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Aging Is Bad for You?

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FROM THE EDITOR

Should Aging Be Treated?

Nicolai Wohns, MD

Aging has long been a source of fear and anxiety, driving many adults to go to great lengths—ranging from cosmetic interventions to fashion choices—to maintain a youthful appearance. The desire to defy time extends beyond aesthetics, reflecting a deeper reluctance to acknowledge the reality of our aging and eventual death. Capitalizing on mortal fear and anxieties has an equally long, and often disreputable, history; marketplaces are stocked with products dubiously claiming to restore youth. What is relatively new, however, is that "anti-aging" has become a legitimate focus of medical science and clinical effort. Indeed, geroscience is a specialty area of biological science that aims to understand and manipulate fundamental processes of aging. With heavy investment from the pharmaceutical industry, private enterprise, and public institutions, a key promise of the field is to develop blockbuster gerotherapies that slow, halt, or even reverse biological aging.[1,2]

Now, impressive advances appear poised to make good on this promise. Human trials of anti-aging interventions are under way, driven by recent discoveries about the basic biology of aging.[3] Yet, while both public and private funding for geroscience has ballooned,[2] little attention has been paid to the social, cultural, and ethical consequences of anti-aging interventions. With older adults projected to outnumber children by 2034 for the first time in US history,[4] the consequences of gerotherapies and their wide availability will only grow in importance for clinicians and patients.

Safe, effective interventions that robustly slow, halt, or reverse biological aging—and their wider ramifications—should be taken seriously by ethicists, clinicians, policymakers, and researchers. *Is it justifiable to devote resources to anti-aging initiatives when other pressing human needs (eg, food insecurity, homelessness, social injustice, and climate change) go unmet? Which principles should be developed and invoked to equitably guide gerotherapeutic innovation and capitalize on the "commodification of aging"? Which advisory and regulatory structures should be in place to check the interests of corporate entities looking to influence public policy?* One might even scrutinize the basis for viewing aging as a "problem" that needs solving by health care at all.

Such inquiry prompts still broader reflection on questions of value. For instance, *What should the inevitability of aging and death teach us about the meaning and value of life?* Other considerations are culturally specific: *Given prevailing narratives that pitch*

aging as bad, at least in the United States, how should we challenge ageism and foster a positive conception of aging as another kind of opportunity for growth? There are also questions of justice (eg, *What do younger generations owe older generations?)* and of identity (eg, *How does aging influence an individual's sense of self?)* While these questions have arguably been neglected in Western thinking, the renewed focus on the ethical complexities and significance of growing older has given impetus to the renaissance now underway in the ethics of aging.

This theme issue takes up these questions, examining the ethical valences of what geroscience suggests about socially, culturally, and historically entrenched patterns of pathologizing and medicalizing aging. Geroscientific advances suggest a need for critical evaluation of whether and to what extent we should think of anti-aging ventures as legitimate enterprises of health care. Perhaps central to this debate are views on the proper scope of medicine, as well as deeply held social and cultural understandings of aging. As the boundaries of biomedicine expand, medicalization of aging risks eroding its fundamental role in shaping how we understand ourselves and our relationships with others, while further stigmatizing aging and growing old.

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CASE AND COMMENTARY: PEER-REVIEWED ARTICLE

What Are the Most Ethically Salient Implications of Epigenetic Age Testing?

Michael Hauskeller, PhD and Liam Shore, MSc

Abstract

This commentary on a case considers how clinicians should help patients interpret results of tests that might be personally meaningful but not clinically actionable. Tests of biological age, for example, can easily lead to patient misunderstandings that can increase risks of psychological harm and make age-related discrimination seem justifiable. This commentary suggests that companies offering epigenetic testing should be more transparent about these tests' reliability and limitations.

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Case

AA is a healthy 56-year-old patient who ordered a direct-to-consumer test online that is a measure of biological age. These so-called "epigenetic clock" tests estimate the likelihood of developing age-related conditions (eg, cancer, cardiovascular disease, and Alzheimer's disease) and predict one's risk of death.

AA received the test's results, which state that he is "biologically 65-years-old." AA follows up on the manufacturer's recommendations to begin courses of the company's brain health and cellular repair supplements. AA has questions, too, and follows up with Dr B, his primary care physician.

AA is worried about his accelerated so-called biological age relative to his chronological age and his reportedly higher risk of age-related diseases and death. "Do I really have so little time, Dr B? Can you help me live healthier and longer? Can you help me age less or more slowly?" Dr B considers how to respond.

Commentary

When we age, our DNA changes. These changes happen on the genetic level through telomere shortening, genetic mutation accumulation, and mitochondrial dysfunction. Other changes are epigenetic, which means that what changes is the way our genes are expressed in our bodies and how well they do the work they are meant to do. That work

consists of creating proteins that are needed for what we consider the normal functioning of a cell, tissue, or organ and creating them when they are needed and not when they are not needed. The older we get, the less reliable those epigenetic biological processes tend to become.[1] This so-called epigenetic drift increases the likelihood of infections (such as pneumonia and COVID-19) and age-related diseases (such as cancer or heart and lung diseases), which in turn puts us at a higher risk of dying.[2] Yet gene expression is influenced not only by genetic factors, but also by environmental conditions and lifestyle choices like what we eat and how physically active we are, which is why 2 people of the same chronological age can be very different in terms of how well their bodies function on various levels. This is what is commonly referred to as a person's epigenetic or biological age: biologically, we do not all age at the same rate. Some people age faster than we would expect on the basis of their chronological age, some age more slowly.

In this commentary, we question the empirical validity of biological age testing and highlight some of the ethical questions arising from it. Patients and the public can easily misunderstand the significance of biological age tests, which increases the risk of psychological harm and makes age-related discrimination appear justifiable. To mitigate these risks, companies offering epigenetic testing need to be clearer about how the tests work, how reliable they are, and what they can and cannot show.

"Biological Age" Is a Fiction

A person's biological age can be assessed in various ways. The most common tests, known as "epigenetic clocks," measure DNA methylation patterns. Methylation is a process that is responsible for the activation and silencing of particular genes. Other tests focus on different biomarkers, such as the length of telomeres. While these tests have been shown to be fairly reliable indicators of a person's risk of developing certain age-related diseases,[3] we should be very clear that they cannot tell us how old we "really" are, as is frequently claimed in the media.[4] The number that those tests come up with and that we are led to believe is our actual age is in fact fictitious because it entirely depends on what biomarkers and what method of computation are being used, which, in the absence of any consensus about what markers and methods *should* be used, undermines the very concept of a person's biological age.[5]

Although biological age is widely treated as a reality, there is no such thing as a particular person's biological age. This is why we are likely to get a different result if we take a different kind of test,[6] and, even if the same kind of test is applied, the result also depends on the type of tissue that is used as the source material, as well as the size of the sample. Your heart might then turn out to be "older" or "younger" than your liver.[7] In fact, those tests don't measure how old our cells are or how old the cells in particular parts of our body are. Our cells are in fact never older than we are (though some of them are chronologically younger), and our age depends on when we were born and nothing else. So, if, like patient AA, we are 56 years old and told that our biological age is actually 65, then all that can possibly mean is that whatever parts of our bodies have been tested are in a worse state than is to be expected for someone our age and that this state is more commonly found in someone who is 9 years older, which is, of course, still a good reason for AA to be concerned about the state of his health and possibly make some changes in his life.

Fiction as Legal Reality

Having this kind of information can no doubt be helpful. Since some of the damage that is measured in these tests is reversible, and since further damage can possibly be prevented or slowed with the right treatment, they can be useful tools for identifying health risks and potential remedies, such as lifestyle changes, pharmacological interventions, or even cellular reprogramming.[8] But to frame the results of these tests as the discovery of one's biological age—especially if biological age is presented and promoted as one's "actual" age—is highly misleading and has far-reaching potential consequences if taken literally. Some bioethicists have already argued that people should be given the right to have their assumed biological age, rather than their documented chronological age, officially recognized as their legal age if there is a difference between them to prevent unjust age discrimination.[9]

This argument has not been accepted by any courts yet, but the more we get used to thinking of our purported biological age as our real age, the more likely it becomes that it will eventually be regarded as a fact demanding legal recognition. But legally recognizing one's biological age as one's actual age would almost certainly also affect the opportunities one has in life. Would someone who is clinically assessed as younger than what their date of birth indicates have to wait until they have reached biological pension age before being able to access their pension? Would someone who is assessed as older find it more difficult to get health or life insurance, find a romantic partner, or even access clinical interventions?

Setting the Record Straight

Even if being told that one's biological age considerably exceeds one's chronological age has no legal implications (yet), many patients will struggle to interpret this claim correctly—namely, as a shorthand for a probabilistic assessment of possible future health problems and resulting life expectancy. Clinicians confronted with a patient who has received a test result seemingly providing a scientific confirmation of accelerated biological aging need to be sensitive to the emotional impact that this piece of information is likely to have on that patient and do everything they can to mitigate it by following well-established guidelines for crisis management following a medical diagnosis.[10] All illnesses are, to a certain extent, crises of meaning that disturb the ill person's understanding of their world,[11] but what is usually most disturbing is an illness that we know—or are being told—will drastically reduce our life expectancy, as happens to AA in the case described above. To be diagnosed as suffering from a terminal illness is bound to come as a shock to any patient and is likely to upend their entire life. To be told that one is actually much older than one thought one was might well have a similar effect because it makes death appear more imminent. In both cases, the time we think we have left in our lives has suddenly shrunk considerably.

Even if the biological age test that AA took was not clinically indicated, it is still within the remit of Dr B's responsibilities to make sure that AA fully understands the results, which do not entail that he will develop morbidity or die earlier than would be expected on the basis of his chronological age. Rather, they merely indicate that certain aspects of his physical condition make it more likely that particular health hazards lie in store for him in the future if not addressed. This explanation should then lead to a discussion of what, exactly, was measured in the biological age test taken by AA and what can be done to prevent the underlying conditions it revealed from compromising AA's health and well-being later.

Balancing Innovation and Trust

However, for this discussion to be possible, Dr B would have to know exactly how the test results were generated, which is harder to determine than it should be because of the proprietary nature of current epigenetic clocks and the economic incentives that accompany them. This problem is both an informational and an ethical one, which can only be solved through greater transparency. Experts outside of the commercial venture are prevented from impartially analyzing the algorithms via a peer-review process, and other independent developers are not allowed to dig into the code to check for flaws and biases. Not only does this secrecy make monopolies more likely and innovation less likely,[12] but many potential users will also find it difficult to trust a technology that is largely protected from public scrutiny,[13] and rightly so. The lack of transparency makes it easier for commercial companies offering epigenetic testing to manipulate the results and provide false positives to sell products that might or might not work. Even if the companies are honest, the suspicion that those companies might offer solutions to problems that wouldn't exist if they had not first created them will not go away until epigenetic testing companies adopt a business model that permits closer external scrutiny of their algorithms. Companies must also give consumers all the information they need to justify their trust that the risk scores provided are accurate and that the recommended supplements and interventions will actually help them. And because companies' success as businesses ultimately relies on the trust of consumers, they would do well to open-source all or part of the epigenetic testing algorithms to gain ideas from the wider community on how to improve the reliability of the score provided, potentially foster innovation via collaboration, and discover and develop new talent or partnerships. In the meantime, clinicians like Dr B should follow existing guidelines regarding the interpretation of direct-to-consumer genetic and genomic testing results, such as the American College of Physicians' position paper, "Ethical Considerations in Precision Medicine and Genetic Testing in Internal Medicine Practice."[14]

Conclusion

Biological age is a fiction that should, at the very least, be clearly identified as such by clinicians when discussing biological age tests with patients to prevent them from becoming confused, upset, or falsely flattered about results purporting to show that their biological age differs from their chronological age. Taking this step would also prevent patients from misinterpreting their supposed biological age as their "real" or "actual" age, with its potentially far-reaching legal implications. Epigenetic testing can, of course, reveal potential or existing health problems and provide valuable information that can be used to improve a patient's health and lifespan. Yet to fully realize the potential of epigenetic clocks in an ethically responsible way, researchers, regulators, and developers must prioritize transparency, accountability, standardization. By open sourcing their algorithms, or parts of them, while maintaining ownership of their platform or tools, companies would be able to balance technological and scientific innovation with the need for accountability and trust. Regulators could support this move by creating a framework to categorize the efficacy of interventions for particular biomarkers and defining and mandating the use of standards to calculate biological age.

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Editor's Note

The case to which this commentary is a response was developed by the editorial staff.

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The people and events in this case are fictional. Resemblance to real events or to names of people, living or dead, is entirely coincidental. The viewpoints expressed in this article are those of the author(s) and do not necessarily reflect the views and policies of the AMA.

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CASE AND COMMENTARY: PEER-REVIEWED ARTICLE

Should Slowing Senescence Be Regarded as a Legitimate Enterprise of Health Care?

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Abstract

Dementia is one of the most common developments in our increasing human lifespan. Preventing and postponing it have been important projects of health care that rely on the approval and use of interventions, sometimes in the absence of clinical or ethical consensus about what constitutes meaningful clinical improvement, outcomes, or risk factor modification. This commentary on a case considers these variables and proposes how to improve the general health and well-being of older persons.

Case

Multiple news stories have been touting so-called "anti-aging effects" of newly approved drugs that affect fundamental physiological processes of aging. DD, a healthy 78-year-old patient, asks Dr C, "I want to live long enough to see my grandchildren grow up, but I am frightened by the possibility of developing dementia. I've seen advertisements about new drugs. Would you prescribe these for me, Dr C?" Dr C wonders what is known about these new drugs' safety and efficacy and considers how to respond.

