All Overview of the Resilience World: Proceedings of the American Geriatrics Society and National Institute on Aging State of Resilience Science Conference
Running Title: Resilience in Older Adults

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Impact Statement: We certify that this summarizes the proceedings of a bench-to-bedside conference that addressed commonalities and differences among the frameworks of resilience most commonly used in aging research in the physical, cognitive, and psychosocial fields. Attendees considered what can be borrowed from each domain to better operationalize the concept of resilience and whether a unified working definition of "resilience" can be developed. Responses to the knowledge gaps and recommended research from this conference could hasten the translation of findings on resilience to the care of older adults.

Key Points:

- Resilience, which relates to one's ability to respond to stressors, typically declines with age and the development of comorbid conditions in older organisms, but health-related

disciplines have differed in their conceptualizations of resilience in older adults and its multicomponent dimensions in response to physical, cognitive, and social stressors.

- Themes of "Overview of the Resilience World," a bench-to-bedside conference, included the intertwined contributors to resilience from the molecular to the societal level, the dynamic nature of resilience throughout the lifespan, and the critical relationships between resilience and health equity.
- Participants recommended longitudinal studies of the impact of exposures to stressors on resilience in older adults; use of new and existing cohort study data, natural experiments (including the COVID-19 pandemic), and preclinical models to enhance resilience research; and translational research to bring findings on resilience to patient care.

Why Does This Matter?

The research gaps identified at this conference and proposed studies could enhance our understanding of resilience and lead to more effective and equitable strategies to promote resilience in older adults.

Abstract
Resilience, which relates to one's ability to respond to stressors, typically declines with age and the development of comorbid conditions in older organisms. Although progress has been made to improve our understanding of resilience in older adults, disciplines have employed different frameworks and definitions to study various aspects of older adults' response to acute or chronic stressors. "Overview of the Resilience World: State of the Science," a bench-to-bedside conference on October 12–13, 2022, was sponsored by the American Geriatrics Society and National Institute on Aging. This conference, summarized in this report, explored commonalities and differences among the frameworks of resilience most commonly used in aging research in the three domains of resilience: physical, cognitive, and psychosocial. These three main domains are intertwined, and stressors in one domain can lead to effects in other domains. The themes of the conference sessions included underlying contributors to resilience, the dynamic nature of resilience throughout the lifespan, and the role of health equity in resilience. Although participants did not agree on a single definition of "resilience(s)," they identified common core elements of a definition that can be applied to all domains and noted unique features that are domain specific. The presentations and discussions led to recommendations for new longitudinal studies of the impact of exposures to stressors on resilience in older adults; the use of new and existing cohort study data, natural experiments (including the COVID-19 pandemic), and preclinical models for resilience research; and translational research to bring findings on resilience to patient care.

Key Words: Resilience, stressors, physical, cognitive, psychosocial

Background

Our ability to respond to health stressors declines with age and is affected by the development of comorbid conditions in older organisms. The term "resilience" is commonly used in gerontological, neurology, and psychosocial literature, but how resilience is conceptualized in response to physical, cognitive, or social stressors has differed among the fields.[1-4]

Figure 1 displays three main domains of resilience: cognitive, physical, and psychosocial. This illustration shows that resilience domains are intertwined and that stressors in one domain can lead to effects in other domains.

"Overview of the Resilience World: State of the Science," a bench-to-bedside conference on October 12–13, 2022, was sponsored by the American Geriatrics Society and National Institute on Aging. This conference explored commonalities and differences among the frameworks of resilience most commonly used in aging research in the physical, cognitive, and psychosocial fields. A multidisciplinary panel of speakers shared differing perspectives and provided insights on the definitions of resilience and approaches to resilience research in their respective disciplines. Attendees considered what can be "borrowed" from each domain to better operationalize the concept of resilience and whether a unified working definition of "resilience" can be developed.

This conference was the first in the most recent series of American Geriatrics Society Bench to Bedside conferences. These meetings provide updates on cutting-edge research, identify research gaps and opportunities, and facilitate networking among experts and promising new investigators from relevant disciplines in the field of aging. Future conferences in this series will address resilience stress tests and novel biomarkers of resilience (Spring 2024), and new interventions to optimize resilience (Fall 2025).

Session 1: Resilience in Action: What We Do (Not) Know: This section summarizes the resilience working definitions, state of the science, and knowledge gaps in resilience from psychosocial, physical, and cognitive fields and discusses how resilience changes in response to exposures in individuals and societies. Topics were deliberately approached from a discipline-specific perspective to lay the groundwork for the multidisciplinary integration attempts discussed in the subsequent sections.

