Executive summary:

The AIM of the Genetic Factors of Osteoporosis (GEFOS) Seventh Framework Programme (FP7) project is to identify osteoporosis susceptibility alleles by meta-analysis of Genome-Wide Association Studies (GWAS) comprising a large collection of osteoporosis genetics cohorts in Europe and outside (n=46.000). Prospective meta-analysis of GENOMOS, a large consortium of (non-GWAS) genetic studies on osteoporosis (n=80.000), is used to assess generalizability of genetic effects and develop sufficient power to quantify even small, but clinically important risks. The improvement in clinical risk-assessment for osteoporosis by adding the diagnostic panel of osteoporosis risk-alleles identified in this project will be quantified in prospective studies including the evaluation of both genetic and classical risk factors.

The project develops within the context of seven work packages including:

-WP1. Assembly GWA datasets;
-WP2. Replication de-novo genotyping;
-WP3. Reiterative meta-analysis;
-WP4. Selection novel phenotypes;
-WP5. Gene-environment interactions;
-WP6. Risk modelling genetic markers; and
-WP7. Field Synopses.

The project management (WP8) is performed by the coordinating centre at Erasmus Medical Centre Rotterdam, The Netherlands.

The GEFOS Project has been in the forefront of the latest genetic discoveries in the field of osteoporosis using the Genome-wide association approach, followed by large scale de-novo replication of hundreds of markers. To date, 56 BMD loci have been discovered of which 14 were found associated with risk for all-types of fracture. Insight into the relations between BMD and fracture has been obtained from associations with other osteoporosis traits, including structural assessments (i.e., pQCT), biomarkers and hormone levels. At present, several initiatives using GWAS are underway for any type of fractures, and site specific forms (i.e. hip, vertebral and wrist). This GEFOS coalition of expert investigators in the field of genetic osteoporosis has brought together more than 150,000 samples arising from more than 50 studies over the world, to become the largest collection worldwide of samples with bone phenotypes.

Project Context and Objectives:

Osteoporosis is a common, age-related disease with a strong genetic component. With increasing age of the population, Europe is facing a substantial increase in osteoporotic fractures, which account for considerable disease-burden and costs. It is estimated that, 30 to 50% of women and 15 to 30% of men experience an osteoporosis-related fracture during their lifetime(1). Osteoporosis-related fractures are associated with increased mortality, morbidity and reduced quality of life. Annual costs of hospitalization for osteoporosis-related fractures exceed those drawn from other expensive non-communicable diseases including stroke, myocardial infarction and breast cancer. Of all fractures, hip fracture is the most ominous complication of osteoporosis as it is associated with increased morbidity and mortality(2). The incidence of hip fracture increases exponentially with age. Survivors of hip fracture experience chronic pain, reduced mobility and increasing degree of dependence. The direct and indirect costs involved with hip fractures alone are substantial. It is estimated that, in Europe, 179,000 men and 611,000 women sustain hip fractures each year and the estimated cost surpasses more than 25 billion EUROS(3). Osteoporosis-related vertebral fractures commonly occur in the lower thoracic or upper lumbar vertebrae. Although the incidence of vertebral fracture increases with age, the true prevalence of vertebral fracture is not known, as only one third of vertebral fractures come to clinical attention(4). The other most frequent type of fracture is that of the distal radius and ulnar, which are commonly seen in both middle aged and elderly women.

Early identification and treatment of subjects at risk can help prevent this, and genetic susceptibility alleles are the most promising risk factors in this respect. Further, increasing the knowledge on the underlying physiopathology of the disease can aid the identification of drug targets and the development of new compounds for the treatment of disease. Recent advances in genotyping technology have enabled the use of the hypothesis-free Genome Wide Association Study (GWAS) approach to detect common gene variants, of modest effect size. In contrast to genome-wide linkage, the GWAS approach does the hypothesis-free screening at a much higher density of DNA markers and does not require related subjects. GWAS are usually based on large sets of cases and controls or on population-based cohorts, using the classical epidemiological tool of association analysis to establish a correlation between the DNA marker and the causative gene of interest. GWAS has been extremely successful in the identification of risk genes for many complex diseases.

This is mostly due to the wide availability of existing and on-going epidemiological study-populations in which the power of novel genomic technologies can be applied. This is also the case in the field of osteoporosis where dozens of well conducted epidemiological studies with DNA collections will allow setting up collaborations where to identify the genetic variants underlying the risk for osteoporosis and fracture. The AIM of the GEFOS Seventh Framework Programme (FP7) project is to identify osteoporosis susceptibility alleles by meta-analysis of Genome-Wide Association Studies (GWAS), comprising a large collection of osteoporosis genetics cohorts in Europe and outside (n=46.000). Prospective meta-analysis of GENOMOS, a large consortium of (non-GWAS) genetic studies on osteoporosis (n=80.000), is used to assess generalizability of genetic effects and develop sufficient power to quantify even small, but clinically important risks. The improvement in clinical risk-assessment for osteoporosis by adding the diagnostic panel

of osteoporosis risk-alleles identified in this project will be quantified in prospective studies including the evaluation of both genetic and classical risk factors. Further, the identification of biological pathways involved in bone biology and the disease process will provide the opportunity to translate this knowledge into compounds use for the treatment of osteoporosis.

The project develops within the context of eight work packages, including:

-WP1. Recruitment of GWAS
-WP2. Replication by de-novo genotyping
-WP3. Reiterative meta-analysis of GWAS
-WP4. Selection and analysis of new phenotypes
-WP5. Gene-environment interactions
-WP6. Risk modelling genetic markers
-WP7. Field Synopses
-WP8. Project Coordination

The project management (WP8) is performed by the coordinating centre at Erasmus MC Rotterdam, The Netherlands.

In addition, the main objective of the coordinating centre (WP8) is maintaining communication between the European Commission and the researchers, organizing periodic meetings and allocating resources for the adequate functioning of the project.

1. Identify osteoporosis susceptibility alleles for fracture risk and for bone phenotypes, by performing meta-analysis of already funded GWA studies comprising greater than 45.000 samples in Europe and outside (WP1, WP3).

2. Seek replication and explore the generalizability of the associations by prospective meta-analysis in the large extended GENOMOS collection of greater than100.000 samples (WP2, WP3).

3. Explore the genetic basis of more novel bone phenotypes such as quantitative ultrasound, bone geometry, and biochemical markers (WP4) and gene-environment interactions (WP5).

4. Seek clinical translation of the results by evaluating identified risk alleles for their predictive power in prospective cohorts with documented classical risk factors for osteoporosis (WP6).

