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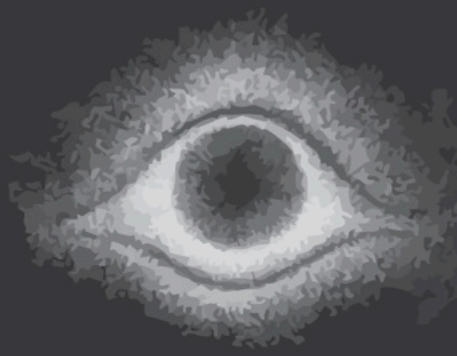

Executive Board

Cover Artwork

Adapted by S.J. Steuart from "Untitled" by Rodolfo Abularach (Artist, Guatemalan, 1933 - 2020). 1966. Image courtesy of the National Gallery of Art. The Cover Artwork is inspired by Issue 10's article: "Crystalline Conundrum: Understanding the Absence of Tumorigenesis in the Human Lens." *Crystalline Conundrum* explores how the human lens does not develop cancer, despite being mitotically active and cancers developing from the lenses of other mammalian species. The article's authors argue this phenomenon, once biologically understood, may offer a lens into future cancer prevention or treatment modalities.

Associate Editors

About HMSR

The Harvard Medical Student Review (HMSR) is student-founded, student-managed, and student-administered under the guidance of faculty and staff. Its mission is to provide a platform for students to contribute to important issues facing health and medicine through a variety of formats, including scholarly articles, editorials, and original artwork. Contributions are invited from the Harvard medical, dental, and public health schools, the rest of Harvard University, and other medical schools.

Dear readers,

We are proud to share Issue 10 of the Harvard Medical Student Review. This edition brings together a range of topics that reflect the breadth of questions facing medicine today, from the promise of regenerative therapies to the potential pitfalls of AI in the clinic. Each piece, in its own way, invites us to think more critically about how medicine is practiced, how it is changing, and who it serves.

A central theme in this issue is the tension between innovation and responsibility. Our contributors examine technologies like stem cell therapy and artificial intelligence not only for their clinical potential, but for the challenges they pose around equity, implementation, and long-term impact. Similarly, the articles addressing aging, sex differences in acute MI, and social determinants of health ask us to consider where gaps in evidence, training, or awareness are leading to real consequences for patients.

We've also included pieces that examine the system itself, including how private equity is reshaping medical practice and whether emergency departments are equipped to respond to diverse socioeconomic needs. Each of these articles reflects the core HMSR aim: to highlight work that is relevant, well-reasoned, and grounded in both science and practice.

Thank you to our authors, editors, and peer reviewers for your time, thought, and commitment to quality. We hope this issue encourages thoughtful discussion in classrooms, hospitals, and beyond.

Sincerely,

Arya Rao
Editor-in-Chief
Harvard Medical Student Review

Contents

Arts

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"Sadness (Tristesse)" by Albert Besnard. Image courtesy of the National Gallery of Art.

Forgotten Fragments

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Keywords

memory loss; cognitive decline; senility; apraxia

When words decayed and thoughts grew dim,
I lost my grip on life's fragile limb
Memory, once a symphony, now a lost hymn,
And darkness seeped beneath my paper-thin skin.

The hours withered like a barren vine,
Leaving me floating on a sea of time,
My recollections vanished, line by line,
Like ink-tipped memories drained by a thirsty pen of mine.

I became a pile of forgotten keys,
Shrouded in a cloak of elusive memories,
A whirlwind of tangled threads and mysteries,
Binding my mind, unraveling life's sweet melodies.

Names and faces now distant shores,
Whose norm I could perceive no more,
Fractured fragments of a life once bore,
Collapsed like a forgotten tapestry of yore.

The man I knew, a mirage of mist,
Drifting through the layers of a life amiss,
A puzzle box with an erased life list,
Each day a ghost, a specter I resist.

My family recoiled, strangers in my gaze,
No longer found in the labyrinths of my haze,
An empty mirror reflecting a vacant maze,
The essence of me, lost in a forgotten haze.

I wandered down corridors of vacant thought,
A haunted mansion of memories unsought,
Whispering echoes of who I once sought,
Lost in the labyrinth of my mind, distraught.

The world a riddle, my mind the key,
Yet I fumble and stumble, unable to see,
A ravenous hunger for clarity consumes me,
But the answers are locked in a forgotten decree.

I long for the embrace of yesterday's light,
To reclaim my thoughts, my essence, my might,
But I'm trapped in a twilight so tragically bright,
Where shadows dance and memories take flight.

In this fractured world, I drift and sway,
A vessel adrift in a turbulent bay,
My thoughts like fragments, drifting away,
Lost in the ether, forever to stay.

But in spite of the pain, the loss, the grief,
In the darkest depths, I find a slight relief,
For even in fragments, there's still belief,
That traces of me may someday find relief.

Perspectives

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"Artificial intelligence, Toshiba, Kawasaki City, Japan" by Lewis Baltz (Artist, American, 1945-2014). 1989–1991, printed 2006. Image courtesy of the National Gallery of Art.

A Guide to AI Challenges and Barriers

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Conflict of interest: The authors declare no potential conflicts of interest.

Keywords

artificial intelligence; social challenges; technology; medical bias; insurance

Abstract

Artificial intelligence (AI) tools are developing quickly and prominently within the U.S healthcare system. It therefore seems essential to understand their weaknesses to practice medicine that is fully informed. The goal of this paper is to overview several key concerns surrounding healthcare AI, as well as some anticipated barriers to its implementation. AI's generalizability is currently limited due to a widely fragmented Electronic Health Record (EHR) and inaccessibility to training data. AI tools are therefore at risk of acting on incomprehensive knowledge and generating inaccurate outputs. They are also extremely susceptible to several different forms of bias. Such bias can result in preferences towards diagnosing some diseases over others and recommending interventions that are only beneficial to certain populations. Privacy and transparency are also of great concern, especially when dealing with private medical data. While "black box" algorithms are criticized for their lack of transparency, innovators are working towards explainable AI (XAI) tools that can "show their work." Developing guidelines make it difficult to predict how liability for AI malpractice may be distributed across parties but has interesting implications for how physicians will change their practice in response. Finally, the current U.S. payment structure does not easily accommodate healthcare AI tools. This challenge raises questions surrounding healthcare AI's reimbursement mechanism as it becomes more widely utilized. While this paper does not provide solutions for the outlined concerns, it emphasizes the importance of understanding and anticipating the shortcomings of new healthcare technologies.

Introduction

As artificial intelligence (AI) becomes increasingly prevalent, so do concerns regarding its ability to accurately and equitably supplement the medical field. Therefore, it is the duty of providers to be aware of both the benefits and harms that healthcare AI may pose towards their patients. This guide overviews some major talking points surrounding healthcare AI's anticipated challenges and implementation barriers.

Generalizability

A major concern within the field of AI research is the generalizability of results. There are a few reasons for this. One is that there is no universal Electronic Health Record (EHR) within the U.S. Most current healthcare AI is supervised, meaning that it requires training on large data sets that are labeled by humans. This training is difficult to accomplish when health data is scattered throughout different

systems. Many programs must settle for smaller amounts of training data. This limitation raises questions regarding the applicability of those systems to larger or different populations of patients. This concern is also prevalent on a smaller scale - AI with great performance using data from one U.S. hospital may fail in another U.S. hospital due to its lack of generalizability (1). One exception to the fragmented American EHR is the VA, the country's biggest integrated healthcare system (2). The vast amount of data stored within the VA EHR makes for an ideal AI training ground. However, the data demographics still leave plenty of room for debate - How generalizable is VA data to the rest of the country?

AI training seems to risk spectrum bias, which refers to a test that is performed and evaluated within a population that is different from the intended population (3). This incomprehensive training leads to limited, incomprehensive knowledge. If medical students are only taught to recognize and treat diseases that are prevalent in their school's state, they will misdiagnose and mistreat the vast array of diseases that are less geographically common. If they are taught only to identify infections on lighter skin tones, they are more likely to miss presentations on darker skin tones. In fact, they may fail to identify the presence of disease altogether because they have had no exposure to it in training. The same problem applies to AI.

Other Biases

In general, a program that is trained on biased data will inherit and reinforce inequalities in its own algorithms. Echoing the concerns of generalizability is diagnosis bias. COVID-19 diagnostic tools that are trained in the U.S. may not have much exposure to lung-related diseases such as tuberculosis and types of pneumonia associated with HIV/AIDS that are more prevalent in other countries. The algorithm then runs the risk of misdiagnosing these diseases as COVID-19 due to their similarities and lack of knowledge of their differences (4).

Bias may also be introduced in disease modeling scenarios. A big mitigation initiative during the peak of the COVID-19 pandemic was disease "mapping" to track spread. These modeling techniques often require specified data inputs that are more challenging to obtain from underrepresented populations. Additionally, the models were used in recommending interventions (such as quarantining and social distancing) that were a lot less attainable in crowded and/or poor sanitary environments. Similarly, treatment selections made through AI tools were less likely to account for social determinants of health that are underrepresented and less accurately documented in the EHR (4).

Infodemic bias is especially prevalent in the age of social media and mass information. AI has increasingly been used to help fact-check and combat the spread of misinformation. However, this integration is mostly done within "easy to mine" data sources such as Twitter and Facebook. While it may be having a positive impact on these platforms, other information sources such as radio and TV are less likely to be fact-checked by AI. Simultaneously, these alternate channels may act as primary information sources for certain countries and populations (4).

Privacy, Transparency and Mistrust

By design, medical AI is going to guide and influence clinical decision-making. As always, it is important for a physician to be able to explain how and why a recommendation is made. This process is made more complex when considering the "black box" tendencies of certain AI technologies. The term "black box" is used to refer to the lack of transparency regarding AI output. It is not always as clear how an AI algorithm generated a particular

output given a specific input. This lack of clarity can lead to an overall mistrust of AI, and especially so within the healthcare field. How can a physician use the medical advice of an algorithm when its reasoning is not available?

These concerns have led to the push for explainable AI (XAI) that is able to reason through its output in an understandable way. There are a wide variety of XAI methods, many of which include visual representations (decision trees, graphs, etc.) of the decision-making process (5). These methods ensure that when a clinician inputs data, they receive the output they are looking for and an explanation for that output. The clinician can use this information in their own professional evaluation of the AI's performance before utilizing its advice in their decision-making process. Given the importance of physician transparency, it will be unsurprising to see XAI continue to grow throughout the field.

Rules, Regulations, and Malpractice

AI has been leveraged by developers through the promise of its increased accuracy, and hence, its ability to reduce medical mistakes. However, the rules and regulations surrounding responsibility for AI mishaps are still developing. Historically, physicians are typically liable for their actions even when under the influence of third-party information. For example, if a physician follows an insurer's recommendation for a procedure plan and harm occurs, the physician is still responsible. Similarly, the physician is responsible for appealing coverage denials if they believe a service to be medically necessary (2). In the case of AI, then, it would seem that physicians should maintain liability for all decision-making. However, the lack of clear guidelines may still leave room for liability to be potentially shared by AI producers. This possibility combined with the hope of increased accuracy puts malpractice in an interesting economic position.

On the one hand, malpractice pressure increases the demand for AI. Physicians may shift towards "defensive medicine," through which they'd push certain decision-making onto AI in hopes of avoiding some amount of liability. This increased demand for AI would result in raised AI prices. Competition increases and product differentiation decreases. Subsequently, AI producers would have to rely more on prices in order to compete and would likely reduce their prices in response. Therefore, malpractice seemingly has two opposite effects on price-setting and profit-making6. While the long-term economic effect is still up for questioning, it does certainly raise social concerns regarding how malpractice will affect physician reliance on AI.

What about insurance?

The already complicated world of health insurance is made more complex when considering how AI can or should be billed for. In general, medical procedures and services are defined by Current Procedural Terminology (CPT) codes that are developed by the American Medical Association (AMA). These codes are divided into three categories (7):

- Category I → Describes a procedure or service that must meet specific criteria. These codes are typically reimbursed by both Medicare and commercial payers.
- Category II → Used for tracking and performance measurement purposes. These codes are not generally reimbursed by Medicare or commercial payers.
- Category III → Codes for developing technology, services, and procedures. These codes are temporary and may be later placed in Category I if the criteria is met. While there are no fees assigned to these codes, reimbursement may be available on a case-by-case basis (8).

To be billed for, a specific AI technology must fall into a CPT category and be defined by a CPT code. AI does not fit well into this type of payment structure. New AI technologies are performing countless and various tasks. It would take a long and tedious amount of time to create a special CPT code for each (7). Simultaneously, one CPT code cannot overlap with another. This rule provides a unique challenge for AI, as many algorithms do work that has historically been performed by humans and is likely already defined by an existing CPT code. For example, an AI tool that detects pulmonary hypertension in medical imaging is performing work that is already covered by CPT code CPT71275: CT angiography, chest (noncoronary) w/ contrast material(s), including noncontrast images, if performed, and image postprocessing (7). One suggestion has been to bundle AI services with their complementary services (in this case, the new pulmonary hypertension AI tool and the already-existing imaging service would be bundled) (9). However, it is still unclear as to what billing trajectory AI will end up following.

Conclusion

The rapid rise of healthcare AI promises big change for the medical field. The associated challenges outlined in this paper are non-exhaustive and subject to change over time. Still, understanding them will guide learning and decision-making when implementing new AI tools into the healthcare system.

