Bone Phenotyping Approaches in Human, Mice and Zebrafish – Expert Overview of the EU Cost Action GEMSTONE (“GEnomics of MusculoSkeletal traits TranslatiOnal NEtwork”)

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Brussels, 13 November 2018

COST 120/18

DECISION

Subject: **Memorandum of Understanding for the implementation of the COST Action "GEnomics of MusculoSkeletal traits TranslatiOnal Network" (GEMSTONE) CA18139**

The COST Member Countries and/or the COST Cooperating State will find attached the Memorandum of Understanding for the COST Action GEnomics of MusculoSkeletal traits TranslatiOnal Network approved by the Committee of Senior Officials through written procedure on 13 November 2018.

MEMORANDUM OF UNDERSTANDING

For the implementation of a COST Action designated as

COST Action CA18139
GENOMICS OF MUSCULOSKELETAL TRAITS TRANSLATIONAL NETWORK (GEMSTONE)

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

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

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

The main aim and objective of the Action is to allow researchers in different European countries and abroad to bring together a wide range of expertise surrounding crucial areas of genetic and functional research in musculoskeletal diseases.. This will be achieved through the specific objectives detailed in the Technical Annex.

The economic dimension of the activities carried out under the Action has been estimated, on the basis of information available during the planning of the Action, at EUR 68 million in 2018.

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

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

TECHNICAL ANNEX

OVERVIEW

Summary

The musculoskeletal system is a key element for healthy aging, being mobility a fundamental component of quality of life, health, and independence of aging individuals. The unprecedented amount of discoveries arising from genome-wide association studies (GWAS) have set a new era full of translational potential in the field of musculoskeletal biology. Coupled to the growing understanding of monogenetic disorders, the GWAS discoveries have set a roadmap characterizing the biological pathways underlying the musculoskeletal metabolism. The musculoskeletal field is now confronted with new biology arising in the form of novel factors clustering in known molecular pathways but also with novel factors whose role and function remains to be elucidated. Several opportunities to increase the amount of discoveries like the imminence of whole-genome sequencing efforts, the advent of a new generation of "very-low cost" GWAS arrays and the availability of very large mega GWAS studies like the UKBIOBANK are now in place. The challenge is now about bringing the knowledge arising from high-throughput analysis of increasingly available BIG DATA to a larger set of researchers, who can both contribute to 1)generating additional genetic discoveries and 2) setting the ground for their functional characterization in order to translate these genetic discoveries into meaningful clinical applications. To do this, GEMSTONE will be the mechanism to reach out to a wider range of researchers active in musculoskeletal biology, in order to fuel the production of discoveries and their biological relevance, which will allow their translation to treatments and new molecular definitions.

Areas of Expertise Relevant for the Action	**Keywords**
● Clinical medicine: Endocrinology and metabolism (including diabetes, hormones) ● Health Sciences: Epidemiology ● Basic medicine: Genetic epidemiology ● Basic medicine: Genomics, comparative genomics, functional genomics	● Genomics ● Musculoskeletal system ● Translational Science ● Osteoporosis ● Molecular Medicine

Specific Objectives

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

Research Coordination

● Setup a roadmap facilitating the identification of drug targets that meet the needs of patients with musculoskeletal conditions composed of a coordinated list of functional assessments of genes (and pathways) influencing musculoskeletal disorders; and activities distributed across expertise groups generated by inventarising skills and competences of the network.

● Bring researchers from at least 15 research groups working on big data, bioinformatic innovation and systems biology in animal and human (cell/organisms) models together, aiming to setup a methodological support framework focused on implementing analytical pipelines of existing methods to efficiently manage, integrate, analyse and interpret functional and big data.

● Seek molecular re-categorization of complex diseases of the musculoskeletal system in humans by integrating the knowledge on disease/phenotype definition across the different expertise groups; generating a phenotype map in the first 2 years of cells/tissues, organisms, and human populations and re-evaluated with the output of functional investigations before year 4.

● Bring stake-holders together to plan and seek translational outreach and dissemination of the activities of the action aiming to achieve personalized diagnosis and targeted treatment of patients affected with musculoskeletal conditions;

Capacity Building

● Draw a capacity map within the network and beyond to pinpoint among the groups the existing strength- (expertise) and lacking- (knowledge and resource gaps) areas; aiming completion of the internal (within GEMSTONE) inventory by year 1 and pinpointing the external by year 2.
● Use the capacity map to facilitate knowledge and expertise transfer between high-impact partners and emerging collaborators per discipline, task and skill; aiming to provide a list of priorities governing the planning of the capacity-building activities.
● Transform the aforementioned knowledge transfer into achieved enhanced capacity of the participating partners, resulting in true teaming-up around the objectives (i.e., efficient prioritization of functional assessments and equitable distribution of functional work across collaborators); with provision of updated capacity maps by years 2 (internal) and 3 (external).
● Enrich the capacity of the network further through widespread knowledge exchange and engagement, linking scientific expertise of academia and industry and patient engagement by securing patient representation across activities (among other stakeholders); aiming broad stakeholder representation in at least 5 yearly sessions during the duration of the ACTION.
● Secure endurance of the network by means of prioritizing young investigators as key players in all previously mentioned capacity objectives, setting the basis of a long-standing intergenerational collaboration; procuring that in all activities at least 1/3 of all participants are young investigators.

TECHNICAL ANNEX

1. S&T EXCELLENCE

1.1. CHALLENGE

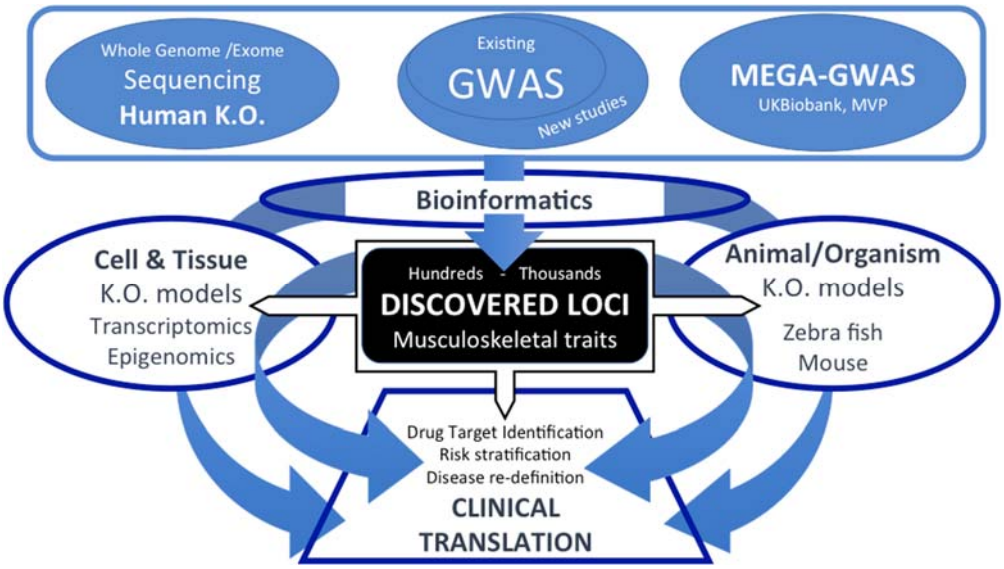
1.1.1. DESCRIPTION OF THE CHALLENGE (MAIN AIM)

