Fragilité

de la clinique à la Géroscience

Pr Yves ROLLAND

Pas de conflit d'intérêt

IHU HealthAge
GEROSCIENCE & PREVENTION

Organisation mondiale de la Santé

Fragilité

de la clinique à la Géroscience

Agenda

- Du concept de fragilité à la Capacité Intrinsèque
- Evaluer la résilience
- La Géroscience – L'expérience de l'IHU HealthAge
- Perspective thérapeutique

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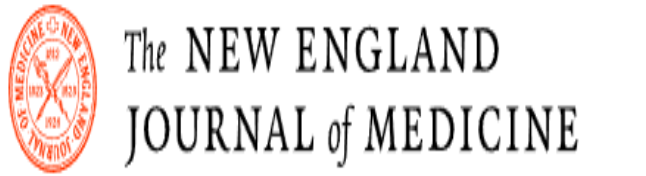
Du concept de fragilité à la Capacité Intrinsèque

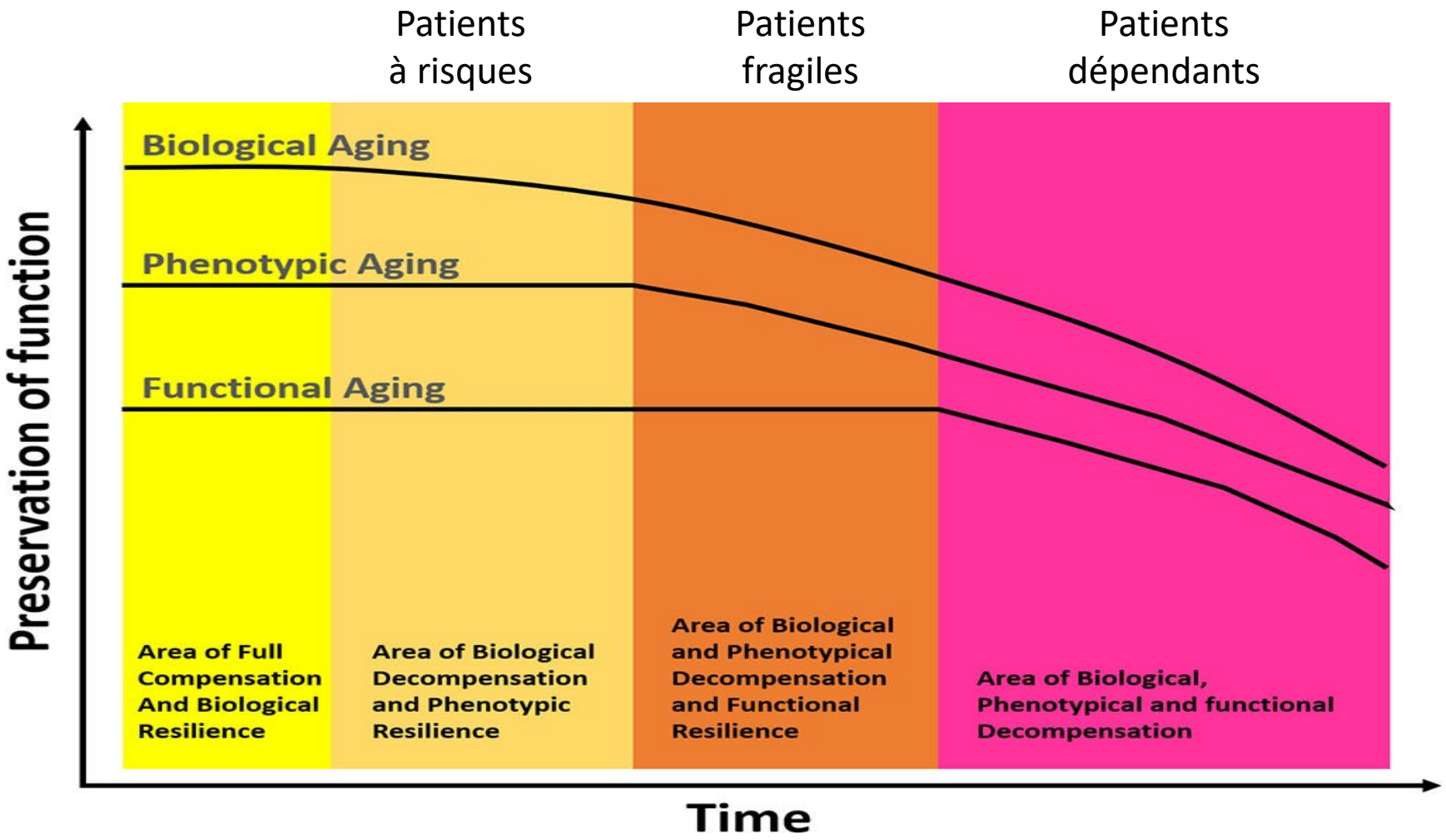


1984

1993

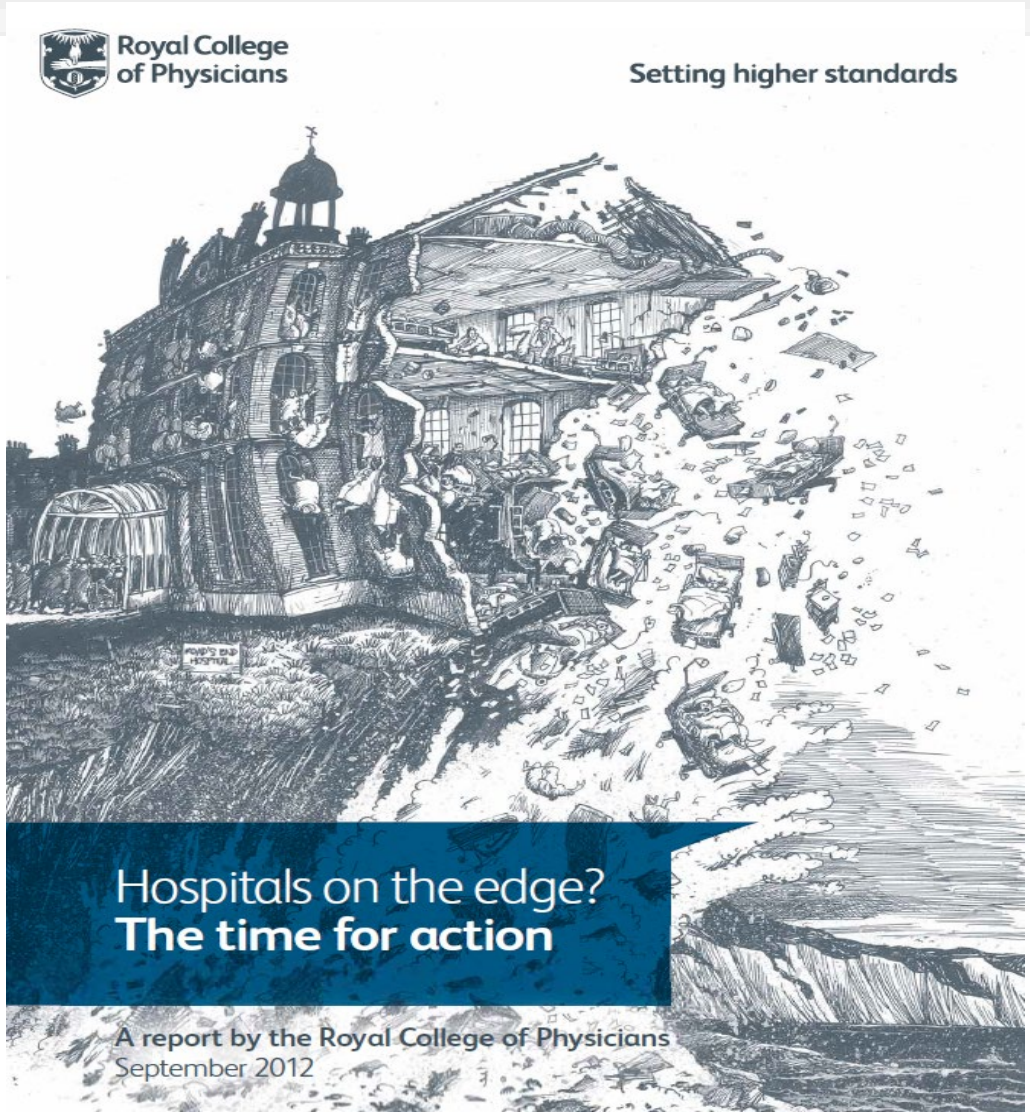
Aout 2024

Du concept de fragilité à la Capacité Intrinsèque



Time and the Metrics of Aging. Ferrucci L et al. Circ Res. 2018

Du concept de fragilité à la Capacité Intrinsèque



SPECIAL ARTICLES

The End of the Disease Era

Mary E. Tinetti, MD, Terri Fried, MD

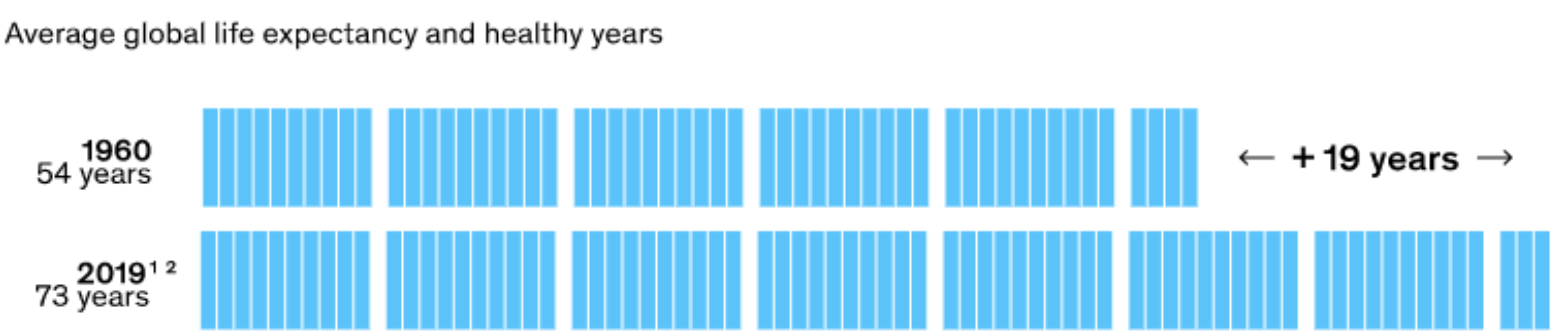
The time has come to abandon disease as the focus of medical care. The changed spectrum of health, the complex interplay of biological and nonbiological factors, the aging population, and the interindividual variability in health priorities render medical care that is centered on the diagnosis and treatment of individual diseases at best out of date and at worst harmful. A primary focus on disease may inadvertently lead to undertreatment, overtreatment, or mistreatment. The numerous strategies that have evolved to address the limitations of the disease model, although laudable, are offered only to a select subset of persons and often further fragment care. Clinical decision making for all patients should be predicated on the attainment of individual goals and the identification and treatment of all modifiable biological and nonbiological factors, rather than solely on the diagnosis, treatment, or prevention of individual diseases. Anticipated arguments against a more integrated and individualized approach range from concerns about medicalization of life problems to "this is nothing new" and "resources would be better spent determining the underlying biological mechanisms." The perception that the disease model is "truth" rather than a previously useful model will be a barrier as well. Notwithstanding these barriers, medical care must evolve to meet the health care needs of patients in the 21st century. **Am J Med. 2004;116:179–185.**

"…**The time has come to abandon disease as the primary focus** of medical care. When disease became the focus of Western medicine in the 19th and early 20th century, the average life expectancy was 47 years and most clinical encounters were for acute illness. Today, the average life expectancy in developed countries is 74 years and increasing, and most clinical encounters are for chronic illnesses or non-disease-specific complaints…"

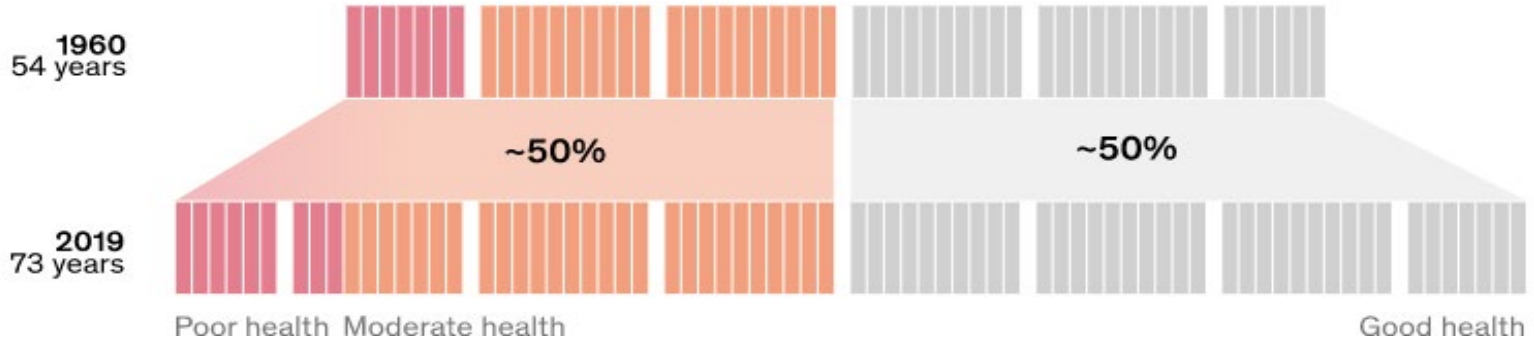
Du concept de fragilité à la Capacité Intrinsèque

YEARS WITHOUT LIFE: Longer lifespan but decreased well-being…

60 Years of Increased Life Expectancy



Has NOT Yielded an Increase in Years of Good Health



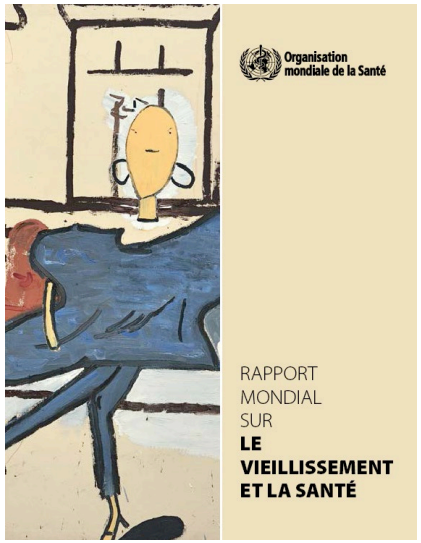
Source: Institute for health Metrics and Evaluation; World Bank; McKinsey analysis

Du concept de fragilité à la Capacité Intrinsèque

	Fit	Prefrailty	Frailty	End-Stage Frailty
Frailty Score	Fried frailty phenotype, 0 points Deficit-accumulation frailty index of <0.10 Score on Clinical Frailty Scale, 1–3	Fried frailty phenotype, 1 or 2 points Deficit-accumulation frailty index of 0.10 to <0.20 Score on Clinical Frailty Scale, 4	Fried frailty phenotype, 3 or 4 points Deficit-accumulation frailty index of 0.20 to <0.55 Score on Clinical Frailty Scale, 5–7	Fried frailty phenotype, 5 points Deficit-accumulation frailty index of ≥0.55 Score on Clinical Frailty Scale, 8 or 9
Goal	Increase physiological reserve	Increase physiological reserve	Preserve physiological reserve and prevent avoidable stressors	Provide comfort
Lifestyle	Exercise and physical activity High-quality diet Social engagement	Exercise and physical activity High-quality diet (protein intake) Social engagement	Less intense exercise may be better tolerated High-quality diet (protein intake) Social engagement	Physical activity as tolerated Diet as tolerated Social engagement as tolerated
Disease Management	Apply disease-based guidelines	Apply disease-based guidelines	Consider trade-off between disease and treatment burden	Deescalate treatments
Preventive Care	Vaccination Cancer screening	Vaccination Cancer screening	Vaccination Individualize cancer screening (time to benefit vs. remaining life expectancy)	Vaccination Stop cancer screening
Interventions for Frailty	?	Treat reversible causes of frailty Exercise and physical activity Nutritional counseling and supplementation CGA and multidisciplinary intervention Comprehensive medication review	Treat reversible causes of frailty Rehabilitation (PT and OT) Nutritional counseling and supplementation CGA and multidisciplinary intervention Comprehensive medication review	Comprehensive medication review