5. Summarize the data from the project in the context of the whole field by publishing data synopses at regular intervals (WP7).

In addition, the main objective of the coordinating centre (WP8) is maintaining communication between the European Commission and the researchers, organizing periodic meetings and allocating resources for the adequate functioning of the project.

Project Results:

During the contract period the Genetic Factors of OSteoporosis (GEFOS) project has achieved most of the objectives and technical goals with relatively minor deviations from those traced at the beginning of the project.

The core of the GEFOS activities have developed within three-main core axes where the activities of the GEFOS consortium developed:

- Setting the largest achievable GWAS discovery setting (GEFOS consortium)

- Assembling the largest centralized DNA collection from osteoporosis studies for replication of the GWAS discovered signals (GENOMOS consortium)

- Launching working-groups across a comprehensive set of musculoskeletal outcomes underlying the physiological and pathological processes underlying the occurrence of osteoporosis and fracture.

CORE ACTIVITY AXES

1. Setting the largest achievable GWAS discovery setting

The GEFOS project has now brought together more than 20 studies worldwide focusing on osteoporosis-related traits. The first GEFOS effort began in 2007(5), putting together five GWAS on femoral neck and lumbar spine BMD, within cohorts of the contractual partners (including 19,175 individuals from the Rotterdam Study, Erasmus Rucphen Family (ERF) study, United Kingdom Twins Study (Twins-UK), Framingham Osteoporosis Study (FOS) and deCODE Genetics). The rationale behind choosing BMD as the first outcome of analysis was based on scientific and statistical considerations. Even though fracture is the most relevant outcome, fractures are complex traits, with moderate heritability, high heterogeneity (multiple mechanistic pathways) and difficult to collect and standardize. In contrast, BMD is the best available measurement used in clinical practice to assess the risk of osteoporotic fracture. BMD is widely available, well standardized and also highly heritable. Although fracture at any site could be attributed to osteoporosis, fractures of the spine, proximal femur and wrist are the most frequent osteoporosis-related fractures. This way, the lumbar spine, hip and forearm are the preferred skeletal sites used to measure BMD and assess fracture risk.

- BMD Measurements

Since the forearm BMD measurements were not available, our first GWAS effort focused on BMD measured at the femoral neck and lumbar spine. Several small-scale GWAS efforts on BMD were attempted before identifying 7 BMD loci associated at genome-wide significant level. The first big leap in discoveries occurred with the initial GEFOS large collaborative effort bringing to 20 the number of discovered BMD loci (5). After that, several efforts on other diverse set of osteoporosis traits have been launched in parallel. Numbers of samples fall drastically across efforts in traits that are much less widely available and will be discussed in detailed within Axis 3 describing the working groups. The second larger effort of the GEFOS project (6) comprised a second round of meta-analysis for femoral neck and lumbar spine BMD in an expanded set of discovery

cohorts (including 17 GWAS approximately 32,000 samples); this time the effort included analysis of the BMD loci in relation to the risk for all-types of fracture and replication in the GENOMOS collection of osteoporosis studies that will be discussed in Axis 2 describing in detail the replication and DNA collection. Once more the GEFOS collaboration provided a major leap in discoveries by more than doubling the identified BMD loci, bringing the number to 56 (of which 32 were novel with regard to all previous efforts). This means that GEFOS has been historically, the driving force behind the identification of 80% (45/56) of the BMD loci. Further, 14 of the BMD loci were shown to be associated with the risk of fracture in the largest set of fractures assembled to date including more than 30,000 cases and 10000 controls.

- Fracture risk

Finding only a fraction (~25%) of the BMD loci associated with fracture risk reflects the higher heterogeneity (diverse mechanistic pathways) leading to bone fracture and the lesser power determined by the difficulty to collect sufficient number of cases. Under this contention, the next goal of the project was to run a GWAS meta-analysis on risk for all-type of fractures (the same definition used to assess the fracture relation of the 56 BMD loci), another on risk for clinical vertebral fractures and subsequently on risk for distal forearm (wrist) fractures. Given the difficulty of collecting sufficiently powered collections these specific GWAS efforts on fracture are still underway.

The GWAS meta-analysis on all-types of fractures has been run on an expanded set of 24 studies including 19,414 cases and summing to 102,873 participants. This effort constitutes the largest study drawn on the genetics of fracture risk. Still pending replication by de-novo genotyping in the GENOMOS DNA collection, this effort has identified variants in known BMD loci (discovered by our GEFOS effort) but also variants in pathways related to endocrine metabolism and neurological pathways. The identified factors constitute susceptibility loci for all-types of fracture, which constitute the more generalizable associations across skeletal sites and types of populations.

Nevertheless, this does not imply that there are no susceptibility loci influencing the risk of fracture at specific skeletal sites. For this reason, the next objective of the project was targeting specific GWAS meta-analyses on risk for hip, vertebral and wrist fracture, which are the most frequently skeletal sites where fractures take place. Some GEFOS partners (personal communication Styrkarsdottir deCODE and Jackson WHI) embarked in relatively large efforts focusing on hip fracture which were fully negative. Such negative experiences hinted on the need of pursuing analysis of fractures at other, but still relevant skeletal sites.

For this reason, the next goal was to focus on the study of vertebral fractures. This type of fractures requires adequate imaging and scoring tools to diagnose them. As described, only a fraction (less than one third) of the vertebral fractures come to clinical attention. Further, the definition of vertebral fracture is challenging and prone to misclassification (particularly for the mild forms). Clinical vertebral fractures with radiographic documentation constitute well-defined phenotypes with low probability of misclassification. Under this contention, the next effort drawn within the GEFOS project was to run a GWAS on a collection of clinical vertebral fractures cases arising from the GENOMOS DNA collection. In total, 1,712 clinical vertebral fracture

cases were identified across 11 studies from Europe and Australia, which were genotyped with the Illumina Omni Express Beadchip at the Genetic Laboratory of the Department of Internal Medicine from Erasmus MC. Controls, were obtained from existing GWAS genotyped sets that were regionally-matched to the cases. The efficiency of the study design was undermined by the different genotyping platforms existing between cases and controls, providing an extra level of complexity to the analysis of the data. This resulted in an extended duration of the project, which at the time of writing of this report has identified one fracture locus. The identified GWAS signal will undergo additional replication, together with some of the suggestive signals by the novo-genotyping in additional cases/control sets. Publication in one major clinical journal will be targeted during 2013.

