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REVIEW

The New Frontier of Perioperative Cognitive Medicine for Alzheimer's Disease and Related Dementias

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Abstract
This is a review of preoperative cognitive assessment and other healthcare gaps in the care of older adults at risk for Alzheimer's disease and related dementias (ADRD) who have elected surgery with anesthesia. It summarizes concerns regarding ADRD perioperative healthcare, perioperative cognitive, and neuronal domains of vulnerability. It also offers a plan for phased preoperative cognitive screening and perioperative cognitive intervention opportunities. An argument is made for why medical professionals in the perioperative setting need fundamental training in cognitive-behavioral principles, an understanding of neurodegenerative diseases of aging, and an appreciation of the immediate and long-term medical risks for such patients undergoing anesthesia. The author's goal is to encourage readers to consider perioperative cognitive medicine as a new frontier for generating evidence-based care approaches for at-risk older adults with neurodegenerative disorders who require procedures with anesthesia.

Keywords Anesthesia · Cognitive disorders · Evidence-based medicine · Delivery of health · Delirium · Neuropsychology

The World Health Organization predicts that by 2050, 2 billion people will be 60 and older, up from 1 billion in 2020 [1]. The number of persons aged 80 years or older is expected to triple and reach 426 million by 2050, with 21% of adults being 85 years and over [2]. Accompanying this change in population age will be increased rates of noncommunicable disorders impacting brain function, including cerebrovascular disease (small and large vessel), neurodegenerative disorders such as Parkinson's disease, dementias such as Alzheimer's disease (AD), and depression. For example, AD is currently diagnosed in at least 1 out of 9 people (11.3%) age 65 and older in the total US population [3]. Between 2020 and 2025, every state in the USA is expected to experience an increase of at least 6.7% in the number of individuals with AD. Certain states in the West and Southeast are projected to experience even more significant increases in dementia; Florida is projected to increase 24% from 2020 to 2025 (from 580,000 to 720,000 individuals age 65 and older with AD) [3].

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ADRD and Perioperative Healthcare Concerns

Increases in population percentage of AD and Related Dementias (ADRD) will impact the function of states' health care systems, including perioperative care. Currently, low- and high-risk surgical procedures are performed annually on more than half a million patients aged 65 and older [4]. At least 20–35% of older patients undergoing surgery have signs of a mild to major neurocognitive disorder [5–7]. Given the expected rate increase of neurodegenerative disorders in the populous, perioperative healthcare systems will face more significant numbers of individuals with early to late-stage AD [8] and other neurodegenerative diseases needing procedures with anesthesia due to severe health-related conditions (e.g., cardiac) or requesting surgeries for quality of life improvement (e.g., joint replacement) [4].

Individuals with memory or cognitive disorders who elect surgery with anesthesia present challenges to providers concerned about decision-making capacity, initial procedural planning, and discharge complications. Researchers report how older individuals classified with major neurocognitive disorder had poor pre-colonoscopy bowel preparation and higher no-show rates for procedures [9], increased use of emergency and rehabilitation services [10], and prolonged hospitalization and complications [11–15]. Preoperative cognitive-behavioral profiles predict postoperative clinical complications, hospital cost, discharge complications, and lost services [16–18]. Failure to identify preoperative cognitive vulnerabilities, therefore, decreases medical care efficiency.