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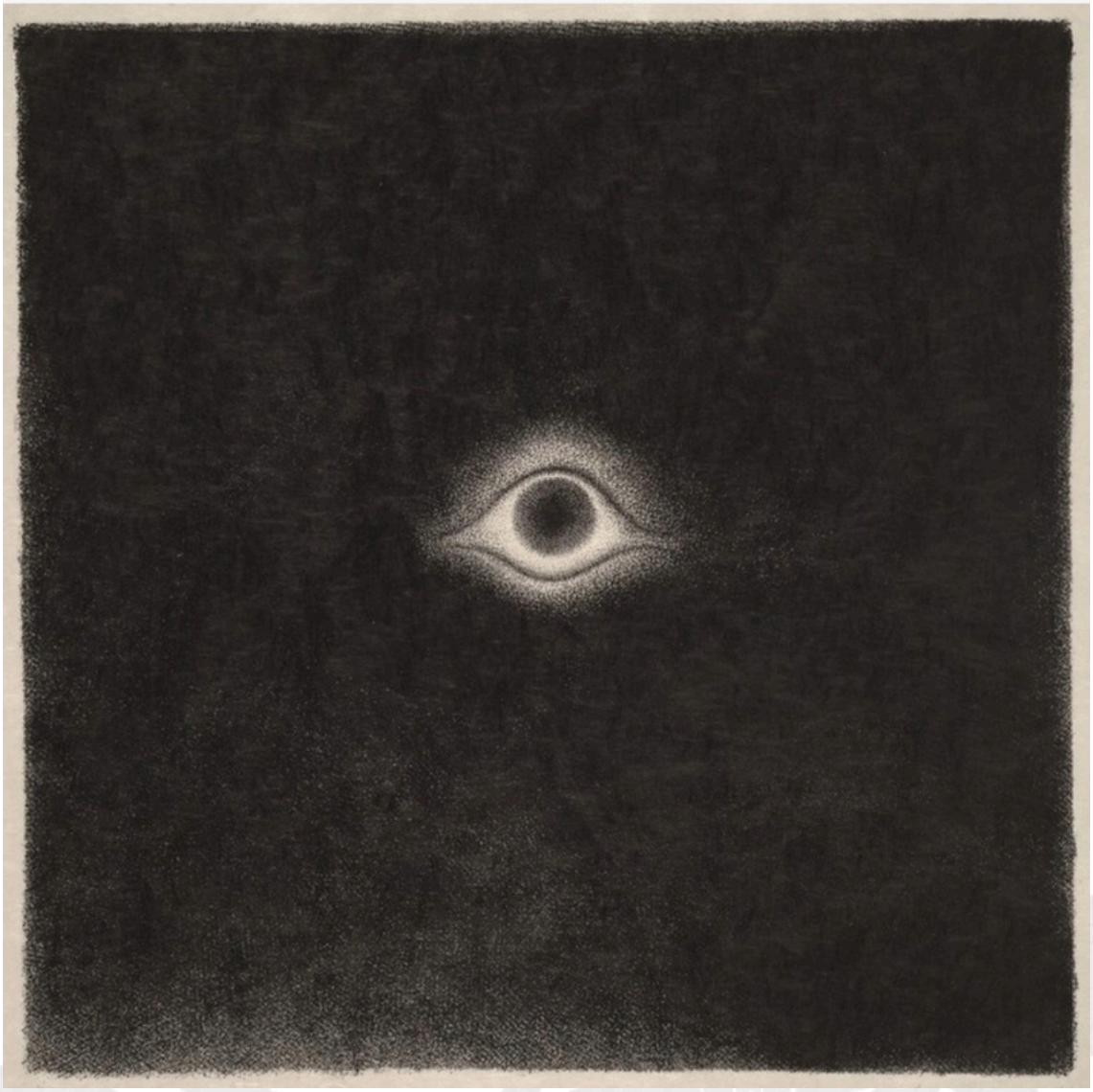

"Untitled" by Rodolfo Abularach (Artist, Guatemalan, 1933 - 2020). 1966. Image courtesy of the National Gallery of Art.

Crystalline Conundrum: Understanding the Absence of Tumorigenesis in the Human Lens

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Keywords

primary lens tumor; tumorigenesis; cancer prevention

Conflict of interest statement: The author declares no potential conflicts of interest.

Abstract

Despite the mitotically active nature of the ocular lens and near-constant exposure to ultraviolet radiation, there have been no reported cases of primary tumors in the human lens. In contrast, such tumors have been induced and reported in the lens of non-human vertebrates, particularly in cats. This report discusses various theories, including the avascular nature of the lens, the presence of barrier properties within the ocular environment, and the lens capsule composition as a potential chemo-mechanical barrier against tumorigenesis. Despite the significant implications for cancer prevention and treatment, there has been limited research into this phenomenon. Identifying protective mechanisms could contribute to a better understanding of human cancer genetics and potentially lead to preventative treatments.

Significance statement

There are no reported cases of primary tumors within the human lens, a phenomenon that is poorly understood and scarcely investigated. This perspective highlights theories for potential tumor-resistant properties and urges researchers to continue investigating. Further research could have significant implications for understanding cancer biology, tumorigenesis, and future preventative treatments.

Over the past century, the absence of primary tumors of the human lens has been remarked upon in the literature but never rigorously investigated (1–4). If true, this observation is noteworthy and certainly remarkable because all dividing cells, even in invertebrates, can develop genetic mutations and form tumors.5 Immediately posterior to the anterior lens capsule lies a single layer of epithelial cells. Within this layer is the germinative zone. As cells divide, they migrate laterally and then displace centrally, losing organelles as they do so, so that they can laminate and incorporate into the clear crystalline lens that refracts light onto our retina (Figure 1).6 By design, this mitosis occurs throughout life and into old age, thus it is curious that such a mitotically active tissue, with near constant exposure to ultraviolet radiation, is seemingly resistant to tumorigenesis.

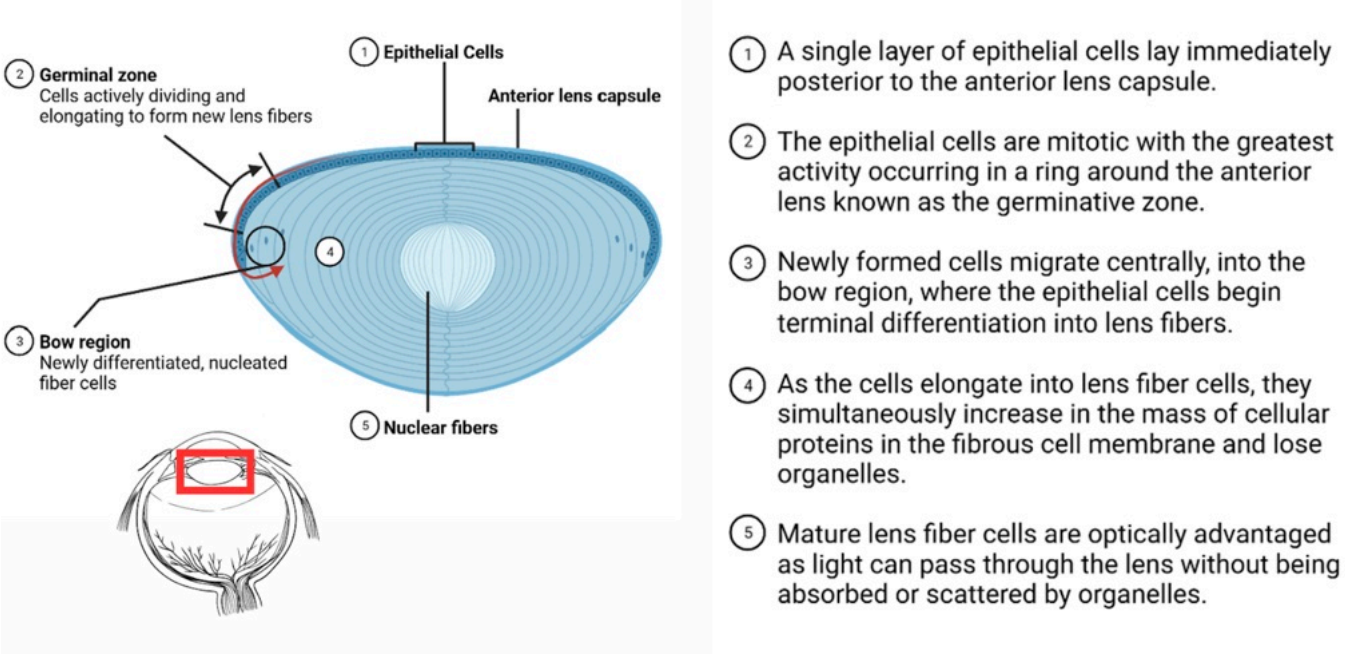

Figure 1. The mitotic cycle of epithelial cells within the normal human crystalline lens (6). Image created using BioRender.com.

Limited research has explored this phenomenon, the results of which are equally perplexing. Malignant tumors of the lens can be induced with exposure to carcinogens (7) and oncogenic viruses (8) and can be engineered genetic defects in transgenic animals (9–11). Strikingly, malignant tumors of the lens can occur spontaneously in other nonhuman vertebrate species (cats, rabbits, dogs, and birds) (12–20).

However, no case of malignant or benign tumor of the human lens has been reported or described in the literature. A review of veterinary databases revealed that in non-human species, malignant tumors of the lens occur most commonly in cats, constituting 4.5% of intraocular and adnexal neoplasms in that species (20). It is established that rupture of the lens capsule is a major risk factor for the development of the tumor, coining the nomenclature of feline ocular post-traumatic sarcoma (a benign neoplasm of lens epithelial origin) (14). Retrospective review of previously unreported cases of primary lens tumors in cats from the University of Wisconsin School of Veterinary Medicine's Comparative Ocular Laboratory collection reveals that all cases showed evidence of lens capsule rupture and most had some degree of uveitis, similar to tumors observed in other vertebrate species (birds, rabbit, and dog) (20).

With awareness of the strong correlation of capsular trauma to tumorigenesis, it is even more shocking that such tumors have not been described in humans. Cataract removal is the most commonly performed surgical procedure in humans (21), and by design, the lens epithelium is traumatized and retained during modern extracapsular cataract extraction. Despite frequent surgical injury to the lens epithelium, no benign or malignant lens tumors have been documented (20). Could genetic protective mechanisms exist? And if so, wouldn't identifying this mechanism hold significant implications to better understanding the genetics of

human cancers and ultimately providing preventative treatment?

Several theories have arisen to attempt to explain this phenomenon. The lens is a naturally avascular tissue, sensibly designed to minimize the scattering of light as it passes through to the retina. As such, the lens acquires nutrients from aqueous and vitreous components passing through the semipermeable membrane of the lens capsule (22). It has long been proposed and accepted that adequate vascular supply is essential for tumorigenesis and progression (23). Solid tumors, irrespective of their source, typically begin as a small cluster of cells relying on nutrients diffusing from nearby tissues (23). As the tumor grows, it eventually reaches a size where simple diffusion is inadequate to support further growth and angiogenesis is needed to facilitate further growth. Hence, it is sensible to assume an avascular tissue, such as the lens, could harbor potential tumors to a minimal size dependent on available resources. Interestingly, however, even proangiogenic colonies of neoplastic cells have not been described (24).

Additionally, another avascular ocular tissue, the cornea, can still be invaded by advancing tumors maintaining their angiogenic factors (25). As such, avascularity alone does not entirely explain the lack of primary tumor formation in the lens. However, unlike the lens, the cornea lacks a capsular barrier. Although, it is hypothesized that the Bowman's layer of the cornea serves as a form of corneal barrier, as tumors in the stroma layer beneath are largely undiscovered despite a notable prevalence of chromosomal abnormalities (26). Hence, it is conceivable that either the ocular environment or the existence of barrier properties could contribute to the absence of tumor development in the lens.

Other theories emphasize this possibility by suggesting the lens capsule is a chemo-mechanical barrier. Among other molecules, the lens capsule is largely composed of collagen types I-IV (27, 28). Fragments of collagens make up endostatins, which are known to act as inhibitors of angiogenesis.29 It is postulated that these endostatin molecules exist near or within the lens capsule to serve a protective mechanism against angiogenesis, both for the purpose of preserving lens transparency but also inhibiting the angiogenesis of tumors (29). Notably, there is evidence indicating that fragments of type IV collagen, the primary constituent of the lens capsule, may impede tumor cell growth (30) and hinder the activation of matrix metalloproteinases (31) in tumor cells believed to contribute to invasiveness. This evidence lends support to the idea that a growth inhibitor associated with the lens capsule could prevent neoplastic transformation in subcapsular epithelial cells.

Interestingly, even highly invasive melanomas and retinoblastomas, sometimes occupying the entirety of the posterior chamber, demonstrate well-defined borders at the lens capsule interface (24). These types of tumors are widely recognized for their infrequent invasion or direct contact with the lens capsule. Instead, the tumor-lens interface becomes filled with debris and fluid (24). Is it possible that these tumors are repelled by an unknown chemo-mechanical property of the lens capsule?

Undeniably, these observations are quite remarkable and impress exciting potential for research to advance cancer prevention and treatment. So then why is there such limited research into this phenomenon? According to NIH.gov, in 2020, the National Institute of Health (NIH), a major research funding agency in the United States, estimated a cost of nearly 6.5 billion dollars to support cancer research efforts. However, a search into the NIH RePORTER database revealed that the NIH has never funded any projects attempting to investigate the seemingly tumor-resistant properties of the human lens capsule epithelium (32). Such research seems to be a prime

candidate for identifying a cancer-inhibiting gene or genes in humans. With current genetic techniques, it should be possible to identify the genes involved in lens tumor formation in other species and to use these as candidate genes in identifying the genes responsible for preventing cancer in the human lens. A genetic protective mechanism is hypothesized to exist, and identifying this mechanism may be of significant value in enhancing the understanding of human cancer genetics.

Given the striking absence of primary tumors in the human lens, several experimental approaches could be employed to elucidate the underlying protective mechanisms, such as comparative genomic transcriptomic analysis, CRISPR-based functional genomics, lens capsule extracellular matrix components, in vivo animal models, epigenetic and regulatory network studies, and organoid and 3D cell culture models (Table 1).

Table 1 | Potential experimental methodologies and genetic approaches for investigating protective mechanisms of the human lens and their associated research benefits.

Experimental approach	Benefits of the proposed method
Comparative genomic transcriptomic analysis	Whole-genome and transcriptome sequencing of human lens epithelial cells compared with lens epithelial cells from species known to develop lens tumors (e.g., cats) could reveal key genetic differences. Identifying differentially expressed genes, particularly those involved in tumor suppression, DNA repair, and apoptosis, could pinpoint genetic factors responsible for the lens' tumor-resistant properties. Additionally, single-cell RNA sequencing (scRNA-seq) could provide insights into unique gene expression profiles of subpopulations within the lens epithelium.
CRISPR-based functional genomics	CRISPR-Cas9 or CRISPR interference (CRISPRi) could be used to selectively knock out or suppress candidate tumor suppressor genes in human lens epithelial cell cultures to determine their role in preventing neoplastic transformation. Conversely, overexpressing these genes in other epithelial cell types prone to tumorigenesis could help assess their protective effects beyond the ocular environment.
Lens capsule extracellular matrix (ECM) analysis	The lens capsule's composition, particularly its type IV collagen content and potential angiogenesis inhibitors like endostatins, could be further explored using proteomics and mass spectrometry. In vitro studies exposing cancer cell lines to isolated lens capsule components could assess whether these elements exert direct tumor-suppressive effects. Additionally, matrix metalloproteinase (MMP) activity assays could determine whether the capsule actively prevents ECM degradation, a key step in tumor invasion.
In vivo animal models	Transgenic animal models could be developed to express human lens-specific genes in species that normally develop lens tumors. If these genes confer tumor resistance, it would provide strong evidence for their protective role. Additionally, lens capsule transplant experiments in animal models with aggressive ocular tumors could test whether the human lens capsule creates a hostile environment for tumor growth.

Epigenetic and regulatory network studies	Investigating DNA methylation patterns and histone modifications in human lens epithelial cells could reveal whether epigenetic regulation contributes to their resistance to tumorigenesis. Chromatin immunoprecipitation sequencing (ChIP-seq) could help identify key transcription factors involved in maintaining the lens' quiescent but mitotically active state without leading to malignant transformation.
Organoid and 3D cell culture models	Engineering lens epithelial organoids or 3D co-culture systems with cancerous cell lines could provide a controlled environment to study potential tumor-inhibitory effects of the lens microenvironment. This approach could be particularly useful for testing the effects of biochemical signals and mechanical properties of the lens capsule on tumor suppression.

By employing these methodologies, researchers could move beyond theoretical explanations and begin identifying actionable molecular targets for preventing tumorigenesis in other tissues. Understanding how the lens naturally resists tumor formation could lead to the development of novel cancer therapies, including biomimetic extracellular matrices, anti-angiogenic compounds, and gene therapies designed to enhance tumor suppression in high-risk tissues.

