In search of "Omics"-based biomarkers to predict risk of frailty and its consequences in older individuals—The FRAILOMIC Initiative

Authors: Jorge D. Erusalimsky[1], Johannes Grillari[2,3], Tilman Grune[4], Pidder Jansen-Duerr[5], Giuseppe Lippi[6], Alan Sinclair[7], Jesper Tegnér[8], Jose Viña[9], Anna Durrance-Bagale[10], Rebeca Miñambres[11], Marcelo Viegas[12], Leocadio Rodriguez-Mañas[13], on behalf of FRAILOMIC Consortium

Affiliations: [1]Cardiff School of Health Sciences, Cardiff Metropolitan University, Western Avenue, Cardiff, Wales CF5 2YB, United Kingdom; [2]Evercyte GmbH, Muthgasse 18, 1190 Vienna, Austria; [3]BOKU – University of Natural Resources and Life Sciences, Dept. of Biotechnology, Muthgasse 18, 1190 Vienna, Austria; [4]German Institute of Human Nutrition, Potsdam-Rehbruecke, Arthur-Scheunert-Allee 114 – 116, D-14558 Nuthetal, Germany; [5]Universität Innsbruck, Research Institute for Biomedical Ageing Research, Rennweg 10, 6020 Innsbruck, Austria; [6]Laboratory of Clinical Chemistry and Hematology, Academic Hospital of Parma,Via Gramsci 14–43126 Parma, Italy; [7]Department of Stroke Medicine, Luton & Dunstable University Hospital, Lewsey Road, Luton, Bedfordshire, UK; [8]Unit of Computational Medicine, Department of Medicine, Karolinska Institutet, Karolinska University Hospital L8:01 SE-171 76, Stockholm, Sweden; [9]Facultad de Medicina y Odontologia, Universidad de Valencia, Avda Blasco Ibañez nº 15, 46010 Valencia, Spain; [10]Niche Science and Technology, 26 Bardolph Rd, Richmond-Upon-Thames, Surrey, TW9 2LH, United Kingdom;[11]Sistemas Genómicos, Parque Tecnológico de Valencia, Ronda G. Marconi, 6 - 46980 Paterna (Valencia), Spain, [12]Lifelength, Miguel Angel 11, Madrid, Spain 28010, [13]Hospital Universitario de Getafe, Division of Geriatrics, Ctra. de Toledo Km. 12,5, 28905-Getafe, Spain

Corresponding author: Leocadio Rodriguez-Mañas, Hospital Universitario de Getafe, Division of Geriatrics, Ctra. de Toledo Km. 12,5, 28905-Getafe, Spain

Phone: +34 6833241

Fax: +346247241

Email: leocadio.rodriguez@salud.madrid.org

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ABSTRACT

An increase in the number of older people experiencing disability and dependence is a critical aspect of the demographic change that will emerge within Europe due to the rise in life expectancy. In this scenario, prevention of these conditions is crucial for the well-being of older citizens and for the sustainability of our health care systems. Thus, the diagnosis and management of conditions like frailty, which identifies the people at the highest risk for developing those adverse outcomes, is of critical relevance. Currently, assessment of frailty relies primarily on measuring functional parameters, which have limited clinical utility. In this viewpoint article we describe the Frailomic Initiative, an international, large-scale, multi-endpoint, community- and clinic-based research study funded by the European Commission. The aim of the study is to develop validated measures, comprising both classical and "omics-based" laboratory biomarkers, which can predict the risk of frailty, improve the accuracy of its diagnosis in clinical practice, and provide a prognostic forecast on the evolution from frailty to disability. The initiative includes eight established cohorts of older adults, encompassing >75,000 subjects, most of whom (~70%) are aged >65 years. Data on function, nutritional status and exercise habits have been collected and cardiovascular health has been evaluated at baseline. Subjects will be stratified as "non-frail" or "frail" using Fried's definition, all adverse outcomes of interest will be recorded and differentially-expressed biomarkers associated with the risk of frailty will be identified. Genomic, proteomic, and transcriptomic investigations will be carried out using array-based systems. As circulating microRNAs in plasma have been identified in the context of senescence, ageing and age-associated diseases, a miRNome wide analysis will be also undertaken to identify a miRNA-based signature of frailty. Blood concentrations of secreted proteins known to be upregulated significantly in senescent endothelial cells and other hypothesis-driven biomarkers will be measured using ELISAs. The Frailomic Initiative aims to issue a series of interim scientific