Commentary

Cognitive decline, including development of dementia, is associated with aging and is a prominent component of senescence. The quest to avoid dementia and especially Alzheimer's disease (AD) appeals to people as they age, drives demand for any help and hope practitioners can offer their patients, and enjoys widespread support for research. The attraction of and search for a pill to avoid age-associated decline seems everlasting.[1]

The author was one of a then-small cadre of dementia practitioners and clinical researchers in the late 1970s when the field of dementia research began to emerge from the backwaters of clinical care and research.[2] We looked for any kind of medication that might offer hope to patients receiving a dementia

diagnosis, as patients and their families wanted to "do something." Popular medications used then included drugs like isoxsuprine and ergoloid, now abandoned because they lacked evidence of effectiveness.[3,4] Their presumed effect of widening blood vessels, and thereby improving circulation, provided a rationale for their off-label use for dementia and allowed physicians to offer tangible help and hope to some. Unlike drugs used for dementia today, these drugs' costs and side effects were minimal and didn't attract much attention.[5]

Over the past 50 years, we have learned a lot more about AD.[6,7] Evidence supporting the efficacy of new drugs, ranging from those that inhibit acetylcholinesterase (as acetylcholine is the neurotransmitter thought to be most involved in AD) to drugs designed to remove brain amyloid, has been accumulating from long-term trials.[6,7] Over several decades, intense research efforts have been based on the notion that buildup of amyloid plaque in the brain is one culprit of neurodegeneration in the brains of persons who develop AD and dementia; slowing the rate of plaque buildup is key to preventing or reducing AD burden. However, there is no consensus on what constitutes clinically meaningful change. This commentary examines this issue and proposes how to improve general health and well-being in older persons.

Statistical, Detectable Differences

The US Food and Drug Administration (FDA) has recommended that researchers use sensitive measures of cognition in clinical trials to evaluate an experimental drug and to test the validity of hypotheses (eg, about the roles of amyloid and acetylcholine in AD).[8] To demonstrate an effect of an intervention—usually on persons in earlier stages of the disease, with mild AD, or with minimal or so-called mild cognitive impairment—cognitive outcomes of treatment and placebo groups are compared over time using standardized psychometric tests. The FDA recommended that such measures be used in multi-year clinical trials[8]; a difference between the treatment and placebo groups' cognitive decline, if statistically significant, is unlikely to be due to chance and is believed to indicate that the intervention is effective, at least in minimizing unwanted cognitive decline.[9] While there is indeed controversy over the effectiveness of AD treatments,[9] it is generally agreed that the benefits shown in clinical trials are, at best, modest, limited to statistically significant but small, mostly imperceptible, differences in rates of decline or in rates of disappointing side effects. Neither of the 2 major classes of drugs (anti-amyloid and anticholinergic drugs) is believed to "cure" the disease.[6] Nevertheless, after decades of work, the field can finally "do something" rather than standing by helplessly as AD progresses.

However, one important question is this: What constitute clinically important differences in trials of drugs designed to slow a progressive disease like AD?[9] Unlike diseases like cancer or life-threatening cardiac diseases that present clear-cut dichotomous outcomes—such as mortality, recurrence of the disease, or of a measurable event—a progressive dementia, like AD, leaves investigators, regulators, clinicians, and patients and their families with a different question: How much difference is worth the cost, effort, and, especially, side effects of

treatment? Should any difference in outcomes that is unlikely to be a chance difference be regarded as clinically significant?

Determining Clinical Significance

An important issue for AD, in common with many other progressive conditions, is whether a statistically significant difference favoring treatment in one or more outcomes can be taken as a threshold for a minimal clinically important difference, or minimal detectable difference. There is no gold-standard method to define or calculate minimal clinically important differences.[9] Regulatory bodies, including the FDA, generally rely on statistically significant changes.[9,10] Clinicians, certainly[9]—and patients and their proxies—likely recognize that a difference, albeit statistically significant, favoring treatment on any trial endpoint might not represent a meaningful clinical benefit. That an FDA expert committee convened to review a highly publicized anti-amyloid monoclonal drug recommended non-approval due to lack of compelling evidence of a treatment effect[11,12]—a recommendation the FDA did not accept—reflects the lack of consensus on a threshold for a clinically meaningful benefit.[9] In 2019, Weinfurt proposed a way to "clarify the meaning of clinically meaningful benefit in clinical research: noticeable change vs valuable change."[13] More recently, Liu et al have proposed a helpful 3-step approach to evaluate clinical benefit of Alzheimer's disease therapies. First, is a change noticeable—that is, "clear, perceptible, and … easily communicated"? Second, is it valuable, or "judged to be important"? And third, is it worthwhile, in the sense that "the value of the change outweighs specific considerations such as side-effects, costs, inconvenience, or required duration"?[9]

In the absence of consensus on what constitutes a clinically important difference, the field uses not only psychometric outcomes but surrogate endpoints like brain amyloid. Together, these outcomes measures are likely to increase the number of treatments in development and approval pipelines. However, except for donepezil, which is now relatively cheap and easy to administer, the newer anti-amyloid antibodies have more serious side effects (eg, infusion reactions, dizziness, falls or stroke, and even death[7,9]). Moreover, in the absence of consensus on what constitutes a clinically meaningful benefit, we are also left with serious resource implications, ranging from costs ($26 500 per year for lecanemab) to infrastructure and resource issues.[14] Indeed, the market for new drugs and the costs of their widespread delivery and monitoring is staggering. Improvements in longevity in higher-income countries and now in lower-income countries have created a new epidemic, what was once called the silent epidemic.[7,15,16] The global estimate of the number of persons living with dementia was 57 million in 2019, and that number is expected to grow to 153 million by 2050.[17] At the time of the approval of the first anti-amyloid antibody drug, aducanumab, in 2021, the US Centers for Medicare and Medicaid Services and the Health Care Financing Administration programmed a 14.5% increase in Medicare Part B premiums[18] to cover the newly approved drug's expected costs, given its widespread market and projected price. The drug company promoting aducanumab has since discontinued this drug as a treatment for AD.[19]

The United States already has much higher health care costs than any other advanced economy.[20] Treatments adopted on the basis of minimal detectable differences will undoubtedly contribute to health care cost inflation. Added to that is the fact that amyloid, the target of these drugs, is not the only culprit implicated in AD and associated neurodegenerative disorders. Most people with AD, especially older persons, have co-occurrences of other neurodegenerative changes: tangles of Tau proteins, microinfarcts, macroinfarcts, Lewy bodies, and other neuropathological changes.[21,22,23] These pathologic changes would not likely be affected by the newer drugs. If anything, the minimal effectiveness of these newer drugs might be because they ignore other, commonly co-occurring pathologic changes seen in AD and related dementias.

Reframing Prevention

Large investments required to market, provide, and monitor drugs of relatively minimal effectiveness—including for dementia—could be used for better purposes. An example is investments to address "moral determinants of health" as outlined by Berwick,[24] which refer to the solidarity required to problematize structural determinants that undermine health and exacerbate inequity. For chronic diseases, including dementia, prevention has become more promising and evidence based. For example, observational studies conducted in high-income countries suggest that age-specific dementia incidence rates have decreased, supporting the notion that prevention is possible, to an extent, and might have already occurred due to improved socioeconomic conditions and education levels, better control of cardiovascular risk factors, and better well-being overall.[25] The third report of the *Lancet*'s Standing Commission on Dementia, published in 2024, identified 14 potentially modifiable risk factors for dementia and concluded: "The potential for prevention is high and, overall, nearly half of dementias could theoretically be prevented by eliminating these 14 risk factors."[7]

An ethical issue posed by relying on minimal detectable differences is that the use of these as evidence of effectiveness in clinical trials and to justify FDA approval decisions has led to the dawn of an era in which expensive treatments of minimal effectiveness will forestall better uses of collective resources. It is relatively easy to prey on people's fear of dementia with appeals like that of the president and chief executive officer of the Alzheimer's Association, who credited a new anti-amyloid drug with giving patients "more months of recognizing their spouse, children and grandchildren"[26] without any good supportive evidence for this claim.[9]

I would argue that for reducing the burden of dementia on individuals and society, prevention or delay of onset of dementia is now on the verge of being deployed in the ways that, many decades ago, led to the decline of heart disease and stroke. An evidence-based strategy to reduce risk factors throughout the life course is likely to be better at preventing or delaying dementia than relying on medications that are judged to be effective based on minimal detectable differences. Evidence-based prevention across the life course addresses a

universal desire to delay senescence without producing socially irresponsible trade-offs that accompany treatments whose minimal benefits are mostly unnoticeable to individuals taking them. Better to do "something" that aging persons can experience and that offers better overall health.

Patient Advice

Based on the above analysis, Dr C should inform patient DD that the new expensive drugs that might offer hope on the basis of minimal detectable differences will not likely prevent the disease or even have much present benefit that DD can perceive. They do come with high individual costs, including side effects and taking time away from other things important to older people. An alternative would be to focus on elements that promote both general health and well-being and, especially, those that reduce risk of dementia and decline. And, of course, DD should enjoy his current relatively good health and grandchildren as they grow into adults.

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The people and events in this case are fictional. Resemblance to real events or to names of people, living or dead, is entirely coincidental. The viewpoints expressed in this article are those of the author(s) and do not necessarily reflect the views and policies of the AMA.

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MEDICAL EDUCATION: PEER-REVIEWED ARTICLE

What Does It Mean for a Patient to "Look Older Than Their Stated Age"?

Chris Gilleard, PhD

Abstract

Documenting one's assessment of a patient's physical appearance during a clinical encounter is regarded as a key element in a clinician's overall judgment of a patient's health. This article considers ethically and clinically relevant uses and misuses of such appraisals in clinical practice when applied to judgments of a patient's agedness. Despite being a possible invitation for negative clinician bias, such appraisals should be part of clinical encounters and training.

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Looking Old

Looking older than one's chronological age is an important health indicator. In most modern societies, where "looks" confer social distinction, older people often report feeling that their aged appearance renders them socially "invisible."[1,2,3] It is unsurprising, therefore, that the default option for most older people's subjective judgments about their age is to consider themselves younger than their chronological age.[4] But in the health care setting, appearing older than one's chronological age carries potentially relevant information, serving as a sign of probable ill-health and warranting further investigation.

At the same time, clinicians working with older patients have long been at pains to distinguish between age and disease, insisting that even those of great age can yet be fit and healthy.[5] Nevertheless, the linkage between the two cannot be gainsaid, even if it has led to a too-ready acceptance of a certain level of morbidity as a "natural" component of old age. The point of this paper is not to support this latter assumption (that older age equates with greater morbidity) but to suggest that clinicians' judgments of patients' agedness—their looking older than their chronological age—possesses clinical value rather than simply reflecting "ageist bias."

Judging an Appearance of Agedness

What, then, should one make of passing clinical judgments about a patient's agedness (as defined above)? Physicians, it is said, are trained to begin their examination "with a general inspection of the patient, which often includes an assessment of whether the

patient 'appears his/her stated age' or 'appears older.'"[6] This, it is said, should be "a component of the physical examination."[7] Little guidance, however, is provided as to how such judgments should be made, and surprisingly little research has been conducted on how accurate such clinical judgments are. If, as research suggests, looking older than one's age is indeed a marker of poor health and a poor prognosis,[8,9,10] it is important that clinicians make such judgments reliably.

One relatively recent review of the literature concluded that "perceived age promises to be a useful predictor of overall mortality and cardiovascular, pulmonary, cognitive and osseous comorbidities."[10] But while most of the studies examined in that review were based on ratings of standardized photographs of the face and head, few were based upon the usual face-to-face encounter typical of clinic appointments. The question remains whether perceptions of agedness made in routine clinical practice are sufficiently reliable to guide routine clinical assessment.

Research on the accuracy of clinical and nonclinical judgments of agedness is not encouraging. While one review concluded that "age estimation of unfamiliar faces can be quite accurate,"[11] accuracy varies according to the similarity—in race and age group—between the observers and the observed.[11,12] Williams and colleagues, for example, observed significant variation in health care students' ability to accurately estimate a patient's age, with one 83-year-old patient being judged anywhere from 55 to 89 years of age, while another 60-year-old patient was judged to be somewhere between 34 to 63 years of age.[13] In general, the accuracy of age judgments is inversely related to the observed person's age, with the ages of older patients less often accurately judged.[14]

A number of contextual factors need to be considered in judgments of patients' appearance, not least the problem of "own-age" bias. Training and experience significantly improve the accuracy of age estimation, especially for older people.[15] Studies of the accuracy of geriatricians' estimates of their patients' age, for example, suggest good inter-rater agreement.[16] Nevertheless, many factors can act as more salient markers of ill-health than clinicians' assessment of their patient's agedness, such as the impact of weight loss, poor sleep, chronic pain, poverty, and self-neglect. All of these factors can contribute to judging someone's appearance as older than their chronological age, and, in a given case, any one of these factors could be the more important marker of ill health. Nevertheless, there is evidence that, setting aside such contextual clues of age as hair and clothing, judgments of facial aging and facial agedness retain some prognostic value.[17]

Health Care and the Question of Ageism

While there are clearly problems with the accuracy of clinicians—particularly, young clinicians—in judging the agedness of the patients they see, consistent evidence that looking older than one's chronological age is a sign, or prognosticator, of ill health suggests a value in retaining this element in the clinical assessment. The benefit of making such judgments remains, however, problematic for reasons other than the reliability of such assessments. That looking older than one's chronological age is a reliable marker of disease is a matter of empirical enquiry. At the same time, judgments that a patient looks older than their age might lead the clinician to a too-ready assumption of the inevitability of their ill-health and a too-ready assumption about the limited prospects of effective treatment.

Ageism has been said to characterize health care settings both in North America and in Europe,[18,19] leading one group of reviewers to claim that "age-based discrimination is common and long-standing among health care providers, within health care systems, and in health care policies."[20] Contributing to such discrimination is not only a widespread, anti-age bias, but also the widespread absence of old and very old patients enrolled in clinical trials. The result is a lack of evidence on which to base appropriate prescription for and treatment of the most aged patients.[21] Evidence-based clinical practice guidelines rarely highlight the particular needs of old and very old patients.[22,23] At the same time, historical assumptions about when and when not to intervene, what and what not to prescribe, and which investigations should or should not be conducted are less easily updated in the absence of such guidelines and related clinical research findings.

