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PRECISION MEDICINE AND TARGETED THERAPIES:
REALITIES AND PERSPECTIVES

Precision medicine
Standardised geriatric evaluation

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Notes are linked to the references page.

All practitioners have encountered the following scenario: two 85-year-old women, with the same pathology, undergo the same surgery; one recovers rapidly and returns home without assistance, the other develops complications with confusion, multiple falls, pneumonia and, finally, loss of autonomy and nursing home placement. What kind of information would have helped to distinguish these two patients prior to surgery? Would it have been possible to improve the outcome of the second patient?

FOR THE SAME CHRONOLOGICAL AGE, THE ELDERLY ARE VERY DIFFERENT

Longitudinal studies have shown that there is extreme heterogeneity among elderly persons and that chronological age is absolutely not a predictor of physiological age.

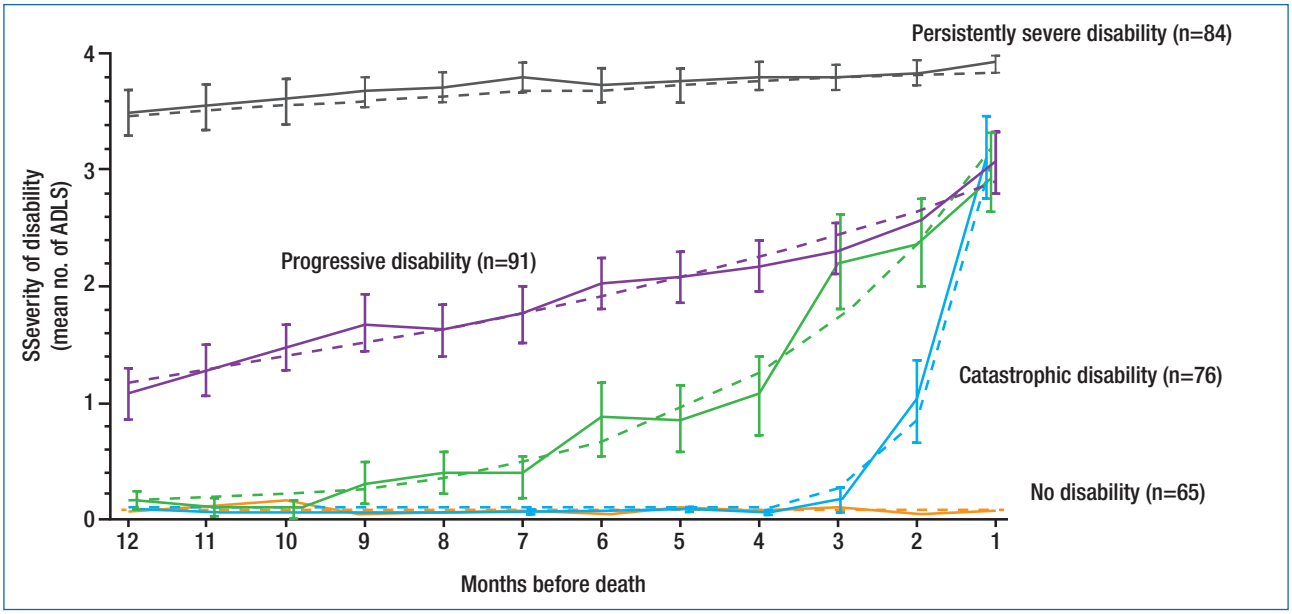
Disability-free life expectancy

Currently in France, a man can expect to live to 79 years, but he will start to develop disabilities from the age of 63 years and will therefore live with them for the next 16 years. Women have a life expectancy of 85 years but will live with disabilities for 20 years or so [1]. All the work of the geriatrician focuses on compressing this period of life with disabilities as much as possible.

