Utility of omic-based biomarkers in characterizing older individuals at risk for frailty, its progression to disability and general consequences to health and well-being - The FRAILOMIC Initiative

Reporting

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Final Report Summary - FRAILOMIC (Utility of omic-based biomarkers in characterizing older individuals at risk for frailty, its progression to disability and general consequences to health and well-being - The FRAILOMIC Initiative)

Executive Summary:
The global population of older people is increasing rapidly. From 2013 to 2060 the proportion of the
population aged ≥65 years is projected to increase from 18% to 28% and the proportion of those aged ≥80 years from 5% to 12%. An aging population raises social and economic challenges and as the number of older people increases, so too will the number of people with age-related disability and dependence.

Frailty is a preventable and reversible condition that marks the transition from robust health and function to age-related disability.

The FRAILOMIC project (2013 – 2018) aimed at identifying and developing clinical instruments (composed by clinical, -OMICs based laboratory, and classical laboratory biomarkers):

1) To predict the risk of frailty.
2) To improve the diagnostic accuracy of frailty in day to day practice.
3) To assess the prognosis of frailty in terms of disability and other adverse outcomes.

To this end, FRAILOMIC sampled biospecimens from a pool of over 75,000 participants from nine established population-based cohorts participating in the study. Nested case-control samples from 4261 participants contrasting frail individuals to prefrail and robust controls were sampled and analyzed in 10 highly specialized European laboratories. In total, 35312 candidate biomarkers were selected to capture the major known biological processes associated with ageing such as metabolics (muscle function, insulin, IGF1 signaling pathway, and stress response), cardiovascular homeostasis, inflammation, regulation of cell proliferation, and regulation of gene expression.

As a result, FRAILOMIC identified 13 biomarkers with promising associations with the diagnosis of frailty beyond classical risk factors measured in the clinic, such as depression, adiposity, and prevalent diseases. These biomarkers moderately improved diagnostic accuracy between 2%-10% upon clinical parameters usually assessed in medical practice.

We conclude that the benefit of analyzing OMIC markers to improve the diagnostic accuracy in frailty is limited. A prevailing assumption and requirement for the success of precision or personalized medicine is the notion that molecular biomarkers will improve diagnostics markedly. But the frailty phenotype is highly heterogeneous and stratification based on molecular markers showed only limited success, highlighting the need of a consensus definition of frailty and encouraging the use of already established criteria, such as the Fried phenotype in clinical praxis.

Project Context and Objectives:
According to the 2012 EU Ageing Report [1], the age structure of the European population is projected to change dramatically in the 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). The population pyramids represent the current and predicted age structure in the EU by 2060. These demographic trends suggest an impending scenario characterized 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. Nevertheless, recent data suggest that this tendency can change, providing the opportunity of living long lives in healthy, functional conditions. Hence, the above demographic scenario entails significant individual and societal challenges and calls for prompt preventive actions.

Once established, disability is hard to reverse. 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. 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.

The FRAILOMIC Initiative adheres to the following basic definition of frailty: ‘an age-associated syndrome characterised 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, hospitalisation and death’. Additionally, in keeping with the definitions released by the International Classification of Impairments, Disabilities and Handicaps, 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 operationalized 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.

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 non-linear, and the onset and presentation of disability cannot be reliably predicted from clinical diagnosis alone. 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 personalized 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 and provides opportunities for intervention. It is becoming increasingly clear that there is a need to expand the concept of frailty from epidemiology to clinical practice.

FRAILOMIC tries to refine, using –omics, the epidemiological-based concept of frailty to make it useful in other (clinical and non-clinical) settings, providing tool-kits to the health workers that allow them to assess the risk of developing frailty (risk biomarkers (BM)), to detect frailty (diagnostic BM), and to assess the evolution of frailty (prognostic BM) and its likely response to treatment (predictive BM), thus bridging the
gap between epidemiology and care practice.

We measure the levels of blood and urine omic-based BM in old people selected from nine cohorts, using standardized and innovative technology. Combining these lab BM with clinical BM, we develop predictive, diagnostic and prognostic models, with its modulation by nutrition and physical activity, in general old population and in old people showing some characteristics that confer a high risk for developing frailty (selected cardiovascular risk factors and diseases). After that, a selected set of BM will be validated prospectively and assessed to find the best-fitted models. These models will guide the development of the ready-to-use kits to be implemented in the clinical settings.

FRAILOMIC is a well-balanced consortium with a strong participation of SMEs distributed over the individual tasks. In summary, FRAILOMIC is original, relevant, pertinent, feasible, and overcomes the usual research bottlenecks on Biomarkers, and fits perfectly with the topics addressed by the HEALTH.2012.2.1.1-2 call in human subjects.

The main objective of FRAILOMIC is to develop clinical instruments (composed by clinical BM, omics based laboratory BM and classical laboratory BM):

1) To predict the risk of frailty.

2) To improve the diagnostic accuracy of frailty in day to day practice.

3) To assess the prognosis of frailty in terms of disability and other adverse outcomes.

In addition, the project has also three secondary objectives:

1) To assess the interactions between –omic based BM and nutrition and physical exercise (useful to know the potential response to treatments) on the natural history of frailty.

2) To test whether the above stated instruments are also useful for special populations: people with diabetes, obesity and people with cardiovascular disease.

3) To test the differential validity of Fried’s criteria as compared with those described in the Toledo Study of Healthy Aging (TSHA) and Three-City-Bordeaux studies.

The main objectives of the project are to find out the role of several –omics based BMs in the characterization of the risk of developing frailty, in the contribution to a better diagnosis of frailty and in the implementation of stronger predictors of the prognosis of frailty. The usual approach in these studies aimed to find biomarkers in clinical practice consists in studying a group of biomarkers potentially related to the disorder studied, check them in exploratory studies with low sample sizes and, when a preliminary panel of BMs has been selected, validate them in larger populations.

The Frailomic project comprises four phases (Exploratory, validation, best fitted model and dissemination/exploitation phase). Figure 2 describes the different phases of the FRAILOMIC study.
In the exploratory phase 35312 candidate BM were selected to capture the major known biological processes associated with ageing such as metabolics (muscle function, insulin, IGF1 signaling pathway, and stress response), cardiovascular homeostasis, inflammation, regulation of cell proliferation, and regulation of gene expression. The BM were measured in 1636 participants from 4 nested case-controls samples from the Toledo Study of healthy Aging, the InChianti Study, the 3 City Study Bordeaux site, and the AMI study. 340 of these participants were classified as “frail” according to the Fried phenotype.

These 35312 BM were reduced after statistical evaluation using machine learning approaches to 59 BM forwarded for validation phase in 2625 participants from 6 longitudinal cohorts (TSHA, MAPT, SARDINIA, EXERNET, SAGE, ENRICA).

Phase 3 describes the statistical evaluation of the relationship between BM and diagnosis of frailty, risk of incident frailty, and prediction of frailty outcomes.

Phase 4 includes all dissemination activities, including scientific communications and non-scientific public presentations. In addition, it includes the exploitations of potentially patentable results and the provision of algorithms in forms of analysis toolkits.

Project Results:
Frailty is traditionally defined as a specific geriatric syndrome characterised by increased vulnerability to unfavourable outcomes, such as falls, disability, hospitalisation and overall mortality, which is a result of the impairment of manifold and interrelating biological pathways, ultimately leading to decreased homeostatic reserve and lower resistance to stressor events, such as therapy or infections. Due to an increasing trend toward ageing of the population (the percentage of people aged ≥ 65 years is projected to increase by 20% in Europe by 2060), frailty will soon emerge as a serious and increasingly important global health burden.