The apparent resistance of the human lens epithelium to tumorigenesis presents an untapped avenue for oncological research, with potential implications for cancer prevention and treatment. The absence of primary tumors in a tissue that remains mitotically active throughout life, despite continuous exposure to ultraviolet radiation and surgical trauma, suggests the existence of unique protective mechanisms. If genetic or biochemical factors within the lens epithelium or capsule contribute to this resistance, identifying these mechanisms could inform strategies for suppressing tumorigenesis in other tissues. For example, if the lens capsule's extracellular matrix components, such as type IV collagen and endostatins, play a role in inhibiting angiogenesis and tumor invasion, similar mechanisms might be leveraged therapeutically in cancers reliant on angiogenic signaling. Moreover, uncovering genetic factors that prevent neoplastic transformation in the lens could contribute to the identification of novel tumor suppressor genes, expanding our understanding of intrinsic cancer resistance in humans. This phenomenon underscores the necessity of further research, as elucidating these protective mechanisms could inspire innovative approaches to cancer prevention and treatment, shifting the focus from reactive therapies to proactive, biologically informed interventions.

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The author would like to acknowledge Anthony Pappas, Ph.D. for introducing this fascinating lapse in knowledge, as well as student doctors Parker Webber and Bosten Loveless for their contributions to the poster presentation Paradoxical lack of investigation into the natural tumor-resistant properties of the human lens capsular epithelium. Their efforts were paramount in sparking interest in this subject and highlighting this notable gap in the literature.

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"The Tax Collectors" by Jean Honoré Fragonard (Artist, French, 1732 - 1806). 1778. Image courtesy of the National Gallery of Art.

The Expansion of Private Equity into Ophthalmology

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Keywords

private equity; ophthalmology; patient care; physician autonomy; private practice; income

Abstract

Throughout the last few decades, private equity (PE) has expanded into the field of ophthalmology at an incredible rate. Acquisitions of private practices by firms have increased with the intention of maximizing profits and patient volume to target the growing demand for medical services and address a fragmented healthcare system. PE investment has proven to greatly benefit PE firms and senior ophthalmologists of well-established practices. However, this trend of PE acquisition has received much criticism despite its seemingly positive short-term outlook. In this commentary, we discuss the potential setbacks of PE advancement in ophthalmology, including the loss of physician autonomy, reduced income for junior ophthalmologists, and decline in quality of patient care – all resulting from the increased focus on maximizing profitability. Furthermore, we consider the ramifications of PE investment on incoming ophthalmologists who are entering an uncertain job marketplace and may struggle to locate stable practice opportunities. This commentary concludes with the evaluation of private equity advancement through the lens of a medical student and an ophthalmologist, as well as a call for medical students and trainees to educate themselves on the matter and promote further research on the long-term consequences of this trend of PE investment.

Commentary

Private equity (PE) has made significant advancements into the field of ophthalmology throughout the past few decades, most notably with a trend of increasing private equity acquisitions of private practices. For medical students, residents, and trainees in the early part of their career, this is an evolving dynamic that requires attention due to its paramount effect on the private practice landscape. This commentary attempts to further educate students, residents, and early career physicians on the impact of private equity's encroachment on physician practices in the ophthalmology space. Private equity firms seek to maximize profit through acquisitions of private practices, with the aim of increasing the value of purchased ophthalmology practices and thereupon selling the practice to another firm that shall do the same. These firms are thus understandably drawn toward more profitable private practices that are highly likely to grow financially (1). Multiple ophthalmology practices may also be consolidated into larger groups under the same PE firm to increase profitability, with the providers of these practices becoming employees under these firms. This expansion of private equity into ophthalmology has been justified with multiple motives, including a growing demand for medical services from an aging United States population and targeting "inherent

inefficiencies present in a relatively fragmented practice environment", the latter statement a reference to the presence of hundreds of individual practices and a general independence from hospital systems (1, 2, 7). PE investment of ophthalmology practices has demonstrated short-term financial success for both senior ophthalmologist providers and the private equity firm itself due to increased profits, increased patient volume, and improved payer mix (3). Nonetheless, there remains much skepticism expressed in literature regarding the true success of private equity acquisitions of private practices in the long-term perspective (3, 10). Despite the beneficial short-term patterns mentioned above, other studies have also demonstrated decreased physician autonomy and physician salaries following acquisition. Due to the uncertainty regarding the fate of junior and incoming ophthalmology colleagues, PE encroachment on ophthalmology practices raises a potentially significant concern for the future of ophthalmology and patient care.

The decrease in physician autonomy results from ophthalmology providers handing clinical operations authority to the private equity firm. PE firms generally purchase 60 to 80 percent ownership of a practice (12). With the acquisition of practices by private equity firms, ophthalmologists must then operate under certain policies imposed by the larger business practice model. Subsequently, these firms then restructure the ophthalmology practice to establish an organization that primarily seeks financial success via high volumes of surgical procedures and cash-pay procedures (e.g., premium IOLs, intravitreal injections, cosmetics) (4, 5, 9). PE firms further maximize profitability of ophthalmology practices by implementing structural changes such as vertical consolidation, or the creation of a vertical referral pathway consisting of optometrists, ophthalmologists, and vitreoretinal surgeons in order to keep patients within an internal network that addresses all eyecare needs (1, 11). Despite demonstrating great efficiency, these strategies may restrict ophthalmologists' ability to make independent clinical decisions, manage their procedural volume, or see a diverse body of patients. In fact, a questionnaire-based study found that 81.4% of vitreoretinal fellows expressed concerns about a loss of autonomy under a PE-owned practice (7). This finding reflects the widespread apprehension among junior and future ophthalmologists regarding the preservation of independence in their practice.

The financial goals of the PE firm may also necessitate tighter control over expenses and ophthalmologist income, especially as salary becomes more linked to the physician's ability to meet procedural quotas. Multiple studies also have suggested that junior and future ophthalmologists are "less likely to succeed financially compared with their contemporaries" (6) due to private equity investment and vulnerability during the buy-in process. Junior ophthalmologists typically join large physician-owned practices with the goal of eventually becoming a partner, a process that requires buying into the practice after a pre-determined employment period. This process often takes several years for both junior and senior ophthalmologists. Both sides must decide if the "marriage" is the right fit. For example, the junior ophthalmologist needs to determine if the practice model, philosophy, the patient clinical and surgical volume, and the practice environment are mutually beneficial. The senior ophthalmologist must decide whether the junior colleague's personality, clinical and surgical expertise, and work ethic align with the practices. Once both sides have mutually decided to pursue a buy-in, a pre-determined price is then paid by the junior ophthalmologist over a period of time, after which subsequent profits of the practice are then appropriately distributed to all of the partners including the new junior ophthalmologist.

Unfortunately, the junior ophthalmologist is susceptible to the risk of a PE firm buying out the practice before the junior physician can secure their buy-in. If a firm does approach the practice while the junior ophthalmologist's buy-in is not yet complete, this ophthalmologist is not considered a partner and hence is excluded from the negotiations with the private equity firm. The junior physician is not included in the payout agreed upon by the partners. Consequently, the junior colleague loses their ability to buy into the practice or become a partner, nullifying their financial investment over the last few years and excluding them from further financial benefits from the sale. Additionally, once the buyout has been completed, the junior ophthalmologist loses autonomy and will likely be asked to streamline clinical operations based on the private equity firm's recommendations.

Through a medical student and future ophthalmologist standpoint, the expansion of private equity into ophthalmology raises concern due to minimal evidence regarding its long-term success. This trend also challenges personalized patient care which has always been synonymous with the concept of private practices. While PE acquisition is associated with increased patient volume, the focus on profit and high procedure volume appears to pressure ophthalmologists to see more patients in less time. Research indicates that PE may hinder patient care through shorter appointments, fewer Medicare and Medicaid patients seen, and greater costs (i.e., PE-owned practices demonstrated a mean increase of 11% in charges per medical claim filed over non-PE practices) (10, 11). Students are inspired by fields such as ophthalmology that entail established and prolonged relations with their patients, but the increasing involvement of private equity in ophthalmology may deter many trainees who are seeking these fond relationships. In fact, according to one research study, 78% of ophthalmology trainees stated that they would not consider employment by a PE-owned practice out of fear of loss of autonomy and reduced quality of patient care (7). Furthermore, the anticipated difficulty of becoming a partner at physician-owned practices and an indeterminate job marketplace present much uncertainty in the future of incoming ophthalmologists (7, 8).

From the perspective of a practicing ophthalmologist, private equity encroachment on ophthalmology practices has been met with mostly negative reviews. The three biggest issues include loss of autonomy and independence, a practice pattern built on profitability, and declining reimbursement. Most private equities, once they purchase a practice, require senior providers who were paid out to remain on board for several years to help the transition to a private equity-owned practice. In this time frame, there is significant clinical reorganization, where metrics such as those mentioned above are implemented to address the financial needs of the organization. Additionally, product replacement and medical equipment purchasing are reduced to offset costs. Some groups may align compensation with patient satisfaction scores which often does not correlate with each other and may even be detrimental; for example, ophthalmologists may overutilize unnecessary procedures to achieve higher satisfaction scores from their patients (11). The difficulty ultimately comes from the fact that the interests of the private equity company usually do not align with those of the physician. Furthermore, solo and independent ophthalmology practices are left to compete against large private equity firm-owned ophthalmology practices who may own more resources and finances to advertise, recruit, and retain patients, staff and physicians. This dichotomy becomes even greater as more practices become absorbed by private equity firms.

With private equity acquisitions on the rise in ophthalmology, it is imperative that medical students, residents, and junior ophthalmologists are knowledgeable on the impact of private equity on the future of this specialty. Information regarding PE, ownership structures, and practice options should be widely provided to trainees pursuing ophthalmology, ideally through small group discussions and on-site learning during residency program education (7). Although several highly accountable publications have analyzed the trends of private equity encroachment on medical practices, additional research investigating the long-term implications of PE acquisition and its impact on medicine must be done.

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"The Voyage of Life: Old Age" by Thomas Cole (Artist, American, 1801 - 1848). 1842. Image courtesy of the National Gallery of Art.

The Medicalization of Aging: Exploring the Ethics and Impacts of Anti-Aging Interventions

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Keywords

aging; gerotherapeutics; biomedical enhancement; personal autonomy; culture

Abstract

This paper explores the ethical implications and societal impacts of gerotherapeutics, which aim to delay aging and age-related diseases. As medical advancements target aging as a condition to be treated, the medicalization of aging raises concerns about reinforcing ageist stereotypes and marginalizing older adults. The growing anti-aging industry, fueled by societal pressures, particularly for women, may lead to economic and healthcare disparities. Misclassifying aging as a disease risks diverting resources away from essential public health needs. This paper argues for a shift in perspective, emphasizing aging as a natural process deserving of respect, rather than a condition to be "cured."

Body

The term gerotherapeutics refers to pharmacological and behavioral interventions that affect biological mechanisms of aging with the intent to prevent or delay age-related diseases and lengthen the time spent without illness or disability (1). According to the National Institute of Aging, the geroscience hypothesis "posits that since aging physiology plays a role in many – if not all – chronic diseases, addressing aging physiology will allow a reduction or delay in the appearance of multiple chronic diseases" (2). The National Institute of Aging was established in 1974 to conduct research focused on improving the health and well-being of older-adults (3). Approximately 13 years ago, the Trans-NIH Geroscience Interest Group was created to study the biological process of aging and its intersection with the biological processes of other common chronic diseases (3). The study of aging is becoming increasingly imperative as the aging population continues growing (4). A study by Donner et al. found that a majority of people wished to live to 120 years of age or longer if health was guaranteed (5). In 2013, Pew Research Center found that 63% of US adults believed that "medical advances that prolong life are generally good because they allow people to live longer" (6). Moreover, the global anti-aging market is estimated to be worth billions (7). Some researchers and policymakers have even proposed classifying aging as a disease in order to direct more funding toward aging-related research and incentivize the development of therapeutic interventions. With all these vested interests in gerotherapeutics, it is critical to evaluate the ethical implications of anti-aging interventions.

Aging has long been studied in relation to health. In Dr. Ilia Stambler's article in Frontiers in Genetics, he discusses that the concept of fighting against aging traces back to approximately 100 BCE with the works of Cicero (8). In the late 1700s-early 1800s German hygienist Christoph Wilhelm Hufeland

described aging as the "enemy of life" (8). In 1903 immunologist Elie Metchnikoff coined the term "gerontology", describing aging as similar to disease and considering it to be a mistake to view aging as physiologic phenomenon (8). In 2021, the World Health Organization (WHO) proposed the inclusion of "old age" in the 11th revision of the International Classification of Diseases (ICD-11) (9). However, WHO decided to use "ageing associated decline in intrinsic capacity" instead of "old age" because their "inclusion of 'old age' in ICD-11 was not intended to cast age or ageing as a disease…the intention was to recognise that the physiological process of ageing has a detrimental effect on a person's intrinsic capacity" (9). However, despite its long history as a natural process, the perception of aging in contemporary society has been significantly influenced by cultural values that often position it as a condition to be avoided or corrected, particularly through the lens of medical and cosmetic interventions.

Societal pressures to maintain a youthful appearance have profoundly influenced perceptions of aging, particularly for women. Wrinkles, body fat, sagging skin, and grey hair have become not only signs of aging but also markers of failure in a culture that equates physical attractiveness with social value (10). Women are inundated with advertising that promises miraculous anti-aging products and procedures, from Botox to chemical peels, creating an industry driven by the fear of becoming "invisible" as they age (11). In North America alone, the anti-aging products market accounted for 30.4% of the global market revenue in 2024, and the anti-aging products market size is projected to reach USD 80.61 billion by 2027, reflecting society's growing investment in countering visible signs of aging (12). It is also important to notice that although women account for the majority of cosmetic procedure patients, indicating a gendered targeting of anti-aging interventions, men are becoming more interested in surgical interventions. According to the 2024 Procedural Statistics Release of Cosmetic Surgery Procedures, while in 2023 males comprised only 5% of lower body lift patients, this number increased to 10% in 2024, a procedure rooted in the weight loss-related body concerns that are coming back along with the increasing interest in taking GLP-1 medications for weight loss (13). The idea that aging bodies are inherently flawed fuels the normalization of interventions that "fix" these perceived imperfections, rendering aging itself a defect requiring correction (10).

These beauty work practices reinforce ageist stereotypes that depict youth as desirable and old age as repulsive or unworthy (11). Social media amplifies these standards by showcasing idealized and often unrealistic images of youthful beauty, compelling individuals to engage in medical or cosmetic interventions as a form of self-care and self-esteem (10). This dynamic reflects a broader rejection of the traditional view that aging, while tragic, is a normal process, and part of the natural order (14). Instead, the medicalization of aging redefines it as a problem requiring intervention, betraying a disregard for older adults and exacerbating their marginalization (14). For example, a cross-national study conducted by the WHO's Ageism Report found that ageism leads to poorer health outcomes, reduced life expectancy, and increased social exclusion for older adults (15).