Psychosocial Resilience

From the perspective of psychological science, especially developmental or lifespan psychology, resilience can be defined as the "capacity of a dynamic system to adapt successfully to disturbances that threaten system function, viability, or development."[5] This definition is broad enough for use by researchers from different disciplines.

Factors that define psychosocial resilience are the challenges threatening the system and how well it responds. These challenges can be acute (e.g., laboratory tests), major events (e.g., loss of a loved one), or chronic (e.g., ongoing health conditions). Resilience outcomes can be recovery (returning or bouncing back from a stressor), sustainability (capacity to absorb perturbations or

disturbances with little or no observable detriment), or growth (increased capacity to cope with future stressors).

Psychosocial resilience is not viewed as a unidimensional phenomenon, and most people have uneven functioning across domains and processes that support resilience. Simultaneous increases, decreases, and maintenance of functioning characterize the development of adaptive capacities throughout life.[6,7] Resilience researchers in social sciences increasingly recognize that resilience is a multidimensional construct that can be heterogeneous and dynamic.

Physical Resilience

Geriatrics research has frequently focused on frail older adults whose reserve capacity is low. But even without phenotypic features of frailty, older adults have different abilities to maintain (resist) or regain function after encountering a health stressor. Frailty is influenced by the resources available to a system, whereas resilience is the extent to which this complex system can recruit those resources when challenged by a stressor. A better understanding of what factors come into play at times of stress, to support recovery from diseases or treatments, is necessary to develop interventions that promote recovery for all. Future interventions may target resilience factors at molecular, domain-specific, or environmental levels.

A clinical understanding of physical resilience can benefit from how resilience has been conceptualized in ecology, where resilience is an emergent property reflecting how well a dynamic and complex ecosystem can remain in equilibrium.[8] A system can be resilient in a desired or undesired stable state, so resilience (in this framework) is not positive if a person predictably returns to an unhealthy condition after perturbations.

Cognitive Resilience

"Cognitive reserve" is a property of the brain that enables better-than-expected cognitive performance, given the degree of aging-related brain changes and brain injury or disease. For example, high cognitive reserve helps people cope (i.e., experience minimal cognitive symptoms) with age-related brain changes and neuronal damage from Alzheimer's disease. Factors associated with cognitive reserve include greater educational or occupational attainment.

Brain maintenance is the relative absence over time of changes in neural resources or neuropathologic changes as a determinant of preserved cognition in older age.[9,10]

Notable in the field of cognitive resilience is that recovery from a stressor is typically considered; the emphasis is on maintaining cognition or function.

Cognitive reserve and brain maintenance can be influenced by multiple genetic and environmental factors that operate at various points or continuously throughout the lifespan. "Resilience," in the cognitive health literature, refers to both cognitive reserve and brain maintenance.

The Exposome as a Stressor

Although many aspects of physical, social, and cognitive resilience are determined by intrinsic factors, they are directly affected by a lifetime of exposures. The "exposome" refers to all of a person's exposures over a lifetime and acknowledges the relationship between these exposures and health. These exposures are external to the biological person, can range from the microbiome to structural racism, might affect people differently, and are commonly influenced by systemic inequities. Interactions between the exposome and an individual's biology throughout the life course result in wellness or disease.

The Area Deprivation Index (ADI) incorporates data on 17 measures of social determinants of health in discrete geographic areas. A study of deeply phenotyped brains showed that people living in the most disadvantaged neighborhood decile, as measured by the ADI, have a greater likelihood and burden of Alzheimer's disease neuropathology.[11,12] The Pennsylvania Department of Health used the ADI to allocate scarce COVID-19 treatments to the most disadvantaged areas, which increased the alignment of resources to need while mitigating health inequities.[13] Tools like the ADI will play a critical role in understanding how the exposome influences resilience across domains and stressors and directing resources to support resilience to specific stressors.

Session 1 Discussion

When resilience is defined as "sustainability of the current state," a suggestion was that this state might or might not be desirable. An opposing view was that this undesirable state is stability rather than resilience.

Attendees also noted that investigators who study cognitive resilience often focus on stressors to which the person was exposed decades earlier. In contrast, those studying physical resilience tend to focus on current stressors, such as surgery, anesthesia, or infection. Linkages between cognitive and physical frailty and resilience involve psychological factors as well. Studies could use a life-course approach or leverage natural experiments, such as the COVID-19 pandemic, to explore the linkages among the resilience domains.