Several lines of evidence attest that frailty can be prevented, or at least delayed, by the establishment of timely and appropriate physical, psychological and therapeutic interventions. The two main drawbacks in managing frailty are the still uncertain definition of this condition, and the challenging clinical assessment (i.e. loss of muscle mass and strength, decay of energy and exercise tolerance, decreased physiological reserve), which makes it impractical for routine use in clinical practice. As for other chronic and prevalent disorders [5, 6], laboratory diagnostics have the potential to help identify those individuals who may be at greater risk of developing this condition later in life, and may also assist the managed care of frail individuals. Over the last few decades many independent studies have attempted to identify predictive, diagnostic and prognostic biomarkers of frailty (i.e. vitamin D, cortisol, testosterone, dehydroepiandrosterone and inflammatory biomarkers among others), but no definitive conclusions can be drawn. This is principally attributable to limitations of the published trials, such as the small sample size, the heterogeneity of entry points and study population, and the use of little validated techniques for biomarker measurement.

Here we summarize the scientific output of the consortium in terms of scientific papers published by members of the consortium funded by by the European Union’s Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 305483, FRAILOMIC Project.

We categorize the publications in 6 groups: Frailty; MicroRNA and Gene Expression; Nutrition, Cardiovascular Disease and Physical Activity; Diabetes, Obesity, and Metabolic Syndrome; and Cognition.
Jointly with the reference we give a short summary and put the publications into the context of FRAILOMICs at its aims.

Frailty:
The FRAILOMIC studies produced overview papers about frailty in general, the care approach in different settings, and the goals of the FRAILOMIC initiative.

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 healthcare 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. The aim of FRAILOMIC is to develop validated measures, comprising both classic 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.


In the latest publication, FRAILOMIC authors compared the Phenotype Model to the Deficit Accumulation model and relate FRAILOMIC to the novel concept of “Intrinsic Capacity”. Frailty in aging populations is associated with increasing evidence of ill health, functional loss, increasing dependency and premature death. The FRAILOMIC Initiative was designed to define, predict and prevent frailty by means of identifying omic markers associated with the diagnosis, risk, and prognosis of frailty. Relating biomarkers associated with frailty to a continuous measure of intrinsic capacity will help in identifying and monitoring at-risk populations. The FRAILOMIC Initiative will provide key insights into the prevention, early detection, and treatment of frailty to reduce the impact of disability in our aging populations.


The PI of the FRAILOMIC project has written an article jointly with one of the original investigators of the frailty phenotype model about the position of frailty in the hospital setting. They conclude that as societies’ life expectancies are approaching natural lifespans, the gains in life-years have been accompanied by an increase in the rates of disability. Disability is the main result of three concurrent factors in older people (older than 60 years): the ageing process, unhealthy lifestyles, and health disorders. Disability is often preceded by a state characterised by reduced capacity to respond to stressors, caused by a decline in functional reserves. This condition—frailty—might precede by several years the development of disability and other clinical outcomes, and is a major risk factor for non-catastrophic disability.


In this line of research looking at frailty in the clinical setting Rodríguez-Pascual et al. investigated the association between frailty and adverse health outcomes in hospitalized patients with stable heart failure. This study examined the association of frailty, diagnosed by well-accepted criteria, with mortality, readmission and functional decline in very old ambulatory patients with heart failure. They conclude that frailty diagnosed in the hospital using the Fried Phenotype criteria was associated with an increased risk of...
1-year mortality, hospital readmission and functional decline among older ambulatory patients with stable heart failure.

One of the five frailty components is grip strength. Given that some of the deleterious effects of uric acid (UA) on health are greater in younger than in older subjects, and that age is strongly associated with skeletal muscle composition and function, García-Esquinas et al. tested the hypothesis that the association between UA and muscle strength differs by age. They found that the association between UA and muscle strength differed depending on age: while a negative link was observed in adults aged 20–40 years, this relationship disappeared later in life, and was reversed after the age of 60.


Frailty and sarcopenia are correlates of musculoskeletal aging that represent a state of vulnerability increasing the risk of negative health outcomes. In fact of the three components that define sarcopenia, two (gait speed and grip strength) are equally included in the frailty definition. Standardized definitions are lacking for both, and sometimes both concepts are used interchangeably. Davies et al. assessed the coexistence of these 2 entities in a cohort of older community-dwelling people. They conclude that frailty and sarcopenia are distinct but related conditions. Sarcopenia is not a useful clinical biomarker of frailty, but its absence might be useful to exclude frailty.


A potential risk factor that has received little attention is the literature is environmental pollutions. While environmental pollution can be prevented on a societal level, for an individual it is often complicated to shield him or herself from it. García-Esquinas y Rodríguez-Artalejo wrote a review about environmental pollutants an frailty in older adults summarizing the existing evidence on the potential associations between environmental pollutants, limitations in physical functioning, and frailty among older adults. They found that only a few studies evaluated the association between specific environmental pollutants and frailty. Cross-sectional studies suggest an association between second-hand smoke and lead exposure with the prevalence of functional limitations and frailty in older adults; they also suggest a link between cobaltum exposure and walking problems. One longitudinal study found an increased risk of frailty after PM2.5 exposure among individuals hospitalized with a myocardial infarction, while another found an inverse association between cadmium and phthalate exposure and hand-grip strength. They identified a clear need for more studies to assess the effects of environmental pollution on physical functioning decline, frailty development, and its progression.


Another environmental factor that is strongly associated with socioeconomic status are housing conditions. García-Esquinas et al. recognizing that housing conditions are an important social determinant of health, systematically assessed the association between housing conditions and physical function limitations in
older adults; moreover, whether they assessed whether this association is independent of the socioeconomic status achieved earlier in life. They found that poor housing conditions, particularly living in a walk-up building and lacking heating, are independently associated with limitations in physical function in older adults and argue that this entails serious inequalities in functional status, which should be firmly addressed.


Pérez-Hernández et al. followed-up on this study in longitudinal cohort. Acknowledging that poor housing conditions have been associated with an increased risk of morbidity and mortality in old age. They defined likewise poor conditions as living in a walk-up building, lacking piped hot water or heating, feeling frequently cold at home, lacking a bathtub/shower, a refrigerator, a washing machine, an own room or a landline. They measured frailty with the Fried criteria, lower extremities performance with the Short Physical Performance Battery (SPPB), and disability in instrumental activities of daily living (IADL) with the Lawton and Brody questionnaire. They found that participants who lived in homes with ≥1 poor conditions showed a higher risk of frailty (odds ratio [OR] = 2.02; 95% confidence interval [95% CI]: 1.09-3.75) and transportation disability (OR = 3.50; 95% CI: 1.38-8.88). Lacking heating and feeling frequently cold were associated with an increased risk of exhaustion (OR = 2.34; 95% CI: 1.00-5.48) and transportation disability (OR = 3.31; 95% CI: 1.07-10.2) respectively. They conclude that prevention programs targeting functional limitations in older adults should ensure that they live in suitable housing conditions.


Disability is often described as the endpoint of the frailty process. As such it is important to also investigate whether it is possible to ameliorate the health consequences associated to this end state of frailty. Martinez-Gomez et al. investigated whether regular physical activity (PA), known to protect against disability onset, also, once the disability is present, attenuates its harmful health consequences. They showed that being physically active (ie, doing any PA) was associated with a statistically significant 26%-37% and 35%-50% lower risk of total and CVD death, respectively, across types of disability. As compared with those being physically active and without disability, those who were inactive and had a disability showed the highest mortality risk from total (hazard ratios from 1.52 to 1.90 across disabilities, all p < .05) and from CVD (hazard ratios from 1.99 to 2.24 across disabilities, all p < .05). Total and CVD mortality risk was similar in physically active participants with disabilities and in inactive individuals without disability. They conclude that In older adults, PA could attenuate the increased risk of mortality associated with physical disability.