Failure to identify preoperative cognitive vulnerability or the presence of neurodegenerative disease also places patients at risk. Older individuals with reduced cognitive functions are at greater risk for postoperative neurocognitive difficulties and mortality. This is most comprehensively explained in a well-written review by Oresanya, Lyons, and Finlayson (2014), summarizing preoperative clinical features associated with mortality and delirium. Of the studies reviewed from 2000 to 2013, authors concluded that the presence of a clinical diagnosis of dementia or impairment on general cognitive screeners was independently associated with perioperative mortality and a 2- to 17-fold increased risk for postoperative delirium (of note, postoperative delirium experience is a significant risk factor to later cognitive decline [19–21] and greater mortality ([22], see [23] for a review)). Neurodegenerative disorders without dementia, such as Parkinson's disease, are also vulnerable [24, 25]. Retrospective studies reviewing hospital or national database systems indicate that a diagnosis of PD is associated with higher rates of postoperative delirium, cognitive decline [26], prolonged hospitalization, increased risk of recurrent dislocation within their first postoperative year, and poor long-term prognosis relative to non-PD patients who underwent the same procedures [27]. Other independent older adult risk factors for neurocognitive complications include fewer years of educational attainment, depression [28–30], frailty [31, 32], and presurgical evidence of a non-symptomatic stroke and presurgical neuroimaging markers of atrophy [33–35]. Overall, preoperative indicators of peripheral and central nervous system integrity correlate strongly with older adults' postoperative surgical success.

Vulnerable Cognitive/Neuronal Systems

Investigations using neuropsychology metrics identify vulnerability in systems of processing speed, working memory, inhibitory function, and episodic memory. Individuals with lower preoperative working memory and episodic learning/memory scores have higher rates of delirium after cardiac and non-cardiac surgeries (e.g., [16, 36]). Rigorous prospective neuropsychology studies assessing type and severity of postoperative cognitive decline for cognitively well older adults after orthopedic surgery report lower post-surgery scores on measures of working memory, inhibitory, and episodic memory relative to non-surgery peers [35, 37]. Authors suggest surgeons can expect 15% of their older adult non-cardiac surgery patients to experience at least mild acute postoperative memory disturbances (1 standard deviation decline from baseline), with approximately 11% of all patients experiencing executive (inhibition/working memory) complications alone or in combination with memory problems [37]. High-risk older individuals undergoing aortic valve replacement reports have lower scores on working memory/inhibition tests at 4 to 6 weeks, relative to older adults with similar cardiovascular disease who did not have surgery [34]. Although postoperative cognitive dysfunction abates by one-year post-surgery for most cognitively well older adults [34, 38–40], the neuropsychology domain findings implicate specific brain systems vulnerable to perioperative stressors.

Prospective perioperative neuroimaging studies provide corresponding evidence. For cognitively well older adults electing orthopedic surgery, the severity of preoperative white matter disease predicts greater pre- to postoperative working memory and inhibitory change [35]. In what is known as the signature of AD-related cortical atrophy [41], thinner structural cortical thickness measurements predict postoperative delirium for individuals without dementia, with predictive power highest in the superior frontal gyrus [41]. Thinner entorhinal cortices, greater volume of white matter disease, and larger ventricles also explain intraindividual variability on two-channel derived EEG measures for older adults electing orthopedic surgery with general anesthesia [42], acute measurements in microstructural intra-extracellular free water [43], and pre- to postoperative functional network changes [44].

Functional brain MRI studies show perioperative change to the cingulate cortex, specifically the posterior cingulate cortex (PCC). The PCC plays a prominent role in pain and episodic memory retrieval, topographic and topokinetic memory (orientation of the body in space), and working memory information transfer. Functional changes occur in the PCC from pre to 6 weeks post-cardiac surgery [45]. Reduced functional connectivity involving anterior and posterior cingulate cortex nodes also occur within 48 h after total knee arthroplasty with general anesthesia [44]. These changes are most noticeable for individuals meeting research criteria for mild cognitive impairment, and the reduction is marked within the PCC and angular gyri [46]. Anesthesia research implicates the PCC during sedation [47, 48], and functional MRI delirium investigations identify abnormal interactions between PCC and the dorsolateral prefrontal cortex [48]—a region necessary for working memory [49]. Cholinergic input to the cingulate cortex and frontal–temporal-parietal cortices is dependent on the Basal Nucleus of Meynert (BNM), an essential nucleus for cholinergic transmission. The cholinergic projections provide the chemical shift between synchronous versus dyssynchronous states of cortical activation mediating consciousness [48] and response to anesthesia [50].