N ENGL J MED 391;6 NEJM.ORG AUGUST 8, 2024

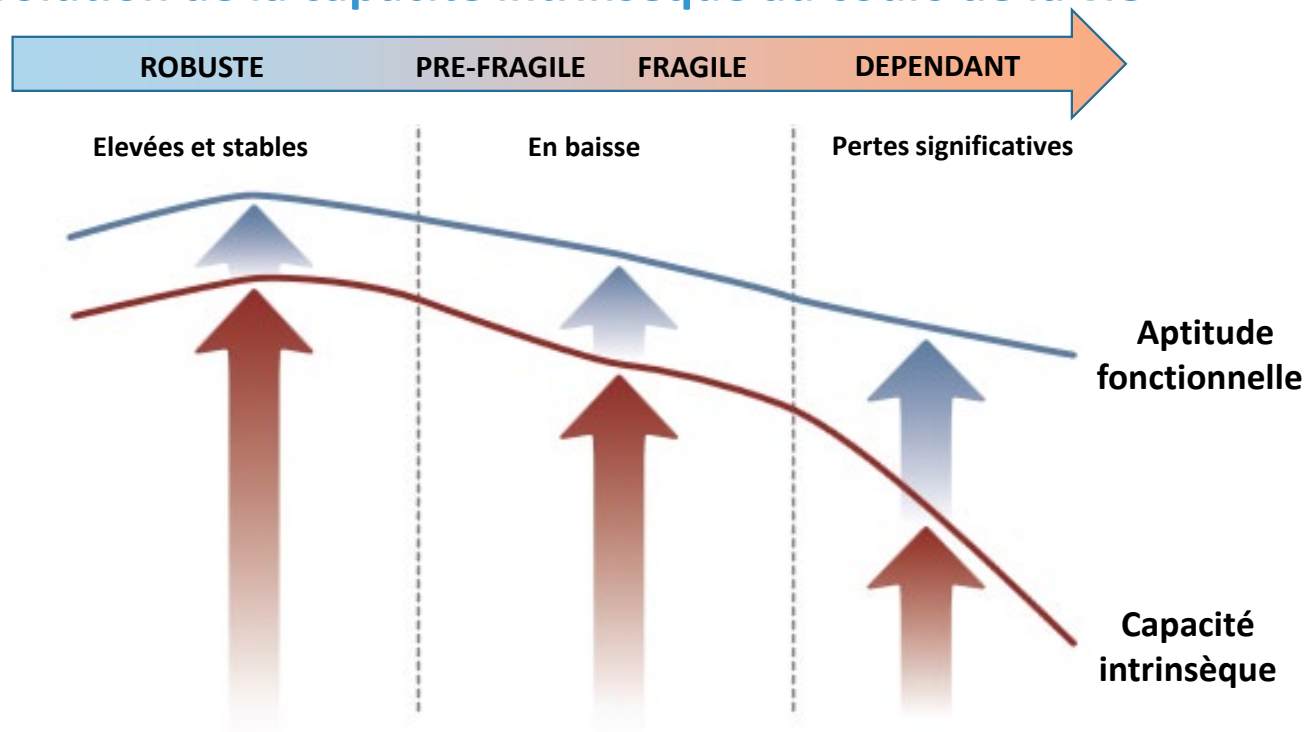
Du concept de fragilité à la Capacité Intrinsèque



Vieillir en bonne santé (O.M.S.) : «Développer et maintenir les aptitudes fonctionnelles qui favorisent le bien-être».

Pour la personne
*«Continuer à être ce qu'elle a été, à faire ce qui est important pour elle, à **conserver ses fonctions**» :*
Mobilité, mémoire, vitalité, capacités psychologiques et sensorielles …

Évolution de la capacité intrinsèque au cours de la vie



OMS: Rapport mondial sur le vieillissement et la santé

Du concept de fragilité à la Capacité Intrinsèque

Step1
Dépistage

Je certifie avoir obtenu l'accord du sujet ☐ **Le :**		**Signature:**
Fonctions	**Tests**	**Résultats**
Cognition	1. Avez-vous des problèmes de mémoire ou d'orientation?	☐ Oui ☐Non
	2. Avez-vous constaté une aggravation de ces troubles ces 4 derniers mois?	☐ Oui ☐Non
	3. Apprentissage de 3 mots : Citron, clé, ballon	☐ Oui ☐Non
	4. Orientation temporo-spatiale :	
	Quelle est la date complète d'aujourd'hui ?	
	- Année	☐ Oui ☐Non
	- Jour de la semaine	☐ Oui ☐Non
	- Mois	☐ Oui ☐Non
	- Jour du mois	☐ Oui ☐Non
Nutrition	1. Perte de poids : Avez-vous perdu involontairement au moins 3kg au cours des 3 derniers mois ?	Poids actuel : ..... Kg ☐ Oui ☐Non
	2. Avez-vous perdu de l'appétit récemment ?	☐ Oui ☐Non
Cognition	Rappel des trois mots: Mot 1	☐ Oui ☐Non
	Mot 2	☐ Oui ☐Non
	Mot 3	☐ Oui ☐Non
Vision	Avez-vous des problèmes avec vos yeux ? difficultés en vision de loin, à lire, pathologie oculaire ou médicament (ex diabète, HTA)	☐ Oui ☐Non
Audition	**Test de Whisper (test de chuchotement)*** :	
	- Oreille droite capable de répéter 3 mots	☐ Oui ☐Non
	- Oreille gauche capable de répéter 3 mots	☐ Oui ☐Non
Psychologie	Au cours des deux dernières semaines:	
	1. Vous êtes-vous senti déprimé ou sans espoir ?	☐ Oui ☐Non
	2. Avez-vous trouvé peu d'intérêt ou une perte de plaisir à faire les choses ?	☐ Oui ☐Non
Mobilité	**Test de lever de chaise**** :	Temps en sec.....
	1. Réalisation des cinq levers?	☐ Oui ☐Non
	2. Si non, combien de levers de chaise réalisés?	
	3. Si aucun, le patient est-il capable de se lever d'une chaise en s'aidant des bras mais sans aide d'autrui ?	☐ Oui ☐Non

Du concept de fragilité à la Capacité Intrinsèque

Phase 1
(2020-2023):

> 50'000 adults age 60+ recruited in Toulouse

Lancet Longevity 2022

Phase 2
(2024-2034):

national extension
2 Mio adults age 60+

Phase 3
(2025-2034):
international extension

Implementation of the WHO integrated care for older people (ICOPE) programme in clinical practice: a prospective study

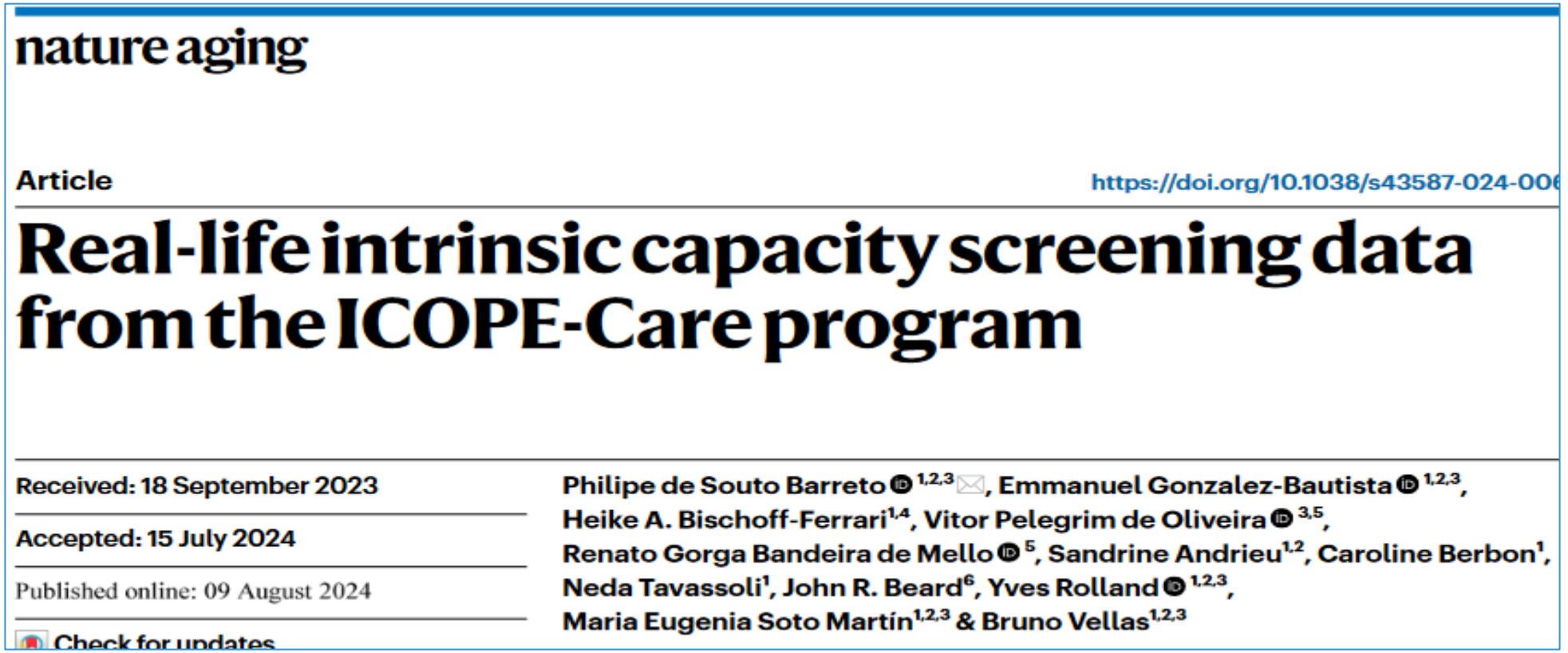
Neda Tavassoli, Philipe de Souto Barreto, Caroline Berbon, Celine Mathieu, Justine de Kerimel, Christine Lafont, Catherine Takeda, Isabelle Carrie, Antoine Piau, Tania Jouffrey, Sandrine Andrieu, Fatemeh Nourhashemi, John R Beard, Maria Eugenia Soto Martin, Bruno Vellas

Du concept de fragilité à la Capacité Intrinsèque

Key points

- 6.201 professionals trained
- > 61 000 older adults (74.2 ± 15.2 years, 63.1% women)

- Screen positive
  - 48.7% cognition;
  - 46.6% hearing
  - 40.5% vision;
  - 36.1% psychology;
  - 28.9% locomotion
  - 18.8% vitality;



nature aging

Article

https://doi.org/10.1038/s43587-024-006

Real-life intrinsic capacity screening data from the ICOPE-Care program

Received: 18 September 2023

Accepted: 15 July 2024

Published online: 09 August 2024

Check for updates

Philipe de Souto Barreto[1,2,3] ✉, Emmanuel Gonzalez-Bautista[1,2,3], Heike A. Bischoff-Ferrari[1,4], Vitor Pelegrim de Oliveira[3,5], Renato Gorga Bandeira de Mello[5], Sandrine Andrieu[1,2], Caroline Berbon[1], Neda Tavassoli[1], John R. Beard[6], Yves Rolland[1,2,3], Maria Eugenia Soto Martín[1,2,3] & Bruno Vellas[1,2,3]

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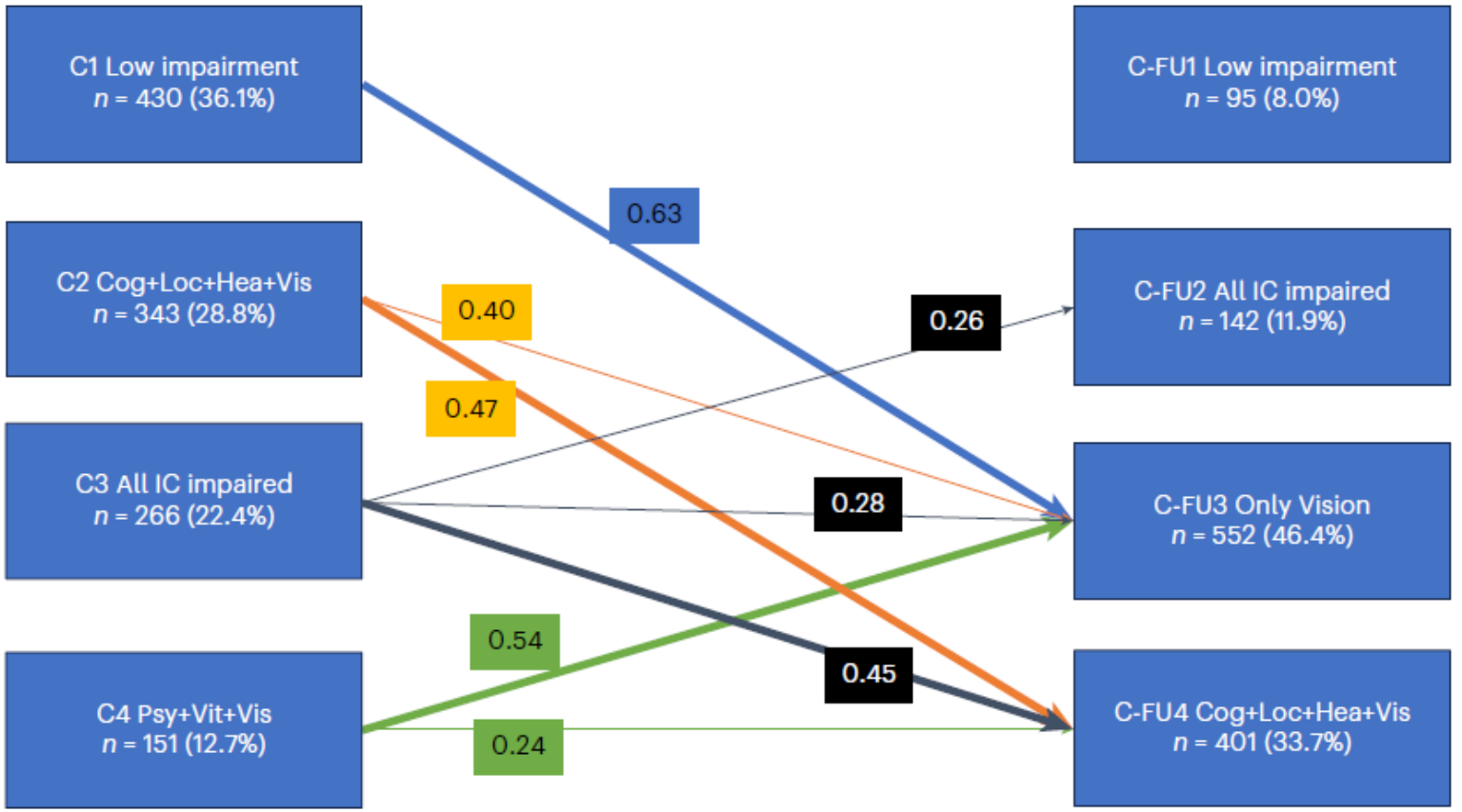

Du concept de fragilité à la Capacité Intrinsèque

Exemple Appétit: incidence, persistance and réversibilité

Analyses Longitudinal – Analyses à 5.5 mois.

