70° CONGRESSO NAZIONALE SIGG LIBERI E LONGEVI

The role of biomarkers in age-related diseases, multimorbidity and frailty

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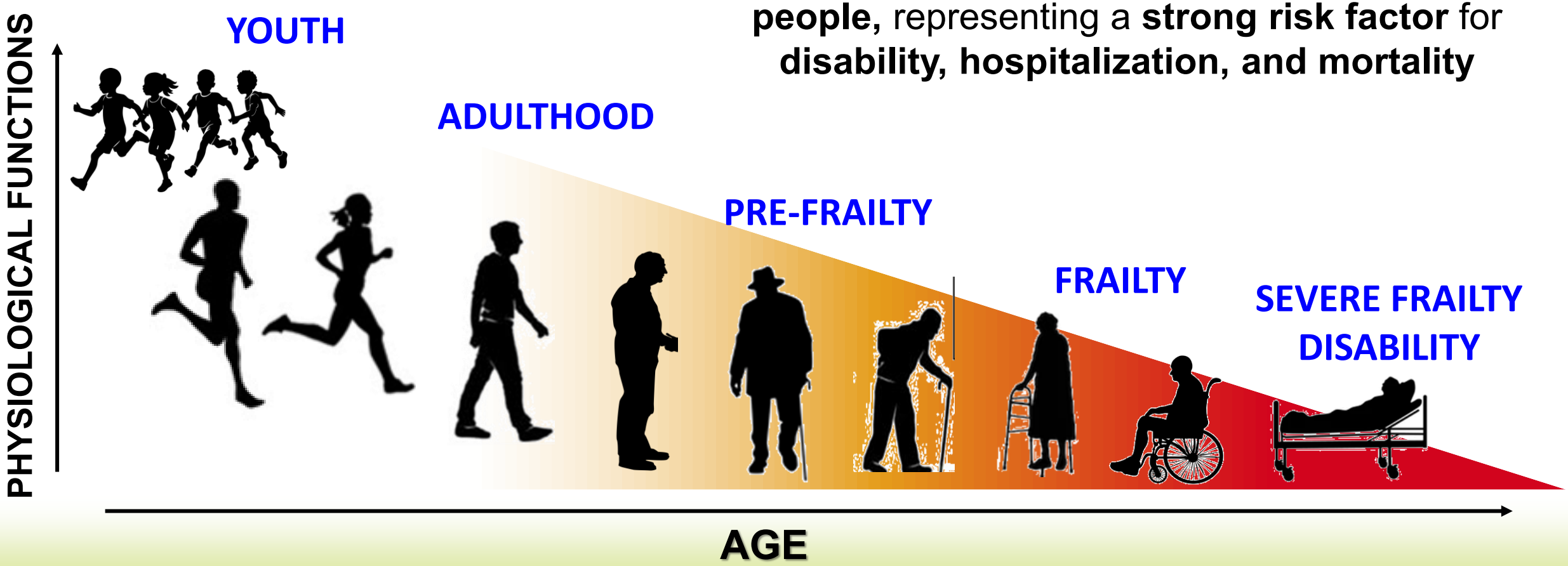
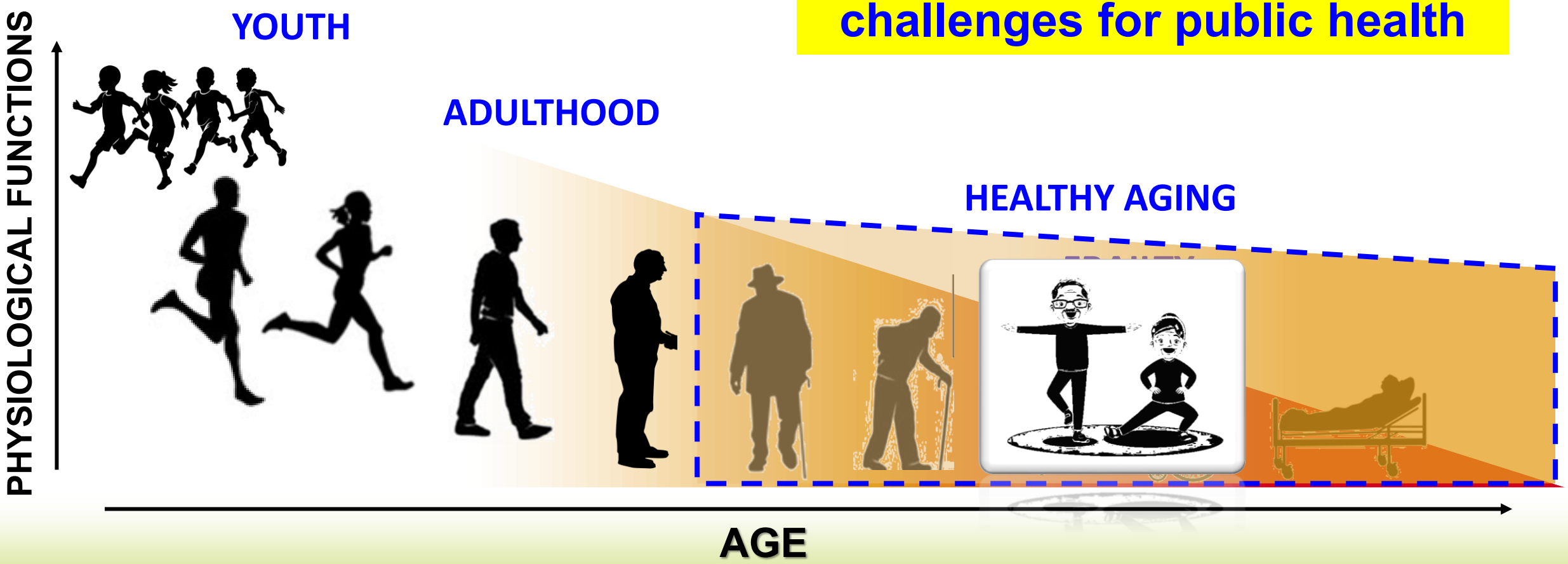
FRAILTY

Frailty is a **complex medical condition** characterized by **decline in physiological functions** and **global health of older people,** representing a **strong risk factor** for **disability, hospitalization, and mortality**



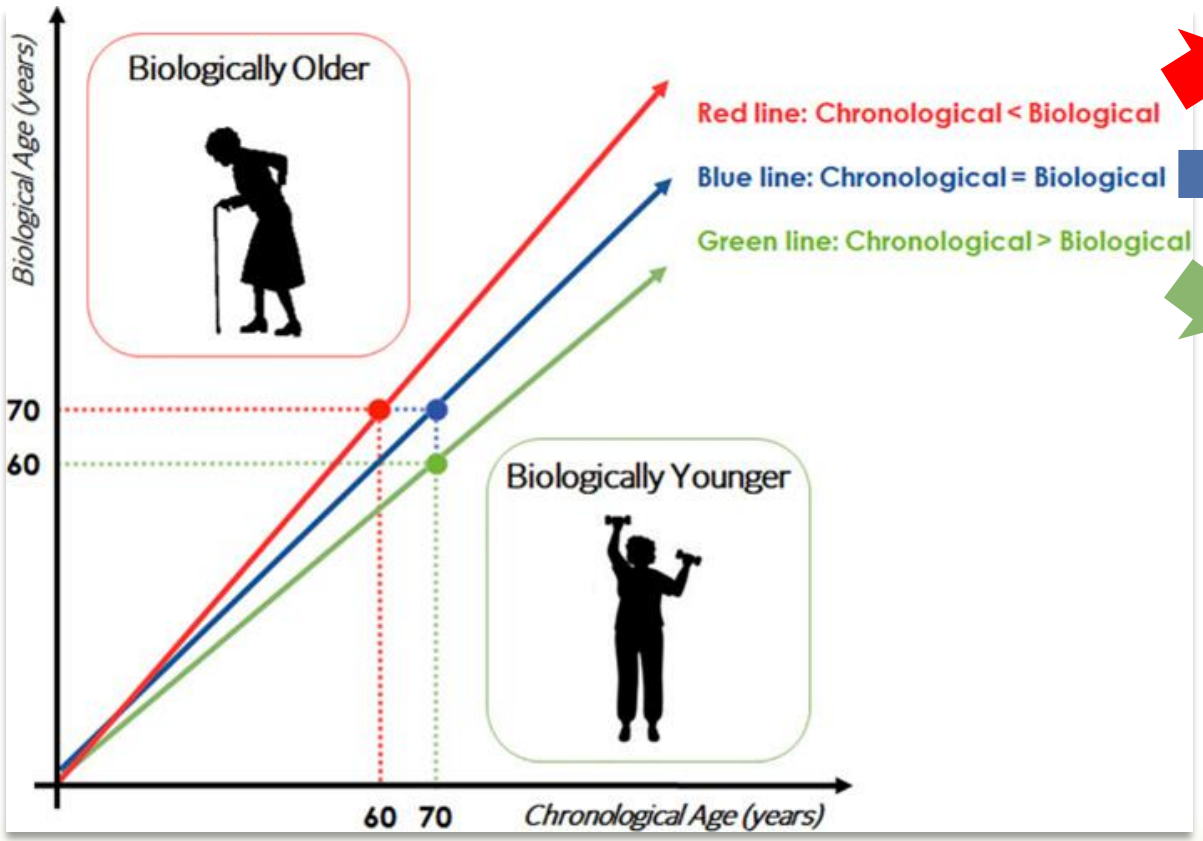
FRAILTY

one of the most significant challenges for public health



The aging process is not homogeneous among older adults

People can be classified as **biologically older (or younger)** than their **chronological age**



