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SPECIAL ARTICLE

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Moving geroscience from the bench to clinical care and health policy

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Abstract

Geriatricians and others must embrace the emerging field of geroscience. Until recently geroscience research was pursued in laboratory animals, but now this field requires specialized expertise in the care of vulnerable older patients with multiple chronic diseases and geriatric syndromes, the population likely to benefit the most from emerging therapies. While chronological aging measures the inevitable passage of clock time that occurs equally for everyone, biological aging varies among individuals, and importantly, it is modifiable. Advances in our understanding of biological aging, the discovery of strategies for modifying its rate, and an appreciation of aging as a shared risk factor for chronic diseases have jointly led to the Geroscience Hypothesis. This hypothesis states that interventions modifying aging biology can slow its progression—resulting in the delay or prevention of the onset of multiple diseases and disorders. Here we wish to report on the Third Geroscience Summit held at National Institutes of Health on November 4–5, 2019, which highlighted the importance of engaging other disciplines including clinicians. Involvement by scientists with expertise in clinical trials, health outcomes research, behavioral and social sciences, health policy, and economics is urgently needed to translate geroscience discoveries from the bench to clinical care and health policy. Adding to the urgency of broadening this geroscience coalition is the emergence of biological aging as one the most important modifiable factors of COVID-19, combined with the inability of our society to once again recognize and confront aging as a priority and opportunity when facing these types of public health emergencies.

KEYWORDS

aging, economy, geriatricians, geroscience, social

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UNRAVELING THE MYSTERIES OF BIOLOGICAL AGING

Aging is no longer the profound mystery or mere fodder for speculation and fantasy it once was. In 1973, only two decades after the publication of the first issue of this journal and a year before the establishment of the National Institute on Aging (NIA), the seeds of geroscience were planted when Dr Bernice Neugarten and Dr Robert Havighurst from the University of Chicago organized a scientific conference focused on the possibility and appropriateness of using knowledge from basic biology to extend longevity in humans.[1,2] Since then, biologists have discovered mutations in genes that radically extend lifespan and rates of aging in simple model organisms such as the nematode worm *C. elegans*.[3] Others observed that mammalian cells have a limited potential for division and that this represents a normal part of aging in vivo.[4,5] It had been speculated, incorrectly, that aging evolved under the direct force of natural selection, and that it reflects simple inherited clock-like mechanisms that might potentially be turned off or on at will. Instead, it is now clear that aging is far more complex with many genes influencing lifespan and/or healthspan.[6]

Key Points

- Geroscience-guided interventions are poised to transform our ability to influence clinical trajectories and improve outcomes in older adults.
- Geriatricians need to remain aware of developments in the field of geroscience.
- Geriatricians and others with expertise in clinical trials, health outcomes research, behavioral and social sciences, health policy, and economics can contribute to moving geroscience-guided discoveries from the bench to the realm of clinical care and ultimately health policy.

Why Does this Paper Matter?

This paper discusses how geriatricians, as well as investigators with expertise in clinical trials, health outcomes research, behavioral and social sciences, health policy, and economics evaluation can help move the field of geroscience from the bench to clinical care and health policy.

DISCOVERING WAYS OF MODIFYING BIOLOGICAL AGING

It soon became apparent that manipulating the rate of biological aging is surprisingly easy using behavioral manipulations, genetic tinkering, and drug-like molecules.

In addition to decades of research demonstrating the benefits of dietary restriction, we also saw the emergence of pharmacological approaches. First among these were studies conducted using simple animal models and then mice, demonstrating that targeting pathways such as mTOR (mammalian target of rapamycin) signaling with drugs or drug-like molecules could also extend lifespan[7] and healthspan.[8] Studies soon followed showing an impact on lifespan and healthspan in animal models with acarbose, the synthetic nonfeminizing steroid 17α-estradiol and many others[9] with sex differences in terms of benefits of some compounds.