Cognitive and neuronal systems implicated in perioperative risk profiles overlap with those observed in common dementias and neurodegenerative disorders (e.g., AD, small vessel vascular dementia, and PD with or without dementia) as well as major depression [51] and chronic pain [52]. For example, the number of cells within the BNM decreases with normal aging. It is accentuated for individuals with prodromal neurodegenerative disorders presenting signs of executive and declarative memory dysfunction (e.g., AD [53, 54] and PD [55]). We can now surmise why preoperative clinical diagnosis of dementia or memory/executive dysfunction has a 2- to 17-fold increased risk for delirium. Preexisting vulnerability places the brain at risk for symptom onset or disease acceleration after perioperative stressors—i.e., brain reserve and the threshold theory [56].

Biomarker Considerations

The perioperative environment is essentially a "stress test" involving at minimum disrupted sleep, activity changes, exposure to new medications, anesthesia, and acute pain. One or more of these "stressors" may contribute to neurodegeneration and increased vulnerability to tau and amyloid-beta accumulation. Although some associations remain controversial [57], studies show how sleep disruption [58, 59] and physical activity levels [60] contribute to increased generation and aggregation of amyloid β in cognitively well older adults. Rodent studies link general anesthesia-induced apoptosis to increased generation and aggregation of amyloid β [61–63] and increased tau hyperphosphorylation [64]. Through the mediation of glucocorticoids, stress responses may stimulate these actions [65–67]. Individual susceptibility combined with stressors within the perioperative experience may result in delirium.

Due to the heterogeneity of dementia and the familial and sporadic neurodegenerative disorders developing in the older adult population [68], it appears too simplistic to rely upon biofluid biomarkers alone for perioperative risk detection. Apolipoprotein E (ApoE) allele 4, the most robust genetic risk marker for late-onset AD, does not predict delirium [69–73] and has mixed findings for predicting postoperative cognitive dysfunction [74–76]. It only indirectly modifies the relationship of delirium when postoperative protein markers of biological stress are considered [73]. Further, associations between the levels of cerebrospinal fluid amyloid and tau biomarkers with disease severity or rate of AD progression remains inconsistent [77–79]. Factors such as age, sex, comorbidities, medications, lifestyle factors, and genetic variation also impact the clinical interpretation of these biomarkers [80]. Future researchers will need to integrate biomarker metrics with patient demographic, clinical, and psychosocial characteristics to improve risk detection and perioperative intervention approaches.

The Translational Call to Action

International and national anesthesiology societies and some surgery position papers are actively recommending providers regularly address perioperative brain health for older adults [81–85]. Although in 2013, the United States Preventive Services Task Force (USPSTF) refrained from recommending routine screening for cognitive impairment (citing stress-related to misdiagnosis and the absence of efficacious treatment to mitigate cognitive decline, thereby reducing the potential benefits associated with early detection of dementia) [86], the new 2019 American College of Surgeons Geriatric Surgery Verification (ACS GSV) Program [87] strongly recommends preoperative and postoperative cognitive and functional status screening for older adults electing surgery. Differentiating delirium from dementia has been particularly challenging in a postoperative setting if the patient has no caregiver or has no medical history and no dementia diagnosis or cognitive screening recorded [88]. Completed preoperative cognitive screening documents should be attached to medical records for postoperative multidisciplinary care teams and primary care physician reviews. Based on the ACS GSV recommendations and the plethora of growing data showing the importance of preoperative cognition on outcomes, perioperative medical teams are now faced with the dilemma of which measure(s) to choose, how to use them in the clinical setting appropriately, and how to adjust individual patient care.

Colleagues in the American Society of Anesthesiology (ASA) and the International Anesthesia Research Society (IARS) are now collaborating with neuropsychologists and geriatricians to address perioperative "brain health" status [89]. Anesthesiologists have pushed the concept of a "perioperative surgical home" for patient care [90–92], emphasizing the triple aims of improving health, improving health care delivery, and reducing the cost of care. Anesthesiologists and surgeons are not trained in brain-behavioral approaches; However, professionals with an understanding of brain-behavioral profiles (e.g., neuropsychologists, geriatricians, and behavioral neurologists) are needed to bridge the gap within the perioperative setting to address brain-anesthesia interactions [5, 93–95].