Disability

Average age-related decline

Healthy aging

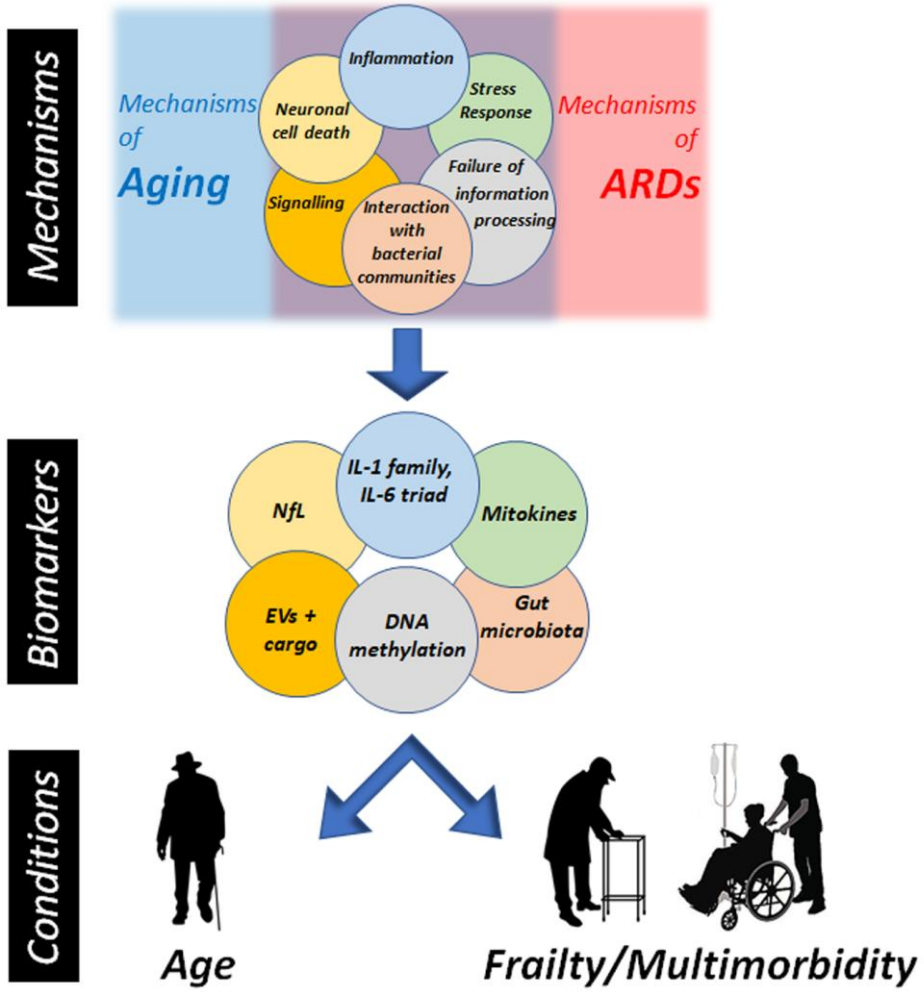
Biological age is a measure of cellular functionality and overall health

Biological age may be a strong predictor of frailty, as it reflects the true physiological state of an individual and the age-related decline.

Salvioli S., et al 2025 doi: 10.3389/fendo.2025.1574133.

BIOMARKERS OF AGING

- **Indicators** of biological age and states, such as healthy or unhealthy aging
- **Identifiers** of individuals with higher risk of developing age-related diseases (ARDs) and **possibly frailty**
- **Tools** to evaluate the efficacy of interventions to promote health life span



Salvioli S., et al 2023 doi: 10.1016/j.arr.2023.102044.

BIOMARKERS OF AGING and FRAILTY

- **Frailty Phenotype** (*Fried et al., 2001 doi: 10.1093/gerona/56.3.m146*)
- **Frailty Index** (*Rockwood et al., 1999 doi: 10.1016/S0140-6736(98)04402-X*)
- **Osteoporotic Fracture index** (*Ensrud et al., 2009 doi: 10.1111/j.1532-5415.2009.02137.x*)

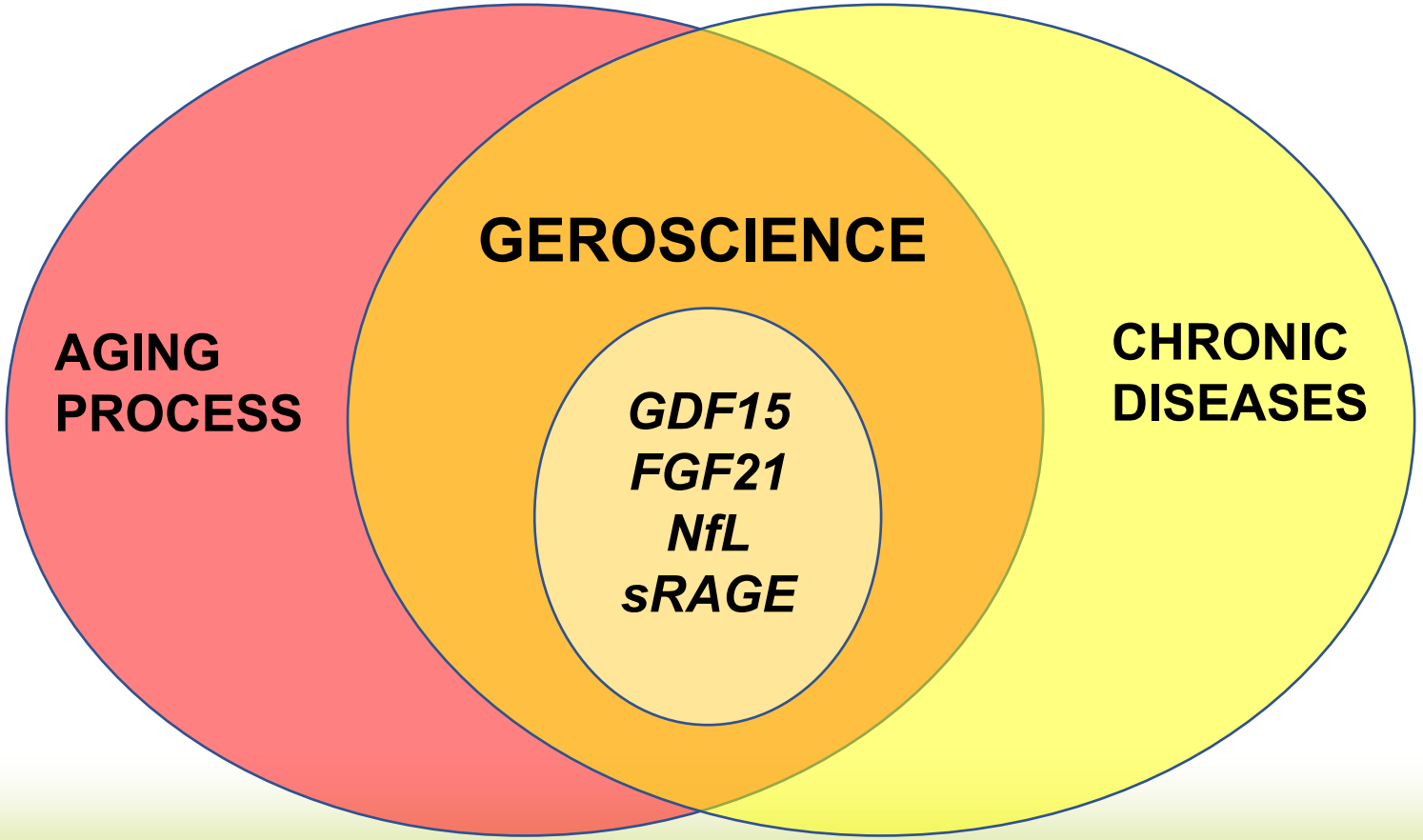
Each of these methods can return a different diagnosis

Is there a way to improve the diagnosis of frailty?

The combination of frailty measurement tools and biomarker detection would complete frailty identification.

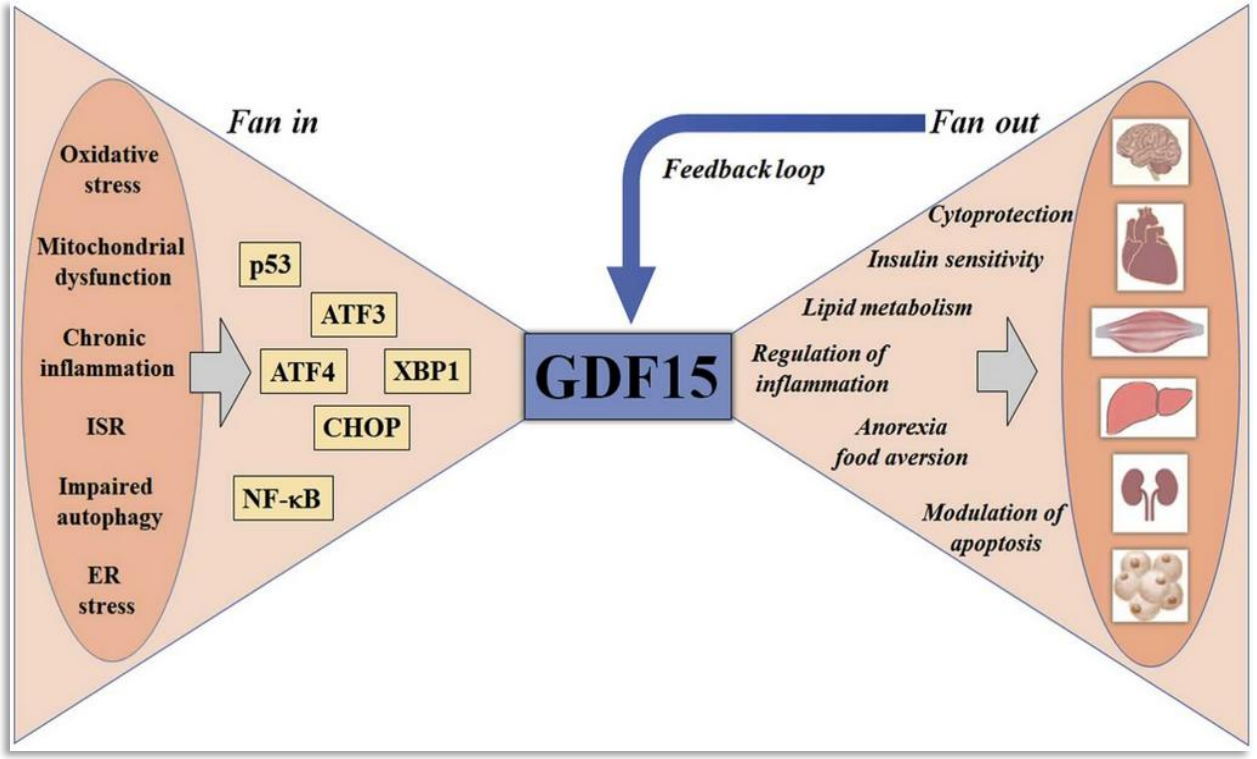
BIOMARKERS OF AGING and FRAILTY

Geroscience: organismal aging and age-associated diseases share the same basic molecular mechanisms.