MicroRNA and Gene Expression

One of the components of frailty's gait speed and physical activity. Falls, a common consequence of frailty, are the origin of many fractures in the elderly. Physical activity is hampered by joint pain and bone disease. Hackl et al. investigated circulating microRNAs also being tested for their association with frailty as
biomarkers for bone disease. MicroRNAs (miRNAs) are the most abundant RNA species to be found in cell-free blood. Encapsulated within microvesicles or bound to proteins, circulating miRNAs are remarkably stable analytes that can be measured using gold-standard technologies such as quantitative polymerase-chain-reaction (qPCR). Nevertheless, the analysis of circulating miRNAs faces several pre-analytical as well as analytical challenges. From a biological view, there is accumulating evidence that miRNAs play essential roles in the regulation of various biological processes include recently results from circulating miRNAs analysis in patients with osteopenia, osteoporosis and fragility fractures have been reported.


Kocijan et al. investigated fragility fractures in patients. Established bone turnover markers do not reflect fracture risk in idiopathic male and premenopausal osteoporosis and the role of microRNAs (miRNAs) in these patients is currently unclear. miRNAs are a class of small non-coding RNAs that regulate gene expression and bone tissue homeostasis. They are considered a new class of endocrine regulators with promising potential as biomarkers. Specific serum miRNA profiles are strongly related to bone pathologies. Therefore miRNAs might be directly linked to bone tissue homeostasis. In particular, miR-29b-3p has previously been reported as regulator of osteogenic differentiation and could serve as a novel marker of bone turnover in osteoporotic patients as a member of a miRNA signature.


Heilmeier et al. Investigated whether Serum-miRNA signatures are indicative of skeletal fracture in postmenopausal women, complementing standard measures of bone density done in clinical practice. Standard DXA measurements, including Fracture Risk Assessment Tool (FRAX) scores, have shown limitations in assessing fracture risk in Type 2 Diabetes (T2D), underscoring the need for novel biomarkers. MicroRNAs (miRNAs) are secreted into the circulation from cells of various tissues proportional to local disease severity and were recently found to be crucial to bone homeostasis and T2D. In vitro functional studies in human adipose tissue-derived mesenchymal stem cells to investigate the effect of miR-550a-5p, miR-188-3p, and miR-382-3p on osteogenesis, adipogenesis, and cell proliferation were done. They found that miR-382-3p significantly enhanced osteogenic differentiation (p<0.001) whereas miR-550a-5p inhibited this process (p<0.001). Both miRNAs, miR-382-3p and miR-550a-5p, impaired adipogenic differentiation, whereas miR-188-3p did not exert an effect on adipogenesis. The data suggest for the first time that miRNAs are linked to fragility fractures in T2D postmenopausal women.


In the same vein, Weilner et al. investigated the relationship between miRNA and osteogenic differentiation after recent fracture. Because of the nature of circulating miRNA, they might not only be useful as
surrogate biomarkers for the diagnosis or prognosis of pathological conditions, but could be actively modulating tissue physiology. They showed that the levels of specific circulating miRNAs change in the context of recent osteoporotic fractures and that such perturbations of "normal" levels might affect bone metabolism or bone healing processes. They also looked at the relationship in mesenchymal stem cells. Because damage to cells and tissues is one of the driving forces of aging and age-related diseases, various repair systems are in place to counteract this functional decline. In particular, the property of adult stem cells to self-renew and differentiate is essential for tissue homeostasis and regeneration. However, their functionality declines with age. One organ that is notably affected by the reduced differentiation capacity of stem cells with age is the skeleton. Here, they found that circulating microvesicles impact on the osteogenic differentiation capacity of mesenchymal stem cells in a donor-age-dependent way. While searching for factors mediating the inhibitory effect of elderly derived microvesicles on osteogenesis, we identified miR-31 as a crucial component. They demonstrated that miR-31 is present at elevated levels in the plasma of elderly and of osteoporosis patients. Endothelial miR-31 is secreted within senescent cell-derived microvesicles and taken up by mesenchymal stem cells where it inhibits osteogenic differentiation by knocking down its target Frizzled-3. Therefore, they suggest that microvesicular miR-31 in the plasma of elderly might play a role in the pathogenesis of age-related impaired bone formation and that miR-31 might be a valuable plasma-based biomarker for aging and for a systemic environment that does not favor cell-based therapies whenever osteogenesis is a limiting factor.


With this accumulating evidence of the validity of miRNA as biomarker for bone and fracture risk and recovery, Weilner et al. reviewed the role of these miRNAs in cellular senescence. They found that evidence exists that associates miRNA with with cellular aging and tissue degeneration. Specifically in regard to frailty, microRNAs have been found to influence the onset and course of age-related musculoskeletal conditions such as osteoporosis, osteoarthritis, and posttraumatic arthritis. Both intracellular and extracellular microRNAs may be suitable to function as diagnostic biomarkers. In particular, they conclude that microRNAs play an important role in orchestrating age-related processes and conditions of the musculoskeletal system.


The opposite of cell ageing, in some respect, is cancer. In cellular senescence is absent in cancer cell. The miR-17-92 cluster, led by its most prominent member, miR-17-5p, has been identified as the first miRNA with oncogenic potential. Thus, the whole cluster containing miR-17-5p has been termed oncomiR-1. It is strongly expressed in embryonic stem cells and has essential roles in vital processes like cell cycle regulation, proliferation and apoptosis. The importance of miR-17-5p for fundamental biological processes is underscored by the fact that a miR17-deficient mouse is neonatally lethal. Recently, miR-17-5p was identified in the context of aging, since it is comprised in a common signature of miRNAs that is downregulated in several models of aging research. Recently, miR-17-5p turned out to be the first 'longevimiR' in an animal model, extending the lifespan of a transgenic miR-17-5p-overexpressing mouse. Here, we summarize the current status of research on miR-17-5p with emphasis on its role in cellular
senescence, aging and cancer, which points to a pleiotropic function of miR-17-5p regulating multiple targets involved in autophagy, cell cycle regulation and apoptosis in a tissue-dependent fashion. In addition, its elevated presence in serum or plasma of a wide range of tumor patients suggests using it as an 'alarmiR', a general indicator of a potential tumor pathology. However, amounts of circulating miR-17-5p of healthy individuals as reference values are still missing, before any miRNA can be classified as such an 'alarmiR'. In conclusion, miR-17-5p is at the crossroads of aging, longevity and cancer and might represent a promising biomarker or even therapeutic tool and target in this context.


Centenarians have long been a model phenotype for studying ageing given that they show exceptional health profiles when compared to the general population. Consuelo Borras et al. compared the transcriptome from centenarians to septuagenarians. Centenarians not only enjoy an extraordinary aging, but also show a compression of morbidity. Using functional transcriptomic analysis of peripheral blood mononuclear cells (PMBC) they identified 1721 mRNAs differentially expressed by centenarians when compared with septuagenarians and young people. They identified Bcl - xL as an important gene up-regulated in centenarians. It is involved in the control of apoptosis, cellular damage protection and also in modulation of immune response, all associated to healthy aging. They conclude that mRNA expression in centenarians is unique and reveals that BcL- xL plays an important role in exceptional aging.