Another discussion topic was the role of the exposome in resilience. The exposome can be a stressor or a resource, and some exposures can have elements of both. Prior experience with stressful conditions might prepare people to cope more effectively with subsequent stressors. In addition, the same person might adapt differently to exposures at different times because of changes in the context.

Participants noted that resilience research already leads to improvements in patient care and population health. When a clinician sees a patient, they not only examine test scores and complaints but also need to understand a patient's life course to incorporate exposures and resilience factors into their plan to optimize future health trajectories.

Table 1 summarizes the key knowledge gaps in the physical, cognitive, and psychosocial domains of resilience.

Session 2: Toward a Holistic Concept of Resilience

Session 2 speakers built on the Topic 1 presentations by exploring the interactive and dynamic concept of resilience. They discussed changes in a person's resilience over time and the complex interactions among systems within individuals and societies. Speakers also explored the roles of societal disadvantage in resilience and shared molecular mechanisms of cognitive and physical resilience.

Dynamics of Resilience

In the early 1990s, John Nesselroade introduced measurement bursts to depict the "warp" and "woof" (terms used in weaving) of developmental dynamics.[14] This analogy suggests that the structure underlying development consists of interwoven threads that denote longer-term trends (warp) and shorter-term variability (woof) around which those trends are built. These longer-term stable attributes include cognitive functioning, emotions, and personality. **Figure 2** summarizes major conceptual frameworks from the three domains discussed in Session 1, acknowledging that Nesselroade's "warp and woof" analogy for short- and long-term dynamics is relevant to most theories of resilience.

Understanding resilience requires determining how short- and long-term processes come together across the lifespan to produce resilient human tapestries and how people might have similar or different trajectories. One approach to address this need is to assess how people do during times of rapid change (e.g., disease progression, menopause, retirement, relocation, or loss of a loved one). Personal characteristics might explain why processes (e.g., vulnerabilities or attributes that enhance adaptive capacity) differ among individuals.

Understanding resilience also requires understanding hierarchical complex systems that contain layers of subsystems spanning multiple spatial and temporal scales. Each subsystem layer has heterogeneous components that interact (nonlinearly) within and across layers in many ways. As a result, the system's response (or adaptation) to external and internal perturbations is difficult to explain, control, and predict. A system is decomposable if it can be divided into subsystems that can be studied in isolation (a process known as "reductionism"). A major advantage of decomposable systems is that they can be studied using traditional, reductionist approaches. However, complex systems are not fully decomposable because they have strong interactions, although some aspects with weak interactions might be almost decomposable.

Ashby's Law of Requisite Variety may provide insights for studying resilience. According to this law, for a system to be stable, the number of states that its control mechanism can attain (its variety) must be at least as great as the number of possible states the system can end up in, i.e. the number of outcome states. This law may suggest a promising framework for developing interventions for healthy aging. For example, promoting variety in the activities of older adults (e.g., through cognitive challenges, physical exertion, social interactions, and spiritual activities) could enhance their resilience.

Resilience and Health Equity

According to a resilience framework that incorporates sociocultural factors (e.g., language, acculturation, and immigration history) into the biopsychosociocultural model used in psychology, risk factors for cognitive impairment and dementia that differentially affect older Black and Latino/a/x adults fall into three categories[15,16]:

- Biological (e.g., comorbid conditions or molecular factors)
- Psychological (e.g., depression, stress, and social isolation)
- Sociocultural and structural (racism and discrimination, socioeconomic status, health care barriers, quality of life, literacy)

Potential resilience factors for cognitive impairment and dementia in minoritized populations can be grouped into the same categories:

- Biological (e.g., genetics related to ancestry, physical activity, nutrition)
- Psychological (e.g., *familismo* [family loyalty and closeness])
- Sociocultural and structural (e.g., acculturation, bilingualism, and social and health policies)

A similar biopsychosociocultural framework could be applied to understanding issues that influence equity across other resilience domains.

Molecular Mechanisms of Resilience

The biological and potential molecular underpinnings of frailty include metabolic dysfunction, chronic inflammation, impaired hypothalamic-pituitary-adrenal axis response, energy homeostasis dysfunction, endocrine dysfunction, mitochondrial dysfunction, oxidative stress, epigenetic alterations, genomic instability, and metabolic dysfunction.[17] Frailty indices based on health deficits outperform age-based metrics based on DNA methylation, and frailty indices can predict biological age.[18] However, frailty might occur too late in the aging process to serve as a marker of resilience.