Growth Differential Factor15

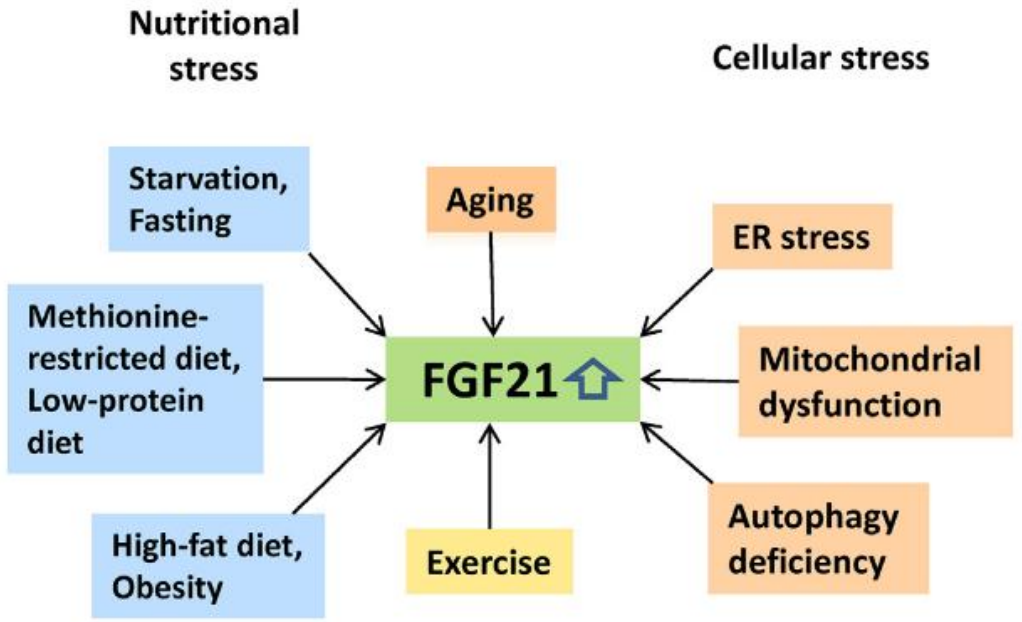
- One of the most upregulated circulating proteins during aging and in several ARDs.
- Component of SASP.
- Produced in response to mitochondrial stress and inflammation.
- Protein with pleiotropic effects.



Conte et al. 2022 doi: 10.1016/j.arr.2022.101569

Fibroblast Growth Factor 21

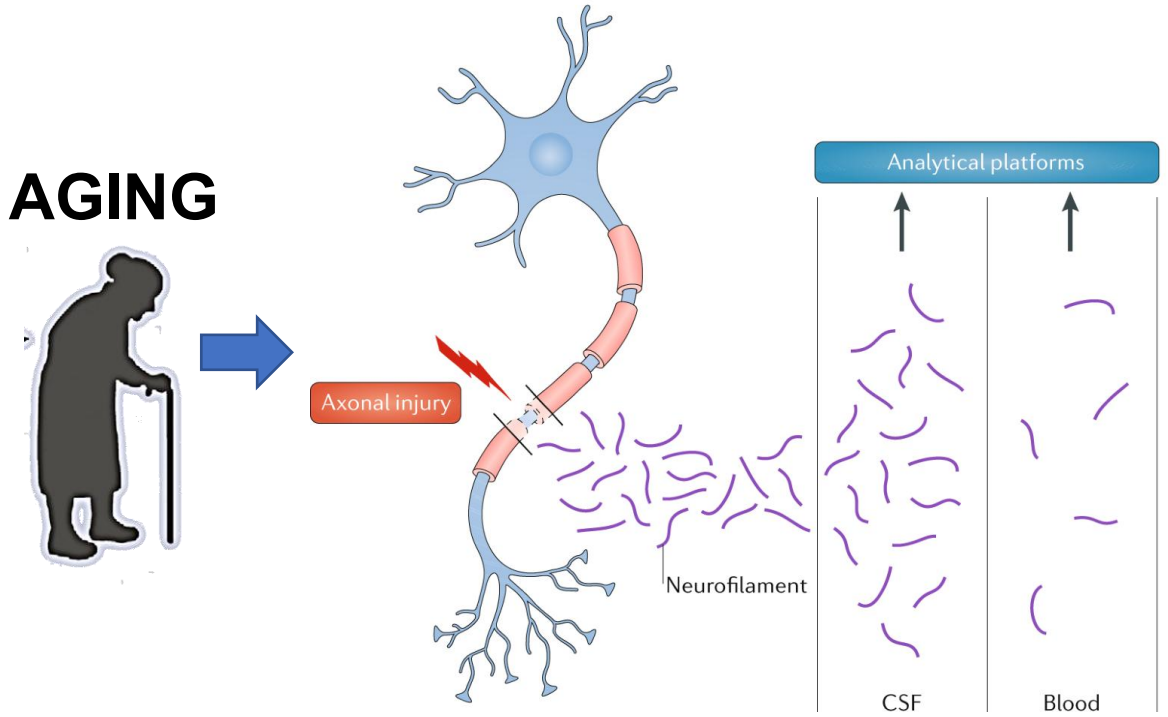
- Its circulating levels increase with aging.
- It counteracts age-related metabolic changes and promotes the maintenance of health and longevity.
- In some cases it has been reported an association with specific pathological conditions.



Salminen et al., 2017 doi: 10.1016/j.arr.2017.05.004

Neurofilament light chain (NfL)

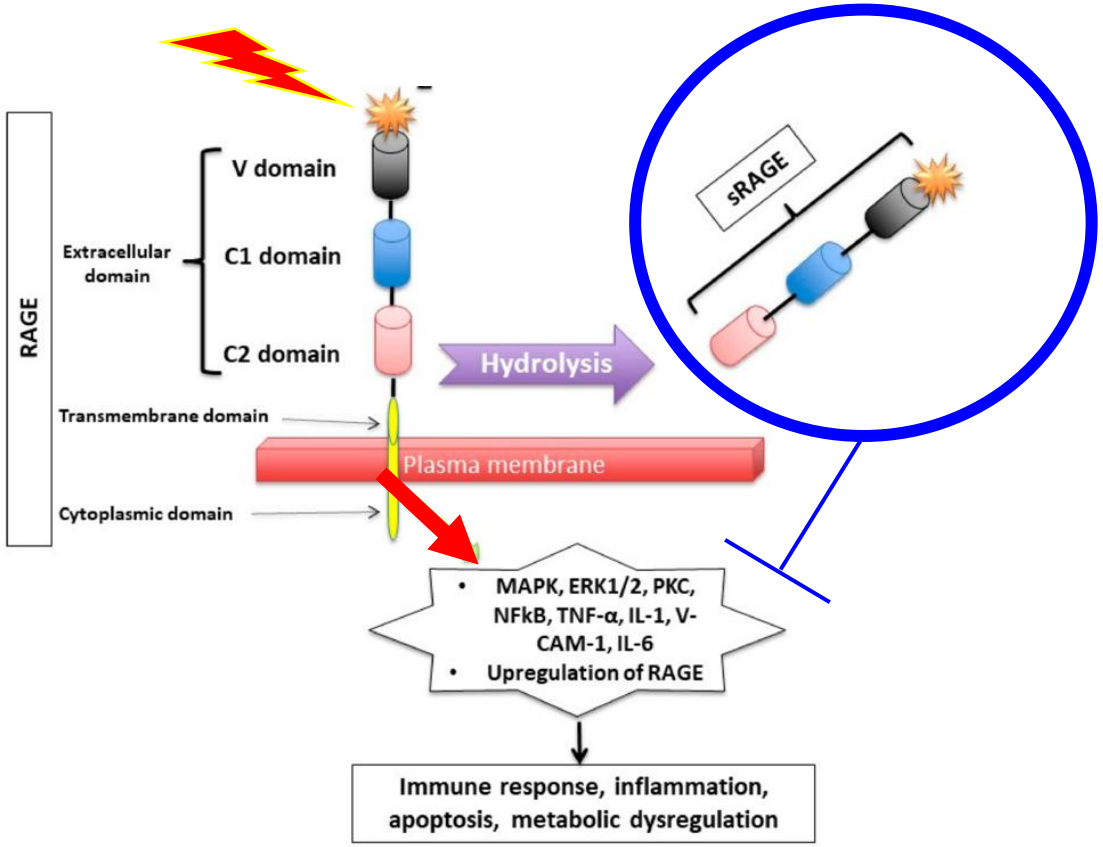
- Fragments of a structural protein of neuronal axons.
- When present in plasma and CSF is a reliable marker of neurodegenerative diseases, cognitive impairment, other non-neurodegenerative conditions, such as physical decline and CVD.



Modified from Khalil et al 2018 doi: 10.1038/s41582-018-0058-z.

soluble Receptor for Advanced Glycation Endproducts

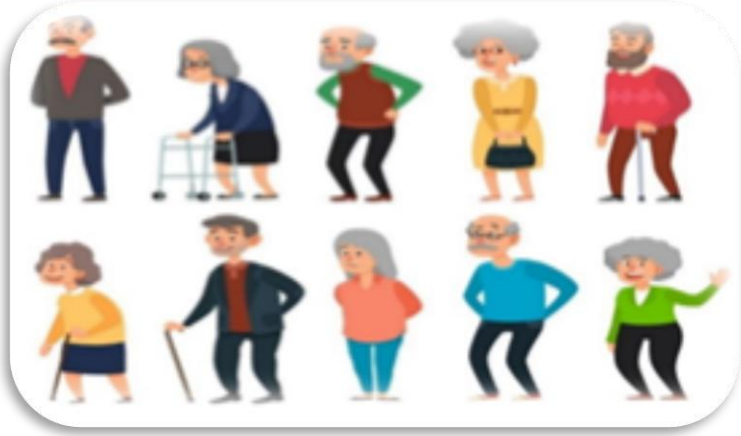
- RAGE is implicated in the pathogenesis and progression of chronic diseases and inflammatory disorders.
- It is a marker of inflammatory reaction
- **Soluble RAGE** is considered to have an anti-inflammatory activity



Modified from Mouanness et al., 2022 doi: 10.1016/j.arr.2017.05.004

COMMUNITY-DWELLING SUBJECTS

463 subjects, mainly from Northern Italy, **aged between 50 and 113 years,** enrolled before the Covid-19 pandemic



❖ Subjects divided into **FOUR AGE GROUPS**:

- 75 **ADULTS** (**A**, age range 50-69 years)
- 117 **OLDER PEOPLE** (**O**, age range 70-88)
- 109 **NONAGENARIANS** (**NG**, age range 89-98)
- 162 **CENTENARIANS** (**C**, age range 99-113)

❖ Subjects also categorized as

- **FRAIL**
- **NON-FRAIL**

based on a **45-item FRAILTY INDEX** according to the **Deficit Accumulation Model**

Rockwood K, Mitnitski A. 2011 Frailty defined by deficit accumulation and geriatric medicine defined by frailty. Clin Geriatr Med. doi: 10.1016/j.cger.2010.08.008.