The COST Action is envisaged from the perspective of the musculoskeletal system as a key element for healthy aging. The foundation of this vision is based on the recognition that mobility is a fundamental component of quality of life, health, and independence of individuals as they age. In the elderly, lack or limited mobility is a trigger for the development of chronic conditions like osteoporosis, diabetes, hypertension and coronary heart disease among several others. During the last 10 years whole-exome sequencing and genome-wide association studies (GWAS) have substantially progressed biological insights on the genetic determinants of monogenic and complex traits [1, 2]. This has also been the case in the musculoskeletal field, particularly for the identification of genetic factors of osteoporosis and associated conditions [3]. Knowledge derived from even more comprehensive GWAS bases on sequenced reference panels [4-6], but also knowledge arising from monogenic disorders presenting with alteration of bone mass and fragility [7, 8] are increasingly providing novel insight on the key regulatory mechanisms governing skeletal physiology. Such abundance of genetic discoveries pleas for the creation of a roadmap characterizing the biological pathways underlying musculoskeletal metabolism, highlighting the opportunities to translate these discoveries in clinical applications (i.e. the development of new medications). Current treatments for osteoporosis reduce fracture risk by only 25-50% [9, 10] and there are concerns regarding side effects and long-term safety. Similarly, patients with osteoarthritis (another limiting locomotor condition) are asymptomatic in the early stages of disease, develop problems only after significant cartilage erosion has occurred and no drugs are available to prevent or delay disease progression. Thus, there is an urgent need to advance understanding of bone and joint disorders and define new molecular pathways that facilitate development of new treatment options. The potential of incorporating genetic information in the search for suitable drug targets has recently been highlighted by a number of studies demonstrating how successful drug mechanisms are predicted by known genetic associations (i.e. the protein product modulated to elicit a clinical response); and how such improved prediction is perceivable across the whole range of the drug development pipeline, from preclinical and clinical phases to launched drugs. One of these studies also showed that the highest degree of genetic support for drug-target indications was related to the musculoskeletal (bone mineral density), metabolic and blood categories. [11] In this context, drug mechanisms with genetic support are shown to succeed twice as often as those without it (from phase I all the way to approval), and that is the case for osteoporosis drugs as illustrated in the same investigation. Altogether, the aim of this COST Action is bringing together multiple disciplines currently active in the field of musculoskeletal research under a coordinated effort, which allows translating the emerging wealth of genetic discoveries into palpable clinical applications that can help setting the ground for personalized medicine (Figure 1). Studies of extreme phenotypes in humans have been instrumental in identifying molecular mechanisms underlying rare single gene disorders as well as common and chronic diseases, including diabetes and obesity. Such studies have resulted in novel treatments that revolutionise the lives of affected individuals [12-15]. The genes identified to underlie several bone disorders aggregating in families (identified through Sequencing) are starting to reveal a large overlap in the biologic pathways affecting monogenic and complex forms of musculoskeletal and other types of conditions [16, 17]. The biologic insight derived from genes identified through monogenic conditions is huge, as they constitute

"human Knock-outs" providing close to unequivocal evidence of involvement of a genetic cause of disease and open an array of translational opportunities. Application of an extreme phenotype approach to identify rare skeletal disorders in humans has led to discovery of SOST and LRP5 as critical regulators of Wnt signalling in bone [18-20] and resulted in the development of new drugs to stimulate bone formation [21].

The push within the field of microarray technology has opened a new series of opportunities to the large number of well-conducted epidemiological studies on osteoporosis and other musculoskeletal outcomes, which have DNA but have not yet been genotyped for GWAS. The advent of "cheap" arrays opens a new era of discoveries offering the possibility to increase the sample size of **Existing GWAS** efforts and allowing the scrutiny of less-frequent genetic variants in much better powered settings.

Figure 1



This means that many researchers in Europe and around the world will be able to apply GWAS to their samples in the near future and keep thriving the number of genetic discoveries. Similarly, very large efforts on genetic epidemiology launched with **huge sample sizes** by current standards are already making **Mega-GWAS** a reality; with examples like the UKBiobank Study genotyped for 500K samples. These studies are not only "game changers" in the field of genetics of complex traits, but are also brought forward under a policy of free public availability. This means two things: one, that the number of discoveries will increase dramatically, and two, that these data will be widely available to be mined by multiple researchers. Several human **bone cell models** are used to mimic bone metabolic processes in vivo. These allow for easy, fast, non-invasive, reproducible and representative analysis of many molecular processes that take place during differentiation and activity of osteoblasts, osteoclasts and osteocytes. Studying differentiation of mesenchymal stem cells (MSCs) is an insightful model of bone formation model by studying molecular and cellular processes related to stem cell decision-making, osteoblast differentiation and mineralization. Similarly, assays using the key-osteoclast enzyme tartrate-resistant acidic phosphatase (TRAP) allow investigating bone resorption. Osteocytes, by far the most numerous cell type in bone and crucial for mechanosensing, exert effector actions on both osteoblasts and osteoclasts. Studying osteocyte marker genes enables novel genes acting in relation to osteocyte-restricted disease models, such as sclerosteosis and several types of rickets. Evaluating cell models (primary or differentiated) is a crucial step to understand the underlying biology pinpointed by the genetic discoveries. GEMSTONE will play a crucial role coordinating the functional evaluations across genes and pathways, promoting interaction and cross feedback between participating centres and specially limiting unnecessary redundancy and duplicate efforts across teams. The bone- and joint-specific extreme phenotype screens in **knockout mice** will (i) identify novel pathways regulating normal bone and cartilage development, maintenance and resilience; (ii) uncover new genetic determinants of disease; and (iii) provide *in vivo* models to elucidate their molecular basis and investigate novel treatments. Skeletal development and maintenance are regulated by systemic and local factors acting in the bone microenvironment. This complexity only occurs in live animals and cannot be modelled ex vivo. In vitro techniques do not offer an alternative because skeletal development and bone turnover are dynamic processes, whilst mechanical forces,

movement and tissue responses to injury modify bone maintenance. Mice are used extensively in studies of the skeleton. Key molecules that regulate cartilage (e.g. Wnt/beta catenin, Ihh, PTHrP, Sox9, FGFR3) and bone (e.g. Wnt/beta catenin, Runx2, FGFR1, osteocalcin, osterix, OPG, RANKL, TRAP, cathepsin K, TNF) in mice have the same functions in man, and human genetic disorders causing abnormalities of cartilage and bone are recapitulated in genetically modified mice. Similarly, endocrine and metabolic control of bone and cartilage is faithfully preserved in mice and humans. With the International Mouse Phenotyping Consortium seeking to screen KO models for all genes and across a vast array of phenotypes, interaction with groups generating the human genetic discoveries is warranted. GEMSTONE will attempt bringing together groups with access to mouse lines and infrastructure for (musculo) skeletal assessments. **Zebrafish laboratory fish models** hold unique potential to open powerful avenues for skeletal research that are challenging in other vertebrate systems. A growing number of studies suggest that genetic homology between zebrafish and mammals, is deeply conserved. For instance, zebrafish possess the physiochemical (e.g., collagen, hydroxyapatite) and cellular (osteoblasts, osteoclasts and osteocytes) hallmarks of mammalian bone; they express core genes mediating mammalian osteogenesis and respond to known osteoactive compounds. While the skeletons of zebrafish and mammals differ in several aspects (e.g., lack of hematopoietic marrow, diminished participation in calcium homeostasis and a reduced role in resisting gravitational loading), it has been established that zebrafish and humans share the same mechanism of bone formation and remodelling during development and throughout life. However, the use of fish models for bone biomedical research has yet to be widely established. Modern technologies have brought forth new opportunities to identify genetic and phenotypic similarities between fish and mammalian skeletons, as well as translate across fish and human bone physiologies. These efforts by the community may be greatly aided by bringing together established and potential fish users with bone researchers from different disciplines, which is one of the aims of GEMSTONE.