reports as key results emerge. Ultimately, it is hoped that this study will contribute to the development of new clinical tools, which may help individuals to enjoy an old age that is healthier and free from disability.

INTRODUCTION

According to the 2012 European Union (EU) Ageing Report [1], the age structure of the European population is projected to change dramatically in coming decades, with older people accounting for an increasing share of the population. The percentage of citizens aged over 65 years is predicted to rise from 18% of the current population to 30% in 2060, whereas the percentage of over-80s will increase from 5% to 12% during the same time-period (Figure 1) [1]. The population pyramids in Figure 2 represent the current and predicted age structure in the European Union (EU) by 2060. These demographic trends suggest an impending scenario characterised by an increase in age-related disability and dependence, which will ultimately impact not only on the wellbeing of the individuals affected, as disability is a major factor determining a low quality of life, but also on healthcare systems, putting at risk their sustainability [2]. Nevertheless, recent data suggests that this tendency can change, providing the opportunity of living long lives in healthy, functional conditions [3]. Hence, the above demographic scenario entails significant individual and societal challenges and calls for prompt preventive actions.

Once established, disability is hard to be reversed. This is one of the main reasons that make prevention the core factor in the fight against disability in older adults, with the identification of conditions preceding the development of disability being an essential requisite to achieve this goal in an effective manner. Frailty is the most important risk factor for the development of non-catastrophic disability [4]. Thus, the identification of risk factors for frailty, the improvement in the accuracy of the diagnosis of frailty and the best knowledge of factors predicting the evolution from frailty to disability are necessary steps to be covered. Currently assessment of frailty relies primarily on measuring functional parameters such as weight loss, gait speed and grip strength. However, it is now becoming increasingly recognised that the clinical utility of such parameters in terms of risk prediction, diagnosis and prognosis of

frailty is limited. To improve this situation we have set up the FRAILOMIC initiative. This is an international, large-scale, multi-end point, community- and clinic-based research study funded by the European commission, whose aim is to develop validated measures of both classical and "omics"-based laboratory biomarkers, which may be able to predict the risk of frailty, improve the accuracy of its diagnosis in clinical practice, and provide a prognostic forecast on the onset of disability. In this viewpoint article we describe the rational, objectives and principal biomarkers that will be measured by the study.

The Frailomic Initiative adheres to the following basic definition of frailty: "*an age-associated syndrome characterized by a decrease of biological reserve and resistance to stressors due to functional decline of several physiological systems and placing the individual at enhanced risk of disability, hospitalization, and death*" [5]. Additionally, in keeping with the definitions released by the International Classification of Impairments, Disabilities and Handicaps-ICIDH (WHO, 1980) FRAILOMIC defines disability as *"any restriction or lack (resulting from an impairment) of ability to perform an activity in the manner or within the range considered normal for a human being".* However, because the participating cohorts have originally operationalised this definition in different ways, for the purposes of this study, incident disability has been defined as the appearance of a new dependency for basic activities of daily living.