Theou, O., et al., 2023. How to construct a frailty index from an existing dataset in 10 steps. Age Ageing. 52(12), afad221. https://doi.org/10.1093/ageing/afad221

Conte et al., 2025 doi: 10.1016/j.mad.2025.112077

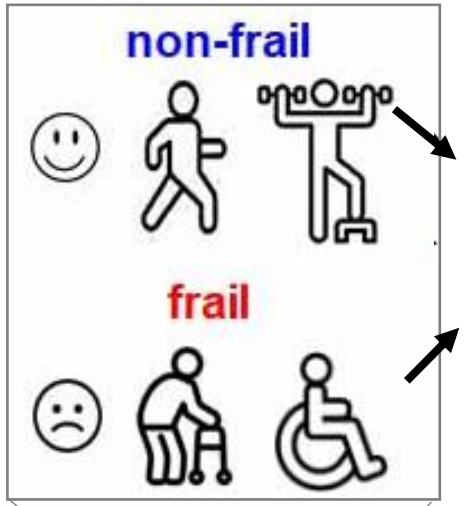
FRAILTY INDEX

FI ≥ 0.25 used as the threshold over which subjects were considered **FRAIL**

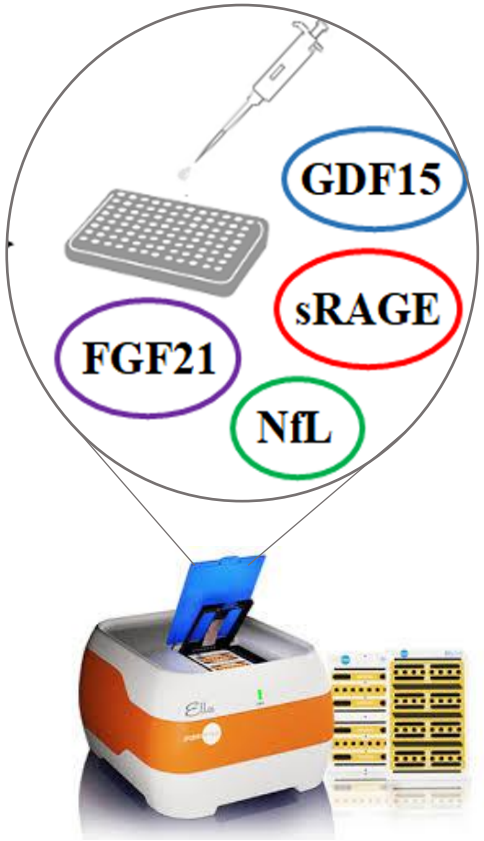
Community-dwelling participants		
CHRONIC CONDITIONS	**SIGNS AND SYMPTOMS**	**LIVING BEHAVIOUR/SOCIAL FUNCTION**
Angina	Falls last year	Eating independently
Anxiety	Weight loss in the last year	Dressing
Arthrosis	BMI	Bathing/Showering
Atrial Flutter/Fibrillation	White blood cells	Moving alone
BPCO	Hemoglobin	Use of toilet
Cancer	Platelets	Incontinence
Chronic renal failure	Glycemia	Smoking
Dementia	Albumin	
Depression	Creatine	
Heart failure	Total cholesterol	**PHYSICAL PERFORMANCE**
Hip femur fracture	HDL	Walk 500 meters without assistance
Hypercholesterolemia	Triglycerides	Up and down stairs without assistance
Hypertension	CRP	Bedridden
Myocardial infarction		Handgrip
Osteoporosis		
Parkinson's disease		**MENTAL HEALTH**
Polypharmacy (N° of Medications)		sensory ability: ability to understand
Stroke/Thrombosis		
Type 2 diabetes		
Venous insufficiency		

Conte et al., 2025 doi: 10.1016/j.mad.2025.112077

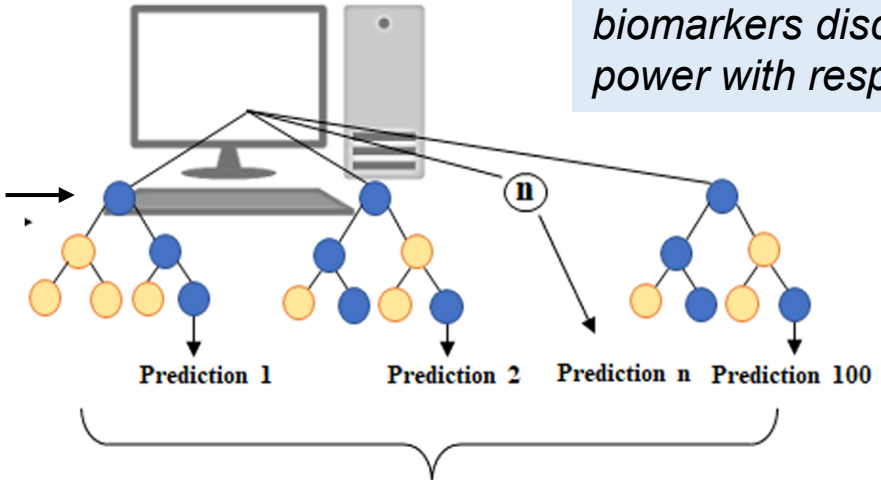
Community-dwelling people



Sample collection Biochemical analysis



Algorithm creation Validation

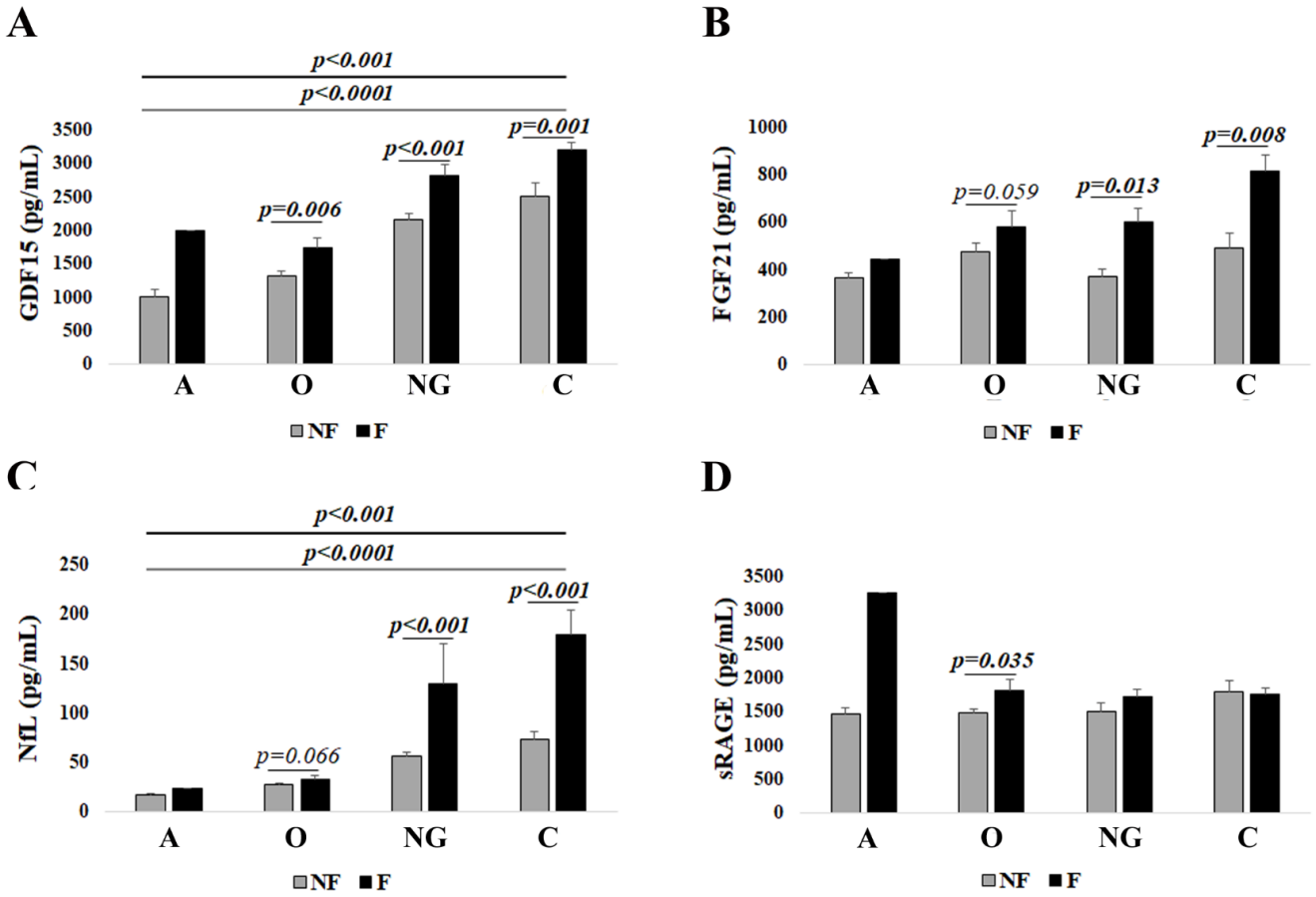


*A **Random Forest Decision model (RFD)** was used to assess the biomarkers discrimination power with respect to FI*

Can the four biomarkers discriminate between frail and non-frail subjects?