Trajectories of disability can be predicted

A study published in 2010 attempted to predict trajectories of disability [2]. Five distinct trajectories were identified in the last year of life: no disability, catastrophic disability, accelerated disability, progressive disability and persistently severe disability (Figure 1). On average, one year before death, three groups of subjects – those with no disability, catastrophic disability and accelerated disability (which together accounted for half of all decedents) – were largely free of disability. Subjects with progressive disability had mild disability and those with persistently severe disability had severe disability. The trajectories of the groups with accelerated disability and catastrophic disability diverged from the trajectory of the group with no disability at about 10 and 3 months before death, respectively. The severity of disability in the progressive disability group gradually increased over the year. For each trajectory, the predicted values of the severity of disability did not differ from the observed values, with only one exception (month 3 in the accelerated disability group).

Figure 1. Trajectories of disability in the last year of life among 383 decedents [2]



The severity of disability is indicated by the mean number of activities of daily living (ADLs) in which subjects had disability. Solid lines indicate the observed trajectories and dashed lines indicate the predicted trajectories.

STANDARDISED GERIATRIC EVALUATION

An article published in 1984 by Larry Rubinstein and colleagues constitutes one of the pillars of modern geriatrics [3]. In this study, elderly patients with loss of autonomy and a high probability of nursing home placement were randomly assigned to a geriatric evaluation unit designed to improve diagnostic assessment, therapeutic management and rehabilitation (experimental group, n=63; control group, n=60). Patients assigned to the geriatric unit underwent a 'standardised geriatric evaluation' (SGE), comprising an assessment of psychosocial status, functional autonomy, and cognitive and nutritional status, the results of which were used to develop a specific treatment plan.

At one year, patients in the geriatric unit had much lower mortality than controls (23.8% vs. 48.3%, P<0.005) and were less likely to have been discharged to a nursing home (12.7% vs. 30.0%, P<0.05) or to have spent time in a nursing home during the follow-up period (26.9% vs. 46.7%, P<0.05). Patients in the control group had substantially more acute care hospital days, nursing home days and hospital readmissions. Patients in the geriatric unit were significantly more likely to have an improvement in functional status and morale than controls (P<0.05).

Rubenstein et al. defined SGE as 'a multidisciplinary approach to assess functional and psychosocial status while taking into account associated pathologies, thus making it possible to identify the specific needs of the most frail individuals and to propose an appropriate treatment and follow-up plan' [3].

There is a large body of work showing that SGE is effective and can recognise the heterogeneity of elderly subjects, independently of chronological age. It distinguishes the 'robust' 80–85-year-old subject who can benefit from the same therapeutic management as a person in their fifties, from the elderly person whose frailty is not readily apparent but who, in response to a stressor event, can decompensate and glide towards dependency. This frail person is the geriatrician's target of interest because frailty is a dynamic phase that can lead to dependency, but is also reversible if it is identified and managed properly [4].

THEORETICAL AND OPERATIONAL DEFINITIONS OF FRAILTY

The detection of frailty is one of the major challenges of our aging societies. Frailty corresponds to a state of decreased physiological reserves and a loss of the capacity to respond to intrinsic or extrinsic stresses [5–8]. The declining ability to adapt to different life stressors increases the risk of adverse outcomes such as hospital readmission, falls, loss of autonomy, nursing home placement and mortality.

There is no consensus on the operational criteria by which to recognise frailty. Nonetheless, in 2001 Linda Fried proposed five criteria to define frailty: weight loss of 5% or greater per year, self-reported exhaustion, low physical activity (no physical activity or fewer than one or two walks per week), slow walking speed (difficulty walking 100 metres), and low grip strength [9]. Frailty was defined as the presence of at least three of these criteria and pre-frailty as the presence of two criteria.

Using these criteria, a study published in 2009 reported that in Europe, 15–20% of the population aged 65 years and older was classified as frail and 35–40% as pre-frail [10].