Gene expression has been part of the risk factor battery investigated in FRAILOMICs. Using data from the FRAILOMIC TSHA cohort El Assar et al. investigated the relationship between candidate genes of aging and frailty. Frailty can be viewed as a loss of functional reserve resulting in increased vulnerability to stressors. They hypothesize that pathways regulating cellular response to stress are potential players in the development of frailty. Among the analyzed genes, lower expression of genes related to cellular response to hypoxia (hypoxia inducible factor-1α) or to cellular response to oxidative stress (nuclear factor erythroid 2-related factor 2 and its target genes heme oxygenase-2, thioredoxin reductase-1, and superoxide dismutase-2), but not to those related to inflammation or vascular physiology, were significantly associated with the presence of frailty after adjustment for age and sex. These associations remained significant after adjustment by type 2 diabetes and Charlson index of comorbidities. Lower expressions of genes involved in cellular response to stress were also associated with increased risk of functional impairment. They conclude that reduced expression of several genes implicated in cellular response to oxidative stress or hypoxia is significantly associated with the presence of frailty.


In summary, important genetic markers exist that can be associated to healthy ageing and frailty. The usefulness in the clinical setting has yet to be evaluated.

Nutrition:
Poor nutritional status is very prevalent in geriatric populations, is one of the main risk factors for the onset of frailty. The prevalence of frailty is ranges from 10 to 15% among elderly people living in the community
and the prevalence of frailty is high among elderly people who are malnourished. FRAILOMIC investigators investigated how nutrition influences on the risk of developing frailty. There is emerging evidence of the role of certain nutrients as risk factors for frailty. However, people eat food, rather than nutrients, and no previous study has examined the association between dietary patterns empirically derived from food consumption and the risk of frailty in older adults. León-Muñoz et al showed that in older adults, a prudent dietary pattern showed an inverse dose-response relationship with the risk of frailty while a Westernized pattern had a direct relationship with some of their components. León-Muñoz LM, García-Esquinas E, López-García E, Banegas JR, Rodríguez-Artalejo F. Major dietary patterns and risk of frailty in older adults: a prospective cohort study. BMC medicine. 2015 Dec;13(1):11.

García-Esquinas E, et al. demonstrated among community-dwelling older adults, that fruit and vegetables consumption was associated with a lower short-term risk of frailty in a dose-response manner. An inverse dose-response relation was also found between the baseline consumption of fruit and risk of exhaustion, low physical activity, and slow walking speed, whereas the consumption of vegetables was associated with a decreased risk of exhaustion and unintentional weight loss. The strongest association was obtained with 3 portions of fruit and 2 portions of vegetables.


The hypothesis that increasing protein rather than pure energy intakes may confer protection against frailty has been suggested, Rahi B et al. assessed the association between frailty and higher protein and energy intakes in the FRAILOMICS 3C cohort. They conclude that a1 g/kg protein intake was associated with a lower prevalence of frailty in French community-dwelling older subjects. This observation adds to the literature, suggesting increasing the daily protein intake to at least 1g/kg for older adults aged 65 and more.

Rahi B, Colombet Z, Harmand MG, Dartigues JF, Boirie Y, Letenneur L, Feart C. Higher protein but not energy intake is associated with a lower prevalence of frailty among community-dwelling older adults in the French three-city cohort. Journal of the American Medical Directors Association. 2016 Jul 1;17(7):672-e7. Following in this line of research and acknowledging that low intake of certain micronutrients and protein has been associated with higher risk of frailty. León-Muñoz et al. assessed the effect of global dietary patterns on frailty. They examined the association between adherence to the Mediterranean diet (MD) and the risk of frailty in older adults. Adhering to the Mediterranean diet was associated with reduced risk of slow walking and of weight loss and in particular higher consumption of fish and fruits reduced the odds of frailty.


One of the goals of the FRAILOMIC project was to investigate special subpopulation as for example people with diabetes mellitus type 2, hypertension, or obesity. In this line, Lopez-Garcia investigated whether a Mediterranean-style diet pattern was associated with lower risk of frailty among older women with diabetes. They showed that adherence to a Mediterranean diet pattern reduced the risk of frailty by 50% in women with type 2 diabetes and found that the largest reduction of risk was associated with the consumption of vegetables and fruits as well as alcohol intake. They conclude that a Mediterranean-style
diet pattern was associated with reduced risk of frailty syndrome in the subpopulation of older women with type 2 diabetes.


Rahi et al. place emphasis on the fact that Mediterranean diet is also considered as a key component for healthy aging, including prevention of age-related disability, while its association with frailty, independent of disability has not sufficiently been addressed. They investigated the relation between adherence to Mediterranean diet and frailty incidence among persons aged ≥75 years in the FRAILOMIC Three-City study. They conclude that, in addition to its well-documented beneficial effects on health, adherence to Mediterranean diet contributed to prevent the onset of frailty, even at late stages of life.


Lana et al. in another study examined the association between consumption of dairy products and risk of frailty in community-dwelling older adults aged 60 and older free of frailty at baseline. Their results showed that a higher consumption of low-fat milk and yogurt was associated with lower risk of frailty and, specifically, of slow walking speed and weight loss. Current recommendations to prevent frailty include protein supplementation; thus, although experimental research is needed, increasing the consumption of low-fat yogurt and milk might prevent frailty in older adults.


Other group of FRAILOMIC investigators investigated the cross-sectional and prospective associations between patterns of serum fat-soluble micronutrients and frailty in four European cohorts (Three-City Bordeaux-France, AMI Gironde-France, TSHA Toledo-Spain and InCHIANTI Tuscany-Italy) of older adults 65 years of age and older and three different patterns were identified: the first pattern was characterized by higher serum carotenoids and α-tocopherol levels; the second was characterized by high loadings for serum vitamins A and E levels and low loadings for carotenoids level; the third one had the highest loading for serum 25(OH)D and cryptoxanthin level and the lowest loading for vitamin A and E. A significant cross-sectional association was only observed between the second PC and prevalent frailty (p 0.02). These findings suggest that some specific micronutrient patterns are markers but not predictors of frailty in these European cohorts of older adults.

Pilleron S, Weber D, Pérès K, Colpo M, Gomez-Cabrero D, Stuetz W, Dartigues JF, Ferrucci L, Bandinelli S, Garcia-Garcia FJ, Grune T. Patterns of circulating fat-soluble vitamins and carotenoids and risk of frailty in four European cohorts of older adults. European journal of nutrition. 2018 Jan 27:1-1. Other study assessed the association between frailty and higher protein and energy intakes. They found that a 1 g/kg protein intake was associated with a lower prevalence of frailty in French community-dwelling older subjects.

Meat is an important source of high-quality protein and vitamin B but also has a relatively high content of saturated and trans fatty acids. Although protein and vitamin B intake seems to protect people from functional limitations, little is known about the effect of habitual meat consumption on physical function. The following study examined the prospective association between the intake of meat (processed meat, red meat, and poultry) and physical function impairment in older adults and the results was that a higher consumption of processed meat was associated with a higher risk of impairment in agility and lower-
extremity function.


One component of the diet that is in the focus of investigators are added sugars in processed food. Laclaustra M, et al. showed that the consumption of added sugars in the diet of older people was associated with frailty, mainly when present in processed foods. The frailty components that were most closely associated with added sugars were low level of physical activity and unintentional weight loss. In necessary future research to determine whether there is a causal relation between added sugars and frailty.


Similar to the consumption of alcohol, common in the Mediterranean in its form of wine, coffee consumption has been attributed with positive health effects. Machado-Fragua et al. investigated the possible association between coffee consumption and functional impairment, frailty, and disability. In this study they showed that in older people, habitual coffee consumption was not associated with increased risk of functional impairment, and it might even be beneficial in women and those with hypertension, obesity or diabetes.