		Perte d'Appétit à 5.5 Mois		
		Oui	Non	Total
Perte d'Appétit à baseline	Oui	133	408	541
	Non	**204**	4275	4482
Total		340	4 683	5 023

Incidence

4.6%

Du concept de fragilité à la Capacité Intrinsèque

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		Oui	Non	Total
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	Non	204	4275	4482
Total		340	4 683	5 023

Réversibilité

75.4%

Du concept de fragilité à la Capacité Intrinsèque

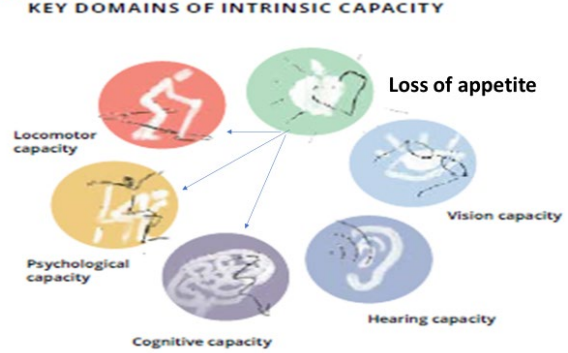
Exemple Appétit: incidence, persistence and reversibility

Analyses Longitudinal: ajustées sur l'âge, le sexe, la poids

Sujets sans déficit à baseline

Appetite loss	Odds ratio	P-value	95% conf. Interval	
Cognition (n=2219)	**1.77**	0.001	1.25	2.51
Locomotion (n=1381)	**1.91**	0.002	1.28	2.85
Vision (n=1,219)	**1.16**	0.444	0.80	1.68
Hearing (n=486)	**0.76**	0.379	0.41	1.41
Psychological (n=3342)	**1.79**	0.002	1.23	2.59
Weight loss (n=4702)	**1.93**	<0.001	1.34	2.76

Integrated care for older adults (ICOPE)



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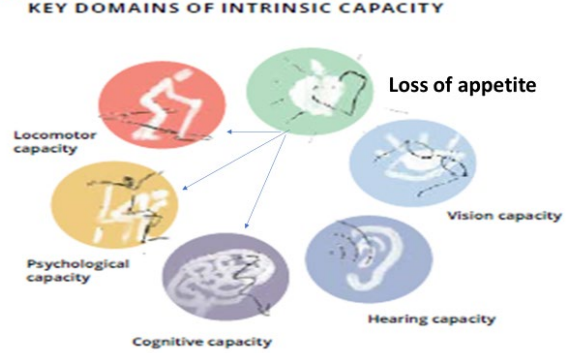
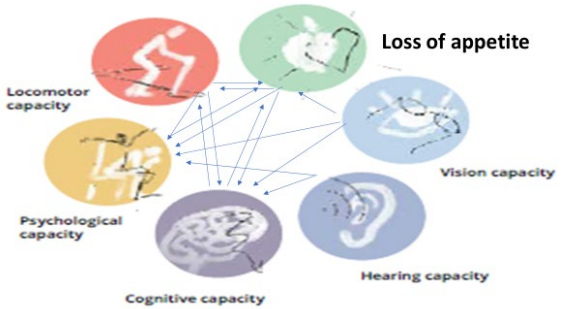




nature aging

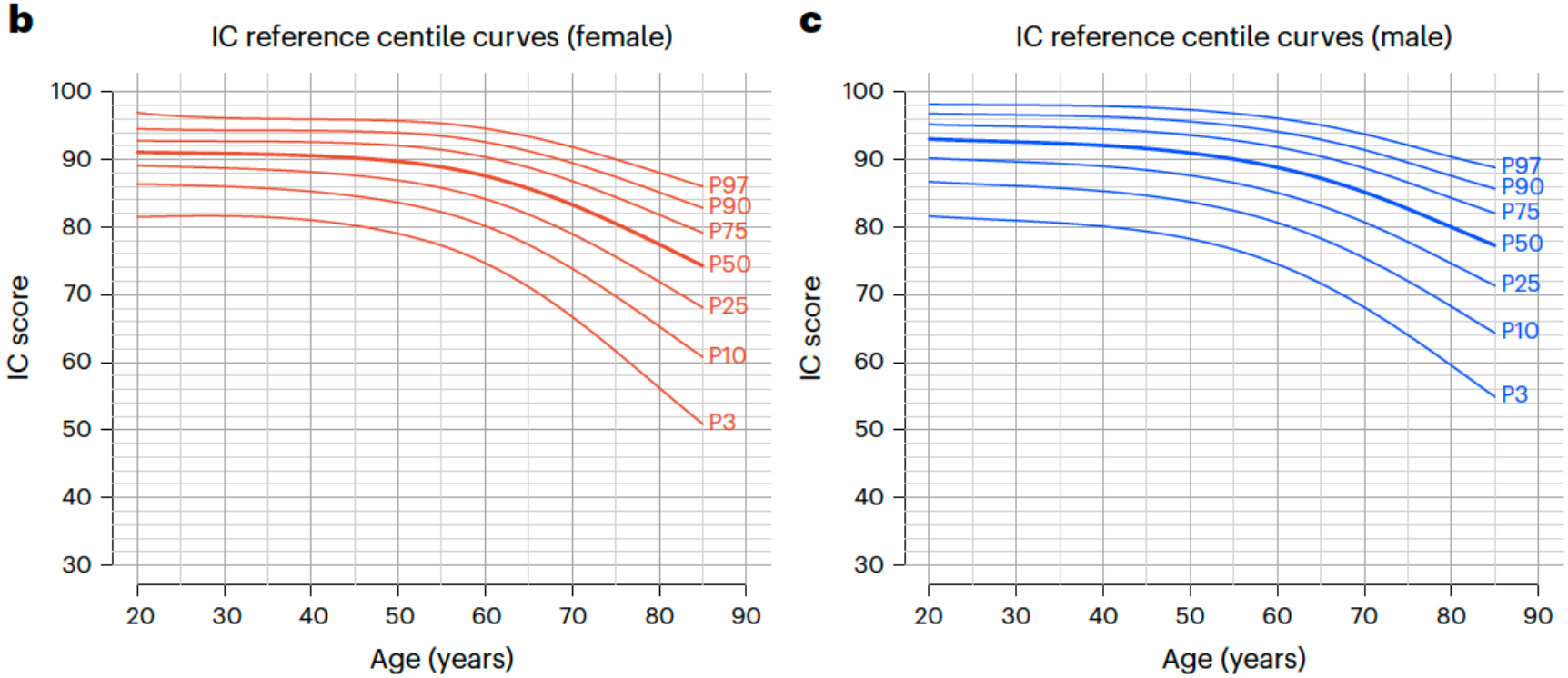
Wan-Hsuan Lu[1,2,3] ✉, Yves Rolland[1,2,3], Sophie Guyonnet[1,2,3], Philipe de Souto Barreto[1,2,3] & Bruno Vellas[1,2,3]

Letter

https://doi.org/10.1038/s43587-023-00522-x

Reference centiles for intrinsic capacity throughout adulthood and their association with clinical outcomes: a cross-sectional analysis from the INSPIRE-T cohort

Courbes de référence de la capacité Intrinsèque



Du concept de fragilité à la Capacité Intrinsèque

‘**Age-related decline in IC**’ was recently added to the International Classification of Diseases (11th Revision) (ICD-11) under code MG2A10T

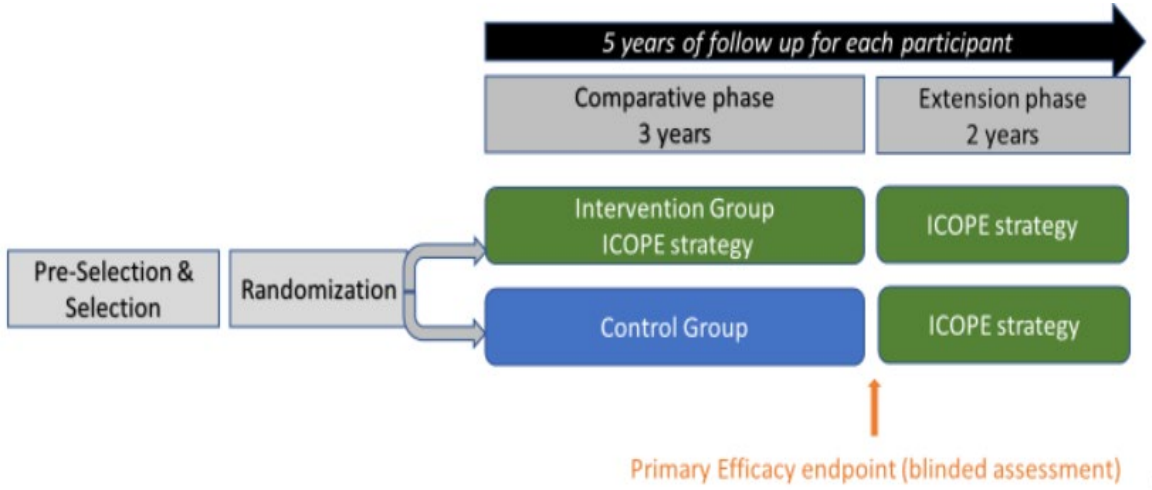
Du concept de fragilité à la Capacité Intrinsèque

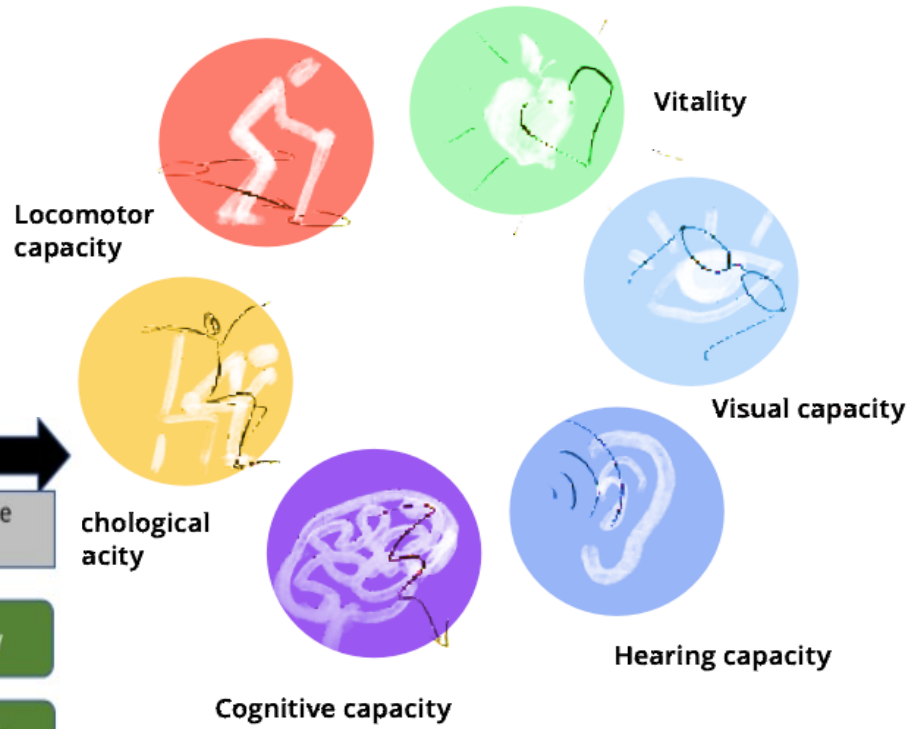
RCT ICOPE

1000 adults age 70 years and older

from **France**

Reduce functional decline over 3 years





Pr. S. Andrieu

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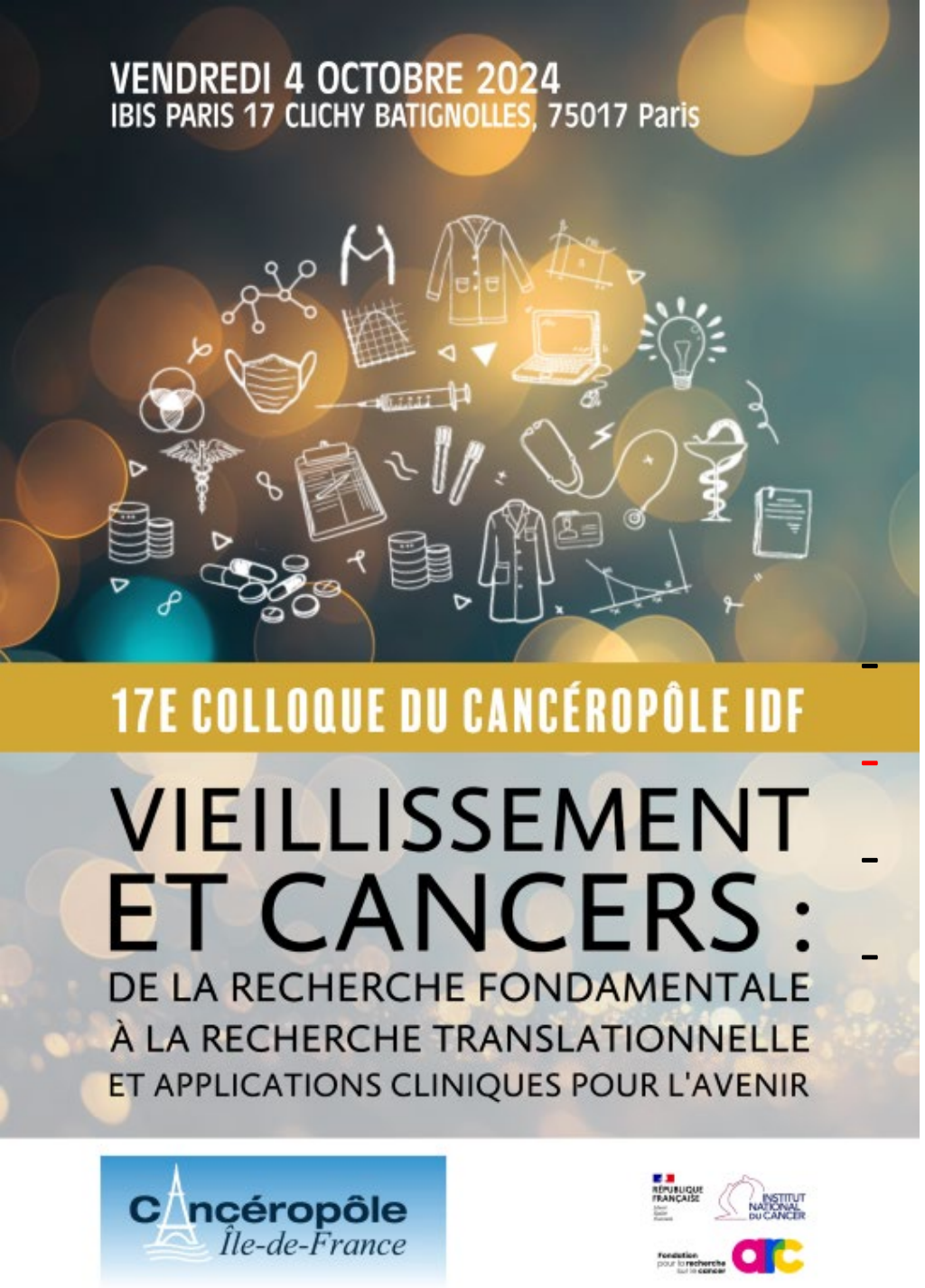

