Emory Undergraduate Medical Review

FEATURING

Fall 2023 • Volume 10 • Issue 1

Cover Image by Alyssa Chen

EMORY UNDERGRADUATE MEDICAL REVIEW

Vol. 10 | Issue 1 Fall 2023

MISSION STATEMENT

The Emory Undergraduate Medical Review publishes student-authored research review articles at the cutting-edge of medicine, science, and public health. Our interdisciplinary articles span all clinical fields and are peer-reviewed by medical professionals from leading academic institutions, including Emory University, Harvard University, and the Baylor College of Medicine.

On and off-campus, EUMR leads a variety of medically-related events & unique initiatives, including frequent collaborations with Emory's School of Medicine and local community partners. Our projects have been featured by Emory's News Center and have caught the attention of President Gregory Fenves.

LETTER FROM THE EDITOR

Dear Reader,

EUMR's Fall 2023 edition marks the beginning of a new chapter of excellence and impact as our journal enters its tenth year. This semester, we celebrated EUMR's tradition of journalistic excellence and medical inquiry and paved new ways for the journal to make an even greater impact on our community. Whether it was reaching new heights with our journal quality or launching several new initiatives, we are proud of the hard work each member of our Editorial Board has put in to make EUMR's fall semester a success.

Interdisciplinary exploration and medical innovation are at the core of EUMR's mission and culture, and our writers continue to impress us with the quality and range of topics covered in our 10th volume. Together we produced a total of 23 articles across our digital and journal platforms, each of which address key questions in maternal healthcare, epidemiology, biotechnology, global health policy, and medicine. Our journal would not be the same without the dedication and talent of our writers, editors, and executive board, and we are endlessly grateful for their work.

Outside of our journal, EUMR's Events and Publicity team continued signature traditions such as the Fall Suture Lab in partnership with Emory School of Medicine, while implementing several new, exciting initiatives.

At the start of the semester, we launched our RISE High School Mentorship program in partnership with Druid Hills High School, under the guidance of Dr. Poornima Amarapu. Through this program, EUMR members guided high school seniors through the medical writing process to ultimately create full length, EUMR style medical reviews, which will be published next year. We also launched our new medical Op-Ed Column: "Medical Matters," in partnership with the Emory Wheel, Emory's student-run newspaper, which features student opinions on the future of healthcare, such medical volunteer licensure restrictions, the ethicality of savior siblings, and more. Other initiatives include our new volunteer partnership with Bethesda Community Clinic, allowing EUMR members to directly serve underresourced patient populations. Finally, we are proud of our new Narcan distribution and education initiative, led by one of our first-year liaisons to improve access to key resources for overdose prevention.

Most importantly, we would like to thank our dedicated Advisory Board who serve as critical members of our journal, without whom our work would not be possible. We are particularly proud to announce the addition of several new advisory board members, Dr. Xinhua Chen, Dr. Judy Gichoya, Dr. Sarah Mitchell, Dr. Joseph Petrosino, Dr. Subadhra Shashidharan, Dr. Sara Turbow, and Dr. Zanthia Wiley. They have replaced several advisory board members who have supported EUMR over the past decade and will be dearly missed. We wish them the absolute best in their careers.

As we look to the second half of EUMR's 10th year as a publication, we are excited to build upon these initiatives and see our team's hard work continue coming to fruition next year. Ultimately, we aim to push forward EUMR's mission of providing students the platform to explore the cutting-edge of current issues facing healthcare and medicine through interdisciplinary journalism & community impact. We cannot wait to work with everyone again this spring.

Cordially,
Shreya Ramanathan & Alyssa Chen
Editors-in-Chief
EUMR 2023-2024

Colonial medicine: A tool of empire and its legacies in present-day health disparities

CLAIRE GONG
Staff Writer

In early 2019, a study on the Ebola epidemic from the Harvard School of Public Health presented survey data from the Democratic Republic of Congo and concluded that individuals refused vaccines and formal medical care due to the belief that the virus was not real (Vinck et al., 2019). The findings were immediately propagated by news media and presented the outbreak as a consequence of misguided beliefs and failure to seek care. While the study provides important population-based insight underscoring the harm of misinformation on public health, it is also a microcosm of how literature on health crises in low-income countries (LIMCs) often ignores complex historical factors and power relations that shape the institutional mistrust and healthcare disparities we see today. The context of colonial history, in particular, is crucial for informed analysis of healthcare in LIMCs (Richardson, 2020). Numerous scholars and medical professionals have linked the current disease outbreaks in these regions with the enduring effects of colonial governments who neglected the development of health services for native populations (Farmer, 1996; Pearson, 2018; Richardson, 2019). In fact, a recent 2021 study in the American Economic Review found that health interventions are less effective in areas with a greater historical exposure to colonial health interventions (Lowes & Montero, 2021). This article will employ a longitudinal approach in illustrating the fraught relationship between disease, medicine, and colonialism, delineating how this impacted indigenous peoples, and presenting the rich and complicated history that continues to impinge on health disparities in former colonies today. Through the critical examination of these historical antecedents, this article will ultimately unearth the role of colonialism as a structural determinant of health.

...literature on LIMCs often ignores complex historical factors and power relations that shape the institutional mistrust and healthcare disparities we see today.

The impetus for medical development in the 18th and 19th centuries largely arose from the reality that death and disease were major barriers for the colonial agenda. Novel "tropical" diseases, such as cholera and malaria, were deadly to the new European arrivals. Some scholars go so far as to contend that malaria was "the largest obstacle to colonization" (Bump & Aniebo, 2022). According to records by military physicians, from 1817 to 1838, the average annual mortality

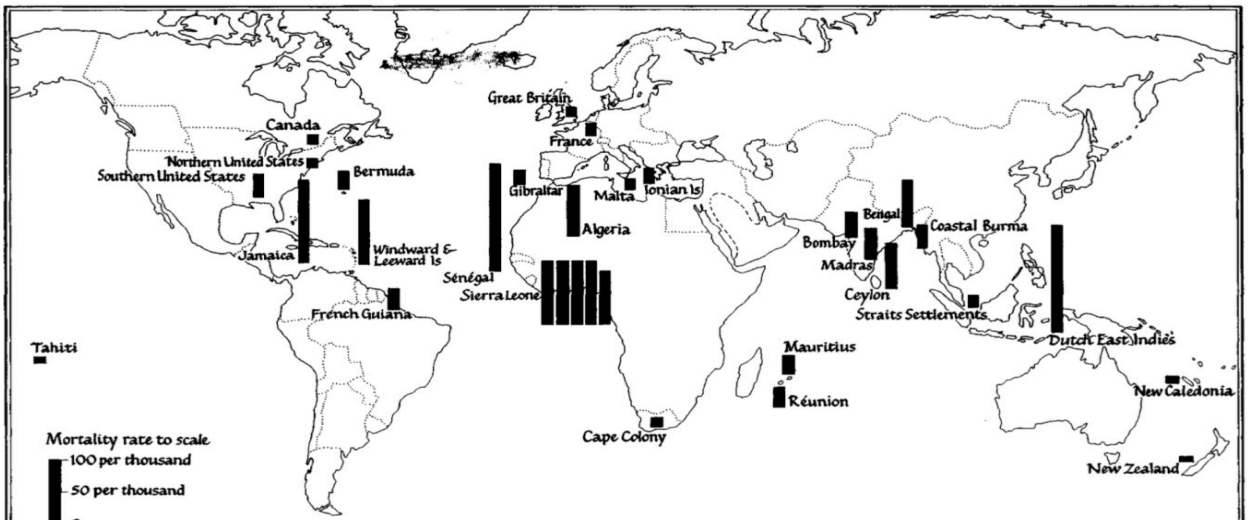

Figure 1. Mortality rates of European troops at the metropole and abroad 1817-1838. (Curtin, 1989)

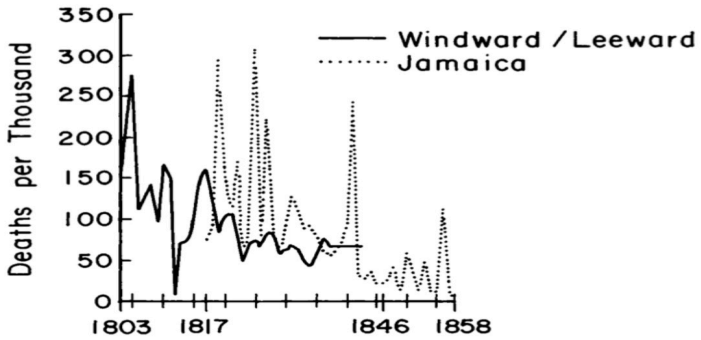

Figure 2. Mortality rates for British troops in Windward and Leeward Islands, and Jamaica, 1803-1858. (Curtin, 1989)

rate was 483 per thousand for European troops in Sierra Leone, where malaria was rampant at the time (Curtin, 1989). Additionally, the relocation cost (percentage change in death rate compared to the rate observed in the metropole) for movement from Britain to the West Indies was 593 percent, 80 percent of which was caused by "tropical fevers" and 15 percent by intestinal diseases.

It is also critical to underscore the fatal diseases brought to the local populations by European settlers. A notable example is the arrival of smallpox in the Americas, carried by European conquistadors, which launched a raging epidemic that tore through the continent in 1775 to 1782. The disease is said to have wiped out 90% of the native American population in Northern Barrens (Hearne, 1968). This widely cited statistic is based on claims made by English explorer Samuel Hearne, who observed and recorded the outbreak. However, a 2012 study placed the number at under 20%, but also acknowledged the limited availability of reliable epidemiological data (Carlos & Lewis, 2012).

Thus, medicine served as a crucial instrument for the advancement of the colonial agenda.

Widespread disease constrained territorial expansion and threatened economic output. Its importance is put simply by Hubert Lyautey, French military official and conqueror of Morocco, "The physician, if he understands his role, is the most effective of our agents of penetration and pacification." (Farmer et al., 2013). That role was not only to maintain the health of colonial troops, but also the enslaved local workforce who propelled the Western economy.

Associated with the significant medical advancements in the 19th century, death rates in colonies began to fall (Curtin, 1989). Previously, relocation costs for Europeans settling in the Tropics increased by upwards of twofold, but with the development of new drugs and more robust public health infrastructure, Europeans were able to advance into regions previously occluded by risks of fatal disease. One such advancement was the introduction of a prophylactic for malaria called quinine, an alkaloid extracted from cinchona bark. In one of the first clinical trials from 1866 to 1868, Quinine and three other cinchona-derived alkaloids achieved cure rates of more than 98% in 3600 patients (Dobson, 2001). A therapeutic triumph, quinine played an indispensable role in enabling the safe occupation and administration of colonies, to the extent that historian Daniel R. Headrick distinguishes the drug as a "tool of empire" (Headrick, 1981). Furthermore, the implementation of public health measures, including immunisation campaigns, water filtration, and sewage disposal, were also important attributes of this period of development and reform that has been dubbed "the great sanitary awakening" (Winslow, 1923, p. 192).

While inhabitants of regions under colonial rule benefited from these Western medical and public health developments, it is reductive to decontextualize this from the targeted agendas that dictated colonial medicine. For example, Joseph Chamberlain, the Secretary of State for the Colonial Office in the United Kingdom, established the London School of Hygiene and Tropical Medicine in 1899, not with the intention of serving the population at large, but in recognition that the health of colonists was essential to the administration and control of the British empire (Greenwood, 2022). In general, Western medicine primarily served European settlers, and was only later extended to the local population under cordon sanitaire policy (Alubo, 2001), which instituted forced administration of vaccines and confinement of locals who were suspected of

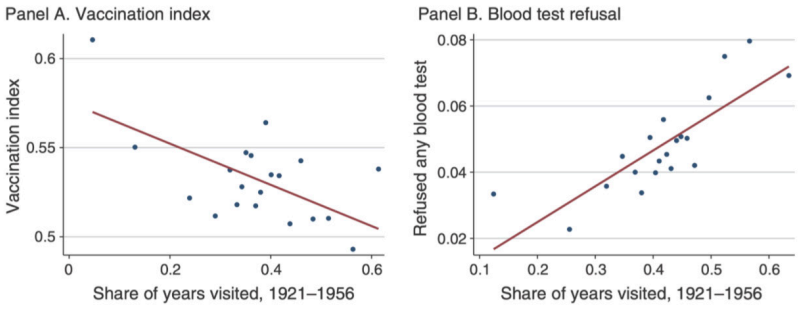

Figure 3. (A) Increased exposure to colonial medical campaigns are negatively correlated with vaccination rates, and (B) positively correlated with refusal of blood test. (Lowes, 2021)

disease in attempt to construct sanitary enclaves for Europeans (Menke et al., 2020). Medical developments were not designed to aid local populations and any improvements in health observed in the group were largely a byproduct of efforts to safeguard European colonists from disease and infirmity — ultimately, to secure the empire.

Colonial medical campaigns were also often disguised under a pretext of saviorism. In congress meetings in 1933, Rabat, Morocco and 1938, Algiers, Algeria, witnesses lauded "the civilizing work of benevolent France in its expansion," and urged colonial powers to "develop the manifestations of modern life, above all from the hygienic point of view" in a region where "everything remained to be done." (Keller, 2007). The colonized were characterized as uncivilized, ignorant, unhygienic, diseased — in need of salvation from White respectability, purity, and altruism.

Colonial medicine was strategically positioned and leveraged to present a scientific basis for racial and ethnic hierarchy. Medical visits served as a means to obtain demographic, behavioral, and biological data on the local population, and were exploited as "crucial instruments for surveillance" (Keller, 2006). The body of empirical evidence was employed in the reinforcement of supremacist ideology — cementing the narrative of non-White individuals being dirty and diseased, ignorant and superstitious, violent and barbarian. Thus, through the authority of science, colonial ideology was reified to indisputable fact and reality. These powerful portrayals and historical antecedents continue to pervade contemporary perceptions and self-perceptions of former colonies. On a larger scale, they inform global power dynamics and resource allocation. Sequestration of medical resources, research, and skilled personnel in Western countries continues to be observed today. While colonial investments in public health infrastructures have benefitted contemporary health (Dell & Olken, 2017; Huillery, 2009), there is also the countervailing force of extractive institutions historically designed for the efficient export of resources to the metropole that continue to impinge on state policies, government attitudes, and economic performance (Acemoglu et al., 2001). Interestingly, these negative impacts have been found to be more prominent in regions where Europeans faced higher mortality rates, often regions with more severe disease environments, due to the heightened need to establish extractive institutions.

Research examining the colonial healthcare inequities that persist to the present is pivotal... into enacting the systemic changes necessary for initiating reparations...

Additionally, a 2021 study on World Bank development projects in the health sector in Central Africa illustrates reduced success in areas with higher exposure to colonial medical campaigns (Lowes & Montero, 2021). The study also analyzed Demographic and Health Surveys and found lower vaccination rates and higher mistrust in medicine (measured by refusal of free, non-invasive blood tests for anemia and HIV) in these areas, controlling for various geographic and individual factors, such as environmental determinants of malaria (e.g. temperature, precipitation), education-level, and wealth. The relationship between colonial experience and elevated levels of mistrust is also corroborated by other literature (Blouin, 2022; Nunn & Wantchekon, 2009; Okoye, 2021). Additionally, mistrust has been identified to primarily stem from internal channels; for example, how severely an individual's ancestors were devastated by colonial experience (Nunn & Wantchekon, 2011). External factors, including deterioration of social, political, and economic structures, contrib-

uted less to levels of mistrust.

The significance of these present-day health disparities and their connection with historical devastations have led scholars to regard colonial experience as a structural determinant of health (Czyzewski, 2011; Ramos et al., 2022; Rodríguez-Díaz, 2020). The colonial past sets newly independent countries in a subordinate position of forced dependency and lack of agency under systemic barriers and adverse living conditions. Therefore, it is essential to historically contextualize the healthcare crises we observe in former colonies and engage in critical scientific inquiry on the enduring effects of colonialism on public health. The scarcity of research in this area can inadvertently reinforce a reductive narrative that implies health crises directly arise from innate culture and beliefs. Epidemics do not form in a vacuum — they are complex and dynamic phenomena that are born at the nexus of historical, geopolitical, social, and biological factors.

Research examining the colonial healthcare inequities that persist to the present is pivotal to building the structural basis and evidence to galvanize institutes and authority into enacting the systemic changes necessary for initiating reparations towards countries that have experienced colonial injustices. This awareness can encourage development of locally specific and accessible medical resources, including implementation of education in cultural competency for physicians, investment in language interpreters, cultural translation of medical materials, and medical research focusing on non-Western countries. Improved patient-centered care, healthcare access, and resource allocation will foster a more trusting relationship between medicine and non-Western populations, and spur progress towards the end-goal of decolonizing medicine. ❧

AUTHOR BIO

Claire Gong is a junior double majoring in Biology and Visual Arts on the pre-dental track. She is interested in how structural and institutional factors perpetuate racial and gender health inequities.