Because the FRAILOMIC project is also committed to overcoming the gender gap in scientific publications and acknowledging that particularly in the elderly the gender dimensions is important Pilleron et al. derived five sex-specific dietary clusters by a hybrid clustering method from weekly frequency of intake of twenty food and beverage items. They showed that the ‘Biscuits and snacking’ cluster was associated with a higher risk of mobility restrictions and limitation in IADL in men and limitation in ADL in women concluding that in this cohort of community-dwellers aged 67+ years, some unhealthy dietary patterns may increase the risk of activity limitation all along the disablement process in older adults.


Similar to coffee, alcohol consumption is often an important cause of disease burden; thus, it is noteworthy that little information is available on alcohol intake among older adults in Europe. But it has also been attributed with positive effects if consumed in limited quantities as part of a healthy diet. Interestingly little was known about the alcohol consumption patterns in Spain. León-Muñoz et al. examined alcohol consumption patterns and their association with demographic and clinical variables in the older population of Spain. They conclude that alcohol consumption among older adults in Spain is frequent and mostly consistent with the traditional Mediterranean drinking pattern. It was found that a proportion of individuals were heavy drinkers and used medication that may interact with alcohol.


Consumption of moderate-to-heavy amounts of alcohol has been associated with lower risk of cardiovascular disease and diabetes. Although both diseases are main causes of the frailty syndrome, no
previous study has assessed the association between alcohol-drinking patterns and risk of frailty in older adults. Ortolá et al. investigated what type of drinking pattern was associated with the risk of frailty. They defined a Mediterranean drinking pattern was defined as moderate alcohol intake, with wine preference (≥80% of alcohol proceeds from wine) and drinking only with meals. They concluded that certain drinking patterns, in particular drinking only with meals and the Mediterranean drinking pattern, are associated with a lower risk of frailty in older adults.


Several studies have found that moderate alcohol intake is associated with lower risk of functional limitations in older adults, this studies showed that in older adults, moderate alcohol consumption, as well as the Mediterranean Drinking Pattern (MDP) in specific subgroups, is associated with lower risk of functional limitation. These results should not serve to promote alcohol intake, because older adults are particularly vulnerable to its harmful effects. Both moderate drinking and the MDP were associated with a lower risk of falls and injurious falls in older adults. And the small association between alcohol consumption and better physical HRQOL found at baseline was not apparent after a few years of follow-up.

Specifically, León-Muñoz et al. acknowledging that several studies have found that moderate alcohol intake is associated with lower risk of functional limitations in older adults, assessed this association in older adults from Mediterranean countries, who show characteristic drinking patterns. Compared with non-drinkers, ex-drinkers showed a higher risk of IADL limitation. By contrast, moderate drinkers had a lower risk of limitations in mobility, agility and IADL. Among individuals reporting poor or fair health, the Mediterranean diet pattern was associated with lower risk of mobility limitations. They conclude that In older adults, moderate alcohol consumption, as well as the Mediterranean diet pattern in specific subgroups, is associated with lower risk of functional limitation. But that these results should not serve to promote alcohol intake, because older adults are particularly vulnerable to its harmful effects.


One of the major risk factors for disability and a consequence of being frail are falls. Ortolá et al. investigated patterns of alcohol consumption and the risk of falls in older adults. The found that both moderate drinking and the MDP were associated with a lower risk of falls and injurious falls in older adults. They state however that advice on alcohol consumption should balance risks and benefits.


A very important aspect of frailty research and geriatrics in general is the focus on quality of life. The shift in perception that it is important how we age and not only that we survived is reflected in the following work from Ortolá et al. associating alcohol consumption patterns, known to be associated with frailty, to health related quality of life. They find that, although a cross-sectional association between alcohol consumption and better health related quality of life exists, the association was not apparent after a few years of follow-up. Medical advice on alcohol consumption cannot be grounded on its effects on HRQOL.

Ortolá R, García-Esquinases E, Galán I, Rodríguez-Artalejo F. Patterns of alcohol consumption and health-

Another risk factor associated with frailty and poor health outcomes is smoking. In particular second-hand smoking has turned into a focus of investigation. Exposure to secondhand tobacco smoke (SHS) is a well-established risk factor for cardiovascular disease and lung cancer in nonsmoking adults. This was the first study to assess the association between SHS and the frailty syndrome in the nonsmoking older adult population. In the US nonsmoking older adult population, exposure to SHS was associated with an increased frequency of frailty. More efforts are needed to protect older adults from SHS, especially at home and in other areas not covered by smoke-free regulations.


Conclusions
A poor nutritional status is associated with an increased risk of several chronic diseases related to age, these diseases can lead to frailty. These findings support that a good eating pattern decreases the risk of the components of frailty in older adults.

Poor nutritional status is associated with the onset of frailty. Screening and early diagnosis of poor nutrition status and frailty in elderly people will help to prevent the onset of disability. Effective treatment is based on correction of the nutrition and physical exercise.

Cardiovascular disease, physical activity
Cardiovascular disease is a major risk factor for frailty in the elderly. Although the directionality is unclear in many cases, cardiovascular disease is recognized as a preventable risk factor that could lead to a reduction in the incidence and progression of frailty. FRAILOMIC investigators investigated risk factors associated with cardiovascular disease, cardiovascular mortality, and frailty as part of their research funded by FRAILOMIC.

Prolonged sitting time has demonstrated consistent associations with increased risk of cardiovascular disease. Prolonged sitting time can be modified, i.e. reduced and if the impact on cardiovascular health is positive in might be able to reduce frailty. For example, Cabans-Sánchez et al. showed that changes in sitting time, one of the major (non) activities in the elderly, were associated with cardiovascular disease mortality. They showed that individuals that spent less time sitting and showed a positive trend towards less sitting time over the course of 2 years had their risk of dying from cardiovascular disease reduce by about 1/3. The conclude that among older adults, maintaining low sitting time should be promoted to reduce cardiovascular disease mortality.


Intimately linked to sitting time is time spent watching television. Acknowledging that Sedentariness is an important risk factor for poor health. García-Esquinas et al. examined the prospective association between television viewing time and indicators of physical function, mobility, agility, and frailty. They found that among older adults, longer television viewing time is prospectively associated with limitations in physical function independently of physical activity.


Inflammation is believed to be at the center of the aging process intimately linked to frailty. To estimate the
association between physical activity, sitting time and death from inflammatory diseases, FRAILOMIC investigators Cabanas-Sánchez et al. examined the independent and combined associations of physical activity (PA) and sitting time (ST) with long-term mortality attributed to inflammatory causes other than cardiovascular disease (CVD) and cancer in a national cohort of older adults in Spain. They found that low PA and high ST were consistently associated with a higher risk of mortality from non-infectious inflammatory causes. Associations of PA and ST with mortality from infectious inflammatory causes showed a similar trend, but most of them did not reach statistical significance. They conclude that low PA and high ST were independently associated with higher mortality from inflammatory diseases other than CVD or cancer in older adults and that interventions addressing simultaneously both behaviors could have greater benefits than those focusing on only one of them.


There is strong evidence that regular physical activity (PA) reduces the risk of CVD mortality in the elderly. Physical activity is one of the few recognized modifiable risk factors amenable to intervention even in the elderly that could reduce the prevalence of frailty. In this line of research, Higueras-Fresnillo et al. showed with data from one of the FRAILOMICs cohorts that older adults who increased or maintained PA levels had lower CVD mortality, but the benefits appeared before among those who remained active. In addition, the beneficial effect of maintaining and increasing PA was greater among those who have better health. These findings highlight the importance of public health strategies to promote PA in older adults, as allowed by their abilities and health conditions. Since PA was self-reported, these findings should be confirmed with objective measurements (e.g. accelerometers).


