**Intrinsic capacity and resilience: taking frailty to the next level**

*Marije Hamaker, Sanne Gijzel, Siri Rostoft, Frederiek van den Bos*

Marije Emilie Hamaker, MD PhD, department of geriatric medicine, Diakonessenhuis Utrecht, the Netherlands

Sanne Gijzel, MD PhD, Vivum Naaderheem Geriatric Rehabilitation Center, Naarden, the Netherlands

Siri Rostoft, MD PhD, Department of Geriatric Medicine, Oslo University Hospital, Oslo, Norway; Institute of Clinical Medicine, University of Oslo, Oslo, Norway

F. van den Bos, MD PhD, department of geriatric medicine, University Medical Centre Utrecht, the Netherlands

Corresponding author:

Marije Hamaker

Diakonessenhuis, department of Geriatric Medicine

Bosboomstraat 1, 3582 KE Utrecht, the Netherlands

[mhamaker@diakhuis.nl](mailto:mhamaker@diakhuis.nl)

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**Abstract**

In addition to frailty, two novel concepts have been introduced in the field of geriatrics to capture the heterogeneous aging process: the first is intrinsic capacity, which uses a community-based, holistic approach and is propagated by the World Health Organization (WHO); and the second is resilience, which provides a more dynamic perspective on the individual’s reserves, injury and recovery. While both concepts are linked to frailty, with all three focusing on reserves in relation to ageing, each approaches this issue from a different point of view. In this paper, we will compare and contrast these three concepts – frailty, intrinsic capacity and resilience – and assess their relevance to future geriatric oncology research as well as daily clinical practice.

**Introduction**

Frailty can be conceptualized as a state of decreased physiological reserve due to the cumulative ageing processes across multiple organ systems, resulting in an increased vulnerability to stressors, such as cancer treatment. Frailty is one of the corner stones of geriatric medicine, and the concept is frequently used in geriatric oncology. There, its introduction has led to a better understanding of the interrelationship between a patient’s vulnerabilities and their response to treatment-induced complications like surgical injury or chemotherapy toxicity.1 Three recent randomized controlled trials found that implementing a geriatric assessment-driven intervention for older adults with cancer was feasible, reduced serious toxic effects and improved QoL.2–5

However, more recently, two novel concepts have been introduced in the field of geriatrics, both aiming to capture the heterogenous ageing process. The first is intrinsic capacity, which uses a community-based, holistic approach and is propagated by the World Health Organization (WHO);6 and the second is resilience, which provides a more dynamic perspective on the individual’s reserves, injury and recovery.7–11 While both concepts are linked to frailty, with all three focusing on reserves in relation to ageing, each approaches the issue from a different point of view. In this paper, we will compare and contrast these three concepts – frailty, intrinsic capacity and resilience – and assess their relevance to future geriatric oncology research as well as daily clinical practice.

**Intrinsic capacity**

The WHO introduced the holistic concept of intrinsic capacity as a way of monitoring ageing and functional ability over time. Intrinsic capacity is defined as the composite of all the physical and mental capacities that individuals can draw on at any point in their life. It is a dynamic construct: lifestyle, injuries, and events at different points across the life course will have a significant impact on the intrinsic capacity trajectory, as will health-related or social interventions.12 While there is a general tendency for intrinsic capacity to decline from mid-adulthood onward,6 there may be significant variation between individuals. Furthermore, intrinsic capacity may wax and wane as an individual experiences various setbacks and potential recoveries in their life course (Figure 1).

Common problems of older age, such as difficulties with hearing, seeing, remembering, moving or performing daily or social activities, may affect functional ability. However, health care professionals are often not aware of such problems until they have progressed to the level of actual impairment or disease. It is believed that intervening in early, sub-clinical stages of decline may enable stabilization or even partial reversal of impairment. Therefore, the WHO recommends longitudinal, community-based monitoring of the intrinsic capacity trajectory over time, with subsequent delivery of comprehensive care using multicomponent interventions aimed at maintaining intrinsic capacity, managing underlying diseases and addressing long-term needs. Such comprehensive care is already at the core of geriatric medicine, but for promoting healthy ageing, WHO recommends a much broader application within the community, in the stages and years before a person’s ageing has progressed to the level of needing geriatric care.6