FRAILTY AS A PRECURSOR OF DISABILITY: A RATIONALE FOR THE FRAILOMIC INITIATIVE

One of the main features that characterises the health status of the elderly is its large heterogeneity in terms of the effects that ageing has on the individuals' quality of life, functional limitation, and the type of diseases and conditions by which they are affected. Although health status is one of the major determinants of disability, the relation is nonlinear

and the onset and presentation of disability cannot be reliably predicted from clinical diagnosis alone [6]. Moreover, the capacity of health status determination and chronic disease to predict disability diminishes as the age of the population increases. It also appears that physical and cognitive factors contributing to functional decline and disability interact, thus suggesting that preventive care and rehabilitation of older people should take into account these cofactors for increased dependence. This would imply the need for a personalised medicine approach, taking into account patient stratification and a deeper understanding of which functional biomarkers may be prognostic of disability in older individuals, and hence offer an opportunity for its prevention. In this scenario, frailty has emerged as a relevant concept, as it predicts the risk for adverse clinical outcomes like death, disability, falls and hospitalisation [7] and provides opportunities for intervention [8]. It is becoming increasingly clear that there is a need to expand the concept of frailty from epidemiology to clinical practice [9]. In this regard, several studies have demonstrated some prognostic usefulness of conceptualising frailty in the context of predicting risk in patients undergoing surgical procedures [10], those receiving treatment for cardiovascular disease [11], and frail older cancer patients likely to develop severe toxicity and side effects in response to aggressive treatment [12].

The above considerations have led to the concept of defining frailty as a precursor to overt disability. According to its definition, frailty is envisaged as a recognisable phenotypic presentation encompassing physiological and psychological changes consequent upon ageing, lifestyle factors, clinical conditions, and interactions among them [6, 13]. In contrast with chronic disease, the predictive capacity of frailty for adverse outcomes like death or disability is known to increase as the age of the population advances [14]. The prevalence of frailty in people aged greater than 65 years is reportedly high and increases with ageing [7, 15].

Irrespective of the conceptual framework, when an individual passes the threshold for frailty and disability emerges, recovery is unlikely - especially as the age of the patient, the degree of disability, and its duration increase further [16]. It is also known that frailty is a major predictor of institutionalisation (odds ratio [OR] versus robust individuals, 8.6; 95% confidence interval [95% CI], 4.9–15.2) and death (OR, 7.3; 95% CI, 4.7–11.4) and that the relative risks persist after adjustment for sex, age, comorbid conditions, and poor self-rated health [17]. Furthermore, in a study that investigated the patterns of functional decline in elderly persons during their final year of life, frailty as an illness trajectory was approximately eight times more likely than sudden death to predict dependency in activities of daily living (OR, 8.3; 95% CI, 6.5–10.7). At the time of death, frail individuals were also relatively more disabled than those who died of cancer and/or organ failure [18]. Frailty may precede disability and other clinical outcomes by many years [7], and its early detection is clearly of importance to prevent disability [8]. Although it is widely recognised that progression from frailty to disability is influenced by multiple determining factors including those of genetic, biological and environmental origin, current research on biomarkers that can predict the development of frailty and its response to treatment is largely inconclusive. Moreover, although there is a considerable agreement about the conceptual definition of frailty (13), when its operational definition is contemplated, some differences emerge [19]. This has led to varying reports of its prevalence in community-dwelling older people, ranging from as low as 2.5% to as high as 25% [15]. Therefore, in order to address these discrepancies, the Frailomic Initiative aims to provide a clinically acceptable nomenclature for frailty, to identify its most prevalent risk factors in an unbiased approach, and to explore and define its consequences in measurable, accurate and reproducible terms, adding to the current criteria new “omic-based” items.

To address these aims, the Frailomic Initiative has designed four partially overlapping study phases. Phase I is being conducted in currently running prospective cohorts where, as well as conventional biomarkers of frailty, potential "omics"-derived or hypothesis-driven laboratory biomarkers for this condition are being explored. In phase II, data emerging from phase I will be validated in validation cohorts, and in phase III, best-fit models for tool kits will be devised. It is expected that the study findings will be disseminated at interim intervals throughout the study period and thereafter (phase IV) and that these will provide healthcare policymakers with the tools to target resources and programmes toward elderly individuals who are at obvious risk of developing frailty, in order to reduce the incidence of new-onset dependence.