Edited by Claire Zegger, Aastha Bansal, and Dr. Xinhua Chen

Placed by Aastha Bansal

REFERENCES

Acemoglu, D., Johnson, S., & Robinson, J. A. (2001). The Colonial Origins of Comparative Development: An Empirical Investigation. American Economic Review, 91(5), 1369–1401. https://doi.org/10.1257/aer.91.5.1369

Alubo, O. (2001). The promise and limits of private medicine: Health policy dilemmas in Nigeria. Health Policy and Planning, 16(3), 313–321. https://doi.org/10.1093/heapol/16.3.313

Blouin, A. (2022). Culture and Contracts: The Historical Legacy of Forced Labour. The Economic Journal, 132(641), 89–105. https://doi.org/10.1093/ej/ueab031

Bump, J. B., & Aniebo, I. (2022). Colonialism, malaria, and the decolonization of global health. PLOS Global Public Health, 2(9), e0000936. https://doi.org/10.1371/journal.pgph.0000936

Carlos, A. M., & Lewis, F. D. (2012). Smallpox and Native American mortality: The 1780s epidemic in the Hudson Bay region. Explorations in Economic History, 49(3), 277–290. https://doi.org/10.1016/j.eeh.2012.04.003

Curtin, P. D. (Ed.). (1989). The Mortality Revolution and the Tropical World: Relocation Costs in the Early Nineteenth Century. In Death by Migration: Europe's Encounter with the Tropical World in the Nineteenth Century (pp. 1–39). Cambridge University Press. https://doi.org/10.1017/CBO9780511665240.002

Czyzewski, K. (2011). Colonialism as a Broader Social Determinant of Health. The International Indigenous Policy Journal, 2(1), Article 1. https://doi.org/10.18584/iipj.2011.2.1.5

Dell, M., & Olken, B. A. (2017). The Development Effects Of The Extractive Colonial Economy: The Dutch Cultivation System In Java.

Dobson, Sm. (2001). Antimalarial chemotherapy: Mechanisms of action, resistance, and new directions in drug discovery. In Infectious Disease. Humana Press Totowa, NJ.

Farmer, P. (1996). Social inequalities and emerging infectious diseases. Emerging Infectious Diseases, 2(4), 259–269.

Farmer, P., Kleinman, A., Kim, J., & Basilico, M. (Eds.). (2013). Reimagining Global Health: An Introduction.

Greenwood, A. (2022). Diagnosing the medical history of British imperialism. The Lancet, 400(10354), 726–727. https://doi.org/10.1016/S0140-6736(22)01648-8

Headrick, D. R. (1981). The Tools of Empire: Technology and European Imperialism in the Nineteenth Century. Oxford University Press.

Hearne, S. (1968). Journals of Samuel Hearne and Philip Turnor between the years 1774 and 1792. New York : Greenwood Press. http://archive.org/details/journalsofsamuel0000hear

Huillery, E. (2009). History Matters: The Long-Term Impact of Colonial Public Investments in French West Africa. American Economic Journal: Applied Economics, 1(2), 176–215. https://doi.org/10.1257/app.1.2.176

Keller, R. C. (2006). Geographies or power, legacies of mistrust: Colonial medicine in the global present. Historical Geography, 34, 26–48.

Keller, R. C. (2007). Colonial Madness: Psychiatry in French North Africa. University of Chicago Press. http://ebookcentral.proquest.com/lib/emory/detail.action?docID=408213

Lowes, S., & Montero, E. (2021). The Legacy of Colonial Medicine in Central Africa. American Economic Review,111(4), 1284–1314. https://doi.org/10.1257/aer.20180284

Menke, H., Pieters, T., & Menke, J. (2020). How Colonial Power, Colonized People, and Nature Shaped Hansen's Disease Settlements in Suriname. Societies, 10(2), Article 2. https://doi.org/10.3390/soc10020032

Nunn, N., & Wantchekon, L. (2009). The Slave Trade and the Origins of Mistrust in Africa. NBER Working Papers, Article 14783. https://ideas.repec.org//p/nbr/nberwo/14783.html

Nunn, N., & Wantchekon, L. (2011). The Slave Trade and the Origins of Mistrust in Africa. American Economic Review,101(7), 3221–3252. https://doi.org/10.1257/aer.101.7.3221

Okoye, D. (2021). Things fall apart? Missions, institutions, and interpersonal trust. Journal of Development Economics, 148, 102568. https://doi.org/10.1016/j.jdeveco.2020.102568

Pearson, J. L. (2018). Introduction. In The Colonial Politics of Global Health (pp. 1–19). Harvard University Press. https://www.jstor.org/stable/j.ctvckq5xf.4

Ramos, J. G. P., Garriga-López, A., & Rodríguez-Díaz, C. E. (2022). How Is Colonialism a Sociostructural Determinant of Health in Puerto Rico? AMA Journal of Ethics, 24(4), 305–312. https://doi.org/10.1001/amajethics.2022.305

Richardson, E. T. (2019). On the coloniality of global public heath. Medicine Anthropology Theory, 6(4), 101–118. https://doi.org/10.17157/mat.6.4.761

Richardson, E. T. (2020). Epidemic Illusions: On the Coloniality of Global Public Health. The MIT Press. https://doi.org/10.7551/mitpress/12550.001.0001

Rodríguez-Díaz, C. E. (2020). Community Resistance as Public Health Activism in Puerto Rico. American Journal of Public Health, 110(10), 1454–1455. https://doi.org/10.2105/AJPH.2020.305884

Vinck, P., Pham, P. N., Bindu, K. K., Bedford, J., & Nilles, E. J. (2019). Institutional trust and misinformation in the response to the 2018-19 Ebola outbreak in North Kivu, DR Congo: A population-based survey. The Lancet. Infectious Diseases, 19(5), 529–536. https://doi.org/10.1016/S1473-3099(19)30063-5

Winslow, C.-E. A. (1923). The Evolution and Significance of the Modern Public Health Campaign. Yale University Press.

IMAGE REFERENCES

Curtin, P. D. (Ed.). (1989). The Mortality Revolution and the Tropical World: Relocation Costs in the Early Nineteenth Century. In Death by Migration: Europe's Encounter with the Tropical World in the Nineteenth Century (pp. 1–39). Cambridge University Press. https://doi.org/10.1017/CBO9780511665240.002

Lowes, S., & Montero, E. (2021). The Legacy of Colonial Medicine in Central Africa. American Economic Review,111(4), 1284–1314. https://doi.org/10.1257/aer.20180284

Treating the patient, not just the tumor: The role of complementary methods in cancer therapy

KRISHNA SANAKA
Staff Writer

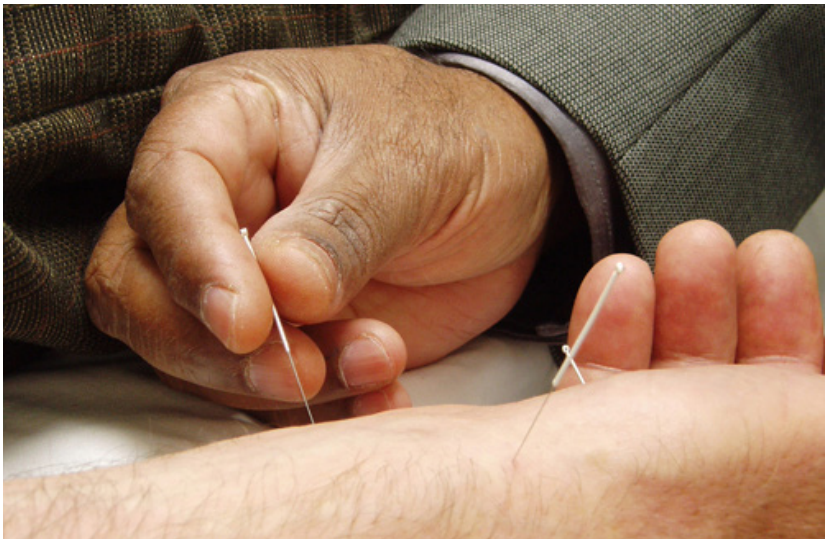

Figure 1. Acupuncture, shown above, involves mechanically or electrically "pricking" patients to affect the neuroendocrine system and reduce pain elsewhere in the body. (Hunter, 2007)

While cancer incidence continues to rise, medical advancements have led to drastic improvements in survival. Since 1991, cancer death rates in the United States have decreased by 33%, resulting in an estimated 3.8 million deaths averted (Siegel et al, 2023). While new therapeutic options and improved detection methods have played a role in this survival benefit, patients with cancer are also increasingly turning to complementary and alternative methods in their treatment plans. An estimated one-third of American patients utilize meditation, yoga, acupuncture, herbal medicine, and supplements (Sanford et al, 2019). Thus, it is important to investigate the role various complementary and alternative interventions play in modern cancer treatment.

Chemotherapy as a first-line treatment for cancer involves the use of systemic medications to kill rapidly dividing tumor cells. Despite its key role in many cancer treatment regimens, chemotherapy causes a variety of side effects including, but certainly not limited to, nausea, vomiting, nutritional deficiencies, hair loss, immunosuppression, nerve damage, and potential for long term organ damage (Altun and Sonkaya, 2018). Pharmacologic interventions to alleviate chemotherapy side effects are often utilized. For example, serotonin inhibitors and corticosteroids have antiemetic properties and are frequently used in the clinical setting (Rao and Faso, 2012). From a complementary medicine perspective, acupuncture is a nonpharmacologic option with potential to relieve chemotherapy-associated nausea and vomiting, cancer-related pain, and other symptoms. This method, based on traditional Chinese medicine, involves placing thin, steel needles at select pressure points across the body to relieve a bothersome symptom (Patel et al, 2020).

Acupuncture may be an effective non-pharmacological option to reduce chemotherapy-induced nausea and vomiting in patients as a sole therapy or as an adjunct to more standard pharmacologic antiemetic practices.

Neuroimaging data shows that acupuncture results in the stimulation of a number of regions in the brain, including the primary and secondary somatosensory, anterior cingulate, prefrontal and insular cortices, amygdala, hippocampus, and hypothalamus (Lu et al, 2009). According to multiple studies, patients receiving acupuncture experienced significantly less nausea on the days of chemotherapy infusions and on subsequent days of the treatment cycle (Lu et al, 2009). Acupuncture may be an effective non-pharmacological option to reduce chemotherapy-induced nausea and vomiting in patients as a sole therapy or as an adjunct to more standard pharmacologic antiemetic practices.

Not only do patients with cancer endure negative side effects related to their therapy, but they also often experience significant mental health concerns with up to 47% of all cancer patients reporting a significant level of distress (Randazzo and Peters,

2016). This distress may be due to fear of cancer-related mortality as well as financial burdens, isolation from friends and family, alterations in lifestyle and more. The rate of depression among cancer patients is estimated at three times that of the general population (Smith, 2015). A number of complementary medicine techniques may be used to treat cancer-related depression and anxiety. Acupuncture may provide improved mental health (Satija and Bhatnagar, 2017). Mindfulness-based meditation, originating in Eastern religious traditions such as Hinduism and Buddhis, involves achieving a state of mind that is aware and in control of the present moment in order to reduce stress and improve overall health (Mehta et al, 2019). Studies have shown that mindfulness-based meditation not only lowers anxiety and depression scores in cancer patients, but it also leads to significant improvements in physical health and the immune response (Mehta et al, 2019).

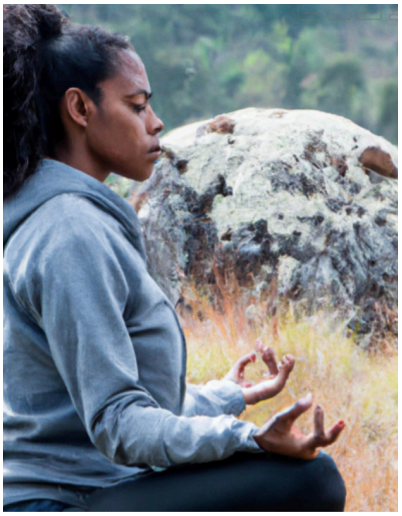

Figure 2. Mindfulness meditation, depicted above, is a practice with extensive history that involves bringing oneself to the present moment in order to alleviate symptoms of anxiety and depression. (Budassi, 2022)

In addition to combating therapy-related side effects and cancer-related depression and anxiety, complementary medicine techniques provide patients with a sense of empowerment. This, in turn, may increase the likelihood a patient completes the standard of care therapy course. Nonadherence to a planned chemotherapy regimen is a significant barrier to improving cancer outcomes. It has been reported that up to one-third of patients who initiate chemotherapy fail to complete more than half of the recommended treatment, which results in worse cancer-specific survival rates (Morris et al, 2007). Chemotherapy nonadherence is also associated with a variety of social factors, including rural geography, low socioeconomic index, and lack of access to high-volume medical professionals (Morris et al, 2007). Addressing therapy nonadherence is clearly a matter of improving cancer outcomes while also closing healthcare disparities among historically vulnerable groups. Complementary medicine interventions may impart an element of choice that helps patients feel a greater level of control over their treatments, potentially improving compliance (Buckner, 2018). Encouraging patients with cancer to pursue adjunctive complementary therapies such as acupuncture, yoga, and meditation, offers them more autonomy over their treatment plan. Studies have shown that when complementary interventions are included, patient adherence to standard medical therapy regimens is improved and direct involvement in disease management is greater (Martin et al, 2005).

Encouraging patients with cancer to pursue adjunctive complementary therapies such as acupuncture, yoga, and meditation, offers them more autonomy over their treatment plan.

Therefore, allowing and even encouraging patients to pursue complementary treatments as an adjunctive to standard of care therapy may be essential in empowering patients. Ultimately, such treatments could significantly improve health outcomes by managing chemotherapy-related side effects, decreasing cancer-related distress, depression, and anxiety, and improving compliance to recommended cancer-directed therapies. ❧

AUTHOR BIO

Krishna is a third year majoring in Anthropology and Human Biology. His interests are the cross-section of public policy and health outcomes, and the potential role of new technologies in healthcare.

Edited by Aastha Bansal Christina Fu, and Dr. Sarah G. Mitchell

Placed by Christina Fu

REFERENCES

Altun İ, Sonkaya A. The Most Common Side Effects Experienced by Patients Were Receiving First Cycle of Chemotherapy. Iran J Public Health. 2018;47(8):1218-1219.

Buckner, C. A., Lafrenie, R. M., Dénommée, J. A., Caswell, J. M., & Want, D. A. (2018). Complementary and alternative medicine use in patients before and after a cancer diagnosis. Current oncology (Toronto, Ont.), 25(4), e275–e281. https://doi.org/10.3747/co.25.3884

Lu, W., Dean-Clower, E., Doherty-Gilman, A., & Rosenthal, D. S. (2008). The value of acupuncture in cancer care. Hematology/oncology clinics of North America, 22(4), 631–viii. https://doi.org/10.1016/j.hoc.2008.04.005

Martin, L. R., Williams, S. L., Haskard, K. B., & Dimatteo, M. R. (2005). The challenge of patient adherence. Therapeutics and clinical risk management, 1(3), 189–199.

Mehta, R., Sharma, K., Potters, L., Wernicke, A. G., & Parashar, B. (2019). Evidence for the Role of Mindfulness in Cancer: Benefits and Techniques. Cureus, 11(5), e4629. https://doi.org/10.7759/cureus.4629

Morris, M., Platell, C., Fritschi, L., & Iacopetta, B. (2007). Failure to complete adjuvant chemotherapy is associated with adverse survival in stage III colon cancer patients. British Journal of Cancer, 96(5), 701–707. https://doi.org/10.1038/sj.bjc.6603627

Patel, M., Urits, I., Kaye, A. D., & Viswanath, O. (2020). The role of acupuncture in the treatment of chronic pain. Best Practice & Research. Clinical Anaesthesiology, 34(3), 603–616. https://doi.org/10.1016/j.bpa.2020.08.005

Randazzo, D., & Peters, K. B. (2016). Psychosocial distress and its effects on the health-related quality of life of primary brain tumor patients. CNS Oncology, 5(4), 241–249. https://doi.org/10.2217/cns-2016-0010

Rao, K. V., & Faso, A. (2012). Chemotherapy-induced nausea and vomiting: optimizing prevention and management. American Health & Drug Benefits, 5(4), 232–240.

Sanford, N. N., Sher, D. J., Ahn, C., Aizer, A. A., & Mahal, B. A. (2019). Prevalence and Nondisclosure of Complementary and Alternative Medicine Use in Patients With Cancer and Cancer Survivors in the United States. Journal of the American Medical Association Oncology, 5(5), 735-737. https://doi.org/10.1001/jamaoncol.2019.0349

Satija, A., & Bhatnagar, S. (2017). Complementary Therapies for Symptom Management in Cancer Patients. Indian Journal of Palliative Care, 23(4), 468–479. https://doi.org/10.4103/IJPC.IJPC_100_17

Siegel, R. L., Miller, K. D., Wagle, N. S., & Jemal, A. (2023). Cancer statistics, 2023. CA: A Cancer Journal for Clinicians, 73(1), 17–48. https://doi.org/10.3322/caac.21763

Smith H. R. (2015). Depression in cancer patients: Pathogenesis, implications and treatment (Review). Oncology letters, 9(4), 1509–1514. https://doi.org/10.3892/ol.2015.2944

IMAGE REFERENCES

Budassi, P. C. (2022, August 3). Mindfulness Meditation [Photograph]. Wikimedia Commons. https://commons.wikimedia.org/wiki/File:Mindfulness_meditation.jpg

Hunter, K. (2007, March 2). Basic Acupuncture [Photograph]. Wikimedia Commons. https://commons.wikimedia.org/wiki/File:Acupuncture1-1.jpg

Flipping the light switch of neurons: Illuminating the discovery and implications of optogenetics

YUNA LEE
Staff Writer

"A major first step, then is to identify the many different types of neurons existing in the cerebral cortex… The ideal signal would be light… This seems rather far-fetched but it is conceivable that molecular biologists could engineer a particular cell type to be sensitive to light in this way" (Crick, 1999).