Plasma levels of biomarkers in non-frail (NF) and frail (F) subjects

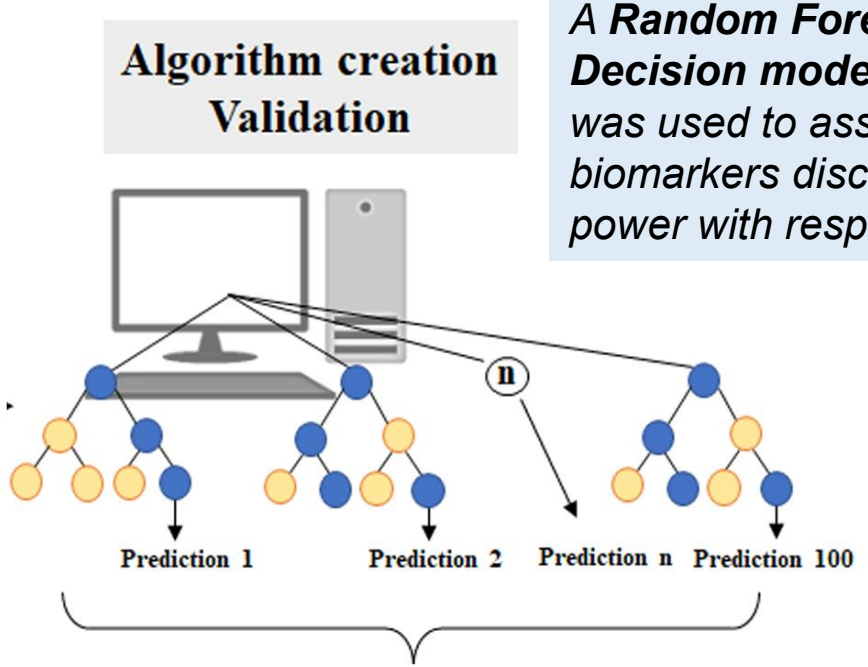
GDF15 (A) - FGF21 (B)
NfL (C) - sRAGE (D)
in NF and F divided by age groups
A = adults
O = older people
NG = nonagenarians
C = centenarians



In A group only one frail subject was present, so no statistical comparison with non-frail subjects was possible.

Data are expressed as mean ± SE, p values were determined by Kruskal-Wallis test with Bonferroni correction.

Conte et al., 2025 doi: 10.1016/j.mad.2025.112077



*A **Random Forest Decision model (RFD)** was used to assess the biomarkers discrimination power with respect to FI*

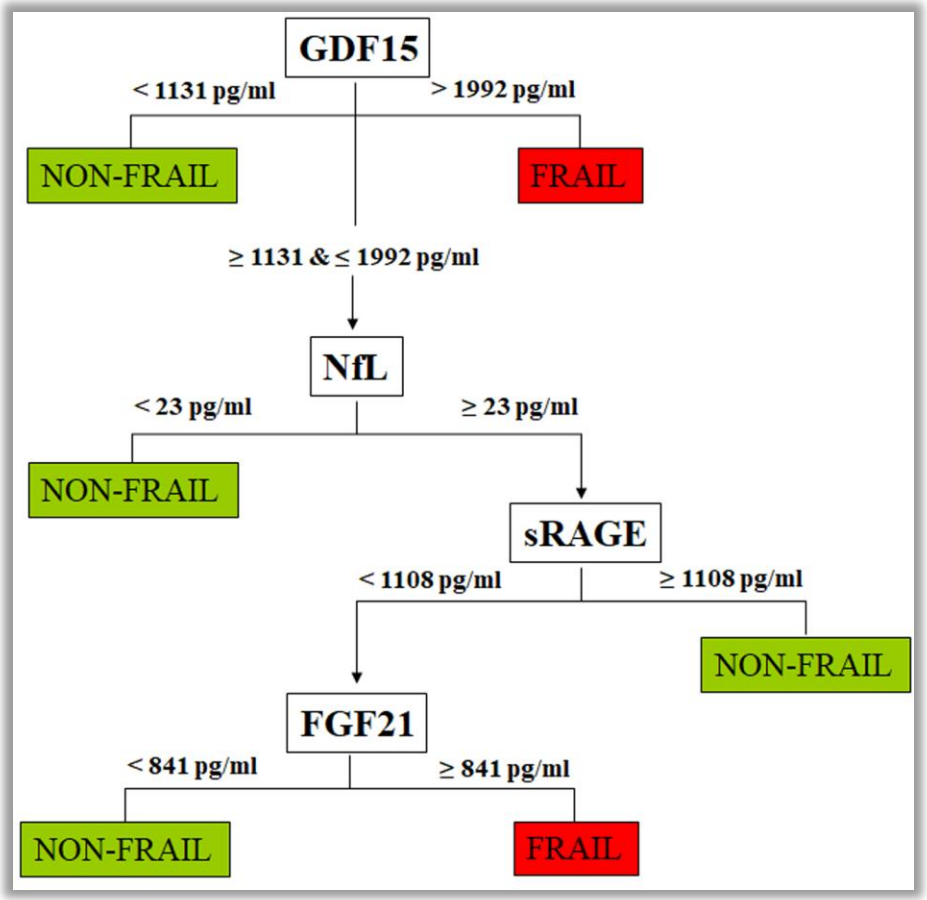
Can the four biomarkers discriminate between frail and non-frail subjects?

The data have been divided in two subgroups:

- **training dataset (334 observations)**
- **validating dataset (129 observations).**

RFD model indicated that GDF15, NfL, sRAGE, and FGF21 represent effective factors for estimating frailty status

The biomarker values with the greatest **predictive capacity (>88%)**.



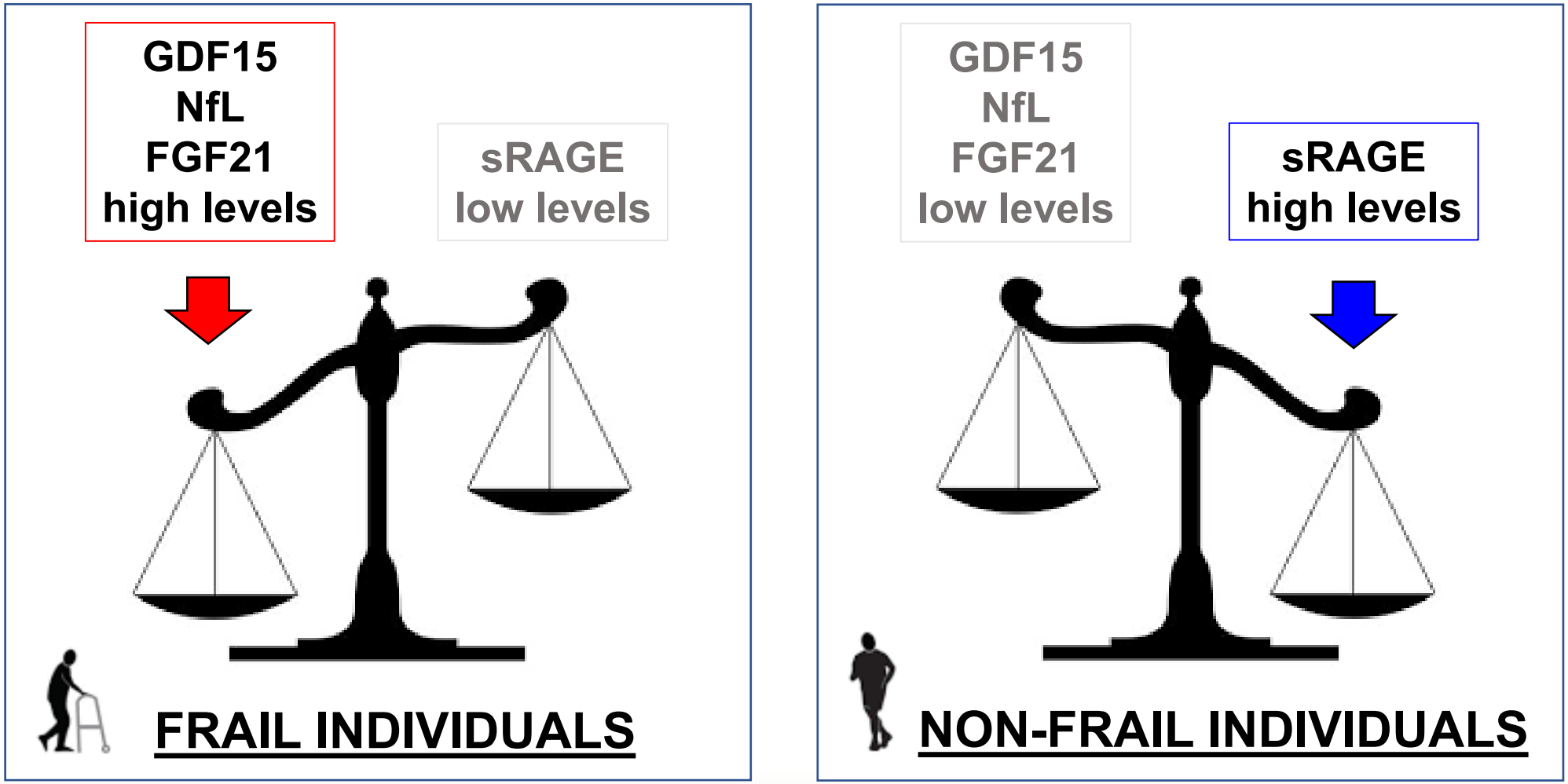
	Random Forest Decision Model	Probability (%)
R1	If GDF15 < 1131 then: **NON-FRAIL**	97.3
R2	If GDF15 = 1131-1992 and NfL < 23 then: **NON-FRAIL**	97.2
R3	If GDF15 = 1131-1992 and NfL ≥ 23 and sRAGE ≥ 1108 and FGF21 < 841 then: **NON-FRAIL**	98.1
R4	If GDF15 = 1131-1992 and NfL ≥ 23 and sRAGE ≥ 1108 and FGF21 ≥ 841 then: **NON-FRAIL**	88.7
R5	If GDF15 = 1131-1992 and NfL ≥ 23 and sRAGE < 1108 and FGF21 < 841 then: **NON-FRAIL**	90.7
R6	If GDF15 = 1131-1992 and NfL ≥ 23 and sRAGE < 1108 and FGF21 ≥ 841 then: **FRAIL**	98.4
R7	If GDF15 >1992 then: **FRAIL**	96.8