Western culture has historically framed aging in opposition to health and vitality, perpetuating narratives of decline and dependency. From as early as the writings of Claudius Galen, aging has been viewed as a "natural condition" distinct from disease, though modern perspectives often blur these lines (16). Anti-aging advocates further complicate this framework by asserting that while aging is natural, it remains undesirable and should therefore be ameliorated through intervention (17). This perspective aligns with Western cultural ideals

that prioritize the optimization of the body and liberation from biological constraints, reinforcing a perception of aging as a process to be resisted rather than embraced (17).

These cultural values also intersect with societal pressures, particularly for women, who are often compelled to equate their worth with physical youthfulness. The moralizing narrative that "letting oneself grow old" equates to "letting oneself go" reflects deep-seated ageism and a rejection of aging as a valued stage of life (10). Ageism perpetuates the assumption that old age is undesirable and fraught with dependency, loss, and unhappiness (11). Framing aging as a universal process, anti-aging proponents argue that it is both knowable and therefore improvable, situating interventions at the intersection of health preservation and restoration (17). However, conflating aging with disease betrays a broader societal discomfort with mortality, further marginalizing older adults while prioritizing biomedical interventions over acceptance of aging as an essential aspect of life (14).

Misclassifying aging as a disease carries significant dangers, particularly in how resources are allocated in healthcare systems. One notable example is the significant venture capital investment in biotechnology firms focused on anti-aging drugs and cellular reprogramming, such as Calico (a Google subsidiary), which has received over $1.5 billion in funding despite limited clinical translation to date (18). In contrast, many public health systems remain underfunded in areas like mental health and chronic disease prevention (19). If aging is regarded as a medical issue that needs treatment, significant resources could be redirected toward anti-aging solutions, potentially neglecting important public health concerns like chronic illness management, mental health services, and preventative care (20). This redistribution of resources might worsen current inequities, mainly favoring those who can afford costly anti-aging therapies, while marginalized groups are left without necessary care (20). In Brazil, for instance, government resources have increasingly supported aesthetic medicine training and clinics, while funding for geriatric primary care and dementia services has stagnated (21). A health system that overly prioritizes the postponement of aging may overlook the intricate and varied needs of senior citizens, potentially sidelining at-risk groups and exacerbating health inequalities. Policymakers and clinicians must find a balance - encouraging innovation in geroscience while ensuring that critical care infrastructure and preventive services for the general population remain well-supported. Mechanisms such as public-private partnerships, evidence-based prioritization, and regulatory oversight can help align longevity research with broader health equity goals.

The economic consequences of viewing aging as a disease go beyond just healthcare. The worldwide anti-aging industry flourishes by taking advantage of societal anxieties about aging, potentially leading to the endorsement of unverified or insufficiently researched treatments (22). This expanding market amplifies socioeconomic disparities, as access to effective gerotherapeutics could be confined to affluent groups, further intensifying inequalities. Moreover, the quest for extending lifespan without emphasizing healthspan might impose significant pressure on social and economic frameworks, such as pensions, long-term care, and workforce stability (23). Focusing on healthspan-oriented approaches can aid in reducing these risks while promoting ongoing economic and social growth.

Ultimately, recasting aging as an illness might reduce societal value for the inherent process of aging, impairing the life quality and contentment of older individuals. Presenting aging as a disease could strengthen ageist views, labeling older adults as fundamentally deficient and reliant. These beliefs might undermine intergenerational connections, diminish the chances for older adults to make

meaningful societal contributions, and sustain the notion that youth is the only life phase deserving of aspiration. In contrast, accepting aging as a natural and worthwhile stage of life enables a more comprehensive view of health, emphasizing the importance of preserving functional independence, social ties, and mental well-being. At the same time, certain medical and public health advances, such as access to geriatric care, fall prevention programs, cognitive health support, and lifestyle interventions like nutrition and physical activity, can meaningfully promote healthy and comfortable aging without framing it as a pathology. Aging, while inevitable, should be viewed not as a condition to be "cured" but as a journey to be navigated with care, respect, and support.

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Reviews

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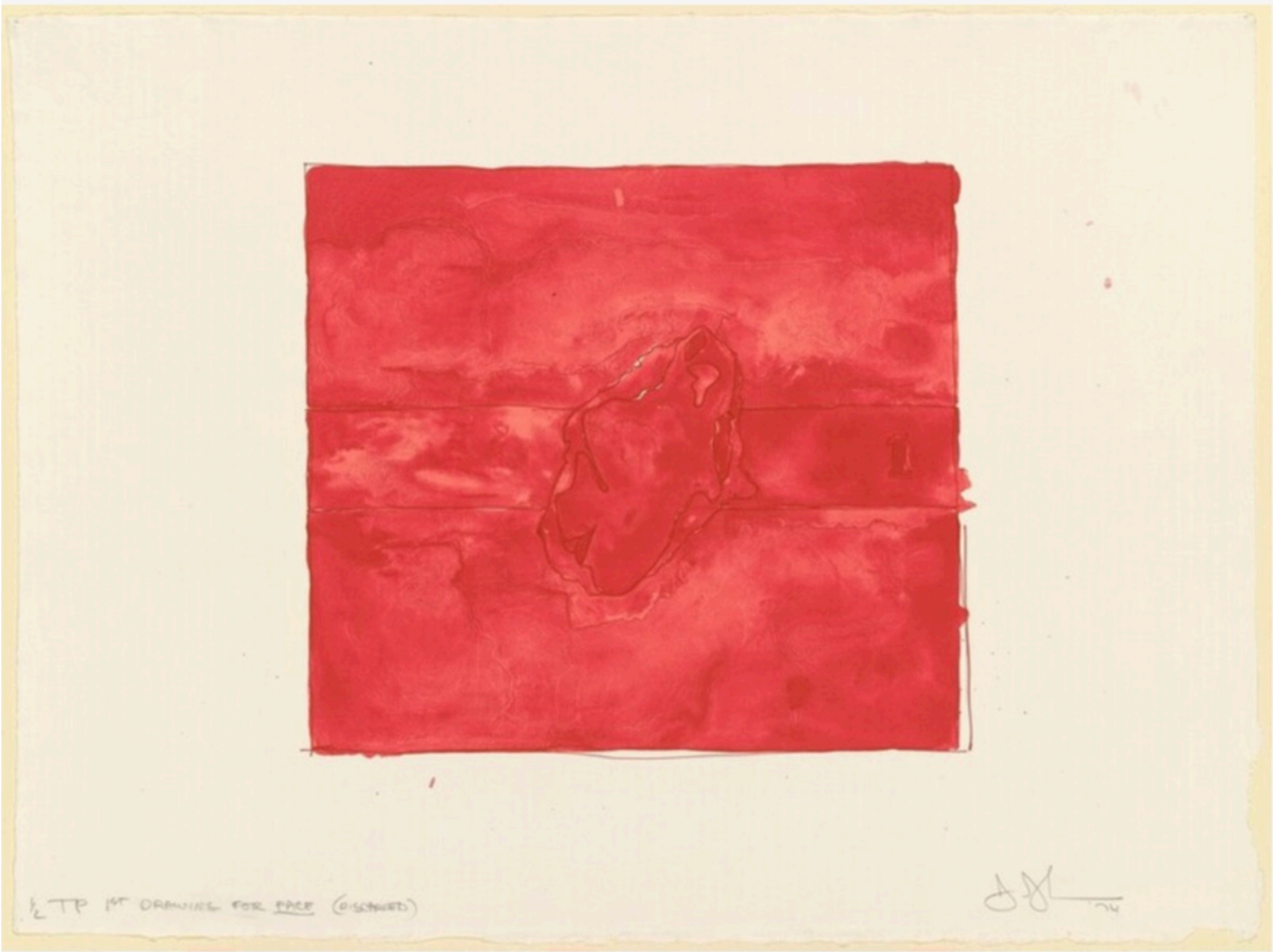

"Face [trial proof]" by Jasper Johns (Artist, American, born 1930). Started 1973, published 1974. Image courtesy of the National Gallery of Art.

Assessing the Need to Educate Prehospital Providers on the Sex Differences in the Clinical Presentation of Acute MI

Keywords

acute MI; sex differences; clinical presentation; prehospital

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Abstract

Medical research has historically underrepresented females. As part of a movement to better represent women in research, U.S. Congress passed the National Institute of Health Revitalization Act of 1993, which mandated the inclusion of women and minority groups in clinical research.1 With the increase in female inclusion, sex differences in the clinical presentations of diseases and responses to medication have emerged. Previous research has found differences in how women and men might present with acute myocardial infarction (MI), with women more often experiencing signs and symptoms that are labeled as 'atypical' or 'nontraditional.'2-8 However, this information has not been robustly incorporated into the prehospital curriculum standards, including education for emergency medical technicians (EMTs) or paramedics.9 This paper investigates whether there is a need for the prehospital curriculum to discuss the lesser-known signs and symptoms of acute MI and the differences in disease presentation between men and women. First, some differences between women's and men's physiology and pathophysiology are explored. Next, the clinical presentation of acute MI is reviewed, including the research supporting the sex differences in clinical presentation. Additionally, the disparities in EMS quality of care will be discussed, as research has shown that women receive lower quality of care in the prehospital setting.10 Social factors that can affect delays to treatment will also be discussed. Since there is substantial evidence that health outcomes of acute MI differ between men and women, EMS education should include and emphasize these topics.

Methodology

This integrative review identified appropriate articles through a search on PubMed with the keywords "acute MI," "sex differences," "gender differences," "sex and gender differences in the clinical presentation," "pathophysiology," "anatomy," "differences in acute MI clinical presentation of transgender individuals," "EMS recognition of acute MI," and "time to treatment and outcome." The PubMed search did not include "chromosomal anomalies," as EMS provider educational standards do not include knowledge of genetic diseases and chromosomal anomalies.9 The search included articles published after 2000. These articles were then assessed and considered relevant if they addressed the following questions:

- Are there sex differences in the clinical presentation of acute MI? Which sexes are discussed in each study?

- Are there anatomical, pathophysiological, or hormonal differences in women and men that affect the development of acute MI? If there are differences, do they affect the signs and symptoms that patients experience?
- Is there an association between time to treatment for acute MI and functional outcomes or mortality? If so, what is the significance in relation to EMS care?
- How accurate is EMS provider recognition of acute MI?
- Is there a difference in the quality of care between EMS providers caring for male and female patients?

Sex and Gender

A person's chromosomal makeup of XX (female) or XY (male) defines one's sex. Other chromosomal anomalies exist, such as XXY (Klinefelter's Syndrome) or X (Turner's Syndrome). Gender is defined as how a person chooses to identify and express themselves. Gender exists as a spectrum and includes categories such as man, woman, transgender man or woman, or nonbinary, as well as others. All the reviewed studies placed patients into binary categories of "male" or "female." None of the reviewed studies included individuals with chromosomal anomalies or those who identify as non-cisgender. Similar to the reviewed studies, this paper will focus on the differences between biological males and females. The conclusion of this paper emphasizes the importance of and the need for acute MI research to encompass a wider spectrum of gender inclusion.

Body

Acute Myocardial Infarction

Most people experiencing an acute MI will present with the well-known signs and symptoms that are taught to healthcare professionals: chest pain, pressure, tightness or discomfort, and diaphoresis. However, numerous studies have found that, compared to men, women more frequently present with additional symptoms that are not as well-taught. Women more commonly present with nausea, vomiting, stomach pain, indigestion, heart palpitations, and dyspnea (2,3). While men more often report pain or discomfort in their left shoulder, women more commonly experience pain or discomfort in their jaw, neck, arms, or between their shoulder blades (2,3). Women are also more likely to have fatigue as their only symptom (3). Although chest pain often accompanies these additional symptoms in both men and women, it may be absent in either sex. However, certain female demographics may disproportionately not experience chest pain at all. Lichtman et al. found that, compared to men, women aged 18 to 55 more often present without chest pain during an ST-elevated acute MI (2). Since EMS providers commonly care for patients experiencing an acute MI, they should be educated about the unfamiliar symptoms that may present with or without chest pain and be informed that women more commonly experience these less frequently emphasized symptoms.

The differences between men's and women's vascular physiology and the development of vascular disease may partly account for differences in clinical presentations, though this relationship has yet to be definitively determined. First, women's coronary arteries are narrower than men's, and women have a higher baseline myocardial blood flow (11). Haider et al. suggest that these two factors could contribute to a higher degree of endothelial shear stress, potentially helping to prevent plaque accumulation in women's coronary arteries (11). The pathophysiology of cardiovascular disease has also

been shown to differ between sexes. A study from 2021 found that plaque erosion is responsible for nearly one-third of acute coronary syndrome (ACS) incidents, including unstable angina and acute myocardial infarctions (12). Plaque erosion occurs when the top endothelial layer of a plaque is lifted, and platelets and fibrin deposit there and form a white thrombus (12). Plaque rupture is responsible for the remaining ACS incidents, which can occur when an atherosclerotic plaque partially lifts off the luminal wall of a blood vessel, and fibrin and red blood cells deposit and form a red thrombus at the site of the break (12). Studies have found that plaque rupture is more often experienced by men, and plaque erosion is more commonly experienced by women (11,13). However, one study found that as women's age increased, the prevalence of ACS due to plaque rupture also increased (13). While there is clear evidence that men's and women's vascular physiology and disease development differ, further research is needed to definitively determine whether differing patterns of plaque buildup and thrombosis directly contribute to differences in men's and women's clinical presentation of acute MI.

In addition to vascular pathophysiology, differences in men's and women's hormonal physiology also affect cardiovascular health. Premenopausal women have more circulating estrogen compared to men or postmenopausal women (13). Estrogen has an anti-inflammatory effect on blood vessels and favors low vascular resistance. Studies have shown that premenopausal women have a lower incidence of cardiovascular disease compared to postmenopausal women and men (11,14). Men have more testosterone than women, but research has found conflicting results regarding the overall effect of testosterone on cardiovascular health (15). More research is needed to determine whether there is a direct link between different hormonal profiles and disease presentation. There are studies examining the effects of estrogenic treatments such as oral contraceptive pills and post-menopausal hormone therapy on acute MI risk; however, this information lies outside the scope of EMS education. An in-depth discussion of hormones requires a high-level understanding of endocrinology, which is generally not included in EMS provider education.

Myocardial infarction pathophysiology also differs between women and men. ACS syndromes are classified as Type 1 and Type 2, with ACS Type 1 accounting for roughly 90% of cases and ACS Type 2 accounting for the remaining 10%. ACS Type 1 is defined as an acute atherothrombotic event. A greater proportion of women experience ACS Type 2, which occurs when an infarction is caused by inadequate myocardial oxygenation without injury to the coronary arteries.3 Inadequate oxygenation can occur due to an increase in oxygen demand and/or a decrease in supply. Tachycardia or hypertension can increase myocardial oxygen demand, and hypoxemia, anemia, and hypotension decrease oxygen supply. Often, ACS Type 2 occurs in the presence of more than one of these conditions (16). For instance, ACS Type 2 is associated with operations, sepsis, arrhythmia, and anemia, which all could reasonably lead to an increase in myocardial oxygen demand and/or a decrease in oxygen supply (17). There is limited information discussing sex differences underlying the mechanism of ACS Type 2. Nevertheless, educating prehospital providers about the potential sex differences in heart disease pathophysiology could facilitate their understanding of the differences in men's and women's clinical presentation.