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Evaluer la résilience

Physical resilience is
the ability to recover function
after a health stressor

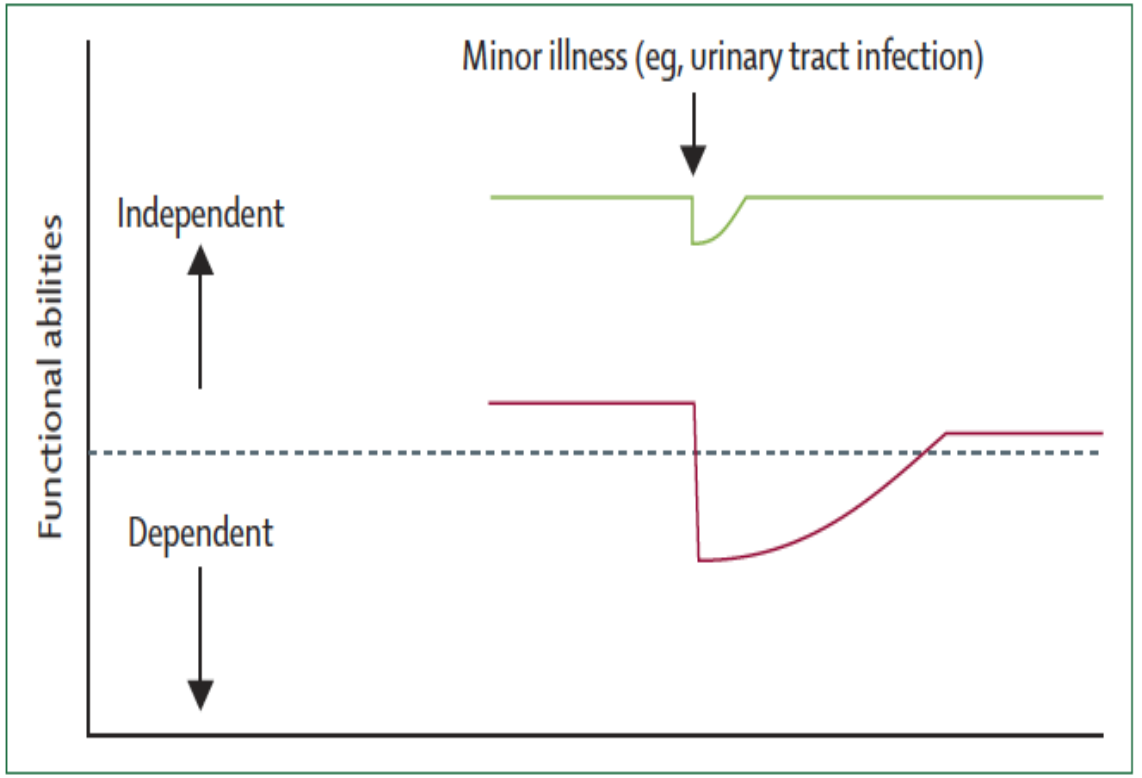


Figure 1: Vulnerability of frail elderly people to a sudden change in health status after a minor illness

Clegg A et al. *Lancet* 2013

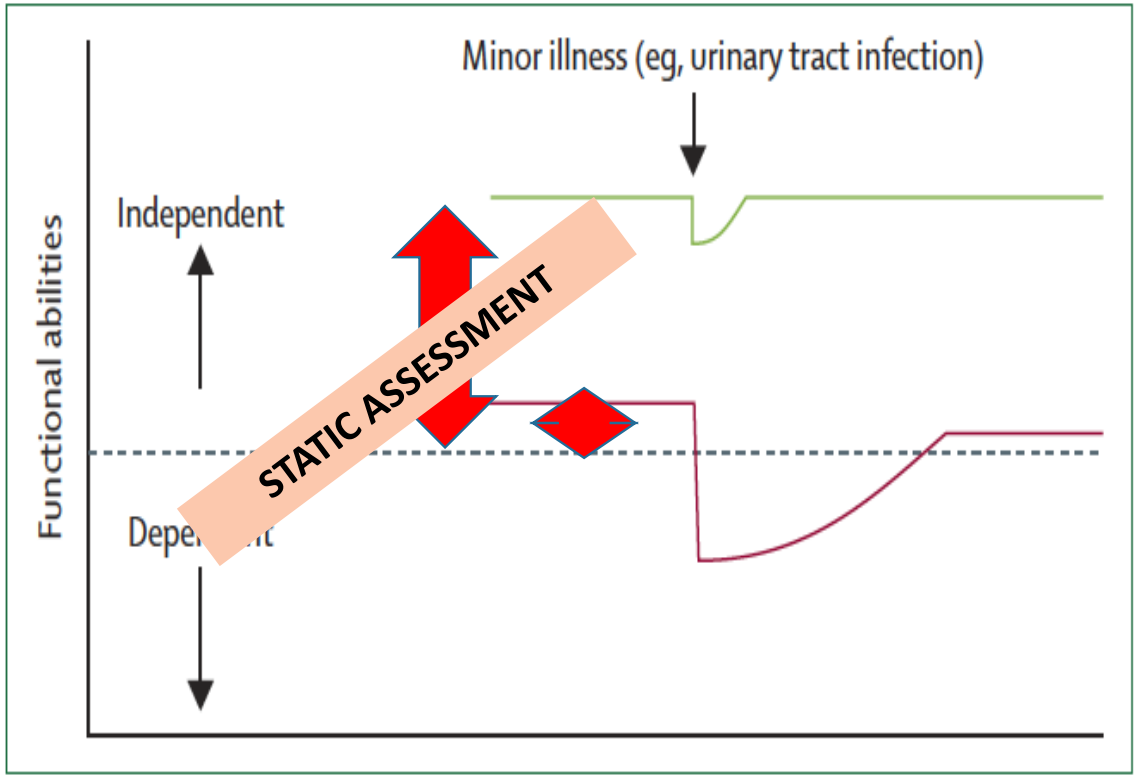
Evaluer la résilience

Reserve

Multiple domains of physiological, physical, psychological, and cognitive capacities at the level of the person that are accessed to respond adaptively to stress.

Stressor

Environment and social support



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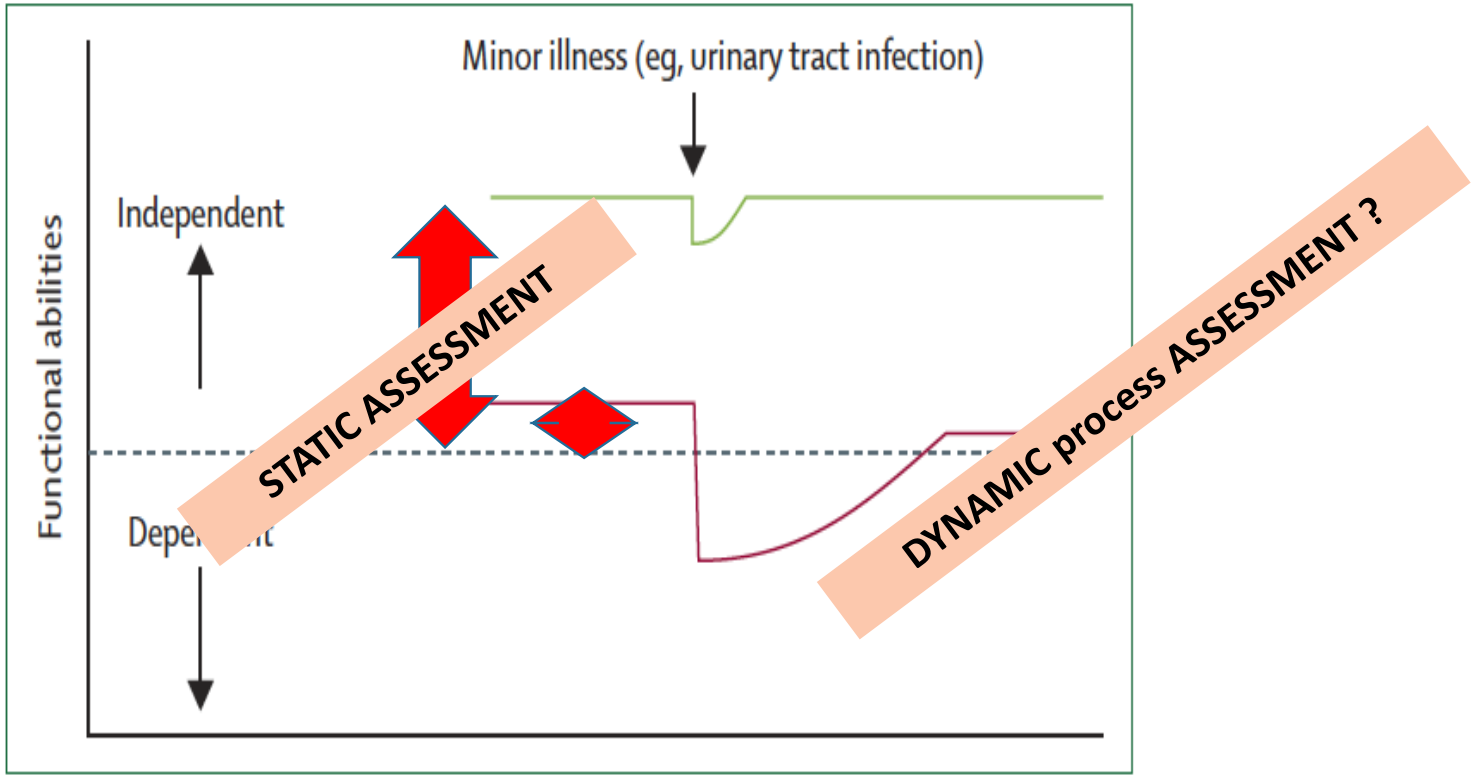

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Clegg A et al. *Lancet* 2013

Evaluer la résilience

Frailty screening methods for predicting outcome of a comprehensive geriatric assessment in elderly patients with cancer: a systematic review

Marije E Hamaker, Judith M Jonker, Sophia E de Rooij, Alinda G Vos, Carolien H Smorenburg, Barbara C van Munster

THE LANCET Oncology

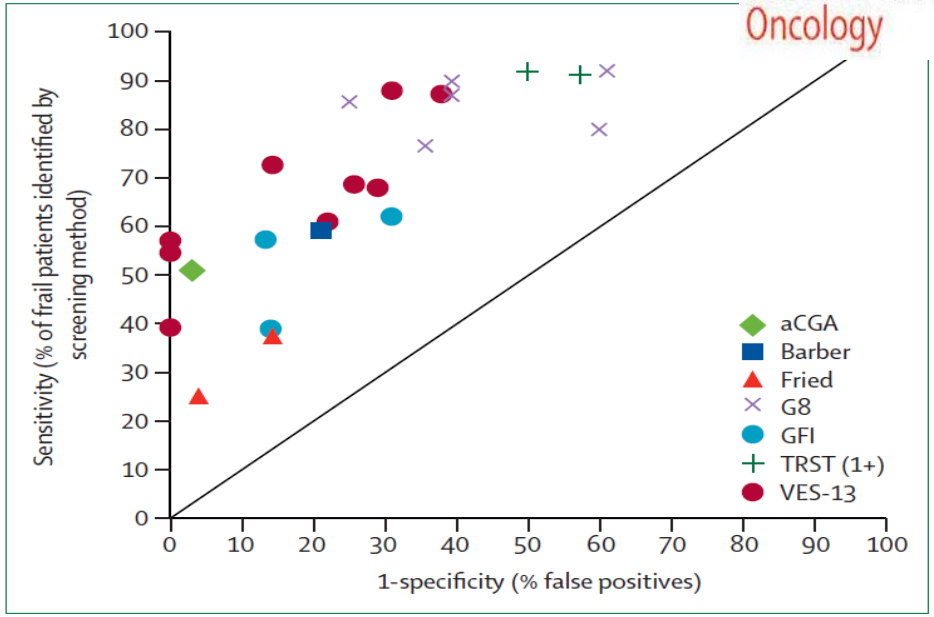


Figure 2: Sensitivity and 1-specificity of screening methods for predicting outcome of comprehensive geriatric assessment

Incorporating Biomarkers of Frailty and Senescence in Cancer Therapeutic Trials

Joleen M. Hubbard and Aminah Jatoi

Department of Medical Oncology, Mayo Clinic, Rochester, Minnesota.

Journals of Gerontology: BIOLOGICAL SCIENCES, 2015, 722–728

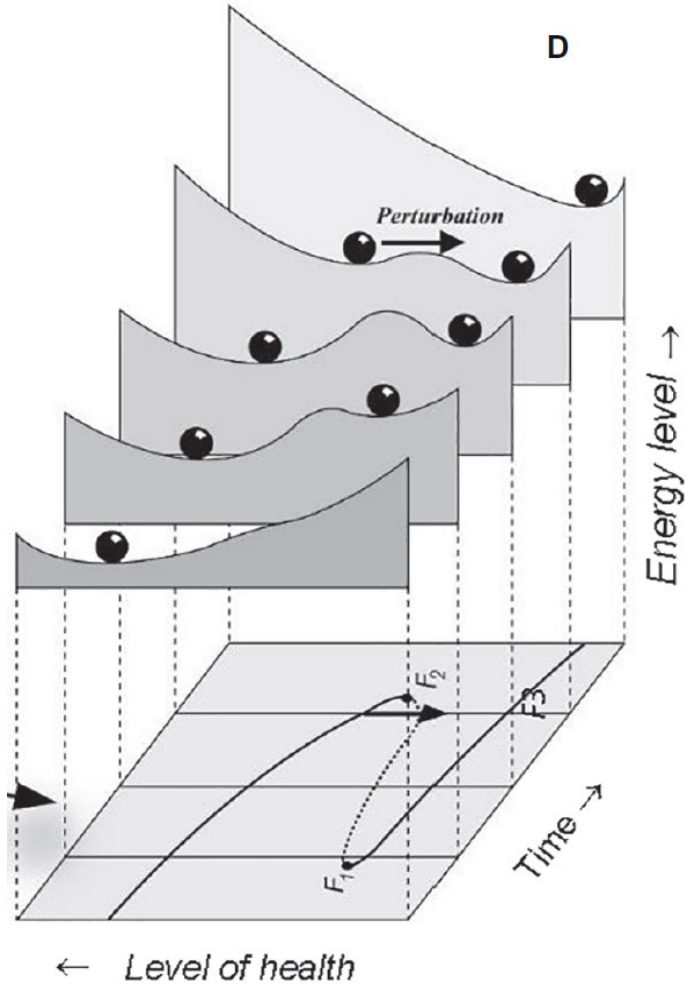
"…Les oncologues sont confrontés au dilemme de savoir comment identifier efficacement les personnes fragiles qui peuvent avoir plus de difficultés à tolérer et à se rétablir d'un traitement systémique contre le cancer. »

« Les mesures statiques de la fragilité n'ont qu'une valeur prédictive limitée pour les complications, les événements indésirables et la mortalité, et une faible valeur prédictive pour le potentiel de guérison et les résultats bénéfiques ».