Biomarkers of inflammation, metabolic and mitochondrial function, and epigenetic dysregulation explain 27% of the variance in physical resilience after hip fracture.[19] Although this finding helps underscore the role of fundamental processes, understanding molecular mechanisms might not be required, because recognition of a low-resilience molecular phenotype could still be used to target resources. This perspective could be useful for developing a range of interventions to maintain and even enhance resilience.

Data from the Religious Orders Study and the Rush Memory and Aging Project have also been used to explore the molecular mechanisms of resilience in brain health. These data show that some people experience rapid cognitive decline, a few have a slower decline, and some have no cognitive decline.[20,21] In one analysis, 10 of 11 pathological indices examined (including markers of Alzheimer's disease, other neurodegenerative diseases, and cerebrovascular conditions) were associated with faster decline and accounted for 2% to 34% of the variation in decline.[22] But more than 50% of the variations in cognitive decline were not explained by the pathologic indices examined.

One study defined resilience as residual cognitive decline, which accounted for about half of inter-person differences in cognition at the end of life.[21] A variety of cellular and molecular mechanisms may underlie this definition of resilience, and these could point toward personalized medicine approaches for maintaining cognitive health. For example, AK4 generated by human induced pluripotent stem cell lines was associated with residual cognitive decline.

Session 3: Tools to Operationalize and Advance the Concept of Resilience

The Trans National Institutes of Health (NIH) Resilience Working Group defines "resilience" as a system's capacity to resist, recover better (grow), or adapt in response to a challenge or stressor. A system can represent various domains (e.g., individual, community), levels (e.g., social, behavioral, physiological), and processes (e.g., aging), or a combination.[23] Over time, a system's response to a challenge might fluctuate in response to the challenge's severity, duration of exposure to the challenge, innate or intrinsic factors, or some combination of these factors. The working group developed the Resilience Research Design Tool, a checklist of requirements for harmonizing the design and reporting of resilience studies at NIH.[24]

Animal models are another resource for resilience research. These models can be used to measure biological and physical parameters that indicate subjective responses. Animal models allow studying the biology of resilience and its interplay with the biology of aging within and across tissues. Physical resilience could provide a useful paradigm for testing the safety and efficacy of emerging interventions that target the biology of aging in animal models. For example, murine models could be used to study age-related changes in resilience measures as a result of anesthesia, chemotherapy, or surgical challenges. The results would be translatable and disease agnostic because they would involve several physiological systems in animal models and, ultimately, humans.

A third resource for resilience research consists of data analytical approaches—bioinformatics and science-informed modeling. The gold-standard way to assess the health of a dynamic system like resilience is dynamic stimulation, which experimentally perturbs the system to determine how it responds. Data on physiologic resilience can be analyzed using dynamical systems models and latent variable analyses grounded in theory positing how physiological systems and their interactions create capacity to respond resiliently. Alternatively, these data can be analyzed using data-driven machine learning techniques seeking to empirically identify determinants of resilient responses. Both theory-based models (e.g., latent variable modeling) and data-driven machine learning modeling are needed to advance knowledge of and develop interventions that promote physiologic (underlying) resilience as well as broader determinants of observed resilience (after exposure to a stressor).

<u>COVID-19 as a Natural Resilience Experiment</u>

Two conceptual models from the Johns Hopkins Pepper Center and the Duke Pepper Center have been recently developed to inform research on physical resilience, or functional recovery after health stressors.[1,25] These models were applied here in a discussion of how the COVID-19 pandemic could be used to advance resilience research. Participants acknowledged that the

pandemic resulted in biological stressors (e.g., the virus and its consequences) as well as psychosocial stressors (e.g., isolation, anxiety).

In the Hopkins model, which depicts a physiological system's pre-stressor capacity to manage stressors and post-stressor functional responses, a robust system maintains its level of function. Although a resilient system might lose some degree of function, it retains its essential function. In contrast, a non-resilient system loses its essential function. According to this model, people who are not perturbed by a SARS-CoV-2 infection are robust, whereas others are perturbed by it but do not develop functional decline. Prevention entails intervention on the physiologic capacity and management entails potential modification of post-stressor responses to promote ultimately resilient outcomes.