In a 1999 edition of the Royal Society Journal, Francis Crick, who co-discovered the structure of DNA, suggested the possibility that one could control neural activity with light (Crick, 1999). Once described as "far-fetched", this concept is now the basis for optogenetics- a technique that enables a genetically based, high-temporal resolution method to control neural activity noninvasively. What is particularly exciting about optogenetics is the amount of control and precision it allows researchers to have over defined cell types (Deisseroth, 2010). Previously, electrodes have been used to stimulate or record neural activity, but lacked the specificity offered by optogenetics- using electrodes stimulates all cells at the insertion site, and cannot be used to turn off neurons with precision. With optogenetics, scientists can selectively activate or inhibit specific types of neurons in the brain by using light to control genetically modified proteins called opsins. By inserting genes encoding opsins into particular neurons and then shining light on those neurons, researchers can manipulate their activity with remarkable precision.

The discovery of optogenetics was dependent on several, seemingly unrelated studies conducted by labs across several academic institutions. Francis Crick had introduced the groundbreaking concept of optogenetics within the realm of neuroscience. He envisioned the potential of utilizing light as a tool for precisely manipulating specific neurons, offering a revolutionary approach to understanding the intricacies of the brain. During this period, though the idea was visionary, practical application remained a challenge due to the lack of techniques for integrating photosensitive proteins into neuroscience methodologies (Deisseroth, 2011). Coincidentally, within the scientific community, microbiologists had already made significant progress in understanding photosensitive proteins. Research conducted by Oesterhelt and Stoeckenius in 1971 and further expanded upon by Matsuno-Yagi and Mukohata in 1977 shed light on the existence of these proteins, which played a vital role in regulating ion flow across the plasma membrane in various microorganisms (Oesterhelt and Stoeckenius, 1971; Matsuno-Yagi and Mukohata, 1977; Deisseroth, 2011). This knowledge provided a foundational understanding of the biological basis of optogenetics.

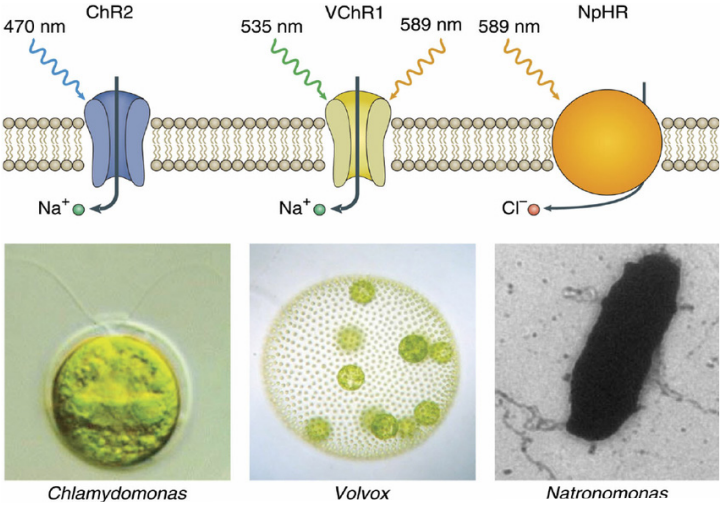

Figure 1. Light-responsive molecules utilized in optogenetics and their corresponding non-vertebrate species. (Farrar et al., 2014)

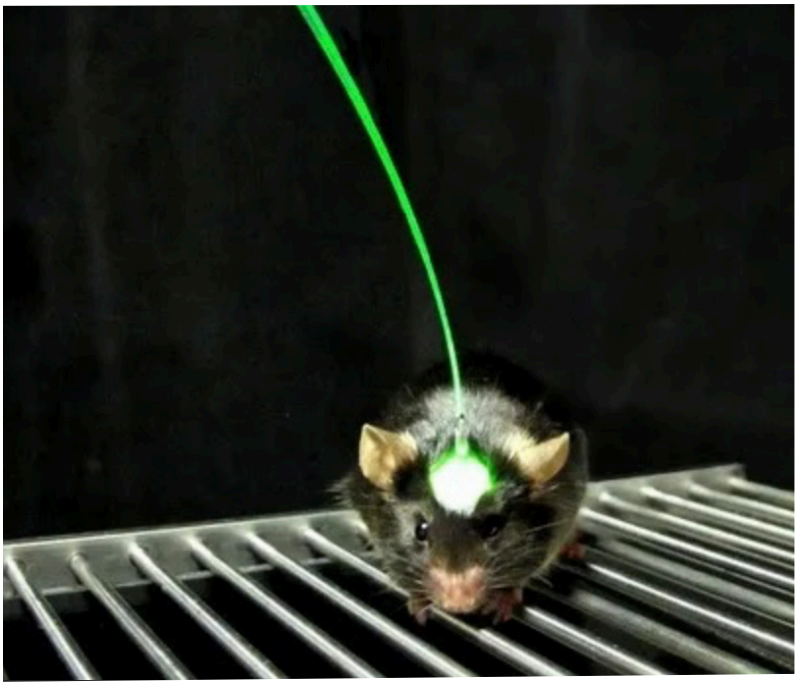

Figure 2. Post-stroke mice brains stimulated using optogenetic technology. (Carr, 2014)

The turning point in the development of optogenetics occurred in 2003 with a pioneering study led by Nagel and colleagues, when they successfully demonstrated the feasibility of expressing microbial opsins, a type of light-sensitive ion channel protein, in non-excitable mammalian cells (Nagel et al., 2003). This breakthrough enabled rapid and precise cell depolarization in response to light stimuli, marking a significant advancement in the field. Building upon Nagel's work, another pivotal study conducted by Boyden and collaborators in 2005 showcased the remarkable efficacy of light in modulating the electrical excitability of neurons (Boyden et al., 2005). Through the expression of microbial opsins in mammalian neurons, they achieved unparalleled spatial and temporal resolution in controlling neural activity. This achievement opened the door to a new era in neuroscience research, offering scientists unprecedented control over neuronal functions with the potential for transformative discoveries. These foundational studies not only illuminated the path for optogenetics but also highlighted the collaborative nature of scientific progress. The collaboration between visionary concepts, biological discoveries, and innovative experimental techniques ultimately propelled optogenetics from a theoretical idea in 1979 to a powerful and transformative tool in neuroscience by the early 2000s.

Through the expression of microbial opsins in mammalian neurons, they achieved unparalleled spatial and temporal resolution in controlling neural activity.

Optogenetics facilitated a new era in neuroscience by enabling precise causal experiments. Initially, when scientists inserted electrodes into animal brains, they observed neurons reflecting specific environmental features, states, or motor movements (Gildenberg, 2009). These observations led to theories about brain functioning, action generation, computation, and information storage. However, the lack of precise tools hindered rigorous testing of these theories until the advent of optogenetics. This technique facilitated gain and loss function experiments, enabling scientists to determine if the activity of specific neurons is necessary and sufficient to explain particular behaviors (Kim et al., 2017). Optogenetic methods have significantly advanced our understanding of a wide array of phenomena in behavior, physiology, and pathology, spanning the domains of sensation, cognition, and action. The emergence of single-component optogenetics as a standard research tool, known for its speed, simplicity, and versatility, played a crucial role in justifying the initiation of large-scale national neuroscience research initiatives such as the BRAIN initiative in 2013 (Deisseroth, 2015). These methods have illuminated the causal roles of specific cell types and projections in both natural and disease-related physiological and behavioral processes, ranging from basic homeostasis to complex cognitive functions. For example, optogenetic techniques have revealed the underlying neuronal mechanisms regulating movement (Petreanu et al., 2009) and identified unexpected bottom-up circuit mechanisms

through which the spinal cord and cerebellum control skilled and voluntary movements (Heffley et al., 2018).

Researchers have also pinpointed patterns of activity in genetically and anatomically defined cells, even when mixed with other cell types, that specifically drive or inhibit fundamental organismal functions such as hunger, thirst, energy balance, respiration, arousal, sleep, and the circadian rhythm (Deisseroth, 2015). For example, a study done on the circadian rhythm used photostimulation to establish a causal relationship between a specific neuron type (Hcrt-producing neurons) to sleep state behaviors of mice (Adamantidis, 2007). Optogenetics has also been extensively applied to the study of primary sensory information transmission, including olfactory, auditory, visual, and tactile processing. A significant development in recent years has been the testing of longstanding and debated models of neural information representation. Using activity-guided expression of microbial opsin genes, researchers have causally identified sparse and distributed population representations (engrams) underlying memory states and the connections among features of these states (Liu et al., 2012). Optogenetic studies have also investigated learning processes in various brain regions, including the ventral striatum, amygdala, and hippocampus. Bypassing the usual pairing of an aversive stimulus with an auditory sensory cue, a study performed a fear conditioning experiment pairing optical control of the LA (lateral amygdala) pyramidal neurons with the sensory cue, finding that the subsequent presentation of the tone produced behavioral fear responses (Johansen et al., 2010). Overall, a common thread in optogenetic research is the identification of specific cell populations or their projections with mechanistic contributions to individual symptom domains, providing causal maps that explain both adaptive and maladaptive states.

Optogenetic techniques have revealed the underlying mechanisms regulating movement & identified unexpected bottom-up circuit mechanisms [that control] skilled and voluntary movements.

In summary, optogenetics' power lies in its ability to selectively activate or inhibit specific neurons with unparalleled precision. This level of control has allowed scientists to unravel the intricacies of various physiological and behavioral processes, ranging from fundamental functions like homeostasis to complex cognitive operations. By manipulating neural circuits with remarkable accuracy, researchers have identified the specific roles of defined cell types and projections in phenomena such as movement regulation, sensory information processing, and learning. Moreover, optogenetics has challenged existing models of neural information representation. Through the manipulation of synaptic plasticity and microcircuit dynamics, scientists have gained new perspectives on memory states and their connections, refining our understanding of learning processes and information flow within the brain. By integrating innovative ideas with biological knowledge and experimental techniques, optogenetics exemplifies the product of collaborative science. As this technology continues to advance, it holds the promise of unlocking further mysteries of the brain, offering not only profound scientific insights but also paving the way for innovative therapies and treatments in the field of neuroscience. ❧

AUTHOR BIO

Yuna Lee is a senior majoring in Neuroscience and Behavioral Biology, and is interested in researching the somatosensory system.

Edited by Neha Bajaj, Zuha Jaffar, and Dr. Zanthia Wiley

Placed by Zuha Jaffar

REFERENCES

Adamantidis, A., Zhang, F., Aravanis, A. et al. Neural substrates of awakening probed with optogenetic control of hypocretin neurons. Nature 450, 420–424 (2007).

Boyden, E., Zhang, F., Bamberg, E. et al. Millisecond-timescale, genetically targeted optical control of neural activity. Nat Neurosci 8, 1263–1268 (2005). https://doi.org/10.1038/nn1525

Crick, F. (1999). The impact of molecular biology on neuroscience. Philosophical Transactions of the Royal Society B, 354(1392), 2021–2025. https://doi.org/10.1098/rstb.1999.0541

Deisseroth, K. (2010). Controlling the Brain with Light. Scientific American, 303(5), 48–55. https://doi.org/10.1038/scientificamerican1110-48

Deisseroth K. Optogenetics. Nat Methods. 2011 Jan;8(1):26-9. doi: 10.1038/nmeth.f.324. Epub 2010 Dec 20. PMID: 21191368; PMCID: PMC6814250.

Deisseroth, K. Optogenetics: 10 years of microbial opsins in neuroscience. Nat Neurosci 18, 1213–1225 (2015). https://doi.org/10.1038/nn.4091

Gildenberg, P. L. (2009b). Neuromodulation. In Elsevier eBooks (pp. 9–20). https://doi.org/10.1016/b978-0-12-374248-3.00003-3

Heffley, W., Song, E.Y., Xu, Z. et al. Coordinated cerebellar climbing fiber activity signals learned sensorimotor predictions. Nat Neurosci 21, 1431–1441 (2018). https://doi.org/10.1038/s41593-018-0228-8

Johansen JP, Hamanaka H, Monfils MH, Behnia R, Deisseroth K, Blair HT, LeDoux JE. Optical activation of lateral amygdala pyramidal cells instructs associative fear learning. Proc Natl Acad Sci U S A. 2010 Jul 13;107(28):12692-7. doi: 10.1073/pnas.1002418107. Epub 2010 Jun 25. PMID: 20615999; PMCID: PMC2906568.

Kim, C. K., Adhikari, A., & Deisseroth, K. (2017b). Integration of optogenetics with complementary methodologies in systems neuroscience. Nature Reviews Neuroscience, 18(4), 222–235. https://doi.org/10.1038/nrn.2017.15

Liu, X., Ramirez, S., Pang, P. et al. Optogenetic stimulation of a hippocampal engram activates fear memory recall. Nature 484, 381–385 (2012). https://doi.org/10.1038/nature11028

Matsuno-Yagi A, Mukohata Y. Two possible roles of bacteriorhodopsin; a comparative study of strains of Halobacterium halobium differing in pigmentation. Biochem Biophys Res Commun. 1977 Sep 9;78(1):237-43. doi: 10.1016/0006-291x(77)91245-1. PMID: 20882.

Nagel G, Szellas T, Huhn W, Kateriya S, Adeishvili N, Berthold P, Ollig D, Hegemann P, Bamberg E. Channelrhodopsin-2, a directly light-gated cation-selective membrane channel. Proc Natl Acad Sci U S A. 2003 Nov 25;100(24):13940-5. doi: 10.1073/pnas.1936192100. Epub 2003 Nov 13. PMID: 14615590; PMCID: PMC283525.

Oesterhelt D, Stoeckenius W. Rhodopsin-like protein from the purple membrane of Halobacterium halobium. Nat New Biol. 1971 Sep 29;233(39):149-52. doi: 10.1038/newbio233149a0. PMID: 4940442.

Petreanu L, Mao T, Sternson SM, Svoboda K. The subcellular organization of neocortical excitatory connections. Nature. 2009 Feb 26;457(7233):1142-5. doi: 10.1038/nature07709. PMID: 19151697; PMCID: PMC2745650.

IMAGE REFERENCES

Carr, J. (2014b, September 16). Optogenetic researchers innovate method to stimulate brain regrowth. The Stanford Daily. https://stanforddaily.com/2014/09/15/optogenetic-researchers-innovate-method-to-stimulate-brain-regrowth/

Farrar, J. (2014, June 20). Gene therapies for inherited retinal disorders. Retrieved from https://www.researchgate.net/figure/Non-vertebrate-light-responsive-molecules-utilized-in-optogenetics-together-with-the_fig3_263289157.

The challenges of diagnosing and treating treatment-resistant depression

ESTHER JUNG
Staff Writer

Currently, about 280 million people in the world are diagnosed with depression, and depression is about 50% more common in women than in men (World Health Organization, 2023). Its symptoms include a depressed mood, anhedonia (a loss of pleasure or interest in activities), poor concentration, disrupted sleep, and more; these symptoms must be present nearly every day for at least 2 weeks to be classified as depressive disorder. However, treatment-resistant depression (TRD) is a diagnosis for patients with depressive disorder whose symptoms do not respond typically to antidepressant medications and/or psychotherapy. Although it is estimated that more than a third of patients treated for depression are treatment-resistant, the official definition of TRD varies from expert to expert, and no consensus remains about how to diagnose TRD as no official definition currently exists in the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 (Pandarakalam, 2018). The most widely accepted definition of TRD is when a patient's depressive symptoms do not improve after being treated with two antidepressants from different classes. However, other experts postulate that TRD may be diagnosed if a patient does not respond to at least four different treatments, including psychotherapy. Since there is no common consensus on how to diagnose TRD, there is no common consensus on how to treat it (Souery et al., 2006). When patients do not respond to certain courses of treatment, what other options do they have left to treat their depression? Medical professionals often recommend combination therapy, which includes combining two different antidepressants, or augmentation therapy, which involves the addition of a non-antidepressant medication to increase, or augment, the effects of another antidepressant the individual is taking. More drastic recommendations include electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), and deep brain stimulation (DBS).

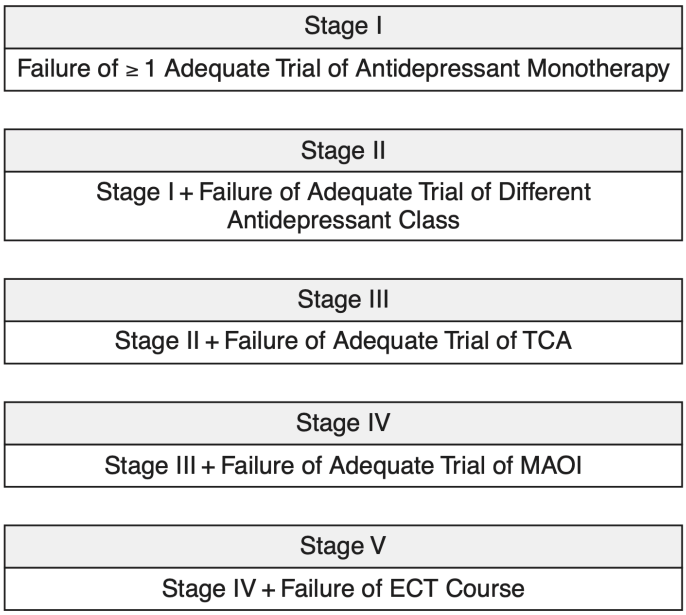

Figure 1. Staging criteria of treatment-resistant depression as a spectrum, rather than one singular diagnosis. (Keller, 2005)

Since there is no common consensus on how to diagnose TRD, there is no common consensus on how to treat it.