Evaluer la résilience

Rerouting Geriatric Medicine by Complementing Static Frailty Measures With Dynamic Resilience Indicators of Recovery Potential

	Measures of resilience	Measures of frailty
Static: list of items questioned or observed	Predict positive outcomes (recovery). Currently, 6 psychological resilience scales are in use (e.g., Conner-Davidson resilience questionnaire)	Predict negative outcomes, e.g., mortality. More than 50 static frailty scales are currently available (e.g., Fraily index or Fraily phenotype)
Dynamic: monitoring stimulus-response over time	Dynamic measures of resilience are not yet available: the hypothesis to develop and validate these is proposed here (e.g., response of blood pressure on orthostatic response over time)	Dynamic measurements of frailty are not available



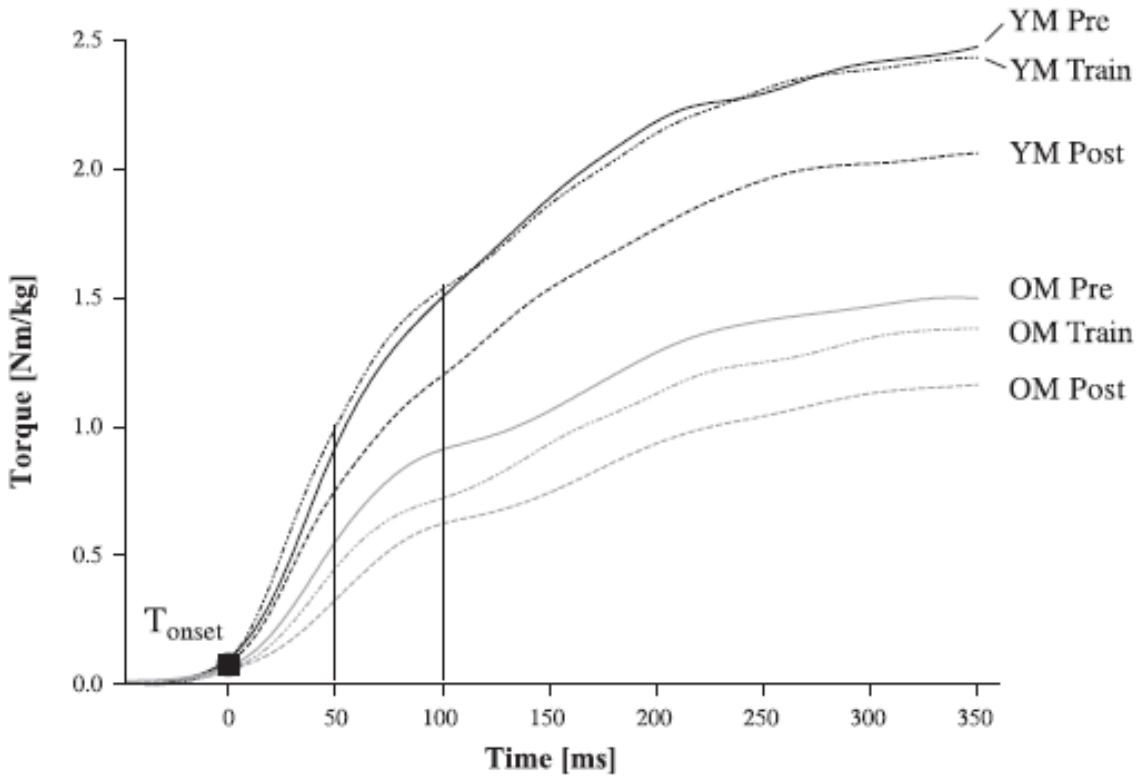
Olde Rikkert M and Melis R, Frontiers in Physiology 2019

Evaluer la résilience

Effect of 2 weeks of immobilization Then 4 weeks of re-training on the quadriceps force

9 elderly subjects (OM: 67.3 years)
11 young subjects (YM: 24.4 years old)
Same level of physical activity

Effects of aging on muscle mechanical function and muscle fiber morphology during short-term immobilization and subsequent retraining.



Hvid et al. *J Appl Physio* 2010

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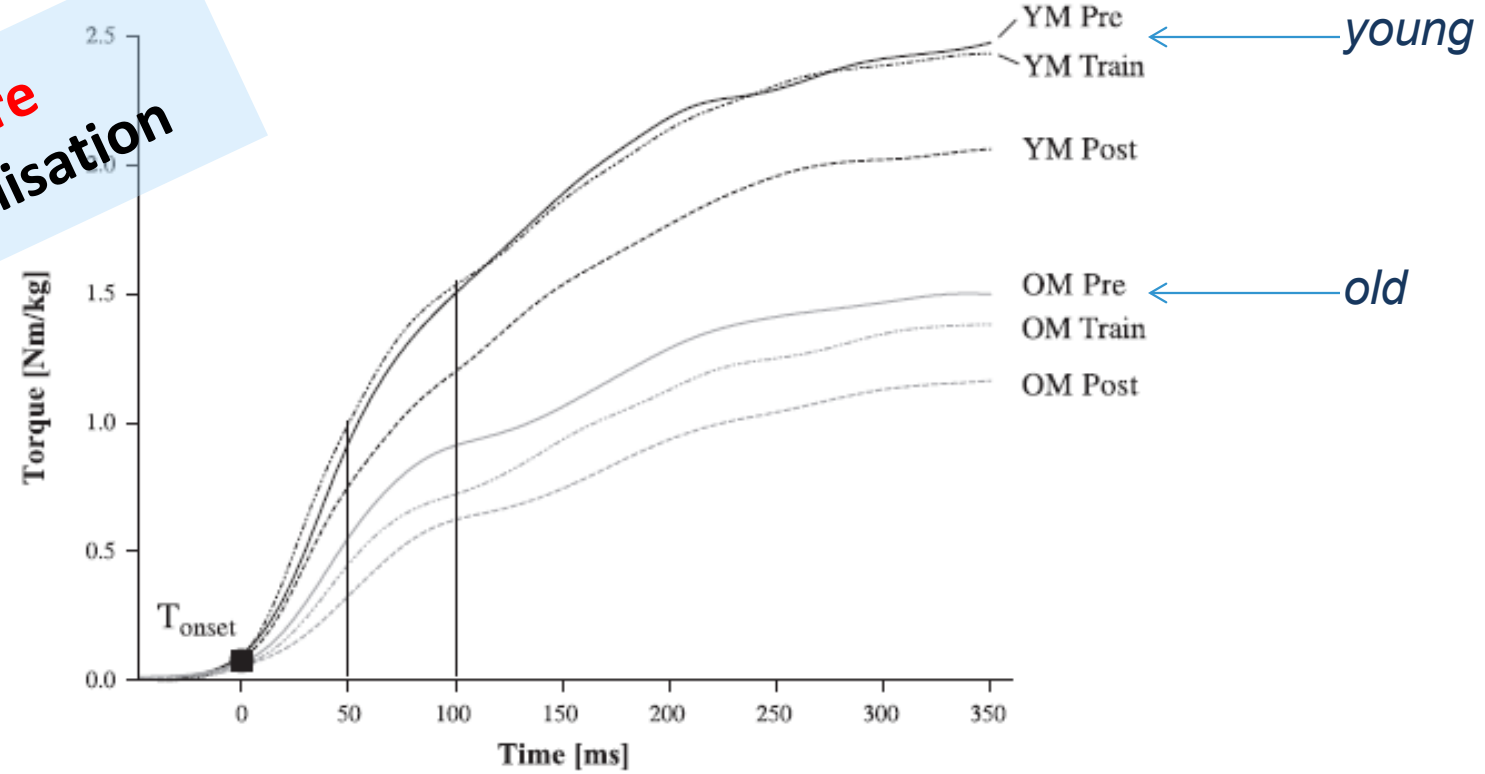
Before immobilisation



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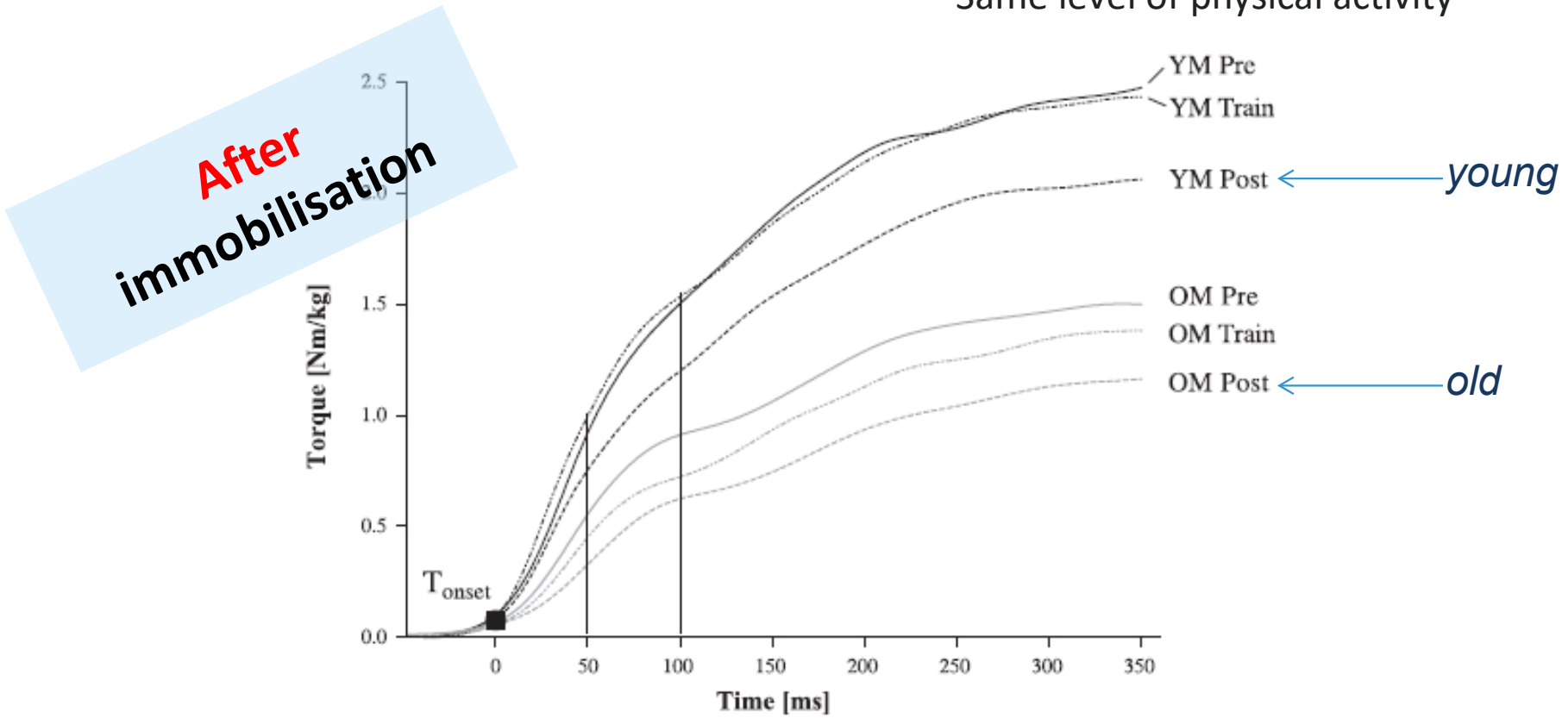

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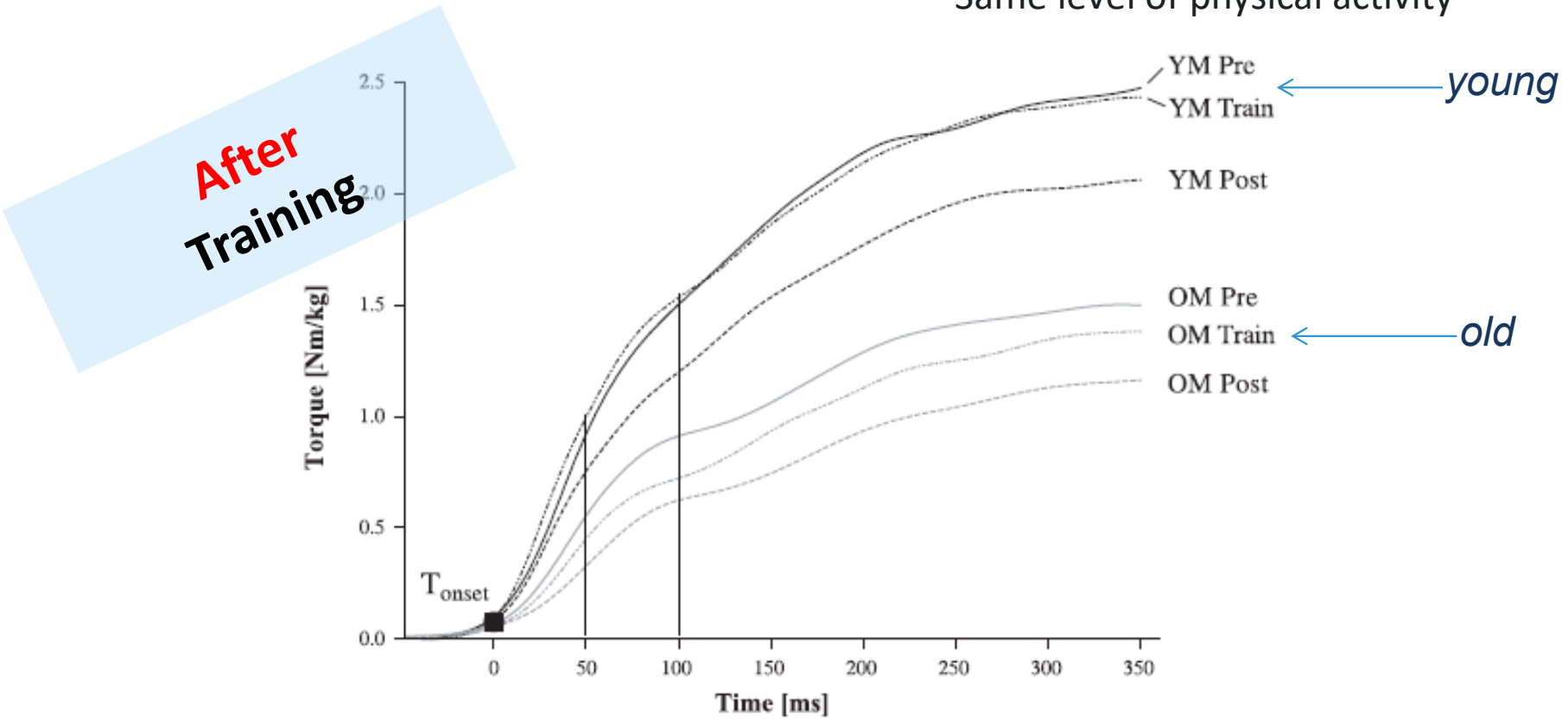
Effect of 2 weeks of immobilization Then 4 weeks of re-training on the quadriceps force

9 elderly subjects (OM: 67.3 years)
11 young subjects (YM: 24.4 years old)
Same level of physical activity

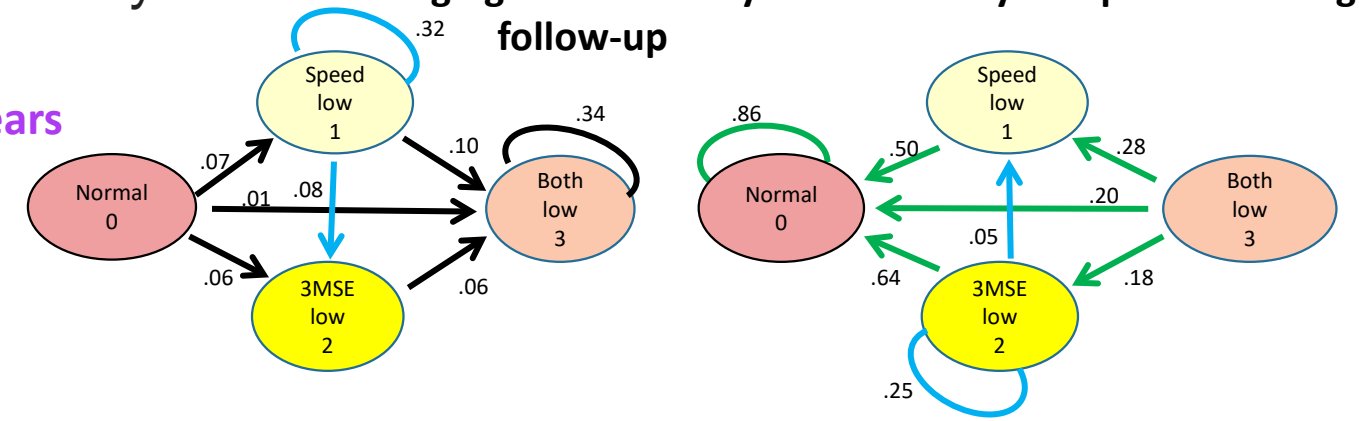


Hvid et al. *J Appl Physio* 2010

Evaluer la résilience

Reversible States of Physical and/or Cognitive Dysfunction: A 9-Year Longitudinal Study. New Mexico Aging Process Study - 598 Healthy independent-living adults, 9 years follow-up

60 ≤ age ≤ 78 years



Qualls C et al. J Nutr Health Aging. 2017

Transitions to improved function decreased with **age,** APOE4 status, BMI, and health status
Transitions to worse function increased with **age,** APOE4 status, BMI, and health status .