One way to measure health status in the elderly population is to count the number of chronic conditions. Martinez-Gomez et al investigated whether physical activity was associated to long-term all cause mortality independent of the number of chronic conditions. They showed that physical activity was associated with a reduction in increased risk of death associated with multimorbidity (ie, coexistence of ≥2 chronic conditions) in older individuals.


High cardiorespiratory fitness (CRF) is strongly associated with longer life among older adults. CRF can be assessed by exercise-based methods, which are not feasible in most clinical settings. Thus, nonexercise algorithms to estimate CRF have been developed, but whether they predict mortality in older adults is uncertain. Algorithms that predict CRF without the need for actually making exercise to measure fitness showed that Higher nonexercise CRF was related to lower risk of death in older women but not in men. Because previous research does not support clear sex-specific association, further research is required to assess whether nonexercise CRF predicts mortality in older adults or new algorithms should be developed for this population, with special attention to older men.


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In a similar vein, the association between frailty and blood pressure a core cardiovascular risk factors has been investigated. Frailty and disability are associated with cardiovascular risk factors, including hypertension, in older people; however, little is known about their association with ambulatory blood pressure (BP). They found that in community-dwelling older adults, frailty and disability were independently associated with lower diurnal SBP, blunted nocturnal decline of SBP, and higher nocturnal SBP. These findings may help explain the higher mortality associated with low clinic SBP in frail older subjects observed in epidemiologic studies.


Graciani et al. from the FRAILOMIC study group investigated the relationship between ideal cardiovascular health as a summary measure of many cardiovascular risk factors and frailty given that major cardiovascular risk factors and existing cardiovascular disease have been linked to increased risk of the frailty syndrome but the association between ideal cardiovascular health and the risk of frailty in older adults is uncertain. They defined ideal cardiovascular health as having 7 ideal metrics: never smoking, physically active, healthy diet, body mass index <25 kg/m², untreated serum cholesterol <200 mg/dL, untreated blood pressure <140/90 mmHg, and untreated fasting serum glucose <100 mg/dL. They showed that the number of ideal metrics showed a tendency to a reduced risk of all frailty criteria. The cardiovascular metrics associated with the greatest reduction of frailty risk were being physically active and ideal body mass index. They concluded that reaching old age in ideal cardiovascular health is associated with a reduced risk of frailty.


In summary, although FRAILOMICs primary focus was on OMIC biomarkers that help in diagnosis, risk prediction, and prognosis of frailty, FRAILOMIC researchers made important contributions to establish a relationship between primary risk factors such as physical activity patterns and proximal frailty risk factors whose association with blood based OMIC can still be evaluated using FRAILOMICs data in the future.

Diabetes, Obesity, and Metabolic Syndrome:

One of the most prevalent diseases in old age are diabetes mellitus type 2 and the metabolic syndrome. Research has shown that although part of the predisposition to diabetes is genetic, and important share can be modified through lifestyle interventions such as healthy diet and physical activity – important interventions known to be associated to the onset and recovery from frailty. To this end, Pérez-Tasigchana et al. Investigated precursors to diabetes type 2, the metabolic syndrome and insulin resistance and their relationship to frailty, establishing targets for monitoring frailty risk. They conclude that metabolic syndrome and insulin resistance were associated with increased risk of frailty. Metabolic syndrome in particular was associated with an increase in the odds of becoming frail of 85% when compared to participants without metabolic syndrome. This work extends the spectrum of harmful consequences of metabolic syndrome, and suggests that preventing or controlling MS may serve to delay frailty.


Rather than to elucidate precursors of diabetes, García-Escquinas et al. opted to evaluated how much of the associated between frailty and diabetes type 2 can be explained by common, preventable risk factors,
because many mechanisms between diabetes and frailty remain to be fully understood. They find using data from one of the FRAILOMIC cohorts that Diabetes mellitus is associated with higher risk of frailty; that this association is partly explained by unhealthy behaviors and obesity and, to a greater extent, by poor glucose control and altered serum lipid profile among diabetic individuals. They conclude that diabetes nutritional therapy could reduce the risk of frailty.


In the same line of research, García-Esquinas et al. combined data from two of the FRAILOMIC cohorts to investigate the relationship between obesity and incident frailty. Obesity has long been identified as a risk factor for diabetes, but its impact on overall health in the elderly has often been questioned ("obesity paradox") In this work, García-Esquinas et al. evaluate for the first time the longitudinal relationship between abdominal obesity and frailty onset. They showed that general and abdominal obesity are associated with incident frailty in the elderly. In particular, compared with individuals with no general nor abdominal obesity, the risk of frailty was more than doubled among individuals with concurrent general and abdominal obesity.


One of the consequences of diabetes type 2 could be the rapid accumulation of advanced glycation end products. AGE are one of the parameters measured in FRAILOMIC as candidate biomarkers for frailty. Pilleron et al. investigated in the FRAILOMIC 3C-Bordeaux study whether advanced glycation end products as assessed by skin autofluorescence is associated to frailty and its components, trying to identify another mechanistic pathway between diabetes and frailty. While they could not find an increased prevalence of frailty nor with the risk of frailty overall, they report an increased risk for two of the frailty components: exhaustion and energy expenditure.


Given that nutritional status is associated with frailty, and that obesity has been associated with higher risk of frailty in older adults, it is necessary to investigate the pathophysiological mechanisms. No previous study has examined the association between leptin, an adipokine, and the risk of frailty in older adults, and whether this association could be explained by insulin resistance or chronic inflammation. In the FRAILOMIC ENRICA cohort higher leptin concentration was associated with greater risk of frailty in older adults. This association was only modestly explained by insulin resistance and chronic inflammation, as measured by CRP.


Cognition:
Frailty is often associated with reduced cognitive function. In fact, authors recently proposed a “cognitive frailty” phenotype because they felt that the cognitive domain of frailty is not sufficiently recognized in the
most widely used frailty definitions.

In order to describe the relationship between cognitive performance and frailty, Rosado-Artalejo et al. used data from a FRAILOMIC cohort to evaluate cognitive performance at distinct stages of the frailty process. In addition, they used 3 different scales to measure frailty: Frailty Phenotype (FP), Frailty Trait Scale (FTS), and Frailty Index (FI). They found that individuals classified with the worst degree of frailty presented complaints in more cognitive domains and to a higher extent than moderate frail and robust participants. Cognitive performance progressively declined across the frailty state, regardless of the instrument used to assess frailty. In prefrail participants, cognitive impairment may be an early marker of frailty-dependent cerebral involvement and could be already subject to interventions aimed at reducing the transition to frailty.


One of the candidate biomarkers measured in all FRAILOMIC cohorts is CCL1 (eotaxin-1). CCL11 is a chemokine classically known to be involved in allergic responses. More recently, this mediator has been implicated in age-related cognitive decline. Here Butcher et al. used data from two of the FRAILOMIC cohorts to elucidate the relationship between CCL11 and cognitive status. They found contrasting results. While there was an association in the AMI cohort with higher levels of CCL11 associated to lower cognitive status, no differences were found in 3C. These results indicated that CCL11 could be a significant independent predictor of cognitive function in older adults residing in a rural environment.