Conclusion

A firm body of evidence indicates that, at least for middle-aged and older people, looking old for one's age is a sign of both present ill health and future morbidity.[10] For that reason, it is understandable that many physical examinations incorporate the clinician's judgments of a patient's appearance and their relative agedness. The question arises whether such judgements in practice lead to more or less effective investigations, interventions, and care. As long as most clinical guidelines base their recommendations on younger rather than older patients, judgments of age and agedness are unlikely to improve, and, if anything, such guidelines might discourage more positive expectations. While looking for signs of agedness in the physical examination might be a very traditional (and evidence-based) practice, the otherwise "invisibility" of both age and agedness in clinical research and evidence-based clinical guidelines seems a tradition in urgent need of change. More particularly, there is a strong case to be made for a more explicit focus on training junior (and mostly young) doctors on how to judge age and agedness accurately and carefully, both to increase the potential value of this element in clinical assessment and to challenge any ageist assumptions about what ageing looks like.

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HEALTH LAW: PEER-REVIEWED ARTICLE

How Old Are You, Actuarily?

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Abstract

Advances in epigenetic age estimation are now applied in actuarial science to make risk assessment more precise. But such health insurance underwriting practices pose ethical and legal questions about discrimination, privacy, and equity in biological data use. Legal adaptations, such as Canada's Genetic Non-Discrimination Act (GNDA) of 2017, aim to protect persons against genetic discrimination but do not evolve as quickly as epigenetic technology. This article examines the GNDA's regulatory limitations and highlights the need for more adaptable legislative strategies.

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The Canadian Context

As health technologies advance, governments will face mounting pressures to regulate insurers' use of novel assessment tools, including epigenetic technologies. Insurers have embraced epigenetic age estimators[1,2] that predict health outcomes (ie, mortality and multimorbidity) based on measures of methylation related to aging. While these technologies offer insurers enhanced risk assessment capabilities, they simultaneously intensify fundamental concerns about privacy and discrimination,[3] echoing issues related to the use of traditional genetic data, such as single nucleotide polymorphisms.[4]

These concerns are particularly pronounced in Canada, where, despite its universal health care system, private insurers increasingly fill critical gaps in meeting citizens' health needs.[5,6,7] While the public system covers basic health services, rising costs and population growth have created a dependence on the private sector for timely access to essential services and emerging treatments.[6] As private insurers gain greater influence over health care access and thus quality of life, the ethical implications of their utilizing genetic and epigenetic information in risk assessment are becoming increasingly significant.

To address concerns about use of genetic information by providers of goods and services, Canada passed the Genetic Non-Discrimination Act (GNDA) in 2017.[8] While the GNDA is groundbreaking in its protection against genetic discrimination, this paper

argues that it contains critical definitional and structural limitations that render it inadequate for regulating emerging epigenetic and future health technologies. By analyzing the act's scope and consent-based framework, we demonstrate that the GNDA's shortcomings could perpetuate inequities as insurers adopt new forms of health data in their underwriting practices. Given Canada's influential position in developing global health policies,[9] examining these regulatory gaps offers valuable insights for creating more adaptive legislation that can evolve alongside rapid scientific advancement.

The Genetic Non-Discrimination Act

The ethical and legal concerns about the use of genetic data did not arise with epigenetic age estimators. When genetic technologies first entered the market, there were anxieties that insurers and other private actors could exploit genetic data for discriminatory purposes.[10,11] Although it is widely accepted that discriminatory practices are foundational to the insurance business—with US state laws variably allowing discrimination based on age, gender, and credit score, for example[12]—genetic information was recognized as fundamentally different, partly given its sensitive nature.[3] It was argued that private insurers should not be able to deny or alter coverage terms on the basis of predictive genetic information, as this practice would constitute genetic discrimination.[13,14] In response to these concerns, Canada passed the GNDA in 2017, thereby granting special protections to genetic data in the hopes of mitigating these privacy and discrimination risks.[9] The act regulates access to and use of genetic test results in contractual settings.[9] It defines a genetic test as one that "analyzes DNA, RNA or chromosomes for purposes such as the prediction of disease or vertical transmission risks, or monitoring diagnosis or prognosis."[9] Under the GNDA, no person can require individuals to undergo or disclose the results of such tests, and any actors, including insurers, must obtain a client's explicit written consent before collecting or processing genetic data.[9] Through this consent-based framework, the GNDA attempts to address ethical concerns about providers' use of genetic data while still permitting its use when individuals voluntarily agree to disclose it.

Despite this protection, concerns persist about the act's ability to adequately regulate emerging health technologies that might also pose ethical risks. This uncertainty is particularly evident when examining whether epigenetic technologies fall within the act's scope. Epigenetic age estimators—which use DNA methylation patterns to gauge an individual's biological age, an indicator of aging at the cellular level—stand out as one of the most prominent recent innovations in aging biology.[15] Current data suggest that the difference between a person's chronological and biological age, known as age acceleration, can serve as a health outcome predictor comparable to mental health indicators or health behaviors.[16]

At first glance, integrating epigenetic age estimation into underwriting might seem less problematic than using genetic information. Measures of age acceleration might appear to be simply an "objective" and streamlined method for capturing data on a characteristic that is similar to characteristics insurers already use in actuarial calculations. These characteristics include smoking habits, exercise patterns, and other self-reported lifestyle behaviors. When employed in underwriting, accelerated age could be used to predict a person's quality of life or lifespan.[2] Yet this apparent simplicity masks deeper concerns, as, much like genetic information, epigenetic data—in addition to being predictive—can be inherited and influenced by factors outside of an individual's

control.[17] Despite the important similarities of epigenetic data to genetic data, it remains unclear whether the GNDA should or does apply to epigenetics.

Limitations of the Genetic Non-Discrimination Act

As technologies continue to push the boundaries of what qualifies as genetic information, it is imperative to clarify the scope of the GNDA. While there has yet to be a determination pertaining to the reach of the act, Canada's Supreme Court has indicated that the scope of "genetic characteristics" is not stagnant and should be broadly interpreted.[18] This opinion lends credibility to speculation on the part of genetic experts that the act would likely apply to epigenetic data.[18] Although epigenetic clocks do not analyze the amino acid sequence of proteins, they do analyze methylation marks found on DNA and could therefore qualify as a form of "DNA analysis," per the GNDA.[15] Moreover, there is abundant evidence to support the "vertical," or generational, transmission of certain epigenetic biomarkers when gametes are exposed to stressors, and genetic tests, per the GNDA, predict "vertical transmission" risks.[19] That said, the strength of this argument is tempered by the fact that epigenetic technologies are not typically used to predict "disease or vertical transmission risks, or [for] monitoring, diagnosis or prognosis."[9] While it seems likely that courts would rule in favor of the GNDA's application to epigenetic data, the narrow terminology used to describe genetic tests leaves room for doubt.

Regardless of whether epigenetic data ultimately fall within the GNDA's scope, long-standing criticisms of the legislative approach taken by the Canadian government persist. The first of these critiques revolves around the consent-based nature of the act, which places the onus on individuals to understand their right to withhold genetic data from insurers and the risks entailed should they provide consent. Without knowledge of the GNDA, clients might feel compelled to share the results of a genetic test even if sharing might not be to their benefit.[20] Such a framework mistakenly treats consent as a sufficient barrier against genetic discrimination, despite mounting evidence that individuals can underestimate the sensitivity of genetic information and might be unaware that private actors are not entitled to such data.[7,20]

The risks of genetic discrimination are compounded by the heritability of genetic information. An analysis of a given client's health data can provide an insurer with significant insight into heritable traits that might also impact that client's blood relatives. While the GNDA is clear about the need for explicit written consent "to collect, use or disclose the results of a genetic test of the individual,"[9] consent is only required of the person to whom the data belongs. This provision leaves open the possibility that one person's health data could be used to inform decisions about another's coverage. Until there is legal clarification on this potential loophole, the consequences for individuals of the use of genetic test results, including estimates of age acceleration, could be significant. Research suggests that age acceleration is heritable,[21,22] meaning that if a parent voluntarily shares signs of rapid age acceleration with an insurer, they might unknowingly expose their children to risk of higher premiums, as an insurer, using a parent's data, could infer health risks in the children and adjust the children's premiums accordingly without needing additional consent. This scenario illustrates how the GNDA's reliance on individual consent fails to account for the collective nature of genetic information and the potential for discrimination against family members. Given the lack of transparency in health insurance underwriting practices,[23,24,25] it remains difficult to determine whether the use of genetic information to discriminate against

family members occurs in practice, underscoring the broader challenge of regulating health data in the private insurance sector.

The limited protection of individuals against discrimination is further magnified at the population level. A growing body of evidence demonstrates that age acceleration varies significantly with sociodemographic background,[26,27,28] revealing how biological markers can reflect broader social disparities. This variation points to a more troubling concern about the risk of discrimination at the population level, such that the use of health data in underwriting could further entrench and magnify preexisting inequities. Factors that disproportionately impact certain populations—including chronic stress from discrimination, limited access to health care, and involuntary environmental exposures from substandard housing—might become embedded in these epigenetic markers.[26,27,28] As a result, individuals from certain racial, ethnic, or socioeconomic groups might face higher insurance premiums not because of personal choices but because their biology reflects the structural disadvantages they have endured. This dynamic, known as proxy discrimination,[29] strengthens the case for granting special legislative protections to certain forms of health data, particularly when similar protections are not extended to other involuntary characteristics.

Keeping Pace

The challenges identified with both familial and proxy discrimination through biological markers highlight the urgent need for legislation to better account for the continued development of health technologies, including biological age estimators. Current definitional and structural limitations that might exclude certain kinds of health data from GNDA protections represent just one facet of a broader problem: the law's struggle to keep pace with rapidly evolving science. While, arguably, epigenetic information could be protected under the GNDA, other adjacent technologies with similar discriminatory potential might fall squarely outside of the act's scope. For example, emerging types of proteomic analysis, which rely not on DNA, RNA, or chromosomes, but on a set of proteins present in a person's body, can now be used to determine biological age as well.[30] As has been observed with epigenetic clocks, results from these new proteomic age estimators also vary with sociodemographic background and, importantly, would not be protected by the GNDA.[31] Such examples illustrate how the same equity concerns raised by the use of epigenetic age estimators extend to the potential use of other health technologies in insurance, pointing to a need for forward-thinking definitions that allow legislation to evolve with science.

Addressing definitional and structural gaps, however, represents only half the solution. Additional accountability and oversight mechanisms will be necessary to protect against the discriminatory impact of shifting actuarial practices. Without adequate transparency regarding the ways biological information is processed by insurers, it is impossible to evaluate the direct link between specific actuarial practices and their impact on genetic discrimination. As is the case with all forms of discrimination, laws might have their limitations but still represent a crucial piece in dismantling inequities. With continual monitoring of actuarial practices, laws and policies can be refined to better meet the needs of the people they are intended to serve and protect.

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MEDICINE AND SOCIETY: PEER-REVIEWED ARTICLE

Life Extension and Civic Virtue

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Abstract

This article argues that inequitable access to interventions capable of dramatically extending human lifespans would undermine individual and collective upkeep of civic virtue. Specifically, intervention maldistribution that normalizes the expectation of differential lifespans based on socioeconomic status undermines the moral agency of persons living with poverty and the commonality of lifespan experiences, such as milestones and events. As a result of their greater access to interventions that significantly increase lifespan, those with wealth might be tempted to regard persons living with poverty as biologically distinct, physiologically inferior, and less deserving of moral consideration than themselves.

Radical Life Extension

Contemporary geroscience has, in recent years, made significant strides toward radical life extension; it is, at the very least, possible that some novel forms of medical intervention—including new gene therapies and senolytic medications—might permit some humans now alive to experience lifespans longer than even those of the most long-lived members of the human species thus far.[1] This possibility brings with it any number of ethical questions—including whether such longevity is, itself, a morally significant good.[2] In this paper, however, I want to examine another moral worry about radical life extension—namely, its effects upon the sorts of civic virtue that seem necessary for stable liberal democratic governance. I will argue that the availability of such therapies in societies characterized by widespread inequality in wealth and power is likely to have a corrosive effect upon such virtues. If medical innovation creates a world in which people with wealth can expect to have lifespans significantly longer than those of persons living with poverty, then the former might be increasingly prone to see the latter as fundamentally alien sorts of creatures—a conclusion that does not make the exercise of civic virtues impossible, but which would make that exercise more difficult. Therapies that bring the possibility of radical life extension into an already unjust social world, in sum, might have significant effects upon the moral character of those found within that world; they might, indeed, serve to make some inhabitants of that world worse people—worse, at least, at those moral tasks required to pursue justice in shared political life.

We might note, by way of introduction, that this paper assumes that the social and political world into which these therapies are to be introduced resembles our own. The speed with which these interventions are being introduced suggests that we are unlikely to create more equal societies—or a more equitable planet—before we have to come to grips with how these interventions are rightly to be distributed. We might note, furthermore, that most societies—including liberal democratic ones—have become more unequal in terms of income distribution over the past 50 years.[3] We might therefore expect that medical interventions with the power to extend lifespans will be introduced into a world in which some people have significantly greater effective power—in the market and in political life—than others. Tellingly, it has been found that those with wealth have greater effective access to highly desirable glucagon-like peptide-1 receptor agonists (GLP-1 RA) drugs for diabetes than persons living with poverty.[4] Similar distributional effects can be seen with other therapies, such as anti-malarial drugs[5] and cancer medications.[6] We might assume that the prospect of radical life extension would prove no less desirable than the promise of disease cure or control and therefore assume that the individuals who receive access to therapeutic life extension are likely to have disproportionate wealth. The focus of the present paper is on what, if anything, is morally distinctive about gerotherapeutics and the longevity gap they might eventually make possible.

Civic Virtue

There is a longevity gap between persons with low and high incomes,[7,8] and making that gap larger would seem plausibly to count as a moral wrong—certainly, much of the literature presumes that such a gap constitutes an injustice.[9] The focus of this paper, however, is the impact of this gap on the civic virtues, which we may understand to be those virtues of minimal altruism and moral motivation required for a citizen to be a successful participant in a liberal polity. That some such virtues are required seems to be accepted by most political philosophers. Some theorists argue that societies cannot engage in good-faith political negotiations without something like patriotism or, at the very least, a felt commitment to the political society as a sort of moral project; one cannot be a good member of a political society, on this view, without something like a proper moral commitment to that country and therefore to the good of its members.[10] John Rawls, in a more modest vein, argues that the stability of a liberal democracy requires something like the commitment to listen to the arguments of one's fellow citizens and to be motivated by the particular interests of those fellow citizens—a concept he develops under the concept of civic friendship.[11] On this latter view, political societies cannot demonstrate stability for the right reasons—that is, cannot be justified as political communities rather than contests of power and violence—unless the citizens demonstrate a continued moral will to take the interests of their fellow citizens as morally significant when considering which policies to pursue, to defend, and to endorse. Liberal democracy, in short, requires at the very least the sort of virtues involved in listening to the voices of one's fellow citizens and taking their words as having moral weight—even when that sort of listening might get in the way of naked self-interest.