DEFINING FRAILTY: FROM CLINICAL TO LABORATORY BIOMARKERS

A number of investigations have proposed several readily assessable surrogate markers of frailty including grip strength [20], gait speed [11], and poor nutritional intake and micronutrient deficiencies [21, 22]. However, there remains neither consensus definition of frailty nor consensual clinical assessment tools [13]. Moreover, although there is a range of frailty indices that may be useful to predict adverse outcomes, these involve collecting data on a large number of clinical variables and hence may be cumbersome and impracticable for everyday application [23].

The most accepted physiological framework to explain frailty and its consequences has been proposed by Fried & Walston [24]. According to their description, frailty results from sarcopenia, energetic imbalance, and feedback between these factors, the so-called "frailty cycle". This state is thought to involve multiple pathways and systems, especially those related to metabolic and nutritional deficiencies, age-associated hormonal derangements and the development of a pro-inflammatory milieu [25]. Examples of these include decline of

mitochondrial function [26]; a decrease in circulating levels of testosterone [27]; increased hydrocortisone (cortisol)–dehydroepiandrosterone (DHEA) ratio [5]; increase in circulating levels of estradiol in women [28]; declining serum levels of growth hormone and insulin-like growth factor (IGF)-1 [29]; elevated interleukin (IL)-6 and soluble receptors of tumour necrosis factor (TNF)-α [30]; vitamins deficiency [22] and increased values of both C-reactive protein (CRP) and D-dimers [31].

Derangement of the oxidant/antioxidant balance leading to oxidative stress is also considered an important determinant of frailty. This notion has been strengthened by recent work using patients from the Toledo Study of Healthy Ageing (TSHA), a constituent cohort of the Frailomic Initiative. The TSHA has shown that in geriatric populations oxidative stress is associated with frailty and not with ageing, thus highlighting the possibility that a set of biomarkers might exist which differentiate ageing from frailty at the molecular level [32].

Alzheimer's disease and cognitive decline [33] as well as cardiovascular diseases [34] and their risk factors, including diabetes mellitus [35], have been associated with frailty. In turn, frailty has been shown to influence the prognosis of acute cardiovascular events [36]. Furthermore, within the context of frailty, studies have emphasised the contributory role of atherosclerosis [34] and endothelial dysfunction [37]. Therefore, the possibility of detecting biomarkers related to vascular endothelial dysfunction and of atherosclerotic plaque growth or instability could provide clues to identifying individuals at risk of becoming frail and thereby improve their prognosis.

Another important pillar of the Frailomic Initiative is based on the increasing awareness that cellular senescence, a biological process underlying ageing at the cellular level is occurring in almost all organisms including mammals. There is circumstantial evidence that cellular senescence drives organismic ageing and thereby provides the basis for the onset of age-

associated pathology and disease. This concept is best illustrated by the demonstration that genetic elimination of senescent cells reduces age-associated pathology in a mouse model of premature ageing [38]. Of particular importance for the Frailomic Initiative concept is the process of endothelial and vascular smooth muscle cell senescence that occurs in the vascular wall. This phenomenon has been extensively described *in vivo* and has been associated with vascular disease, [39]. Cellular senescence can be observed with increasing age in a variety of other tissues. The occurrence of senescent cells correlates well with age-associated diseases and conditions, such as chronic obstructive pulmonary disease, the metabolic syndrome, kidney diseases, Alzheimer's disease, and skin ageing. Senescent cells are known to secrete a large panel of bioactive proteins, including proinflammatory cytokines and metalloproteases, referred to as the "senescence-associated secretory phenotype" (SASP) [40]. It is conceivable that components of the SASP contribute to tissue damage, considered as a driving force for age-associated functional decline.

AIMS OF THE FRAILOMIC INITIATIVE

The principal aim of the Frailomic Initiative is to develop validated measures comprising both classical and omics-based laboratory biomarkers to predict the risk of frailty, improve the diagnostic accuracy of frailty in day-to-day clinical practice, and assess the benefits of a prognostic forecast of frailty on the onset of disability and other adverse outcomes. In order to identify predictive biomarkers, the European Union-funded Frailomic Initiative follows an "omics" approach (genomics, transcriptomics, proteomics and metabolomics, for example), using existing large datasets from previous "omics" initiatives [41]. These studies have created a wealth of data that, so far, have not been used in the field of frailty research.