Last but not least, one of the success stories was the result of a comprehensive evaluation across multiple musculoskeletal phenotypes of one of the identified genetic factors mapping to the WNT16 locus (see description of work package 4 below). This locus is one of the 56 BMD loci identified by the second GEFOS BMD effort carried out in tenths of thousands of individuals(6). In that setting, variants in WNT16 were also found associated with risk for all types of fracture. Among all the studied traits, variants in this locus were associated with forearm BMD measurements(7). This association with forearm BMD postulated wrist fractures as a suitable and logical next trait to be studied by the consortium. In the same paper, association of WNT16 variants with forearm fracture were examined in 2,023 cases and 3,745 controls de-novo genotyped across three studies. One of the SNPs mapping to the WNT16 locus were associated with 1.33 (95%CI: 1.20-1.46, P value =7.3x10-9) increased risk per copy of the minor allele. Based on this successful experience, it was decided that GWAS genotyping would be pursued in the largest DNA collection of wrist fractures from the GENOMOS collection, (i.e. Swedish UFO study). The study included approximately 1,000 cases and 1,000 controls. Genotyping was performed using the Illumina Omni Express Beadchip at the Genetic Laboratory of the Department of Internal Medicine from Erasmus MC. The original proposal of the GEFOS project planned to use as discovery 1,736 cases with GWAS data. Assuming an average minor allele frequency of 0.20, to achieve sufficient power (80%) this initially proposed setting (i.e. 1,736 cases/approximately 4,000 controls) would be powered to identify variants with effect size (odds ratio) of only 1.35 or higher.

This constitutes a similar low power scenario, to that of the de-novo genotyping strategy described in Zheng et al. (7); yet, combining the originally proposed setting with that arising from the UFO genotyping will result in a discovery set with 2,736 cases and 5,000 controls, which would allow the identification of variants associated at genome-wide significant level (p less than 5x10-8) with effect sizes (odds ratio) of 1.27 or higher. This would constitute the highest power scenario setting available for the discovery set. After de-novo genotyping wrist fracture case sets of the GENOMOS collection, the design will have sufficient power to identify associated variants with effect sizes (odds ratio) of 1.17, justifying the approach. The meta-analysis of wrist fractures is currently underway and will be finalized shortly after the general effort on all-types of fracture.

2. Assembling the largest centralized DNA collection from osteoporosis studies for replication of the GWAS discovered signals (GENOMOS consortium)

The GEFOS project has been built upon the already existing organization of the GENOMOS Fifth Framework Programme (FP5) project consortium which tackled most of the shortcomings of individual candidate gene association studies. Only a limited number of polymorphisms in the most prominent candidate genes of osteoporosis (including ESR1(8), VDR(9), COLIA1(10), TGFB1(11) and LRP5/6(12)) were scrutinized, but provided large-scaled evidence about their involvement. Such setting included between 20,000 and 45,000 DNA samples. Nevertheless, the GENOMOS effort was restricted to known polymorphisms and did not interrogate the genetic contribution to osteoporosis at a genome wide level as is currently down with the GWAS approach of the GEFOS project. A worldwide inventory of osteoporosis studies was performed at the time of the GEFOS proposal with the ambitious goal of recruiting close to 90,000 DNA samples (including those of the original GENOMOS collection which were not readily available after the Fifth Framework Programme (FP5) project). During the course of the project a more detailed survey on available phenotypes and sample sizes across studies was assembled. This is a web-based questionnaire, which can be queried online, to identify studies suitable for collaborations across different working groups (see http://www.gefos.org online). The website and the phenotype inventory database were optimized through a grant of the OBIBA project and McGill University. The original plan in the GEFOS proposal was to have the de-novo genotyping activities performed by several contractual partners, or even by the GENOMOS collaborators themselves in particular situations. Nevertheless, after careful consideration, subcontracting of the genotyping activities turn out to be the most beneficial strategy for the project. This decision was driven by the prolific set of markers discovered associated at genome-wide significant level with BMD in the second GEFOS effort(6) which performed de-novo genotyping in more than 100 markers at the replication stage.

This decision was further supported considering that additional outcomes like fracture and other skeletal phenotypes, will also bring up the need to genotype additional markers. Such number of identified loci and variants taken forward for replication are much more than expected in the original GEFOS plan. Constrained by the project's budget limitations several scenarios were scrutinized to identify the best alternative allowing optimizing the GEFOS resources. Several genotyping centres capable of performing flexible (able to receive SNP selections across different time periods), high quality and high-throughput genotyping were asked to provide a quotation with the lowest possible cost which would allow taking the highest number of markers (of clear scientific interest) to follow-up replication. After comparing the offers from four independent genotyping centres, we selected the UK-based company KBioscience / LC-GENOMICS as the best available facility to perform the core of the de-novo genotyping activities. The selection procedure complied with the conditions of transparency and equal treatment described in the Seventh Framework Programme (FP7) Financial Guide (Article II.7.2). Additional genotyping centres from contractual partners included the University of Queensland in Australia and deCODE Genetics in Iceland, who genotyped sets from studies already present in their collections. All together, the second GEFOS BMD effort included close to 80,000 samples from 37 studies, of which close to 50,000 were genotyped at Kbiosciences.

This collection is continuing to expand and at the moment holds up to 120,00 DNA samples at the centralized facility of Kbiosciences. After

publication, the genotype information of their samples is sent back to the contributing cohorts who can use them in their own research initiatives. This DNA collection constitutes an invaluable common resource facilitating the discovery and scrutiny of genetic variants arising from (but not limited to) GWAS efforts. This collection also offers the opportunity to bridge fields of knowledge and has set the foreground for upcoming efforts requiring large populations to mine datasets and facilitate discoveries (i.e., approaches working with sequencing technologies, cell biology and/or organism models).

3. Launching working-groups across a comprehensive set of musculoskeletal outcomes underlying the physiological and pathological processes underlying the occurrence of osteoporosis and fracture.

As described above, osteoporosis and the derived risk for fractures while heritable constitute very complex traits, requiring very large sample sizes to uncover the weak, yet true genetic effects underlying their aetiology. The aetiology is multifactorial involving huge environmental influence and genetic factors. This way, the mechanistic pathways leading to fracture can arise from a diverse set of components from the musculoskeletal system.