With the Duke model, resilience is a dynamic response that entails a complex system's process to regain health or equilibrium after exposure to a stressor. This model defines prestress reserve as a set of domains that include the person's psychological, physiological, and cognitive capacities to respond adaptively to a health stressor. The COVID-19 vaccines can boost prestress reserve, for example. The Duke model emphasizes that opportunities to intervene and bolster the resilient response occur before, during, or after a stressor, such as COVID-19 exposure.

Aside from exposure to the virus or an active infection, the COVID-19 pandemic has disproportionately impacted older adults in nursing homes due to long-term lockdowns, for example, yet this population remains understudied. Effects on nursing home residents may include worsened mood and increased use of psychotropic medications.

According to a recent study, approximately one third of older adults described frequent feelings of loneliness throughout the first 6 months of the COVID-19 pandemic, and more than half attributed their increased loneliness to pandemic-related restrictions.[26] Rates of reported loneliness decreased over time, suggesting that older adults had high levels of resilience, especially if they used coping strategies and assistive technologies.[27] However, a subgroup of older adults struggled with increasing loneliness over time, particularly if they showed discomfort with technology, anxiety, or depression.

Topic 3 Discussion

An adaptive response does not require growth in the affected domain. For example, someone can adapt to losing a leg by improving their function and quality of life, even if they will never regain use of that leg.

The NIH framework does not explicitly link resilience with positive outcomes because resilience is on a scale. Perhaps "resilient" should be distinguished from "resilience" (capacity to build a stronger system that can better respond to a stress exposure, which is positive).

Longitudinal studies were another major discussion topic during the conference. In the resilience schema, remaining at the baseline level is regarded as a success, and experiencing a loss without returning to that condition is a failure. If responses are measured at more time points (i.e., in a longitudinal study), they might show that people's responses to stressors vary, and those whose

condition deteriorates might do better over the long run than those whose condition remains the same as at baseline. Experimental models should be used to measure responses at repeated time points.

Attendees recommended that longitudinal studies introduce a stressor and measure responses using a type of burst design. Giving people an opportunity to master their response to an acute stressor could affect their responses to future stressors (or bursts).

Final Discussion

Defining "Resilience"

A common definition of "resilience" for use in all domains could have a set of core concepts but include other terms that can be customized for each domain. Such a definition might list different stressors and outcomes for each domain. Another approach is to agree on what resilience is *not*.

Suggested features of a common definition of "resilience" were:

- Identify the person or group who defines a "good" outcome or response to a stressor (i.e., acknowledge that the care team might value an outcome not highly valued by a patient or care partner)
- Emphasize the process and capacity in addition to the outcome.
- Make any medical definition consistent with existing definitions, such as "resilience" and "resistance," in common English.

Participants identified two potential unifying definitions of "resilience":

- Attainment of a valued outcome after exposure to a stressor that is expected to diminish that outcome.
- The capacity, process, or outcome of achieving a valued result after an exposure.

Participants used the different trajectories of older adults who develop COVID-19 as examples for contemplating what resilience is and is not. Some attendees argued that if someone develops symptomatic COVID-19 without interruptions in their activities of daily living (ADLs), they are probably resilient (at a cellular level). However, their ADLs alone would not show their resilience if "resilience" requires losing and then regaining function or stability. According to some participants, a flat trajectory after exposure to a stressor always indicates resilience because something made these people withstand the stressor. However, someone who experiences no COVID-19 symptoms might not demonstrate resilience, if an asymptomatic infection is not even considered a stressor. Alternatively, people with an apparently flat trajectory might have taken a hit in an unmeasured domain. Whether a phenotype of change is identified sometimes depends on the measure used.

Perhaps resilience should be distinguished from robustness. A flat trajectory in the COVID-19 example might indicate robustness, whereas someone with resilience would show a change without lasting loss of function. In other words, a resilient person can regain their pre-stressor function even though it took a hit. Alternatively, the flat trajectory could be called "maintenance of functioning," a trait of adaptive functioning but not resilience (according to some

frameworks). Attendees agreed that future researchers should avoid applying "resilience" as a catchall term. Recognizing that multiple conceptual models and definitions already exist, attendees recommend that future researchers specify their definition of resilience and adhere to it precisely.

Patient Perspective

Participants noted that some patients might object to being labeled as "not resilient" because they view this term as a negative construct. This terminology could alienate important stakeholders (patients and caregivers) and make them feel disempowered. An attractive feature of resilience is that it is a positive construct, and studying a positive construct can be more appealing than studying risk factors and predictors of bad outcomes.