The approach taken by the Frailomic Initiative is to predict the risk of frailty, to improve the diagnostic accuracy of frailty in terms of day-to-day clinical practice and to assess the

prognosis of frailty in terms of disability and other adverse outcomes. This will allow clinicians to go beyond the traditional disease-based approach to healthcare strategy and toward a strategy based on comprehensive quality-of-life, since the impact will be on reducing disability. Secondary objectives of the Frailomic Initiative include assessing interactions among putative biomarkers, nutrition, exercise and their effects on the natural history of frailty. In addition, the potential therapeutic usefulness of identifying frailty status in special older populations such as those with metabolic syndrome, diabetes and cardiovascular disease will be examined. The Frailomic Initiative aims to provide useful tool kits for care providers that will allow them to assess the risk of an older individual developing frailty (i.e., "risk biomarkers") as well its identification (i.e., "diagnostic biomarkers"), clinical course (i.e., "prognostic biomarkers"), and likely response to treatment (i.e., "predictive biomarkers") thus bridging the gaps between epidemiology and clinical practice.

Participating older adults in the Frailomic Initiative will be recruited from eight established community based cohorts, seven of which are European, (Inchianti, Toledo Study of Healthy Ageing (TSHA), ENRICA Study, SardiNIA Study, Three-Cities (3-C), AMI Cohort, and the Collaboration on Ageing in Europe [COURAGE]), and one, the Study of Global Ageing and Adult Health (SAGE), representing people from across the globe. These cohorts comprise a total of >75,000 subjects, most of whom (n=51,860) are aged >65 years. Baseline data (e.g. functional and nutritional status, exercise habits and cardiovascular health) for each of the FRAILOMIC participants will be obtained from the original cohort surveys. The main descriptors of the cohorts are summarized in Table 1. In addition, during the study, all adverse outcomes (disability, hospitalisation and death) will be systematically recorded. In phase I of the Frailomic Initiative, exploratory study subjects will first be stratified as "non-frail" or "frail" using Fried's definition such as the presence of at least three criteria presented in Table 2. In non-frail subjects one of the aims of the study will be to identify

biomarkers that are associated with the risk of developing frailty; that is, the expression of these biomarkers will be differentiated between subjects who do and those who do not develop frailty during a 3 year follow up period. Another study aim in frail and non-frail subjects (matched by sex, age and time of follow-up) is to improve the diagnosis of frailty by identifying biomarkers that are differentially expressed between these two groups, using conditional logistic regression analysis. Lastly, another study aim will be to characterise, using Cox regression analysis, the prognosis of subjects with frailty at baseline by documenting their incidence rates of disability, hospitalisation and death thereafter. Statistical analysis of the data will aim to identify significant relations between target biomarkers and study endpoints, taking into account their diagnostic accuracy (by using Receiver Operating Characteristic [ROC] curves), diagnostic odds ratio (DOR), positive and negative likelihood ratios, positive and negative predictive power as well as sensitivity and specificity. A statistical method devised in-house by the Frailomic Initiative researchers [42] will be adapted to the Frailomic Initiative in order to minimise false positive associations and multiple testing challenges occurring when analysing several datasets.