As such the musculoskeletal system can then be seen as a heterogeneous set of processes melting into a 'funnel' leading to the occurrence of fracture. This mixed set of etiological pathways is the basis of its complexity, and the reason of why such large collection of studies is needed to achieve a sufficient sample size that allows identifying the underling weak genetic effects. Bone mineral density (BMD) measurements were prioritized to be studied by the consortium considering they are the best available predictors of fracture in the clinical setting. The GEFOS studies on BMD presented a high yield of genetic discoveries relevant for the understanding of bone biology. Such high yield is likely the result of constituting a highly heritable, quantitative, precise and widely available trait. Nevertheless, BMD is not the only determinant of fracture and in fact, close to 50% of fractures occur below the osteoporosis threshold. For that reason, additional working groups have been launched across different outcomes with the objective of pursuing the dissection of the largest amount of underlying pathways leading to fracture.

Actually, the working group organized by trait of interest has constituted the driving force of the scientific activities of the GEFOS consortium. Such organization allows assembling teams of researchers composed of experts in the specific fields in both the epidemiological and genetic aspects. Further, although not described in the original proposal, numerous collaborations were established with at least five groups providing resources of basic research providing functional evaluations for the identified loci. These included the Broad Institute (US) with the GRAIL connectivity analysis tool(13), McGill University (Canada) with expression of culture osteoblast cell lines(14), deCODE Genetics (Ijsland) with lymphocytic and adypocyte expression profiles(15), University of Oslo (Norway) with phenotype- expression profile correlation from hip biopsies(16). Such partnership allowing integrating the clinical/epidemiological findings with the contributed functional workup contributed in many instances to the understanding of the genetic associations. A synopsis (described below WP7) of the functional evidence supporting the association and implication of a given gene, ranged among a broad spectrum, extending from those pinpointing

genes playing critical roles in bone biology with functional evidence at multiple levels, to those with very limited functional evidence revealing potential novel bone pathways.

Such plethora of working groups focusing on different musculoskeletal traits is one of the richest aspects of the GEFOS consortium. The potential of this integration of multiple phenotype studies has been exemplified by the findings surrounding the 7q31 WNT16 locus. This locus has now been catalogued as an important factor involved in different aspects of bone biology. Within GEFOS working groups, variants from this locus were shown to be associated with several traits including: BMD of the femoral neck and lumbar spine in the elderly (6) and in premenopausal women(16); wrist BMD (7); total body and skull BMD in children and adults(17); cortical thickness from pQCT of the Tibia (7), and quantitative ultrasound (Kaptoge/Moayyeri personal communications). Further two other publications also found the locus associated with finger BMD and confirmed the total body, forearm, lumbar spine and femoral neck BMD association. Nevertheless, the reported GWAS signals arise within short distance of at least three different genes including WNT16, FAM3C and C7orf58, none of which can be disregarded as underlying the associations. Additional functional work from a mouse model (7, 17) and expression profiling (18) helped to pinpoint the involvement of WNT16 and C6orf58, but not FAM3C, arising from independent GWAS signals. This way, the creation of different working groups and close interaction between their activities has been proven as a powerful strategy to provide insight into the mechanistic pathways underlying the risk of fracture.

WORK PACKAGE ACTIVITIES

WP1. Recruitment of GWAS

Most of the activities of WP1 comprised the work described above focusing on assembling the largest achievable GWAS discovery settings for the studied traits. This work package was coordinated by ErasmusMC Rotterdam, The Netherlands in person of Prof. Dr. Andre Uitterlinden and Dr. Fernando Rivadeneira. The most useful resource for the success of this activity was the web-based inventory of samples sizes and measurements/outcomes availability. A web-based interface for the analysis of genome-wide association datasets has been constructed in Erasmus MC and made available to GEFOS collaborators to aid the analysis of their data(19). After assembling the largest effort on BMD ran to date in the field of osteoporosis, the consortium has achieved its largest expansion to date for the analysis of risk for all types of fracture. This ongoing effort has now brought together 24 GWAS, including 19,414 cases and summing to 102,873 participants. As described above, relevant fracture sites with limited number of case collections like clinical vertebral and wrist fracture were subject to GWAS genotyping with the objective of guaranteeing suitable discovery sets with reasonable power. All the fracture efforts are currently underway awaiting replication with de-novo genotyping.

WP2. Replication by de-novo genotyping

The collection and preparation of DNA samples from the GENOMOS cohorts (no GWAS genotyping) was coordinated by ErasmusMC Rotterdam, The Netherlands in person of Dr. Fernando Rivadeneira and Dr. Karol Estrada, with support of the University of Ioannina in person of Dr. Evangelis Evangelou and Dr. Evangelia Ntzani. As for the recruitmen of GWAS, the web-based inventory of samples sizes and measurements/outcomes availability played a pivotal role in the inclusion of studies in the consortium. While contractual partners deCODE genetics and Brisbane University carried out genotyping activities for a limited set of studies, the core of the de-novo genotyping replication activities of the GENOMOS studies were carried by LGC-Genomics/KBiosciences in the UK under a subcontracting agreement. Genotyping of more than 100 markers on sets of more than 50,000 participants has been carried out to date for diverse working groups. The current inventory of potential GENOMOS cohorts now approaches greater than 100,000 samples from 38 or more studies, while at least 5 additional studies are expected to join currently ongoing efforts. As sustained above, putting together this DNA collection as a shared resource is one of the biggest achievements of the GEFOS project, which will no doubt enable additional discoveries from all type of efforts make use of it. We expect that this resource will be used by subsequent round of GWAS and upcoming sequencing efforts. Yet, this is also a resource suitable for basic science researchers who want to evaluate their discoveries arising from cellular or organism (animal) models, at the human population level. A research steering committee (RSC) for the GENOMOS DNA collection is in place to coordinate the access and adequate management of the samples to guarantee the best use of the resources. The RSC is composed of Prof. Dr. Bente Langdahl, Prof. Dr. Barbara Obermayer-Pietsch and Prof.Dr. Jonathan Reeve. The DNA samples remain property of the researchers (and their institutions) and are always asked in advanced to 'opt in' or 'opt out' of the genotyping efforts. Contributing parties are asked to have their DNA samples undergo whole genome amplification (WGA) to secure sufficient material towards the future. Considering the joint venture and large-scale number of

samples achieved by the consortium, the costs of genotyping and WGA services are obtained at preferential price, in what constitutes a great use of resources.

WP3. Reiterative meta-analysis of GWAS

Meta-analysis of several GWAS datasets has been performed for several traits as a reflection of very active working groups. The University of Ioannina, Greece, coordinates this working package in person of Prof. Dr. John Ioannidis and Dr. Evangelos Evangelou. This work package provided analytical and methodological support across most of the GWAS efforts. Several activities were also carried under the supervision of Dr. Evangelia Ntzani and the work of Dr. Kostas Tsilidis, Dr. Despina Kontopoulos, Dr. Foteini Kavvoura and Orestis Panagiotou. Furthermore, the analysis of the replication and subsequent meta-analysis with the discovery datasets was also supported by this work package assuring that appropriate methodology was incorporated and adhere to in the analysis plans. The core of the activities in the work package included data management, organization of datasets, quality control and meta-analysis in close interaction with all other work packages.