It follows that citizens must be willing to get less than they could, from time to time, because of the moral importance ascribed to the other members of the political community. This sort of moral motivation, however, is itself a learned skill, as Rawls himself emphasized in his account of these virtues; and, like all skills, it must be developed and maintained through time.[12] Rawls argues that citizenship in the liberal state provides any number of opportunities to practice the virtue of seeing fellow

citizens as morally significant. We vote together, argue together about politics, and so on, and, in so doing, we remind ourselves of the moral reality of those with whom we are in political fellowship.[13] It is also plausible, however, that there exist standing pressures to regard these fellow citizens as morally unlike ourselves—as aliens or as lesser forms of human beings. There is some evidence, in particular, that those with great wealth are prone to dehumanizing explanations of poverty and, indeed, of those experiencing poverty; they tend to favor explanations of wealth that begin with the moral incapacity of those experiencing poverty or even something quite like biological difference.[14,15] There is something like a standing moral risk that the bodies and the lives of those who have been marginalized are taken as presumptively inhuman by those who are given more central places within social life generally. One example is the pseudo-scientific colonial logic whereby Indigenous persons were construed as members of separate and inferior race.[16] Another is when other forms of bodies—such as the bodies of achondroplastic dwarves or disabled bodies more generally—are taken to be imperfect or pathological.[17] Those who are more powerful have a tendency to regard that power as natural and often as the result of basic differences in biology.[16] The contention of this paper, though, is that such ideological deformation can occur not simply with reference to the physical body but with reference to the lived experience of aging and mortality; dehumanization can result not simply from physical differences but from differences in chronological expectations as well. This tendency to dehumanize those who have been marginalized makes civic virtue more difficult; it is hard to preserve civic friendship, after all, when one has decided some members of the polity are not entirely human.

Longevity and Civic Virtue

At this point, we might return to the issue of life extension and ask how this possibility might affect civic virtues. There is not space here to expound on a general theory of the factors that might help maintain the skill of moral recognition over time. We can, however, say that something like recognition of the common narrative structure of most human lives is one means by which this moral skill is preserved. What is meant by "recognition of a common narrative structure" is that we are more likely to see each other as morally worthy of concern when we are able to understand the ways in which we often lead quite similar lives; again, Rawls emphasizes some particular commonalities in his analysis of public reason and mutual respect.[18] However different those with wealth and those experiencing poverty might be, there are many ways in which the narrative arc of their lives is quite similar; both face similar milestones throughout their lives—from the fact of being born in vulnerability to particular others, to the experience of loving particular people, to the demands of choosing a profession and a practical identity. Indeed, we might extend these ideas to the temporal process of seeing one's choices play out against the backdrop of an expected story of how a life develops and how it necessarily ends. Not all of us have the same sorts of experiences—some of us are denied love or a career—but many of us have similar moments, and we react to them in markedly similar ways. We have, as it were, a certain framework of narrative similarity; those with wealth and those experiencing poverty can both expect to have 30th and 50th birthdays, and they react to those birthdays with similarly complicated sets of emotions on the basis of socially available stories about what being 30 and 50 mean. Through the similarities in the narrative arc of our lives—common milestones, common social meanings of these milestones, common joys and sorrows—we can come to recognize something about the ways in which the people with whom we do politics are, in fact, creatures very much like ourselves. Charles Dickens describes this phenomenon well, having Fred Scrooge—Ebenezer's less miserly nephew—note that, at Christmas, people are inclined to look at one another less as "another race of

creatures bound on other journeys" and more as "fellow-passengers to the grave"[19]—a recognition of similarity that might stand, to some degree, as support for the skill of moral recognition at a time when such recognition between those with wealth and those experiencing poverty was becoming strained.

These worries are not unique to issues of longevity. Earlier discussions of medical augmentation of height noted that such therapies had the potential to exacerbate existing inequality, as class differences affected access to enhancement of socially desirable characteristics, such as being tall.[20] Life-extending therapies, however, can be a profoundly damaging instantiation of this problem by increasing privileged citizens' sense of biological difference and eroding that sense of narrative similarity that stands against it. Imagine that therapies come to exist that double expected longevity (including both number of years and the number of healthy years)—from, say, 80 years to 160 years, on average—and imagine that these therapies are provided, in the first instance, disproportionately to those with wealth. Under these circumstances, it is plausible to imagine that the stock of narrative similarities between those with high and low incomes might become more strained; the social meaning of being 50, for instance, is unlikely to be the same when one's expected lifespan is 80 and when it is twice that number. These ideas can be amplified by noting the ways in which chronological age and narrative self-construction might come apart as human lifespans become more varied. One's chronological age might no longer indicate much of anything about how much time one can be expected to have left—or even what sorts of experiences one can be presumed to have had in the time one has lived.[21]

Indeed, experiences as ordinary as choosing a career or a romantic partner might seem fundamentally different when one has twice as much time in which to either enjoy what one has built or try something entirely new. If there is already a risk of democratic decline that emerges from profound inequality of wealth—if, that is, civic virtue becomes somewhat frayed by the tendency of those with wealth to ignore the moral humanity of those experiencing poverty—then it is likely that such decline might be exacerbated, at the very least, by an increased sense that these 2 groups do, in fact, exist as different sorts of creatures and can expect radically different sorts of stories to be told about—and in—the lives they lead.

We may conclude by noting that nothing said here should constitute a dispositive reason to condemn radical life extension; it might be true that there exist significant enough reasons to pursue life-extending interventions and even to accept their necessarily unequal availability. This paper intends only to assert that potential injustices might emerge by means of the introduction of those interventions into any world as unequal as our own and that, if we do choose to develop them, we ought at the very least to be cognizant of how they might affect civic virtue—and, indeed, the possibility of justified governance such virtue makes possible.

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MEDICINE AND SOCIETY: PEER-REVIEWED ARTICLE

Should Clinicians Be Agents of Anti-Aging?

Sarah McKiddy

Abstract

Pursuit of longevity has become both a biomedical frontier and a booming consumer enterprise. Popular "anti-aging" products—ranging from dietary supplements to skin care and hormone therapies—are commonly promoted as slowing or even reversing aging. At the same time, scientific advances in geroscience are yielding candidate gerotherapeutics and biomarkers for aging that will increasingly generate questions about their applicability, utility, safety, and ethical integration into care. While geroscience holds promise for extending health span, its impact will depend on how this knowledge is integrated into practice and aligned with individual values and priorities, health equity, and prevention of age-related conditions across the lifespan. This article explores the implications of geroscience, particularly for the care of older adults, by examining clinicians' role in ethical incorporation of gerotherapeutics in practice and concludes by making systems-level recommendations.

"Anti-Aging" vs Geroscience vs Gerotherapeutics

In public and commercial discourse, *anti-aging* typically refers to a broad range of products and practices intended to combat often visible or perceived signs of aging.[1] These include cosmetic treatments, hormonal and dietary supplements, "age-defying" fitness regimens, and other interventions related to rejuvenation. In popular discourse, *anti-aging* carries connotations of aging as a medical problem by presenting aging as a condition in need of intervention as opposed to a natural and heterogeneous lifelong process. While anti-aging marketing, geroscience, and gerotherapeutics share a focus on aging, they differ in intent and conceptual framing.

Geroscience is an interdisciplinary field of biomedical research focused on understanding the genetic, molecular, and cellular mechanisms that underlie biological aging and age-related diseases.[2] Geroscience emerged from the recognition that aging processes (such as cellular senescence, mitochondrial dysfunction, epigenetic changes, and chronic inflammation) are major risk factors for many chronic illnesses in older adults.[2] Geroscience is grounded in the hypothesis that interventions targeting biological mechanisms of aging might delay the onset of age-related diseases, functional impairment, cognitive decline, and loss of physiological resilience over time and, in so

doing, extend health span—the period of life spent in good health and with functional independence—and possibly overall lifespan as well.[3,4] Accordingly, rather than targeting one disease at a time, geroscience research targets fundamental aging pathways in order to prevent or delay the onset of multiple age-related conditions simultaneously.[5]

Emerging from geroscience research are proposed gerotherapeutics. These interventions (often pharmacological) are intended to modulate aging-related biology and thus delay age-associated diseases.[6] For example, gerotherapeutics include senolytics—drugs that selectively clear senescent cells—which are implicated in aging and chronic inflammation.[7] Studies have shown that senolytic compounds can extend health span and even lifespan in mice by reducing adverse effects of senescent cells.[8]

Another oft-cited gerotherapeutic strategy is the use of caloric restriction mimetics such as metformin or rapamycin (an mTOR inhibitor).[9] These drugs, originally developed for other indications, have shown potential to influence aging pathways (eg, by improving metabolic and immune function in animal models) and are being used in trials such as the Targeting Aging with Metformin (TAME) study, which seeks to test whether metformin can delay age-related diseases by targeting biological mechanisms of aging.[10] Rapamycin, in particular, has been shown to potentially increase lifespan in organisms from yeast to nonhuman mammals, and there is now growing interest in its potential effects on human aging as well.[11] Notably, no gerotherapeutics have been approved for "anti-aging" purposes in humans, and aging is not currently classified as a disease by regulators; there is broad consensus in the gerontological field against medicalizing a natural and multifaceted life process.[12]

The translation of gerotherapeutics from bench to bedside, while promising, requires interdisciplinary reflection on how such tools might reshape the meaning and management of aging. As geroscience continues to deepen our understanding of the biological mechanisms of aging, it opens new possibilities for treating and preventing age-related conditions. This article does not question the value of these discoveries but rather asks how clinicians and health systems should respond to them by examining the broader clinical and societal domains that determine who benefits, how care is delivered, and what it means to age well.

Clinicians' Roles in Anti-Aging Narratives

Health care is participating in a convergence of accelerating geroscience research and a surging consumer anti-aging market.[13] Breakthroughs in the biology of aging offer hope that we will someday have tools to prevent or treat age-related conditions in fundamentally new ways.[14] Such hope raises the question, however, of how such interventions should be regulated and promoted and, more fundamentally, how they might affect our conception of what is normal and what is abnormal. While drugs require premarket approval from the US Food and Drug Administration (FDA), cosmetics (aside from most color additives) and dietary supplements do not; instead, manufacturers are responsible for ensuring product safety, and FDA oversight largely occurs after these products enter the market.[15,16]

As human trials and approval of gerotherapeutics might occur in the future, clinicians eventually might incorporate them in practice. In the meantime, a practical strategy for delaying or treating age-related conditions would be to align prescribing of drugs approved for treatment of particular diseases with the principles of evidence-based prevention: if the drug demonstrates safety and efficacy for delaying the onset of

multiple diseases, it could be considered a valuable anti-aging intervention.[17] Until therapies are validated for this purpose, however, other effective approaches remain relevant for supporting longevity, such as maintaining a healthy diet, staying physically active, remaining socially engaged, and managing chronic conditions. Even as drugs with gerotherapeutic properties become more widely adopted, lifestyle approaches are likely to act synergistically with them; exercise and metformin, for example, activate distinct but overlapping biological pathways.[18] The tech-infused discourse regarding geroscience and "biohacking" (a wide range of practices intended to optimize biological function)[19] might sometimes divert attention from these foundational health measures.

In navigating ethical issues raised by off-label prescribing of disease-targeting drugs to delay or treat age-related conditions, clinicians might find it worthwhile to draw on approaches from the fields of geriatric medicine and palliative care, which emphasize holistic, patient-centered decision-making. For example, the Age-Friendly Health Systems movement promotes the "4 *M*'s" framework, which addresses what matters, medication, mentation, and mobility.[20] This approach emphasizes that high-quality care for older adults involves aligning care with the individual's goals and priorities (what matters), deprescribing or optimizing medications to avoid harm (medication), maintaining mental health and cognition (mentation), and preserving physical function (mobility). Any intervention for or health encounter with an older adult should ideally be evaluated in light of these broader domains. In prescribing any novel therapy, it is also important to consider the *therapeutic illusion* (overestimation of benefits due to optimism or patient demand) and remain clear-eyed about the uncertainties.[21] Navigating the boundary between openness to innovation and regulatory reality might surface as one of the key challenges in the emerging field of gerotherapeutics.

Policy- and System-Level Recommendations

Policymakers, clinicians, scientists, research funders, regulatory agencies, and educational institutions all have a role in ensuring that longevity science is translated into meaningful public benefit.

Here are some key areas for consideration:

1. *Require robust evidence and regulatory oversight*. Before anti-aging therapies are widely promoted or integrated into practice, they should meet stringent evidence standards. For example, if a company seeks approval for or markets a "longevity" drug, it should be evaluated on outcomes such as postponement of specific age-related diseases or improvement in functional health and not just on affecting a biomarker change that might not hold much value to the individual. Conditions such as frailty and multimorbidity, which are not discrete diseases, could be used as clinical endpoints in trials of drugs intended to prevent or treat multiple age-related conditions.[22]

2. *Promote more equitable access to gerotherapeutics*. As geroscience breakthroughs occur, their benefits must not be limited to those with the greatest resources. Public and private payers should proactively evaluate truly effective aging-related interventions for insurance coverage. Health care professionals, researchers, and policymakers should advocate for inclusive research and equitable distribution of validated gerotherapeutics so that extending health span does not become solely a luxury good. Additionally, government and academic research funding should support interventions that

can be delivered at scale and at reasonable cost, including nonpharmacological strategies. Community-based programs that contribute to quality of life and health span (eg, exercise classes, nutrition support, social engagement initiatives) also merit funding, expansion, and attention.