Biomarkers' concentration are expressed in pg/ml

A subject is considered **non-frail** in the first five cases (**Rules 1-5**), **frail** in the last two cases (**Rules 6-7**)

Conte et al., 2025 doi: 10.1016/j.mad.2025.112077

RFD model indicated that GDF15, NfL, sRAGE, and FGF21 represent effective factors for estimating frailty status



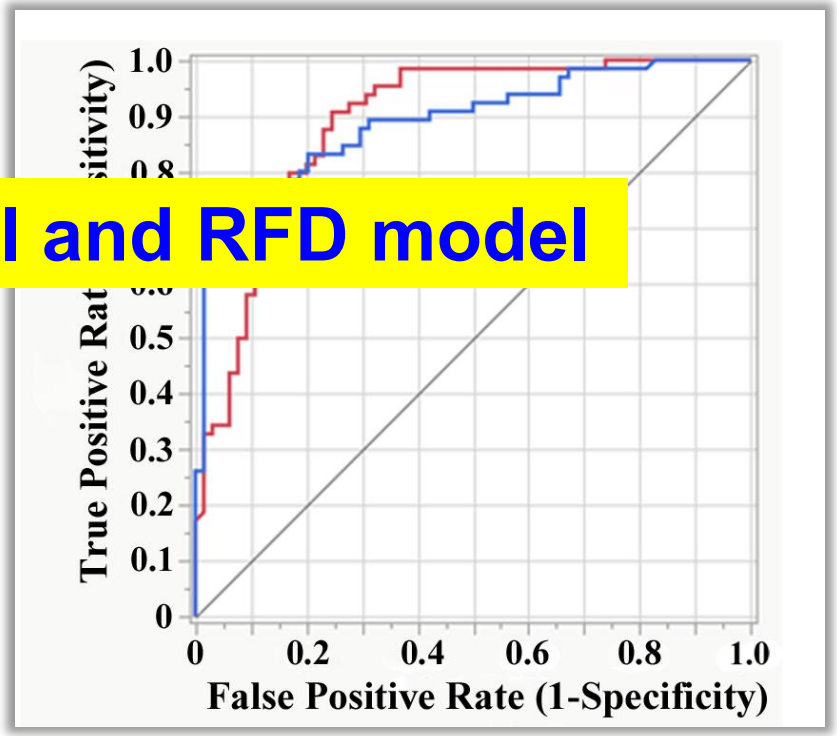
The predictive power of the model in the validation group

	VALIDATION GROUP (N=129)		
	Predicted Frail	Predicted Non-Frail	Total
FI ≥ 0.25	49 (TP)	16 (FN)	65 (TP+FN)
FI <0.25	7 (FP)	57 (TN)	64 (FP+TN)
Total	56 (TP+FP)	73 (FN+TN)	129 (N)
Sensitivity	0.75		
Specificity	0.89		
F-Score	0.81		

Some cases are discordant between FI and RFD model

Note:
Accuracy = (TP+TN)/(TP+FP+TN+FN);
Precision = TP/(TP+FP);
Sensitivity = TP/(TP+FN);
Specificity = TN/(FP+TN);
F-Score = 2 x ((Precision x Sensitivity)/(Precision + Sensitivity)).
TP: true positive counts; TN: true negative counts; FP: false positive counts; FN: false negative counts.

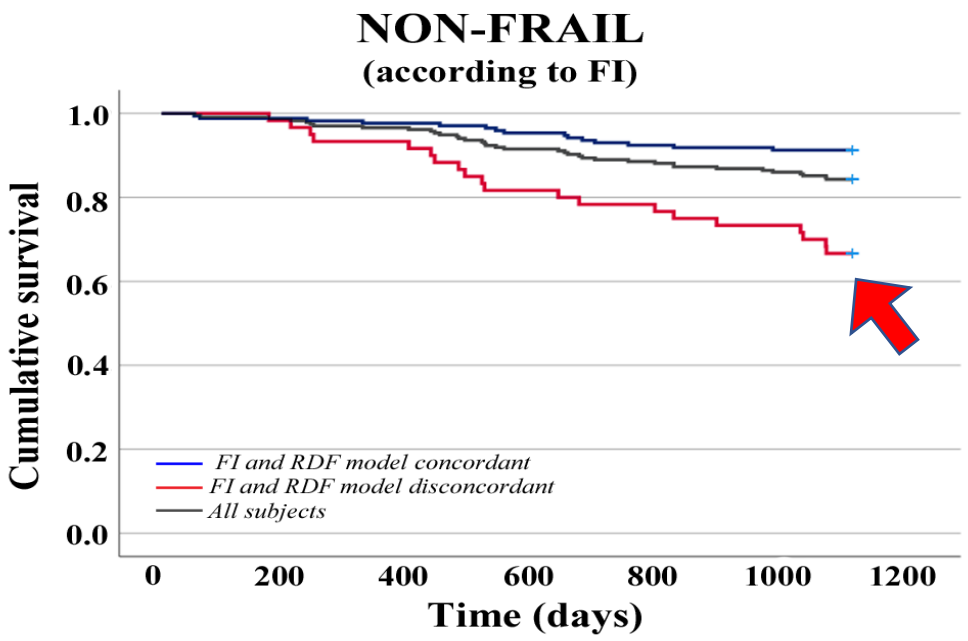
Comparison of ROC **curves of frail (blue)** and **non-frail subjects (red)** from the random forest model



The ROC curves reveal an **Area Under the Curve equal to 0.91**, corresponding to a **high level of accuracy**

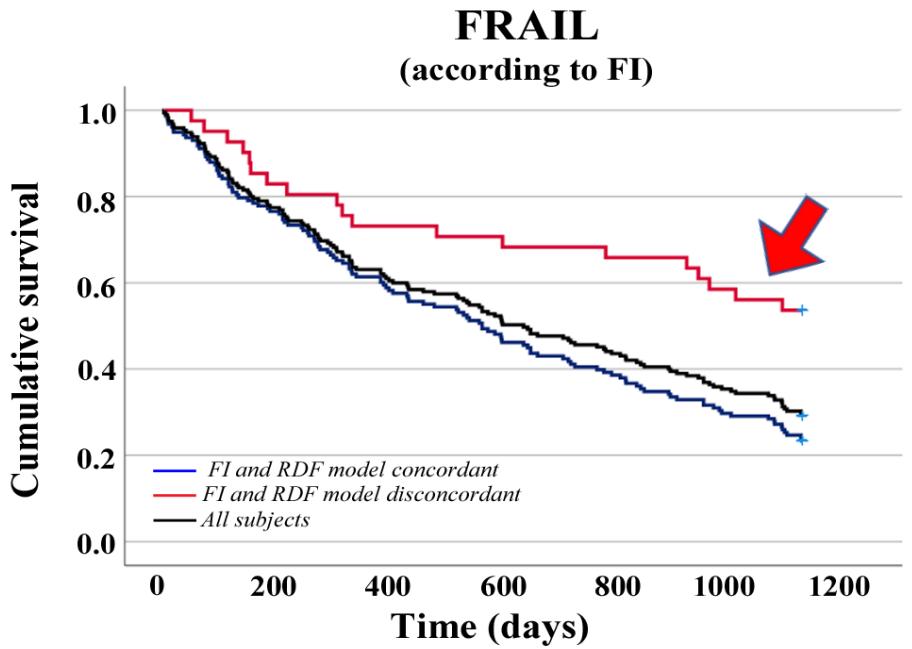
Can RFD model help refine survival prediction on FI?

people who are NF according to FI but are **F according to the RFD model**



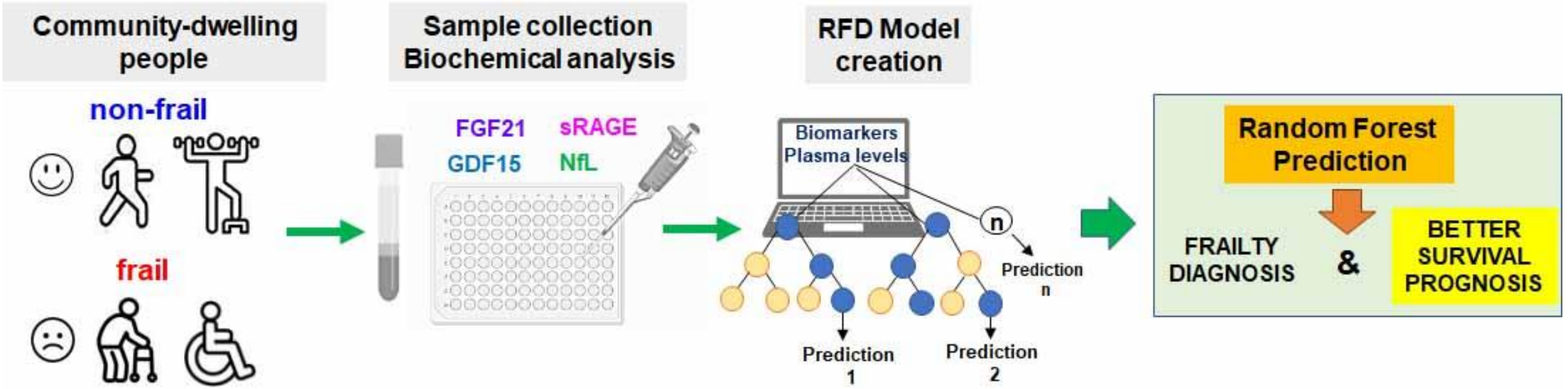
grey line: all NF subjects; **light blue line:** subjects in which FI and RFD model are concordant in defining non-frailty; **light red line:** subjects in which FI and RFD model are discordant in defining non-frailty

people who are **F according to FI** but are **NF according to the RFD model**



black line: all F subjects; **blue line:** subjects in which FI and RFD model are concordant in defining frailty; **red line:** subjects in which FI and RFD model are discordant in defining frailty.