WP4. Selection and analysis of new phenotypes

The core of the activities was focused on the identification of those phenotypes, other than fracture and BMD measured at the hip and spine that would be suitable and relevant to be studied by the GEFOS consortium. This work package was coordinated by the University of Gothenburgh, Sweden in person of Prof. Dr. Claes Ohlsson with the assistance of Dr. Liesbeth van den Put and Dr. Matttias Lorentzon. The coordinators of this work package are also involved in leading the wrist fracture working group. The so-called 'novel' phenotypes are those where the limitations of the two dimensional BMD and X-ray evaluations can be overcome by 3-D evaluations of bone structure and quality. Several publications on peripheral quantitative computerized tomography (pQCT) arose from this work package, providing further insight on the genetic effects on bone structure, which was not achievable by DXA-based BMD assessments. Several publications have resulted from pQCT (7, 20, 21) and sex hormones(22, 23). Several other publications are expected on Lean mass, Heel ultrasound and serum markers/hormones relevant to bone metabolism. Further, the study of genetic determinants of total body and skull BMD in pre-pubertal children(17) can also be seen as a novel approach to study bone health and early determinants of osteoporosis.

WP5. Gene-environment interactions

As described above, osteoporosis and its derived risk for fractures are very complex traits whose aetiology is multifactorial, meaning it involves huge environmental influence and a broad range of genetic factors. This work package was coordinated by Prof. Dr. Jonathan Reeve and Dr. Stephen Kaptoge from Cambridge University in the United Kingdom. The work package leaders have also been involved in the coordination of the ultrasound working group. The main effort of this work package envisaged launching powerful gene x environment analyses using the candidate SNPs identified by the meta-analysis of the GEFOS/GENOMOS. This effort was launched aware of the contention that if very large sample sizes are need to uncover the weak, yet true genetic effects underlying the aetiology of the different traits, testing for interactions with environmental factors would be even more challenging. Within the GEFOS

project Gene x Age interactions were identified for variants in the WNT16 locus by employing a life-course epidemiological approach(17). Then, a gene by sex interaction effort was attempted within a large setting including 25,353 individuals from 8 cohorts, followed by replication of 12 top single-nucleotide polymorphisms (SNPs) in an additional set of 24,763 individuals(24).

However, despite the large collaborative effort, there was no evidence for genome-wide significant interaction in the joint analysis. This already implied that any existing gene-by-sex interactions for BMD probably represent weak effects, accounting for less than 0.08% of the variation per implicated SNP. Age and sex are covariates of widespread availability. In contrast, environmental variables suitable to be tested for gene x environment interactions are, on the other hand, not uniformly distributed or measured across populations. This adds another level of complexity, since this makes it extremely difficult to collect a set of sufficient sample size. Power calculations allowing for 0.1% type-I error (i.e. p less than 0.001) indicate the need for a substantial increase in numbers above the 100,000 individuals for many of the studied variables. After an initial questionnaire survey to assess the extent of exposure information available, studies were invited to contribute individual data to the WP5 coordinating centre for uniform harmonization. The study-level response rate to the invitation was nearly 90%. Most of the studies that were unable to participate cited IRB restrictions to contributing individual-level data, but were willing to provide summary information or to locally conduct the analyses for inclusion in the meta-analysis. Among the 33 studies that provided individual-level data, the availability of exposures varied from 100% for anthropometric variables, to less than 10% for some biomarkers and nutrients. This work package has laid the foundation towards achieving a powerful discovery setting for GxE interactions. Nevertheless, additional efforts are required to achieve sufficient sample size and consistency in data harmonization and analyses. Publication of these efforts will be sought in the course of 2013.

WP6. Risk modelling genetic markers

The objective of this work package is developing a novel risk algorithm for fracture prediction by combining genetic risk factors for fracture with other clinical variables included in the WHO FRAX algorithm, applied prospectively to predict fracture risk in the general population. This work package is coordinated by Prof. Dr. John Kanis and Prof. Dr. Eugene McCloskey from the University of Sheffield, in the United Kingdom. The work and the activities of this GEFOS work package were undertaken by Professor Anders Oden and Dr Helena Johansson, statistical consultants under the long-established auspices of the WHO Collaborating Centre for Metabolic Bone Diseases. The WHO Collaborating Centre for Metabolic Bone Disease has carried out research activities of significant international impact on the field of skeletal diseases, particularly for osteoporosis.

Within the second GEFOS effort on BMD (18) a first attempt was made to use an allelic gene score to predict BMD levels, osteoporosis status and fracture risk. These allelic score were modelled in the PERF Study, an independent population not part of the GWAS or replication meta-analysis. Less individuals of the population carry few (first quintile) or many (fifth quintiles) BMD-decreasing alleles, following a relative normal distribution. A gradient between the first quintile is seen for BMD levels, risk of osteoporosis and fracture risk, suggesting that the

allelic-score is able to predict disease status. Nevertheless, the inclusion of variables like age, weight alone(AUC=0.75 [0.73-0.77]) perform better than the allelic score (AUC= 0.59 [0.56-0.61]). This gives the foundation for implementing an algorithm than can integrate genetic factors and clinical variables for the prediction of fracture like FRAX. In these models, the outcome is incident fractures captured in prospective cohorts; the same cohorts need data on risk factors available at baseline to permit the calculation of FRAX probabilities (the WHO algorithm mentioned in the objectives). The risk factors are listed below which will be combined with the genotypes of interest.