Biomarkers to be initially examined in the Frailomic Initiative, listed according to their biological functions are shown in Table 3. Although most of these molecules have not been previously studied within the context of frailty, each of them was included after a careful review of the literature having shown a suggested relationship with this condition, its domains or its potential pathophysiological routes. Genomic and transcriptomic investigations of proposed candidate genes will consist of genotyping single nucleotide polymorphisms (SNPs) and assessing gene expression levels. More candidate genes will be investigated as they come to light in the future. SNPs will be analysed using the VERACODE platform, that allows the analysis of 48, 96, 144, 192 or 384 SNPs by an allelic discrimination reaction, extension reaction and multiplex PCR with universal primers while gene expression will

be analysed using the OpenArray platform, an array-based system that applies the real-time polymerase chain reaction (RT-PCR) technique, and then subjected to bioinformatics analysis. Labelling of telomeres in interphase nuclei will be performed using high-throughput quantitative fluorescence *in situ* hybridisation (HT-FISH) so as to determine the percentage of cells with critically short telomeres (43). Frequency of critically short telomere length has been demonstrated to be a more useful determinant of telomere dysfunction than the average telomere length [43]. Since circulating microRNAs in serum or plasma have been identified in the context of senescence, ageing and age-associated diseases [44] a miRNome wide analysis of circulating miRNAs will be investigated in order to identify a miRNA based signature of frailty. Along the same lines, proteins known to be secreted by senescent endothelial cells will be investigated. In addition, serum levels of HIF-α will be determined and compared with the expression of a panel of target genes. Finally, conventional and innovative laboratory biomarkers will be assessed with standardised and reference techniques, according to the best laboratory practice.

THE FRAILOMIC INIATIVE SPECIAL POPULATIONS

The Frailomic Initiative will try to assess if there are some population groups that are at high risk for developing frailty and disability. These are mainly those populations with a high cardiovascular risk profile, which exhibit some differential characteristics regarding the general population of older adults.

CONCLUSIONS

The EU places a high priority on healthy ageing. In 2011, with the EU's agreement to launch the Joint Programming Initiative "*More Years, Better Lives*", the European Commissioner for Research and Innovation Máire Geoghegan-Quinn stated that "*Europe must work together to tackle challenges such as its ageing population*". The EU went on to make 2012 the

"European Year of Active Ageing and Solidarity between Generations" [45]. The challenges related to an ageing European population have changed over the years. Although there is clear evidence that people are living longer, future forecasts suggest that life expectancy will not be increased substantially, whereas old age dependency ratio is set to show enormous growth. Hence the, achievement of protracted life expectancy seems less important for the future than reaching an old age that is healthy and potentially free from major disease and disability.

The above mentioned aims of the Frailomic Initiative will refine the epidemiological concept of frailty using omics-based research methods. Thus, the discovery of biomarkers associated with this condition may provide new biological insights into its aetiology. Furthermore, It will allow us to develop clinical instruments that could be used in the clinic to predict the risk and improve the diagnostic accuracy of frailty as well as assess its prognosis. In this respect the early detection of subclinical changes afforded by these potential biomarkers could be crucial in allowing for early interventions to prevent/delay frailty and consequently the future onset of disability (8). The practical outcomes of the Frailomic Initiative promise to build a solid bridge between standard "care of elderly people" as provided by today's healthcare workers and a more personalised approach to healthcare of older people that would allow us to target limited medical and nursing resources to the individual needs of the patient. The Frailomic Initiative is an ongoing, international, large-scale, multi-endpoint, community- and clinic-based research programme and aims to issue a series of interim scientific reports as key results emerge over the next few years.

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CONFLICT OF INTEREST STATEMENTS

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Marcelo Viegas: Dr. Marcelo Viegas is Chief Scientific Officer at Life Length, Inc. (www.lifelength.com), Madrid, Spain.

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Table 1. Main descriptors of the cohorts participating in the FRAILOMIC Initiative