In 2019, the Society for Perioperative Assessment and Quality Improvement (SPAQI) convened experts in neuropsychology, geriatric medicine, and anesthesiology to review the literature and compile a comprehensive list of cognitive screening tools used within primary care and preoperative settings. The team identified seven cognitive screenings previously used in preoperative settings with administration time ranging from 1 to 10 min [94]. These tests included clock drawing (to command and copy conditions) [96], the Mini-Cog© [97], mini-mental state exam [98], months backward [99], short-blessed test, and the short orientation memory concentration test [100, 101], telephone

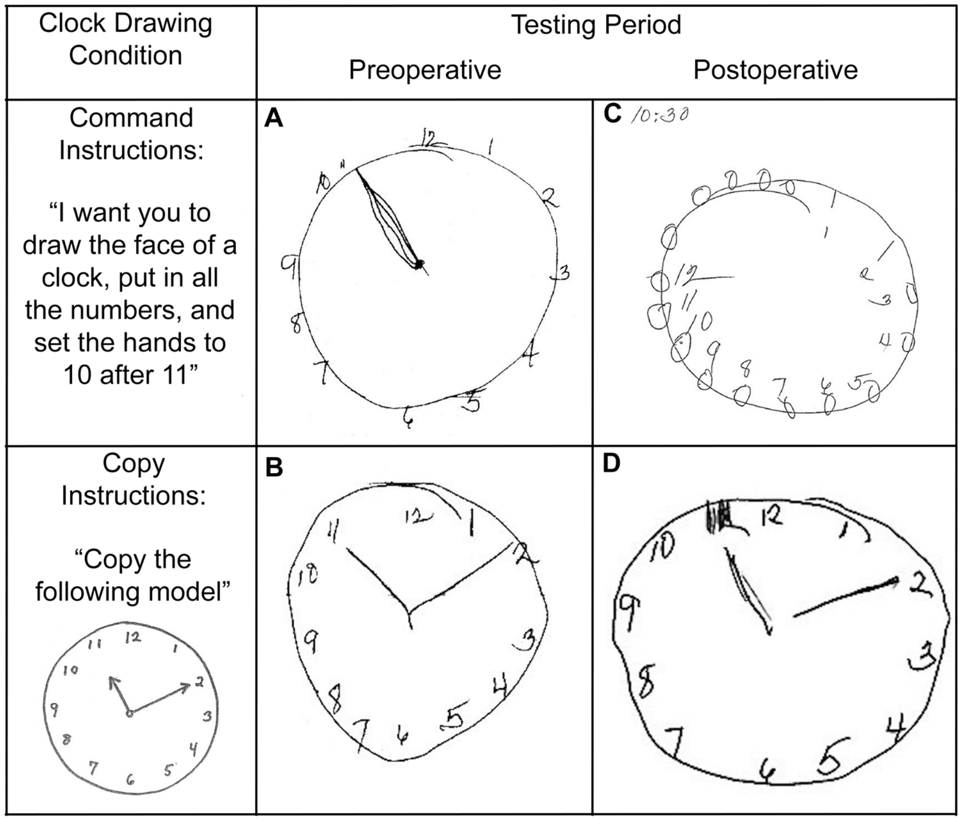

Fig. 1 Clock drawing test to command and copy conditions completed preoperatively (7 days before surgery) and postoperatively (42 days postoperatively) in a 76-year-old individual. Preoperative drawings show frontal compromise on the command condition (**A**, incorrect hand placement, gap in number spacing) and subtle signs in the copy condition (**B**, hands touching numbers, hands equal in length, gap in number spacing). Postoperative drawings show frontal impairment in command condition (**C**, increased perseverations, intrusions, incorrect number placement, missing hands) with subtle signs in the copy condition (**D**, hands of equal length, number gaps, self-correction of hand and number)

interview for cognitive status [102], and time and change [103]. Of these, tests with some element of clock drawing are the most reported in the perioperative literature [5, 6, 11, 17]. This is likely due to its long history as a rapid cognitive screener (particularly for dementias [96, 104]), a wide variety of scoring options, and the stimulus value a patients' drawing provides for rapid recognition of cognitive impairment (Fig. 1). However, the test is associated with interrater reliability difficulties [105, 106] unless error analyses are used.