- Country and ethnicity
- Age in years
- Sex (0 : men, 1 : women)
- BMI (kg/m2)
- Previous fracture (0 : no, 1 : yes)
- Parental history of hip fracture (0 : no, 1 : yes)
- Current smoker (0 : no, 1 : yes)
- Glucocorticoid use (0 : no, 1 : yes)
- Rheumatoid Arthritis (0 : no, 1 : yes)
- Secondary osteoporosis (0 : no, 1 : yes)
- Alcohol 3 or more units a day (0 : no, 1 : yes)
- Femoral neck BMD (T-score or BMD value with machine type)

SNP Locus Closest Gene/Candidate
rs4233949 2p16.2 SPTBN1
rs6532023 4q22.1 MEPE/SPP1
rs4727338 7q21.3 SLC25A13
rs1373004 10q21.1 MBL2/DKK1
rs3736228 11q13.2 LRP5
rs4796995 18p11.21 FAM210A
rs6426749 1p36.12 ZBTB40
rs7521902 1p36.12 WNT4
rs430727 3p22.1 CTNNB1
rs6959212 7p14.1 STARD3NL
rs3801387 7q31.31 WNT16
rs7851693 9q34.11 FUBP3
rs163879 11p14.1 DCDC5
rs1286083 14q32.12 RPS6KA5
rs4792909 17q21.31 SOST
rs227584 17q21.31 C17orf53

Since the studies need to have this information, the power of this analysis will be lower than the ones employed in the discovery to identify the association of genotypes with variables such as fracture and BMD in a cross-sectional design. The power can be maximized by identifying the maximum number of suitable cohorts and ensuring that the latest data on incident fractures are included to increase the number of outcome events. We chose 16 SNPs from the 14 BMD loci associated with risk for any type of low-trauma fracture and are listed below:

Approximately 70 GEFOS cohorts were contacted to determine which fulfill the criteria for integration into the analysis. A response was obtained from 29 cohorts with 5 of these declaring their cohorts unsuitable for inclusion. A total of 24 cohorts will contribute to the analysis, comprising approximately 78,000 individuals and listed below. Of these, 8 cohorts do not wish to provide individual level data but will conduct the

same statistical analysis plan and provide coefficients and summary statistics to the final meta-analysis.

Cohort
AGES Reykjavik study
EPOS
MrOS Sweden
AUSTRIOS-A/B FLOS
MrOS USA
Cabrio-C/CC
Framingham
PERF
CaMOS
GOOD
PROSPER/PHASE study
DOPS
Hertfordshire
UFO
EDOS
HK Community elderly
WGHS
EMAS
KOR-amc
OPUS
EPIC-Norfolk
MRC-HIP
Rotterdam Study

Of these, 18 contributing cohorts have provided information on the FRAX variables available at baseline as presented above. All cohorts have age, sex, BMI and information about fractures during follow up in different levels of detail. Relevant genotypes (ranging from 4-16 SNPs) are available across these cohorts. The final analysis of WP6 will be completed and submitted for publication within 2013.

Cohort	Prev fx	Family history	Smoke	Steroids	RA	Sec OP	Alcohol	FN BMD
Austrios-A/-B	X	-	X	X	X	X	X	-
CaMOS	X	X	X	X	-	X	X	X
EDOS	X	X	X	X	X	X	X	X
EMAS	X	-	X	X	-	X	X	X
EPIC-Norfolk	-	-	X	-	-	-	X	-
EPOS	X	X	X	X	-	X	X	X
Framingham	X	-	X	X	X	-	X	X
HCS	X	X	X	X	-	-	X	X
KOR-amc	X	X	X	X	X	X	X	X
MrOS Sweden	X	X	X	X	X	-	X	X
MrOS USA	X	X	X	X	X	-	X	X
PERF	X	-	X	X	X	X	X	X
PROSPER/PHAS	-	-	X	X	X	X	X	-
UFO	X	-	X	X	X	X	X	-
Rotterdam Study	X	-	X	X	X	X	X	X
WGHS	X	X	X	X	X	-	X	-
OPUS	X	X	X	X	X	X	X	X
MRC-hips	X	X	X	X	X	-	-	X

WP7. Field Synopses

This work package is coordinated by the University of Edinburgh in the United Kingdom in person of Prof. Dr. Stuart Ralston with support of Dr. Nerea Lopez-Alonso. The coordinators of this work package are also involved in leading the clinical vertebral fracture working group. Several osteoporosis synopses were performed during the duration of the project including a systematic evaluation of 150 candidate genes in relation to BMD and fracture(25), and a comprehensive review of the field published in the journal 'Endocrine Reviews' (26). Activities of this work package also included a synopsis of the functional evidence existing for the multiple identified loci, which was part of the second GEFOS BMD effort (6).

WP8. Project management

Management of the project was performed by the coordinating center at Erasmus MC Rotterdam, The Netherlands in the persons of Dr. Fernando Rivadeneira and Prof. Dr. Andre G. Uitterlinden, together with Maria Jongerden, Financial advisor, and the support of Dr. Karol Estrada, who worked on his PhD project during the course of the contractual period. Several other PhD students, post-docs, IT support staff and administrative personnel worked at different periods throughout the project.

The core of the activities of this work package consisted (but was not limited) to:

1. Setting up and managing the GEFOS website
2. Organizing GEFOS/GENOMOS investigator meetings
3. Organizing GEFOS research steering committee (RSC) meetings
4. Communicating with the European Commission and allocating grant funds

1. Setting up and managing the GEFOS website and file sharing

The GEFOS website is available at http://www.gefos.org and is fully functional and has undergone restructuring from its original design. The website was renovated through a grant from McGill University for the OBIBA project in person of Dr. J. Brent Richards Consortium member through the Kings College, a contractual partner of the project. The web-based phenotype survey and study inventory are part of the website, allowing each collaborator to administer its own information while sharing the summary of the data with the rest of researchers in the field of bone research. The website is physically hosted at a server property of the coordinating centre in ErasmusMC Rotterdam. Most of the coordination and information exchange is currently running through the website (i.e., exchange of meeting minutes, analysis plans, supplementary material from manuscripts and release of meta-analysis results to the scientific community). There is a GEFOS members secure section where confidential documents can also be shared (i.e. Research steering committee meeting minutes, summary results, specific survey information). In addition, secured file-share areas have been enabled which are now at service of the different trait working groups starting their meta-analyses. Minutes and slides of the meetings are shared with all GEFOS consortia members and not only among contractual partners. Even though there is still a website for GENOMOS collaborators http://www.genomos.eu/ we have now implemented in the website structure the possibility to combine both the GEFOS and GENOMOS information. File sharing server directory have also been provided for the different working groups to upload in a centralized repository the individual study results.

Different access levels are provided to preserve confidential information (e.g. result of GWAS) as such until a more active participation/contribution of the GENOMOS partners has been achieved.