Equity also necessitates challenging the underlying ageist and ableist narratives that equate aging with decline and imply that only certain types of existence are "worth" extending. The pursuit of longevity, then, potentially engenders social hierarchies if aging "well" becomes a moral obligation tied to wealth or access. As scholars in aging have made increasingly clear, aging is as much a social and moral category as it is a biological process, and the medicalization of aging must be interrogated through this theoretical lens.[23] Policymakers and research funders can support the goal of equity by incentivizing participation in research of underrepresented populations (eg, through community-based recruitment models), calling for equity metrics in trial designs, and supporting coverage-with-evidence development models through agencies like the Centers for Medicare and Medicaid Services.

3. *Integrate more geroscience, geriatrics, and lifespan frameworks into health professions curricula*. Health professions education and health care delivery offer an opportunity to more fully integrate principles of lifespan health into care by training clinicians in the biology of aging and geroscience. In this way, students are exposed to emerging therapies and trends, as well as geriatric care principles and frameworks.[24] Professional societies could also create guidelines or repositories of resources on longevity or health span for patients, analogous to chronic disease management plans, which would review evidence-based preventive strategies (eg, vaccinations, exercise), discuss advance care planning, and recommend selective use of gerotherapeutics when appropriate. Whether emerging therapies in this area meaningfully improve health outcomes remains an open question that hinges on how health span is operationalized and measured.[25] As novel therapies are integrated into practice, health systems have an opportunity to implement monitoring processes to evaluate their clinical utility and ensure that they bolster, rather than fragment, the delivery of high-quality care.

Conclusion

As geroscience and its connotations of health span gain attention as a promising frontier, it is worth exploring whether their scope should remain limited to biology or also encompass the broader ecosystem of aging, such as housing, food security, and policy. This notion prompts reflection on how we conceptualize health span. Is it a biological duration of low disease burden or a dynamic sociocultural state in which people are able to live well according to their own values? While interpretations may differ across disciplines and worldviews, clarifying the conceptual scope of health span will be essential as it gains traction within both clinical and commercial spheres.

The unique challenge of anti-aging interventions is that the target (ie, aging itself or associated physical changes) might not fit neatly into conventional definitions of treatable disease, which, as discussed, complicates regulatory oversight and norms of aging. This challenge makes it all the more important for clinicians and health systems to center patient values in care delivery and to promote approaches that support function and adaptability across changing health states.

Geroscience reminds us that the biology of aging is deeply entangled with many chronic diseases, but it is the field of gerontology that elucidates how aging is experienced variably, contextually, and irreducibly. No two individuals age identically, biologically or socially. Against this backdrop, the cultural impulse to "overcome" aging can foster an insatiable drive for incremental biomedical gains, sometimes eclipsing the more fundamental commitments required to improve the everyday realities of older adults. Meeting these commitments requires grappling with the interdependence of social and caregiving contexts. By acknowledging this reality, geroscience can position itself to be a means of shaping the very systems and environments that will define our own aging trajectories. An important measure of progress will be how well advances in geroscience are translated into interventions and systemic support that help address existing health inequity.

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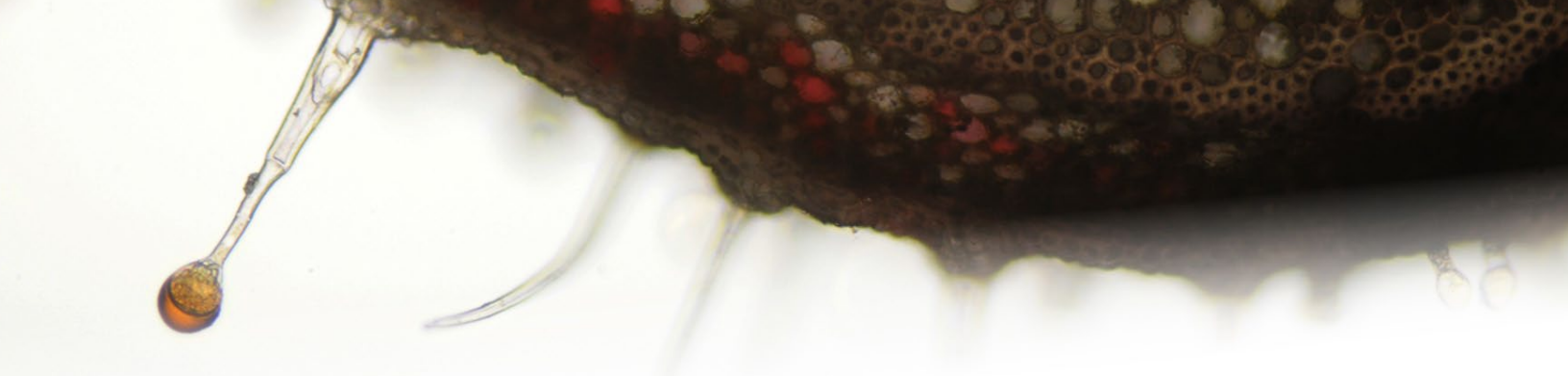

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HISTORY OF MEDICINE: PEER-REVIEWED ARTICLE

Lessons for Responsible Geroscience From the History of Longevity

Nicolai Wohns, MD and Daniel Promislow, DPhil

Abstract

Advances in public health, medicine, and technology since the mid-19th century have redefined what is considered "natural" for human beings. This article situates contemporary geroscience in that historical context. The development of gerotherapies must be guided by historical insight, ethical foresight, and a commitment to justice. Since extending lifespans has important societal consequences, how aging research will affect future generations should be prioritized. Equitable access to gerotherapies, as well as an emphasis on social responsibility and the influence of community on health and longevity, must remain central to any vision of the future of aging.

Transformation of Longevity

Aging and longevity have undergone a profound transformation over the centuries, driven by remarkable advances in science, technology, and public health. Once plagued by high rates of infant mortality and the ever-present threat of infectious diseases, the global population in the modern era has seen average lifespan nearly double in the past 2 centuries.[1] In this article, we explore the historical context of lifespan extension and then turn our attention to efforts by geroscientists to extend lifespan by tackling the underlying biological processes of aging itself. We highlight important lessons from the history of longevity, arguing that equitable access to gerotherapies, as well as an emphasis on social responsibility and the influence of community on health and longevity, must remain central to any vision of the future of aging.

Historical Gains in Lifespan

For most of human history prior to the modern era, life expectancy at birth was relatively constant.[2] As recently as 1860, a person born in the United States could expect to live 39 years.[3] Over the subsequent 100 years, however, life expectancy rose dramatically. More people were surviving birth and childhood, thanks to ambitious social, economic, and public health initiatives. Revolutions in sanitation and nutrition played integral roles.[4] Access to clean water and proper waste disposal reduced the spread of waterborne diseases like cholera and typhoid. Agricultural yields increased dramatically, leading to increased caloric intake and better nutritional states. Improved neonatal care reduced child mortality rates. Furthermore, the development and widespread use of vaccines reduced mortality from childhood infectious diseases like smallpox, polio, and

measles.[4] The discovery of penicillin and other antibiotics dramatically decreased deaths from bacterial infections, which were leading causes of death for much of human history.[4] In addition to medical, sanitary, and nutritional improvements, economic and social development played a centrally important role in increasing longevity. Specifically, rising incomes, better housing, and higher levels of education led to better health literacy and healthier lifestyles.[4] These society-wide interventions were a success; by 1960, life expectancy at birth in the United States had increased to 70 years.[3]

As more people survived to old age, cancer, cardiovascular disease, and neurodegenerative diseases emerged as leading causes of mortality and, as a result, became targets for research and intervention.[5] Further gains have been made over subsequent years—average life expectancy at birth was 78.4 years in 2023[6]—in part due to improved treatments for cardiovascular disease and cancer that are both more widespread and more efficacious.[4]

Questioning "Natural" Human Lifespan

Given these dramatic historical changes in lifespan, how then should we conceive of a "natural human lifespan"? Even within a single population, quantitative genetics tells us that, at the individual level, differences in lifespan potential among people are shaped not only by the environmental factors discussed above, but by the genes they have inherited from their ancestors. But these heritable factors account for only 20% to 30% of the variation in human lifespan,[7] and only one or two genes are known to have large effects on life expectancy worldwide.[8,9,10] This fact underscores that the majority of the variation in lifespan among individuals within populations, as well as between populations, is shaped by environmental factors, many of which are modifiable.[11,12]

In this light, natural human lifespan might be conceived as the maximum lifespan, under optimal conditions, for a given genotype. Optimal conditions, to be clear, here refer to environmental features associated with prolonged longevity for a given population, including modifiable behaviors (eg, avoiding cigarette smoking, optimizing nutrition and exercise, sleeping well, maintaining an active social life, pursuing personally rewarding activities), minimizing pathological infectious diseases and risk of accidents, and so on.[11] Thus, "natural" becomes an expression of intrinsic longevity potential modified by extrinsic environmental interactions. Whether or not this view is ultimately correct, it is helpful in one clear way: it brings into focus the contemporary emphasis on aging as a fundamentally malleable and modifiable condition.[13]

But this contemporary emphasis is not entirely new. The idea that environmental factors and lifestyle choices can promote greater health and longevity resonates with similar claims from antiquity. Hippocrates, for example, spoke of the impact of climate, geography, and water quality on health and disease in his treatise, *Airs, Waters, and Places*, which dates from the 5th or 4th century BCE.[14] He also advocated a balanced diet, regular exercise, and moderation in habits as critical for maintaining health and longevity. Cicero, in his essay *De Senectute* from 44 BCE, similarly gives prudent advice regarding diet, exercise, and social interaction for the purposes of healthy aging—advice that would sound familiar to a contemporary reader.[15] Nevertheless, the unrivaled gains in lifespan over the last 2 centuries demonstrate that systemic societal and environmental changes (eg, sanitation, nutrition, workplace reforms) and scientific advances (eg, vaccines, antibiotics) were necessary to make significant progress.

Social and Systemic Dimensions of Lifespan Extension

Three important points emerge from these observations. First, many of the factors that, historically, have increased life expectancy (eg, sanitation, nutrition, workplace reforms, mass vaccinations) do so for everyone; these are societal benefits. The contrary is also true, however: fewer community resources and a relative lack of health infrastructure lead to worse health and shorter longevity.[4] Indeed, in addition to increasing life expectancy, the last 2 centuries saw increasing disparities in longevity between rich and poor countries.[4] Racial disparities in longevity and the socioeconomic inequity that contributes to them remain stark, with certain racial groups experiencing greater improvements in longevity than their racially marginalized counterparts.[16] Access to quality health care, education, and nutritious food often correlates with higher income levels—those with such privileges lead longer, healthier lives.[17,18] Thus, a second important point is that population-wide gains in longevity can mask within-population differences in longevity that reflect and perpetuate social divisions. The health and well-being of those around you—your community—and your community's infrastructure and resources are pivotal determinants of your own lifespan. These points underscore the collective dimension of health and longevity, highlighting that individual well-being is deeply intertwined with communal care.

The history of lifespan extension also teaches us that increasing population-wide life expectancy has deeply enmeshed systemic consequences, affecting family structures, social security systems, health care costs, and workforce dynamics.[19] Societal modernization and growing wealth accumulation and economic opportunities have led to delayed marriage and childbearing, as well as fewer offspring, all of which have reshaped traditional family planning and patterns of schooling.[20] At the same time, the retiree-to-labor force ratio has grown, leading to a rise in the number of years that social security benefits are paid out, which strains the financial viability of the program.[21] Additionally, extended lifespans have historically led to longer periods of managing chronic diseases.[22] Indeed, there is evidence that gains in lifespan have not been matched by proportionate gains in so-called health span.[23] These 3 points—that advances in public health extend life as a collective good yet can deepen social inequities and also drive broad social and economic change—are among the most important takeaways from the history of longevity.

Three Novel Features of Gerotherapy

Looking to current and future efforts, the difficulty in further increasing life expectancy should not be underestimated.[24] Childhood mortality in developed countries is now so low (roughly 5.6 per 1000 live births in the United States in 2023)[6] that further improvements in early-life survival, while of course worth pursuing, will have little impact on overall life expectancy. Furthermore, it has been estimated that even by eliminating all deaths from both cardiovascular disease and cancer, life expectancy at birth would still be less than 90 years.[25]

It is in this light that the emerging era of geroscience represents a fundamentally new approach and offers the potential for further increases in longevity. While there are no current gerotherapies proven to be effective in slowing, halting, or reversing biological aging in humans, numerous clinical trials are ongoing to study their effects.[26] These include studies of the effects of senolytics, which target and eliminate senescent cells that accumulate with age,[27] and of mTOR inhibitors, which appear to mimic the beneficial effects of caloric restriction by reducing inflammation, increasing fatty acid oxidation, inducing autophagy, and enhancing expression of key mitochondrial

proteins.[28,29] In 2006, Shinya Yamanaka made the Nobel prize-winning discovery[30] that a set of 4 transcription factors can reprogram mature cells back to an embryonic-like "pluripotent" state; in recent years, geroscientists have suggested that the Yamanaka factors might also be able to turn back the clock on aging.[31]

There are many potential distinctions between traditional public health interventions and gerotherapeutic approaches. Here we discuss three. First, gerotherapy primarily targets mid-life and old age, instead of the conditions of early life. For example, senolytics, mTOR inhibitors, and Yamanaka factors are specifically designed to address and counteract the cumulative effects of aging processes that become more salient as we grow older.[28,31] Second, the *direct* impact of gerotherapeutics is novel, as traditional public health advances have primarily had an indirect impact. Important public health interventions increase lifespan by decreasing mortality from extrinsic sources through the manipulation of disease ecology. For instance, big public works projects like sewer systems, water chlorination, and mass vaccination campaigns all disrupt the transmission of pathogens, leading indirectly to benefits observed at the population level. In contrast, gerotherapeutics are designed to alter the intrinsic mechanisms of aging itself. Rather than mitigating extrinsic mortality risk, these interventions aim to modulate cellular and molecular mechanisms that constitute the very process of biological aging, with direct effects on individual risk of age-related disease. Finally, the era of gerotherapeutics embodies an *individualized* approach to longevity, which contrasts with the public health initiatives of the 19th and early 20th centuries. Senolytics and mTOR inhibitors are being developed as treatments for individuals,[28,31] similar to contemporary treatments for cardiovascular disease and cancer. Taken together, these 3 distinguishing features of gerotherapies mark a shift in strategy vis-à-vis longevity, one that makes it all the more vital to reflect on the historical trajectories that brought us here and the lessons they offer for guiding the future of aging science.