For clinical utility, intrinsic capacity has been decomposed into subdomains that can inform clinical responses, including mobility/locomotor, cognitive, sensory, psychosocial, and vitality/energy domains (Table 1).6 In a large longitudinal study on ageing in general populations, these five subdomains and their composite were powerful predictors of future care dependence, even after accounting for chronological age and the presence or number of key health conditions.13 While there are numerous instruments available for assessing overt losses of capacity,6 these may not be suited to capture more subtle changes over time, especially in individuals who still have a fairly high level of functioning.12 Similarly, although recommendations for early intervention are available for each subdomain, the quality of the evidence ranges from very low to moderate,14 and the overall effect on intrinsic capacity has not yet been studied. Thus, while theoretically well-founded, the practical application of intrinsic capacity in promoting healthy ageing and well-being still remains to be clarified.

*Example: Mr C is 75 years old. He is a former high school history teacher, who lives with his wife and two dogs in a small village. He has a son who lives at a distance, so they do not see each other frequently, although they do call each other every week or so. Since his retirement, Mr C became increasingly interested in gardening and hiking in the countryside with his dogs. He describes himself as quite fit and healthy, but over the past years, some of the more strenuous tasks in the garden are being put off until they are more or less unavoidable, and the stints out with the dogs have shortened somewhat. His other hobby is playing chess at the local club, but he is thinking about quitting because he does not like to be out in the evenings. It might also be because his hearing is making it more difficult to carry on conversations with all the background noise; additionally, his wife thinks chess may have become less satisfying to him now that he is losing more often than he was used to, but she hasn’t brought this up with her husband.*

In this case, there is no overt impairment or disease, and Mr C’s overall functioning is still at a quite high level. However, there are several signs of declining intrinsic capacity including issues with vitality, hearing and cognition, that may be amenable to intervention had they been brought to light by longitudinal monitoring.

**Frailty**

While intrinsic capacity focuses on the evolution of reserves over time, a frailty assessment is a snapshot taken at a specific moment (Figure 1). Through an evaluation of geriatric domains, a patient’s vulnerabilities are uncovered and used as input for modifying treatment as well as implementing interventions to optimally support the patient.2,3,15–20

In geriatric oncology, the most commonly assessed geriatric domains include the ability to perform basic and instrumental activities of daily living (ADLs and IADLs), mobility, nutritional status, cognition, mood, and social support, in addition to comorbidity and related medication use. Of these domains, nutritional and functional status including mobility appear to have the strongest association with negative oncologic outcomes, such as surgery-related complications, toxicity of chemotherapy, functional decline, and mortality.21 Recent studies have also demonstrated that while frailty and the underlying ageing processes are not easily reversible, modifying treatment and providing additional support to the patient during the treatment trajectory can nonetheless improve outcomes.2–4 For example, the recently published landmark trial GAP70+ showed that in older patients being considered for chemotherapy, a frailty assessment with subsequent web-based management recommendations was able to significantly decrease the proportion of patients experiencing grade 3-5 toxic effects in the first three months of treatment (51% compared to 71% in usual care, p<0.001).3 In surgery, geriatric co-management based on the evaluation of frailty led to an increased use of inpatient paramedical support services and a decrease in postoperative mortality after colorectal surgery (4.3% vs. 8.9% with usual care, p<0.001).23 However, there was no effect on surgical complication rates.

Thus, assessing frailty provides a cross-sectional measurement of physical, functional and psychosocial reserves, which allows for estimating risks of treatment as well as implementation of supportive interventions that may improve outcomes.