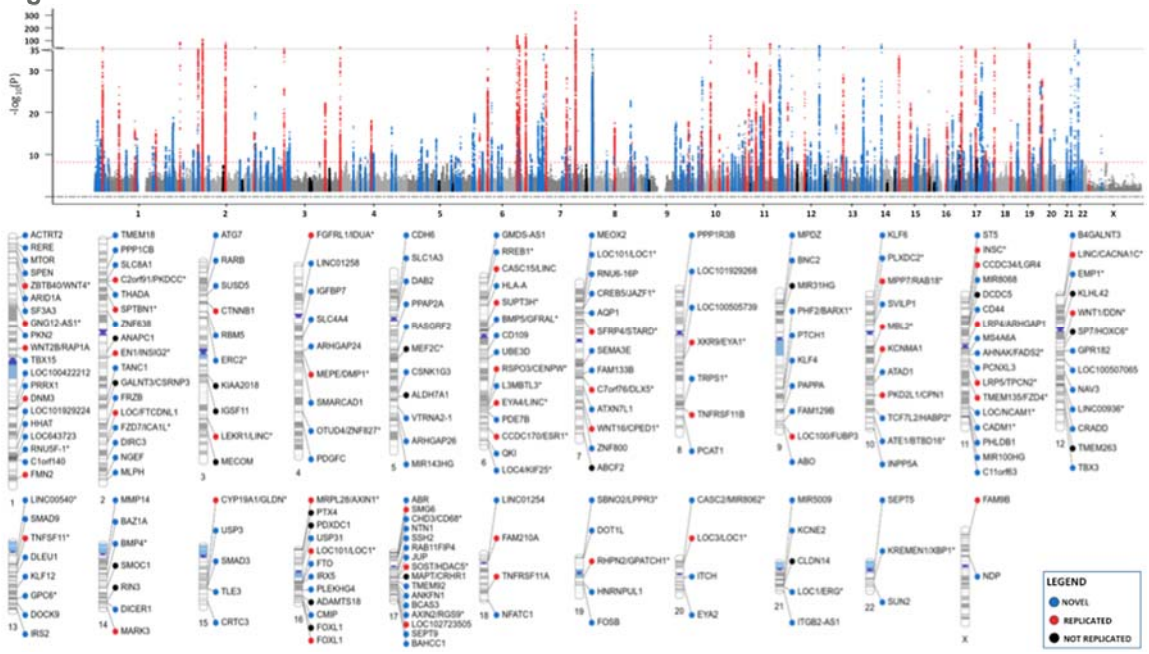
Altogether, this means that the potential to advance the field of musculoskeletal research is huge; yet, faces several limitations that this GEMSTONE COST Action proposes to overcome. To begin with, all upcoming activities intended to be covered by this COST Action requires the organization of the existing expertise across centres, seeking to make an inventory across registered partners in GEMSTONE but also reaching out to eligible groups not included as secondary proposers but that can participate as partners in the future. Yet another limitation is related to the lack of knowledge with regard to the potential advent of a large amount of new GWAS emerging in the near future. As the microarray technology starts to become affordable, this COST Action can expect more than 100K samples from studies on musculoskeletal traits to be GWAS'ed in the near future. Similarly, the provision of large sets of GWAS from large efforts (i.e. UKBiobank, which are made publicly available, requires that several research groups that will be entering directly or indirectly in the "GWAS era" are TRAINED in the use of such data. In addition, the results from the large-scale sequencing efforts and the GWAS also require interpretation and functional follow-up, initially through the use of **bioinformatics** resources allowing high-throughput database mining of the discoveries; followed by the integration of functional studies on prioritized variants and candidate genes. Yet, there are two big limitations hampering the advancement of current and/or future functional evaluations: 1) the lack of certainty surrounding the gene candidacy underlying the associations and 2) the lack of systematic large-scale functional screening that can bout the very high yield in sheer number of discoveries derived from the genetic studies. Being able to achieve functional integration of the genetic discoveries will bring forward the most promising potential of this GEMSTONE COST Action. Namely, being able to translate these discoveries into palpable clinical applications, mostly as the identification of novel drug targets and at later stages, with the identification of biomarkers, strategies allowing risk stratification and molecular disease redefinition. This will be a tangible approximation towards different aspects of personalized medicine. Therefore, this GEMSTONE COST Action will aim integrating and disseminating expertise across multiple disciplines, which is a crucial step to reach its purpose of preventing musculoskeletal disease or treating patients better.

1.1.2. RELEVANCE AND TIMELINESS

We are currently living an unprecedented buoyant period of genetic discoveries that it is almost overwhelming (**Figure 2**). Hundreds (and soon thousands) of genetic leads requiring scrutiny through bioinformatics in-silico and functional in-vivo follow-up is now a reality. Given the very recent and nearing activities uprising in the field of sequencing and GWAS genotyping of musculoskeletal conditions, this GEMSTONE COST Action is fully pertinent to the musculoskeletal field. GEMSTONE will provide the basis for a better understanding of human musculoskeletal diseases and allow the development of new strategies for their prevention and therapy. This will be done thanks to this GEMSTONE Action, which will bring together a pan-European (and near global) platform where the

expertise of researchers in the field of genetics and epidemiology, will be combined with that from researchers working on functional assessments of the musculoskeletal system. This synergistic Action will allow advancing the field of musculoskeletal research closer to personalized medicine applications. The timeliness of this COST Action is also evident as this COST Action will profit from the large current amount of emerging discoveries, will potentiate them even further towards the future, and very importantly will allow to coordinate functional efforts to make the best use of the different expertise and resources.

Figure 2 – UKBiobank GWAS



1.2. OBJECTIVES

1.2.1. RESEARCH COORDINATION OBJECTIVES

GEMSTONE is setup with the aim of allowing researchers in different European countries and abroad to bring together a wide range of expertise (surrounding crucial areas of genetic and functional research in common complex diseases) in a synergistic manner. This is needed to deal with the overwhelming amount of discoveries arising from recent large-scale genetic investigations of the musculoskeletal system and the scarce functional workup following them. Rather than having the expertise scattered throughout Europe (and abroad) working independently, this COST Action will embrace a well-coordinated transnational team, providing expertise and exchanging knowledge within a common objective, which allows the best use of resources. In this context, the main research coordination objectives of GEMSTONE are to:

A. Setup a **roadmap** facilitating the identification of drug targets that meet the needs of patients with musculoskeletal conditions composed of a coordinated list of:

- **Functional assessments of genes** (and pathways) influencing musculoskeletal disorders generated by inventorying, harmonizing and standardizing the wealth of genetic discoveries arising from (past and upcoming) GWAS and sequencing studies in the field of musculoskeletal research; targeting scrutiny of at least 150 genes in 5 years.

- **Activities distributed across expertise groups** generated by creating inventories of skills and competences that will result in a relevant, equitable and efficient coordination of activities allowing to maximize the functional scrutiny of targeted genes (and pathways); assigning to each participating group at least 10 genes in 5 years.

B. Bring researchers from at least 15 research groups working on big data, bioinformatic innovation and systems biology in animal and human (cell/organisms) models together, aiming to setup a **methodological support framework** focused on implementing analytical pipelines of existing robust/standardized methods to efficiently manage, integrate, analyse and interpret functional and big data; sharing program codes/webtools along the project.

C. Seek molecular **re-categorization of complex diseases** of the musculoskeletal system in humans by integrating the knowledge on disease/phenotype definition across the different expertise groups; generating a phenotype map in the first 2 years of cells/tissues, organisms, and human populations and re-evaluated with the output of functional investigations before year 4.