Can RFD model help refine survival prediction on FI?



Finanziato dall'Unione europea NextGenerationEU | Ministero dell'Università e della Ricerca | Italiadomani PIANO NAZIONALE DI RIPRESA E RESILIENZA | Age-It Ageing well in an ageing society | SPOKE 3 Age-It

These data suggest that plasma levels of **GDF15**, **NfL**, **sRAGE** and **FGF21** can be proposed as parameters that can provide **additional information** about **frailty status** and **survival** with respect to FI alone in community-dwelling older subjects.

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journal homepage: www.elsevier.com/locate/mechagedev

The combination of GDF15, FGF21, sRAGE and NfL plasma levels can identify frailty in community-dwelling people across old age

Maria Conte [a], Federica Sevini [a], Giuseppe Conte [b], Monica Tognocchi [b], Erika Ciurca [c], Lorenzo Trofarello [a], Antonio Chiariello [a], Miriam Capri [a], Claudio Franceschi [d], Daniela Monti [e], Mirko Di Rosa [f], Antonio Cherubini [g,h], Fabiola Olivieri [f,h], Stefano Salvioli [a,i,*]

WHAT ABOUT PATIENTS WITH ACUTE ILLNESS?

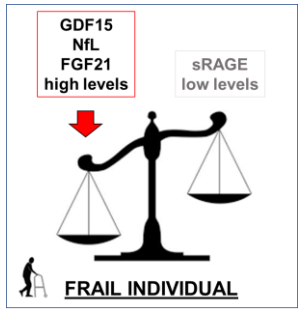
Hospitalized patients over 65 years of age admitted to the acute care wards

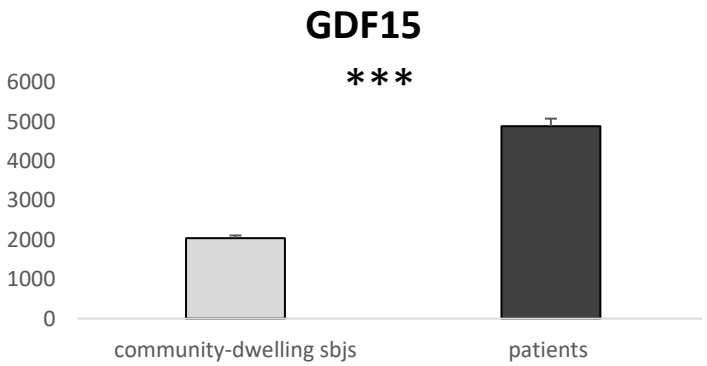
(from INRCA hospitals)

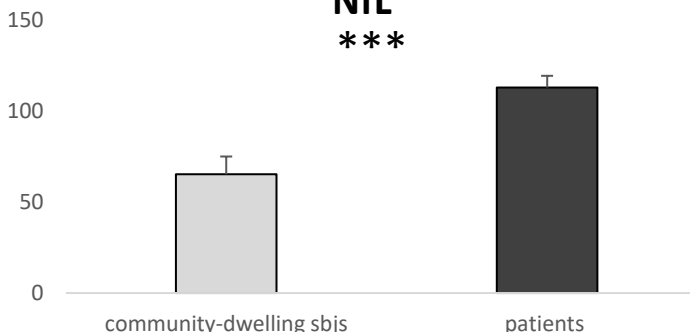
In collaboration with IRCCS INRCA e UNIVPM, Ancona, Italy

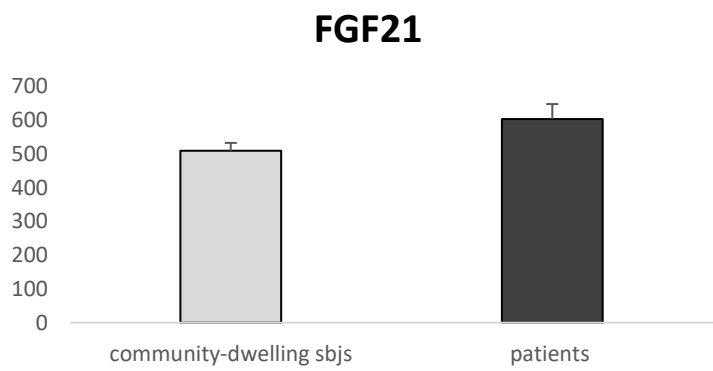
WHAT ABOUT PATIENTS WITH ACUTE ILLNESS?

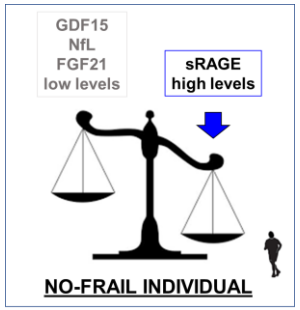
community dwelling-subjects *versus* hospitalized patients

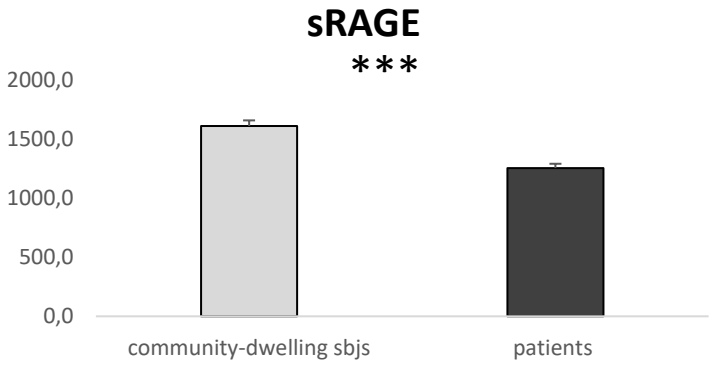


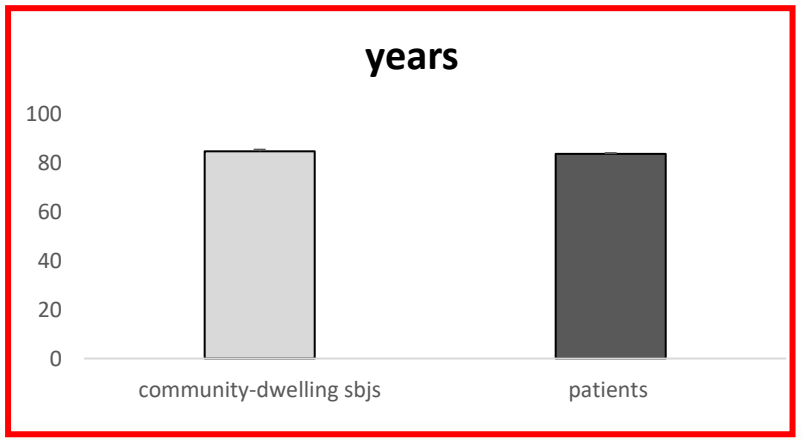












In collaboration with IRCCS INRCA e UNIVPM, Ancona, Italy

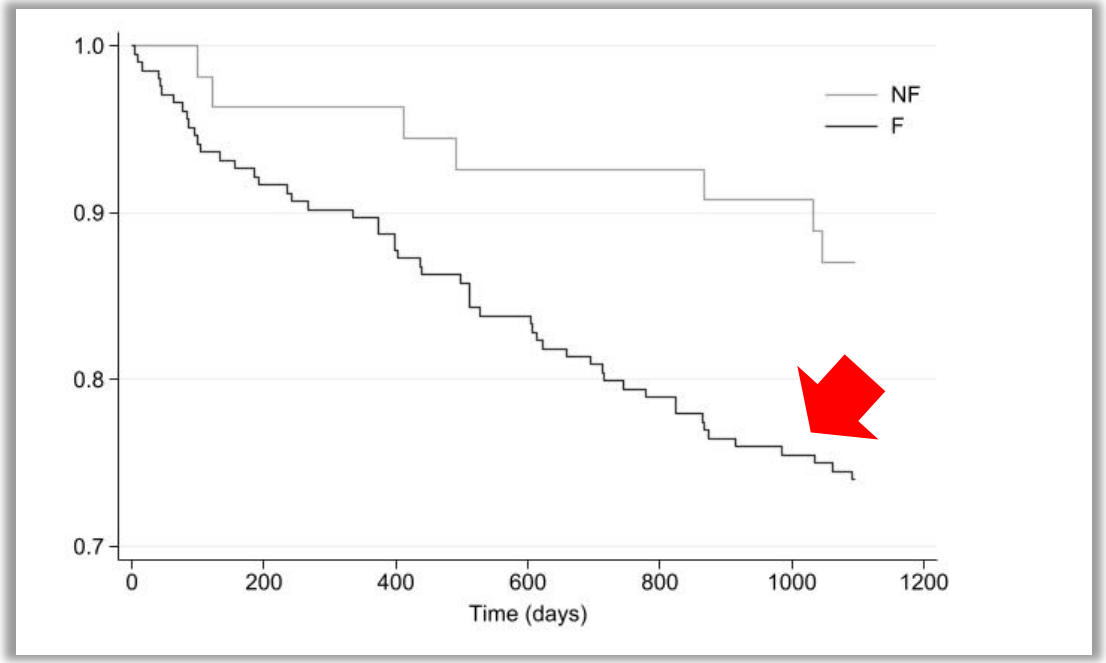
WHAT ABOUT PATIENTS WITH ACUTE ILLNESS?