*Example: It’s four years later: Mr. C is now 79 years old. He has recently been diagnosed with a stage II tumor in his ascending colon, which was discovered after he presented with anemia. A geriatric assessment is performed to determine if he is eligible for surgery. On the G8 frailty screening, he scores 12 out of 17 points, meaning he is potentially frail. Further assessment shows he has become increasingly housebound and now requires some help from his wife for transportation, shopping, housework, and managing finances. He has had no recent falls but does have difficulties walking a block. His wife has urged him to stay more active but he finds it hard to motivate himself for this. His appetite is good but he has lost a few kilograms over the past year. He has mild cognitive impairment with a Mini-Mental State Examination score of 26 out of 30. While he does not have signs of a depression, he says that he finds life increasingly boring. He has very limited social activities, but a loving relationship with his wife, who provides excellent social support.*

*Based on this assessment, the treatment team determines that there will be an increased risk of surgical complications because of his limited physical performance and mobility, and his care dependence in IADLs. The weight loss is likely explained by deconditioning and subsequent muscle loss due to inactivity. His mildly decreased cognitive reserves are not a contraindication for surgery, but do increase his risk of post-operative delirium.*

*A hemicolectomy is scheduled, and additional support is provided by a physiotherapist and a nutritionist; delirium prevention measures are put in place during the hospitalization phase.*

**Resilience**

In addition to intrinsic capacity and frailty, the concept of resilience has been introduced. Oncologic treatments inherently carry risk, even in the fittest of patients. These risks are deemed acceptable given the expected benefit and with the underlying assumption that the patient will be able to recover sufficiently from the injury caused by the cancer treatment. Frailty assessment has thus far proven most valuable in predicting the risk of toxicity or complications,21 but this is only half the story: what is also important, is whether a patient will be able to recover to an acceptable level after the impact of treatment. For example, in a study of women aged 65 years and older with stage I-III breast cancer receiving adjuvant chemotherapy, 42% had functional decline at the end of the chemotherapy.24 At one year, nearly half of these patients had recovered to their baseline level of function while for the other half, loss of function was permanent.24 Thus, while both groups experienced similar negative effects of treatment at three months, the end-result - and with that perhaps the acceptability of these effects – differed significantly.

*Example: Being diagnosed with cancer has been a shock to Mr. C. While initially feeling overwhelmed, the support that was offered by the oncology team, the physiotherapist and nutritionist as well as his family motivated him to become more active in preparation for the hemicolectomy. He received a training program to increase his physical condition, and while time prior to the surgery was limited, he felt empowered by the thought that his own efforts could have a positive impact on the overall outcome.*

*Surgery was relatively uncomplicated, although he experienced some disorientation in the first two nights. (The usual enhanced recovery protocols post-surgery were implemented.) To support his recovery, he was discharged to a rehabilitation facility. Daily physiotherapy, continued nutritional support and the social environment had a positive effect on his overall functioning, mobility and mood. When he returned home after five weeks, he was able to maintain his more positive, active and outgoing attitude.*

Being able to assess and incorporate recovery potential into oncologic treatment decision-making will allow for further precision in tailoring of treatment. This recovery potential is captured in the concept of physical resilience. Physical resilience is a characteristic at a whole-person level which determines an individual’s ability to resist functional decline or recover physical health following a stressor.7 It not only requires having sufficient physiological reserves, but also draws on resources from the person’s social environment, their mindset, and ability to manifest adaptive behavior, as well as support resources provided through care or interventions. If the spectrum from robustness to frailty reflects the amount of physiological potential one has to react to stressors, physical resilience refers to the actualization of that potential (Figure 1).7–11 With its focus on strengths, resources and ability, resilience takes a more positive perspective on an older adult’s health status.

A person’s recovery potential is best observed when an external stressor disturbs their equilibrium, by seeing the subsequent dynamic response over time. One way to test this is by means of a stimulus-response test, which involves standardized probing of a physiological function with an experimental stressor and monitoring the response.25 A well-known example is heart rate analysis during an exercise test, where longer recovery times (return of heart rate to resting levels) were found to be associated with mortality or frailty in older persons.26–29 Evidence on the association between such dynamic response tests and outcomes of oncologic treatment is limited.30 In addition, it is a challenge to develop stimulus-response tests that are reasonably safe and practically feasible for older or vulnerable patients.31

An alternative strategy, circumventing the drawbacks of ‘artificial’ stimulus-response tests, is to use the fact that a person is constantly subject to natural perturbations from the environment and must respond to these tiny challenges to maintain homeostasis.31–34 When continuously monitoring parameters like heart rate or blood pressure, dynamic responses to everyday challenges can be captured. In clinic, asking a patient about response to recent stressors (for example, recent illness, previous surgery, or symptoms related to cancer, such as anaemia) also provides insight in a patients vulnerability and recovery potential.