BIOLOGICAL AGING AS THE GREATEST MODIFIABLE RISK FACTOR FOR CHRONIC DISEASES

Aging is now recognized as the largest risk factor for most chronic diseases, including diabetes, cardiovascular diseases, cancer, dementia, and many others that contribute to lost function and decreased quality of life at later ages. Could it be that by understanding the biological mechanisms of aging itself we would find ways to influence the course of these diseases? This question became more meaningful when it became apparent that the biological processes being studied that influence lifespan were similar to those being studied as causes of individual diseases. Intracellular signaling pathways such as those that respond to nutritional status (the mTOR and insulin response pathways) or stress (molecular chaperones, autophagy) that were having profound effects on the lifespan of simple invertebrate models, were also the focus for causal studies of diseases as diverse as cancer and Alzheimer's disease.[6,10]

THE GEROSCIENCE HYPOTHESIS

The interface between chronic disease studies and normal aging became known as geroscience.[11–13] This multidisciplinary field is grounded in the Geroscience Hypothesis which states that strategies designed to modify biological drivers of aging will not only slow the progression of biological aging but will also prevent or delay the onset of multiple chronic diseases. An earlier version of geroscience first appeared under the label of the Longevity Dividend[14]—but the logic behind these concepts is identical. We have since learned a great deal about the commonality of normal aging mechanisms and the

earliest events in the etiology of age-related diseases. Nonetheless, to this day very few clinicians involved in the care of older adults are aware of the existence of this field of research or its implications for their patients. Given geriatricians' specialized expertise in the care of vulnerable older adults with multiple chronic diseases and geriatric syndromes, the population most likely to benefit from geroscience-guided therapies, there is now a tremendous opportunity for geriatricians to become integrally involved in the development of the geroscience field.

AREAS OF COMMON GROUND BETWEEN GEROSCIENCE AND GERIATRIC MEDICINE

Given the origins of geroscience in the biological sciences, one would expect that professional interactions between basic scientists studying the biology of aging and clinicians providing care for older adults would be rare. Nevertheless, a variety of common threads involving shared interests, common goals, and conceptual principles have emerged. After the Third Geroscience Summit organized in 2019 by the trans-NIH Geroscience Interest Group (GSIG), authors of this report gathered to consider such implications.

Geroscience targets multiple morbidity

The Geroscience Hypothesis is focused on multiple morbidity since it seeks to delay the onset and progression of multiple chronic conditions simultaneously.[11] While improvement in multiple disparate chronic diseases represents the goal of geroscience, researchers studying multiple chronic conditions have struggled with efforts to move from descriptive studies to the development of effective interventions. Moreover, since geroscience seeks to achieve its goals by targeting shared biological mechanisms (aging) and their influence on multiple disease endpoints, the geroscience approach is highly congruent with earlier studies that had focused on the contribution of shared risk factors involving declines in physical and sensory performance for the development of common geriatric syndromes such as falls, urinary incontinence, and functional dependence.[15] Similarly, geroscience is congruent with evidence that interventions such as diet, exercise, and increased physical activity can improve varied downstream clinical outcomes.[16–18] Therefore, geroscience and research into multiple morbidity will likely inform each other, accelerating progress in both fields.

Geroscience needs to emphasize function and healthspan

While geroscience was created more as a vision based on recent advances in our understanding of the basic biology of aging,[12,19] a wealth of animal model studies now support these concepts.[7] Moreover, a geroscience-guided approach to medicine shares geriatricians' focus on health, function, and multimorbidity as opposed to traditional single disease paradigms (Figure 1). Over time, advances in geroscience have indicated that in multiple different animal models of aging, and related chronic diseases, longevity could be manipulated by a variety of genetic, behavioral, and pharmacological means. Most importantly, in most of those paradigms, there was a very strong correlation between extension of lifespan and enhancement of health (the so-called healthspan).[20] Thus, basic biologists turned eager to test these ideas further. As a result, it soon became obvious that further advances in geroscience would necessitate the recruitment of clinicians working in the field, because ultimately, clinicians and others skilled in conducting clinical trials will need to translate to humans hypotheses put forward by basic scientists. As an early example of this synergism, a consortium funded through the Division of Aging Biology of the NIH, and active between 2013 and 2016, came out with a series of proposals for the clinical advancement of geroscience principles.[21] Nevertheless, it is clear that geriatricians can offer important guidance into the use of tools for measuring functional performance from the perspective of mobility, cognition, and social and behavioral factors when testing geroscience-guided therapies.