Furthermore, perceptions of stressors, and acceptable or expected reactions to them, vary by culture. Stressors and their impact on health outcomes can be measured objectively, and cultural and contextual factors are modifiers.

Population-Based and Individual Interventions

Because the systems in which people live do not always promote resilience, building resilience requires investments of resources at the individual, community, and systems levels. However, population-based interventions for enhancing resilience are distinct from individual interventions. The CMS decision to provide additional funding to hospitals that treat large numbers of patients from disadvantaged communities, for example, is in a different category of intervention from a treatment to promote the resilience of a patient undergoing chemotherapy.

Table 2 lists key knowledge gaps related to a holistic concept of resilience.

Conclusions

"Overview of the Resilience World," a bench-to-bedside conference, addressed various conceptualizations of resilience in older adults across physical, cognitive, and psychosocial health domains. Presentation and discussion themes included a biopsychosocial understanding of resilience mechanisms, the dynamic nature of resilience throughout the lifespan, and the relationship between resilience and health equity. Participants agreed that no single definition of "resilience" can achieve consensus. However, common core elements of a definition that can be applied to all domains include a stressor, a response to that stressor, and response outcomes that have value to the person or system. Research questions and high-priority gaps were outlined. Participants recommended new longitudinal studies of the impact of exposures to stressors on resilience in older adults; use of new and existing cohort study data, natural experiments (including the COVID-19 pandemic), and preclinical models for resilience research; and translational research to bring findings on resilience to patient care.

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- Opening Session: Peter Abadir, MD, Johns Hopkins University; Heather Whitson, MD, Duke University
- Resilience in Action: What We Do (Not) Know: George Kuchel, MD, University of Connecticut; Anthony Ong, PhD, Cornell University; René Melis, MD, PhD, Radboud University Medical Center; Yaakov Stern, PhD, Columbia University; Amy Kind, MD, PhD, University of Wisconsin
- Toward a Holistic Concept of Resilience: Peter Abadir, MD, Johns Hopkins University; Cindy Bergeman, PhD, University of Notre Dame; Ravi Varadhan, PhD, Johns Hopkins University; Monica Rivera Mindt, PhD, Icahn School of Medicine at Mount Sinai; Bruce R. Troen, MD, University of Kansas and VA Kansas City Healthcare System; David Bennett, MD, Rush University Medical Center
- Tools to Operationalize and Advance the Concept of Resilience: Daniel Davis, PhD, Hassell; LaVerne Brown, PhD, Office of Dietary Supplements; Nathan LeBrasseur, PhD, MS, Mayo Clinic; Kenneth Schmader, MD, Duke University; Ashwin Kotwal, MD, MS, University of California, San Francisco; Karen Bandeen-Roche, PhD, Johns Hopkins University

Author Contributions

PA and HEW helped prepare the manuscript. KB-R, CB, DB, MC, DD, BE, AK, NL, YS, and RV reviewed and provided feedback on manuscript drafts.

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Tables

Table 1. Physical, Cognitive, and Psychosocial Domains of Resilience: Key Knowledge Gaps	
Physical	How are physical systems on several spatial and temporal scales involved in the emergence of resilience to health stressors in older adults?
	How does physical resilience develop?
	What are the relationships between human systemic resilience and subsystem resiliencies?
	How does physical resilience change across the lifespan?
	What is the relationship between physical resilience and stressor type, intensity, and timing?
	How can a physical stressor's intensity be quantified?
	What are the links between biology and the exposome?
	How does the person's biology interact with the environment or exposome in ways that lead to wellness or disease (social-biological phenotyping)?
	Can we predict which resilience trajectory a person will follow in response to a health stressor initially and during recovery?
	How can we use physical resilience in the clinical management of older adults to support their health?
	If downstream effects of anesthesia exposure are negative, can they be mitigated?
Cognitive	Which genetic and lifelong factors influence cognitive resilience? When do these factors operate in the lifespan? How do they interact?
	What occurs during neural implementation of brain maintenance and cognitive reserve, including differential structural changes?
	What occurs during neural network connectivity at rest?
	What are individual differences in the efficiency, capacity, and flexibility of task-related neural networks to characterize the neural implementation of cognitive reserve?
	Can animal studies provide insights into basic biological mechanisms underlying brain maintenance and cognitive reserve as well as mechanisms underlying cognitive reserve at the molecular, cellular, and network levels?
	Can studies of people with Alzheimer's disease who do better than expected contribute to an understanding of resilience?
	Can studies that use structural and functional brain imaging; studies that incorporate genetic, exposomal, and other analyses; and natural experiments provide useful information on cognitive resilience?
Psychosocial	How can a multilevel analysis perspective account for short- and long-term changes in psychosocial resilience?
	Can intensive measurement-burst study designs that intersperse intensive repeated measures with longitudinal assessments be used to characterize dynamic psychosocial resilience processes?
	Which sociocultural factors affect psychosocial resilience?
	How do dimensions of diversity, social support and engagement, and discrimination and persecution affect psychosocial resilience?