**Integration and implications**

Cancer mostly affects older adults, and the dilemma of how to treat older patients with cancer led to the incorporation of geriatric concepts in oncology. Assessing a person’s reserves in relation to the ageing process has become a standard component of the work-up of an older person with cancer. The three concepts discussed in this paper – intrinsic capacity, frailty and resilience – all focus on the development of person-centered care and all lead to tailored care through assessing reserves, but each does so from a different perspective (Table 1). Frailty, which can be seen as a cross-sectional measurement of intrinsic capacity, has proven fit for purpose in this setting. Assessing frailty can inform and modify the decisional process. It predicts outcomes like toxicity and other treatment-related complications, and uncovers shortcomings in the health status that may be amenable to intervention.21 However, the static frailty assessment cannot inform us fully about how a person will recover from a major stressor. A patient with many deficits can still be resilient, while for another patient without comorbidities the recovery may turn out badly. To optimize decision making and patient support, it would be valuable if the doctor's clinical judgement could be supplemented by objective measurements that predict meaningful outcomes in daily clinical practice.

In clinical geriatric oncology, the community-based, longitudinal concept of intrinsic capacity, with its emphasis on healthy ageing and pre-clinical decline, may be less useful. However, while frailty is generally measured at a single time point, intrinsic capacity highlights the importance of the trajectory of deficits, and as such may add useful strategies for interpreting the frailty assessment. For example, when a patients presents in a wheelchair, it could be a sign of frailty if caused by slowly developing muscle wasting with subsequent functional decline and mobility problems. If it is caused by an accident during childhood, and the person has adapted and is still fully functional, it may not be associated with frailty at all. Likewise, severe anaemia due to colorectal cancer can cause exertional dyspnea that leads an otherwise healthy older person to opt for a wheel chair at clinic. In the same way that intrinsic capacity focuses on reserves over time, assessing frailty should include a timeline and the most likely origin or cause of impairments.

Additionally, being able to assess and incorporate recovery potential into oncologic treatment decisions will allow for further precision in tailoring of treatment, and this is captured beautifully in the concept of resilience. Asking about earlier health challenges and the subsequent recovery trajectory can provide important insight.35 In the course of a cancer diagnosis and oncologic work-up, patients can be faced with multiple stressors (cancer-related symptoms, multiple hospital visits, invasive procedures like biopsies or endoscopies) that can be used to assess impact and recovery time. In addition, initiating prehabilitation (for example, exercise training) and observing whether this leads to improvement in physical capacity will give relevant clues to the recovery that can be expected post-treatment.

Finally, the concept of resilience highlights that frailty should be interpreted in a broader sense, not only focusing on the deficits but also on resources, magnitude of the stressor, and mindset: all of which may affect recovery. For example, a patient with cognitive impairment with a good support system may not encounter problems in daily living and may be resilient, while a physically fit patient with a depression may struggle to cope.

Thus, by adding certain practical aspects to daily clinical care, it is possible to take frailty assessment in older patients with cancer to a higher level (Table 2).

**Implications for research**

For research in geriatric oncology, incorporating resilience is probably one of the largest and most exciting challenges for the coming years. It has the potential to improve patient education and shared decision making, enhance pretreatment assessment of older patients with cancer and refine prognostication, and to optimize selection of patients for prehabilitation and other interventions.

Firstly, adding patient-centred outcomes and their trajectory over time to the usual oncologic research outcomes (survival, progression) will allow for the construction of injury-recovery trajectories. For this, patients should not only be monitored frequently before and during the treatment trajectory, but also during the recovery phase.34 Understanding the severity of decline across various domains (for example, physical, cognitive, social), the duration of the recovery trajectory and the proportion of patients who are unable to recovery fully will allow for better patient education. This information is essential if we want to optimize shared decision making in the older population, particularly as these patients often prioritize functioning over oncologic outcomes. At the moment, few studies include functional recovery as an outcome, and follow-up is often limited to the duration of treatment.