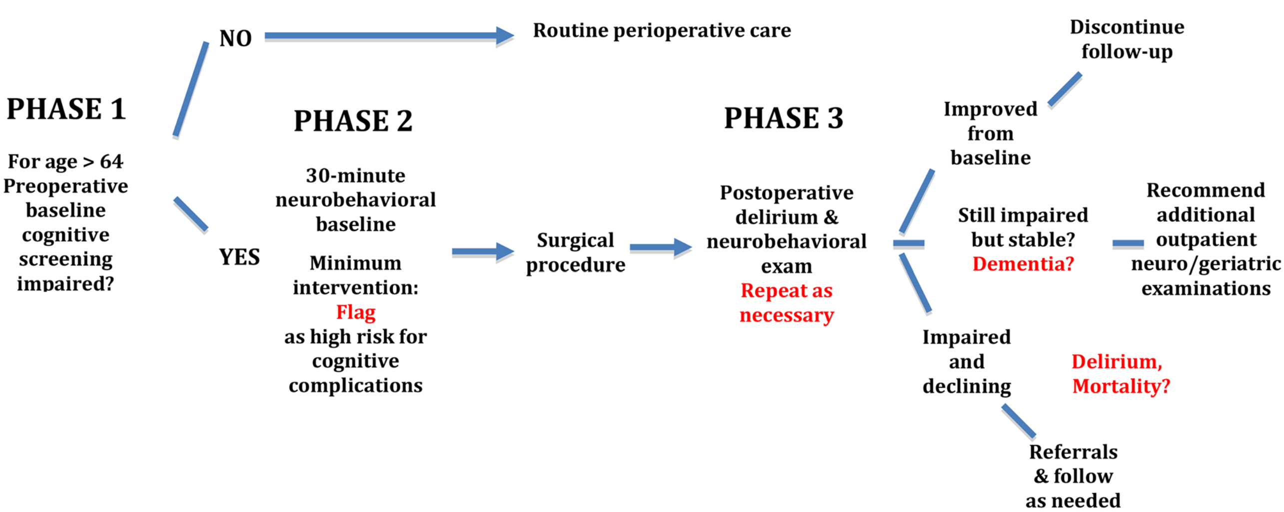

Fig. 2 A staged model of perioperative care for adults age 65 or older electing major surgery with anesthesia and entering a preoperative anesthesia clinic. Phase one and two are currently active at the University of Florida, Gainesville, Florida. Phase three involves geriatric medicine provider assessment using baseline evaluation from phase two as a preoperative reference