Evaluer la résilience

Reversible States of Physical and/or Cognitive Dysfunction:
A 9-Year Longitudinal Study. New Mexico Aging Process Study - 598 Healthy independent-living adults, 9 years follow-up

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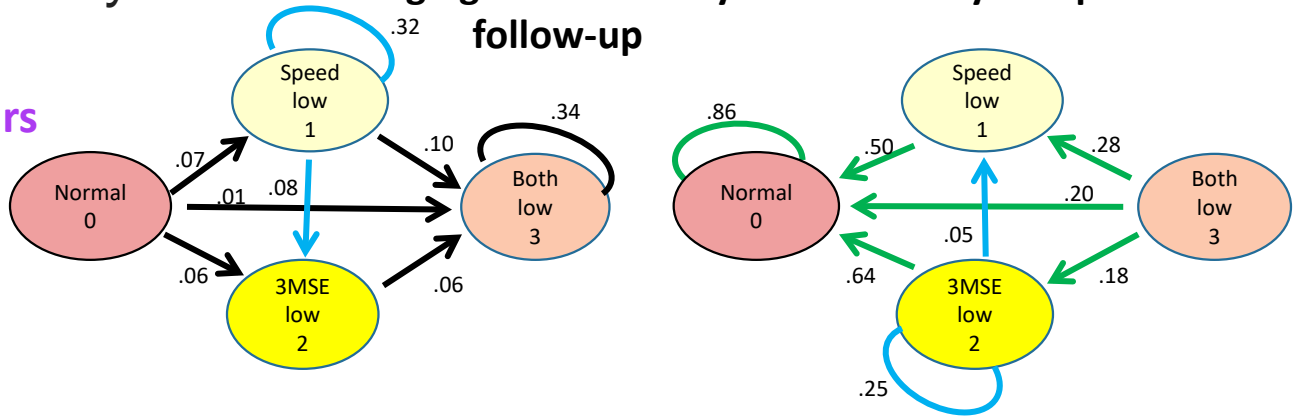
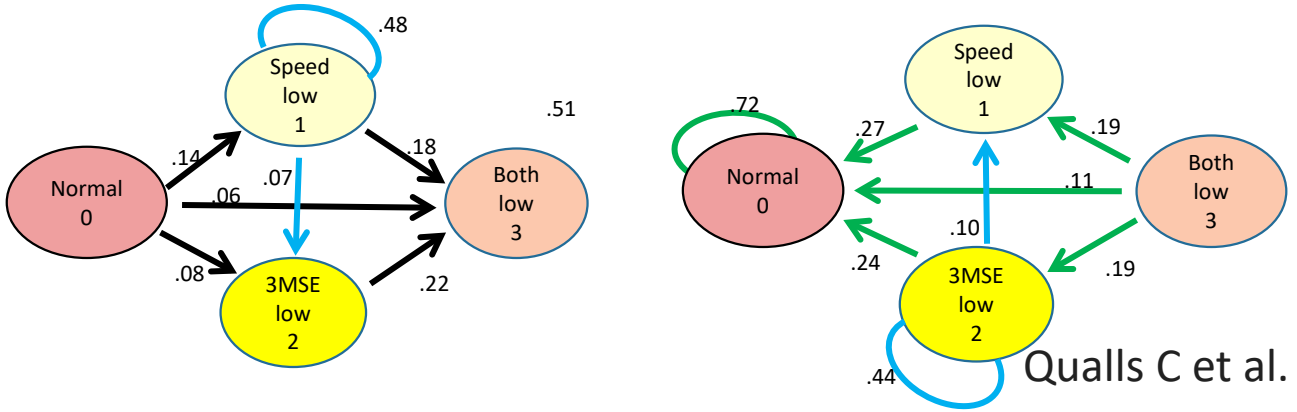


Older 78 +



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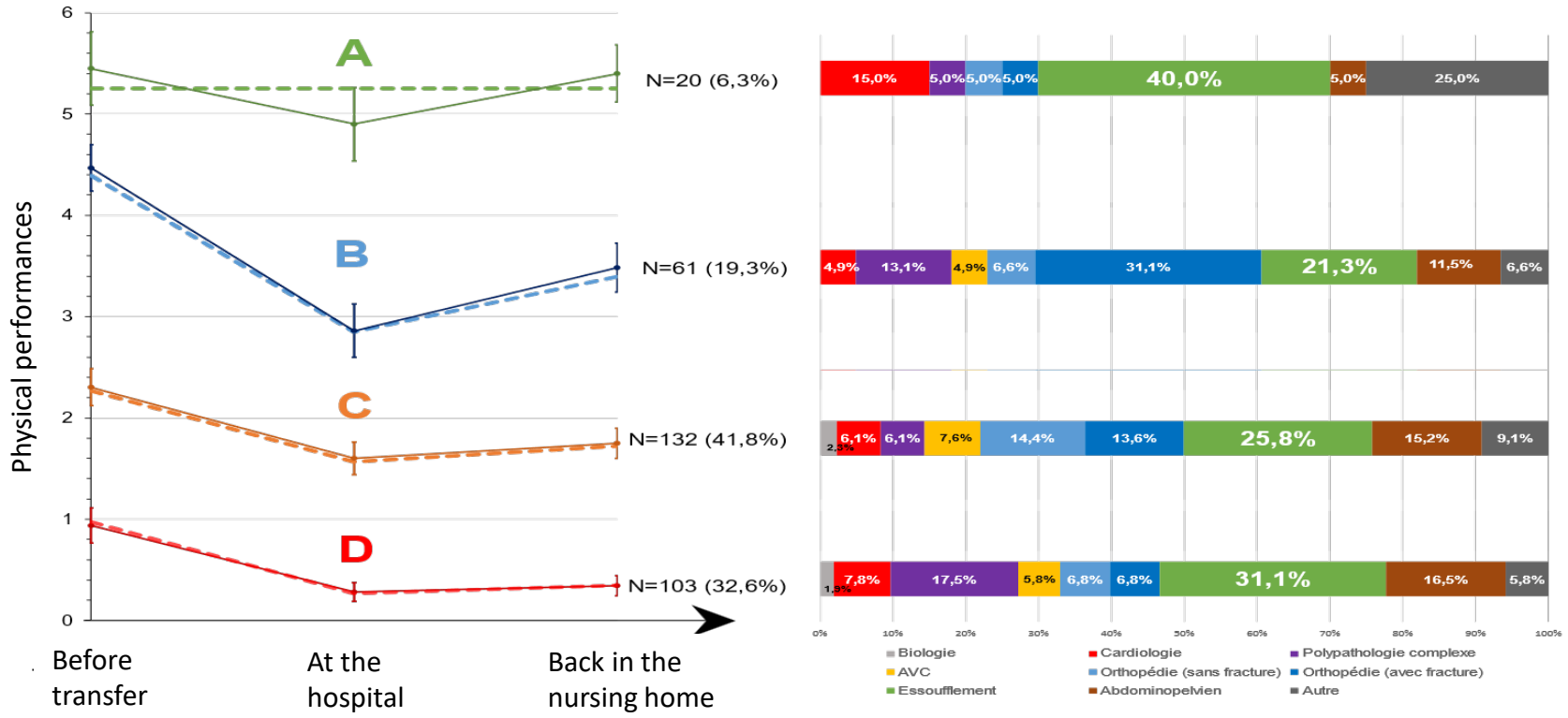
Evaluer la résilience

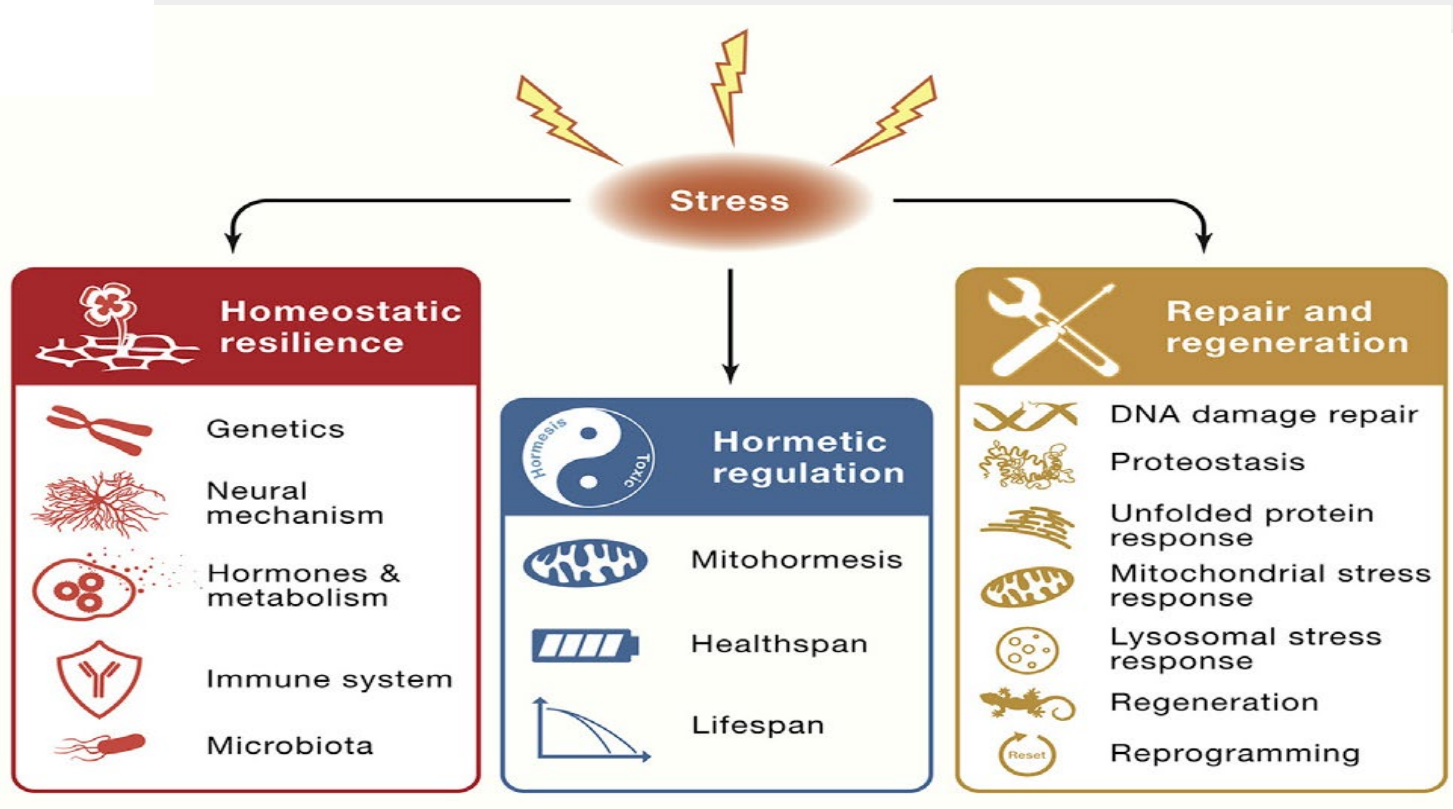
Nursing Home Residents' Functional Trajectories

1037 NHRs transfered to 17 Emergency Departments



Guion V, De Souto Barreto P, Rolland Y
J Am Med Dir Assoc 2021

Evaluer la résilience

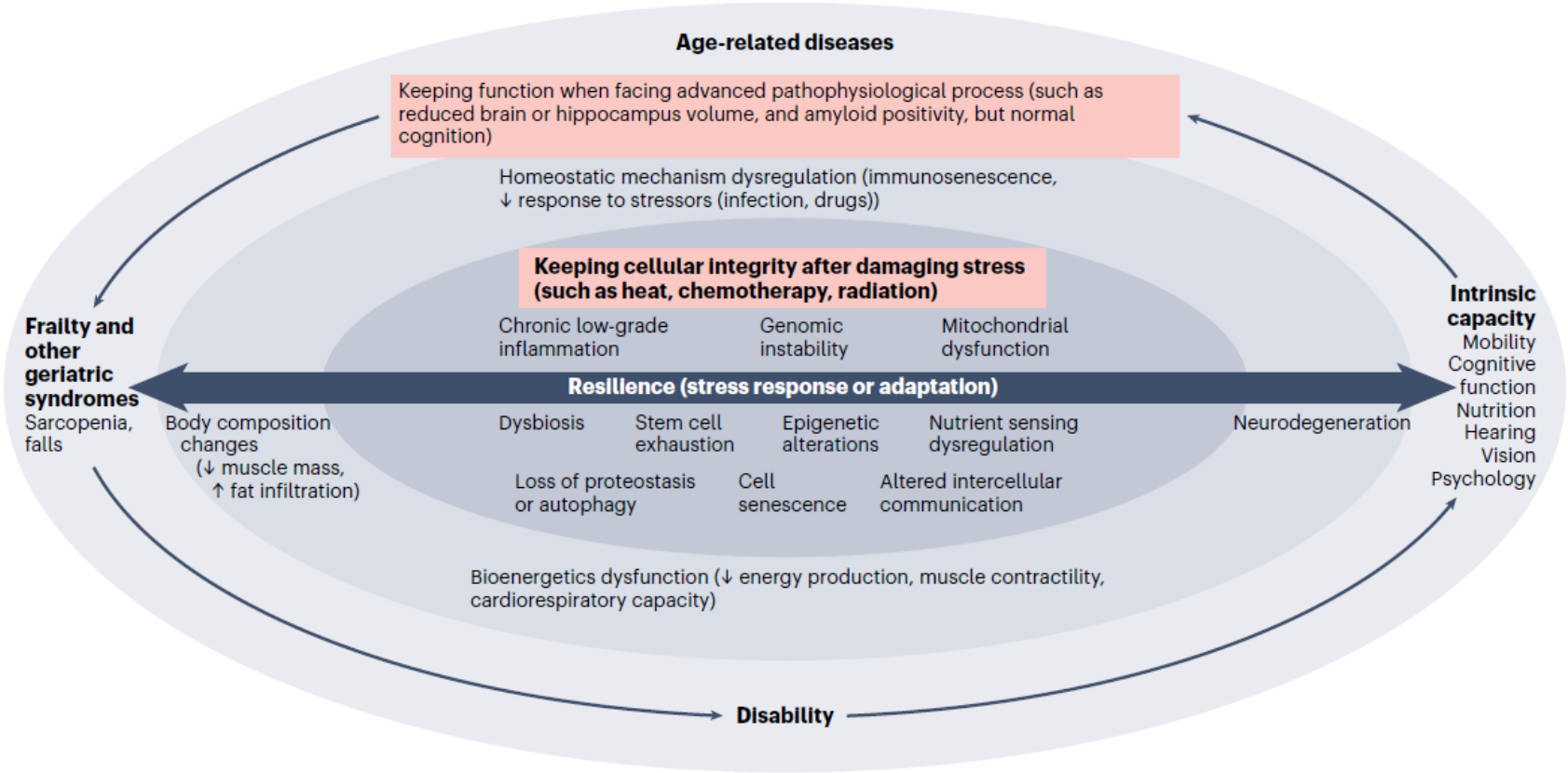


Carlos Lopez-Otın and Guido Kroemer, Hallmarks of health, ***Cells*** 2021

Loss of resilience occurs **much earlier than clinical signs of frailty**
Biological tests might **predict future health** ?
Geroprotective interventions that target hallmarck of aging could modulate resilience