Table 2. Toward a Holistic Concept of Resilience: Key Knowledge Gaps	
Stressors	Can additional exposome metrics be developed that have rigor, validity, and generalizability? Can these metrics be valid across the life course?
	What are the links between the exposome and human biology?
	Which factors and interventions promote resilience in the setting of an adverse exposome?
	How can measures of resilience be supplemented by people's appraisals of stressors to assess their resilience?
	What are the order parameters of the stress and affect systems? What is the interface between these systems?
	What are the types and qualities of contextual influences in conjunction with dynamic psychobiological systems for assessing the precursors, concomitant influences, and effects of stress and resilience on cognitive, health, and well-being outcomes in the face of adversity?
	Can population-level inferences be made from studies of stressors if perceptions of stress are highly subjective?
	Can resilience occur in the absence of a stressor?
Characteristics of resilience	Is resilience always desirable? Can a person who remains in a stable but undesirable state have resilience?
	Is resilience more modifiable at certain windows of development?
	Do people who live very long lives inherit high levels of resilience?
	Are resilience measures specific to pathways and molecular systems? Do they correlate with clinical outcomes?
	Is cellular senescence a proxy for resilience?
	Which factors can boost prestress reserve?
	Is resilience an observable or latent reserve?
	Which characteristics of older adults and populations are associated with a resilient response to acute and post-acute COVID-19?
COVID-19 as a natural experiment	Which molecular and immunological mechanisms underlie reserve and resilience with aging to acute and post-acute COVID-19?
	What are optimal analytical approaches to address questions regarding resilience and COVID-19?
	Which factors and mechanisms underlie long-lasting immunity to COVID-19 vaccination in older adults?
	Which clinical measures can be used to assess resilience before, during, and after SARS-CoV-2 infection?
	How can the duration of COVID-19 vaccine efficacy be prolonged?
	What are the mechanisms of SARS-CoV-2 cell entry and replication in the cells of older adults?
	How can computational and informatics methods be used to integrate emerging multi-modal data for COVID-19 diagnosis, prevention, and treatment in older adults?
	Which interventions before, during, or after COVID-19 can augment reserve and resilience and improve health outcomes?

	Are people who never had a functional decline after developing COVID-19 resilient?
	How has the COVID-19 pandemic affected older adults in different living situations and in different communities in the United States and other countries?
	Can studies (e.g., natural history studies) combine assessments of current and historical stressors?
Methods and study designs	Is it possible to capture what a stressor did to a system and how that system regulated itself?
	Can stress tests in each of the three domains (or a single stress test for all domains) be developed for resilience research?
	Can more diverse clinical trial and cohort study populations provide better information on the scope and distribution of different resilience outcomes?
	Can data be collected and models be developed that can be used jointly to assess the interplay between short- and long-term factors in resilience development?
	Can existing cohort study data be leveraged to investigate resilience? If so, it is expected that extensive data science efforts will be needed to bring these to data analytic readiness and produce valid findings from them: Can generalizable pipelines be developed?
	Can theories about the mechanisms governing physiologic (underlying) resilience be refined and evaluated when fit to coarse human data?
	Can social-biological phenotyping be standardized by promoting more routine inclusion of the exposome in traditional biological assessments? Can the scientific capacity to conduct this work expand?
	Which hybrid data analytic methods can leverage the best aspects of both theory-driven and empirical approaches?
	Which creative study designs can be used to measure subsets of samples intensively to determine what drives missingness and correct for it?
	Can a framework developed for resilience in one domain (i.e., cognitive, physical, or psychosocial) apply to resilience in other domains?
	Are subgroup-specific approaches needed to promote resilience?
	Which hybrid models can be used with the best theory-driven, empirical approaches?
	How can findings from resilience research be translated into patient care?
Translational research	Will understanding the factors that affect resilience help clinicians better assess a patient's resilience or lack thereof?
	Which population-scale approaches can enhance resilience?
	Can promoting variety in the activities of older adults enhance resilience?
	Can high-intensity interval training promote resilience?
	How can resilience research lead to interventions to improve outcomes that matter to patients?
	Can the cost of resilience be shifted from the person to the system to create a form of facilitated resilience?