FRAILOMIC investigators Ajana et al. also investigated the association between plasma Lutein and zeaxanthin and cognitive function in the FRAILOMIC 3C Bordeaux Cohort. The analysis suggested that higher L+Z concentrations were significantly associated with higher cognitive performances.


In summary, FRAILOMIC has contributed a vast amount of publications to the literature to date. It is true though that due to restrictions in time and delays in the shipment of some of the biological sample, many more publications using primary FRAILOMIC data are to be published in 2018 and 2019.

Potential Impact:

Part of the dissemination activities was clearly focused on the web and new media. FRAILOMIC Dissemination Leader (Beneficiary #9 -Niche Science & Technology, NST-), designed and maintained the web page (www.frailomic.org) and a twitter feed (https://twitter.com/frailomic?lang=en). This twitter feed and the webpage were used to update regularly about the advances in FRAILOMIC and in the field of frailty in general. The idea is to maintain the webpage and the twitter feed beyond the actual duration of the EU funded project. Many of the most exciting findings from FRAILOMIC are still to be published and these already established platforms can be used to extend the legacy of the project and maybe enable data sharing practices.

Key messages describing the fundamental aspects of FRAILOMIC were developed at the start of the project and adapted as the project progressed. Project pre-mortem analysis conducted in mid 2017.
indicated that it was highly unlikely that research findings would be available for dissemination before the end of the agreed timelines. Therefore, the dissemination plan was amended to include bespoke message vehicles. Between Jan 2017 and July 2018 Niche prepared over 20 short bespoke message vehicles. A press release package was created for each, including a summary, letter of introduction and specifically designed, royalty free graphic (designed by the Niche team) and was distributed to known web-based news services, published on www.fyi-news.co.uk and re-posted on Linkedin, Facebook and Twitter.

Several videos were created for message dissemination and to maintain share-of voice while the project awaits critical findings for dissemination. These included a lay-person’s description of the FRAILOMIC Initiative and interviews with partners. These were posted on LinkedIn, Twitter, YouTube and Facebook. In addition, Niche participated at several conferences and workshops including: Accelerating Innovation (AIM) Day, University of Oxford (July 2017), Viral Gene Therapy Revolution Congress, Oxford (April 2018) and Health Tech Innovations Conference, London (June 2018).

Another part of the dissemination activities was targeted more towards traditional media outlets such as printed press, radio, and television, as well as life appearances on national and local events to create awareness about ageing and the aims of the FRAILOMIC EU-funded research.

One of the main scientific findings of the FRAILOMIC project is that current geriatric assessment techniques, for example the Fried Phenotype for measuring frailty, can only be improved marginally by adding expensive OMIC measures. While this is discouraging from the point of view of a personalized medicine approach in that we could not identify an outstanding OMIC predictor of frailty so far, it is encouraging because it means that no costly new interventions that require equipment and consumables are required to significantly improve the health and care of the elderly.

Geriatric medicine focuses on the prevention, diagnosis, treatment and rehabilitation of pathologies associated with aging. It is integral and multidisciplinary, dealing with acute illness in healthy elderly people or with some basic pathology, also of their situation or risk of dependence (promoting autonomy, rehabilitation if necessary), physical illness or cognitive, and without ignoring the particular problems of each person in different areas (nutrition, social status).

An Integral Geriatric Assessment considers all aspects that affect an individual’s health from physical, cognitive or social needs. As a result a plan of care and objectives are defined by multidisciplinary team that work in a coordinated manner including geriatricians, nurses, occupational therapists and / or physiotherapists, psychologists and social workers.

Because FRAILOMIC researchers identified a generalized gap in knowledge about ageing and its consequences in the population, FRAILOMIC has done a lot of dissemination activities around healthy aging, trying to create consciousness in society that a) aging is not equivalent to frailty and disability, and b) that by maintaining an active life style and a healthy diet successful aging could be the norm accessible to anyone.

The dissemination activities were supported by the acquisition of two gerontologic simulation suits (GERT, http://www.age-simulation-suit.com).
The age simulation suit GERT (Figure 1) offers the opportunity to experience the impairments of older persons even for younger people. The age-related impairments are:

- opacity of the eye lens
- narrowing of the visual field
- high-frequency hearing loss
- head mobility restrictions
- joint stiffness
- loss of strength
- reduced grip ability
- reduced coordination skills

The suit can be used for two important purposes: to create awareness about the consequences of aging and the benefits of leading an active lifestyle and a healthy diet (“Individual Prevention”); to create consciousness of the "invisible" limitations of ageing such as reduced hearing, slower gait, joint stiffness, grip ability and understand the sometimes inexplicable behavior of elderly members of society in daily routine situation, e.g. supermarket, metro station, etc. (“Societal Understanding”).

Individual prevention is important. Unlike for dementia, frailty can be prevented by leading a healthy lifestyle. This includes a healthy diet, e.g. Mediterranean diet. Unlike dementia, frailty can be reversed by introducing physical activity interventions. In conversations held with many people of the lay audience it became obvious to the FRAILOMIC investigators that many people consider ageing and bad health to be intimately associated and believe that healthy ageing is not achievable for the “normal” citizens. In fact, many people equated old age with disability and the need to be taken care of by ones relatives or social services: an outcome that was unanimously declared as undesirable.

By simulating the limitations of old age using the GERT simulation suit, we could convince many participants that taking care of one’s diet and lifestyle is worthwhile. The suit in itself weights about 20kg simulating the loss of muscle power with advanced age. By explaining to the audience that what they experience was the natural course of ageing but that it dependent on them whether at age 80 they carry and additional 5kg, 20kg, or 40 kg virtually on their shoulders the became conscious of the ability to modify their own ageing trajectory.

Another important message was that it did not matter the age, physical activity could always lead to improvements in physical function. Many of the younger participants almost jokingly carried the additional weight of the suit, while many of the elderly participants were really tired after 15min. Many of the elderly participants initially thought that it was useless to start with exercise at age 65 and that “all was lost” already. This widespread believe could be counteracted by FRAILOMIC investigators.

Societal Understanding was another key focus of the outreach activities. By experiencing first hand the limitations of old age, that are most often invisible, many of the participants stated that they would change their attitude towards their parents and elderly people in general.

The inability to see well when walking, the immense isolation by hearing loss, and the feeling of being lost
and alone when walking with the GERT suits particularly in settings full of people, made them reconsider the common behavior of impatience. One of the main problems of aging is that younger people cannot understand the inherent limitations of age that make elderly react slower in order to e.g. not fall, etc. After the GERT experience, participants voiced that they were astonished by what they have had experienced and would change their attitude.

In total, we have reached an audience of 24.2 million person (as estimated by Kantar Media) through different channels: traditional written press (5.1 mio) radio (2.6 mio) and TV (16.6 min).