Typically, patients with non-treatment-resistant depression are treated with various types of antidepressants. The most common class of antidepressant prescribed is selective serotonin reuptake inhibitors (SSRIs), which work to prolong the neurotransmitter serotonin's effects. Another class of antidepressant is selective serotonin-norepinephrine reuptake inhibitors (SNRIs); these drugs work similarly to SSRIs, but they also block the reuptake of norepinephrine along with serotonin, prolonging the effects of both serotonin and norepinephrine. to last longer. How-

ever, most patients with TRD have demonstrated a resistance to antidepressants, so administering these drugs is typically ineffective in treating depressive symptoms in these patients.

To combat this issue, there exist two pharmaceutical treatments for TRD: combination therapy and augmentation therapy. Combination therapy can be effective by utilizing other less commonly used antidepressants in addition to medications like SSRIs or SNRIs. Monoamine oxidase inhibitors (MAOIs) are one class of antidepressants that have declined in popularity with the continuing increase in the number of available antidepressants (Fiedorowicz & Swartz, 2004). Generally, MAOIs are not widely prescribed due to potential adverse side effects — some of which may be life threatening — along with the added risk for dietary and drug interactions (Thomas et al., 2015). However, multiple studies have demonstrated the efficacy of MAOIs in combination with other antidepressants for the management of TRD (Thomas et al., 2015). Augmentation therapy is another pharmaceutical therapy that works by adding another drug — typically not an antidepressant — to enhance the effects of an antidepressant. For example, some antipsychotics, particularly aripiprazole, have been shown to be particularly effective in augmenting treatment with an SSRI (Philip et al., 2010).

Because there is no official diagnosis for TRD in the DSM-5, estimates of the proportion of patients affected by TRD range anywhere from about one third (Fava & Davidson, 1996) to up to 50% to 60% (Fava, 2003). Clinicians have found some characteristics to be associated with TRD, including symptom severity, suicidality, higher number of lifetime depressive episodes, comorbid anxiety, and anhedonia, symptoms vary from person to person (Kverno & Mangano, 2021). Some clinicians have proposed conceptualizing TRD as existing on a spectrum, "from failure to respond to one standard antidepressant trial, to failure of multiple antidepressant classes or augmentation strategies, to failure of ECT" (Philip et al., 2010). The lack of agreement on TRD's diagnosis has led to inconsistency in TRD research; a 2019 literature review conducted using 260 articles identified that the most common criteria for a diagnosis of TRD required a minimum of two prior treatment failures with confirmation of prior adequate dose and duration. However, the same review found that only 17% of intervention studies enrolled participants that met the most frequently cited criteria for TRD (Gaynes et al., 2019). Although there is a lack of consensus about the number and frequency of treatments an individual must have attempted before being diagnosed with TRD, it appears that a majority of these individuals have attempted treatment with antidepressants.

When pharmacuetical therapies prove ineffective. patients with TRD must turn to more drastic alternatives.

When pharmaceutical therapies prove ineffective, patients with TRD must turn to more drastic alternatives. Electroconvulsive therapy (ECT) is one option that can be effective for patients with TRD. ECT is administered to patients under general anesthesia by electrically stimulating the brain. The electrical currents are passed through multiple electrodes attached to the scalp at precise locations (American Psychiatric Association, n.d.). Transcranial magnetic stimulation (TMS) is also an option for treating TRD; TMS uses magnetic fields, rather than electrical stimulation, with an electromagnetic coil to stimulate specific areas of the brain. However, repetitive TMS is likely not as efficacious as ECT (Xie et al., 2013). The most experimental option to treat TRD is deep-brain stimulation (DBS). This procedure is a neurosurgery that involves implanting electrodes into specific areas of the brain to stimulate them and attaching the electrodes to a battery pack, which is typically implanted under the skin in the upper chest (American Association of Neurological Surgeons, n.d.).

Currently, DBS is most commonly performed to alleviate symptoms associated with movement disorders (e.g., dystonia, essential tremor, and Parkinson's disease), epilepsy, or obsessive-compulsive disorder. Changes in subcallosal cingulate (SCC) activity in the brain have been associated with antidepressant response to a variety of treatments, making the SCC a particular region of interest for TRD patients. Studies done at Emory School of

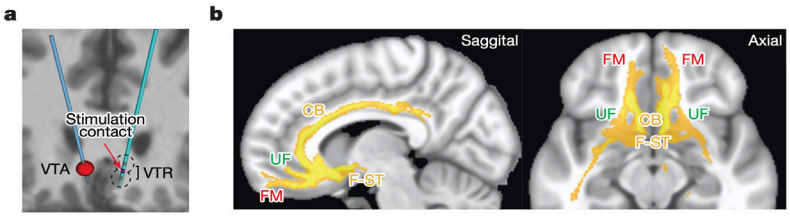

Figure 2. a. Coronal view of a deep-brain stimulation lead targeting the subcallosal cingate in an example patient. The red sphere indicates the volume of tissue activated (VTA). b. Common activation pathway patterns from stimulation at 6 months. (Alagapan et al., 2023)

Medicine using DBS have found that stimulation of the SCC can mediate antidepressant response in TRD patients and lead to a stable decrease in depression symptoms (Riva-Posse et al., 2014). The SCC continues to be the most studied region for DBS in TRD patients, and some outcome data for patients receiving more than 6 years of chronic SCC DBS suggest significant and lasting antidepressant efficacy (Riva-Posse et al., 2014),

However, there are significant consequences and barriers to consider for each treatment option. ECT poses challenges since it must be conducted in a clinic that provides anesthesia and monitoring. ECT is associated with cognitive side effects that can be significant in a minority of patients (Delaloye & Holtzheimer, 2014). Meanwhile, TMS requires daily treatments over several weeks, which can be a logistical barrier for some patients. DBS remains the riskiest option to treat TRD; the treatment is an invasive neurosurgery that is much more experimental than TMS or ECT, as ECT and TMS remain more accessible and less risky than DBS. Furthermore, there are multiple target areas in the brain that could be related to TRD but have yet to be investigated fully. Some other brain regions that have been implicated in depression pathology are the ventral striatum, nucleus accumbens, and the medial forebrain bundle (Riva-Posse et al., 2014). Furthermore, DBS requires very precise mapping of the brain to determine the best stimulation sites for electrodes to be placed; if the electrodes are placed in the wrong position or location, they could have unintended neurological side effects.

Depression is a leading contributor to the global burden of disease, and better understanding its nuances is crucial to alleviating its burden. From 1990 to 2010, depression has advanced worldwide from 15th to 11th place in contributing to years lost due to disability (Delaloye & Holtzheimer, 2014). Depression rates have increased 49.9% from 1990 to 2017, and with that, cases of TRD are likely climbing as well (Liu et al., 2020). As TRD continues to remain overlooked or undiagnosed, patients suffer from disproportionate burdens, escalating medical and mental healthcare costs, clinician time, and personal suffering (Sackeim, 2001). Therefore, it is of crucial importance that clinicians and researchers devote more time to understanding the diagnosis of TRD. As no clear consensus exists for defining adequacy of either dose or duration of treatment when diagnosing TRD, clinicians must urgently agree upon a consensus definition of TRD that addresses how best to specify the number of prior treatment failures and the adequacy of dose and duration (Gaynes et al., 2019). Although promising treatments do exist for patients with TRD, a fundamental lack of research on these treatments still impedes current knowledge of how to treat TRD to ensure that patients do not continue to suffer from mental health symptoms.

AUTHOR BIO

Esther is a fourth year majoring in Neuroscience Behavior and Biology. Her interests are in neurology, psychology, and genetics

Edited by Joseph Park, Madeline Proctor, and Dr. Sarah Caston

Placed by Madeline Proctor

REFERENCES

Deep Brain Stimulation. AANS. (n.d.). https://www.aans.org/en/Patients/Neurosurgical-Conditions-and-Treatments/Deep-Brain-Stimulation

Delaloye, S., & Holtzheimer, P. E. (2014). Deep brain stimulation in the treatment of depression. Dialogues in Clinical Neuroscience, 16(1), 83–91. https://doi.org/10.31887/dcns.2014.16.1/sdelaloye

Fava, M. (2003). Diagnosis and definition of treatment-resistant depression. Biological Psychiatry, 53(8), 649–659. https://doi.org/10.1016/s0006-3223(03)00231-2

Fava, M., & Davidson, K. G. (1996). Definition and epidemiology of treatment-resistant depression. Psychiatric Clinics of North America, 19(2), 179–200. https://doi.org/10.1016/s0193-953x(05)70283-5

FIEDOROWICZ, J. G., & SWARTZ, K. L. (2004). The role of monoamine oxidase inhibitors in current psychiatric practice. Journal of Psychiatric Practice, 10(4), 239–248. https://doi.org/10.1097/00131746-200407000-00005

Gaynes, B. N., Lux, L., Gartlehner, G., Asher, G., Forman-Hoffman, V., Green, J., Boland, E., Weber, R. P., Randolph, C., Bann, C., Coker-Schwimmer, E., Viswanathan, M., & Lohr, K. N. (2019). Defining treatment-resistant depression. Depression and Anxiety, 37(2), 134–145. https://doi.org/10.1002/da.22968

Kverno, K. S., & Mangano, E. (2021). Treatment-Resistant Depression: Approaches to Treatment. Journal of Psychosocial Nursing and Mental Health Services, 59(9), 7–11. https://doi.org/10.3928/02793695-20210816-01

Liu, Q., He, H., Yang, J., Feng, X., Zhao, F., & Lyu, J. (2020). Changes in the global burden of depression from 1990 to 2017: Findings from the global burden of disease study. Journal of Psychiatric Research, 126, 134–140. https://doi.org/10.1016/j.jpsychires.2019.08.002

Pandarakalam J. P. (2018). Challenges of Treatment-resistant Depression. Psychiatria Danubina, 30(3), 273–284. https://doi.org/10.24869/psyd.2018.273

Philip, N. S., Carpenter, L. L., Tyrka, A. R., & Price, L. H. (2010). Pharmacologic approaches to treatment resistant depression: A re-examination for the modern era. Expert Opinion on Pharmacotherapy, 11(5), 709–722. https://doi.org/10.1517/14656561003614781

Riva-Posse, P., Choi, K. S., Holtzheimer, P. E., McIntyre, C. C., Gross, R. E., Chaturvedi, A., Crowell, A. L., Garlow, S. J., Rajendra, J. K., & Mayberg, H. S. (2014). Defining critical white matter pathways mediating successful subcallosal cingulate deep brain stimulation for treatment-resistant depression. Biological Psychiatry, 76(12), 963–969. https://doi.org/10.1016/j.biopsych.2014.03.029

Sackeim H. A. (2001). The definition and meaning of treatment-resistant depression. The Journal of clinical psychiatry, 62 Suppl 16, 10–17.

Souery, D., Papakostas, G. I., & Trivedi, M. H. (2006). Treatment-resistant depression. The Journal of clinical psychiatry, 67 Suppl 6, 16–22.

Thomas, S. J., Shin, M., McInnis, M. G., & Bostwick, J. R. (2015). Combination therapy with monoamine oxidase inhibitors and other antidepressants or stimulants: Strategies for the management of treatment-resistant depression. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 35(4), 433–449. https://doi.org/10.1002/phar.1576

What is electroconvulsive therapy (ECT)?. Psychiatry.org - What is Electroconvulsive Therapy (ECT)? (n.d.). https://www.psychiatry.org/patients-families/ect

World Health Organization. (2023, March 31). Depressive disorder (depression). World Health Organization. https://www.who.int/news-room/fact-sheets/detail/depression

Xie, J., Chen, J., & Wei, Q. (2013). Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for major depression: A meta-analysis of stimulus parameter effects. Neurological Research, 35(10), 1084–1091. https://doi.org/10.1179/1743132813y.0000000245

Xie, J., Chen, J., & Wei, Q. (2013). Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for major depression: A meta-analysis of stimulus parameter effects. Neurological Research, 35(10), 1084–1091. https://doi.org/10.1179/1743132813y.0000000245

IMAGE REFERENCES

Alagapan, S., Choi, K. S., Heisig, S., Riva-Posse, P., Crowell, A., Tiruvadi, V., Obatusin, M., Veerakumar, A., Waters, A. C., Gross, R. E., Quinn, S., Denison, L., O'Shaughnessy, M., Connor, M., Canal, G., Cha, J., Hershenberg, R., Nauvel, T., Isbaine, F., … Rozell, C. J. (2023). Cingulate Dynamics Track Depression Recovery with Deep Brain stimulation. Nature, 622(7981), 130–138. https://doi.org/10.1038/s41586-023-06541-3

Keller M. B. (2005). Issues in treatment-resistant depression. The Journal of clinical psychiatry, 66 Suppl 8, 5–12.

Nanopores: A tool for disease diagnosis and analysis of single biomolecules

ZACH PAIKAN
Events Chair

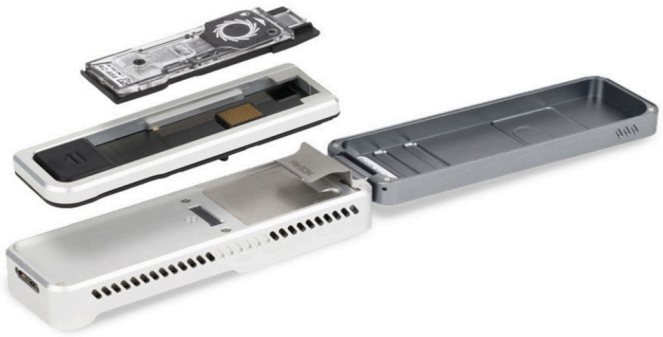

Figure 1. Nanopore chip developed by Oxford Nanopore for DNA sequencing reads. (Oxford Nanopore, 2019)

Single biomolecules, including DNA, RNA, and proteins, have been analyzed and sequenced by the same general methods without variation for more than a generation. Protein analysis is heavily dependent on mass spectrometry, either of the full intact protein or peptide fragments. DNA and RNA analysis involves PCR followed by various sequencing techniques. While these techniques for analysis of single biomolecules have seen substantial improvements in recent times, progress, especially in the domain of proteomics, necessitates exploring new avenues, one of which merely comprises a small hole in a sheet of silica. These small holes, termed nanopores, have the potential to revolutionize our understanding of the genome and proteome while also transforming disease diagnosis and understanding.

The underlying mechanism of analysis by nanopores is relatively simplistic, which allows for broad application of the principles to analysis of various molecules. An ion current flow is induced through nanopores on the surface of a silica sheet upon application of a voltage. Disturbances in this current, caused by any molecule flowing through the nanopore, including ribonucleases and proteins, can be measured and graphed. The magnitude and duration of these aberrations in the ion current is monitored (Dekker, 2007). To apprehend how nanopores could be employed for careful analysis, one must note that the characteristics of a signal are far more nuanced and specific to a type of molecule than might be intuitively reasoned. Based on the exact characteristics of a current disruption, various properties of a sample can be inferred, including polarity, charge, size, and shape (Wen et al., 2021). This principle provides the groundwork for how nanopores might be able to differentiate between molecules, like different amino acids — a small, nonpolar amino acid like glycivne will produce a very different signal from bulky and polar tryptophan, to give an example. The employment of machine learning technology can allow for careful characterization of the nanopore signal specific to an analyte, allowing for development of known standards against which samples can be compared for identification purposes (Taniguchi et al., 2021). Machine learning, with repeated training, can determine all the characteristics of a signal that constitute a specific molecule flowing through a nanopore and rapidly identify the molecule with great accuracy.

These small holes, termed nanopores, have the potential to revolutionize our understanding of the genome.

The construction of nanopore chips is a feat in itself, warranting brief discussion before addressing the applications of this technology in the realm of medicine and analysis of biological specimens. The nanopore workflow is entirely localized on a small chip a few millimeters in diameter. Nanopores themselves may be only a few hundred nanometers wide, and the chemical properties of the channels surrounding the nanopore must be carefully designed with consideration of characteristics like polarity to ensure molecules move through the nanopore properly (Taniguchi et al., 2021). The ability to manufacture such a complex system on the nanoscale is difficult to fathom but allows for high-resolution signal data, enabling the usefulness of the

nanopore.

Nanopore technology can be applied to sequence DNA much like the workflow of PCR followed by various next-generation sequencing techniques. Nanopore sequencing can read up to 880 kb of DNA bases (Delahaye and Nicolas, 2021), and with no need for amplification by PCR or outside labeling (Branton et al., 2008), nanopore technology could significantly reduce the time and cost investment associated with genome sequencing. Nanopore sequencing, however, currently suffers from lower accuracy compared to other next-generation sequencing technologies. Next-generation sequencing products by companies like Illumina have a 99.9% accuracy rate, compared to a 87-98% accuracy rate for PromethION, a popular nanopore-based product from Oxford Nanopore Technologies (Lin et al., 2021). Continued improvement in nanopore technology may bridge this gap and allow for the effective elimination of error in DNA base identification, as seen with other sequencing technologies.

The most intriguing application of the nanopore to DNA, however, lies in the possibility of sequencing beyond the order of DNA bases — unlocking the epigenetic code may be facilitated by nanopore technology. Abnormalities in DNA methylation can be found in a variety of tumors, and proposed assays using nanopores have the potential to diagnose the methylation state of individual nucleotides, similarly without the use of outside labels or amplification (Lin et al., 2021). Modification of RNA nucleotides, which are associated with cancers and neurological diseases, have also been characterized through changes in the ion current signal in the nanopore (Wang et al., 2022). The high specificity associated with nanopore signal blocking can render existing sequencing technology for characterization of nucleic acids anachronistic, especially when detection specificity can be fully optimized by the incorporation of machine-learning technology.