Geroscience reconciles biological reductionism with geriatric complexity

Real-world patients rarely resemble hypothetical case studies taught in medical school. Training, clinical, and research programs have always been organized along neat and seemingly logical lines guided by a focus on individual organs or provider skillsets. Yet, clinical presentations, needs, and personal preferences of older patients often defy and come into collision with these silo-based approaches to clinical care. These issues resonate especially powerfully in the context of multiple morbidity involving common chronic diseases, and geriatric syndromes. The multifactorial complexity of common geriatric syndromes such as frailty, delirium, falls, and urinary incontinence has long hindered the development of strategies for prevention or treatment that would be guided by any specific mechanisms. Moreover, all of

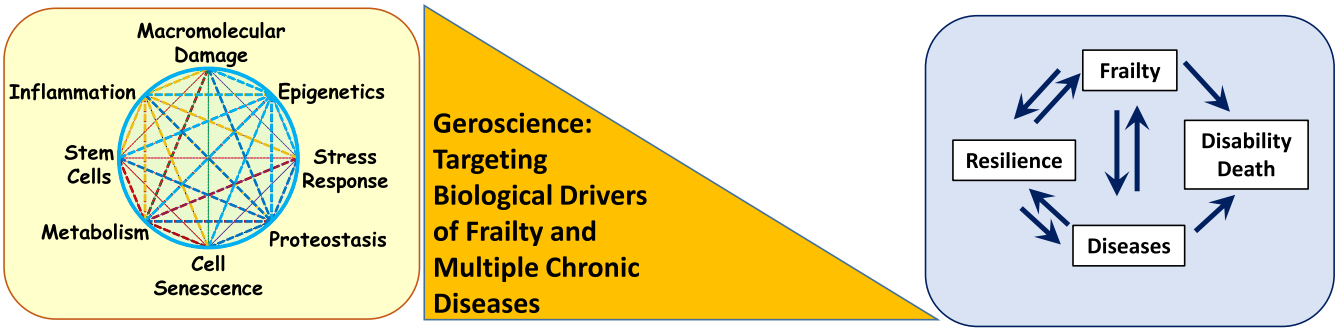


FIGURE 1 A geroscience-guided approach to medicine shares geriatricians' focus on health, function, and multimorbidity as opposed to traditional single disease paradigms. Biological hallmarks of aging (yellow) contribute to the progression from resilience to frailty, varied chronic disease, and disability (blue) impacting function and providing opportunities for geroscience-guided approaches (orange) designed to slow the onset and progression of chronic diseases and disability

these concerns and obstacles are further amplified by additional complexity and inter-individual heterogeneity introduced by the coexistence of clusters of co-existing chronic conditions that differ between individuals.

Most experienced clinicians tend to be justifiably skeptical of "magical" solutions to the vexing real-world clinical challenges outlined above, especially when these seem naively simplistic. In fact, reductionist principles upon which most basic science is based often seem in direct opposition to the multifactorial nature of all aspects of geriatric care.[22] In this context, it seems almost nonsensical to speak of clinical solutions grounded in studies of a single gene, molecule, biological pathway, or theory of aging.[22] For example, most studies of Alzheimer's disease pathogenesis have focused on the role of single gene mutations on the development of plaques and tangles in young animals, ignoring the impact of biological aging and related pathologies such as vascular disease.

The interplay between aging biology and disease is complex and mutual, where not only is aging biology the main driver for most chronic diseases, but progression of such conditions can significantly accelerate the aging process, leading to a vicious cycle where the additional of each disease or condition further accelerates the appearance of the next one.[23] Treating each disease as it appears conforms to what is in medical textbooks: treat that disease as specifically and as early as possible! This approach was successful against acute diseases of defined external etiology representing the major scourges of humankind before the 20th century. However, a similar approach will not be as effective against the chronic diseases of complex etiology of the 21st century. In addition, our arsenal is unfortunately not perfect, and in the case of chronic diseases the treatments are often insufficient. As a result, even if it is under control, that disease, combined with the advancing age of the patient, will often contribute to the appearance of a second condition, then a third, etc., each one at an accelerating pace relative to the previous one. Regrettably, under this scenario, attacking one disease at a time is akin to a game of Whac-A-Mole, where no matter how many moles you can whack, more will appear, and furthermore, many treatments (e.g., gonadal ablation for prostate cancer) have unintended sequelae that may further compromise the patient and the effectiveness of available treatments, a concept referred to as competing risks in epidemiology.