2. Organizing GEFOS/GENOMOS investigator meetings

With the main objective of keeping investigators of the GEFOS and GENOMOS consortia in close communication, regular periodic meetings were organized. They took place biannually during the two most important meetings of bone research in Europe and the Americas: the European Calcified Tissue Society (ECTS) and the American Society for Bone and Mineral Research (ASBMR). This setup provided ample opportunities for the investigators to be in close contact, and within a reasonable investment considering that many collaborators attend these meetings on a regular basis. These meetings were also open to the GENOMOS collaborators and actually constituted for them a follow-up of the Fifth Framework Programme (FP5) GENOMOS Project allowing them to be part of the GEFOS activities. During the meetings work package activities were discussed together with the proceedings of the different working groups. The following is the list of project meetings, dates and venues organized by the coordinating center during the contractual period:

- 1st GEFOS 'Kick-off' meeting in Rotterdam, The Netherlands
March 7th, 2008
- 2nd GEFOS / 12th GENOMOS Investigators Meeting in Barcelona, Spain
May 25th, 2008 (ECTS)
- 3rd GEFOS / 13th GENOMOS Investigators Meeting in Montreal, Canada
September 14th, 2008 (ASBMR)
- 4th GEFOS / 14th GENOMOS Investigators Meeting in Vienna, Austria
May 24th, 2009 (ECTS)
- 5th GEFOS / 15th GENOMOS Investigators Meeting in Denver, CO, US
September 15th, 2009 (ASBMR)
- 6th GEFOS / 16th GENOMOS Investigators Meeting in Glasgow, UK
June 29th, 2010 (ECTS)
- 7th GEFOS/17th GENOMOS Investigators Meeting in Toronto, Canada
October 19th, 2010 (ASBMR)
- 8th GEFOS / 18th GENOMOS Investigators Meeting in Athens, Greece
May 7th, 2011 (ECTS)
- 9th GEFOS / 19th GENOMOS Investigators Meeting in San Diego, CA, US
September 19th, 2011 (ASBMR)
- 10th GEFOS / 20th GENOMOS Investigators Meeting in Stockholm, Sweden
May 20th, 2012 (ECTS)
- 11th GEFOS / 21st GENOMOS Investigators Meeting in Minneapolis, MN, US
October 11th , 2012 (ASBMR)

The 11th GEFOS meeting was the first meeting, taking place after the contractual period ended. The meeting was co-organized by the ErasmusMC Rotterdam, The Netherlands, McGill University Montreal, Canada and the Hebrew Senior Life/Harvard University Boston, MA, US collaborators. This meeting counted with the presence of Grigorij Kogan, European Commission Scientific Officer of the GEFOS Seventh Framework Programme (FP7) Project, together with William Sharrock and Joan McGowan, representatives of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), NIH. During the meeting the past activities of the project were reviewed, followed by a discussion about the future of the GEFOS consortium in terms of research goals and funding opportunities in a global setting. Both NIH/NIAMS and EC officers witnessed the wealth of data and value of the collaboration.

3. Organizing GEFOS research steering committee (RSC) meetings

The RSC committee meetings took place on a monthly basis. The dynamics of the trait working groups ran smoothly and never sought the need of having the RSC involved other than for the allocation of the genotyping resources. Such harmony within the trait working groups is probably the result of the consortium agreement guidelines that have been provided by the RSC to the groups. For this allocation, each working group had to provide a request including the number of SNPs, the rationale and robustness of the selection and a statistical power analysis how the de-novo replication genotyping had a sufficient chance of success. Another important and frequent activity of the RSC involved the evaluation and approval of data access requests to the results of the published meta-analysis. To date dozens of requests have been discussed and approved and are currently in the process of publication. These requests also came from groups working outside the bone field or on basic research. Considering the high demand to access the results of the meta-analyses it was decided by the RSC to make all the results publicly available to general research community. In these efforts, the contribution of the GEFOS consortium will be recognized, by co-authoring as a collective unit in the resulting publications, while the European Commission funding of GEFOS should be included in the acknowledgements.

4. Communicating with the European Commission and allocating grant funds

The coordinating centre has been the first line of communication between the partners and the Commission through our Scientific Officer Grogorij Kogan. All issues have been acted upon and solutions provided in a timely fashion if needed. Payments to partners have been done timely. The only major modifications to the original project description were to subcontract the genotyping activities of the project and the request for six months extension to the duration of the project. Both requests were approved by the European Commission and have allowed a better use of the resources allocated to the project and completion of the planned activities. As justified in the request for extension, the successful identification of the very high number of discovered osteoporosis-related loci (greater than100) was the main motivation to request an extension.

In summary, the GEFOS project developed as planned with quite a successfully high yield in discovered loci. No major deviations from the planned milestones and deliverables were observed.

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Potential Impact:

Osteoporosis is a silent but frequent and devastating age-related disease: 50% of subjects that fracture their hip after age 80 years die within 12 months after the event. Actually, women older than 65 years are at greater risk for death after hip fracture than after breast cancer. While the consequences of osteoporosis are well established, the causes of the disease remain elusive. The disease is strongly genetically determined, but the responsible genes were largely unknown until the advent of the GWAS approach less than a decade ago. The first GWAS efforts identified a handful of loci related to the risk of osteoporosis. It was only until a coalition of researchers and studies embarked in the large-scale collaboration of the GEFOS project that major leaps in genetic discoveries have occurred in the field of osteoporosis. There are several degrees of impact at the clinical, scientific and societal level.

- Clinical Impact

The GEFOS project has now identified dozens of genetic factors clustering in novel and known pathways playing key roles in bone biology. In addition to the known proteins and pathways the discoveries arising in the GEFOS project are confronting us with completely new biology that merit further investigations. Nevertheless, only a small fraction of the variation in the osteoporosis or fracture traits is explained by these discoveries. From this perspective we have shown there is still limited application predicting the occurrence of osteoporosis and or fractures for a given individual in the overall population. Despite this, we have also shown that for a very small and specific fraction of the population their genetic makeup can indeed represent differences in susceptibility. As compared to women carrying the normal range of genetic factors for example, individuals with an excess of bone mineral density (BMD)-decreasing genetic variants have up to 56% higher risk of having osteoporosis and 60% increased risk for all-types of fractures; similarly, individuals with a smaller number of variants have a lower chance (protective risk) against developing osteoporosis or sustaining fractures.

As has been established at an epidemiological level, though predictive, BMD has an imperfect relation with fracture risk (i.e., about 50% of individuals without osteoporosis as diagnosed by DXA, still suffer fractures). This is also one conclusion derived from our genetic studies on BMD. By itself, BMD is useful allowing the identification of a large amount of factors involved in bone biology. Yet, there is still discrepancy between the effect sizes of the genetic associations of fracture and those of BMD.