FRAILTY: A LITERATURE REVIEW

Frailty is certainly an unstable state, but above all it is a reversible state, which opens the way towards preventive strategies. A literature review published in the Lancet in 2013 states that it is important to think about the organisation of our healthcare systems, which are essentially based on the concept of disease, whereas frailty is not a disease but a clinical state [11].

Frailty and mortality

The impact of frailty on mortality has been widely documented. The Canadian Study of Health and Aging evaluated the 5-year mortality risk in 2305 diabetic subjects older than 70 years [12]. The study aimed to compare the relative prognostic impact of chronic disease, particularly diabetes, on mortality. In reality, the investigators were surprised to find that frailty was a stronger predictor of 5-year mortality than diabetes (hazard ratio (HR): 2.72 vs. 1.42, respectively).

This link between frailty and mortality was recently confirmed in a meta-analysis [13]. All the studies analysed suggested that a higher frailty index (FI) was significantly associated with a higher mortality risk (pooled HR per 0.01 FI increase 1.039, 95% confidence interval (CI) 1.033–1.044, P<0.001; pooled HR per 0.01 FI increase 1.282, 95% CI 1.258–1.307, P<0.001; pooled odd ratios (OR) per 0.01 FI increase 1.054, 95% CI 1.040–1.068, P<0.001; pooled OR per 0.01 FI increase 1.706, 95% CI 1.547–1.881, P<0.001).

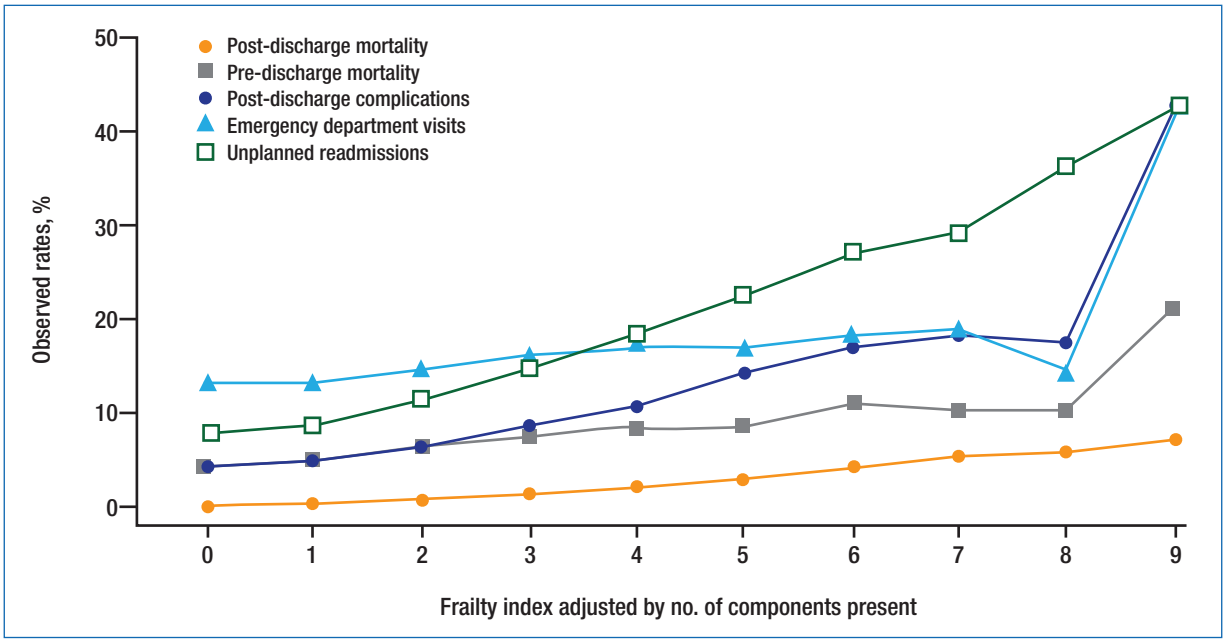
Frailty and surgery

A literature review published in 2016 compiled 23 studies evaluating frailty and postoperative mortality in subjects aged 75 years and older [14]. The results showed that regardless of the methods used to measure frailty, the strongest evidence in terms of the number of studies, consistency of results and study quality was for associations between frailty and increased mortality at 30 days, 90 days and one year, postoperative complications and length of stay. A small number of studies reported a significant association of frailty with discharge to institutional care, functional decline and lower quality of life after surgery.