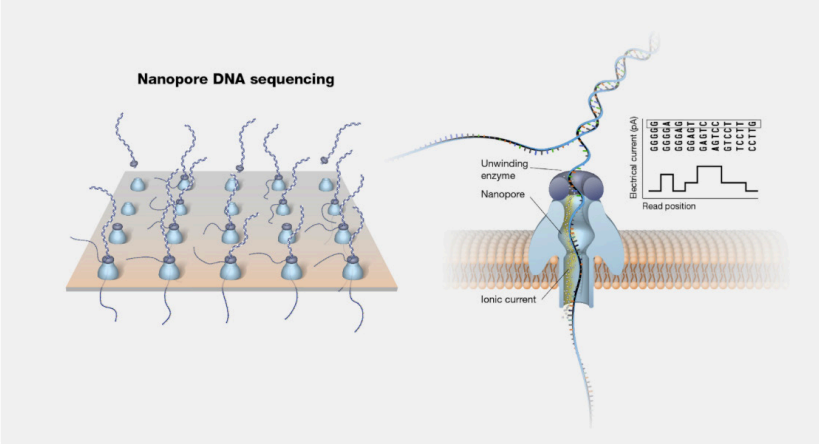

Figure 2. Clear visualization of how biomolecules can be threaded through a nanopore and analyzed. (NHGRI, 2023)

SMPS, or single-molecule protein sequencing, involves identification of the sequence of amino acids in a protein, which is vital for a variety of reasons, including greater physiological understanding of the roles played by specific proteins in the cell and the development of drugs. SMPS currently depends on mass spectroscopy for protein identification, as well as the use of chemical probes to label amino acids. 93.2% of proteins theoretically encoded in the human genome have been detected, but given the sheer number of proteins encoded in our DNA, 1,343 proteins remain completely "missing" (Omenn et al., 2023). In the universe of eukarya, 43.2% of theoretical proteins are part of the so-called "dark proteome," meaning that characterization has not been sufficient in allowing for three-dimensional modeling (Perdigão and Rosa, 2019). Identification of lower-abundance proteins in the cell is difficult using mass spectroscopy, and characterization of post-translational modifications and alternative splicing of DNA to produce new forms of proteins are lacking (Alfaro et al., 2021). While various chemical probes exist for more reactive amino acids like cysteine and lysine, many less reactive amino acids are not able to be labeled. The development of reactions that attach unique and identifiable probes selectively to a single amino acid provides extraordinary challenge, and the devel-

Continued improvement in nanopore technology may bridge this gap and allow for the effective elimination of error in DNA base identification.

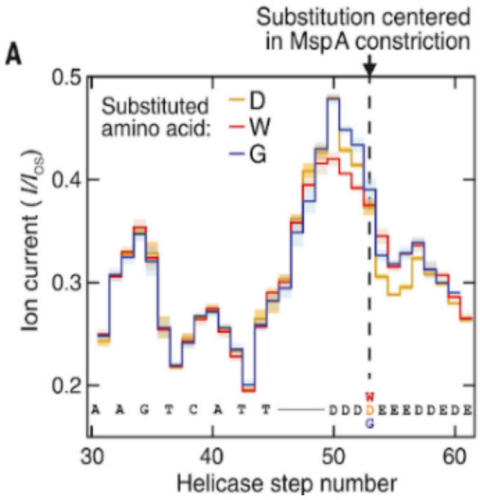

Figure 3. Graph of the ion current demonstrating slight changes in signal upon single amino acid substitution (aspartic acid, tryptophan, or glycine). (Brinkerhoff et al., 2021).

opment of these bioconjugation methods is high-impact work; the development of a methionine probe a few years ago was perceived as a significant discovery (Lin et al., 2017).

While various research groups are working to develop probes for selective enrichment of all amino acids, nanopores could allow for SMPS without enrichment. If the resolution of the ion current through a nanopore is sufficiently high, the unique structure and electronics of each amino acid could be discerned as a peptide is threaded through the nanopore (Hu et al., 2021). The upshot could be immediate protein sequencing and identification of all twenty amino acids, with nanopore protein sequencing being as facile as DNA assays. Such expansive SMPS with the nanopore is mostly theoretical, although identification of single amino acid substitutions in peptide has already been accomplished. Substitution of aspartic acid with tryptophan or glycine produced a noticeable change in the current through the nanopore (Brinkerhoff et al., 2021). Shortly following this work, a group was able to design a nanopore capable of discriminating all twenty amino acids with 98.6% accuracy, as well as the post-translational modifications of methylation, acetylation, glycosylation, and phosphorylation, with the assistance of a machine-learning algorithm, made possible by high signal resolution (Wang et al., 2023). 50-90% of human proteins have undergone at least some form of post-translational modification (PTM), and these PTMs are essential for biological function and can serve as markers for cancer and other diseases (Doyle and Mamula, 2001). While peptides were fully digested into constituent amino acid residues to make this work possible, the rate at which nanopore technology is improving will enable larger proteomics applications in the future.

The rate at which nanopore technology is improving will enable larger proteomics applications in the future.

The ability to differentiate proteins as they move through the nanopore additionally has applications in disease diagnosis. Many existing tests to diagnose pathogens involve blood or tissue cultures and test results are only delivered a few days later. Nanopore-based diagnoses, however, can be returned in as little as six hours, enabling prompt prescription of targeted antibiotics to improve patient outcomes (Zhang et al., 2023). The improper prescription of antibiotics due to the difficulties associated with characterizing the pathogen causing an infection has continued to plague the medical world, yet nanopores provide a potential for swift pathogen identification. The COVID-19 pandemic provided ample opportunity for improvement of disease diagnosis methods, and the incorporation of the nanopore into these techniques is not surprising. PCR, currently considered the most effective method for detection of SARS-CoV-2 proteins, involves the amplification of viral RNA, which can then be easily detected. Current nanopore diagnosis, which does not require any amplification, surprisingly has a similar time-cost relative to PCR. With that said, PCR suffers from false negative results owing to the lower sensitivity of the assay. Nanopores are capable of detecting much smaller amounts of viral genetic material and therefore exhibit far greater sensitivity. Empirically, a study in Wuhan found that nanopores were able to detect 96.5% of positive cases, far outpacing the less-sensitive PCR, only identifying 80.2% of cases classified as positive (Li

et al., 2022). The utilization of nanopores for pathogen identification has broad scope, and the diagnosis of COVID-19 is a good proof of concept for the real-world applicability of the nanopore, with the potential to improve patient outcomes through higher specificity in diagnosis and faster test return times.

The theoretical scope of the nanopore's impact can be summarized with a single word: detection. Whether it be DNA, RNA, or a protein, any molecule can be threaded through a nanopore with the blocking of the ion current producing a distinctive signal, which through advanced analysis techniques incorporating artificial intelligence and high resolution signals, can rectify various limitations in genomics, proteomics, and disease diagnosis.

Given the sheer pace at which nanopore technology has advanced, a future in which amino acid PTMs, epigenetic modifications, the sequence of DNA bases, and the pathogens causing a disease can all be accurately perceived through a nanopore-based workflow in less than a few hours is likely fast approaching. ❧

AUTHOR BIO

Zach is a second year majoring in Biology. His interests are in internal medicine, specifically surgical cardiology.

Edited by Madeline Proctor, Joseph Park, and Dr. Muhammad Azeem

Placed by Joseph Park

REFERENCES

Alfaro, J. A., Bohländer, P., Dai, M., Filius, M., Howard, C. J., Van Kooten, X. F., Ohayon, S., Pomorski, A., Schmid, S., Aksimentiev, A., Anslyn, E. V., Bedran, G., Cao, C., Chinappi, M., Coyaud, E., Dekker, C., Dittmar, G., Drachman, N., Eelkema, R., … Joo, C.. (2021). The emerging landscape of single-molecule protein sequencing technologies. Nature Methods, 18(6), 604–617. https://doi.org/10.1038/s41592-021-01143-1

Branton, D., Deamer, D. W., Marziali, A., Bayley, H., Benner, S. A., Butler, T., Di Ventra, M., Garaj, S., Hibbs, A., Huang, X., Jovanovich, S. B., Krstic, P. S., Lindsay, S., Ling, X. S., Mastrangelo, C. H., Meller, A., Oliver, J. S., Pershin, Y. V., Ramsey, J. M., … Schloss, J. A.. (2008). The potential and challenges of nanopore sequencing. Nature Biotechnology, 26(10), 1146–1153. https://doi.org/10.1038/nbt.1495

Brinkerhoff, H., Kang, A. S., Liu, J., Aksimentiev, A., & Dekker, C. (2021). Multiple rereads of single proteins at single–amino acid resolution using nanopores. Science, 374(6574), 1509–1513. https://doi.org/10.1126/science.abl4381

Dekker, C.. (2007). Solid-state nanopores. Nature Nanotechnology, 2(4), 209–215. https://doi.org/10.1038/nnano.2007.27

Delahaye, C., & Nicolas, J.. (2021). Sequencing DNA with nanopores: Troubles and biases. PLOS ONE, 16(10), e0257521. https://doi.org/10.1371/journal.pone.0257521

Doyle, H. A., & Mamula, M. J. (2001). Post-translational protein modifications in antigen recognition and autoimmunity. Trends in Immunology, 22(8), 443–449. https://doi.org/10.1016/s1471-4906(01)01976-7

Hu, Z., Huo, M., Ying, Y., & Long, Y.. (2021). Biological Nanopore Approach for Single-Molecule Protein Sequencing. Angewandte Chemie International Edition, 60(27), 14738–14749. https://doi.org/10.1002/anie.202013462

Li, X., Li, C., Du, P., Li, S., Yu, L., Zhao, Z., Liu, T., Zhang, C., Zhang, S., Zhuang, Y., Dong, C., & Ge, Q. (2022). Rapid and accurate detection of SARS coronavirus 2 by Nanopore Amplicon sequencing. Frontiers in Microbiology, 13. https://doi.org/10.3389/fmicb.2022.735363

Lin, B., Hui, J., & Mao, H.. (2021). Nanopore Technology and Its Applications in Gene Sequencing. Biosensors, 11(7), 214. https://doi.org/10.3390/bios11070214

Lin, S., Yang, X., Jia, S., Weeks, A. M., Hornsby, M., Lee, P. S., Nichiporuk, R. V., Iavarone, A. T., Wells, J. A., Toste, F. D., & Chang, C. J. (2017). Redox-based reagents for chemoselective methionine bioconjugation. Science, 355(6325), 597–602. https://doi.org/10.1126/science.aal3316

Omenn, G. S., Lane, L., Overall, C. M., Pineau, C., Packer, N. H., Cristea, I. M., Lindskog, C., Weintraub, S. T., Orchard, S., Roehrl, M. H. A., Nice, E., Liu, S., Bandeira, N., Chen, Y.-J., Guo, T., Aebersold, R., Moritz, R. L., & Deutsch, E. W.. (2023). The 2022 Report on the Human Proteome from the HUPO Human Proteome Project. Journal of Proteome Research, 22(4), 1024–1042. https://doi.org/10.1021/acs.jproteome.2c00498

Perdigão, N., & Rosa, A.. (2019). Dark Proteome Database: Studies on Dark Proteins. High-throughput, 8(2), 8. https://doi.org/10.3390/ht8020008

Taniguchi, M., Minami, S., Ono, C., Hamajima, R., Morimura, A., Hamaguchi, S., Akeda, Y., Kanai, Y., Kobayashi, T., Kamitani, W., Terada, Y., Suzuki, K., Hatori, N., Yamagishi, Y., Washizu, N., Takei, H., Sakamoto, O., Naono, N., Tatematsu, K., … Tomono, K.. (2021). Combining machine learning and nanopore construction creates an artificial intelligence nanopore for coronavirus detection. Nature Communications, 12(1). https://doi.org/10.1038/s41467-021-24001-2

Wang, Y., Zhang, S., Jia, W., Fan, P., Wang, L., Li, X., Chen, J., Cao, Z., Du, X., Liu, Y., Wang, K., Hu, C., Zhang, J., Hu, J., Zhang, P., Chen, H.-Y., & Huang, S.. (2022). Identification of nucleoside monophosphates and their epigenetic modifications using an engineered nanopore. Nature Nanotechnology, 17(9), 976–983. https://doi.org/10.1038/s41565-022-01169-2

Wang, K., Zhang, S., Zhou, X., Yang, X., Li, X., Wang, Y., Fan, P., Xiao, Y., Sun, W., Zhang, P., Li, W., & Huang, S.. (2023). Unambiguous discrimination of all 20 proteinogenic amino acids and their modifications by nanopore. Nature Methods. https://doi.org/10.1038/s41592-023-02021-8

Wen, C., Dematties, D., & Zhang, S.-L.. (2021). A Guide to Signal Processing Algorithms for Nanopore Sensors. ACS Sensors, 6(10), 3536–3555. https://doi.org/10.1021/acssensors.1c01618

Zhang, Y., Lu, X., Tang, L. V., Xia, L., & Hu, Y. (2023). Nanopore-targeted sequencing improves the diagnosis and treatment of patients with serious infections. mBio, 14(1). https://doi.org/10.1128/mbio.03055-22

IMAGE REFERENCES

Brinkerhoff, H., Kang, A. S., Liu, J., Aksimentiev, A., & Dekker, C. (2021). Multiple rereads of single proteins at single–amino acid resolution using nanopores. Science, 374(6574), 1509–1513. https://doi.org/10.1126/science.abl438

Nanopore DNA Sequencing. (2023). National Human Genome Research Institute. Retrieved October 2, 2023, from https://www.genome.gov/genetics-glossary/Nanopore-DNA-Sequencing.

Oxford Nanopore chip for DNA/RNA sequencing. (2019). Oxford Nanopore. Retrieved October 2, 2023, from https://nanoporetech.com/about-us/news/oxford-nanopore-launches-flongle-rapid-smaller-dnarna-sequencing-tests-any.

The *Wolbachia* Method: An environmentally sustainable way to reduce disease transmission

ANITA OSURI
Staff Writer

Zika: Microcephaly defects. Chikungunya virus: Potential chronic arthritis. These have been pressing headlines seen in recent news. With global rises in temperatures causing rise in mosquito reproduction and survivability, news coverage has reported on mosquito borne viruses and failures in known disease mitigation methods including vaccine deployment and insecticide treatment; as well as lack of sustainability and self-sustaining quality in known approaches. As we look towards more effective solutions, the *Wolbachia* method has emerged as a strong contender with its possibility of limiting the spread of infectious diseases such as Dengue Fever, heartland virus, and Zika from the crux of the issue. This article will describe the critical need for solutions that mitigate spread of infectious diseases at the human-animal interface; the mechanism of the Wolbachia method including its effectiveness, and future directions for this science.

Importance of Limiting the Spread of Mosquito-Borne Viruses

Rising temperatures and changes in seasonal patterns have caused mosquito borne diseases transmission to increase, especially for endemic diseases such as chikungunya, Zika, malaria, and yellow fever (Allgoewer, 2022). In fact, it is estimated that approximately 390 million people are infected each year with dengue, and many more affected with Zika and yellow fever (World Mosquito Program, 2023). Zika is a virus mainly found in tropical Africa, Southeast Asia, and the Pacific Islands (Center for Disease Control, 2019). It presents with minor symptoms of headaches, fever, and joint pain, but can also lead to more serious consequences such as microcephaly (smaller head size), Guillain-Barre syndrome (damage to the nervous system), and meningoencephalitis (Shariff et al., 2023). The virus is not only spread by an increased number of mosquitoes, the vector of transmission, but also through sexual contact, breastfeeding, and blood transfusions (Huy et al., 2019).

Dengue fever is mainly found in the Americas, Southeast Asia, and Western Pacific regions with an estimated 3.9 billion people at risk of infection (World Health Organization, 2023). Dengue can lead to "fever, nausea, vomiting, skin rash … and in severe cases, shock and death" (Lun et al, 2022). Regions with the highest disease prevalence also tend to be underserved areas due to less established industrial sanitation systems, leading to more standing bodies of water where mosquitoes breed. In addition, decreased healthcare infrastructure leads to increased spread and long term consequences from the illness because there are not enough healthcare personnel or technologies to assist patients to make a full recovery. This leads to an additional burden on the healthcare system and more disease transmission. Thus, the increase in arboviral spread has disproportionate effects on underserved populations (World Health Organization, 2023).

Mechanism of the Wolbachia Method

Scientists introduced the *Wolbachia* Method in the early 2010s in an effort to examine whether this tiny bacteria could potentially be the sustainable weapon to fight the infectious disease surges caused by temperature fluctuations. *Wolbachia* was originally discovered in reproductive tissues of *Wolbachia pipientis* mosquitoes, and later found to lead to numerous infections via cytoplasmic incompatibility (Guruprasad et al., 2014). The cytoplasmic incompatibility can best be explained as a process where the "Wolbachia infection renders males sterile when they mate with uninfected females, but not infected females [rescue mating]" (Chen et al., 2020). Specifically within *Aedes Aegypti* mosquitoes that spread dengue and chikungunya viruses, their replication is inhibited with the *Wolbachia* bacteria. The *Wolbachia* strain *w*Melpop has been shown to delay mortality of Drosophila melanogaster flies by protecting against RNA strain viruses. Introducing *Wolbachia* *w*albB strain into *Ae. aegypti* vector reduces proliferation of the dengue virus by altering the

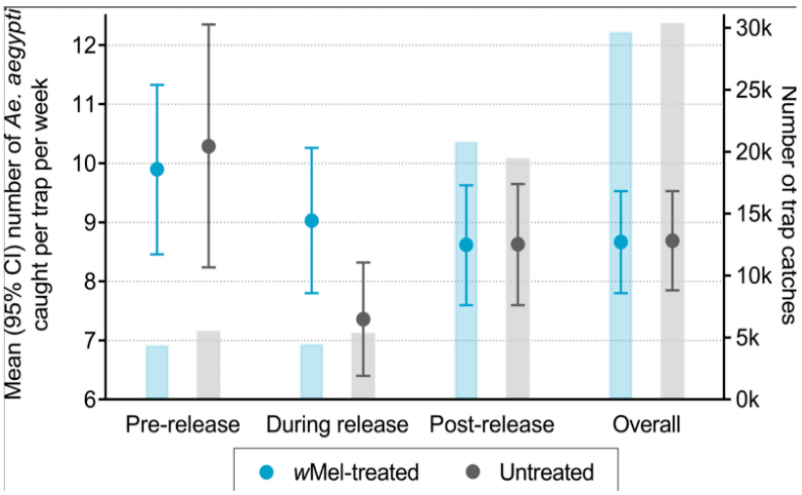

Figure 1: Number of Ae. aegypti trap catches pre-release, during release, and post-release. The bars represent the amount of mosquitoes captured using the BG-sentinel trap. (Tantowijoyo et al., 2022).