Once we understand the injury-recovery trajectory on a group level, we can try to determine which geriatric domains are associated with negative treatment outcomes, such as prolonged recovery time or permanent loss of functioning. Current frailty research has focused on predicting negative outcomes, but is unable to inform us about the associations with recovery. Important first steps are now taken in elective joint surgery, with a recently published template of dynamical tests for various resilience components during surgery and subsequent recovery.8

On an individual level, resilience research could focus on developing easy-to-use dynamic response tests that capture an older patient’s recovery potential. Expanding patient evaluations already in use – such as the preoperative cardiopulmonary exercise test30 – to include recovery time, may provide interesting insights. Additionally, measurements from wearable and non-wearable electronics may bring a new perspective on the dynamics of resilience, opening up another exciting new field within geriatric oncology that warrants further exploration.36–41

Finally, understanding which patients are at risk of poor recovery also allows for optimizing patient support before and during treatment, for example by offering specific interventions to optimize impairments and negate negative treatment effects. Improving patient selection is especially relevant for time-intensive interventions such as (p)rehabilitation. While on a group level studies regarding prehabilitation often fail to be successful, particularly in frail patients, on an individual level significant benefits can be seen.42 Resilience research could help us understand the characteristics of patients who recover well, and which frailty characteristics will be amenable to (p)rehabilitation. Ultimately, this could be an important step in improving outcomes for older patients with cancer.

**In conclusion**, adding principles from intrinsic capacity and resilience to frailty assessment provides opportunities to further personalize treatment and improving outcomes by looking longitudinally at recovery potential instead of deficits. Further research is needed to increase our understanding of the interrelatedness of these concepts and their association with outcomes of cancer treatment. However, with some easy tweaks to the frailty assessment, resilience and intrinsic capacity can help take the care for older patients with cancer to a higher level (Table 2).

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*Author roles*

Conception and design: Marije Hamaker, Frederiek van den Bos

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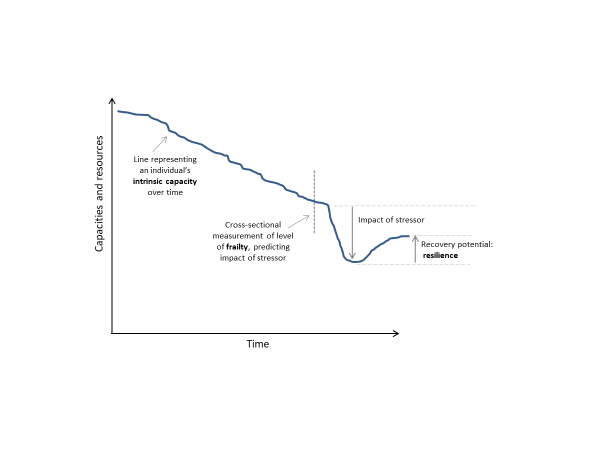
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Figures and tables:

**Figure 1: Time perspective of intrinsic capacity, frailty and resilience** 

**Table 1. Differences between intrinsic capacity, frailty and resilience**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Intrinsic capacity | Frailty | Resilience |
| Aim | Prevention | Risk assessment and prognostication | Assessing ability to recover |
| Focus | Resources | Deficits | Recovery potential |
| Included domains | -Mobility/locomotor  -Cognition  -Sensory status  -Psychosocial status -Vitality/energy | -Basic and instrumental activities of daily living  -Mobility  -Nutritional status  -Cognition  -Mood  -Social support | Any domain can be included, as long as the triad of system, state and stressors is clearly specified. |
| Outcomes | - Monitoring ageing  - Functional ability | -Functional status -Quality of life -Toxicity -Complications | -Resilience stratification groups  -Recovery trajectories of, for example, functional status, quality of life - Dynamic response |

Table 2. **Applying intrinsic capacity, frailty and resilience in clinical practice**

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| * Perform a geriatric assessment for assessing impairment and deficit (frailty) |
| * Establish a timeline for each impairment to differentiate between impairment due to frailty and impairment due to cancer (intrinsic capacity) |
| * Inquire into resources and the patient’s context (resilience) |
| * Ask about response to prior stressors (resilience) |
| * Assess response to prehabilitation (resilience) |
| * Incorporate recovery trajectories in research and shared decision making (resilience) |