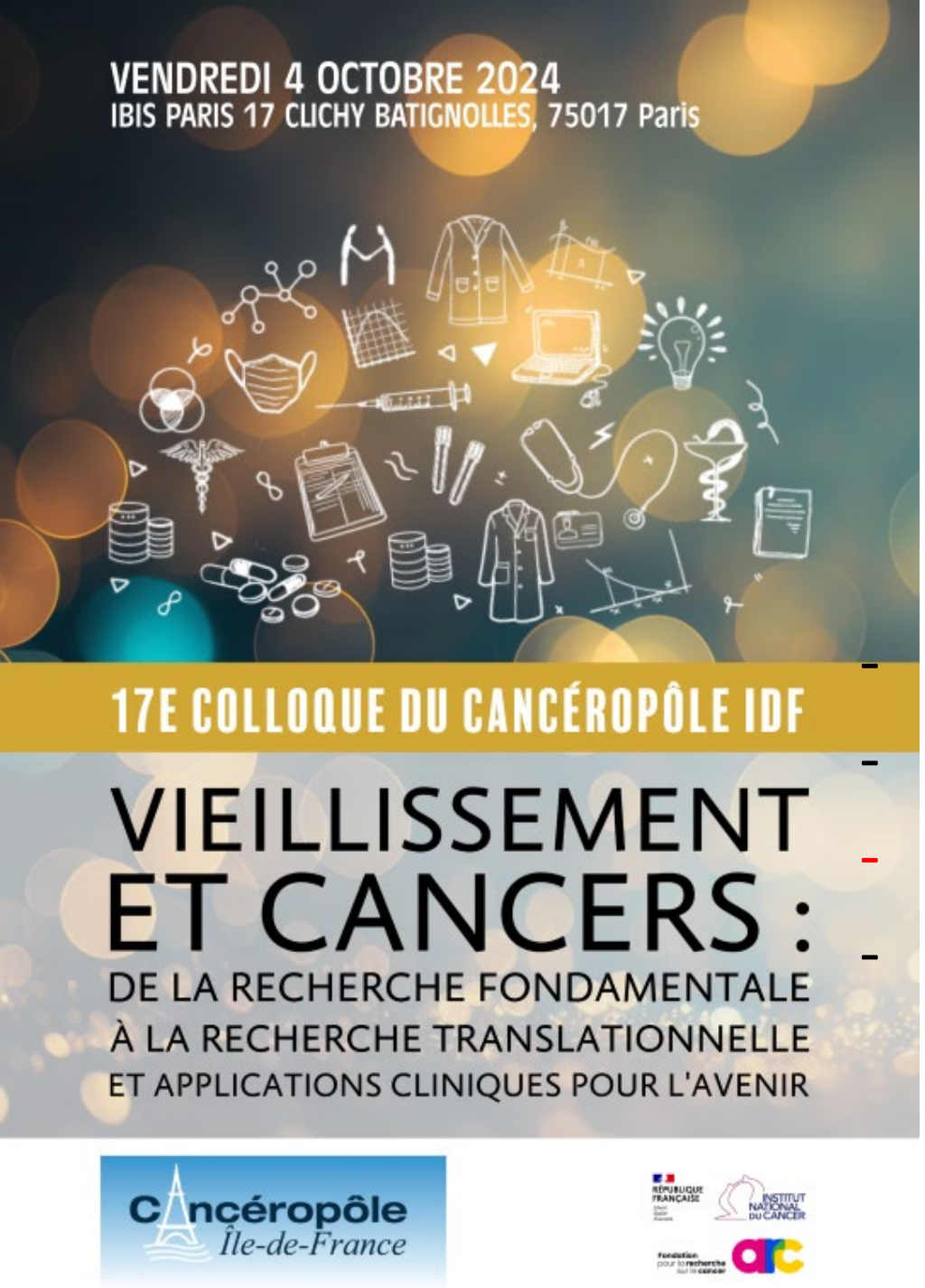
Evaluer la résilience

Looking at frailty and intrinsic capacity through a geroscience lens: the ICFSR & Geroscience Task Force



nature aging

Philipe de Souto Barreto[1,2,3] ✉, Yves Rolland[1,2,3], Luigi Ferrucci[4], Hidenori Arai[5], Heike Bischoff-Ferrari[1,6], Gustavo Duque[7], Roger A. Fielding[8], John R. Beard[9], John Muscedere[10], Felipe Sierra[11], Bruno Vellas[1,2,3] & Nathan K. LeBrasseur[12,13]



Fragilité

de la clinique à la Géroscience

Agenda

- Du concept de fragilité à la Capacité Intrinsèque
- Evaluer la résilience
- La Géroscience – L'expérience de l'IHU HealthAge
- Perspective thérapeutique

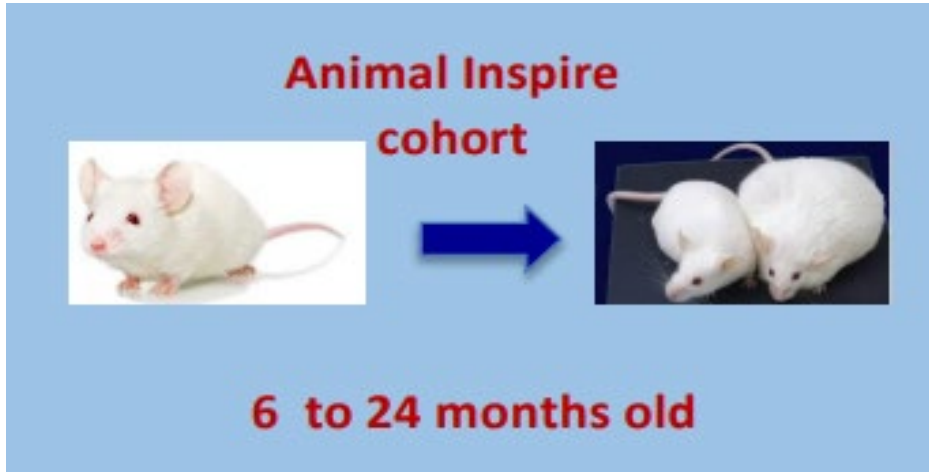
IHU HealthAge
GEROSCIENCE & PREVENTION

Organisation mondiale de la Santé

La Géroscience – L'expérience de l'IHU HealthAge

A unique « mirror » Animal and Human cohort

Angelo PARINI/ Yohan Santin

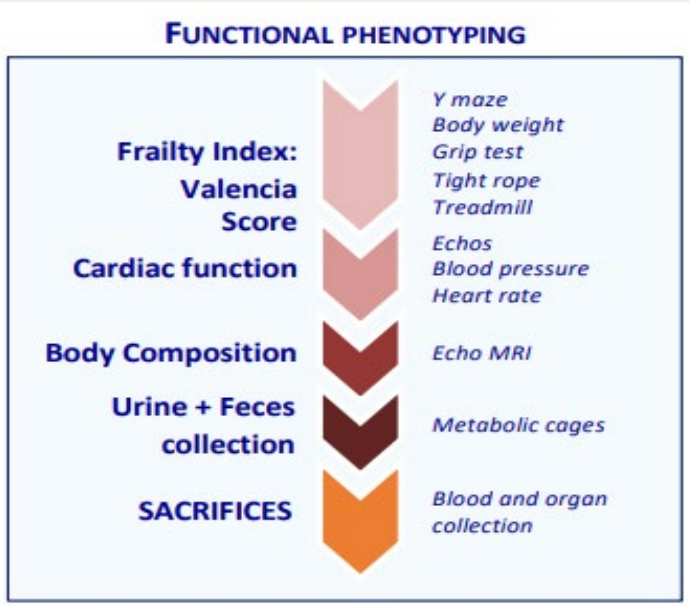


(health status and chronological age)

Normalization and optimization of clinical and biological parameters

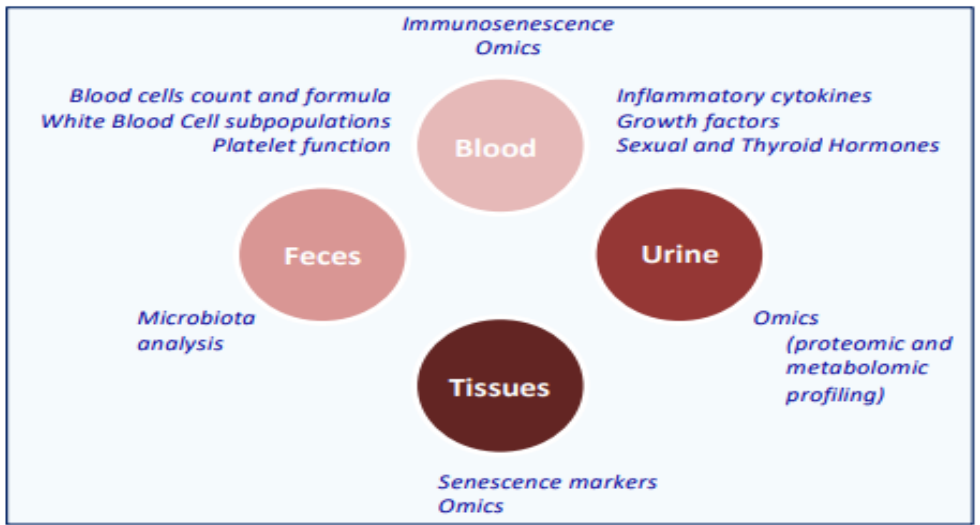
Common dataset with equivalent clinical tests (eg, cognitive function, mobility), and biological tests

New techniques/technologies *(eg, lymphocytes' profiling, imaging..)*



1 568 Swiss Mices

- Functional phenotyping: 120 000 data points
- Spontaneous/voluntary mobility: Between 97 millions and 388 millions of points/2 years

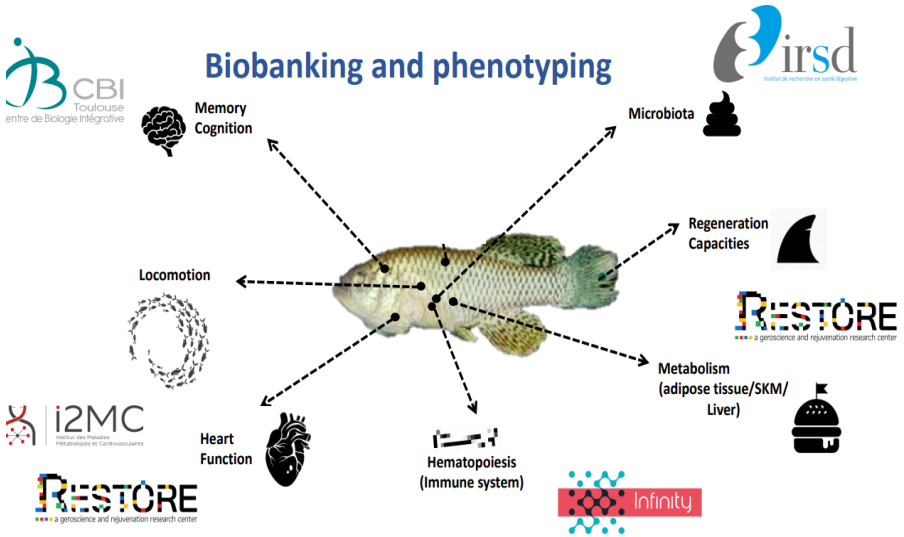


La Géroscience – L'expérience de l'IHU HealthAge

A unique « mirror » Animal and Human cohort

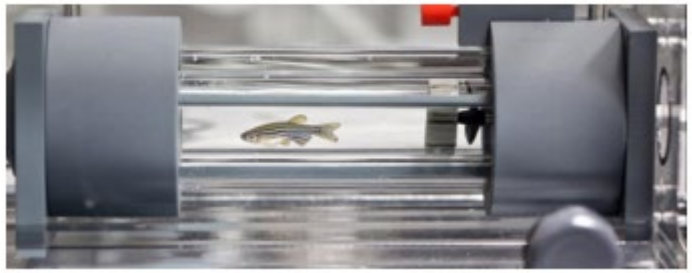
Cohort of Nothobranchius (Killifish)

C Dray, JP Pradère, P Valet

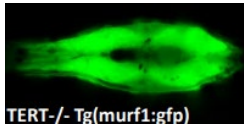


Mobility

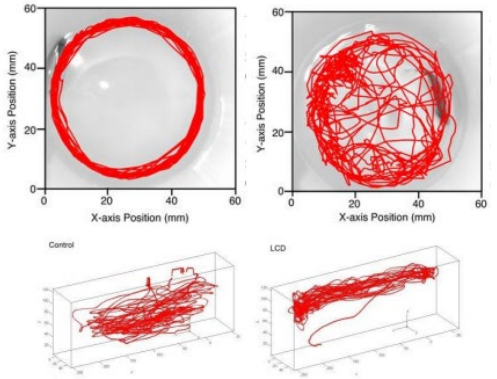
Forced activity+ Gasometry



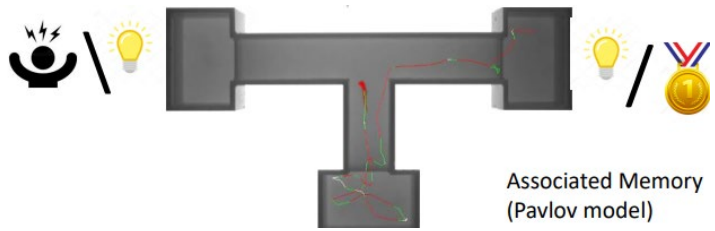
sarcofish (atrophy-related gene)



Behavior



Cognition



La Géroscience – L'expérience de l'IHU HealthAge

A unique « mirror » Animal and Human cohort

The INSPIRE Translational Human cohort

Research objectives

- **To recruit 1000 individuals of several chronological ages (from 20y with no upper limit of age) and functional capacity levels (from robust to frail), with baseline and follow-up biological, clinical, imaging and digital data over 10 years**
- **To explore and identify a set of biomarkers of aging, age-related diseases and IC evolution**