Lessons for Responsible Geroscience

The history of longevity holds several important lessons for thinking about the future. First, serious consideration must be given to how gerotherapeutic interventions could affect future generations. Although it is a matter of some debate whether or not advances in gerotherapy will lead to increased health spans, increased lifespans, or both,[32] we must nevertheless anticipate that if gerotherapies are successful, further shifts in a society's demographic profile will similarly provoke profound disruptions across the socioeconomic landscape. Addressing these diverse effects requires an interdisciplinary approach that draws on the expertise of economists, political scientists, sociologists, health systems specialists, and geriatricians, among others. Second, equity and justice must be taken into account, as the goal is to improve health and longevity for all.[33] If gerotherapies are only available to the privileged, then they will exacerbate inequalities and social divisions. This possibility is particularly important, given the individualized nature of gerotherapy. Third, we must continue to protect, maintain, and expand the population-wide, systemic initiatives that have enabled the great gains in longevity since the 19th century, some of which are under increasing threat. For example, progress in expanding access to proper sanitation facilities appears to be stagnating worldwide, with the absolute number of people without access continuing to rise.[34] Vaccine hesitancy, misinformation, and political polarization are decreasing immunization coverage.[35] And cuts to maternal and child health programs and limited access to reproductive health care in some regions threaten to undo progress in reducing maternal and infant mortality rates.[36] Moreover, we must advocate for these interventions for the health and well-being not only of others, but of ourselves. The

health of one's community and environment plays a critical role in determining one's own lifespan. While geroscience represents a fundamentally novel approach to extending lifespans, its success must be complemented by preserving and strengthening foundational public health measures, thereby fostering a future in which longevity gains can be better shared across all segments of society.

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ART OF MEDICINE

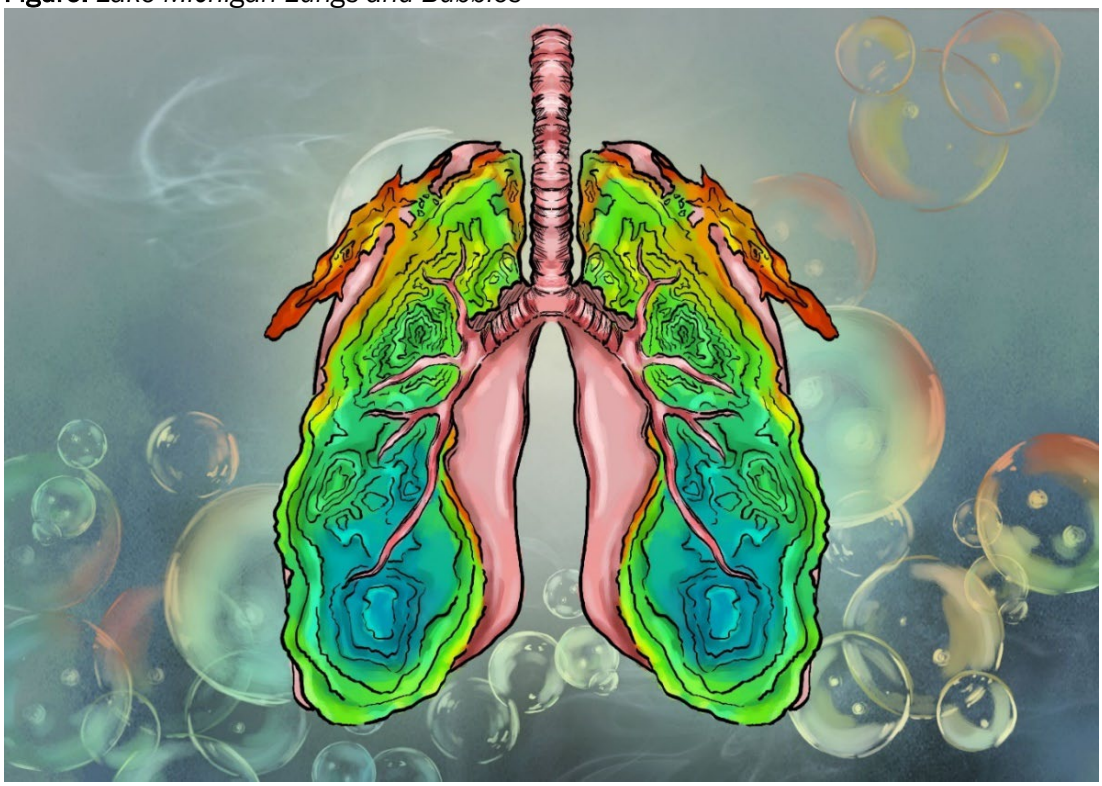
Great Lakes Eutrophication and Respiratory Health Harms

Anaid Kassidy Corona-Andaverde

Abstract

This digital drawing of satellite images showing the eutrophication of Lake Michigan visually explores relationships among respiratory health, algae blooms, and aerosolized cyanotoxin exposure.

Figure. *Lake Michigan Lungs and Bubbles*



Media

Digital illustration using Krita and Wacom® Cintiq.

This digital drawing of satellite images represents the eutrophication of Lake Michigan. Despite advocacy and statewide monitoring initiatives,[1,2,3] harmful algae blooms (HAB) continue to contribute to exposure to cyanotoxins, produced by cyanobacteria,[4] in the Great Lakes. HAB exposure extends beyond contaminated recreational water bodies, as aerosolization transports toxins inland. Indeed, 15% of global asthma trigger responses annually result from aerosolized HAB toxin inhalation in shoreline areas.[5] The most frequent symptoms include cough, allergy, malaise and fatigue, headache, shortness of breath, hypertension, acute pharyngitis, and acute upper respiratory infection.[4,6] Cyanotoxin inhalation will likely be exacerbated by ongoing climate change and more frequent algae blooms.

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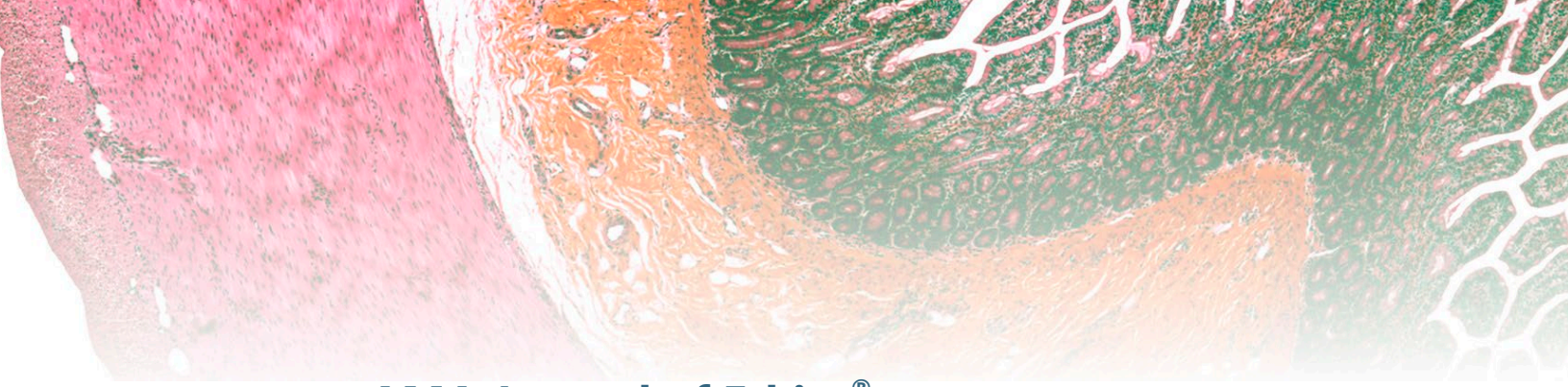

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LETTER TO THE EDITOR

Response to "Is the UDN N-of-1 Enterprise Ethically Justifiable?"

Undiagnosed Diseases Network

We write to respond to several inaccuracies and claims (summarized in italics) in the Gordon and Kearns article[1] regarding processes, risks, and benefits of the Undiagnosed Diseases Network (UDN).

1. *With a centralized institutional review board (IRB), there is no case-by-case review of participants*. Case-by-case reviews, including of adherence to eligibility criteria, consent practices, and design and execution of clinical evaluations, are performed at each UDN site by principal investigators who report to institutional and central institutional review boards (IRBs).

2. *Participants may not understand N-of-1 research or outcomes; parents may feel internal pressure to continue participation*. The UDN consent processes adhere to established ethics best-practices,[2] including facilitating understanding of both the research and the possibility of not obtaining a diagnosis or treatment.

3. *Participants' symptoms are difficult to anonymize, and data sharing can threaten insurance coverage*. External sharing of UDN phenotypic data in data repositories involves deidentified data and standardized Human Phenotype Ontology terms and is compliant with IRB and legal requirements. Claiming that insurance coverage might be affected by data sharing adds an unsubstantiated barrier to already-distressed families' participation.

4. *Minority and rural participants are not well-represented in the program; cost is a barrier to participation*. Lack of minority representation affects many clinical trials. The UDN has recently established community partnerships to enroll participants with health disparities and has always prioritized NIH funds to cover patient costs for under- and uninsured participants.[3]

5. *Need for network external advisors.* Although UDN primary investigators are experts in rare and ultra-rare diseases, since its initiation the network has also had an external scientific advisory panel comprising non-UDN experts in rare and ultra-rare diseases and genomics to provide guidance to the NIH.[4]

6. *The UDN benefits few participants.* Rare and ultra-rare diseases affect approximately 30 million people in the United States,[5,6] many of whom remain undiagnosed. Although the UDN cannot evaluate all individuals, its methods and

successes provide scientific and clinical models for both diagnosed and undiagnosed rare disease research.[7,8,9,10,11]

7. *UDN federal funding is not justifiable due to the small and selected group of individuals helped.* This argument overlooks its initiatives to increase equity.[3] It also employs zero-sum thinking by casting individuals with undiagnosed diseases as less deserving of federal funding, and it disregards the contribution of rare disease research to more common conditions.

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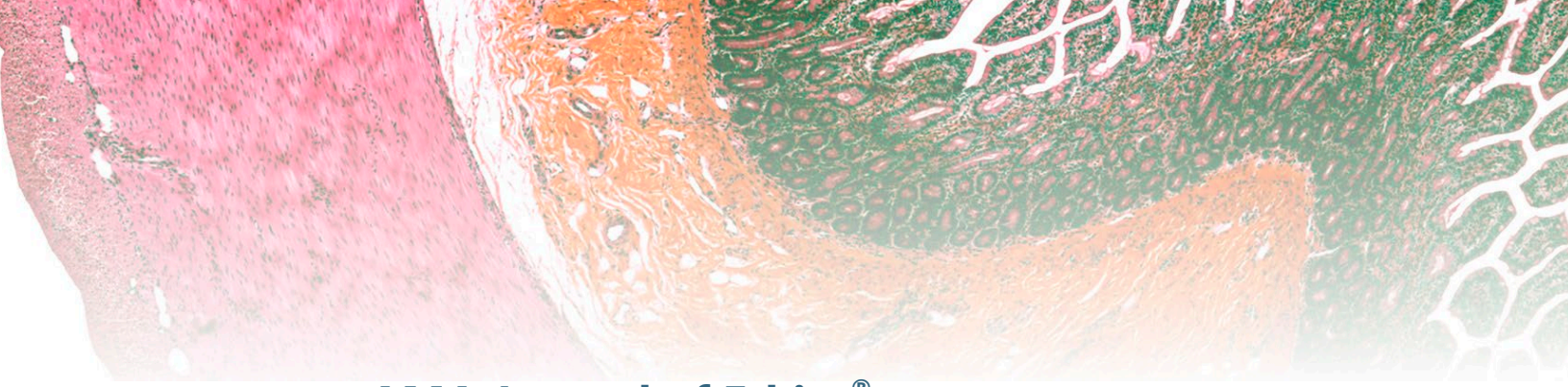

AMA Journal of Ethics®
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LETTER TO THE EDITOR

Patient Voices on Diagnostic Research

Undiagnosed Diseases Network Foundation Participant Engagement and Empowerment Resource

The October 2025 issue of the *AMA Journal of Ethics* explored the ethics of diagnostic research, focusing heavily on the National Institutes of Health's Undiagnosed Diseases Network (UDN). One notable absence was the patient voice. We write as the UDN's affiliated patient advisory board, UDN Foundation Participant Engagement and Empowerment Resource (UDNF PEER). We are patients and caregivers living the diagnostic journeys examined in those articles. While we appreciate the emphasis on training students to care for patients thoughtfully and empathetically with undiagnosed conditions,[1] articles that called into question the value, ethics, and utility of diagnostic research did not reflect our experience with the UDN.

Some articles speculated about the value of participation without resulting treatments.[2,3] For us, the UDN's value was not limited to a diagnosis or treatment. While some UDNF PEER members have found clear answers in the form of a diagnosis or treatment, others have not. But we benefitted from individualized attention to and comprehensive evaluation of our cases. Because of the UDN's benefit to us and our families, we want clinicians who are considering UDN referrals to understand its value.

Ethical concerns raised about informed consent did not reflect our experiences.[2,3] Each of us clearly understood that the UDN is a research program, a diagnosis was not guaranteed, and we could withdraw at any time. We knew that the odds are stacked against us. While we hope for breakthroughs in our cases or our children's cases, we also hope that the UDN's findings help others.

Most concerning is one article's call to end the UDN's public funding.[3] While the article raises interesting points about program access,[3] we believe that increasing opportunities is a better answer than eliminating public programs. Critiques of the UDN's complexity and cost should also consider that the UDN's NIH funding for under- and uninsured patients translates to cost savings for the private health care system.[4] Ending public funding would dismantle the only national model offering such coordinated investigation. Having walked this road, our hope is that the next patient who could benefit from the UDN's model has more opportunities to participate—not fewer.