The patient's self-reported history can significantly impact the prehospital provider's understanding of the patient's condition. Interestingly, Lichtman et al. found that women were more likely to perceive their symptoms as anxiety or stress, whereas men were more likely to perceive the symptoms as muscle pain (2). Therefore, a woman with chest pain and lesser-

known acute MI symptoms may tell the prehospital provider that her symptoms are anxiety-related. If the EMS believes the patient is experiencing acute anxiety and does not evaluate for an acute MI, several unfortunate scenarios could result in worse outcomes for the patient. Theoretically, EMS may fail to perform an EKG, assign the patient as low priority, which places the patient at risk of seriously deteriorating as they wait for an emergency department (ED) assessment. Or worse, EMS may recommend that the patient try to remain calm at home and call 911 again if they still have symptoms later. In either case, the patient would experience a delay in treatment and potentially worse outcomes. Another factor that may contribute to more women misperceiving their symptoms is that, compared to men, more women had visited their primary doctor for symptoms related to an acute MI before being hospitalized (2). During these visits, women were more often told that their symptoms were not heart-related and instead were likely gastrointestinal or stress-related (2). If a patient explains to EMS that their doctor said their symptoms are gastrointestinal or stress-related, the prehospital provider may believe the patient and may not perform investigative interventions. Prehospital providers should be made aware of how patients may perceive their symptoms. This knowledge may enable EMS providers to overcome bias brought on by the patient's symptoms and history.

Conscious or unconscious gender biases can affect a prehospital provider's clinical decisions. Previous studies have found discrepancies in the performance of EMS interventions between male and female patients. For instance, a national study by Lewis et al. found that compared to men younger than 65 years old, women under 65 were significantly less likely to receive aspirin or nitroglycerin for chest pain (18). This study did not control for reasons not to administer these medications, such as patient administration before EMS arrival or an allergy (18). However, another possible reason not to administer medication for chest pain is a low suspicion of a cardiac event, which may be due to unconscious provider bias or inadequate training. Another observed discrepancy between women and men is that, for patients with chest pain, women under 65 were less likely to be transported using lights and sirens compared to men of similar age (18). Occasionally, a patient will request not to be transported with lights and sirens, but otherwise, lights and sirens are used to transport high-priority patients. These discrepancies in treatment and transport methods likely involve gender bias or disbelief of symptoms. Bringing awareness to discrepancies surrounding prehospital interventions may affect EMS providers' patient care decisions, which ideally should be equally performed for women and men.

Failure to investigate the patient's signs and symptoms could also lead to a delay in treatment. When paramedics suspect a cardiac emergency, they should perform an electrocardiogram (EKG). EKGs can show ST-elevated myocardial infarctions (STEMIs) or non-ST-elevated myocardial infarctions (NSTEMIs). The EKG reading can help paramedics assign a patient's priority level, which EMS uses in their report while en route to their destination hospital. EMS providers assign patients experiencing a life-threatening medical emergency with a high priority. Once an EMS provider calls the destination hospital and gives a verbal report, the ED will prepare a room and the appropriate resources for high-priority patients before they arrive at the ED. Assigning a patient with a high priority likely decreases their time to imaging and/or treatment compared to patients assigned with lower priority. One concern that may arise is that basic life support crews (BLS), who are unable to conduct EKGs, may unnecessarily make an acute MI notification to the destination hospital based purely on signs and symptoms. The hospital may use

unnecessary resources, and the patient may undergo avoidable stress from the experience. While it is best to send an advanced life support (ALS) crew to someone experiencing an acute MI, BLS crews may be sent if all other ALS crews in the area are busy. Nevertheless, both BLS and ALS providers should be aware of unfamiliar signs and symptoms of life-threatening disease states so that they may perform appropriate investigative interventions and decrease the possibility of delaying hospital evaluation.

During an acute MI, time to treatment can impact a patient's outcome. Lichtman et al. found that women aged 18-65 had a longer time from symptom onset to hospital presentation (2). Deluca et al. found that each 30-minute delay from the onset of acute MI symptoms to a primary angioplasty was associated with both an increased relative risk of mortality in one year and an increased risk of having a pre-discharge ejection fraction of less than 30%.19 A normal ejection fraction is 52% to 72% for men and 54% to 74% for women (20). Per the American College of Cardiology, an ejection fraction below 30% is considered severely dysfunctional (20). A low ejection fraction indicates that the left ventricle is unable to pump blood to the rest of the body effectively, which can lead to further heart complications. Though EMS does not spend hours with a patient, they can potentially shorten the time to treatment if they recommend that the patient go to the hospital. Obtaining an EKG may especially benefit patients experiencing an MI who present with unfamiliar signs and symptoms and attribute their symptoms to other causes.

In addition to provider recognition of a patient's disease severity, social factors can also influence a patient's time to treatment. Patient characteristics associated with prehospital delay include non-white race, low socioeconomic status, diabetes, and hypertension (21). A non-white race or low SES may be associated with a prehospital delay due to a lack of medical knowledge and mistrust in the healthcare system. Additionally, women are more likely to have a longer delay in seeking care (21). The reasons for the prolonged time to seek medical attention also tend to differ between women and men. Men who reported a mismatch between their expected and actual symptoms of an acute MI, had a low education level, did not call 911 or did not ride in an ambulance tended to have a prolonged time to seek treatment21. Meanwhile, women with a longer delay were older, single, alone during symptom onset, or did not want to trouble anyone (21). Interestingly, men with a history of an acute MI had a shorter delay in seeking treatment, while women with this history had a longer delay in seeking treatment (21). Though prehospital providers cannot impact these social factors, they potentially expedite getting the patient to definitive imaging and care. Suppose prehospital providers are aware of less common acute MI presentations. In that case, they may be able to advocate for a patient with a less common presentation and eliminate delays in the ED.

Conclusion

Since women are more likely to present with lesser-known signs and symptoms of acute MI and are less likely to receive the highest quality of care, there is a need to implement the above findings in prehospital education. This may be through classroom curriculum for future EMS providers and continuing education classes for current providers. EMS providers who understand that acute MI can present with lesser-known signs/symptoms may be more likely to obtain a detailed history and perform interventions, which subsequently may paint a clearer picture for emergency department providers.

The goal of educating the prehospital provider about sex differences in acute MI is to increase

awareness of how life-threatening conditions can manifest beyond the well-known textbook definitions and encourage providers to deliver higher-quality patient care. The curriculum should discuss trends in men's and women's clinical presentations and emphasize how women more often experience unfamiliar symptoms. To supplement this information, discussing underlying differences in male and female physiology could provide greater context for different trends in presentation. The physiology discussion should be tailored to either a more basic level for EMTs or a more detailed level for paramedics. The curriculum should also emphasize the current discrepancies in performing interventions and providing high-quality care between patient sexes. Due to these current discrepancies, the course should review EMS protocols for suspected acute MI. Additionally, the curriculum should reframe the language used to describe lesser-known signs and symptoms. Labeling the symptoms more commonly experienced by women as 'atypical' or 'non-traditional' diminishes their clinical importance. Emerging literature and curriculum should consider placing these signs and symptoms into a category that frames them as likely and valid disease indicators, such as 'additional signs and symptoms.'

In addition to cisgender women and men, future research is needed to assess whether acute MI presents differently in non-cisgender individuals. About 1.6% of the U.S. population identifies as transgender or nonbinary, with a greater proportion under 30 years old (22). Transgender people may undergo hormone treatment or gender reconstruction surgery, and these procedures may affect the risk of developing acute MI. For instance, one study found that transgender men undergoing gender-affirming hormone therapy had an increased risk of MI compared to cisgender women and men (23). Transgender women undergoing gender-affirming hormone therapy may have an increased risk of an MI (23). Due to these increased risks, it may be helpful to compare the acute MI presentation of transgender populations to cisgender women and men. Another challenge that future research may face is collecting patient information. Transgender and non-binary patients do not always disclose their true gender identity to providers. For instance, the U.S. Transgender Survey reports that almost one-third of transgender people did not inform their healthcare providers that they were transgender (24). There are many reasons that people may not wish to disclose their gender, including prior discrimination, fear of mistreatment, and avoiding invasive questions (24). The transgender and non-binary individuals have especially experienced negative interactions with healthcare providers. The responsibility to make a patient feel comfortable falls on the medical provider, and, therefore, providers should have adequate training on how to care for transgender and nonbinary populations. The medical community must continue to acknowledge its biases and adjust providers' approach to patient care so that patients of all genders may one day receive similar quality of care.

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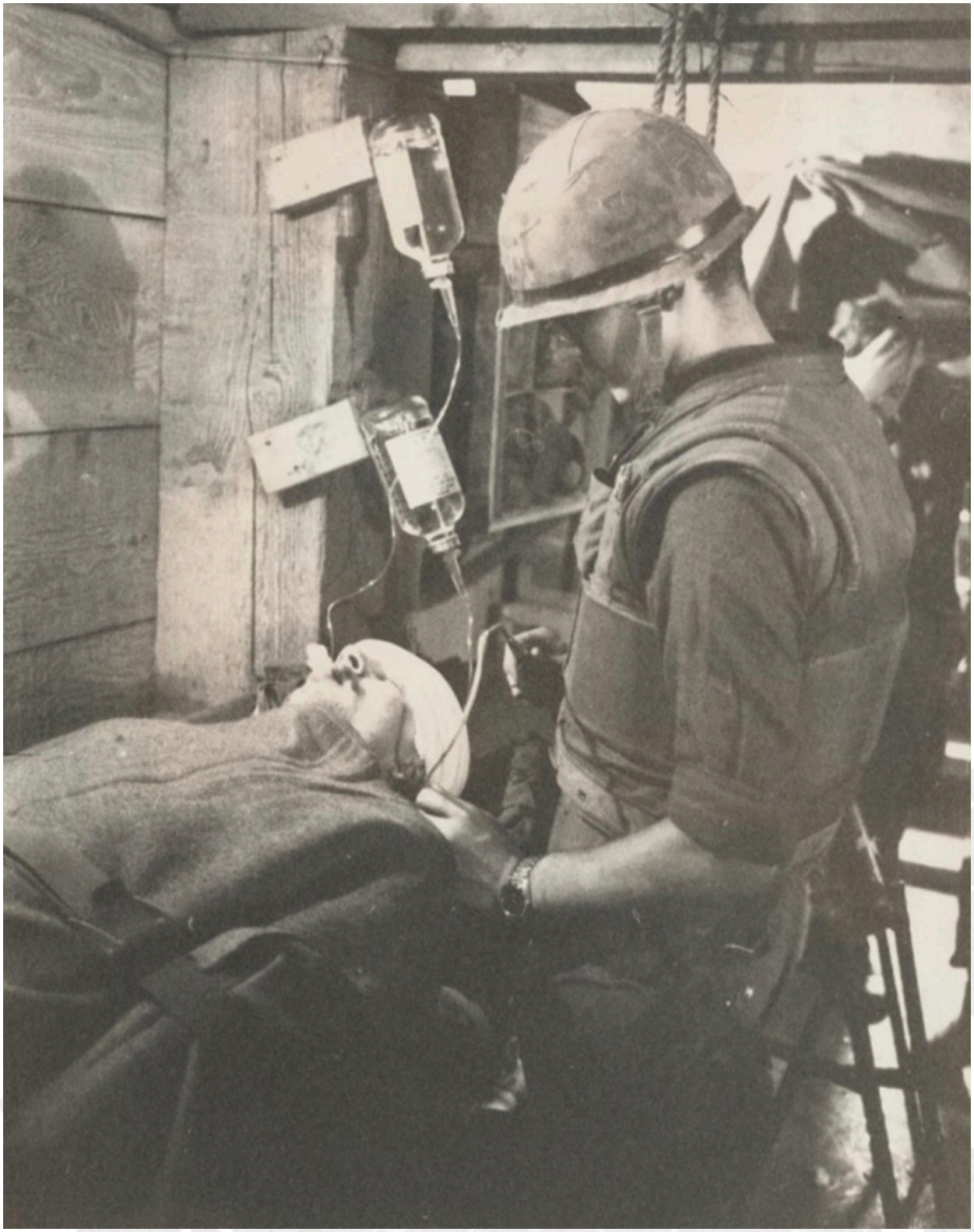

"Caring for a Casualty" by John T. Wheeler (Artist, American, 1925 - 2013). March 8, 1968. Image courtesy of the National Gallery of Art.

Current Practices in ED Social Determinants Screening and Care Connection: A Literature Review

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Keywords

emergency medicine; social determinants of health; screening; community resources

Abstract

Social determinants of health (SDOH) screening in emergency departments (ED) is a promising method to capture and address individualized social needs of a broad patient population, ideally lowering emergency department readmissions while reducing health disparities. With new Joint Commission guidelines requiring social determinants to be addressed and integration of SDOH-related Z-codes into ICD-10 coding, the time is now to implement robust screening and referral programs. This narrative literature review strives to identify best practices prior to the implementation of social determinants screening in the ED of University Medical Center, New Orleans. We investigate current screening tools and their integration with electronic health records, discuss survey formats, detail referral processes, and resource navigation post screening, and describe care connection models from screening to referral. Key conclusions include the identification of the Protocol for Responding to & Assessing Patients' Assets, Risks & Experiences (PRAPARE) as the ideal screening tool, and that electronic screening tools led to higher levels of social needs reporting compared to paper counterparts. Similar success of written resource referrals and referrals given by a navigator in reducing social risk factors was also identified, highlighting the importance of high-quality, written resource referrals. Lastly, challenges to formation of a successful, integrated screening and referral pathway such as loss to follow-up, even in a transition care coordination model that assists patients throughout levels and types of care, are identified.

Introduction

Emergency room services play a critical role in public health. According to Ordonez et al. (1), patients with food insecurity, lower education levels, limited access to primary care services, members of racial and ethnic minority groups, and Spanish-speaking patients with limited English proficiency were all correlated with higher ED utilization. Such groups experience systemic barriers in access to care and emergency care transitions. This may lead to greater health disparities, which tend to be strongly associated with increased adverse SDOH (2). SDOH strongly impacts one's quality of life and life expectancy. According to Alley et al. (3), measurable health outcomes such as mortality and morbidity receive approximately 55% contribution from social, economic, and environmental factors.

This literature review is being conducted as a review of current practices prior to the introduction of a

revamped SDOH screening and referral system in the ED of University Medical Center, New Orleans (UMC). New Orleans and its people are uniquely positioned to reap the benefits of this intervention for many reasons. According to the New Orleans Community Health Improvement Plan (6), only 65% of New Orleanians have a primary care provider, yet chronic conditions are commonplace, with ⅓ of residents suffering from hypertension or hypercholesterolemia and ⅔ of residents considered obese. New Orleans is the second most food insecure city nationally and nearly ¼ of its residents live in poverty, with the city's average household income being $41,604, over $20,000 under the national average (6). Using the ED to connect New Orleanians to necessary resources such as food banks, housing resources, mental health care, preventative healthcare services, and more will hopefully address some of these issues while lowering ED readmission rates by tackling root causes of admission.