These observations also hold true for ambulatory surgery and for surgeries considered to be better tolerated, such as transcatheter aortic valve implantation (TAVI). In a study published in 2017, frail individuals undergoing TAVI had a mortality rate of 34 deaths per 100 patient-years compared with 19 deaths per 100 patient-years in non-frail patients [15].

A Canadian team published a retrospective cohort study of adult patients who underwent surgery between 2007 and 2015 for orthopaedic, general and vascular conditions with a postoperative length of stay between 2 and 30 days [16]. The study sample included 236,957 surgical procedures. The frailty index was associated with readmission (OR 1.11, 95% CI 1.10–1.12). Unadjusted rates of 30-day readmissions (11.1%), post-discharge emergency department visits (14.4%), inhospital (5.9%) or post-discharge (6.3%) complications, and post-discharge mortality (0.8%) varied by frailty in a dose-dependent manner according to the number of individual frailty components (Figure 2).

Figure 2. Postoperative outcome at 30 days according to weight of the frailty components [17]



However, prevention strategies are possible. For instance, the same Canadian team recently published a study of the impact of a frailty screening initiative (FSI) on mortality and complications by comparing surgical outcomes in a cohort of 9153 patients treated before and after implementation of the FSI [17] in the JAMA. This initiative which began in 2011 provides for assessment of preoperative frailty in all patients scheduled to undergo surgery. Overall 30-day mortality decreased from 1.6% to 0.7% (P<0.001) after implementation of the FSI. Improvement was greatest among frail patients (mortality decreased from 12.2% to 3.8%, P<0.001) although mortality rates also decreased among robust patients (from 1.2% to 0.3%, P<0.001).

Frailty and cancer

In oncology, the results of studies assessing the impact of frailty on patient outcomes are also consistent for both solid tumours and haematological malignancies: frailty is a major independent pejorative factor, sometimes more important than the disease itself [18].

STANDARDISED GERIATRIC EVALUATION

Screening to be able to offer specific care plans

Many recent studies from different fields such as cardiology, lung diseases, endocrinology, rheumatology, surgery and intensive care highlight the fact that SGE, by detecting frailty, is an important step in individual risk stratification and prognosis assessment in specific situations.

Tools for detection of frailty

Simple and rapid screening tools are needed to identify subjects accurately who could most benefit from SGE. For example, oncologists use a seven-item frailty scale called G7 and refer the patient to geriatrics if the score is positive.

In a first step, the task of identifying frail patients could fall to general practitioners (GPs), but also nurses. Over the last several years we have developed a collaborative protocol at Toulouse University Hospital for geriatric evaluation performed by nurses. In a second step, the help of a geriatrician and a multidisciplinary team can be offered for a comprehensive evaluation.

Walking speed

The walking speed test is performed over a distance of 4 meters. A walking speed of more than 5 seconds (0.8 ms–1) is associated with an increased risk over 2–7 years of loss of autonomy/dependency (x4), cognitive decline and Alzheimer's disease (x3), mortality (x2), institutionalisation (x2) and hospitalisations (x1.5).

This test could therefore be useful to identify subjects rapidly who could benefit from SGE to detect frailty [19].

Toulouse questionnaire

The gerontopole frailty screening tool (GFST) was specifically designed for use by GPs but it can also be used by paramedical personnel, pharmacists, etc. With six questions, it allows simple and rapid identification of the main frailty criteria (Figure 3). When one or more signs of frailty are present, the GP is invited to express his/her clinical opinion on the frailty status of the individual. Only if the GP considers the patient frail can they be referred to a frailty clinic.