D. Bring stake-holders together to plan and seek **translational outreach and dissemination** of the activities of the action aiming to achieve personalized diagnosis and targeted treatment of patients affected with musculoskeletal conditions; aiming to provide by the start of year 4 lists of: 1) at least 3 druggable targets of interest for the industry, 2) genes to be considered in the diagnosis of monogenic conditions by caregivers and 3) strategies to improve the care of patients.

1.2.2. CAPACITY-BUILDING OBJECTIVES

The COST Action aims at bridging the different fields of science and disciplines of their members (genetic epidemiology, molecular/systems biology, big data/bioinformatics and clinical medicine), into one network that will allow advancing the field of musculoskeletal conditions using a multidisciplinary approach and cross-fertilization of the expertise of its members. Equally important, this COST Action will allow young investigators in the field to broaden their perspectives, learning to embrace collaboration and capitalize from the benefits of working within a network of experts from different disciplines under a common objective. To do this, GEMSTONE will capitalize on the existing local funding endeavours of the partners, and will also foment new applications from the members of the network under a common goal; by definition, this will end up strengthening the applications to each independent national funding agency and maximizing the capacity-building at a national and European level. In this context, the main capacity-building objectives of GEMSTONE are to:

E. **Draw a capacity map** within the network and beyond to pinpoint among the groups the existing strength- (expertise) and lacking- (knowledge and resource gaps) areas; aiming completion of the internal (within GEMSTONE) inventory by year 1 and pinpointing the external by year 2.

F. Use the *capacity map* to facilitate **knowledge and expertise transfer** between high-impact partners and emerging collaborators per discipline, task and skill; aiming to provide a list of priorities governing the planning of the capacity-building activities.

G. Transform the aforementioned *knowledge transfer* into **achieved enhanced capacity** of the participating partners, resulting in true teaming-up around the objective of the action (i.e., efficient prioritization of the functional assessments and equitable distribution of the functional work across collaborators); with provision of updated *capacity maps* by year 2 (internal) and year 3 (external).

H. Enrich the capacity of the network further through widespread knowledge exchange and engagement, **linking scientific expertise of academia and industry and patient engagement** by securing patient representation across activities (among other stakeholders); aiming broad stakeholder representation in at least 5 yearly sessions during the duration of the COST Action.

I. **Secure endurance of the network** by means of prioritizing young investigators as key players in all previously mentioned capacity objectives, setting the basis of a long-standing intergenerational collaboration; procuring that in all activities at least 1/3 of all participants are young investigators.

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

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

Researchers in Europe and around the world are confronted with an overwhelming amount of genetic discoveries facilitated by the emergence of high-throughput genotyping and sequencing technologies, which (with few exceptions) are run under a policy of free public availability, making *big data* available to be mined by multiple researchers. The European Commission has spent millions of euros supporting well-conducted follow-up functional work (https://cordis.europa.eu/projects/home_en.html) focusing on genetic discoveries. Yet, these efforts are currently underway in a slow and competitive way. Such functional investigations are taking place within isolated efforts, which results in gaps of knowledge that slow down the field, in comparison to the proactive feedback and coupling that emerges from working in a network of multidisciplinary experts. GEMSTONE will seek cross-fertilization with existing funded efforts, procuring to setup a network allowing the mining of resources extending from the cell (derived from human and mouse bone samples) to other organism (like mouse and zebra fish) models in a coordinated way. GEMSTONE will attempt this by bringing together diverse centres specialized in functional assessments of the (musculoskeletal system) using such cell and organism models [22-25]. Similarly, the GEMSTONE action seeks embracing the potential of setting up a synergistic collaboration between researchers capable of rapid-throughput skeletal phenotyping of a large set of identified genes knocked-out in cells, zebra fish and mouse models in relation to musculoskeletal phenotypes and place them in the context of investigations at the human population level. Such integration of resources will allow translating gene identification in model cells and organisms to human disease and vice versa. Similarly, monogenic musculoskeletal conditions are also subject of intense investigation with high-throughput technologies, solving many, but also leaving a large fraction of unexplained conditions with still-to-be elucidated genetic origin. Instead of approaching patient care under the context of “one size fits all” policy in terms of diagnosis and treatment, stratifying disease based on novel molecular definitions, and bringing forward novel targeted treatments (which are safer and more efficacious than those developed and formulated broadly), GEMSTONE will enable a research framework going beyond the state-of-the-art.

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

GEMSTONE will procure bridging the different fields of science and disciplines of their members (genetic epidemiology, molecular biology, bioinformatics and clinical medicine), into one network that will allow advancing the field of musculoskeletal conditions by using such multidisciplinary approach. It has recently been demonstrated that using the knowledge arising from genetics (either GWAS discoveries or the knowledge from genes underlying monogenetic conditions) to define drug targets will potentiate the success of the process [11]. GEMSTONE is bringing an unprecedented number of experts in their specific fields into a network working under a unified objective. The knowledge derived from the genetic discoveries will only be materialized after the integration with functional work, fuelled by *big data,* bioinformatics innovation and systems biology approaches, shedding clear translational potential. More than just capitalizing *per se* on the deliverables from the new state-of-the-art technologies available in the field of complex diseases described above, GEMSTONE approaches the challenges with a broader aim, i.e., translating genetic discoveries into tangible clinical applications. Initially, with the most promising venture of identifying new drug targets within the discovered biological pathways, and on the long term, by redefining disease definition on the basis of enhanced understanding of molecular processes. Altogether, GEMSTONE will result in a translational breakthrough in the field, allowing to bring genetic discoveries several steps closer to the patient in the direction of personalized medicine.

1.3.3. INNOVATION IN TACKLING THE CHALLENGE

This GEMSTONE action represents a powerful synergistic strategy to identify novel disease susceptibility genes in humans and to provide disease models for investigation of molecular mechanisms underlying human diseases of the musculoskeletal system. GEMSTONE is innovative in creating a unique multi-disciplinary network of researchers in the fields of genetic epidemiology, molecular/systems biology, big data/bioinformatics and clinical medicine, who in a joint effort will bridge knowledge gaps. The COST Action also extends to other stakeholders involving the participation of several patient organizations and the pharmaceutical industry. GEMSTONE will in this way tackle the major hurdles hampering innovation in care and cure, which is needed to address the

clinical needs of musculoskeletal disorders. The action also extends to stake holders and involves the participation of the pharmaceutical industry and patient organizations. Even though the challenges confronted in the musculoskeletal field is not specific to it, to our knowledge such a pan-coordinated multidisciplinary COST Action has not been applied in the context of other complex diseases. This also means that given the innovative nature of GEMSTONE, this COST Action will serve as a model for future efforts drawn for other complex disorders.

1.4. ADDED VALUE OF NETWORKING

1.4.1. IN RELATION TO THE CHALLENGE

GEMSTONE has a very powerful multidisciplinary network embracing the areas of expertise needed for a successful COST Action. All researchers have recognized trajectories in their respective fields of expertise. GEMSTONE incorporates experts in the fields of musculoskeletal phenotyping including state-of-the-art imaging techniques and clinical definitions of disease; clinical medicine including insightful aspects of therapeutics and diagnostics; monogenic disease of the musculoskeletal system; genetic epidemiology including de GWAS and next generation sequencing areas; bioinformatics including ENCODE project partners; and molecular biology including functional models of (mouse and human) bone cells, organisms (zebra fish and murine), pharmacology and molecular medicine. The strength of GEMSTONE arises from the synergy potential of bringing all this partners and groups into the same network, with common objectives traced by a coordinated plan, setup to maximise the best use of the expertise and resources. As described along the Working Groups, there will be close interaction between the different levels of expertise. In fact, no group of experts in its own will be able to achieve what GEMSTONE can do by placing them in a synergistic platform.