Hospitalized patients over 65 years of age admitted to the acute care wards

We selected patients (n° 258/500) classified as
NON FRAIL based on FI assessment
For these patients a mortality follow-up is available

The RFD model classified as FRAIL 204 patients out of 258 based on biomarker values

these patients showed a
significantly lower survival
on a three-year follow-up
compared to the 54 patients classified as non-frail



In collaboration with IRCCS INRCA e UNIVPM, Ancona, Italy

Unpublished data

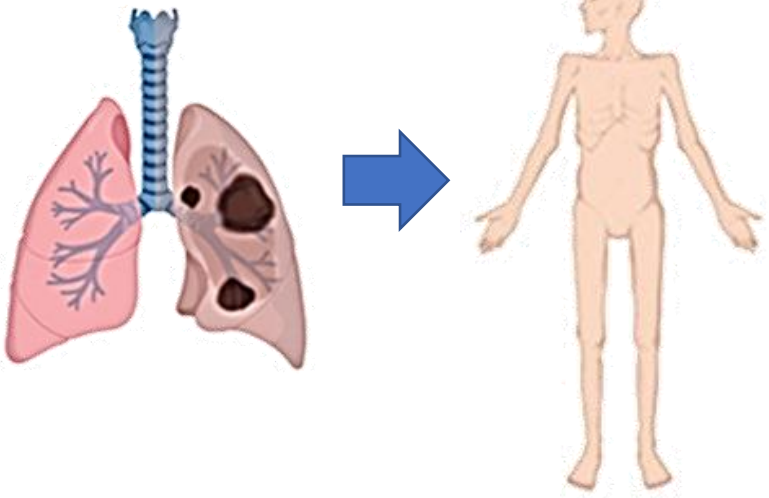
WHAT ABOUT PATIENTS WITH ADVANCED DISEASE?

The considered parameters are indeed dynamic ones
(they provide a snapshot of the present health status)

PATIENTS WITH

NSCLC

SARCOPENIA/ CACHEXIA

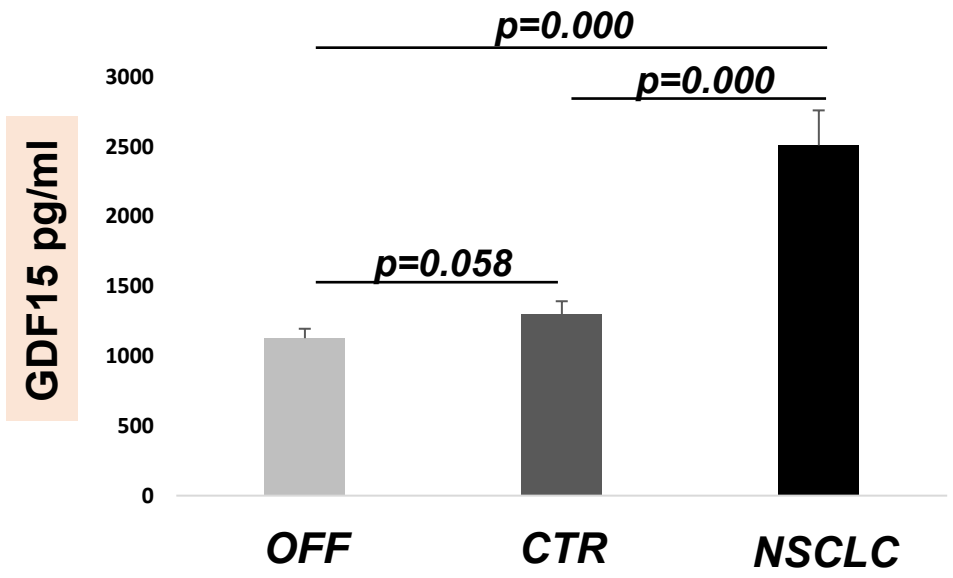


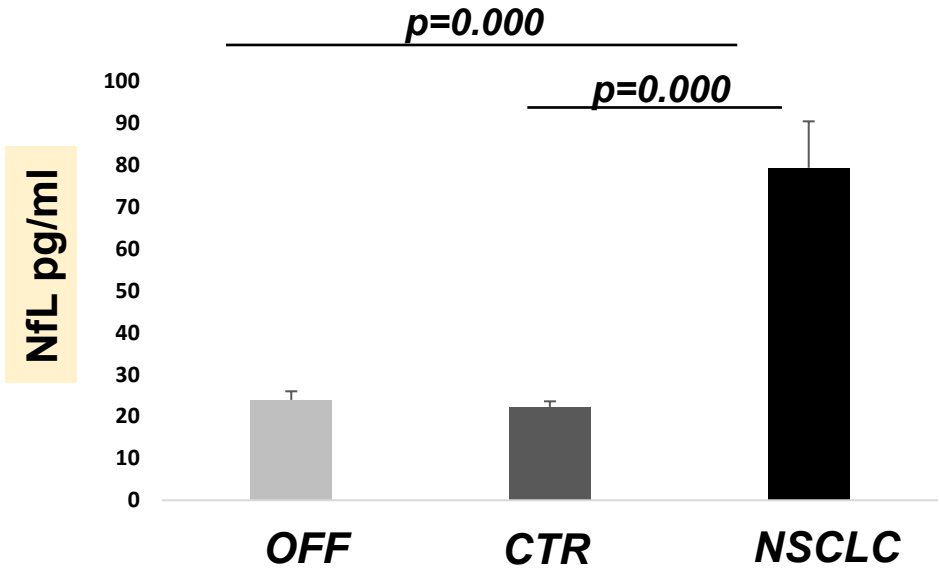
N° 40 NSCLC PATIENTS (stage IIIb-IV)
(mean age 70.00 ± 8.63 – age range 49-83)
(sampling before starting therapy)

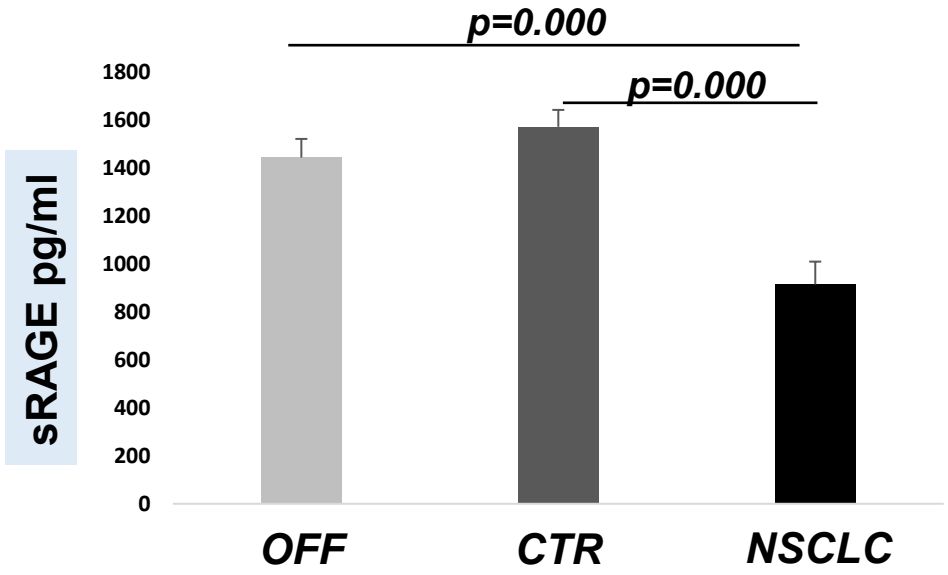
COMMUNITY-DWELLING SUBJECTS

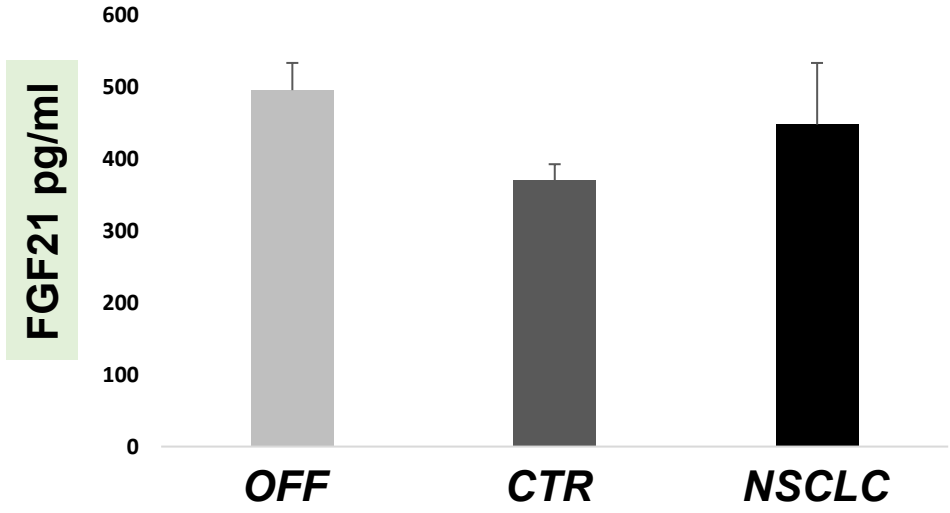
- **N° 93 CONTROLS**
  (mean age 69.95 ± 5.14 – age range 50-83)
- **N° 93 SUPER CONTROLS** - CENTENARIANS' OFFSPRING
  (mean age 70.67 ± 7.38 – age range 50-83)

COMMUNITY-DWELLING SUBJECTS versus NSCLC PATIENTS









De Giglio, Conte et al., in preparation

CONCLUSIONS

- ✓ Biomarkers related to biological age can be associated with physical frailty.

- ✓ A combination of 4 biomarkers such as GDF15, NfL, FGF21 and sRAGE can identify frail subjects with a 82% accuracy in community-dwelling people.

- ✓ Such a combination can help refining the prognosis of survival in a medium-term follow-up, not only in community-dwelling people but also in acute patients.

- ✓ Such a combination could also provide information about the health status of patients with severe chronic diseases (further studies are ongoing).

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Ministero dell'Università e della Ricerca

Italiadomani PIANO NAZIONALE DI RIPRESA E RESILIENZA

Age-It Ageing well in an ageing society

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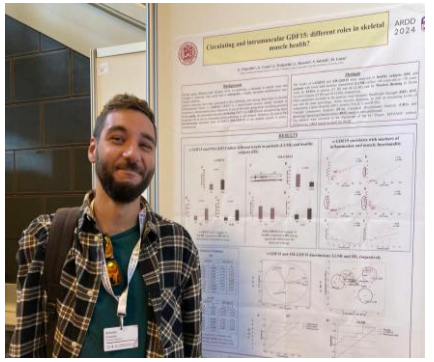

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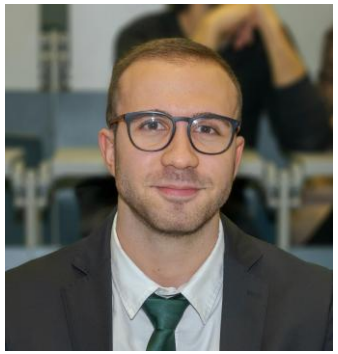

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