Figure 3. Gerontopole frailty screening tool

	Yes	No	Doesn't know
Does your patient live alone?	❒	❒	❒
Has your patient involuntarily lost weight in the last 3 months?	❒	❒	❒
Has your patient become more tired in the last 3 months?	❒	❒	❒
Has your patient experienced increased mobility difficulties in the last 3 months?	❒	❒	❒
Has your patient complained of memory problems?	❒	❒	❒
Does your patient present slowed walking speed (i.e. >4 seconds to walk 4 meters)?	❒	❒	❒
If you have answered YES to one or more of these questions: Do you think your patient is frail? If YES, is your patient willing to be assessed for frailty status at the day hospital? Screening date: …… Appointment scheduled for: …….. Primary physician informed: ❒ Yes ❒ No To make an appointment, please call 05.61.77.66.29	 ❒ ❒	 ❒ ❒	

The GFST was recently approved by the Haute Autorité de Santé as a national tool for frailty screening in individuals aged 65 years and older. A self-reported screening tool for community-dwelling older persons with frailty (FiND questionnaire) has also been validated recently.

TAKING FRAILTY INTO ACCOUNT WHEN ESTIMATING THE EXPECTED BENEFIT OF A TREATMENT

The SGE allows the identification of the specific needs of the most frail subjects so as to be able to propose an appropriate treatment and monitoring plan.

Take the example of a new cancer treatment. In a robust elderly individual, the reference treatment confers a survival gain of 160 days at the cost of 20 bedridden days and 30 days with limitations. The patient therefore gains 110 days of independence. The new treatment, on the other hand, confers a survival gain of 200 days of which 40 days are spent in bed and 30 days with limitations, or 130 days of independence, i.e. 20 days more than the reference treatment. The new treatment can therefore be considered beneficial for a robust elderly person.

In a frail individual as in a robust individual, the reference treatment confers an extra 160 days of survival with 20 bedridden days. However, the frail individual will remain in a state of fatigue for a longer time and will have 60 days with limitations. The reference treatment therefore confers 80 days of independence. With the new treatment, the survival gain will be 200 days, as for the robust individual, but with 40 days in bed and 120 days with limitations. Altogether, then, the new treatment will cause a loss of 40 days of independence compared with the reference treatment. Therefore, the new treatment does not seem advisable for the frail elderly person.

What would be the case if a new treatment was as effective but better tolerated than the reference treatment? The robust patient will gain 200 days of survival at a cost of 20 days in bed and 30 days with limitations with the reference treatment, and 10 days in bed and 15 days of limitations with the new treatment. Altogether, the robust subject will gain 25 more days of independence. The frail patient will also have a survival gain of 200 days, including 20 bedridden days and 60 days with limitations with the reference treatment, and 10 days in bed and 40 days with limitations with the new treatment. The gain in independence is therefore 30 days with the new treatment, i.e. more than in the robust subject.

CONCLUSION

Personalised therapeutic management of frail patients is all the more necessary as we witness the accelerated aging of the population, with 21,000 new centenarians each year. We also know that functional status has an impact that is all the greater with advancing age.

Optimising the care path offered to elderly individuals can only be envisioned if the decision is carefully thought out in a multidisciplinary fashion and based on a SGE. Even though there is not yet a consensus on the tools and disease-specific measurement thresholds, national and international learned societies recommend a SGE before any proposal of a care plan in order to maintain or improve functional status and quality of life. The National Health Service in Great Britain has taken an important step in this direction by requiring GPs to detect the most vulnerable among their patients aged 75 years and older.

To conclude, I will quote this citation from Hippocrates which appears well suited to the clinical medicine that we offer in geriatrics: '*It's far more important to know what person the disease has than what disease the person has.*'

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