Geroscience offers a path to disease-modifying interventions in geriatrics

Geroscience approaches to slow human aging have begun the march from the laboratory to general medical practice, buoyed by the exciting promise that a single "geroprotective" therapy that slows aging could delay multiple age-related diseases. Guided by research on the cellular hallmarks of aging, model organism studies are yielding treatments that slow the accumulation of deterioration in cells and organs.[24] If successful, this approach carries great potential for offering more than mere palliation, which would allow clinicians for the first time the capacity to modify the trajectory and progression of multiple chronic conditions of aging by targeting biology. The result for patients could be that youthful vigor will be preserved for a longer time period, it will take longer to grow old, and resulting infirmities associated with old age will be compressed into a shorter time frame. While geroscience offers a disease-modifying path in geriatrics, it also represents an exciting opportunity for a new form of preventative medicine at all ages. By implementing anti-aging interventions throughout life, perhaps we can anticipate a delay or suppression of the development of disease in older adults.[25]

Opportunities in designing and implementing geroscience-guided clinical trials

Geroscience-guided or inspired therapies are gradually making their way to become part of clinicians' toolbox. For example, the ClinicalTrials.gov website provides an ever-growing list of ongoing phase 2 and 3 studies evaluating in humans therapies grounded in sound geroscience discoveries including older adults with common geriatric syndromes, and related conditions. Such studies test geroscience-guided therapies as varied as rapamycin, metformin, NAD precursors, and compounds known to possess senolytic properties. Over the horizon beyond tests of these first generation geroscience therapies are efforts to study in humans even more precise and effective compounds. Moreover, the proposed TAME (Targeting Aging with Metformin) clinical trial would offer revolutionary insights into these issues by moving beyond a traditional single disease emphasis to a design which incorporates for the first time, multiple chronic disease endpoints (e.g., cardiovascular diseases, cancer, and dementia) as an aggregate primary outcome measure.[26,27]

Need and opportunities for behavioral and social science perspectives in geroscience

Effective translation of the geroscience agenda into meaningful improvements for our patients and society can only be achieved by incorporating five goals that have emerged from the behavioral and social science of aging (Figure 2).

Moving gero-protective therapies from animals to clinical trials requires grappling with the fact that human aging is influenced by unique behavioral and social factors. People who score high on the personality trait of conscientiousness (who have high levels of self-control, are diligent, planful, and organized) tend to practice health-preserving behaviors, stay healthier longer, have fewer morbidities, and die at older ages. The same is true for people who have better lifelong intellectual abilities, who attain more education, who have stronger social connections and routinely survive to later ages.[28] If participants who volunteer, adhere, and finish a trial are highly conscientious, intelligent, educated, stress-free, socially connected, and psychiatrically robust, the trial will not tell us much about how to slow the aging of people who account for the disproportionate burden of age-related diseases. Gero-protective trials need behavioral expertise in inclusive sampling, adherence, and retention, as well as promoting new-treatment adoption in healthcare settings.

Prospective longitudinal studies document that declines in organ integrity occur years before disease diagnosis therefore gero-protective primary prevention may need to be used by midlife, rather than trying to reverse older adults' established organ damage. However, gero-protective trials face a uniquely human barrier when it comes to outcome measures and traditional trial endpoints such as disease diagnosis or death may be too distant to serve as outcome measures. Clinical trials and longitudinal cohort studies are needed to measure each participant's personal pace of biological aging, and test whether a gero-protective therapy has changed that pace. Gero-protective trials need measures of aging and outcome metrics that are noninvasive, inexpensive, repeatable, reliable, and highly sensitive to biological change, because waiting many years before declaring a therapy efficacious, or not, is unreasonable. Also, with gero-protective clinical trials it is not sufficient to include such measurements only at baseline and immediately upon completion. Interim measures may help establish rate of change while repeated measurements performed upon long-term follow-up can address the stability of these changes. An important application of these tests is to inform trial designers as to which participants have been aging fast or slow before joining the trial. The Dunedin Multidisciplinary Health & Development Study is a longitudinal study of a birth cohort now entering its fifth decade.[29] It has provided unique insights into the impact of aging on broad functional measures, together with tracking a panel of biomarkers to attempt to provide a measure of the rate of aging, onset of functional declines and mortality.[30]