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

GEMSTONE is a new independent network of multidisciplinary experts seeking to embrace all groups willing to share their expertise. Within the GEMSTONE Action, there are several isolated efforts that are under way within a local setting, providing resources, which can be capitalized by this COST Action. Some of them include large ventures like emerging collections of whole-genome sequence samples of the extremes of the BMD distribution; the availability of the UKBIOBANK resource to the international community (holding bone phenotypes); functional groups with access to specimens (e.g. International Mouse Genetics consortium) with state-of-the-art phenotyping facilities for mouse and similarly for zebra fish models. Many of these large-scale projects are made publicly available, reason why a setup like the one proposed by GEMSTONE will facilitate that those groups within Europe and abroad will profit from such derived knowledge. Additional small funding is spread across the network to perform a limited number of functional evaluations (i.e. zebra fish, cell models) making a case in favour of GEMSTONE, to make the best use of resources, allocating the functional evaluations where they are needed to cover the existing gaps in knowledge and to avoid inefficient use of resources due to redundancy and duplicate efforts arising due to lack of coordination. In addition, GEMSTONE will also encourage the application of different research groups for funding at a local setting but embraced within the common objective of the COST Action. This strategy will also make the application to the local funding agencies much more likely to be funded, both because of the transfer of knowledge within the network but also by the larger benefit of synergy at a broader level with other initiatives. Last, but not least GEMSTONE will reach out and embrace funded work carried out by past and current efforts on musculoskeletal research across Europe and beyond (in particular seeking cross-fertilisation with FP5, FP7 and H2020 projects listed in CORDIS including GENOMOS, GEFOS, TALOS, MOSAIC, AGEING SKELETON, BONEMATCH, RESCBONE and PoCOsteo.

2. IMPACT

2.1. EXPECTED IMPACT

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

In the short-term and at a **scientific** level, the COST Action will greatly contribute in positioning Europe in the forefront of research in the field of genetics of osteoporosis and musculoskeletal disorders. More specifically, the COST Action will bring together international researchers within a

global collaborative framework where European, Australasian, Canadian and US-American funding agencies co-sponsor simultaneously concerted initiatives with common goals and objectives thus stimulating co-investment in common resources under a cost-effective strategy. Moreover, the COST Action will facilitate the communication and knowledge bridging between several dozens of studies on musculoskeletal conditions from at least 25 (21 COST Countries) that have their populations genotyped with state-of-the-art technology and/or phenotypic assessments specialized on musculoskeletal content. Within the COST Action's framework, a unique scientific milieu will be conditioned where several aspects of musculoskeletal disease heritability will be set forward including trans-domain features like patient involvement and cohort build-up, phenotype enhancement, outcome prioritization, development of new drugs and assays. The long-term impact of the COST Action at a **scientific** level will be the identification of genes and gene networks that contribute to musculoskeletal diseases. Fundamental principles of systems biology, i.e., pathway interactions, gene-environment interactions, gene regulatory networks will be studied and the molecular basis identified. These discoveries will allow the European research community to make a major scientific contribution to the field of complex genetics, systems biology and generation of experimental model systems for human diseases. The knowledge created will allow a better understanding of the biological mechanisms that cause musculoskeletal disease and thus, to devise new strategies for diagnosis, prevention and therapy. The establishment of a common phenotype database transcending the diagnosis of musculoskeletal conditions in humans and extending to the model cell and organism level will allow exploring new types of genotype-phenotype relationships at a new level of more comprehensive and yet unprecedented complexity. New tools will be developed that will aid the analysis of human diseases in human cohort and case-control studies, with the ultimate intention to translate this to the clinical setting, in the form of personalized medicine strategies focusing on drug target identification and novel redefinition of disease at a molecular level. Equally important, this COST Action will allow young investigators in the field to broaden their perspectives, learning to embrace collaboration and capitalize from the benefits of working within a network of experts from different disciplines under a common objective.

The short-term impact of the COST Action at a **technological** level will be plentiful, bringing novel analytical approaches and providing access to technologies to countries and/or institutions lacking them. The advent of technological skills will be accelerated by means of access opportunities facilitated by the network. The theoretical knowledge surrounding the use of technological applications will be coupled to actual execution of tasks either at a local down-scaled feasible context or become possible for actual task execution by means of visiting opportunities (i.e., STSMs). In the short-term, the scientific activity fostered by the COST Action will potentially identify new bone metabolism pathways which will be of great interest for the industry as novel drug targets. In addition, if fracture risk prediction is improved by combining genetics with markers of bone turnover or bone structure, this would also create interest from the companies that produce assays or instruments that can measure these markers. In the long-term, the impact of the COST Action at a **technological** level will allow expediting patient care since the scientific activity fostered by the COST Action will potentially identify new bone metabolism pathways, which will be of great interest for the industry as novel drug targets. In addition, if fracture risk prediction is improved by combining genetics with markers of bone turnover or bone structure, this would also create interest from the companies that produce assays or instruments that can measure these markers (i.e., as pursued within the H2020-funded PoCosteo project among others). Furthermore, creation of an osteoporosis or osteoporosis-muscle or osteoporosis-muscle-fragility genetic chip would also generate interest from industry, enriched with pharmacogenetic applications.

The COST Action is expected to have a multidimensional **socioeconomic** impact. In the short-term, the COST Action is expected to raise public awareness about musculoskeletal disorders in general and their genetic risk more specifically, as well as to identify patient-important outcomes for prioritization in shaping the future musculoskeletal research agenda. Besides the dissemination of the scientific progress achieved during the COST Action per se, the workshops and events that will include the general public, patients and patient organizations are expected to communicate the importance of early detection and precise, personalized treatment of major musculoskeletal complex disorders such as fracture. Moreover, the COST Action will reach out to patient organizations of rare monogenic musculoskeletal disorders and spread the word that the list of rare variants with very large effects is now greatly enriched and that risk identification will be feasible for still-unresolved cases. In the long-term, the COST Action will serve the collaborative effort of burden of disease attributed to musculoskeletal disorders being decreased through enhanced primary and secondary prevention and better quality of care. Thus, beyond the personal impact on millions of people around the world, the COST Action is expected to alleviate the major and continuously growing socioeconomic burden of

osteoporotic fractures and of other less common but equally severe musculoskeletal disorders (i.e., osteoarthritis, sarcopenia and frailty); Direct costs for medical, hospital and surgical care are expected to be reduced, indirect costs that result when patients lose their independence and require nursing care either at home or in institutions are expected to be controlled, loss of work days and income among adults who are still active in the work place are expected to decrease as well as the lower opportunity costs for (family) caregivers. By providing networking opportunities in Early Career Investigators, the COST Action is expected in the short-term to greatly enhance capacity building in the field of musculoskeletal disorders by connecting high-quality scientific communities throughout Europe and worldwide; and training young scientists from different fields and of different mentalities within the same framework. In the long-term, the COST Action will contribute in forming a generation of scholars and health professionals adequately trained and sufficiently interlinked to rise up to the challenges of Big Data generation, handling, analysis and translation with the ultimate goal of a targeted, optimized health care specifically in relation to musculoskeletal conditions. Finally, the COST Action is expected to increase the impact of research on policy makers, regulatory bodies and national decision makers as well as on the private sector. In the long-term, the COST Action will contribute in formulating a global taskforce where all stakeholders will be involved each reaching out to interact productively into a smooth bench-to-bedside translational circle. From a health policy perspective, all the aforementioned impact aspects will ultimately lead to personalized, evidence-based, cost-effective treatment strategies for musculoskeletal disorders.