Name of the Study	InChianti	SardiNIA	3-C	AMI	TSHA	ENRICA	SAGE	COURAGE
Phase(s) where the data will be used	I	II	I	I	I and II	II	II	II
Country of origin	Italy	Italy	France	France	Spain	Spain	China, Ghana, India, Mexico, Russian Federation, South Africa	Finland, Poland, Spain
Cohort type	community, selected from city registries	60% from Sardinia and Lanusei	community	community, rural	community	community	community, multinational	community, multinational
Number of participants by setting	1453	6100 (877 < 65 yrs)	2104	1002	2480	3500 (≥60 yrs)	~45,000	12000
Number of individuals with available biological samples	1453	to be determined	457	1002	1750	3500	to be determined	12000
Possibility to get new biological samples	yes	yes	no	yes	yes	yes	yes	yes
Presence of Diabetes	yes	yes	yes	yes	yes	yes	yes	yes
Presence of Ischaemic Heart Disease	only MI	yes	yes	yes	yes	yes	yes	yes
Presence of stroke	yes	yes	yes	yes	yes	yes	yes	yes
Presence of Peripheral	yes	yes	yes	yes	yes	yes	yes	yes

Artery Disease								
Presence of Hypertension	yes	yes	yes	yes	yes	yes	yes	yes

Table 2. Frailty phenotype as proposed by Fried *et al*. [2001]

Criterion	Measure
Shrinking	Weight loss unintentional >4.5 kg (10 lbs) in prior 1 year
	Sarcopenia
Weakness	Grip strength lowest 20% by sex/body mass index
Exhaustion	"Exhaustion" self-reported
Slowness	Walking time 4.6 m (15 ft) lowest 20% by sex/height
Low activity	Energy expenditure (kcal/week) lowest 20%
	Male, <383 kcal/week
	Female, <270 kcal/week

Table 3. Biomarkers examined by the Frailomic Initiative

Biological process	Biomarker	Rationale for selection	Method of analysis
Metabolism / Muscle function			
	ACE	Association of genotype with muscle mass, response to muscle power training and longevity	Veracode (SNP)
	ACTN3	Association of genotype with response to muscle power training, muscle mass and risk of falling in older females	Veracode (SNP)
	CNTF	Association of genotype and grip strength in older Caucasian women	Veracode (SNP)
	GDF8	Association of genotype with muscle mass in elerly women	Veracode (SNP)
	IL6	Implicated in muscle repair after exercise. Association between genotype and human longevity	Veracode, Openarray (SNP and mRNA)
	mtDNA	Association between genotype and longevity in different populations	Veracode (SNP)
	VDR	Association of genotype with muscle strength and rate of falling in the elderly	Veracode (SNP)
Metabolism/ Insulin/IGF1 signaling pathway		Reducing the activity of this pathway protects from ageing-associated pathologies and extends life-span in animal model systems	
	AKT1	Association of genotype with human longevity	Veracode, Openarray (SNP and mRNA)
	FOXOs	Association of genotype with human longevity	Veracode, Openarray (SNP and mRNA)
	mTOR		Veracode, Openarray (SNP and mRNA)

Metabolism /Stress response			
	HIF1	Modulation of life-span in *C. elegans*	Openarray (mRNA); ELISA
	PGC1α	Association of genotype with diabetes, with age of onset of neurodegenerative diseases and with longevity	Veracode (SNPs)
	SIRT1	Over-expression delays ageing phenotypes and extends life-span in model organisms; genotype associated with lipid profiles in humans	Veracode, Openarray (SNP and mRNA)
	SOD2	Reduced expression associated with ageing phenotypes; genotype associated with survival in very old women	Veracode, Openarray (SNP and mRNA)
Response to stress			
	TP53	Increased expression is associated with ageing phenotypes in mice	Openarray (mRNA)
	SESN2	Inactivation in Drosophila results in an ageing phenotype	Openarray (mRNA) ;
Cardiovascular homeostasis			
	AGT	Association of genotype with hypertension	Veracode (SNP)
	NOS3	Association of genotype with disability in the elderly	Veracode (SNP)
Inflammation			
	AGEs	Increased in ageing, diabetes and cardiovascular diseases; increased levels associated with reduced grip strength	ELISA
	sRAGE	Decreased in diabetes; inverse association with atherosclerosis	ELISA
	CCL11	Increased with ageing; elevated levels	ELISA