Finally, research into the behavioral and social determinants of health makes clear that to reduce society's burden of disease, any benefits arising from the geroscience agenda must be extended to people most in need. Disadvantaged social groups age fastest and die youngest, so they need gero-protective therapeutics most. Since most volunteers who enroll in gero-protective clinical trials are socially advantaged,[31] gero-protective trials need to address existing health disparities in order to lengthen healthspan for the population, not just the privileged few.

The Longevity Dividend and the need for health outcomes and policy research

A slowdown in the rate of biological aging as proposed through the Longevity Dividend/geroscience initiatives would positively and dramatically alter the future course of health. Models of the future health of the US population demonstrate that if heart disease and cancer show

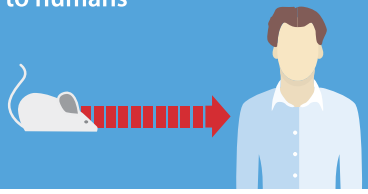
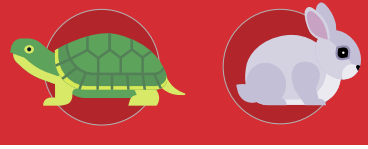
GOAL	CHALLENGE	IMPORTANCE FOR CLINICAL TRIALS
Translate animal models to humans 	Human aging has unique causes (e.g., conscientious personality, health behaviors, cognitive ability, education, social connectedness, adverse childhood experiences, mental illness).	Uniquely human social/ behavioral causes of aging also influence clinical-trial success (i.e., participation, adherence, drop-out).
Recruit midlife as well as older-adult trial participants, to prevent as well as treat disease 	Many social/behavioral causes of human aging begin early in life.	Slowing aging before organ damage may be easier than reversing aging after organ damage. Geroscience interventions can prevent as well as treat late-life diseases.
Develop measures of pace of aging for young to midlife, as well as older, trial participants 	Clinical endpoints of disease and death are too far in the future.	New outcome measures for testing treatment effectiveness of gero-protective prevention trials.
Assess if trial participants' pace of aging is slow or fast at baseline 	Slow agers at ceiling may be unable to show benefit; fast agers may be treatment-resistant, or treatment-sensitive.	Pre-register statistical analyses of baseline pace of aging as a moderator of treatment effect within trial arms, or pre-select trial participants to reduce heterogeneity in pace of aging.
Bring the benefits of geroscience to people who need it most 	Disadvantaged groups age fastest, die youngest, and are unlikely to participate in trials.	To extend healthspan population-wide, gero-protective treatments cannot be restricted to the privileged few.

FIGURE 2 Social and behavioral considerations relevant to the implementation of a geroscience agenda. In considering five distinct goals and respective challenges pertaining to the effective translation of the geroscience agenda from the realm of research to clinical care and population health, a number of key considerations emerge from the world of behavioral and social sciences of aging

linear declines through 2030, the absolute number of healthy people aged 65 and older will rise to about 76 million from 32 million today.[32] If a minor deceleration in the rate of aging occurs, the projected size of the healthy population aged 65+ would rise instead to at least 85 million, and even higher when taking into account the influence of interventions on communicable diseases known to attack compromised immune systems. The economic gains for the United States alone from a minor slowdown in aging—originally estimated in 2013 to be about $7.1 trillion by 2060—would be considerably higher today. Moreover, these estimated benefits could be significantly greater if geroscience-guided interventions also diminished the risk of severe COVID-19 and future pandemics involving other pathogens. With all of these considerations, it is evident that health outcomes and policy research geriatricians and other clinicians must become involved.

FINALLY, WHY IS THE OBVIOUS AND PRESUMABLY GOOD SO OFTEN IGNORED?