"extrinsic incubation period of dengue virus" (Guruprasad et al., 2014).

The World Mosquito Program, a not-for-profit group of companies owned by Monash University, currently runs one of the largest programs specifically for deploying *Wolbachia* infected mosquitoes into the field worldwide. Currently, the World Mosquito Program has deployed Wolbachia in Oceania (New Caledonia [Mont-Dore and Dumbéa]), Americas (Brazil [Petrolina and Campo Grande], Colombia [Aburrá Valley]), and Asia (Vietnam [Thu Dau Mot and My Tho], Indonesia [Yogyakarta], Laos [Vientiane]), and is currently receiving government approval for many more deployments worldwide (World Mosquito Program, 2023).

Feasibility and Effectiveness

The idea of introducing an unfamiliar bacteria into a species where it does not already inhabit led to much controversy when the *Wolbachia* Method was first introduced. However, after reviewing field data demonstrating immense effectiveness of the method, many of these doubts were halted. According to the program, in 2022 they reached the milestone of protecting 10 million people living in 12 countries where the *Wolbachia* Method was implemented. In other cities where the technology has been deployed such as Bello, Medellín and Itagüí, dengue incidence has declined 94-97% compared to the pre-release period (World Mosquito Program, 2023).

There was a 77% reduction in dengue incidence in Wolbachia infected areas compared to those without treatment.

As evidence of the effectiveness of the method, in Yogyakarta, Indonesia, there was a parallel non-blinded cluster randomized control trial, where 12/24 clusters in Yogyakarta , Indonesia were randomly chosen to receive Wolbachia deployments, with all other dengue prevention strategies remaining constant. After the release of the *Wolbachia* infected mosquitoes, the overall number of mosquitoes captured had increased due to reproductive hindrance from cytoplasmic incompatibility (Anders et al., 2018). In Figure 1, the bars represent the amount of mosquitoes captured using the BG-sentinel trap. After adjusting for the wet/dry season, there was an average of 4 traps/km2 for treated Wolbachia clusters and 5 traps/km2 for untreated clusters during pre-release. Compared to post-release, there was an average of 16 traps/km2 and 15 traps/km2 respectively. This demonstrates that *Wolbachia* treated mosquitoes are easier to capture and therefore control the population due to reproductive hindrance. In turn, there was a 77% reduction in dengue incidence and an 86% reduction in dengue hospitalizations in *Wolbachia* infected areas compared to those without treatment.

Alternative solutions

Other alternative solutions to the *Wolbachia* Method include insecticide spraying, Sterile Insect Technique (SIT), vaccination, and more. However, these potential solutions are neither self sustaining, nor completely effective. For instance, insecticide spraying must be done consistently, damages the environment and may have limited effect on *Aedes aegypti* mosquitoes due to immunity. In addition, SIT is a technique where irradiation (gamma rays & X-rays) are used to sterilize male mosquitoes so they cannot reproduce. There needs to be more research done

	Sustainability	Effectiveness	Scalability	Affordability	Current Use
WMP Wolbachia Method	Self-sustaining	Only need to release mosquitoes once	Scale of cities/hundreds of kilometers	Affordable, one time	In 14 countries
Insecticide Spraying	Not self-sustaining	Constant reapplication	Scale of towns/cities	Expensive, continuous application	In most countries highly affected
Sterile Insect Technique (SIT)	Not self-sustaining	Constant reapplication	No published evidence	Expensive, continuous application	Piloted in 5 countries
Genetic Modification	Not self-sustaining	Depends on specific method	Up to several square kilometers	Expensive, continuous application	Used in Brazil

Figure 2: Analysis of sustainability, effectiveness, scalability, affordability, and current use of proactive methods affecting mosquitoes spreading infectious disease. Adapted from World Mosquito Program chart (World Mosquito Program, 2023).

to confirm whether it is effective, as it is not very cost-effective and requires a large number of male mosquitoes to be captured and later sterilized. This process must also be continually done. Lastly, vaccination is a solution that should be used in combination with these other methods. The main challenge for vaccines for mosquito-borne viruses is that many of them have serotypes that often cannot be covered completely by one vaccine. For instance, dengue fever has four different serotypes and chikungunya has three different strains (European Centre for Disease Prevention and Control, 2023). Viruses such as dengue have extremely fast mutation rates, leading to a multitude of variants, leading to an almost impossibility to have a vaccine that completely covers these bases. Vaccines also tend to be extremely costly and underserved communities often are the last to receive these vital supplies. Therefore, taking a preventative approach in combination with a proactive approach is often recommended by epidemiologists. These potential solutions and factors to consider are summarized in Figure 2.

Despite these major advances in science with the *Wolbachia* self-sustaining bacteria, there are some limitations. Scientists have brought up the concern about *Wolbachia* resistant mosquitoes. ThewMel and wAlbB strains of *Wolbachia* only provide partial protection against severe dengue or other viruses. For instance, after feeding *Wolbachia* treated mosquitoes blood from affected patients, infection was detected in the abdomen (53-61%) and saliva (6-12%) (Edenborough et al., 2021). These statistics were determined to be relatively high compared to what the World Mosquito Program claims is "self sustaining". In addition, the Wolbachia method is of unequal nature as it mainly protects against dengue serotypes 2,3,4 and less for DENV-1 (Edenborough et al., 2021). Another concern is the large cost of infecting mosquitoes with the *Wolbachia* bacteria, but this argument has often been shut down because of the self-sustaining aspect of the method. In fact, *Wolbachia* has been found to be sustained in a community for decades due to the limited changes in wMel strain and mitochondrial genomes in *Ae. aegypti* (Ross et al., 2022).

Conclusion

Overall, the *Wolbachia* method is a novel way to sustainably reduce mosquito-borne viral transmission worldwide. There are numerous advantages and evidence of its effectiveness through field trials, although there are drawbacks that need to be addressed. In the context of the other biotechnological methods to reduce viral transmission, it is crucial to continue investigating the other solutions such as SIT to see potential combination solutions. For instance, *Wolbachia* could be used in combination with vaccination programs or insecticides. Ultimately, more research must be conducted on this topic and it will require the collaboration of numerous stakeholders worldwide such as governments, scientists, and local health leaders to raise awareness about mosquito-borne infectious diseases. ❧

AUTHOR BIO

Anita is a second-year Anthropology & Human Biology major with a minor in Quantitative Sciences. She is passionate about mitigating healthcare inequities and new sustainable biotechnologies .

Edited by Neha Bajaj, Zuha Jaffar, and Dr. Judy Gichoya

Placed by Zuha Jaffar

REFERENCES

ALLGOEWER, K. (2022). Determinants of public interest in emerging and re-emerging arboviral diseases in Europe: A spatio-temporal analysis of cross-sectional time series data. J Prev Med Hyg, 63(4). https://doi.org/10.15167/2421-4248/jpmh2022.63.4.2736

Anders, K. L., Indriani, C., Ahmad, R. A., Tantowijoyo, W., Arguni, E., Andari, B., Jewell, N. P., Rances, E., O'Neill, S. L., Simmons, C. P., & Utarini, A. (2018). The awed trial (applying Wolbachia to eliminate dengue) to assess the efficacy of Wolbachia-infected mosquito deployments to reduce dengue incidence in Yogyakarta, Indonesia: Study protocol for a cluster randomised controlled trial. Trials, 19(1). https://doi.org/10.1186/s13063-018-2670-z

Annual Review 2022. World Mosquito Program. (n.d.-a). https://www.worldmosquitoprogram.org/en/wmp-annual-review-2022

Centers for Disease Control and Prevention. (2019, October 7). Overview on Zika. Centers for Disease Control and Prevention. https://www.cdc.gov/zika/about/overview.html#:~:text=Zika%20virus%20was%20first%20discovered,Asia%2C%20and%20the%20Pacific%20Islands

Chen, H., Zhang, M., & Hochstrasser, M. (2020). The Biochemistry of Cytoplasmic Incompatibility Caused by Endosymbiotic Bacteria. Genes (Basel), 11(8). https://doi.org/10.3390/genes11080852

Edenborough, K. M., Flores, H. A., Simmons, C. P., & Fraser, J. E. (2021). Using wolbachia to eliminate dengue: Will The virus fight back? Journal of Virology, 95(13). https://doi.org/10.1128/jvi.02203-20

Factsheet about Chikungunya. European Centre for Disease Prevention and Control. (2017, June 12). https://www.ecdc.europa.eu/en/chikungunya/facts/factsheet#:~:text=There%20are%20three%20major%20genetically,to%20the%20Americas%20in%202013

Guruprasad, N. M., Jalali, S. K., & Puttaraju, H. P. (2014). Wolbachia-a foe for mosquitoes. Asian Pacific Journal of Tropical Disease, 4(1), 78–81. https://doi.org/10.1016/s2222-1808(14)60319-4

How our method compares. World Mosquito Program. (n.d.-b). https://www.worldmosquitoprogram.org/en/learn/how-our-method-compares

Huy, B. V., Hoa, L. N., Thuy, D. T., Van Kinh, N., Ngan, T. T., Duyet, L. V., Hung, N. T., Minh, N. N., Truong, N. T., & Chau, N. V. (2019). Epidemiological and clinical features of dengue infection in adults in the 2017 outbreak in Vietnam. BioMed Research International, 2019, 1–6. https://doi.org/10.1155/2019/3085827

Lun, X., Wang, Y., Zhao, C., Wu, H., Zhu, C., Ma, D., Xu, M., Wang, J., Liu, Q., Xu, L., & Meng, F. (2022). Epidemiological characteristics and temporal-spatial analysis of overseas imported dengue fever cases in outbreak provinces of China, 2005–2019. Infectious Diseases of Poverty, 11(1). https://doi.org/10.1186/s40249-022-00937-5

Mosquito-borne diseases. World Mosquito Program. (n.d.-c). https://www.worldmosquitoprogram.org/en/learn/mosquito-borne-diseases#:~:text=While%20the%20mosquito%20may%20not,Zika%2C%20chikungunya%20and%20yellow%20fever

Ross, P. A., Robinson, K. L., Yang, Q., Callahan, A. G., Schmidt, T. L., Axford, J. K., Coquilleau, M. P., Staunton, K. M., Townsend, M., Ritchie, S. A., Lau, M.-J., Gu, X., & Hoffmann, A. A. (2022). A decade of stability for WMEL Wolbachia in natural aedes aegypti populations. PLOS Pathogens, 18(2). https://doi.org/10.1371/journal.ppat.1010256

Shariff, S., Kantawala, B., Hamiidah, N., Yadav, T., Nazir, A., & Uwishema, O. (2023). Zika virus disease: An alarming situation resurfacing on the Radar – a short communication. Annals of Medicine & Surgery, 85(10), 5294–5296. https://doi.org/10.1097/ms9.0000000000001183

Tantowijoyo, W., Tanamas, S. K., Nurhayati, I., Setyawan, S., Budiwati, N., Fitriana, I., Ernesia, I., Wardana, D. S., Supriyati, E., Arguni, E., Meitika, Y., Prabowo, E., Andari, B., Green, B. R., Hodgson, L., Rancès, E., Ryan, P. A., O'Neill, S. L., Anders, K. L., … Simmons, C. P. (2022). Aedes aegypti abundance and insecticide resistance profiles in the applying Wolbachia to eliminate dengue trial. PLOS Neglected Tropical Diseases, 16(4). https://doi.org/10.1371/journal.pntd.0010284

World Health Organization. (n.d.). Dengue and severe dengue. World Health Organization. https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue#:~:text=Dengue%20(break%2Dbone%20fever),body%20aches%2C%20nausea%20and%20rash

IMAGE REFERENCES

Tantowijoyo, W., Tanamas, S. K., Nurhayati, I., Setyawan, S., Budiwati, N., Fitriana, I., Ernesia, I., Wardana, D. S., Supriyati, E., Arguni, E., Meitika, Y., Prabowo, E., Andari, B., Green, B. R., Hodgson, L., Rancès, E., Ryan, P. A., O'Neill, S. L., Anders, K. L., … Simmons, C. P. (2022). Aedes aegypti abundance and insecticide resistance profiles in the applying Wolbachia to eliminate dengue trial. PLOS Neglected Tropical Diseases, 16(4). https://doi.org/10.1371/journal.pntd.0010284

World Mosquito Program?

Direct primary care: A solution to the complexity of American healthcare?

EMILY BUSH
Staff Writer

Figure 1. A comprehensive study of 116 DPCs estimated average monthly prices based on average highs and lows of monthly fees, visit fees, and enrollment fees. (Eskew and Klink, 2015)

Today, modern medicine seems to be constantly improving and expanding. and disease screening rates relative to other countries (Gunja et. al, 2023). However, in many respects the modern American healthcare system is also costly and flawed. Studies have shown that the U.S. ranks last compared to other high income countries in healthcare access and quality, while ranking at the top for per capita expenditures (Rice et. al, 2013). Additionally, the United States is the only high-income country that does not provide universal healthcare coverage for citizens, which can create challenges for low-income and uninsured individuals. Complex insurance policies can create an overwhelming landscape for patients to navigate. For some doctors, the best solution to the difficulties imposed by the healthcare system comes in the form of direct primary care (DPC), where payment for health insurance is established directly between doctors and patients without insurance company involvement. Though DPC shows promise in promoting physician-patient relationships and upholding the rights of the patient, whether it is a feasible solution to the challenges posed by the healthcare system must be more deeply investigated. In considering a doctor's ethical obligations to their patients as well as the complex landscape of American healthcare, it can be argued that DPC provides a promising solution; however, DPC also has community context-dependent limitations that must be understood and addressed to achieve its full potential.

Though less individualized, community-based advocacy programs have the power to impact the community on a larger scale than the doctor-patient relationship alone.

The physician has a direct duty to care for their patients and makes a commitment to beneficence and non-maleficence in their career. Implicit within this commitment is an ethical duty to act in the best interests of the patient, which includes ensuring a patient receives the care they need. A crucial component is patient advocacy, which the Patient Advocate Certification Board defines as "a professional who provides services to patients and those supporting them who are navigating the complex healthcare continuum" (What is a patient advocate?, n.d.). However, in many contexts, patient advocacy is limited beyond the exam room, and both resources and time are limited for physicians in our healthcare system. Furthermore, it can be argued that doctors have a social responsibility to look after their patients in ways beyond treatment, promoting awareness of determinants of a patient's health, and advocating for their well-being beyond the exam room.

The WashU Institute for Public Health asserts that "to be a physician means [to come] from a somewhat privileged space," and therefore it becomes possible for physicians to "leverage their influence" beyond the traditional scope of patient treatment to address other circumstances impacting an individual's health as well as their larger community (Luft 2017). Dr. Leanne Luft of the University of British Columbia adapts the definition

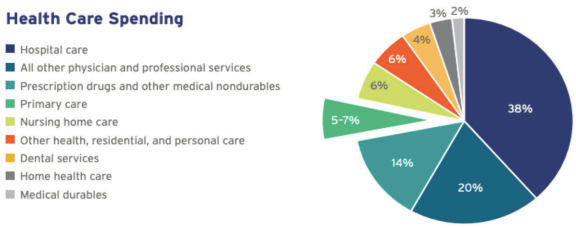

Figure 2. The majority of healthcare spending in the U.S. is directed towards hospital care, while primary care is one of the lowest portions. (Jabbarpour et. al, 2019)

of patient advocacy to encompass "action by a physician to promote those social, economic, educational, and political changes that ameliorate the suffering and threats to human health and well-being that he or she identifies through his or her professional work and expertise" (Luft 2017). She outlines the importance of self-aware physicians who take time to consider how a patient's social circumstances may impact their experiences and challenges in seeking healthcare.

Patient advocacy is divided into two planes, the first being individual patient advocacy, which operates at the patient-physician level and encompasses the physician addressing a patient's immediate medical and social health needs. Community-based advocacy is the other essential component to improving the healthcare system. Though less individualized, community-based advocacy programs have the power to impact the community on a larger scale than the doctor-patient relationship alone. Establishment of DPCs involves patient advocacy on the community level by providing treatment with the aim to increase physician-patient interaction, accessibility, affordability, and care quality.