Additionally, with the introduction of a new National Patient Safety Goal by The Joint Commission targeting health equity, hospitals, and other healthcare institutions are more directly incentivized to address social determinants than ever (7). Effective July 1st, 2023, this goal requires institutions to assess patients' health-related social needs, analyze quality and safety data to identify specific disparities, and develop action plans to improve health equity (7).

Results

Section 1: Discussion of Current Screening Tools

Henrikson et al. (9) reviewed literature published from 2000 and 2018 to yield 21 unique screening tools for social risk factors in a clinical setting and assessed them on their psychometric and pragmatic characteristics. Tools that are deemed psychometrically strong are able to "accurately and precisely identify social risk domains, characterize their associations with relevant outcomes, and measure changes in risk over time and in response to interventions" (8). Tools that are pragmatically strong were deemed as having favorable pragmatic properties such as ease of administration, low cost, and shorter lengths (9). The top 3 scoring tools for psychometric testing were: Urban Life Stressors Scale, Protocol for Responding to & Assessing Patients' Assets, Risks & Experiences (PRAPARE), and Social Needs Checklist (Henrikson et al., 2019). According to Henrikson et al. (2019), the top 3 scoring screening tools for pragmatic testing were: Survey of Well-Being of Young Children, Safe Environment for Every Kid, and WeCare.

In a systematic literature review conducted by Chen et al. (5), 4 main SDOH screening tools were focused on. These were the PRAPARE tool, the Accountable Health Communities (AHC) Screening Tool, the Health Leads Screening Tool, and the HealthBegins Upstream Risks Screening Tool.

According to the literature review, all 4 of the above screening tools cover the 5 key domains outlined by Healthy People 2020, a 10-year program launched by the United States Department of Health and Human Services (HHS) with an objective of improving health through goals like reducing health disparities and reducing preventable disease. These key domains were economic stability, neighborhood and built environment, health and health care, education, and social and community context (5). The review noted that PRAPARE covered the most measures in every domain except health and health care. In this domain, PRAPARE focused on insurance status while the other 3 screening tools focused on needs for assistance, physical activity, diet, and mental health status (5).

Other studies 10 have shown success with utilization of the SDOH screening tool native to EPIC. Benefits included question alignment with other institutional EPIC users, easy access to EPIC population health tools, and quick accessibility of survey responses to team members.

Utilization of surveys native to mobile apps was also reported (11), including use of HelpSteps, a self-administered screening tools which allows users to choose from 22 different domains of social determinants with accompanying referral options, and simply select their most important, and secondary need domains. This survey was combined with the widely adopted AHC Health-Related screening tool (Table 1).

Table 1.

Top Ranked Screening Programs	
Urban life stressors	Whole- A 21-item screening survey for adult patients designed for a primary care setting. It assesses economic security, social and community context, and neighborhood and physical environment. It was determined as one of the top 3 screening surveys for psychometric testing by Henrikson et al. (2019).
PRAPARE	A 36-item screening survey for adult patients in a primary or specialty care setting. It assesses economic security, education level, social and community context, health and clinical care access, and neighborhood and physical environment. It was determined as one of the top 3 screening surveys for psychometric testing by Henrikson et al. (2019).
Social Needs Checklist	A 12-item screening survey for adult patients in a primary care setting. It assesses economic security, social & community context, health and clinical care, and neighborhood & physical environment. It was determined as one of the top 3 screening surveys for psychometric testing by Henrikson et al. (2019).
Survey of Well-being of Young Children	A 10-item screening survey for adult and pediatric patients in primary care and pediatric settings. It assesses education level, neighborhood & physical environment, and food insecurity. It was determined as one of the top 3 pragmatically strong screening surveys by Henrikson et al. (2019).
Safe Environment for Every Kid	A 20-item screening survey for pediatric patients in a primary care setting. It assesses social & community context, health and clinical care, and neighborhood & physical environment, and food insecurity. It was determined as one of the top 3 pragmatically strong screening surveys by Henrikson et al. (2019).
WeCare	A 10-item screening survey for pediatric patients in a primary care setting. It assesses economic security, education level, neighborhood & physical environment, and food insecurity. It was determined as one of the top 3 pragmatically strong screening surveys by Henrikson et al. (2019).
Health Leads Screening Tool	A 7-item screening survey for all patients in a primary care setting. It assesses economic security, education level, social and community context, food insecurity, and neighborhood and physical environment.

Accountable Health Communities (AHC)	A 26-item screening survey designed for Medicare/Medicaid patients in a primary care setting. It assesses economic security, social and community context, food insecurity, and neighborhood and physical environment.
HealthBegins Upstream Risks	A 28-item screening survey for all patients in a primary care setting. It assesses economic security, education level, social and community context, food insecurity, and neighborhood and physical environment.

Section 2: Discussion on Formats of Surveys: Electronic versus face-to-face screening surveys

A study conducted by Gottlieb et al. (12), used both electronic and face-to-face screening surveys in a pediatric ED to assess the difference between the two formats.

The study identified significant differences between the responses from the computer-based surveys and face-to-face interviews, with people being more likely to report social needs items in the computer-based surveys (12). Respondents reported higher levels of stress related to interpersonal violence (p=0.03) in their homes through computer-based surveys (12). The survey also included higher levels of reported substance use in the home (p=0.05) through computer-based surveys (12). This study is important in demonstrating the significance of the methods of data collection as these methods can affect accuracy and disclosure rates of the patients. A key takeaway from the study is the advantages of using computer-based screening tools, which may be more advantageous as they eliminate feelings of shame or judgment towards patients that may be associated with answering these questions posed directly by a medical provider.

Electronic screening allows surveys to be implemented in a universal fashion, with all patients screened to eliminate non-response bias, as less staffing and administrative resources are needed for administration. This aids in the prevention of certain patients not being screened due to external appearance or demographics. One study (12) found a significant difference in financial insecurity between social screening respondents and non-respondents.

Section 3: Use of Referrals and Resource Navigation

After SDOH screening through an EHR-integrated tool, results should be used to connect patients to appropriate services. A study conducted by Gottlieb et al. (14) explored the effectiveness of in-person social services navigation assistance in comparison to sharing standardized written information regarding available social resources. The purpose of this study was to investigate methods to make long-term care more feasible and effective in a pediatric urgent care clinic by addressing social risk factors.

The study randomized patients to receive either written resources or written resources plus in-person assistance. The written resources were prewritten informational handouts that listed local resources from relevant government, hospital, and community social service organizations. The in-person assistance consisted of navigators who also provided other forms of assistance to caregivers such as help with scheduling appointments and completing forms.

The study found that there were no significant differences between the two groups, but that both groups had significant decreases in reported social

risk factors (examples included food insecurity, housing insecurity, and transportation access) as well as improved child and caregiver health. According to Gottleib et al. (14), the results of the study were unexpected as a previous study conducted by the same authors had shown that in-person navigation of resources was significantly more effective. Gottleib et al. (14), discussed that the potential reason for the difference in results could be attributed to the improved quality of information given in the resource sheets. In this study, the navigators incorporated 2 techniques that were recommended by the Agency for Healthcare Research and Quality. These techniques were to include specific contact names at the organizations given and highlight the resources that are most relevant to the social risks identified (14). High-quality written resources may be a sufficient social risk intervention in pediatric populations.

Applications that automatically generate referrals based on screening responses have also been used, and can be combined with an optional social work consultation. A study (11) with this approach reported that 14% of the study population reached out to a social support organization.

Community partners, defined as pre-existing organizations that may address specific social determinants of health such as food banks, shelters for the unhoused, or domestic violence prevention programs in addition to programs that focus more broadly on coordinating social needs interventions, are an invaluable resource in executing resource referrals. The strategic utility of these organizations in ensuring high follow-up rates and connection to care cannot be overlooked and strong relationships between healthcare providers and high-use community partners should be cultivated (15). A large academic medical center set up data sharing with an existing community resource directory organization, United Way of Salt Lake City's 2-1-1. Of the 129 patients with 1 or more stated needs, 73 (56.6%) asked for referral to 2-1-1 and 32 (43.8%) were reached by 2-1-1 within 1 week of emergency department discharge (14).

A study conducted by Hsieh (16), showed that resource navigators could link patients to primary care providers and other emergency providers. This would allow for continuity and advocacy for the patient's social concerns. For many high-risk patients, resource navigation may not be sufficient, and establishing ongoing care is a more effective way to intervene in the complex medical issues these patients may be facing.

Section 4: Putting it All Together: Use of Care Connection Models

Some papers have described their processes for addressing social needs from start to finish, from initial screening to connection to care or provision of social services.

A systematic review conducted by Yan et al. (17) explored current literature that investigated the process of integrating SDOH or social needs screenings into EHRs and subsequent care connections. They identified three main approaches to identifying and addressing social needs. The simplest approach involved healthcare providers identifying social needs and distributing community resources or referrals as they deemed appropriate. The second approach involved healthcare providers identifying social needs and then, using patient navigators to connect patients to external resources or social services. The third approach, the most complex, involved a transition care coordination model that assisted patients throughout levels and types of care at multiple facilities. Overall, Yan et al. (17) found that while many studies explored the process of integrating SDOH screenings, few studies actually reported health outcome measures. They noted that several studies did report positive impacts on healthcare costs and utilization

measures, however, these studies were mixed in their ability to provide conclusive evidence.

This is congruent with a study conducted by Wallace et al. (18). In this study, the authors evaluated the reach and implementation of integrating SDOH screening and referral to resources in an ED. Between January 2019 to February 2020, ED registration staff screened patients for social needs. They used a 10-item, low-literacy, English-Spanish electronic questionnaire that generated automatic referrals. Wallace et al. (18) found that of the 4608 patients approached, 61% of patients completed the screening questionnaire. Of these patients, 47% indicated a need for one or more social services and 34% of those agreed to be followed up with a resource specialist (18). Only 20% of those who agreed to be followed up with were reached out to by outreach specialists for referrals. Only 7% of patients completed the process from screenings to referrals. This overall low completion rate should be considered when implementing referral processes. The article then explored the challenges that arose during this process such as patient stigmatization and staff reluctance. Detailed evaluation of the process determined that patients desired a better understanding of their needs and had felt concerns regarding privacy and being stigmatized from the screening staff. The screening staff expressed discomfort and that they were questioning the usefulness of screening for social needs.

Some authors have described utilizing automation to increase efficiency from screening to referral. An article by Rogers et al. (19) described a custom screening tool they built into Epic EHRs. The screening tool used was reflective of the AHC screening tool, mentioned in Section 1. Rogers et al. (19) customized the tool by integrating it with a Community Resource Network Management Software-as-a-Service (CRNM SaaS). The steps of the process began with the AHC screening tool. Then, these responses were recorded in the patient's EHR and transmitted from EHR to CRNM SaaS platform. The CRNM software reviews the screening results and automatically generates a customized community resource sheet (CRS) that can be given to the patient with their After Visit Summary (AVS). This tailored CRS includes community service providers (CSPs) in the patient's ZIP code or nearest ZIP code that could assist with each SDOH identified in the AHC tool. The strengths of this program were the reduced burden on healthcare staff. Additionally, providing patients with a customized CRS can help account for language or literacy barriers that may prevent the patient from using the information listed on the sheet.

Section 5: Our Proposed Intervention as Informed by the Literature

Table 2.

Section of literature review	Incorporation into proposed intervention
Section 1: Discussion of Current Screening Tools	Similar to the successful screening tools, like PRAPARE, described by Chen et al. (5) , our selected survey covers the 5 key domains outlined by Healthy People 2020. Because of its EPIC integration, it enjoys the benefits described by Peretz et al. 10 like access to population health tools and easy accessibility to care team members.

Section 2: Discussion on Formats of Surveys: Electronic versus face to-face screening surveys	The screening survey is first offered in an electronic format that the patient can fill out alone. This follows recommendations from Gottlieb et al. (12), whose research showed patients were more likely to disclose social needs through electronic formats.
Section 3: Use of Referrals and Resource Navigation	The screening survey is paired with the tool FindHelp which can be used to curate a written list of community organizations and referrals that will be sent home with the patient based on the identified SDOH. This follows recommendations from Gottleib et al. (14) who demonstrated that patients given written resources or written resources plus in- person assistance had similar significant decreases in reported social risk factors and improved child and caregiver health.
Section 4: Putting it All Together: Use of Care Connection Models	When implementing our survey the recommendations of Rogers et al. (19) were used. Rogers et al. (19) described a custom screening tool they built into Epic EHRs and customized by integrating it with a community resource network tool that included resources in the patient's After Visit Summary. At our institution this was similar to the program FindHelp, mentioned above. This was designed to preemptively address common challenges, such as the burden on healthcare staff, that other institutions had faced when implementing screening tools.

As described in Table 2 above, we recommend implementing a program similar to the one described by Rogers et al (19). Based on the demographics in New Orleans and the patient population at UMC, we propose utilizing a social determinants screening tool built into EPIC as well as the integration of a program called FindHelp into Epic. FindHelp uses a unique platform to connect people to local resources and programs. We have outlined a flow chart of our proposed intervention in Figure 1.