Given all the above considerations, why has geroscience not yet involved more clinicians? Historically, scientists studying fundamental aging processes and investigators exploring mechanisms underlying individual chronic diseases rarely interacted. Furthermore, investigations within individual chronic diseases typically either ignored or controlled for chronological age—ironically removing from all consideration the one major risk factor shared by all adult chronic diseases.

Traditional disease-based paradigms which have provided the foundations for our society's approach to health have failed to take into account the multifactorial complexity and growing heterogeneity that defines aging as well as chronic diseases of aging, multimorbidity and common geriatric syndromes.[22,33] Beyond limitations of disease-specific paradigms, there is accumulating evidence of growing inter-individual differences (heterogeneity) in all facets of aging, from biological and physiologic to social and behavioral domains. Increasing heterogeneity with aging leads to the critical observation that the existence of varying disease clusters in different older adults likely has implications for matching individuals with explicit interventions (targeting), a core principle of precision medicine and ultimately treatment effectiveness.[34] The ability of scientists to conceptualize and validate well-defined biological aging pathways that represent shared, yet varying mechanisms worthy of targeting via geroscience-therapies will require the evolution of multidisciplinary team science capable of tackling such multifactorial complexity in a systems-based fashion. Furthermore, we cannot ignore the fact that multitudes of different genetic, lifestyle, social, behavioral, economic, pharmacological, and clinical factors influence how each of us ages. Geroscience-guided approaches also cannot ignore personal preferences and care goals which also become more heterogeneous with aging, requiring scientists to identify and better understand such preferences, and compelling clinicians to better implement these individual choices into individualized clinical care plans.[33]

The 2019 NIH Inclusion Across the Lifespan Policy represents an essential step forward in involving greater numbers of individuals of advanced age in clinical trials and observational studies.[35] However, this policy might not ensure that older adults recruited into NIH-funded clinical research will necessarily reflect the clinical complexity and social/behavioral heterogeneity found in increasingly older populations, including the presence of varying clusters of chronic conditions.[35] Such heterogeneity is much more typical of real-world medicine, and geroscience-guided therapies will be required to demonstrate effectiveness across different populations of older adults in order to be adapted into routine clinical care, and thus ultimately impact human health at the level of entire populations.

Other challenges to testing the Geroscience Hypothesis more rigorously include a lack of financial incentives for investors and others in the private sector to finance aging research given the focus of FDA's congressional mandate on the diagnosis and treatment of diseases, combined with the fact that aging cannot be viewed as a "disease."[27] To that end, the proposed TAME (Targeting Aging with Metformin) trial is designed to demonstrate the feasibility of delaying the onset and progression of an aggregate of chronic diseases through a proof-of-concept geroscience-guided intervention.[27] Moreover, we are also likely to see geroscience-guided strategies designed to improve other aging-related conditions such as sarcopenia, thymic involution, early menopause/infertility, and attenuated responses to vaccination among others. Finally, in addition to training all health providers in clinical approaches to the care of older adults that are based on the latest high quality scientific evidence, we must also train and support a new workforce in geroscience that will include investigators with expertise in geroscience as well as clinicians (geriatricians) with the specialized knowledge needed to prescribe geroscience-guided treatments to the most complex older patients in the same manner that clinical oncologists guide the use of the most sophisticated cancer therapies.[36,37]

Even more fundamentally, in order to make real progress in advancing the discovery, validation and

implementation in daily clinical care of novel geroscience-guided therapies, we must as a society and as health care providers and scientists also fundamentally re-evaluate how we view aging in the context of human health and lifespan. The term "ageism," coined more than 50 years ago by Robert N. Butler, MD, the founding director of the National Institute on Aging at NIH, describes three interconnected elements: prejudicial attitudes towards older people, old age and the aging process; discriminatory practices against older people; and institutional practices and policies that perpetuate stereotypes about older adults. These elements of ageism continue to be perpetuated to this day in the broadcast media, as well as in most clinical, research, and educational settings. Geriatricians and gerontologists have clearly devoted their careers to the care of older adults and the study of aging. However, for many other clinicians, scientists, policy makers, and others for whom aging is not a primary passion, issues surrounding ageism must be confronted.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

All authors made significant conceptual contributions to the manuscript, provided editing, and approved the final manuscript.

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Not applicable.

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