2.2. MEASURES TO MAXIMISE IMPACT

2.2.1. PLAN FOR INVOLVING THE MOST RELEVANT STAKEHOLDERS

The COST Action will endorse a standardized procedure for stakeholder involvement following the Concannon 7Ps of Stakeholder Engagement and Six Stages of Research, covering all listed categories, balancing different perspectives, and being representative. The various stakeholder groups will be invited to participate in the planned Working Group not on a linearly proportional fashion but after consideration of their relevant weight in the Working Group activities. For example, patient groups will be more heavily involved in the phenotype-related Working Group compared to the bioinformatics Working Group. We now have GEMSTONE participants who joined as COST Action representatives of local and pan-European patient organizations from monogenic musculoskeletal conditions including skeletal dysplasias and disease specific ones, like osteogenesis imperfecta. From the seven groups we also have network members representing the pharmaceutical industry, who joined the network with the intention of taking part in the training venues in a bidirectional manner. They will aim presenting to researchers the goals laid out by the industry, and researchers will couple them with the genetic discoveries facilitated by the COST Action. A structured Stakeholder Involvement Strategy will be implemented from the very beginning of the COST Action, which will include interacting steps: a) visioning sessions, key informants interviews and formation of a Stakeholder Advisory Committee, b) participatory mapping, c) surveys, workshops, and focus groups, d) social media boosters, tools cafes, and citizen science targeting that all instances have equal opportunity and access to the capacity building resources and the scientific production of the network. Special attention will be placed on the transfer of knowledge and skills to sectors and partners of COST Inclusiveness Target Countries (ITC).

2.2.2. DISSEMINATION AND/OR EXPLOITATION PLAN

Stakeholder	Measures and channels	Anticipated outcome
Scientists	Open access publications in high –impact journals and announce preliminary findings in international conferences and meetings described below.	Uptake of GEMSTONE output to advance research in the field of musculoskeletal research
Healthcare professionals	In-conference meetings and round-tables will be pursued at major venues (like the meetings of the European Calcified Tissue Society and International Osteoporosis Foundation,	Uptake of GEMSTONE output by implementation of startegies directed to improve patient care in Europe and worldwide.
Patient organisations	The ACTION will seek drawing new initiatives to increase the knowledge on musculoskeletal diseases and will work with National and European organizations to disseminate results in their media (magazine, web, social media).	Patient empowerment by advancing knowledge of scientific developments & feedback patient perspectives on current unsolved needs.
Pharmaceutical industry	Brainstorming sessions within the ACTION and in outside venues (scientific congresses) allowing knowledge exchange that will translate genetic discoveries into substantial contributions to healthy aging and personalized treatment.	Uptake of ACTION output in the development of novel drug pipelines.
Policy makers	Drafting two positions (White) papers at the beginning and in the end of the ACTION, in high-impact field-specific journals stating goals, objectives and achievements of the ACTION.	Uptake of ACTION output for improving locomotor health of citizens in Europe and worldwide. Containing costs for health systems, societies, but specially the individual (patient).
Young investigators	Training sessions at co-located and co-organized meetings, workshops, conferences, training schools and short term scientific missions (STSM)	Preparing our next generation of scientists to become leaders of tomorrow who will perpetuate the missions of the ACTION.
General public	The ACTION activities and meetings will be followed by newsletters, bulletins and letters to the lay press.	Promotion and dissemination of the GEMSTONE ACTION and of its results and achievements.
All	Finally, the ACTION-specific website will serve as a repository of ACTION-related data and events; as a training resource;; and as a dissemination portal to the outside world.	Wide-spread uptake of the ACTION within and among at all stakeholder levels and inviting non-participants to join.

2.3. POTENTIAL FOR INNOVATION VERSUS RISK LEVEL

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

The COST Action will be implemented under the best available circumstances. The network will embrace remarkable scientific output resulting publication-wise in high impact genetic and musculoskeletal speciality journals. Moreover, the COST Action will provide the new network with the unique opportunity to gain momentum and advance its activities up to the next level of translational dynamics and full muti-domain involvement. The scientific activities facilitated by the COST Action are expected to contribute to the identification of new molecular pathways underlying musculoskeletal conditions like osteoporosis, fracture, sarcopenia and frailty; they will build up from developing coordinated innovative evaluations in cellular and animal models, extending to drawing strategies to reassess current strategies for the: 1) management of disease risk and progression, 2) development of improved diagnostics using molecular definitions of disease, and 3) identification of novel therapeutic targets.

Despite its high-profiled, ambitious scientific objectives, the COST Action-related activities will safe-guard against risks related to the pursuit of innovation. These risks may emerge around: 1) the choice of genetic discovery leads; 2) the capacity potential of the Working Groups; 3) the coordination of interaction activities and deliverables between the working groups; 4) the general timeliness of the proceedings within the COST Action; and 5) failure to transcend outside the network. The network is in a powerful position to handle risks related to non-completion or under-performance of the scientific activities due to the established record of international collaboration among the members, yielding breakthrough scientific contributions. Organizational, financial and turbulence risks will be stabilized

given the well-organized management and contingency plans (described below) and the considerable experience of the network in working with large-scale projects.

3. IMPLEMENTATION

3.1. DESCRIPTION OF THE WORK PLAN

3.1.1. DESCRIPTION OF WORKING GROUPS

WG1 "Study populations and expertise groups": The objective of this Working Group is to create, maintain an update the studies and group of experts conforming the network. The European research groups will be central to these organizations but will also reach to an international setting in the Americas and Australasian regions, procuring to maximize the enrichment of the network. Also, the conditions and phenotypes that will be studied will not be confined to specific populations groups. On the contrary, the multidisciplinary network will hold expertise within a broad outreach to the target populations including aspects of age (where both children and adults will be study, the former more in the context of health aspects); sex distribution (where conditions in men and women will be weighted equally) and ethnic or social aspects (reaching out to studies performed not only in European populations. The WG will focus on collecting information on the expertise of the distinct research groups active on musculoskeletal research in Europe and abroad. Such inventory will allow pinpointing focus groups defined by phenotype, functional and methodological expertise. The information collected by the inventory assembled by WG1 will be the backbone for allocating the appropriate emphasis and resources to follow-up studies and knowledge exchange, procuring to recruit and couple the different levels of expertise existing in the network. **DELIVERABLES:** D1. GEMSTONE Ecosystem Report: Network map, inventory, balance assessment, capacity and resources; Stakeholder Analysis Report; and Target Populations Analysis Report (website, documents).

WG2 "Phenotyping": The objective of this Working Group will be to describe ways to decompose the phenotypes of the different genetic studies into meaningful components that will aid the interpretation of the identified biological pathways. A "think tank" will be assembled across different layers of expertise including clinical definitions of disease (i.e. fracture, sarcopenia, etc), imaging applications and molecular definitions in humans, but also through the information derived from other cell and organism models on disease processes; the interaction of the different members of the "think tank" will enable the possibility of integrating the different approaches into one working definition of musculoskeletal disease. This Working Group will allow tracing a phenotypic roadmap to dissect the heterogeneous components of disease into more homogeneous and molecularly defined processes. This will allow re-defining disease towards a better understanding of the underlying process and this way having a better likelihood of being able to tailor treatments. This is one step away from the rule "one prescription fits all" and closer to palpable personalized medicine strategies. This Working Group will also be crucial to establish the transportability of disease mechanisms and phenotyping between species, which is an important step to allocate resources to efforts that are most likely to have an impact on the understanding of disease mechanisms. Further, training on phenotyping techniques will be pursued across the expertise hubs of the network, seeking the setup of a phenotype map in the across cells/tissues, organisms, and human populations. **DELIVERABLES**: D2. Position paper on phenotypic variability and endophenotype definitions of osteoporosis in humans and skeletal traits in animal models (document).