We cannot speak for every participant; however, diagnostic research has benefited us as patients and caregivers, even those of us without diagnoses. As Hall et al write in this

issue, medical professionals' "duty of care is independent of the patient having an established diagnosis."[5] We agree. When there is no standard of care for a patient's condition or symptoms, the availability of diagnostic research options is critical. Each discovery expands medical knowledge, informs future clinical practice, and shortens the diagnostic odyssey for others.

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Undiagnosed Diseases Network Foundation Participant Engagement and Empowerment Resource is an 11-member patient advisory group that advises Undiagnosed Diseases Network leadership and site teams on patient experiences and publishes materials to support the Undiagnosed Diseases Network Foundation mission of improving access to diagnosis, research, and care for all individuals living with ultra rare or undiagnosed conditions. More information about the Undiagnosed Diseases Network Foundation Participant Engagement and Empowerment Resource is available here.

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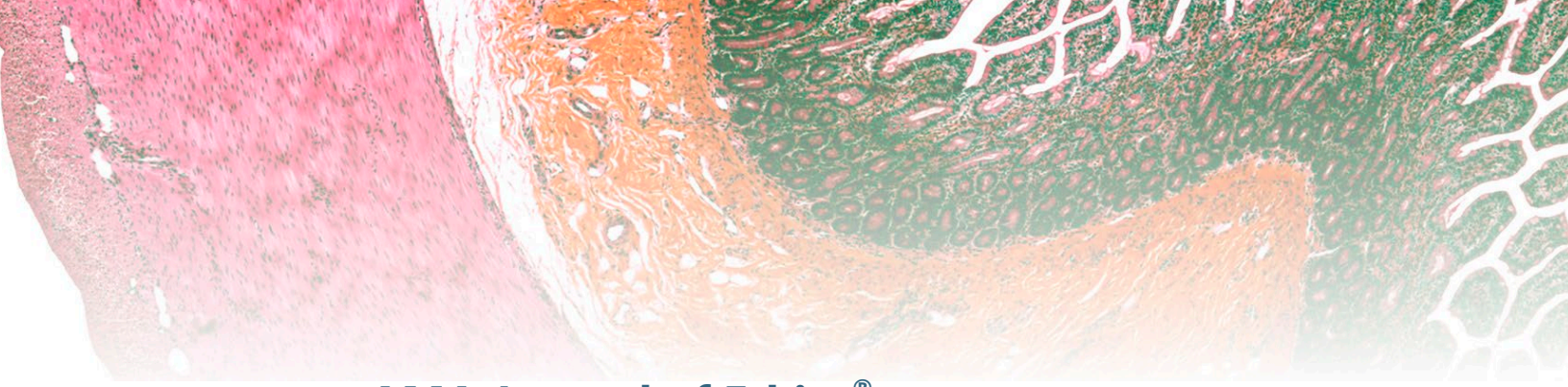

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LETTER TO THE EDITOR

Response to "Response to 'Is the UDN N-of-1 Enterprise Ethically Justifiable?'"

Gianna Gordon and Lisa Kearns, MS, MA

Based on our review of the correspondence from the Undiagnosed Diseases Network (UDN) regarding our article, "Is the UDN N-of-1 Enterprise Ethically Justifiable?" we give a point-by-point response to their summaries of our arguments (in italics) below.

1. *With a centralized institutional review board (IRB), there is no case-by-case review of participants*. We appreciate the strict system-level oversight of consent processes that sites employ yet worry about the application of those processes at the participant level. Extremely heterogeneous patient populations ethically require close oversight by clinicians and researchers with appropriate expertise.

2. *Participants may not understand N-of-1 research or outcomes; parents may feel internal pressure to continue participation*. Our concern is whether ethical best practices are sufficient for the UDN's participants. They are in an especially vulnerable position, as is anyone with a rare disease. It is an ethics issue if patients feel pressure to stay in a study because they have built up, in their own minds, the potential benefits of the study.

3. *Participants' symptoms are difficult to anonymize, and data sharing can threaten insurance coverage*. Because UDN patients have such rare conditions and data may be requested from family members, guaranteed anonymity of data is not possible, even with safeguards in place. (This is true of other databanks.) It is not our intention to distress families, but withholding potential consequences of a data breach violates ethical principles of autonomy and beneficence. Our mentioning the effects of a potential privacy violation isn't distressing, but the fact that it could happen is.

4. *Minority and rural participants are not well-represented in the program; cost is a barrier to participation*. We agree that underrepresentation is an ongoing ethical concern in all drug development in the United States. Even with assistance, UDN participants could still be on the hook for patient services costs steep enough to prevent their participation.

5. *Need for network external advisors.* We're not clear about what the authors are referring to here. To bolster patient protections, especially for informed consent, we suggested that the UDN create a dedicated oversight committee comprising members with relevant expertise. They would provide guidance to UDN researchers, physicians, and patients, not to the National Institutes of Health.

6. *The UDN benefits few participants.* We agree, and we applauded both the UDN's creation of foundational knowledge and its freely sharing it. We also mention the benefits to undiagnosed patients of having certain conditions ruled out.

7. *UDN federal funding is not justifiable due to the small and select group of individuals helped.* We did not say or imply that patients with undiagnosed diseases are any less deserving than anyone else. Rather, we question the ethics of *publicly* funding the UDN, given the limited resources available for health care in this country. We also would never disregard the contributions of rare disease research. UDN patients are not less deserving of public funding but rather, according to the ethical principle of justice, conditions affecting larger groups of the population—some comprising hundreds of thousands of people—may warrant a larger share of limited resources. We add that we find the United States' choice to limit resources for health care to be ethically indefensible.

We thank the authors for their careful reading of our article and for their comments. We admire the UDN's efforts and the impressive success it has achieved. As we acknowledged, the low percentage of patients helped are actual patients and families, whose arduous search for a diagnosis was ended by the UDN's researchers.

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Lisa Kearns, MS, MA is the senior research associate in the Division of Medical Ethics at NYU Grossman School of Medicine in New York City and the associate director of the division's High School Bioethics Project. She is also a member of the division's working groups on Compassionate Use and Preapproval Access and on Pediatric Gene Therapy and Medical Ethics. For the past 10 years, she has studied ethical issues in preapproval access to investigational drugs, including gene therapies and individualized genetic interventions.

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ART OF MEDICINE

What Makes a Good Physician? Asclepius and the Rhetoric of AI

Audiey C. Kao, MD, PhD

Abstract
Visual symbols such as the rod of Asclepius possess rhetorical power by illuminating core values—in the case of medicine, those qualities that make a good physician. Patients expect their physicians to demonstrate skill and judgment, as well as to comfort with compassion and empathy. With the emergence of artificial intelligence, questions abound about how this technology will transform and disrupt the practice of medicine and, ultimately, the therapeutic relationship between physicians and those whom they are committed to serve.

Figure 1. *Allegory of Rhetoric*, 1650, by Laurent de La Hyre

Media
Oil on canvas.

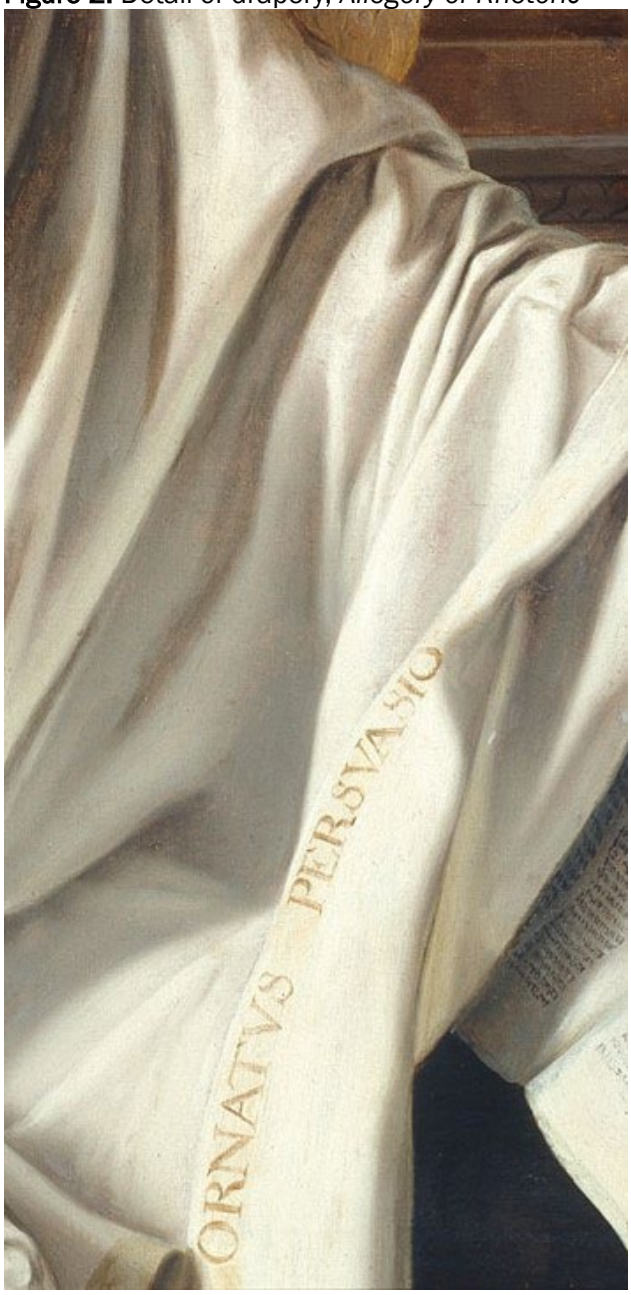
Commissioned for Gédéon Tallemant (1613–1668), an influential administrator in the French court of King Louis XIV, the *Allegory of Rhetoric* (1650, oil on canvas) was one of

7 paintings representing the liberal arts by Baroque artist Laurent de La Hyre (1606-1656).

In addition to capturing rhetoric, La Hyre painted other female figures embodying grammar, logic, arithmetic, music, geometry, and astronomy, which combined were the foundational elements of classical education in the era of Antiquity.

La Hyre modeled the figures after illustrations in Cesare Ripa's book, *Iconologia*, published in 1603.[1] Ripa's work greatly influenced writers and artists employing symbolic imagery to convey complex ideas and moral lessons.

Figure 2. Detail of drapery, *Allegory of Rhetoric*



The edge of the figure's skirt is embroidered with the phrase *ornatus persuasio*. This phrase generally translates to "decorated with conviction" or "rhetoric is persuasion," denoting the function and power of rhetoric.

Aristotle (384-322 BCE) saw the art of persuasive power as one's arguments grounded in 3 areas: ethos, pathos, and logos.[2] Ideally, these persuasive appeals are all drawn upon to form what later rhetoricians called the rhetorical triangle.

Figure 3. Detail of head, *Allegory of Rhetoric*

Ethos, or ethical persuasiveness, refers to a speaker's or writer's character when making an argument. Do they possess the authority and credibility to address this topic? Do they seem to be knowledgeable and reasonable? Do they appear to be honorable and trustworthy? Draped in a robe, wearing a garland, and sitting in a throne-like chair, this figure is adorned with authoritative and honorific symbols.

Figure 4. Detail of hand, *Allegory of Rhetoric*

An outstretched arm seemingly gesturing to and reaching out to an audience, *pathos*, or emotional persuasiveness, appeals to the feelings and imagination of the listener or reader. How does the speaker or writer establish a relationship with the audience? Which emotions are evoked in connecting with the audience? What circumstances can the audience relate to or imagine?

Figure 5. Detail of Caduceus, *Allegory of Rhetoric*

Symbolized by a book propped open by the figure's left hand, *logos*, or logical persuasivness, appeals to reason. What facts and evidence have been brought to bear in this tome? Are they relevant to the argument? Do the conclusions make sense?

Along with the revealed book, a staff with 2 winged snakes is pinched upright by the figure's left thumb. From the 16th to the 19th centuries, such a staff was commonly used as a symbol for rhetoric.[3] Over the millenia, this staff, known as the Caduceus, has come to symbolize various human endeavors—including, if mistakenly, the art of doctoring and the medical profession.

Figure 6. Roman fresco from the eastern wall of the triclinium in the *Casa dei Vettii* ("House of the Vetii", VI 15, 1) in Pompeii, Fourth Style (60-79 CE)

The staff of Caduceus originated with the Greek god Hermes.[4] As the patron god of negotiation, trade, and commerce, Hermes was also regarded as the cleverest of the

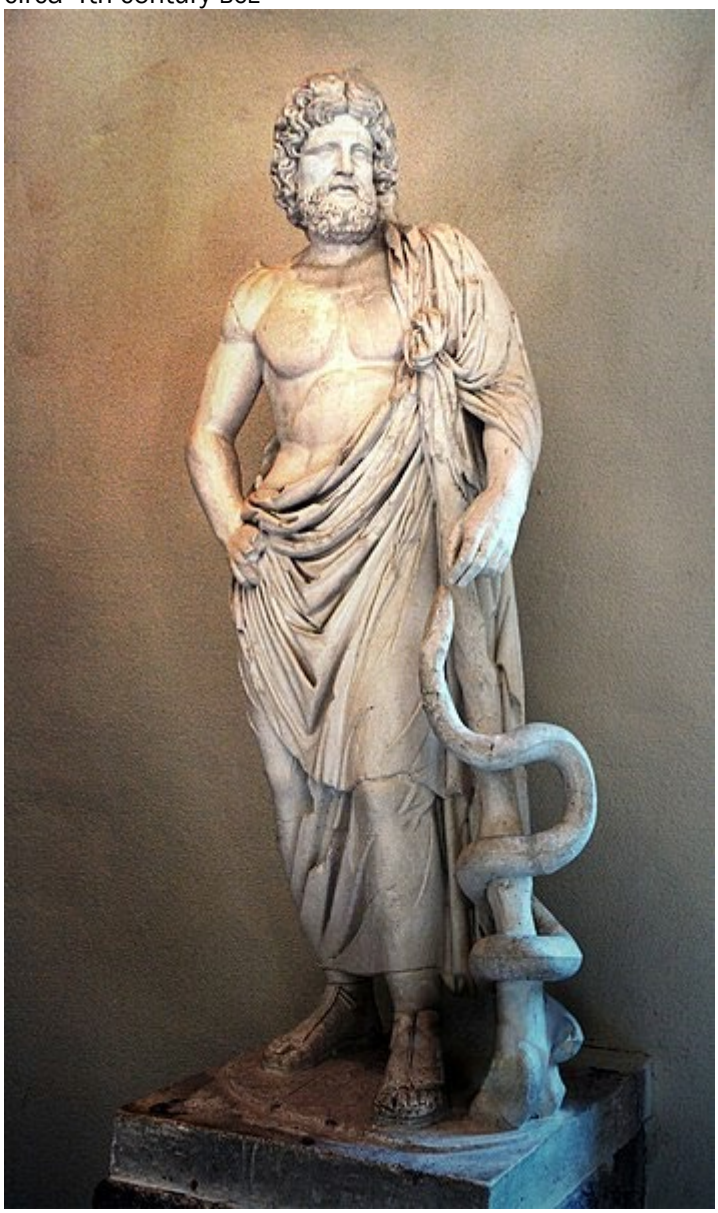
Olympian gods and as a protector of thieves, merchants, and orators, all of whom probably relied on sly actions and clever persuasion in their line of work.