An approach centered around patient advocacy makes for better-informed and better quality physicians. However, American physicians and patients must also coexist in an increasingly complex healthcare landscape that complicates the goal of patient advocacy. The third-party payment system often "insulates" both patients and physicians from the staggering realities of healthcare costs. Insurance companies often restructure payments such that extremely costly tests end up yielding the same copay, or cost to the patient, as inexpensive tests (Engineering a Learning Healthcare System, 2011). Dr. Rita Redberg of the University of San Francisco states that "when … asked about the prices of the tests [physicians] order …, [they] rarely know what the tests cost. In an academic medical center, the costs of testing and new technology are invisible because doctors are removed from the payment system and insulated from the cost of healthcare" (Engineering a Learning Healthcare System, 2011). This becomes an even greater issue when considering the implementation of new technologies and medications in the hospital system. Although many are considered of better quality and accuracy than older technology, they also carry a higher price tag that drives up costs for patients.

Thus, doctors and patients alike are impacted in great measure by the influence of insurance policies on the healthcare system.

Thus, doctors and patients alike are impacted in great measure by the influence of insurance policies on the healthcare system. A possible solution to this challenge is direct primary care. Primary care physicians charge patients a periodic fee to cover the expenses of providing care, and any additional fees for visits do not exceed the value of the periodic fee (Eskew and Klink, 2015). The typical third-party role that insurance companies play in the healthcare landscape is eliminated, and the result is more affordable primary care for the patient with reduced paperwork and increased time for physicians to spend engaging in direct patient care. Other benefits of the DPC model include increased access to required care and increased time spent between physician and patient, leading to higher quality care, and reduced overhead and administrative costs. One study of 141 DPC practices nationwide found that the vast majority (82%) have cost information readily available online, making transparency and commitment to affordability a much clearer goal than profit-driven incentives of insurance companies (Wu, 2010). These qualities of DPC practice strongly support the goal of patient advocacy and work to reduce the challenges patients face.

However, DPC practices often correlate with reduced patient loads. One study found that the typical 2500 patient load was downsized to a few hundred

in the DPC model, thus reducing accessibility to healthcare (Doherty 2015). However, this seems much more to be a feature of a relatively new model rather than a permanent fixture in DPC organization, especially as proven by the emergence of multisite DPCs in the past two decades. Corporate entities like Iora Health and paladina Health have overall patient panels of tens of thousands (Wu, 2010). As the DPC practice model continues to grow and garner attention, it can be expected that these numbers will increase as more sites become established and new corporations are founded with similar goals to expand the DPC model to a wider population.

Growth of the DPC model also has the potential to produce a greater emphasis on primary care infrastructure in the American healthcare system. American physicians like Dr. Barbara Starfield have argued that creating a more robust primary care infrastructure can create more equitable health outcomes among American citizens (Fleming, 2011). By creating more opportunities for Americans to receive primary care, such as screenings and checkup visits, the costs incurred upon citizens and the healthcare system by preventable diseases, including diabetes, heart disease, or stroke, can be greatly reduced. Support for such a line of reasoning is also evidenced by European countries like the Netherlands, UK, and Germany, all of which have made strengthening of primary care a core policy goal. Potential benefits of a strong primary care foundation include a longitudinal physician-patient relationship, lower barriers to access, and ability to coordinate care across a more comprehensive range of services. One study published in Family Practice found that longitudinal primary care significantly reduced hospitalizations due to preventable conditions (van Loenen et. al, 2014). Considering the evidence in favor of strengthened primary care systems, the establishment of DPCs provides a potential for improved patient outcomes.

There is also the concern that DPCs are exclusionary to patients who cannot afford to pay out of pocket in full, despite reduced fees. While accessibility is certainly an area that must be improved upon with the DPC model, its structure alone does not preclude lower-income patients from taking part. One of the greatest challenges posed to low-income patients is the buildup of costs that accompany a lack of quality primary care and consequent expensive treatments for otherwise treatable conditions. In 2019, the two largest contributors to healthcare costs in the U.S. were hospital care, at 38% of total expenditures, and prescription drugs, comprising 20% of spending (Jabbarpour, 2019). Primary care comprised 5-7% of total spending. When considering the benefits resulting from emphasized primary care, it is reasonable to consider that allocating a greater proportion of resources towards primary care could reduce the high costs incurred by hospitalizations, expensive surgeries, and pharmaceutical treatments. Furthermore, while some DPC fees certainly create a cost barrier considering the expectation to pay in full, many new practices are emerging with the primary intent to improve accessibility to the model. Access Healthcare Direct, a DPC practice now with over 800 clinic locations, is providing primary care coverage through subscription fees and doctor's visits with highly reduced rates, as low as $25 per month and $5 to see a physician in 2015 (Huff, 2015). With models such as these emerging, there is great potential for DPC to extend to populations who need affordable coverage most.

One study... found that longitudinal primary care significantly reduced hospitalizations due to preventable conditions.

The DPC model is nowhere near perfect yet. Only a small proportion of primary care practices follow this model, and though it has been suggested to reduce rates of physician burnout, the healthcare field has yet to develop an expanded model that is compatible with the rest of the existing system. Healthcare coverage beyond primary care, for instance, often still must fall under insurance coverage, and thus can leave the patient at higher risk for other out-of-pocket charges (Doherty, 2015). However, models of DPC that support high patient panels and lowered costs of care directly uphold the commitments doctors make to accessible, quality care that deepens the physician-patient relationship and supports the patient's right to viably receive primary and preventive

uphold the commitments doctors make to accessible, quality care that deepens the physician-patient relationship and supports the patient's right to viably receive primary and preventive healthcare. The landscape of the current healthcare system is vast and complex, but with directed efforts on the part of the physician to consider how they can best support and advocate for their patients in their practice, American healthcare can be headed in a better direction. ❧

AUTHOR BIO

Emily is a third year majoring in Neuroscience Behavior and Biology. Her interests are in neurodegenerative diseases and intersdisciplinary medical topics.

Edited by Advaita Krishnan, Siya Malhotra, and Dr. Zanthia Wiley

Placed by Siya Malhotra

REFERENCES

Cleveland State University Ohio. (n.d.). What is a patient advocate?. What is a Patient Advocate? https://health.csu hio.edu/continuing-education/what-patient-advocate

Doherty, R. (2015, December 15). Assessing the Patient Care Implications of "Concierge" and Other Direct Patient Contracting Practices: A Policy Position Paper From the American College of Physicians. ACP Journals. https://doi.org/10.7326/M15-0366

Eskew, P. M., & Klink, K. (2015, November 1). Direct primary care: Practice distribution and cost across the nation. American Board of Family Medicine. https://www.jabfm.org/content/28/6/793.short

Fleming, C. (2011, June 13). Remembering Barbara Starfield: A primary care champion. https://www.healthaffairs.org/content/forefront/remembering-barbara-starfield-primary-care-champion

Gunja, M., Gumas, E., & Williams, R. (2023, January 31). U.S. health care from a Global Perspective, 2022: Accelerating spending, worsening outcomes. U.S. Health Care from a Global Perspective, 2022 | Commonwealth Fund. https://www.commonwealthfund.org/publications/issue-briefs/2023/jan/us-health-care-global-perspective-2022

Huff, C. (2015, January 1). New practice model evolves: "direct care." ACP Internist. https://acpinternist.acponline.org/clinical_information/journals_publications/acp_internist/2015/01/practice.htm

Jabbarpour, Y. (2019, July). Investing in primary care - primary care collaborative. Thepcc.org. https://thepcc.org/sites/default/files/resources/pcmh_evidence_report_2019_0.pdf

Luft, L. M. (2017, June 30). The essential role of physician as advocate: How and why we pass it on. Canadian medical education journal. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5661729/

Redberg, R. F., Stead, W., Chase, M., & Deutschendorf, A. (2011). Healthcare system complexities, impediments, and failures. Institute of Medicine (IOM). https://www.ncbi.nlm.nih.gov/books/NBK61963/

Rice, T., Rosenau, P., Unruh, L., & Barnes, A. (2013, May 1). United States of America: Health System Review. Health systems in transition. https://pubmed.ncbi.nlm.nih.gov/24025796/

van Loenen, T., van den Berg, M. J., Westert, G. P., & Faber, M. J. (2014, September 12). Organizational aspects of primary care related to avoidable hospitalization: A systematic review. OUP Academic. https://academic.oup.com/fampra/article/31/5/502/539081

IMAGE REFERENCES

Eskew, P., & Klink, K. (2015). Average Monthly Cost of DPCs. jabcm.org. Journal of the American Board of Family Medicine. Retrieved October 25, 2023, from https://www.jabfm.org/content/jabfp/28/6/793/F2.large.jpg.

Jabbarpour, Y., Greiner, A., Jetty, A., Coffman, M., Jose, C., & Peterson, S. (2019). Health Care Spending. Patient-Centered Primary Care Collaborative. Retrieved October 25, 2023, from https://thepcc.org/sites/default/files/resources/pcmh_evidence_report_2019_0.pdf.

Machine to molecule: Piezo signaling in alveolar physiology

GRACE WARD
Staff Writer

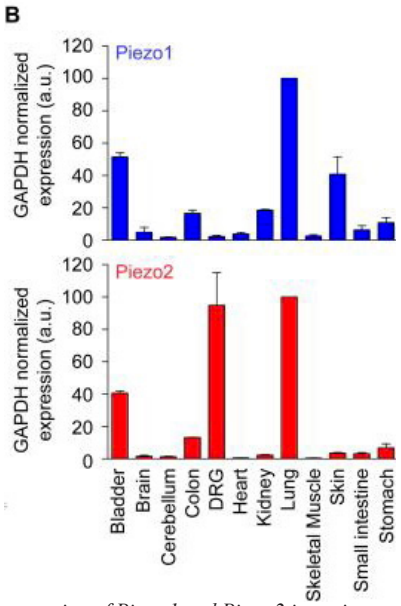

Figure 1. Relative mRNA expression of Piezo 1 and Piezo 2 in various murine tissue types demonstrrates a high level of expression of both channels in lung tissue. (Coste et al., 2010)

Mechanotransduction, the process by which cells translate mechanical stimuli into chemical signals, is pivotal to the body's ability to detect somatic sensations such as touch and pain and its ability to maintain homeostasis in tissues exposed to mechanical stress. The Piezo family, a group of mechanically sensitive calcium ion channels discovered in 2010, is known to be one of the most prominent players in mechanotransduction. Despite the recency of their discovery, Piezo1 and Piezo2 already have a vast array of known functions in a wide variety of tissues and contexts. For one, Piezo channels are predominantly expressed in the respiratory tract, and Piezo1 is known to play a significant role in regulating mechanical stress in alveoli, tiny sacs in the lungs in which gas exchange occurs. As such, this review seeks to understand the function of Piezo channels, especially Piezo1, in mechanical cellular signaling within the context of alveolar physiology.

Piezo1 functions in the cellular repsonse of stretch and shear stress (the force associated with imposed stress that is parallel to the cell surface) (Lai et al., 2022).

Coste et al. discuss their identification of a family of mechanosensitive cation channels known as the Fam38, or Piezo, channels (Coste et al., 2010). The family, named after the Greek word "píesh" (pressure), consists of Piezo1, which is implicated in a wide variety of cellular functions, and Piezo2, which is largely involved in somatosensation (touch/pain sensation and interoception). In mice, both Piezo1 and Piezo2 constitutive knockouts result in early death (embryonic or natal, respectively), demonstrating their necessity for normal physiological function (Volkers et al., 2015). Mechanically, the channels are activated via lateral membrane tension. That is, conformational change in the plasma membrane surrounding the channel (for instance, the 'flattening' of the membrane that might occur when the cell is stretched) causes the channel to open, allowing for the flow of Ca2+ ions (Lin et al., 2019).

Our understanding of Piezo2, which is principally expressed in dorsal root ganglia (DRG) and pulmonary neuroepithelial cells (Figure 1), is relatively focused on its primary role in touch and pain sensation (Nonomura et al., 2017; Volkers et al., 2015). However, studies on Piezo1 have uncovered a diverse array of functions and downstream targets, including endothelial stability, bladder volume regulation, and red blood cell morphology. As such, it is generally understood that Piezo1 functions in the cellular response of stretch and shear stress (the force associated with imposed stress that is parallel to the cell surface),

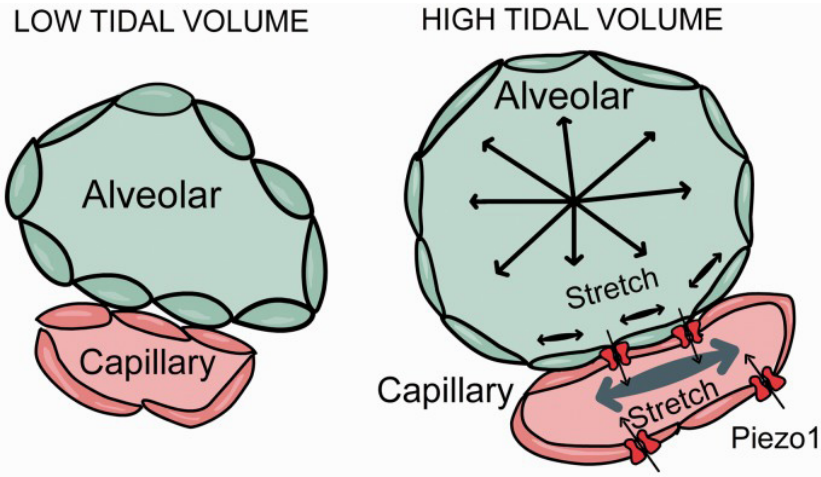

Figure 2. Alveolar epithelial (green) and pulmonary endothelial (red) cellls experience mechanical stress in the form of stretch during inhalation (high tidal volume). (Zhong et al., 2018)

but scientists have yet to fully uncover the extent of its role in various organs and tissues (Lai et al., 2022).

Coste et al. further found that lung tissue has the highest relative mRNA expression (raw mRNA expression normalized by the expression level of a gene that is always expressed, like GAPDH) of both members of the Piezo family, indicating that the channels may be important players in lung physiology (Figure 1). The primary function of the lungs is gas exchange, which, at the macroscopic level, occurs via cyclical filling and emptying of air in the lungs. On a smaller scale, gas crosses the blood-gas barrier by traveling through alveolar epithelial and endothelial cells, which line the alveolar space and surrounding blood vessels, respectively (Novak et al., 2021). Upon investigating Piezo expression in various pulmonary cell types, Nonomura et al. found that Piezo2 is almost exclusively expressed in pulmonary neuroepithelial cells, suggesting a role in neuronal stretch signaling and further confirming Piezo2's identity as a sensory/neuronal signaling factor (Nonomura et al., 2017). On the other hand, Liang et al. (2019), among other groups, detected that Piezo1 is primarily expressed in the alveolar epithelium, and Zhong et al. (2018) indicate Piezo1 expression in alveolar endothelial cells.

The surface area of the alveolar endothelium and epithelium increases by 25% during normal breathing, accounting for the cyclical stretch of these cells (Zhong et al., 2018).

Alveoli are surrounded by two types of epithelial cells. Type I alveolar cells (ATIs) are squamous cells that partially make up the barrier through which gas exchange occurs. Type II alveolar cells (ATIIs) release surfactant (a lubricant that relieves surface tension) and regenerate ATIs. Surrounding the epithelium is the parenchyma/interstitium, mainly made up of extracellular matrix (ECM) and other connective tissues (Novak et al., 2021). The ECM helps maintain alveolar architecture during inhalation and exhalation while also exerting further mechanical input on surrounding cells (Deng et al., 2020). Beyond the pulmonary interstitium are endothelial cells, through which gas exchange with the bloodstream occurs. Like epithelial cells, endothelial cells are subject to mechanical stressors from changes in alveolar volume, such as stretch and shear force (Novak et al., 2021). In fact, the surface area of the alveolar endothelium and epithelium increases by 25% during normal breathing, accounting for the cyclical stretch of these cells (Zhong et al., 2018).

These results indicate that much of the structure (and accordingly the function) of alveoli and their surrounding architecture is heavily informed by a host of mechanical and physical inputs. These environmental demands of cells and tissues in the lungs are particularly unique due to the constant mechanical stress exerted on epithelial and endothelial cells by fluctuating alveolar volume during breathing (Figure 2). As such, alveolar cells must be equipped to respond to this constant homeostatic stress accordingly. Among other mechanisms, Piezo channels play an important role in regulating this stress.

Piezo2 channels expressed in the airway play an essential role in the Hering–Breuer mechanoreflex by sensing lung overinflation and regulating tidal volume (the amount of air that normally leaves/enters the lungs) (Nonomura et al., 2017). However, the

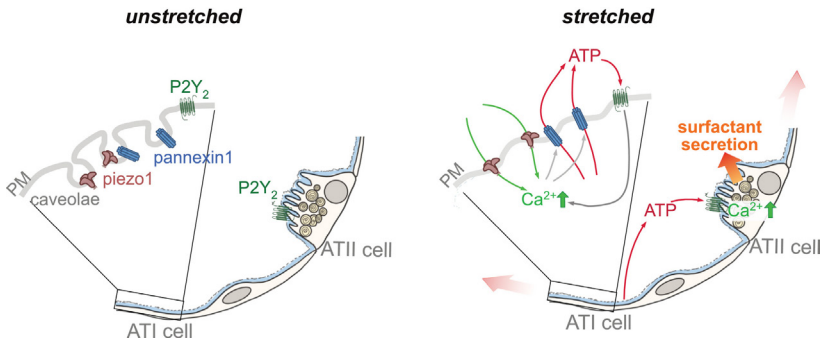

Figure 3. Mechanism of Piezo1-associated purinergic signaling and surfactant production and localization of Piezo1 in caveolae, as proposed by (Diem et al., 2020).

expression of Piezo1 in various alveolar cell types possibly indicates further Piezo-mediated regulation of inspiratory stress. First, an in vitro study demonstrates a functional relationship between ATI Piezo1 expression and surfactant production, which is visually represented in Figure 3. ATI plasma membranes are characterized by a type of invagination called caveolae, which are implicated in mechanosensation. The study finds that Piezo1 tends to colocalize in the plasma membrane with caveolin-1, the protein responsible for caveolae formation. Scientists suggest that these caveolae may flatten when the cell undergoes mechanical tension to expand membrane surface area. This conformational change could account for the lateral tension that activates caveolae-localized Piezo1 channels. The study elucidates that stretch-induced Ca2+ influx via Piezo1 triggers a signaling cascade that ultimately leads to the production and release of adenosine triphosphate (ATP) from ATIs. This purinergic signal ultimately results in the release of surfactant from ATIIs (Diem et al., 2020). Since surfactant decreases surface tension and reduces stress on pulmonary epithelial cells, this finding demonstrates a central role of Piezo1 signaling in maintaining healthy alveolar integrity.