Figure 1. Domains of Resilience in Older Adults

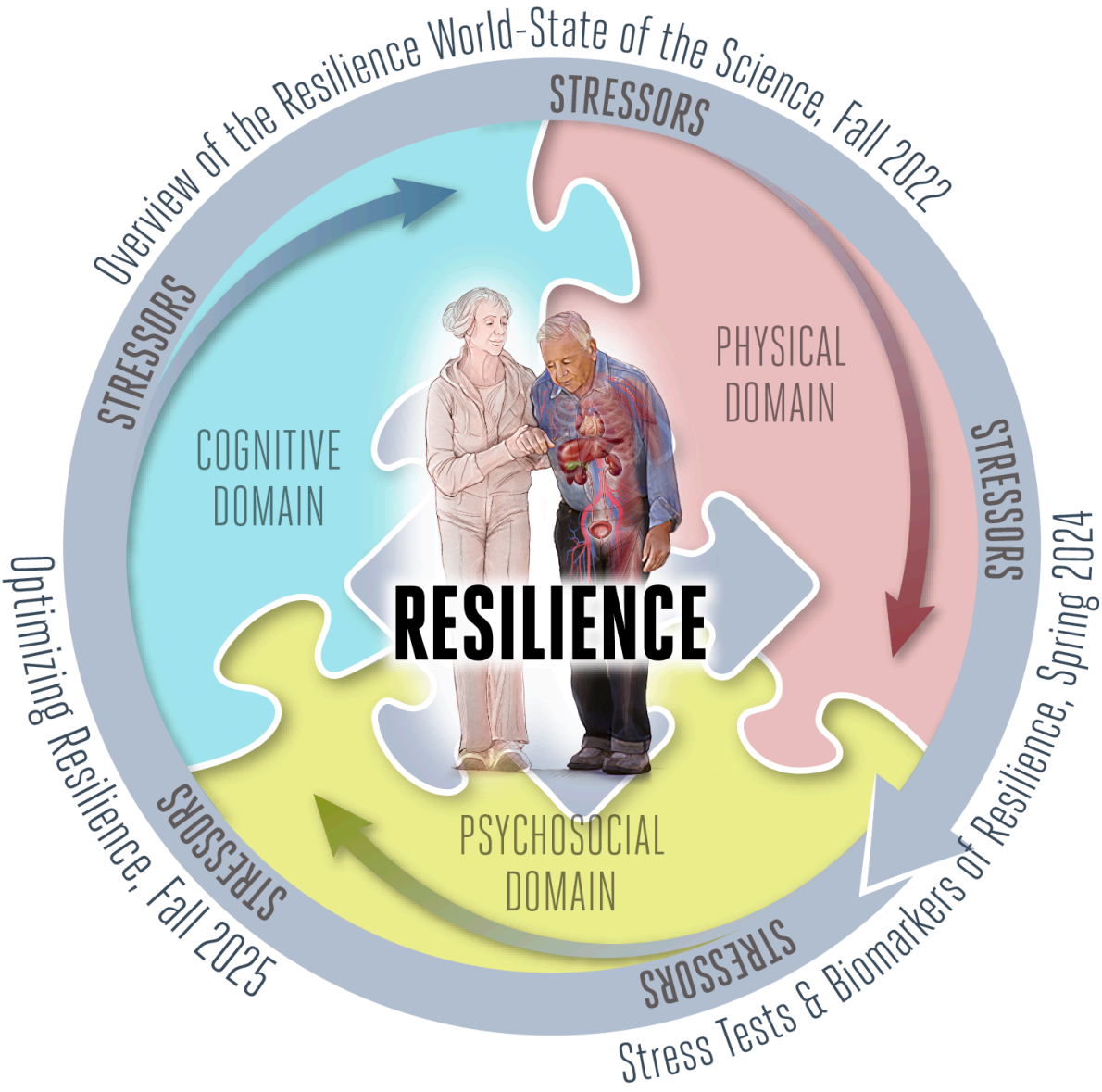

Figure 2. Summarizing frameworks of Resilience that are prominent in different domains of aging research, at the center are dynamics of resilience across life span illustrated by the "warp and woof" analogy to describe the short and long term changes in resilience over time.