Figure 7. *Mercury*, 1611, by Hendrik Goltzius

Media
Oil on canvas.

Similarly, the Caduceus represented Hermes' Roman counterpart, Mercury.

Figure 8. Statue of Asclepius, Exhibited in the Museum of Epidaurus Theatre, circa 4th century BCE

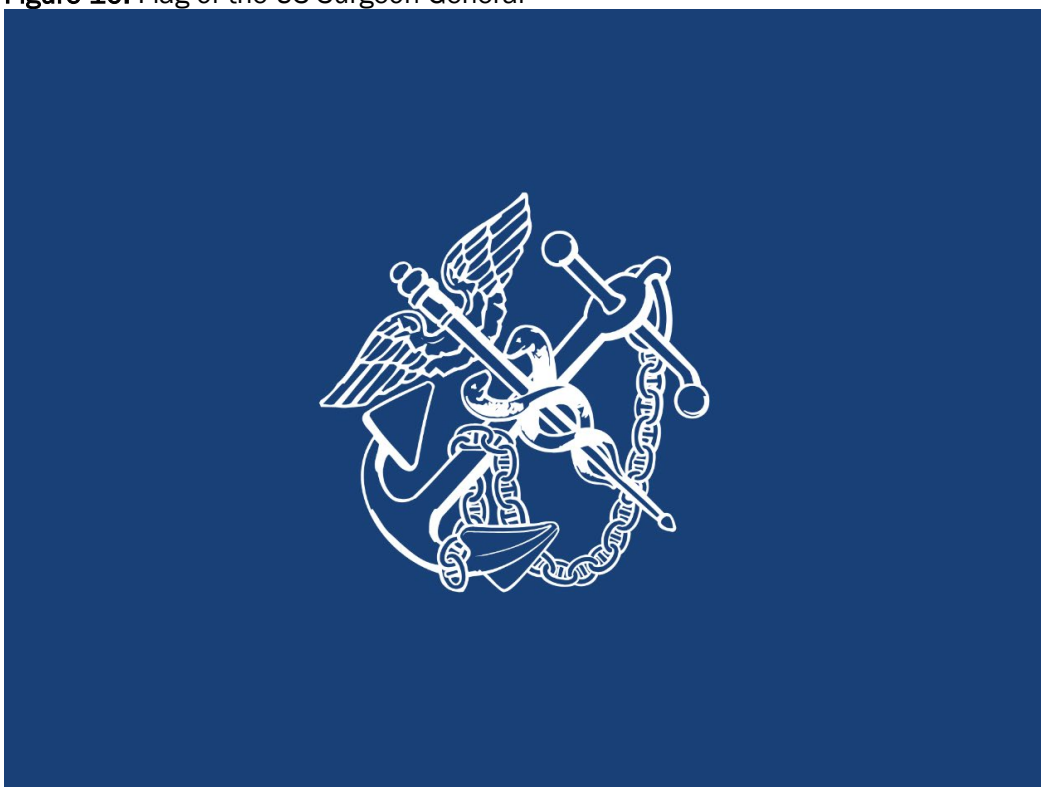


In Greek mythology, a single serpent-entwined staff was wielded by Asclepius, son of Apollo, and a god associated with healing and medicine. The rod of Asclepius has symbolized Western medicine into modern times.[5]

Figure 9. US Army Medical Corps Branch Plaque, 1902

Despite the symbolic origins of the rod of Asclepius, the 2-serpent staff of Caduceus has been misused to represent medicine for well over a century and probably much longer than that. In 1902, the US Army incorrectly used it for its Medical Corps logo.[6]

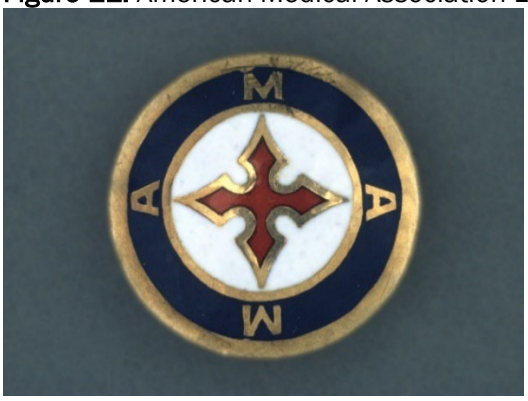
Figure 10. Flag of the US Surgeon General



Are 2 snakes better than one? The US Army Medical Corps logo has never been corrected and likely spawned more mistaken uses over the years, including the current seal and flag of the US Surgeon General. Some claimed that the American Medical

Association (AMA) also used the Caduceus in its logo,[7] but that logo claim defies logos and evidence.

Figure 11. American Medical Association Logo, 1898



Courtesy of the American Medical Association Archives.

Founded in 1847, the AMA adopted its first official logo in 1898. Designed by Dr Richard French Stone of Indiana,[8] the logo was a circular shield with a spear-pointed cross design symbolizing the protective armor of ancient times. Notable is the acronym MAMA on the perimeter, which stood for member of the American Medical Association.

Figure 12. American Medical Association Logo, 1903

Courtesy of the American Medical Association Archives.

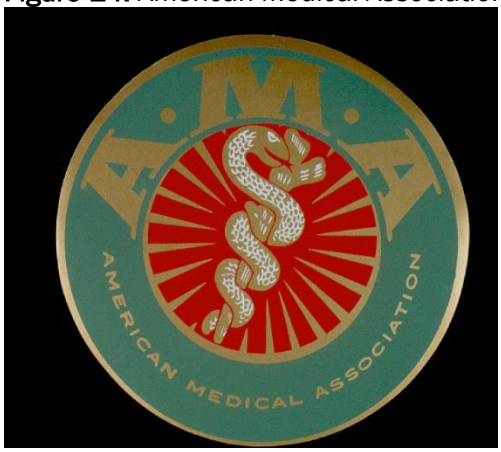
In 1903, the AMA logo was modified to incorporate a red cross, which was used by other health-related organizations at the time, including the American Red Cross and the International Anti-Tuberculosis Association, a forerunner of the American Lung Association.

Figure 13. American Medical Association Logo, 1910

Courtesy of the American Medical Association Archives.

In 1910, the rod of Asclepius officially became part of the AMA logo. The Committee on Insignia stated that "the true ancestral symbol of the healing art is the knotty pine and the serpent of Aesculapius."[9] Scarlet and gold were chosen as the primary logo colors, given their association with medicine dating back to ancient Greece. Some committee members wanted to include an eagle, but that idea was not adopted.[10]

Figure 14. American Medical Association Logo, 1953



Courtesy of the American Medical Association Archives.

Refinements to the AMA logo were approved in 1953.

Figure 15. American Medical Association Logo, 1966

Courtesy of the American Medical Association Archives.

The logo was refined again in 1966.

Figure 16. American Medical Association Logo, 1991

Courtesy of the American Medical Association Archives.

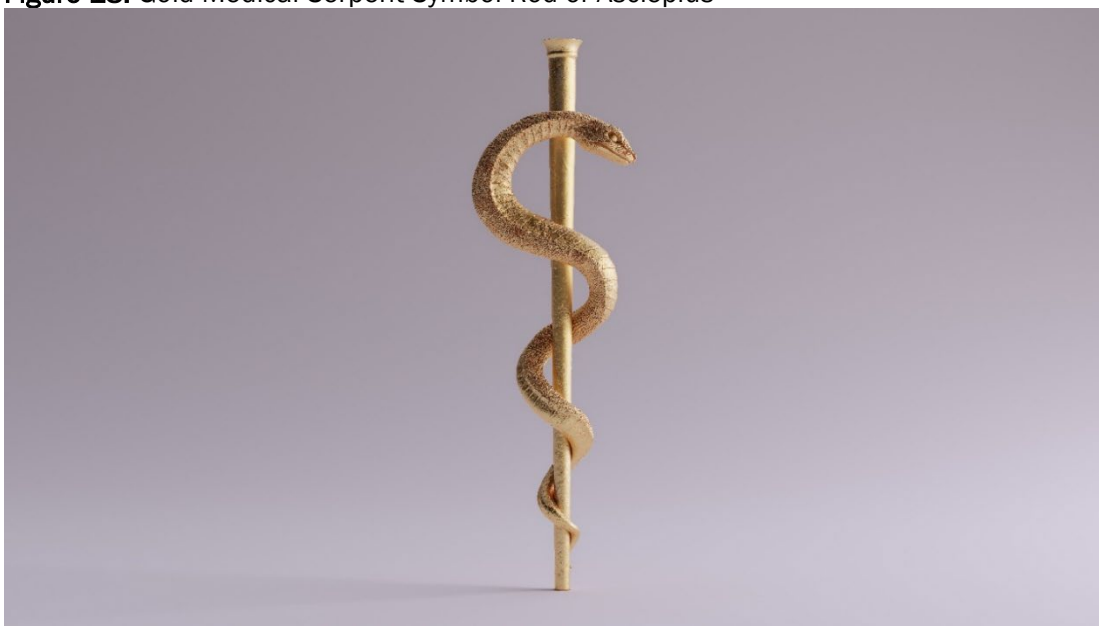
It underwent another change in 1991.

Figure 17. American Medical Association Logo, 2005

In 2005, the AMA's logo was modernized and remains its logo today. The then-AMA chief executive officer remarked that "the more modern visual of the staff of Aesculapius captures the proactive and aggressive role the AMA will play on behalf of our physician members. The purple color connotes unity and balance, and communicates science, creativity and tradition."[11]

With its various logo incarnations over the years, the symbolic integrity of the AMA logo ultimately rests on the AMA's organizational actions and their moral proximity to the ideals of medicine. Should the AMA stray too far or too long from these ideals,[12] its appropriation of the Asclepian rod would be false and misleading advertising.

Figure 18. Gold Medical Serpent Symbol Rod of Asclepius



80's Child/Shutterstock.com.

As artistic shorthand for moral ideals, visual symbols possess potency by illuminating core values—in the case of medicine, those qualities that make a good physician. In seeking medical care, patients expect their physicians to demonstrate competence and judgment, as well as to comfort with compassion and empathy in service to the sick and injured.

Thus, it should be alarming that the Caduceus has been used by some to represent the medical profession, inadvertently perpetuating the practice of medicine as more a business than a calling and its practitioners as merchants providing a commodity like any other in an economy.

Figure 19. Power Loom Weaving., 1835, illustrated by T. Allom and engraved by J. Tingle

During the Industrial Revolution in the 18th and 19th centuries, mechanical inventions like the power loom transformed the nature of business, commerce, and production-oriented work. In this century, intelligent machines such as artificial intelligence (AI) technologies are again poised to fuel workplace transformations and labor market disruptions,[13] provoking concerns and questions about their impact on knowledge-centered work like medicine.

For example, will AI evolve to support patient-centered expectations and physician professionalism? While AI can aid physicians in their work, could physicians be supplanted by AI?[14] What does it mean to be a good physician in the age of AI?

Figure 20. Detail of head, *Allegory of Rhetoric*

Rhetorically arguing for a health care system in which physician colleagues could never be replaced by AI would be self-serving. Whether being up-front about this protective bias enhances my ethos, it's important to acknowledge that while AI can perform some medical tasks as well as or better than physicians,[15,16] the benefits of AI should be focused on how to augment the efficiency and quality of physician work.

Given that AI developers often cannot fully understand how their own AI tools[15,16] arrive at their outputs,[17] entrusting such "black box" technologies to wholly replace physicians' skills and judgment would not be in society's enlightened self-interest. Thus, health care AI demands human oversight and accountability.[18,19]

Figure 21. Detail of hand, *Allegory of Rhetoric*

It may be hard to accept that some patients consider encounters with an AI chatbot to be more satisfying than those they have with a physician. Studies have found that

patients feel chatbot responses to be more empathetic than those provided by health care professionals.[20] But it's one thing for an AI chatbot to deliver a persuasive moment of empathy and something completely different for a patient to initiate and sustain a therapeutic relationship with a human physician.

In the United States, uninsured and underserved patient populations are usually groups that have little or delayed access to the newest health care technologies and innovations.[21] Thus, it would be ironic if historically marginalized patients have no option but to settle for an AI chatbot without access to a physician.

Figure 22. Detail of Caduceus, *Allegory of Rhetoric*

While evidence grows on how AI can help physicians be better diagnosticians,[22,23] there is also emerging data suggesting that use of AI can result in physicians losing their clinical skills (deskilling), trusting and defaulting to AI with its attendant errors and biases (mis-skilling), or never acquiring fundamental skills of doctoring (never-skilling).[24,25]

Educational strategies for enabling physicians to acquire and maintain the skills and competencies that they need to be good physicians are critical if we expect to rely on human oversight of and accountability for AI use in health care.[26]

Figure 23. Image from "Abolitionist Reimaginings of Health," 2022, by Michael Shen

Reprinted from the *AMA Journal of Ethics*.

On November 30, 2022, AI exploded into public consciousness with ChatGPT. AI has sparked feverish optimism at the prospects of tackling long-standing ills in our health care system such as wasteful spending and medical errors.[27] Whether these benefits of AI are realized without serious harms will require fidelity to the core values of the medical profession and what it means to be a good physician.

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