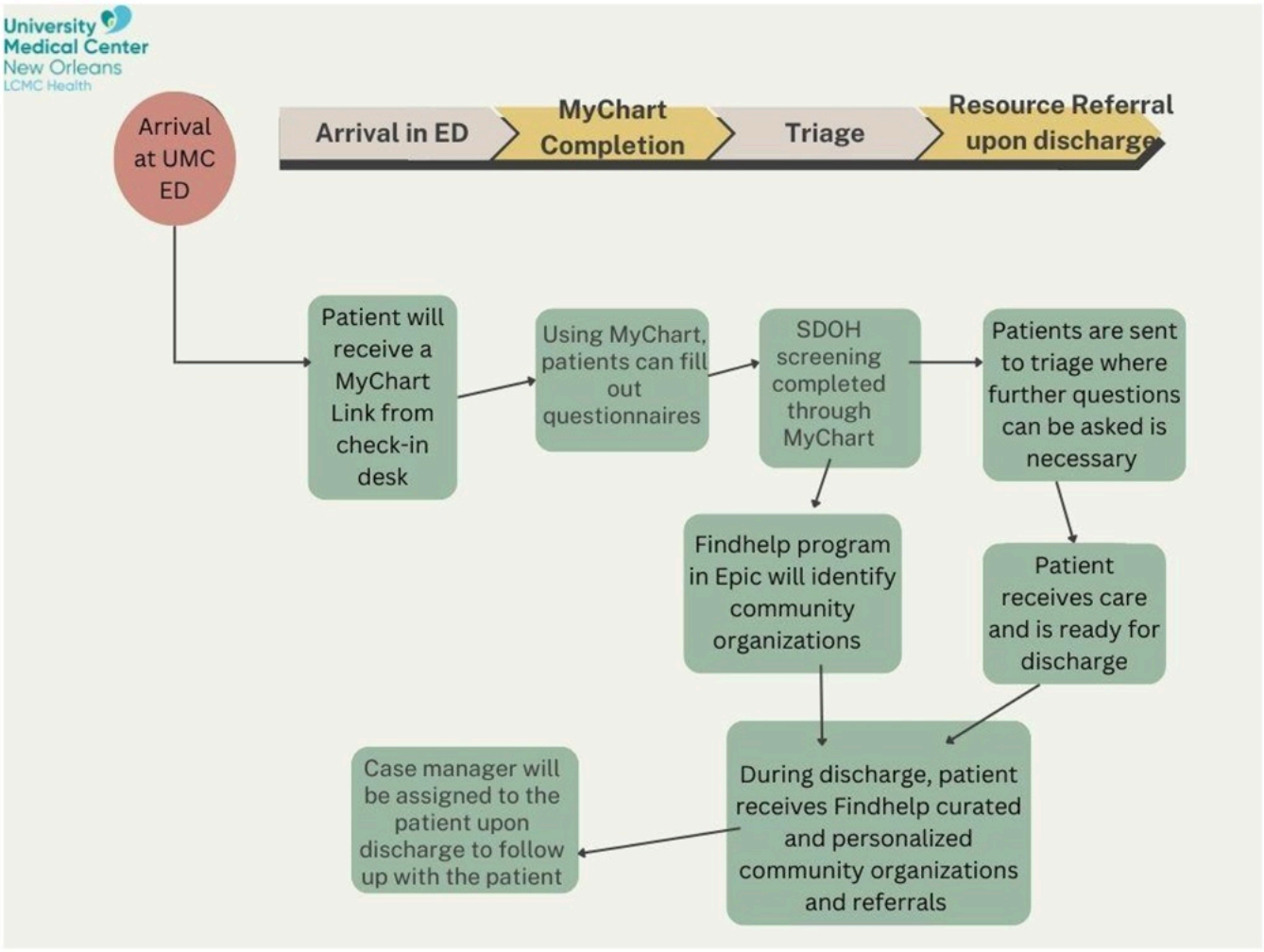

Figure 1. Flow chart through patient arrival at ED to resource referral upon discharge.

The recommended process will be as follows. When a patient arrives at the UMC ED, they will receive a link to MyChart. MyChart is a secure location that stores a patient's health information including medications, medical bills, test results, and appointments. Through MyChart, the patient will be able to complete a SDOH screening survey (Figure 2).

Figure 2. SDOH screening survey to be implemented.

Physical activity

- On average, how many days per week do you engage in moderate to strenuous exercise (like a brisk walk)?
    - 0 days
    - 1 day
    - 2 days
    - 3 days
    - 4 days
    - 5 days
    - 6 days
    - 7 days
    - Patient refused
- On average, how many minutes do you engage in exercise at this level?
    - 0 min
    - 10 min
    - 20 mins
    - 30 mins
    - 40 mins
    - 50 mins
    - 60 mins
    - 70 mins
    - 80 mins
    - 100 min
    - 120 min
    - 130 min
    - 140 min
    - 150+ mins

Financial resource strain

- How hard is it for you to pay for the very basics like food, housing, medical care, and heating?
    - Very hard
    - Somewhat hard
    - Not very hard
    - Not hard at all
    - Patient refused

Housing stability

- In the last 12 month, was there a time when you were not able to pay the mortgage or rent on time?
    - Yes
    - No
    - Patient refused
- In the last 12 months how many places have you lived (open response).
- In the last 12 months, was there a time when you did not have a steady place to sleep or slept in a shelter (including now)?
    - Yes
    - No
    - Patient refused

Transportation needs

- In the past 12 months, has lack of transportation kept you from medical appointments or from getting medications?
    - Yes
    - No
    - Patient refused
- In the past 12 months has lack of transportation kept you from meetings, work, or from getting things needed for daily living?
    - Yes
    - No
    - Patient refused

Food insecurity

- In the past 12 months, you worried that your food would run out before you got the money to buy more?

Figure 2, cont.

- Never true
- Sometimes true
- Often true
- Patient refused

- Within the past 12 months, the food you bought just didn't last and you didn't have money to get more?
  - Never true
  - Sometimes true
  - Often true
  - Patient refused

Stress

- Do you feel stress- tense, restless, nervous, or anxious or unable to sleep at night because your mind is troubled all the time- these days?
  - Not at all
  - Only a little
  - To some extent
  - Rather much
  - Very much
  - Patient refused

Social connections

- In a typical week, how many times do you talk on the phone with family, friends or neighbors?
  - Never
  - Once a week
  - Twice a week
  - Three times a week
  - More than 3 times a week
  - Patient refused
- How often do you get together with friends or relatives?
  - Never
  - Once a week
  - Twice a week
  - Three times a week
  - More than 3 times a week
  - Patient refused
- How often do you attend church or religious services?
  - Never
  - 1 to 4 times per year
  - More than 4 times per year
  - Patient refused
- Do you belong to any clubs or organizations such as church groups, unions, fraternal or athletic groups, or school groups?
  - Yes
  - No
  - Patient refused
- How often do you attend meetings of the clubs or organizations you belong to?
  - Never
  - 1 to 4 times per year
  - More than 4 times per year
  - Patient refused
- Are you married, widowed, divorced, separated, never married or living with a partner?
  - Married
  - Widowed
  - Divorced
  - Separated
  - Never Married
  - Living with partner
  - Patient refused

Intimate Partner Violence

- Within the last year, have you been afraid of your partner or ex-partner?
  - Yes
  - No
  - Patient refused

Figure 2, cont.

- Within the last year, have you been humiliated or emotionally abused in other ways by your partner or ex-partner?
    - Yes
    - No
    - Patient refused
- Within the last year, have you been raped or forced to have any kind of sexual activity by your partner or ex-partner?
    - Yes
    - No
    - Patient refused

Alcohol use

- How often do you have a drink containing alcohol?
    - Never
    - Monthly or less
    - 2-4 times a month
    - 2-3 times a week
    - 4 or more times a week
    - Patient refused
- How many drinks containing alcohol do you have on a typical day when you are drinking?
    - Patient does not drink
        - 1 or 2
        - 3 or 4
        - 5 or 6
        - 7/9
        - 10+
        - Patient refused
- How often do you have six or more drinks on one occasion?
    - Never
    - Less than monthly
    - Monthly
    - Weekly
    - Daily or almost daily
    - Patient refused

Utilities

- In the past 12 months has the electric, oil, or water company threatened to shut off services in your home?
    - Yes
    - No
    - Already shut off
    - Patient refused

Figure 2. SDOH screening survey to be implemented.

The patient will then be sent to triage where the triage nurse will verify survey's completion or answer any questions to facilitate its completion. The survey tool will be added to the EPIC toolbar for easy accessibility to staff. If the survey is not completed pre-triage, or during triage, it can also be completed afterward while waiting for care. Once the patient has been treated and is ready to be discharged, a curated list of community organizations and referrals will be sent home with the patient based on the SDOH FindHelp identified from the survey. A case manager will also be assigned to the patient to follow up with them and provide any additional assistance.

Potential weaknesses of this program include its reliance on patients having a mobile device to access the internet. The MyChart link will be sent to a patient's phone either through text or email. If a patient does not have a phone, we hope to have ED iPads that can be used to fill out the screening surveys. Another weakness is that this program may be difficult for patients with low literacy levels, low proficiency in English, or disabilities. Providing iPads with accessibility features could help combat this issue but would require staff to be available to assist these patients.

Discussion

SDOH screening is an important and growing objective in social Emergency Medicine. Beyond its importance in reducing hospital readmission rates by addressing root cause of disease or ED presentation, screening efforts address the new National Patient Safety Goal by The Joint Commission and have recently been integrated in ICD-10 coding.

Z codes are a separate set of ICD-10 codes that can be used to document patients' SDOH.22 They include a wide range of issues such as education & literacy, employment, housing status, access to food, access to safe drinking water, occupational hazards, and more.22 The Centers for Medicare & Medicaid Services' Office of Minority Health23 released a report in June 2023 that maps out steps to effectively using Z codes. The steps they recommend are the following: (1) collect SDOH data, (2) document the SDOH data in the patient's record, (3) map SDOH data to Z codes, (4) use SDOH Z code data, (5) report SDOH Z code data findings. There are several benefits to collecting this information such as helping the hospital and healthcare staff identify the most commonly used Z codes. Identifying top Z codes can help focus referrals and resources in those specific areas and help to efficiently reduce SDOH.

There is also ample room for future research in this arena, such as an evaluation of follow-up rates with referral services to determine if the resources are being used and to what extent. Future research can also be done to explore SDOH screening implementation in settings other than critical/urgent care settings.

The role and efficacy of healthcare systems in implementing their own social needs interventions that do not require support from community organizations is another area the literature is lacking. Social determinants screening data can potentially be used to tailor interventions relevant to hospitals' unique patient populations. For example, a large proportion of patients indicating food insecurity during screening may indicate that a hospital-run food pantry would be beneficial. By implementing interventions without the reliance on partner organizations post-referral, healthcare entities may be better able to follow-up with patients and connect them to resources in a timely manner post-screening.

Following these recommendations for the SDOH screening process in the ED of UMC, robust collaboration, feedback, and training will be needed to ensure this new process is streamlined and effective for all stakeholders. After its complete rollout, data analysis and quality improvement initiatives will be necessary to ensure completion rates are as high as possible and that patients are being connected to needed resources in a timely and efficacious manner.

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"Metamorphose (Metamorphosis)" by André Masson (Artist, French, 1896 - 1987). 1963. Image courtesy of the National Gallery of Art.

The Role of Stem Cell Therapy in Treating Type 1 Diabetes and Scientific Advances in Evading an Immune Response

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Keywords

human embryonic stem cells; stem cell therapy; type I diabetes; immune system

Abstract

Considering the increasing prevalence and healthcare costs associated with diabetes mellitus (DM), the disease has become an essential subject of continuing research. In particular, type 1 diabetes (T1D) has garnered great interest since current treatments are limited to following a strict diet and insulin regimen or involve approaches that are inaccessible or inappropriate for use by the public. While studies have shown promising effects of stem cell therapy in treating diabetes-induced nephropathy/retinopathy, further research is underway to find a cure for the disease itself. Human embryonic stem cells hold promise for treating T1D because they can effectively differentiate into endocrine and pancreatic cells without encapsulation. However, the likelihood of rejection has shifted focus onto novel techniques that could allow stem cell-derived β-cells to circumvent the immune system. Targeting Human Leukocyte Antigen (HLA) molecules using gene editing techniques such as CRISPR/Cas9 system would allow for an increased graft tolerance. This promising system, combined with encapsulating stem cells to physically separate them from the immune system, could support long-term cell survival and thus increase the likelihood of finding a cure for T1D.

Introduction

Approximately 415 million people around the world are affected by diabetes mellitus (DM) and this number is expected to grow to 642 million by 2040 (1). The worldwide expenditure from diabetes is estimated to be 802 billion U.S. dollars in 2040, with 423 billion dollars attributable to type 1 diabetes in particular (1, 2). Diabetes affects nearly every body system and often leads to microvascular complications such as nephropathy, retinopathy, and neuropathy, and thereby reduces life expectancy by an average of 13 years (3-7). DM is identified as a metabolic disease that results in hyperglycemia, characterized into two etiologies: type 1 and type 2.1 Type 2 diabetes (T2D) is associated with insulin resistance and an inability of the pancreatic beta (β) cells to meet insulin demand, perpetuated by environmental factors such as obesity, smoking, and lack of physical activity.8 Approximately ten percent of the population currently affected by DM presents with type 1 diabetes mellitus (T1D) which is characterized by the autoimmune destruction of insulin-secreting beta-cells, which requires exogenous insulin to avoid deleterious glycemic fluctuations (9).

Effectively controlling elevated glucose levels with exogenous insulin decreases the risk of secondary complications, but comes with increased risk of

hypoglycemia, stemming in part due to inconvenience and poor patient acceptability of multiple insulin injections each day (10). As a result, there is a distinct need for effective therapies beyond exogenous insulin that more closely mimic the native physiological response to hyperglycemia (6). Novel therapies, such as pancreatic transplantation, are limited by donor availability (11, 12). Human pluripotent stem cells (hPSCs) has driven intense research, as their pluripotency allows them to differentiate into insulin-producing β-cells (11). Therefore, a patient can use their own regenerative stem cells to differentiate into large numbers of insulin-producing β-cells reactive to glucose levels, bypassing the problem of donor scarcity (11, 12). Novel therapies, such as pancreatic transplantation, are limited by donor availability and the need for immunosuppression (8). As a result, techniques like genetic engineering and islet cell encapsulation for transplantation are being explored to evade the immune system response that often results in graft rejection and therapy failure (12).

This paper reviews advancements in the treatment of T1D, exploring current transplantation strategies and stem cell-derived therapies. We discuss the immune response associated with diabetes and stem cell therapies, current methods limiting the need for immunosuppression, and newer techniques like genetic modifications with CRISPR/Cas9 and encapsulation delivery methods, highlighting their potential benefits.

Current Therapeutic Strategies for Treating T1D

As healthcare costs and human costs related to diabetes mellitus continue to rise, it is essential to consider options to treat and cure the disease (6). T1D results from the autoimmune destruction of insulin-producing β-cells (9). Symptoms include polyuria and polydipsia, confirmed with tests revealing high levels of blood glucose, C-peptide deficiency, increased amount of hemoglobin glycosylation (HbA1c), and the production of autoantibody markers (13-15). The current treatment regimen for T1D combines intensive diet treatments (such as limiting sugar intake) with the need for lifelong exogenous insulin administration, either via multiple daily doses or using insulin pumps (16). A recent FDA-approved intervention involves an infusion pump providing precise doses of insulin and glucagon, responding to glycemic fluctuations; however, the infusion pump was found to increase the risk of severe hypoglycemic responses (6).

Pancreatic and islet cell transplantation have emerged as alternatives to exogenous insulin administration. Pancreatic transplantation is generally only considered when a patient has severe complications of diabetes mellitus with frequent and severe hypoglycemia and poor quality of life refractory to insulin (17). Risks include thrombosis, bleeding, graft pancreatitis, graft failure, pancreatic-enteric fistula, intra-abdominal abscess, and graft rejection, managed with immunosuppressants (17). Stronger immunosuppressive agents may allow functional graft survival for several years, with patients achieving metabolic control with little to no insulin administration (8). However, pancreatic transplantation is not a primary treatment option for children and adolescents, as they rarely suffer the severe sequelae of type 1 diabetes that would qualify them for transplantation (18). Furthermore, donor availability is on the decline as well.19 Transplantation requires young, non-diabetic, non-obese donors; with the increasing rates of diabetes and obesity in the USA, the availability of deceased donors suitable for pancreatic transplantation has undoubtedly been affected (19). Even if donor availability is not an issue, transplantation and immunosuppression face minor complications such as mouth ulcers, diarrhea, and acne, as well as

longer-term risks like malignancy and infection (20). The Edmonton Protocol, which infuses isolated pancreatic islets into the portal vein of adults with T1D, is now clinically implemented worldwide. Coupled with consistent immunosuppression and induction, the Edmonton Protocol has significantly improved insulin independence over the last ten years (8). While most patients in the first clinical trial achieved over one year of insulin independence, only about 10% maintained insulin independence after five years (8). All other participants achieved insulin independence for an average of 15 months, with the primary cause of failure being antibody development (8). To avoid islet cells trapping in portal capillary sinusoids, research continues in other administration sites, including muscle, the renal subcapsular space, pancreas, omentums, eyes, and testes (6). Overall, current treatments and their complications have shifted focus to other avenues, such as stem cell and cellular replacement therapies to treat T1D.