		associated with decreased cognitive function and lower grip strength	
	LGALS3	Association of genotype with cognitive function at old age	Veracode (SNP)
	JAG1	Secreted by senescent endothelial cells	ELISA
	VCAN	Secreted by senescent endothelial cells	ELISA
Regulation of cell proliferation			
	IGFBP6	Secreted by senescent endothelial cells	ELISA
	Telomere	Association of telomere length with age-associated diseases and life-span	HT-QFISH
Regulation of gene expression			
	miR-24, miR-130, miR-94	Longevity-associated miRNAs	miRNome profiling
	miR-17, miR-19b, miR-20a, miR-106a	Ageing and senescence associated miRNAs	miRNome profiling
	mir-31miR-10a-5p, miR-10b-5p, miR-22-3p, miR-133b, miR-328-3p, let-7g-5p	Osteoporosis related circulating miRNAs	miRNome profiling

FIGURE LEGENDS

Figure 1. Elderly population in Europe: trends 2010 through 2060. Source: EUROPOP 2012 [47]

Figure 2. Population pyramids showing frequency of age groups in EU countries as of current data and those projected for 2060.

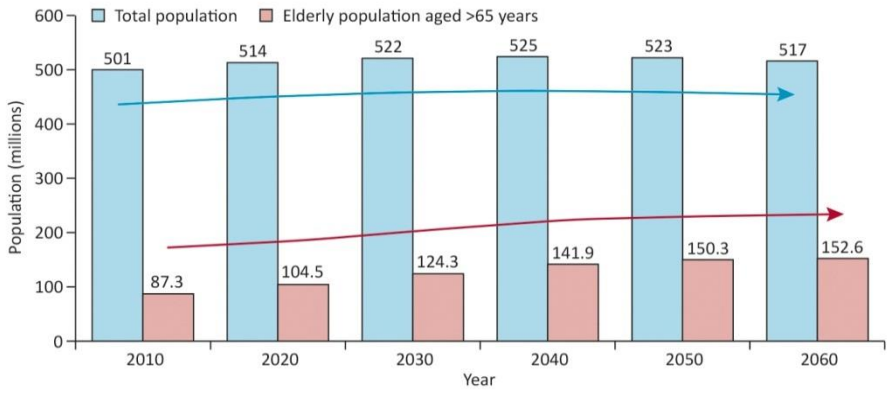
Total population
Elderly population aged >65 years
Population (millions)
600
500
400
300
200
100
0
501
514
522
525
523
517
87.3
104.5
124.3
141.9
150.3
152.6
2010
2020
2030
2040
2050
2060
Year

Fig. 1

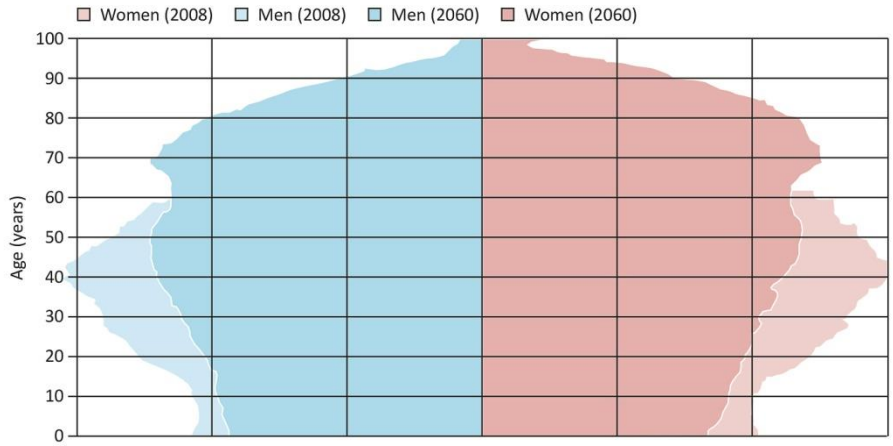
Women (2008)
Men (2008)
Men (2060)
Women (2060)
Age (years)
100
90
80
70
60
50
40
30
20
10
0

Fig. 2