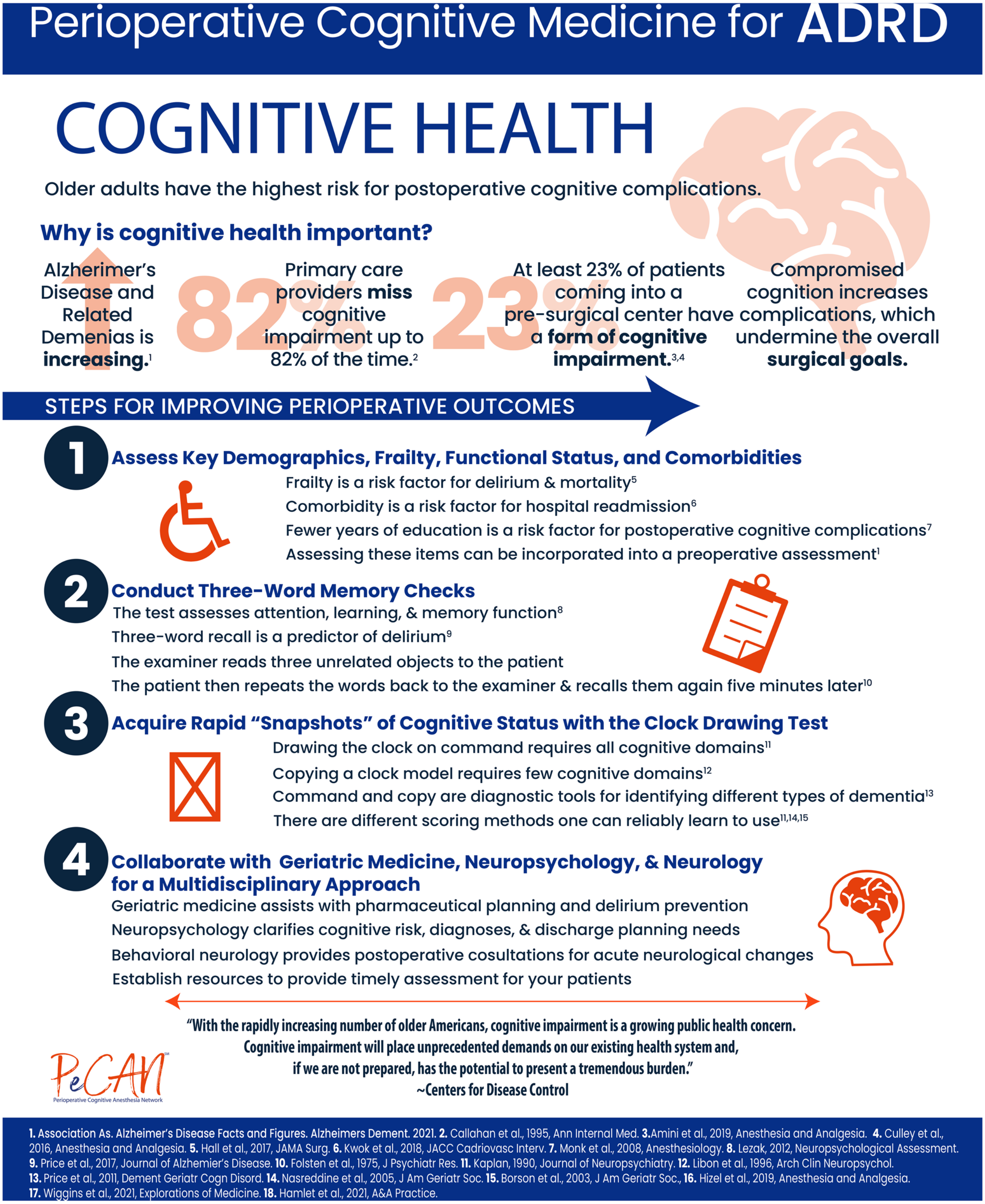

Fig. 3 Information graphic summarizing statistics and rationale for a perioperative cognitive medicine program for ADRD with cognitive screening stages

The Future of Digital Cognitive Capture Tools

Researchers have begun to explore the value of digital capture tools for data gathering field [107] to assist with the cognitive screener time constraints and interrater scoring difficulties. For example, research teams have employed digital technology to assess preoperative nuances during the visuoconstruction of clock drawing for adults aged 65 or older electing surgery with anesthesia [17, 107, 108]. Using a set of normative data from cognitively healthy adults [109] and cluster classification [110, 111], teams show how specific timed metrics and graphomotor features within the command and copy clock condition provide insight into neurodegenerative disorders [111, 112]. Applying this digital technology research in the perioperative setting reveals subtle behaviors predictive of postoperative outcome, including length of stay and hospital cost after certain surgeries [17]. Key elements of the clock drawing change after surgical procedures [108]. Relative to the command condition, the copy condition appears most beneficial for predicting outcome [5, 17], supporting previous assertions that command and copy conditions provide specific information about brain-behavioral profiles and as a unit are diagnostically meaningful [106, 113]. The field faces challenges with rapid digital test applications for disease detection in perioperative settings. We know little regarding clock drawing profiles in patients from diverse backgrounds such as non-Native English speaker status, individuals with few to years of formal education, and reading difficulties [94]. These issues require careful consideration before large-scale digital technology application.