Stem Cells in Treating Diabetes

While long-term stem-cell based solutions have shown promising results in treating primary T1D through transplanting islet cells reactive to blood glucose levels, these results stem from clinical trials that are years away from being incorporated in clinical practice (21). Therefore, short-term solutions that alleviate diabetes-induced microvascular complications through stem cell-derived therapies remain the focus of this review. Bone marrow-derived mesenchymal stem cells (BM-MSCs) for autologous cell transplant have shown therapeutic value in treating diabetic nephropathy through their vascular repair abilities, which offsets the pathogenesis of diabetic sequelae (7, 22). In one preclinical trial, T1D-induced mice regained renal function after one dose (25 million per kilogram of body weight) of systemically administered mesenchymal stem cells (MSCs), ultimately regenerating β-cells and avoiding renal damage (5).

Autologous BM-MSCs have shown to be effective and safe in treating diabetic retinopathy, particularly during the nonproliferative stage (7). MSCs have also delivered promising results in treating diabetic neuropathy through regulation of spinal neuroinflammatory cascades and reversing associated sensorial dysfunction in diabetic mice (4).

As more studies look at stem cells as a possible treatment for diabetes-induced microvascular complications, several optimistic studies focus on a long-term treatment for the disease itself. Currently, islet and pancreatic cell transplants risk rejection and tumor formation (12). Also, donor availability is limited (11, 12). In theory, MSCs derived from adipose tissue (hAD-MSCs), bone marrow (BM-MSCs), or from the umbilical cord (UC-MSCs), which all have similar morphology, phenotypic expression, self-renewal capabilities, and multi-lineage potential, as well as induced pluripotent stem cells (iPSCs), would concurrently address rejection risk and donor availability (6, 23, 24).

Human embryonic stem cells (hESCs) and iPSCs have been differentiated into functional islets through expression of specific pancreatic transcription factors such as PDX-1, MAFA, Neurod1, and NGN3 (Figure 1) (25, 26). Despite the theoretical risk reduction in autologous transplantation, iPSCs may still be rejected due to neoantigens or other epigenetic factors (27). Ensuring that stem cell-derived β-cells are identical to those endogenous to the pancreas remains a challenge.

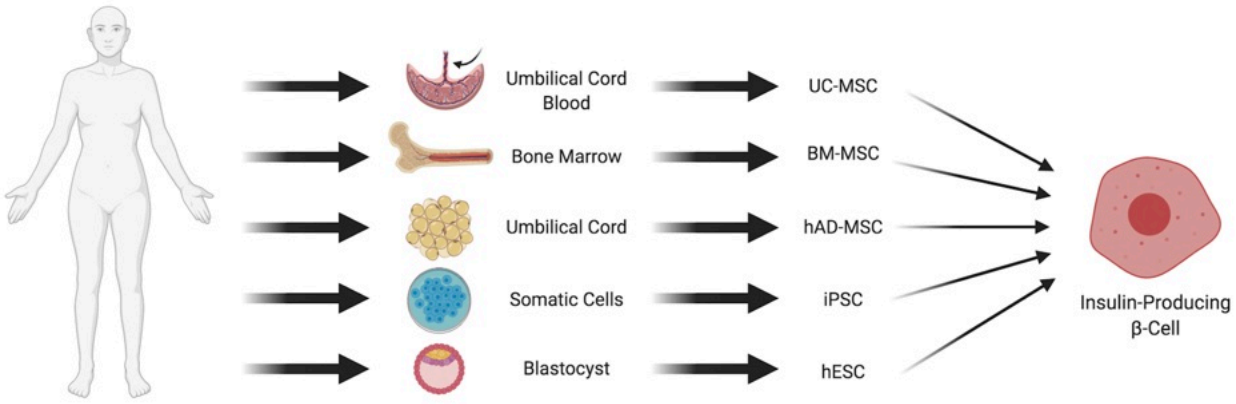

Figure 1: Sources of Stem Cell-Derived β-cells. Mesenchymal stem cells (MSCs) can come from a variety of sources in the human body. Adipocytes and bone marrow MSCs are primarily used to suppress the immune response against β-cells and improve diabetic retinopathy, respectively. Induced pluripotent stem cells (iPSCs) can come from any somatic cell in the body, while human embryonic stem cells (hESCs) are derived from the blastocyst. Both iPSCs and hESCs are differentiated through the expression of pancreatic transcription factors - PDX-1, MAFA, Neurod1, and NGN3 (25, 26). Image created with BioRender.com.

hAD-MSCs appear to be more promising in terms of mitigating rejection caused by neoantigens without entirely suppressing the immune system. hAD-MSCs elicit an upregulation in regulatory T-cells (Tregs) and TGF-β1, which diminishes the autoimmune response in T1D, and suppresses $CD4$ TH1 (T helper) cells that are responsible for destroying pancreatic islets in T1D (28). However, hAD-MSCs have not shown long-lasting effects in preclinical trials; after nine weeks, blood glucose levels steadily rose in mice, reaching concentrations above 300 mg/dL (28). Furthermore, while hAD-MSCs are considered immune-privileged, it is imperative to consider that recognition and eventual rejection of these cells by the immune system cannot be disregarded in the long term (28). Until they are effective in not only avoiding an immune response altogether, but also remaining functional overtime, we must rely on other methods of treatment, such as genome editing via CRISPR/Cas9 and encapsulation. Encapsulation of stem-cell derived β-cells is a promising approach in protecting these cells from the immune system.

The Immune Response to Stem Cell-Derived β-Cells

Transplanted stem cell-derived β-cells are attacked by the innate and adaptive immune systems through autoimmune and alloimmune mechanisms (12). The pathogenesis of type 1 diabetes involves an intricate interplay between the immune system and the β-cells of the pancreas (12). Autoreactive T cells recognize self-determining molecules Major Histocompatibility Complex (MHC) or Human Leukocyte Antigen (HLA) on the surface of cells. Studies on the NOD mouse, which is highly prone to developing T1D, reflect the essential role of MHC class II allele I-Ag7 in the development of

autoimmune diabetes (29). In humans, T1D heritability was found to be linked to two HLA class II haplotypes, HLA DR3 (DRB1*0301-DQA1*0501-DQ*B10201) and HLA DR4-DQ8 (DRB1*0401-DQA1*0301-DQB1*0301) (30). A study on identical twins and HLA-identical siblings showed that the individual with T1D rejected islet transplants from their non-diabetic sibling, showing that the disease process is due to an autoimmune process (31). This process is characterized by autoantibody production and an infiltration of lymphocytes in pancreatic tissue (29). Once bound to these molecules, autoreactive T-cells can either directly destroy β-cells or indirectly through an innate response, driven by natural killer (NK) cells and macrophages, leading to β-cell destruction (12). Evidence shows that MHC class I expression on the surface of β-cells plays a role in initiating the process of β-cell autoimmune destruction by activating CD8 T-cells (32). Antigens presented by HLA class II molecules on the surface of antigen-presenting cells (APCs) are recognized by CD_4 T cells, which are then activated to produce chemokines and cytokines, leading to inflammation (27). The damage to β-cells due to inflammation does not immediately alter glucose levels. A compensatory process of hormone secretion occurs in order to maintain glucose homeostasis until there is a significant decrease in β-cells, at which point T1D manifests (33). Diabetes-associated MHC class I and II alleles also play a role in allowing self-reactive lymphocytes to avoid the negative selection process in the thymus. Autoreactive CD_4 T cells detect specific MHC molecules and destroy the β-cells by a similar autoimmune process (34).

Alloimmunity occurs when the immune system encounters a cell that presents non-self HLA molecules at its surface, such as is the case with transplanted allogeneic stem cells. Similarly to autoimmunity, alloimmunity is largely mediated by CD_4 and CD8 T cells (12). To bypass the alloimmune response, the HLA markers of the donor must match the markers found on the recipient. However, HLA genes have one of the most polymorphic loci in the human genome, thus rendering the mechanisms of susceptibility difficult to clearly elucidate.30 Further illustrating this sensitivity, it has been noted that in order to avoid donor-derived cells from being targeted by the host's T cells, the transplanted cells should not strictly express any mismatched HLA since T-cell receptor αβ (TCRαβ), which is required to bind to MHC class I for the initiation of islet allograft destruction, is extremely sensitive to HLA complexes on the target cell (11, 35).

Novel Methods to Circumvent a Stem Cell-Induced Immune Response

To date, chronic immunosuppression remains necessary in circumventing graft failure. Despite its essential role in protecting the graft from an immune attack, immunosuppression does not seem to be strictly beneficial (11). It significantly increases the risk of infection with pathogens and is strongly correlated with diabetogenicity and β-cell dysfunction (11). Recent studies uncover the benefits of targeting antigen presentation and cytotoxic T lymphocyte activation to subvert chronic immunosuppression in patients with T1D who undergo stem cell therapy. hESCs expressing low levels of HLA were protected from the effects of an autoimmune response.36 However, this same study showed that increased IFNIγ and hESCs differentiation to β-cells both upregulated HLA expression, which was directly correlated with a higher vulnerability to an autoimmune attack.36 Genome editing techniques, such as CRISPR/Cas9, have emerged as promising therapeutic strategies in the treatment of T1D through a selective targeting of HLA genes (37). Overall, zinc finger endonucleases, CRISPR/Cas9, and encapsulation have all shown potential in improving immune tolerance of transplanted stem cells (6, 35, 37). A 2012 study shows that zinc finger endonucleases can

eliminate HLA-A gene expression in T-cells, allowing them to evade destruction by other healthy cytotoxic T cells (35). Low or no levels of HLA-A, however, were not sufficient to completely avoid an immune response. In fact, allogeneic cells that present no HLA molecules are prone to attacks by natural killer (NK) cells according to the "missing self" theory (35, 38, 39). This NK recognition was avoided in the 2012 study by enforcing the expression of non-classical HLA molecules in the transplanted cells such as HLA-A2 , providing HLA compatibility and rendering them unrecognizable by the immune system (35,39). The results from this initial experiment on T cells were used in hESC transplantation, which is usually complicated by HLA matching between the donor and the recipient, and even to autologous iPSCs, which may also induce an immune response as mentioned earlier (27, 35).

The clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated (Cas) protein 9 (CRISPR/Cas9) system is a simple and efficient method for targeting virtually any locus in the genome by directing the Cas9 endonuclease using short-guide RNAs to the specific gene locus (11). This technique allows the disassembly of MHC molecules in β-cell-derived stem cells with the same goal of circumventing the autoimmune and alloimmune responses (12). One preclinical trial showed that human iPSCs become minimally immunogenic after their MHC class I and class II molecules are inactivated by knocking out the accessory chain beta-2-microglobulin (B2M) and by targeting its transcriptional master regulator using CRISPR/Cas9.38,40 Another recent study used CRISPR/Cas9 to eliminate both human MHC class I genes HLA-A and HLA-B from iPSCs. The remaining HLA-C was sufficient to avoid detection by T-cells and destruction by NK cells while maintaining the ability to present antigens (41). In the future, we believe CRISPR could be used endogenously to increase the expression of pancreatic transcription factors (TFs) such as PDX1, MAFA, Neurod1 and Neurog3 (42). These necessary factors are found in endocrine progenitor cells and control cell differentiation into islet cells (42). Using CRISPR/Cas9 in a mouse model, one preclinical trial identified RNLS as a gene that makes β-cells resistant to autoimmune killing (43). Therefore, combining immunomodulating gene therapy with CRISPR/Cas9 could significantly improve stem cell therapy in patients with T1D by improving immune tolerance of stem-cell derived β-cells without subjecting patients to immunosuppressive therapies.

While gene editing techniques are extensively studied, encapsulation, a novel method for delivery of stem cells, is a newer therapeutic approach for T1D. The main goal of encapsulation is to eliminate the need for chronic immunosuppression in patients undergoing islet transplantation, by using a physical barrier to protect β-cells.6The early results of Phase I/II clinical trial indicate promising results (6). In these studies, an encapsulation device surrounds hESCs and, after implantation in subcutaneous space, selectively allows for diffusion of nutrients while preventing direct cell-cell contact with immune cells (6). The most recent encapsulation device allows for external vascularization, which improves oxygenation of the implanted cells but increases access of transplanted β-cells to immune cells (6). Therefore, continued research is necessary to fine-tune the balance between allowing for oxygenation of transplanted cells while minimizing autoimmune response, with the ultimate goal in mind of eliminating an autoimmune response entirely.

Conclusion

In short, the pursuit of stem cells as an alternative therapy for treating T1D arises in part from the relative dearth of available donors for organ and

islet cell transplants, but also from the complications associated with current therapies. Consistent exogenous insulin administration via an artificial pancreas seems to greatly increase the risk of a hypoglycemic response. Moreover, islet cell transplantation has its own issues since transplants have a risk of rejection as well as a limited shelf life of the transplanted islet cells. With over 200 million people anticipated to be newly diagnosed with diabetes mellitus over the next twenty years, developing new treatments is of the utmost concern.

The flaws associated with current treatments may potentially be solved with the use of stem cells. MSCs allow for an individual's own body to become the solution to their disease. Bone-marrow derived MSCs have been shown to improve diabetic nephropathy and retinopathy. Adipose-derived MSCs have been shown to minimize an autoimmune response and to mitigate β-cell destruction through multiple mechanisms, however, they are ineffective in the long run. hESCs and iPSCs have also been transformed into insulin-producing β-cells. Graft failure due to elimination by the immune system is a major hurdle to successful stem cell therapy in treating diabetes and diabetes-induced complications. Currently, the only treatment to avoid autoimmune and alloimmune attacks on stem cells is the use of immunosuppression in engrafted patients. While effective in reducing the immune response, immunosuppression is associated with a significant increase in infection risk and is strongly correlated with β-cell dysfunction. Two recent scientific advances – genetic engineering and cell encapsulation – have shown promise in decreasing chances of graft failure by evading the immune system. Inducing tolerance with genetic engineering and protecting cellular cargo with encapsulation can potentially circumvent the immune system in patients with diabetes treated with stem cells. Genetic editing using novel CRISPR/Cas9 technology would allow an individual to maintain the integrity of their immune system while ensuring the protection of stem cell-derivedβ-cells. This could be achieved by specifically targeting HLA class I and class II genes, considering that low levels of MHC molecules on the surface of cells minimize the chance of an immune response. Encapsulating stem cell-derived β-cells in hypoimmunogenic capsules also seems to be a promising therapeutic strategy for type 1 diabetes by creating a barrier between the therapeutic cargo and the host immune system. Further research must be done to verify the safety of these techniques in a clinical setting, but we remain optimistic that science is leading us in the right direction to ultimately find a cure for type 1 diabetes.

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