Study Population

1000 individuals in Toulouse area

- **Inclusion criteria**
  - Aged 20 years-old or over; both sexes
  - Affiliated to a social security scheme

- **Exclusion** of people having
  - Severe disease compromising life expectancy at 5 years (or at 2 years for frail elderly subjects and subjects aged 80 years-old or over)

La Géroscience – L'expérience de l'IHU HealthAge

A unique « mirror » Animal and Human cohort

The INSPIRE Translational Human cohort 10 years folllow-up

Clinical assessment

	Before inclusion	Inclusion	Each 4-month the first year; then every 6-month	Yearly Visits	Biannual visits
ICOPE Monitor App (IC domains)		✓	✓	✓	
Functional status (ADL, IADL)		✓		✓	
Cognitive status (MMSE, cognitive composite score for people < 70 y)		✓		✓	
Physical performance (SPPB, Chaire rise test (30 sec))		✓		✓	
Depressive symptoms (PHQ-9)		✓		✓	
Nutritional status (MNA, food frequency)		✓		✓	
Oral status (OHAT)		✓		✓	
Participant-reported outcomes for cognition (CFI) and mobility, fatigue and social isolation (PROMIS)		✓		✓	
Objective physical activity and sleep parameters (activPAL accelerometer)		✓		✓	
Vision assessment (WHO simple eye chart, Amsler grid)		✓		✓	
Adverse events (new diagnosis, SARS COV-2 diagnosis, influenza, fracture)		✓	✓	✓	

Large Bio-banking

	T0	Each year	Every 2 years	Nb theoretical subjects	Nb theoretical aliquot or sample /subjet	Freq	Total theoretical aliquot
Blood (PBMC)	X	X		1,000	20 -26 (0,5 ml) 2 (1 ml)	10	250 000
Urine	X	X		1,000	20	10	200 000
Saliva	X	X		1,000	10	10	100 000
Dental plaque	X	X		1,000	4	10	40 000
Nasopharyngeal swabs			X	400	2	5	-
Skin samples (swabbing, delamination)			X	500	4	5	10 000
Optional							
Skin biopsy	X		X	120	-	2	240
Cells	X		X	180	-	2	360
Feces	X		X	300	-	5	1500
Hair bulb	X		X	300	-	2	600
							602 700

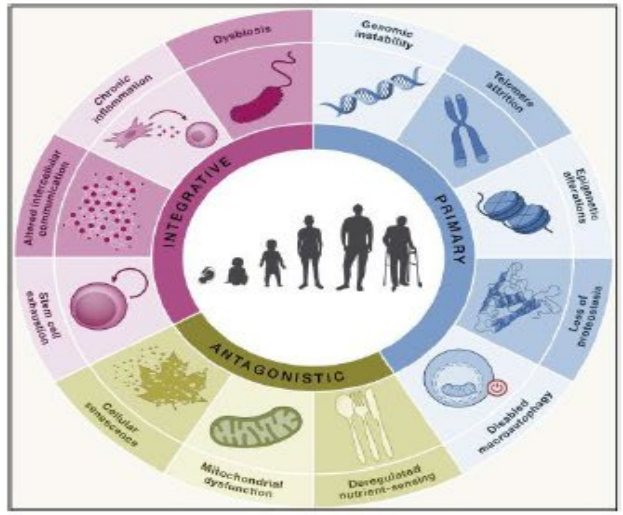
La Géroscience – L'expérience de l'IHU HealthAge

INSPIRE-T aging biology comprehensive phenotyping: Open Science

DONE

Epigenetic alterations
DNA methylation aging clocks
(Horvath, Hannum, Levine, GrimAge)

Chronic inflammation
Inflammatory aging
clock iAge



IN PROGRESS

Mitochondrial dysfunction
Mitochondrial
bioenergetics/metabolism (SCENITH)

Cellular senescence
SAPS biomarkers

Epigenomics
Metabolomics

Genomics
Transcriptomics
Proteomics

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IHU HealthAge
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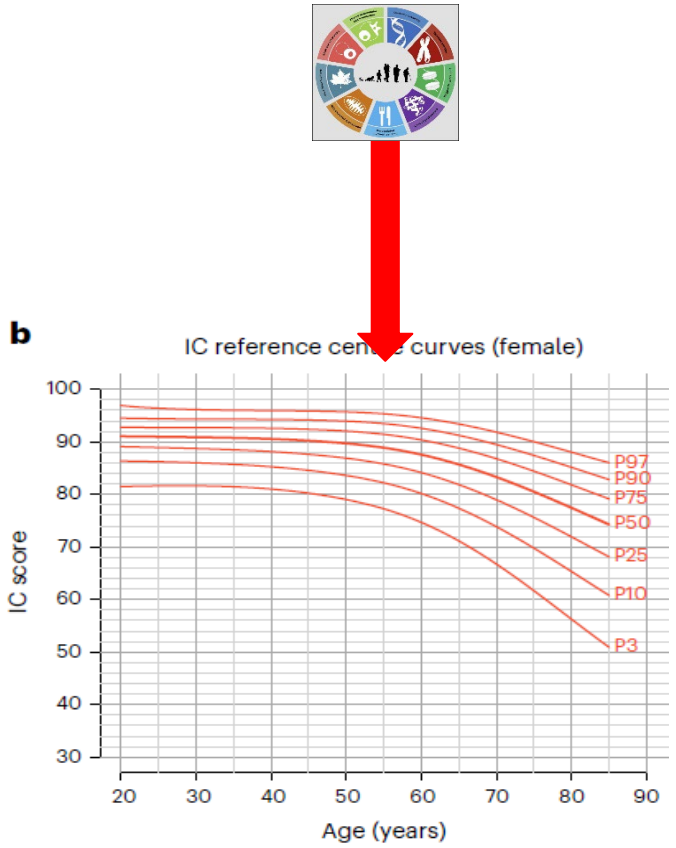
Perspectives thérapeutiques

Prévenir le déclin de patients à risque



Prévention dans des situations à haut risque

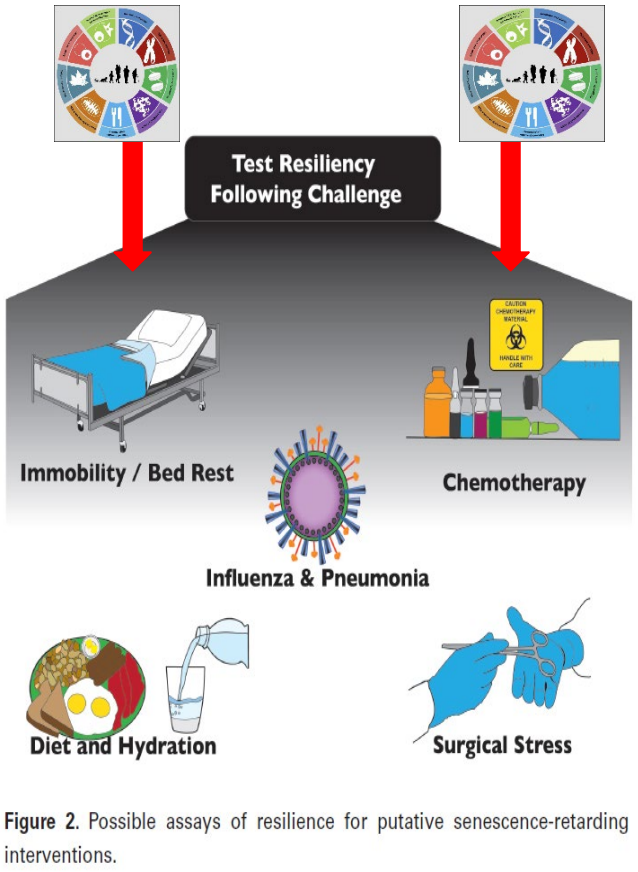
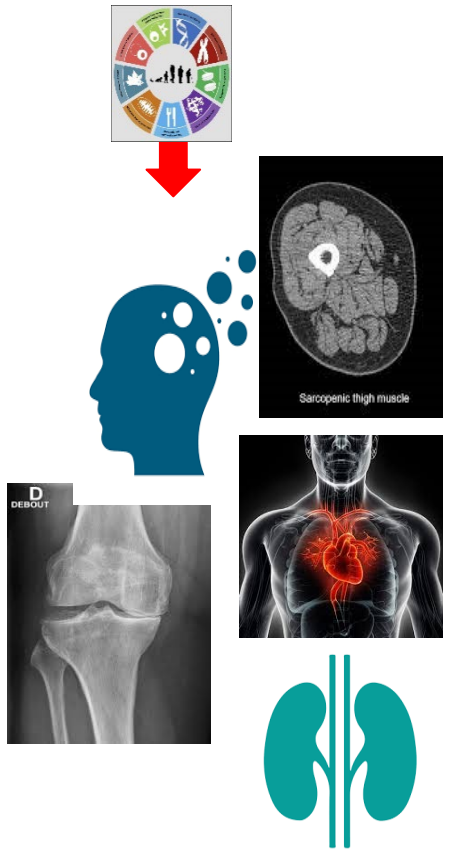


Figure 2. Possible assays of resilience for putative senescence-retarding interventions.

Traitement de conditions somatiques

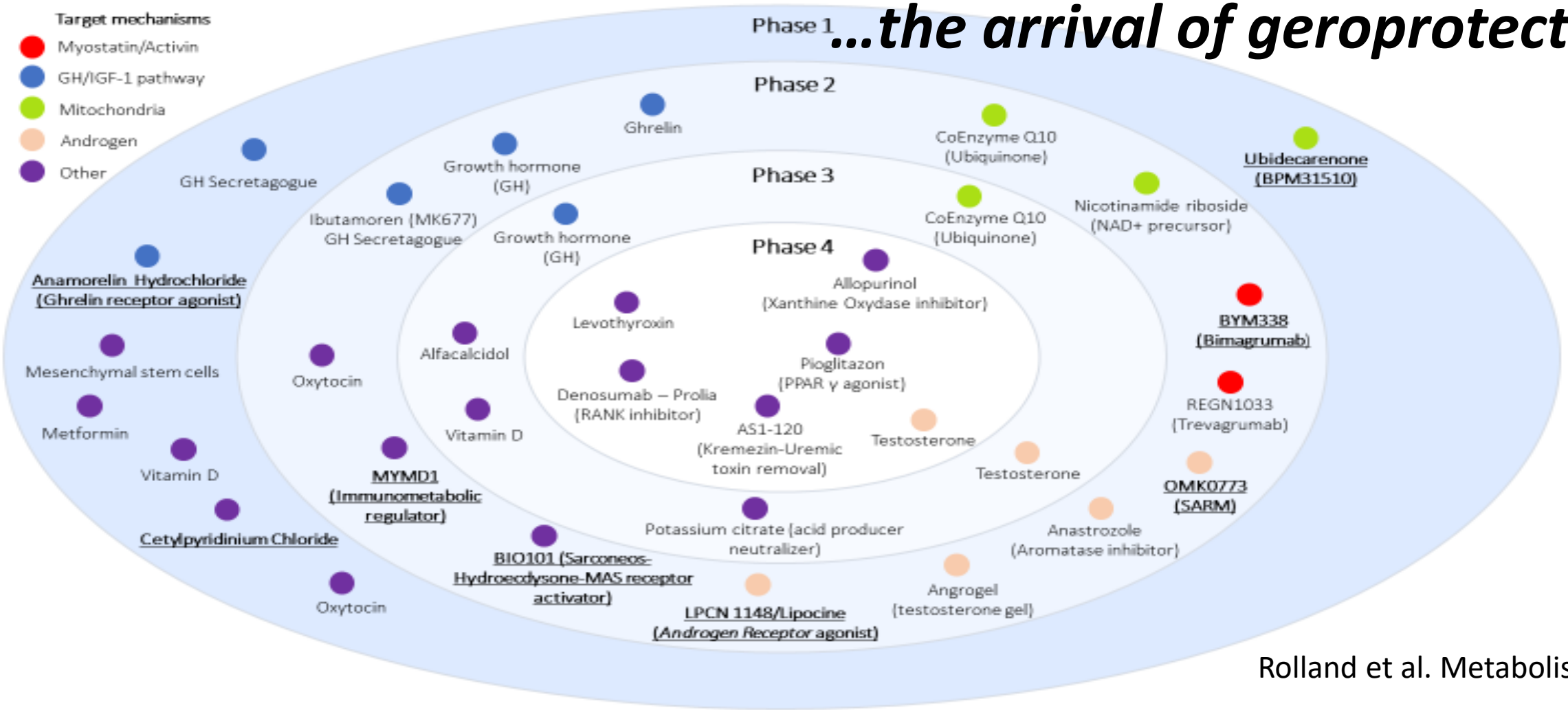


Rolland et al. Nature comunication, 2023
Ferrucci L et al. J Endocrinol Invest 2002;25:10-5
Singh M et al. Mayo Clin Proc 2008;83:1146-53
Derek M. Huffman et al. J Gerontol A Biol Sci Med Sci, 2016

Perspectives thérapeutiques

Example of the potential new drugs for sarcopenia *(Clinicaltrial.gov – March 2023)*

…the arrival of geroprotectors



Rolland et al. Metabolism 2023

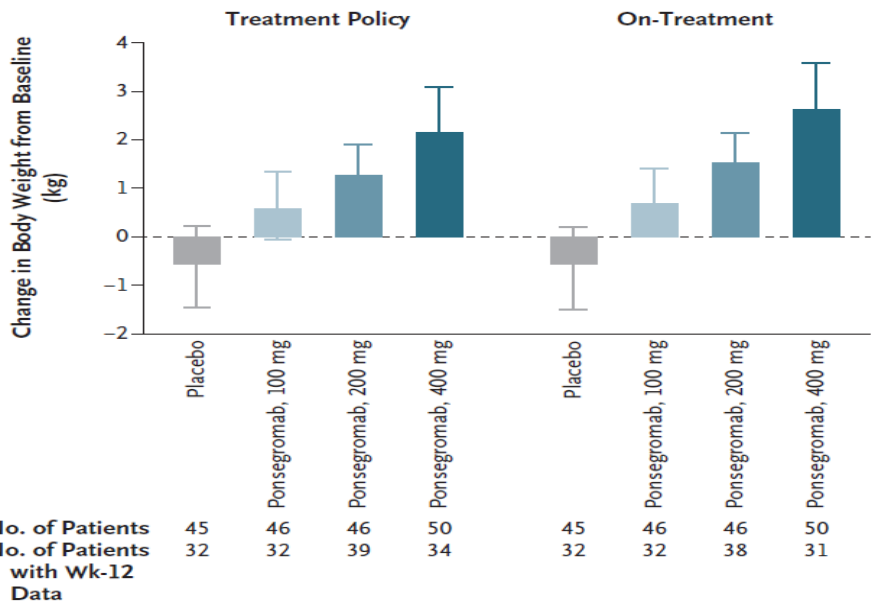
Perspectives thérapeutiques

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ponsegromab for the Treatment of Cancer Cachexia

John D. Groarke, M.B., B.Ch., M.P.H., Jeffrey Crawford, M.D.,



A humanized monoclonal antibody inhibiting GDF-15

Among patients with cancer cachexia and elevated GDF-15 levels, the inhibition of GDF-15 resulted in increased **weight gain** and overall **activity level** and reduced cachexia **symptoms**