WG3 "Monogenic conditions- human KO models": The objective of this Working Group up will initially be to make an inventory of all the genes underlying monogenic conditions presenting with a clear musculoskeletal phenotype. After this, the main focus of WG5 will be to evaluate the overlap between this list of genes and those genes characterized by WG4 and trace them back into common biological pathways. This WG will also liaise with WG3 and WG4 providing lists of genes that can be taken forward for functional follow-up and bioinformatics mining. **DELIVERABLES:** D3. Monogenic disorders database (website) and Monogenic disorders genes and mutation report (document). D4. Report of the monogenic disorders public event summit with participation of members from the scientific network and other stakeholders (meeting).

WG4 "Functional investigations": The objective of this Working Group is to initially liaise with WG1 to make an inventory of the expertise across functional groups of the network with a trajectory on "wet lab" cell and organism models of the musculoskeletal system. Then, in cooperation with WG2 it will work on coupling and establishing correspondence between the phenotype characterizations at the

human population and clinical case level and the different functional models arising from the cell and organism models. Finally, it will also perform an assessment of the very numerous genetic discoveries and procure classifying them into “functional units” within biological pathways but also considering the existing expertise across the groups. This “functional units” will be the building blocks to distribute the workload of functional efforts across the different groups available with the aim of avoiding redundancy and facilitating complementary activities. Exchange of skills and knowledge between the participating groups will be procured in close interaction with WP6. **DELIVERABLES:** D5. Report of the biological pathway integration summit (meeting) with participation of representatives from all the Working Groups of the network (document). D6. Report on the “functional units” methodological framework (including principles, applicability, generalizability (document); Functional Units Analysis Results for Bone Disease (document).

WG5 “Bioinformatics”: The objective of this Working Group will initially be to make an inventory of all the genetic discoveries arising from the distinct efforts. This will be followed by the integration of databases and resources from the public domain, but also those assembled from the different functional Working Groups of the network as inventoried by WG2, which will allow the mining and characterization of the discoveries extending from genetic variant to gene implication, to biologic pathway involvement, all up to phenotypic determination. This WG will also liaise with WG3 providing lists of variants and genes, which can be taken forward for functional follow-up. Exchange of skills and knowledge between the participating groups will be procured in close interaction with WP6. **DELIVERABLES:** D7. GEMSTONE Knowledge database creation and (website) implementation with writing of a database report (document). D8. Report of the knowledge database summit (meeting) with participation of representatives from all the Working Groups of the network (document).

WG6 “Translational outreach”: The objective of this Working Group is to make a synopsis of the knowledge derived from the integration of activities and expertise provided by WG1, WG2, WG3, WG4 and WG5, in order to constitute a roadmap for the identification of drug targets by means of pinpointing molecules and factors within biological pathways that can be suitable for future investigations in a potential therapeutic context. This will be done by reaching out to active researchers within the pharmaceutical industry using genetic resources, asking them to share their expertise and knowledge with the GEMSTONE network, by means of web-based seminars, workshops at scientific meetings and/or research partner mobility schemes to their centres. **DELIVERABLES** D9. GEMSTONE translational potential report on pathways and factors with inventory of relevant interested stakeholders (document). D10. Report of the drug targets summit (meeting) with participation of representatives from all the Working Groups of the network. D11. Report of the GEMSTONE translational public event summit with participation of members from the scientific network and other stakeholders (meeting).

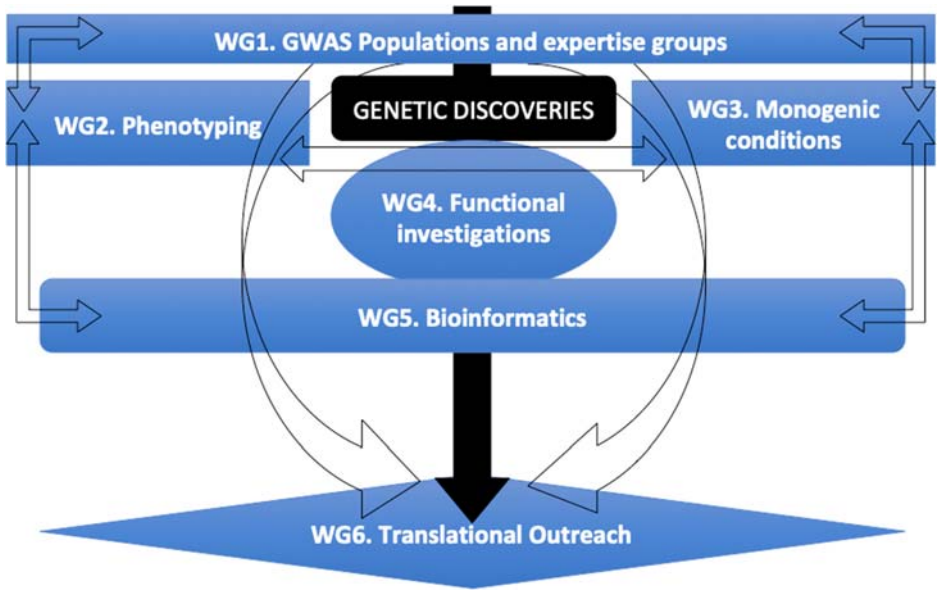
GEMSTONE COST Action - GLOBAL DELIVERABLES PER OBJECTIVE

Objective	Description	Deliverable	WG's involved	Due
A1	Functional assessment of genes	List 150 genes	WG**4**, 1, 3, 5	Years 2-4
A2	Activity distribution across functional groups	List 10 genes p/year - p/group	WG**1**, 4	Yearly 1,2,3,4,5
B	Methodological support framework	Sharing program codes/webtools	WG**5**, 6	Years 2-5
C	Re-categorization of complex diseases	Phenotype Map 1 Phenotype Map 2	WG**2**, 3,4	Year 2 Q1 Year 4 Q1
D	Translational outreach and dissemination	- 3 drug targets - list Dx genes - care strategies	WG**7**, 3,4,8	Year 4 Q3 Year 4 Q1 Year 4 Q3
E	Draw of internal and external capacity map	Inventory 1 (Int) Inventory 2 (Ext)	WG**6**, 1,2,4,5	Year 1 Q4 Year 2 Q4
F	Knowledge and expertise transfer	Priority list capacity building	WG**6**, 1,2,3,4,5	Year 2 Q4 Year 3 Q4
G	Achieved enhanced capacity	Update capacity map/inventories	WG**1**, 6	Years 1-4
H	Linking expertise academia/ industry & patient engagement	Broad stakeholder representation	WG**6**, 2,3,4	Years 1-5
I	Secure endurance of the network w/ young investigator engagement	1/3 participation	WG**6**	Years 1-5

3.1.2. GANTT DIAGRAM

WG	DESCRIPTION	YEAR 1				YEAR 2				YEAR 3				YEAR 4			
		Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
1	Study populations and expertise groups																
2	Phenotyping																
3	Functional Investigations																
4	Bioinformatics																
5	Monogenic conditions																
6	Translational outreach																