In total we achieved a minimum of 6 written articles on a national level Spain (4), China (1), and North America. All of these articles were published also online and are often accompanied by a short video clip.

https://elpais.com/ccaa/2017/02/22/madrid/1487752901_853162.html
https://www.noticiasparamunicipios.com/municipios-madrid/getafe-sentirse-anciano-traje-encejecimiento
http://ecodiario.eleconomista.es/salud/noticias/9216406/06/18/Investigadores-del-Hospital-de-Getafe
http://www.pearvideo.com/video_1063631?st=1&from=singlemessage&isappinstalled=1

In total we achieved 7 appearance in Spanish national radio achieving a total of 1h 6min and 50s of airtime discussing FRAILOMIC, EU funding, and the importance of frailty in the ageing society.

https://www.ondacero.es/programas/mas-de-uno/audios-podcast/entrevistas/marta-checa-doctora_20170921
https://www.ondacero.es/emisoras/comunidad-madrid/madrid/asi-funciona-el-simulador-de-encejecimiento
https://www.cope.es/programas/mediodia-cope/noticias/piel-anciano-anos-20170228_37542
http://cadenaser.com/emisora/2018/06/19/ser_madrid_sur/1529408459_422541.html
https://www.facebook.com/COPEMasMadrid/videos/1649518591731548/?autoplay_reason=gatekeeper&video_con

In total, over a period of 6 month, we were present in 16 TV programs. 11 of these programs were national daily news with an average airtime of little over 1 min. One program “El Hormiguero” is a popular Spanish talk shows with an audience of 3Mio and 13min of active promotions of healthy ageing. Another show was
a reality show that aimed at achieving life style change. The remaining 3 programs were general programs related to health and society. In total we achieved an airtime of 1h 1min and 50s with a cumulative audience of more than 16.6Mio viewers.

http://rtve.es/v/4146678


https://www.antena3.com/noticias/salud/unos-trajes-simulan-los-sintomas-de-la-artrosis-el-parkinson-

https://www.telecinco.es/informativos/sociedad/Salud-Ciencia-Investigacion-Simulador-Biomedicina-Env


Apart from these very mediatic appearances we also presented FRAILOMIC and the project goals in local events all over Spain.

One of the most interesting events, was the industry sponsored “Foro premios Albert Jovell” (Figure 2) (http://www.foropremiosalbertjovell.es/ediciones/2017). This symposium sponsored by Janssen yearly discusses the benefits of a more humanitarian approach toward medicine putting the patient and not the disease into the focus of care. We had a 30min slot to talk about the challenges of an ageing society, frailty and FRAILOMIC, and were able to create consciousness about the ageing process and in a group of 700 attendees from the news media, industry, and policy makers.

Other events were related to health promotions in the city of Getafe (Oct. 2017), Hematogeriatria (Feb 2018), Red Cross in Avila (Abril 2018).

Another industry sponsored event was the Deloitte Innovation Lab: “The value of social Services” (Figure 3). At this meeting stakeholders from NGOs and decision makers from politics and industry discussed the value and the function of Social Service in an ageing society. The GERT simulation suit was used to illustrate the most common limitations of ageing and to allow the participants a first-hand experience of being old, creating the appropriate context of the meeting in combination with the provision of basic statistical and demographic information about the ageing society.

The impact of the FRAILOMIC project at the end of the project is limited in socio-economic terms, given that the final study results are not yet published. The dissemination activities that involved the GERT Simulation suit had an economic equivalent of at least €2.2mio.

In addition, according to the provisions of the Dow, FRAILOMIC has been the subject of an intense dissemination activity among the clinical and scientific community and relevant stakeholders through the participation of several of its participants in related national and international congresses and conferences.
Thus, FRAILOMIC has been presented and spread out in the most important events on aging and frailty, such as those listed below:

International Conference on Frailty & Sarcopenia Research (ICFSR) 2017. Barcelona. 27-28-29 April 2017
EIP AHA. Coordination meeting; Action Group A3 on frailty. Valencia 28-29 June 2017.
Euskadi summer School.
World Congress of IAGG, International Association of Gerontology and Geriatrics 2017. San Francisco. 22-25 July 2017
International meeting "Active Aging and Frailty". Pamplona 24, 25 November 2017
Frailty conference at Royal Academy of Medicine of Valencia. 8 February 2018
International Conference on Frailty & Sarcopenia Research (ICFSR) 2018. Miami 1, 2, 3 March 2018.

List of Websites:
The Frailomic study web address ([http://frailomic.org/](http://frailomic.org/)) was registered immediately after study approval; a simple holding page was produced and uploaded to the website. Updates and expansion of the functionality of the web page have been undertaken periodically to reflect milestones of study progress. In addition, a link was added to the BSWC website where documents related to the study are being stored. Partners are regularly asked for news updates or publications that can be posted on the website. The newsletters (figure 1) are also being posted on the website.

Project logo:
Work on the design of the Frailomic logo project was initiated by NST in the early days of the study. Various design options were developed and tested with representatives of the various partner organisations. Once consensus was achieved, the brand identity was finalized and used to create an identity for internal study documents, slide sets, posters, web presence and other media. Figure 2 show the latest version of the logo for Frailomic project

Newsletters: Two Frailomic newsletters (figure 3) have been produced and distributed among the wider Frailomic team. The newsletters have continued to include information that updates the consortium with partner news and provide a platform for the Frailomic community to share information on their progress and key learnings. Although the information in the internal newsletters has been considered ‘too sensitive’ to share freely on the Frailomic website, we have continued to release less-detailed ‘news’ through our public ‘Frail-feed’ email newsletter and Twitter forum as well as targeted news releases for publication on web-based public news sites.

Members of partner organizations have been invited regularly to submit news pieces and information they want to share to the newsletter’s editor. They have also been asked to provide names of colleagues they feel they might want to receive the newsletter.

Social media and press releases importance of dissemination: In September 2016, NST created the Twitter feed ‘Frail-feed’ dedicated to sharing news from and among partners of the Frailomic initiative. Efforts invested in development of Frail-feed were three-fold. First, research was conducted to identify all
consortia partners already involved in social media – and they were invited to follow Frail-feed; this invite was intended to get the partners to engage in the dissemination process. Twitter was searched to identify members expressing an interest in frailty, gerontology and/or ageing to establish a ready audience. A process of engagement was adopted in ‘following’ candidates with the appropriate profiles and/or interests. This process has continued and we currently have an active audience of 170 followers and we are following 200 Twitter accounts. Effectively, these network connections have been used to target ‘news’ releases and key scientific publications as they emerge from our scientific partner organisations. Frail-feed currently posts 4–5 therapy area stories each week to keep the audience engaged (590 articles tweeted so far). Where possible we have employed these vehicles to initiate ‘interest’ by relating to their impact on FRAILOMIC and the potential impact FRAILOMIC may have on them. NST also scans several news feeds to identify ‘stories’ that could be tweeted through the Frail-feed network channel. Finally, stories, news and updates relating directly or referring to FRAILOMIC have been reported on the NST news website; FYI News. From here, news stories are echoed on Facebook, LinkedIn and Twitter as part of the dissemination activities.

Video engagement:
The FRAILOMIC Study: A script was developed that explained the five key elements of the FRAILOMIC study in layman’s terms. The aim was to make the study objectives more accessible to the broader public. The NST Medical Writing team created a graphic storyboard to capture the key messages associated with FRAILOMIC in pictures. A whiteboard animation technique was employed to create video footage. The script was recorded separately and video-editing techniques employed to combine the audio and video components into a final short animated film. A draft version of the video was approved by the FRAILOMIC partners at the final consortium meeting in Madrid (June 2018). The final product was posted on YouTube (https://www.youtube.com/watch?v=McSl9dl7egk) and promoted on Linked in, Facebook and www.fyi-news.co.uk.

Partner interviews: Prior to the final consortium meeting in Madrid, 2018, NST developed a series of questions to ask partners about the role they had played in FRAILOMIC and the legacy they expect to emerge from the project. At the meeting, NST undertook video interview sessions with 12 representative partners. These interviews were edited into slick 1–2 minute promotional video bites. With the FRAILOMIC Study explainer project, the videos were used in a series of postings on Linked in, YouTube and Facebook to promote the study. Release of the material was combined with a burst-recycling approach of all previously prepared messaging materials through all available channels.

Related documents

- final1-project-logo.pdf
- final1-dissemination-figures.pdf
- final1-description-of-the-project-figures.pdf
- final1-web-figures.pdf