This is also reflected by the limited fraction of BMD loci being associated to fracture. Although BMD is an important determinant in the mechanistic pathway leading to fracture, low BMD is neither a sufficient or necessary cause of fracture. Therefore, after studying BMD, our current efforts are focusing on fracture as an outcome; while also seeking insight from other assessments not picked up by the DXA-derived BMD measurement (i.e. pQCT, biomarkers, ultrasound, etc).

From a different perspective, great impact can be expected from pinpointing many factors in critical molecular pathways which are candidates for therapeutic applications of osteoporosis. Such potential is highlighted by the identification (among others) of genes encoding

proteins that are currently subject to novel bone medications. Several factors (colored orange) have been identified by the GEFOS GWAS efforts and involving biological pathways currently targeted (compounds in blue) for the treatment of osteoporosis. This is the case for denosumab (commercial name Prolia), a human monoclonal antibody against RANKL which is a protein inhibiting bone resorption. Even more interesting is the identification of several factors which can constitute targets for true bone-building drugs. They make part of a new generation of treatments that have the potential of exceeding the benefit, and possibly overcome some side effects, of compounds inhibiting bone resorption. One example of such potential is already evident with the identification of variants in the sclerostin gene, associated with both BMD and fracture risk, and for which, an anti-sclerostin antibody is expected soon to be available in the market.

- Scientific Impact

Also from a research perspective, the GEFOS project has had great impact on facilitating the research of investigators inside and outside the bone field. The GEFOS/GENOMOS DNA collection is a common resource which can be used by researchers from the field of basic sciences extending to clinical setting in human populations. All members of the consortium can trace a plan to genotype variants in the collection to test diverse hypothesis arising from different types of approaches (GWAS, sequencing, expression profiling) at the cellular, tissue organism or population level. Further, some valorisation aspects can be derived from providing paid access to third part profit-oriented instances willing to use the resources to test their own hypothesis. Any income obtained from such ventures is planned to be used in sponsored genotyping activities proposed within the consortium. In addition, all meta-analysis results are made available to the scientific community securing confidentiality of the participants' identifiers. Consortium membership is also used by researchers of the consortium in the form of letters of support of their grant applications, where it is stated they can make use of the resources.

Given the high costs of genotyping DNA samples with SNP arrays and the relatively modest predictive value of SNPs, some critics have stated that GWAS have been a waste of time and money. The GEFOS project/consortium is a successful venture, by itself a counterargument on how this effort is clearly an example of money well spent. The achievements of the project are also subject to extrapolation to the study of other complex traits and common diseases, and include:

1) After more than two decades of unfruitful attempts, the field of genetics of osteoporosis has moved from having a few genetic factors conclusively involved in the occurrence of the disease, to in little more than 5 years, identify dozens of variants convincingly involved in the aetiology of osteoporosis and fracture.
2) Applying the GWAS approach has opened up our molecular understanding of complex diseases like osteoporosis, by convincingly identifying, a large number of genetic factors in known biological pathways influencing bone metabolism, which include known drug targets
3) The discovery of novel biology is an important hallmark of applying the GWAS approach in GEFOS (with close to half of the findings concern genomic regions with unknown function or genes not linked to the disease). It will be a matter of time to unravel and appreciate the

involvement of these factors, and is likely they will constitute new drug targets
4) All the achievements of the GWAS approach were obtained by scrutinizing only 0.3% of the human genome, ranging from 5 to 20% of the variance explained of the disease (as compared to 0% for genetic markers for complex disease before GWAS). This also constitutes evidence of the huge potential of targeting in future ventures a more comprehensive assessment of the genome (i.e., sequencing).
5) GWAS has also provided a very large impetus to change the way good scientific research is done in human genetics and beyond, i.e., in collaboration and by replicating experiments and findings. This is typically the case for a large scale project of world wide scope, like the GEFOS project, whose achievements are the result of embracing principles of collaboration and high standard scientific practices.

The project has also had impact on the formation of young researchers by allowing PhD students and post-docs to play leading roles in the functioning of the GEFOS consortium. One PhD thesis has been produced on research mostly taking place within the consortium, while several publications were used as chapters of several theses. In addition, scientific mobility has been achieved by stimulating student international exchanges to acquire skills and expertise at other centres. This was the case for students of University of Ioannina (Greece), Erasmus MC Rotterdam (The Netherlands) and University of Edinburgh (United Kingdom). Several courses taking place every year at the coordinating centre in Rotterdam involved presentations of the research activities of the GEFOS Project. During these courses partners from the University of Edinburgh (Prof Stuart Ralston), King's College London (Prof Tim Spector) and University of Ioannina (Prof John Ioannidis and Dr. Evangelos Evangelou) participated as lecturers.

Through the end of 2012 the work of the GEFOS consortium has given rise to 50 presentations at the most prestigious scientific meetings in the field of genetics and bone research at worldwide level, including:

- European Calcified Tissue Society 2009 (3)
- American Society of Bone and Mineral Research 2009 (1)
- American Society of Human Genetics 2009 (3)

- European Calcified Tissue Society 2010 (3)
- American Society of Bone and Mineral Research 2010 (7)
- American Society of Human Genetics 2010 (1)

- European Calcified Tissue Society 2011 (1)
- American Society of Bone and Mineral Research 2011 (11)
- American Society of Human Genetics 2011 (3)

- European Calcified Tissue Society 2012 (4)
- American Society of Bone and Mineral Research 2012 (10)
- American Society of Human Genetics 2012 (3)

Further, 19 publications in top ranked scientific journals derived from the GEFOS project and acknowledging the European Commission funding, are testimony of the high scientific throughput of the consortium. Many more are in the process of being published, while the preservation of the consortium activities will keep generating publications into the future. Last but not least, media coverage at a world-wide level has also been achieved, highlighting the work of the GEFOS consortium in an

international context, including coverage for medical, scientific but also general audiences (see PDF attached).

In conclusion, several foreground and dissemination activities have been pursued and logically all of them are acknowledging the European Commission Seventh Framework Programme (FP7) funding of the project, without which setting up the consortium would have not been possible.

- Societal Impact

At the current stage, it is difficult to ascertain if a direct benefit derived of the results of the project has been obtained for the general population. Nevertheless, the high likelihood of having our discoveries translated into clinical applications in the future turns all more into a question of 'when', rather than 'if'.

Among other societal implications the workforce statistics of the project show that close to 40% of the scientific staff involved in the project are of female gender, with a similar distribution in Europe and the Americas. This can be seen as a rising model of involvement of female researchers in high qualified (and in many instances leading) positions guaranteeing the success of the project.

List of Websites:

http://www.gefos.org/