3.1.3. PERT CHART



3.1.4. RISK AND CONTINGENCY PLANS

The COST Action will be implemented in a well-orchestrated, plan-in-advance fashion covering the following. Risk (R) and Mitigation plan (M): **R1**. Choice of genetic discovery leads is not sound – M1: while some leads may fail the large amount of discoveries provides new opportunities and improve through learning process; **R2**. Capacity potential of the Working Group is suboptimal - M2: Redundancy of expertise is tolerated allowing back-up plans; **R3**. Coordination of interaction activities and deliverables between the Working Groups fails – M3: Close monitoring of the proceedings of the COST Action will be warranted to secure deliverable flow; **R4**. General timeliness of the proceedings within the COST Action – M4: delays along the project are not highly prejudicial allowing interventions pinpointed by close monitoring; and **R5**. failure to transcend outside the network – M5: members of the GEMSTONE network are part of distinct scientific networks. For each Working Group and besides the Working Group Leader, a deputy leader will be assigned who will be able to support or substitute the leader's duties. Stakeholders' involvement will be safeguarded by the creation of a stakeholder reserve list so that additional event participants can be promptly summoned in case of unexpected absences. A similar approach will be implemented for the participation of young investigators where every nominated young investigator will in turn nominate another junior colleague who will fill-in in case of attrition.

3.2. MANAGEMENT STRUCTURES AND PROCEDURES

Within the COST framework, research groups from more than 17 COST Countries studying bone disorders will collaborate and disseminate knowledge with a special focus on embracing new and young researchers. The COST Action will bring together the expertise of groups already funded by national research councils and European resources but will also aim at extending the number of participants who will need to secure further funding to conduct research. The instruments applied towards that end will be scientific meetings and workshops, training schools and Short-Term Scientific

Missions (STSM). The **Management Committee** (MC) will coordinate the COST Action with at least one member from each participating country and one Working Group representative on board. A MC chair will be appointed for the general organisation of the COST Action and the representation of the COST Action towards the EU and the public. There will be two MC meetings per year where decisions will be reached about activities to be held and organization thereof. Moreover, the MC will be taking executive decisions related to allocation of funds according to the emerging scientific needs. It will be the responsibility of the MC to prepare the major MILESTONES, the annual reports and the final report. There will be a kick-off MC meeting where the objectives, goals and deliverables will be finalized and where the WGs will take their final form and commence their activities. Once a year, a **General Assembly** (GA) will be summoned with accompanying plenary symposia and/or workshops. There will also be a concluding conference highlighting the COST Action's outputs. The WGs will cover the major activity domains, will involve both junior and senior researchers, will appoint a WG leader and will be coordinated by the **Steering Group** (SG) formed by the Working Group Leaders. Beside the perpetual Working Group interactions, targeted WG activities and meetings as steered by the MC will be held at least twice yearly and will a) bring together the WGs for sharing knowledge and methodology, b) allow for the occasional participation of non-COST participants, c) plan further collaboration and STSMs, d) appoint special purpose committees, and e) facilitate dissemination of knowledge to societal end users. The WG leaders will be responsible for providing biannual reports to the SG and the MC. All activities and meetings besides the closed MC and SG meetings will be open to the scientific community and the public and will be promoted as such. STSMs are critical for supporting visits of early-stage researchers. A concluding conference, publications, position papers, biannual meetings and STSMs will serve as intermediate milestones. To facilitate knowledge and expertise exchange between members of the network a Training School Coordinator will work with at least two Early Career Investigators to create a think tank that will dictate the priority topics addressed by the activities of the action (e.g., supporting individual research groups, which are new to genetic investigations using GWAS and sequencing data, training of young researchers in the fields of genetic research, phenotyping, functional (models) techniques and bioinformatics) and in charge of identifying suitable training experts to give courses to the different research groups involved in the network and mentors for the activities of young investigators. In addition, this think tank will work with the MC to oversee the review of applications, selection of candidates and training activities to be funded. The **COST Action specific website** will serve as a repository of COST Action-related data and events; as a training resource; as an invitation to join the COST Action; and as a portal to the outside world. The **COST Action** will be in **liaison and interaction** with national efforts in other countries, yet differing in their objectives and expected outcomes, and therefore, without effort duplication. The MC will place **Gender balance** and the involvement of **Early Career Investigators** as a standard item on all its agendas, providing them with logistic support to organize among others, a Young Investigators' Network (website); Young Investigators' Induction Event (meeting); and at least two young Investigators' Assembly & Conferences. Finally, the Training School Coordinator will be in charge of producing a Young Investigators' Network Analysis Report (document).

3.3. NETWORK AS A WHOLE

The initial network included 55 members from institutions in 17 COST countries, one (1) Near-Neighbour Country (NNC) Institution and three (3) COST International Partners, with 52.7% female proposers, and achieving outreach in 35,3% of ITC's. All the partners from Inclusiveness Target Countries (ITC) are actively involved with at least one of the core activities of GEMSTONE including functional studies, National biobanks with genomic assessments, study of pedigrees of monogenic conditions, bioinformatics, medical education and translational or clinical medicine, reflecting clearly the multidisciplinary spread of knowledge that is targeted. The aim is to increase further the number of participating ITCs through active promotion, organisation of events in ITCs, and using the COST Targeted Network BESTPRAC resource (www.bestprac.eu) during the first year to promote the project in all ITCs; asking the BESTPRAC members to spread the word on GEMSTONE in their countries through their channels. Additional partners COST countries will also be included in the network. The COST Action is likely to grow with the inclusion of more researchers within spans across different domains including but not limited to clinical scientists, geneticists, functional scientists, epidemiologists and the industry. There is a combination of young and senior leadership from networks in the most active musculoskeletal research scientific societies spanning from young investigators networks to members of the board of the societies and journals. ECIs will be significantly represented in all COST Action activities and meetings, seeking to carry forward and lead the WG-related activities, to identify and disseminate the innovative output of the COST Action, to interact with each other and create a network within the network with much more intense activity and feedback. All partners have an

impressive record of competitive funding accrual by either the EU or other national funding agencies. The network has reached out to National and European patient groups and organizations who are now members of the GEMSTONE network. There are also close links to policy makers, who will be involved in the COST Action's activities mostly through partners active in the board of the European Calcified Tissue Society (ECTS) and the International Osteoporosis Foundation (IOF). Last but not least, we have network members from the industry who are pioneers and leaders in the use of genetic information for the optimization of drug target discovery. In addition, the GEMSTONE COST Action will appoint a Science Communication Manager who together with the MC will be in charge of coordinating the outreach and dissemination activities. The Science Communication Manager will foresee that a global overview of the on-going activities is available to the members of the network in order to avoid duplication of efforts and warranty the best use of resources. The Science Communication Manager will work with the MC to ensure the best scenarios are present to facilitate the interaction of researchers within the network and to procure outreach to clinicians and other stakeholders. For the latter, meetings will be organized either at a distance (web forums or teleconferences) or within face-to-face meetings (dedicated or in parallel to congresses of the musculoskeletal and/or genetic societies) procuring the highest participation possible of network members. Outreach to clinicians will be procured through the organization of targeted venues during congresses, while the dissemination of results and advances will be done through websites and/or bulletins. In conclusion, this COST Action will provide an important collaborative activity boost to small scale and transient collaborations already existing between small nodes of the network, which are expected to grow into a well-coordinated, solid and long-term global network. At the network level, the partnerships will also provide direct access to additional funding opportunities for NCC and ITC partners and thus an expanded international offering, open up new regions for early investigator mobility between these groups of partners, foster and strengthen partnerships and engage with new fields of international research, thriving GEMSTONE into a global leading effort in the field of personalized medicine.

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