A Multidisciplinary Approach

Suppose clinical screening with a brief test such as the Mini-Cog© field [11] or command/copy clock drawing field [5] can be incorporated into a preoperative anesthesia clinic. In that case, the next question involves what to do with the acquired information. Some sites have developed staged assessment programs. Duke University refers patients to geriatricians for optimization (e.g., Perioperative Optimization of Senior Health, POSH) [18] to reduce negative postoperative outcomes [114]. The University of Florida has embedded neuropsychology practitioners into a preoperative anesthesia clinic to provide immediate neurobehavioral differential diagnosis, perioperative recommendations, and post-operative referrals (i.e., Perioperative Cognitive Anesthesia Network, PeCAN; [115, 116]; Figs. 2 and 3).

The PeCAN clinic, for example, works in stages. Phase one involves medical staff acquiring information on a patient's years of education years, frailty [117], clock production to command and copy [96, 118], and 3-word recall [119]. If signs of compromise are noted per screening guidelines, providers immediately refer the patient to an on-site neuropsychologist who conducts an interview and neurobehavioral status exam [120]. The evaluation concludes with immediate patient feedback with recommendations and a routed to the surgical team and primary care providers. The review does not recommend surgical cancellation but rather highlights risks and recommendations for discharge planning [95, 115, 116]. The POSH and PeCAN program provide opportunities for tailored individual care with the perioperative medical team (e.g., [114, 115]).

These preoperative cognitive clinical services also provide crucial venues for cross-pollination between disciplines for education and research purposes. Multidisciplinary team members engage in clinical science problem solving by addressing preoperative, intraoperative, and postoperative cognitive care dilemmas. This focused preoperative clinical setting can also assist with ADRD perioperative research investigation recruitment (see [121] for a review of traditional recruitment challenges).

Summary

Anticipated ADRD rates will challenge our healthcare system. Providers will observe increased rates of delirium and postoperative cognitive complications (accelerated cognitive change) in our older adult population within the hospital and after discharge. This is mainly because individuals with ADRD are not sufficiently identified preoperatively, and care systems lack evidence-based perioperative medical approaches for ADRD. Consequently, preoperative identification of ADRD is critically essential for enhancing recovery from surgery in every facet.

Healthcare systems currently have limited fundamental staff with training in cognitive-behavioral principles, neurodegenerative disease profiles, delirium, and medication interactions. To date, the brain is not routinely considered a vital organ to preoperative assessment. However, it is the organ directly targeted by general anesthesia, essential for sympathetic and parasympathetic responses, and experiences traumatic transformation with neurodegenerative disorders. Anesthesiologists are leading the call for older adult brain health awareness. The American Board of Anesthesiology's exam includes a few questions on geriatric anesthesia/aging relative to fifteen or more for pediatrics (https://theaba.org). Geriatric clinical care also appears to be dwindling for older adults. For the past 5 years, geriatric medicine has had one of the lowest match rates for fellowship specialty training [122]. There are no evidence-based care methods addressing anesthetic agents or doses for individuals with ADRD. Hospitals are not routinely integrating behavioral strategies for reducing the risk of cognitive complications such as delirium [123]. Further, delirium training is minimal within most hospitals [124], and delirium assessments are not routinely performed [125].

We can improve healthcare services and quality by expanding the perioperative clinical team to include neuropsychologists and geriatricians well-versed in cognitive-behavioral profiles and intervention planning. Multidisciplinary high-risk surgery committees may improve perioperative decision-making, particularly for high-risk ADRD surgical patients [126]. This goal is consistent with The United Nations General Assembly who declared 2021–2030 the Decade of Healthy Ageing [127] and the Anesthesia Brain Health Initiative. Identifying ADRD preoperatively is critically important if we are going to enhance recovery from surgery. This could be the most significant benefit of this new frontier in medicine.

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