Further studies suggest Piezo1 involvement in epithelial proliferation and barrier integrity. Epithelial cells, such as ATIs and ATIIs, are turned over or regenerated at incredibly high rates. However, due to their function as barriers, epithelial cells undergo a process called extrusion when they die, which coordinates cell division with cell death in order to preserve the epithelial barrier. In kidney epithelium, Piezo1 activation was shown to be associated both with extrusion during epithelial crowding as well as stretch-induced proliferation (Gudipaty et al., 2017). Piezo1-mediated extrusion is also demonstrated in colon epithelium and epidermis (Eisenhoffer et al., 2012). It is posited that these opposing functions of Piezo1 depend on the nature and location of channel activation. While this phenomenon has not been examined specifically in alveolar epithelium, Piezo1 is heavily expressed in lung tissue, which is approximately 99% ATIs and ATIIs (Crandall & Matthay, 2001). It is likely that Piezo1 plays a similar homeostatic role in alveoli. Along these lines, Piezo1 activation has been connected with shedding of junction molecules and growth factors, which may be associated with similar effects on division/extrusion to those observed in other epithelia (Grannemann et al., 2023).

These environmental demands of cells and tissues in the lungs are particularly unique due to the constant mechanical stress exerted on epithelial and endoehtlial cells by fluctuaing alveolar volume during breathing

Within the context of alveolar endothelial cells, Piezo1 plays a significant role in barrier maintenance and permeability. Much like its seemingly contradictory role in epithelial homeostasis, scientists have demonstrated that Piezo1 activation promotes barrier stability in response to stress as well as endothelial hyperpermeability (Friedrich et al., 2019). Seemingly, the pathway that Piezo1 activates "can be explained by the direction and magnitude of mechanical forces experienced by [endothelial cells]", similar to the case with epithelial proliferation (Zhong et al., 2020). In more general terms, endothelial Piezo1 is also known to be involved in vascular relaxation and blood pressure regulation (Zhong et al., 2018).

Piezo1 is implicated in a variety of pathologies of the lung, most prominently cancer and pulmonary fibrosis. As might be

predicted by its role in epithelial proliferation, the channel is an oncosuppressor in small cell lung cancer and non-small cell lung cancer, as decreased expression of Piezo1 is connected with decreased cell adhesion and metastatic activity. Not only were depleted levels of Piezo1 mRNA observed in lung tumor cells, Piezo1 knockdown induced in vitro migration and in vivo tumor growth (Huang et al., 2019; McHugh et al., 2012).

Piezo1 is also known to play a role in pulmonary fibrosis, especially acute respiratory distress syndrome (ARDS)-associated fibrosis, which arises as a result of excessive alveolar stress during mechanical ventilation treatments. Specifically, the release of ATP from ATIs downstream of Piezo1 activation (Figure 3) mediates an increase in epithelial-mesenchymal transition, a process in which epithelial cells lose adhesion and are (in this case) converted into myofibroblasts. This results in an increase in fibroblastic activity and ECM stiffness (Fang et al., 2022). Here, pulmonary fibrosis inhibits the mechanical functionality of the lungs, and it is a significant chronic health concern in relation to a variety of environmental factors and respiratory diseases besides ARDS. The association of Piezo1 with these various pulmonary diseases makes it a significant potential target for novel treatment methods. It is important to continue research on Piezo1 in pulmonary cell types so that we can better our understanding of its role in conditions like cancer and fibrosis and expose other Piezo1-associated etiologies.

Only five years ago, Zhong et al. (2018) speculated the role of Piezo channels in lung inflation responses. Though it was known that the channels were widely expressed in lung tissues, their physiological role was largely unexplored. Since then, the scientific community has accumulated a great deal of information regarding Piezo channels in the lungs, especially in alveoli. However, the findings detailed in this review only scratch the surface of Piezo1's vast array of functions in the mechanically demanding alveolar environment, and we have much yet to discover. As we continue to discover more about the extensive role of the Piezo family in lung physiology and other contexts, it becomes increasingly clear just how integral these channels are to the body's interaction with the physical and mechanical world around—and within—it. ❧

AUTHOR BIO

Grace is a third year majoring in Biology and Anthropology with Human Biology. Her interests are in biomedical research and plans to pursue a PhD after graduation.

Edited by Advaita Krishan, Samir Lohana, and Dr. Arri Eisen

Placed by Samir Lohana

REFERENCES

Coste, B., Mathur, J., Schmidt, M., Earley, T. J., Ranade, S., Petrus, M. J., Dubin, A. E., & Patapoutian, A. (2010). Piezo1 and Piezo2 Are Essential Components of Distinct Mechanically Activated Cation Channels. Science, 330(6000), 55–60. https://doi.org/10.1126/science.1193270

Crandall, E. D., & Matthay, M. A. (2001). Alveolar Epithelial Transport. American Journal of Respiratory and Critical Care Medicine, 163(4), 1021–1029. https://doi.org/10.1164/ajrccm.163.4.2006116

Deng, Z., Fear, M. W., Suk Choi, Y., Wood, F. M., Allahham, A., Mutsaers, S. E., & Prêle, C. M. (2020). The extracellular matrix and mechanotransduction in pulmonary fibrosis. The International Journal of Biochemistry & Cell Biology, 126, 105802. https://doi.org/10.1016/j.biocel.2020.105802

Diem, K., Fauler, M., Fois, G., Hellmann, A., Winokurow, N., Schumacher, S., Kranz, C., & Frick, M. (2020). Mechanical stretch activates piezo1 in caveolae of alveolar type I cells to trigger ATP release and paracrine stimulation of surfactant secretion from alveolar type II cells. FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology, 34(9), 12785–12804. https://doi.org/10.1096/fj.202000613RRR

Eisenhoffer, G. T., Loftus, P. D., Yoshigi, M., Otsuna, H., Chien, C.-B., Morcos, P. A., & Rosenblatt, J. (2012). Crowding induces live cell extrusion to maintain homeostatic cell numbers in epithelia. Nature, 484(7395), Article 7395. https://doi.org/10.1038/nature10999

Fang, X.-Z., Li, M., Wang, Y.-X., Zhang, P., Sun, M.-M., Xu, J.-X., Yang, Y.-Y., He, Y.-J., Yu, Y., Li, R.-T., Zhou, T., Reng, L.-H., Sun, D.-Y., Shu, H.-Q., Yuan, S.-Y., Xu, J.-Q., & Shang, Y. (2022). Mechanosensitive ion channel Piezo1 mediates mechanical ventilation-exacerbated ARDS-associated pulmonary fibrosis. Journal of Advanced Research. https://doi.org/10.1016/j.jare.2022.12.006

Friedrich, E. E., Hong, Z., Xiong, S., Zhong, M., Di, A., Rehman, J., Komarova, Y. A., & Malik, A. B. (2019). Endothelial cell Piezo1 mediates pressure-induced lung vascular hyperpermeability via disruption of adherens junctions. Proceedings of the National Academy of Sciences, 116(26), 12980–12985. https://doi.org/10.1073/pnas.1902165116

Grannemann, C., Pabst, A., Honert, A., Schieren, J., Martin, C., Hank, S., Böll, S., Bläsius, K., Düsterhöft, S., Jahr, H., Merkel, R., Leube, R., Babendreyer, A., & Ludwig, A. (2023). Mechanical activation of lung epithelial cells through the ion channel Piezo1 activates the metalloproteinases ADAM10 and ADAM17 and promotes growth factor and adhesion molecule release. Biomaterials Advances, 152, 213516. https://doi.org/10.1016/j.bioadv.2023.213516

Gudipaty, S. A., Lindblom, J., Loftus, P. D., Redd, M. J., Edes, K., Davey, C. F., Krishnegowda, V., & Rosenblatt, J. (2017). Mechanical stretch triggers rapid epithelial cell division through Piezo1. Nature, 543(7643), Article 7643. https://doi.org/10.1038/nature21407

Huang, Z., Sun, Z., Zhang, X., Niu, K., Wang, Y., Zheng, J., Li, H., & Liu, Y. (2019). Loss of stretch-activated channels, PIEZOs, accelerates non-small cell lung cancer progression and cell migration. Bioscience Reports, 39(3), BSR20181679. https://doi.org/10.1042/BSR20181679

Lai, A., Cox, C. D., Chandra Sekar, N., Thurgood, P., Jaworowski, A., Peter, K., & Baratchi, S. (2022). Mechanosensing by Piezo1 and its implications for physiology and various pathologies. Biological Reviews, 97(2), 604–614. https://doi.org/10.1111/brv.12814

Liang, G.-P., Xu, J., Cao, L., Zeng, Y.-H., Chen, B.-X., Yang, J., Zhang, Z.-W., & Kang, Y. (2019). Piezo1 induced apoptosis of type II pneumocytes during ARDS. Respiratory Research, 20(1), 118. https://doi.org/10.1186/s12931-019-1083-1

Lin, Y.-C., Guo, Y. R., Miyagi, A., Levring, J., MacKinnon, R., & Scheuring, S. (2019). Force-induced conformational changes in PIEZO1. Nature, 573(7773), Article 7773. https://doi.org/10.1038/s41586-019-1499-2

McHugh, B. J., Murdoch, A., Haslett, C., & Sethi, T. (2012). Loss of the Integrin-Activating Transmembrane Protein Fam38A (Piezo1) Promotes a Switch to a Reduced Integrin-Dependent Mode of Cell Migration. PLOS ONE, 7(7), e40346. https://doi.org/10.1371/journal.pone.0040346

Nonomura, K., Woo, S.-H., Chang, R. B., Gillich, A., Qiu, Z., Francisco, A. G., Ranade, S. S., Liberles, S. D., & Patapoutian, A. (2017). Piezo2 senses airway stretch and mediates lung inflation-induced apnoea. Nature, 541(7636), 176–181. https://doi.org/10.1038/nature20793

Novak, C., Ballinger, M. N., & Ghadiali, S. (2021). Mechanobiology of Pulmonary Diseases: A Review of Engineering Tools to Understand Lung Mechanotransduction. Journal of Biomechanical Engineering, 143(110801). https://doi.org/10.1115/1.4051118

Volkers, L., Mechioukhi, Y., & Coste, B. (2015). Piezo channels: From structure to function. Pflügers Archiv - European Journal of Physiology, 467(1), 95–99. https://doi.org/10.1007/s00424-014-1578-z

Zhong, M., Komarova, Y., Rehman, J., & Malik, A. B. (2018). Mechanosensing Piezo channels in tissue homeostasis including their role in lungs. Pulmonary Circulation, 8(2), 2045894018767393. https://doi.org/10.1177/2045894018767393

Zhong, M., Wu, W., Kang, H., Hong, Z., Xiong, S., Gao, X., Rehman, J., Komarova, Y. A., & Malik, A. B. (2020). Alveolar Stretch Activation of Endothelial Piezo1 Protects Adherens Junctions and Lung Vascular Barrier. American Journal of Respiratory Cell and Molecular Biology, 62(2), 168–177. https://doi.org/10.1165/rcmb.2019-0024OC

IMAGE REFERENCES

Coste, B. (2010). Piezo1 and Piezo2 Are Essential Components of Distinct Mechanically Activated Cation Channels. Science. Retrieved October 5, 2023, from https://pubmed.ncbi.nlm.nih.gov/20813920/.

Diem, K. (2020). Mechanical stretch activates piezo1 in caveolae of alveolar type I cells to trigger ATP release and paracrine stimulation of surfactant secretion from alveolar type II cells. FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology. Retrieved October 5, 2023, from https://pubmed.ncbi.nlm.nih.gov/32744386/.

Zhong, M. (2018). Mechanosensing Piezo channels in tissue homeostasis including their role in lungs. Pulmonary Circulation. Retrieved October 5, 2023, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6024292/.

Demystifying the ozempic controversy

SRINIVAS SOWMI-YANARAYANAN
Staff Writer

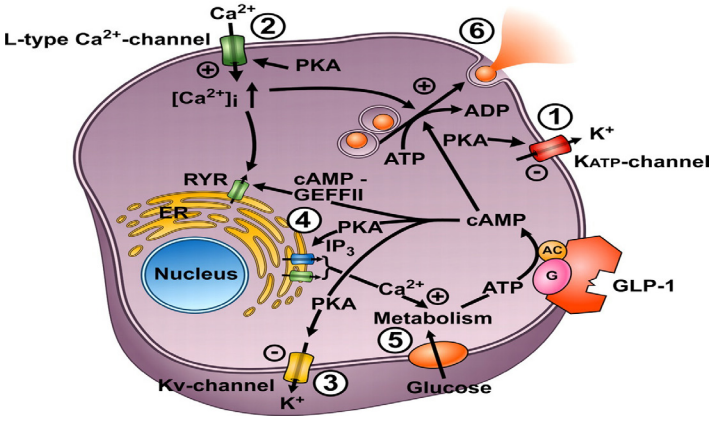

Figure 1: Binding of the ligand to the GLP-1 receptor activates adenylyl cyclase, producing cyclic AMP that ultimately promotes the secretion of insulin from pancreatic beta cells. (Holst, 2007)

Diabetes and obesity are some of the most prevalent chronic medical conditions in the United States and significantly increase individuals' risk for developing cardiovascular disease and mortality (CDC, 2022 & 2023). Expanding the array of treatment options for these diseases is imperative, given the diseases' severity. Ozempic and Wegovy are two new prescription drugs developed by Novo Nordisk to treat type 2 diabetes and chronic weight management, respectively (FDA, 2023). They both contain the active drug, semaglutide, which is a member of the drug class, glucagon-like peptide-1 (GLP-1) receptor agonists. The binding of semaglutide to the GLP-1 receptor causes downstream effects that are useful for treating diabetes and weight reduction. Although Ozempic and Wegovy contain the same active drug, they differ in dosing and the conditions that they are approved to treat (FDA, 2023). With supply shortages in the past year, there has been an uptick in off-label prescriptions of Ozempic for weight loss. Moreover, the promotion of these medications by online influencers for weight loss has led to the spread of misinformation about the drug (Blum, 2023). This article will begin by exploring the current landscape of type 2 diabetes treatments. It will then discuss how semaglutide works in the body, followed by a comparison of Ozempic and Wegovy. Finally, this article will address major misconceptions about these medications and how they are used.

Type 2 diabetes is a disease affecting the body's regulation of glucose metabolism via the peptide hormones, insulin and glucagon. Typically, patients with type 2 diabetes have some degree of insulin resistance and produce insufficient insulin which when combined, leads to elevated blood glucose levels since insulin signals cells to transport glucose into the cells from the blood (Kahn et al., 2014). When cells are not sensitive to insulin, glucose cannot be transported into them from the bloodstream which when severe enough, can cause significant physiological harm. Prior to the development of semaglutide and other GLP-1 receptor agonists, the landscape of type 2 diabetes treatments included lifestyle modifications, insulin, metformin, thiazolidinediones (TZDs), and sulfonylureas, among others. These treatments are often used in conjunction with each other and they are not all effective for every patient, especially since diabetes can present differently depending on the individual (Kahn et al., 2014). Metformin works to decrease the liver's glucose production and increase insulin sensitivity, TZDs "[increase] insulin-stimulated glucose uptake by skeletal muscle cells," and sulfonylureas magnify insulin secretion by pancreatic beta cells (Inzucchi, 2002). These different medication classes have different mechanisms of action which allows healthcare providers to combine these treatments with dietary changes and exercise to help patients with diabetes manage their blood glucose

There is an ever growing need for effective online medical communication which should involve clinicians and healthcare governing bodies that can provide the necessary context about novel drugs.

levels. Having more therapeutic tools allows clinicians to fine-tune treatments to each patient's individual needs. The discovery of GLP-1 receptor agonists has further expanded the landscape of diabetes treatments.

GLP-1 receptor agonists are a new class of type 2 diabetes medications that were approved in 2005 and are another tool for clinicians to use along with the existing treatments mentioned earlier (Nauck et al., 2021). GLP-1 receptor agonists mimic GLP-1 which is a peptide that our body secretes when we consume food to help manage blood sugar levels by promoting insulin release (Holst, 2007). This effect is relevant as a therapeutic tool for managing type 2 diabetes since patients with the condition often cannot produce sufficient amounts of insulin, leading to elevated blood glucose levels.

Notably, "GLP-1 receptor agonists reduce hyperglycemia by increasing insulin and decreasing glucagon secretion in a glucose-dependent manner" (Davies et al., 2017). Glucagon is the hormone that is responsible for increasing blood glucose levels by stimulating the liver to produce glucose from glycogen. By regulating glucagon dynamically, GLP-1 agonists can decrease blood glucose levels with a lower risk of hypoglycemia than sulfonylureas (Zhao et al., 2022). In addition, "GLP-1 receptor agonists also provide significant weight loss by reducing appetite" (Davies et al., 2017). This is in comparison

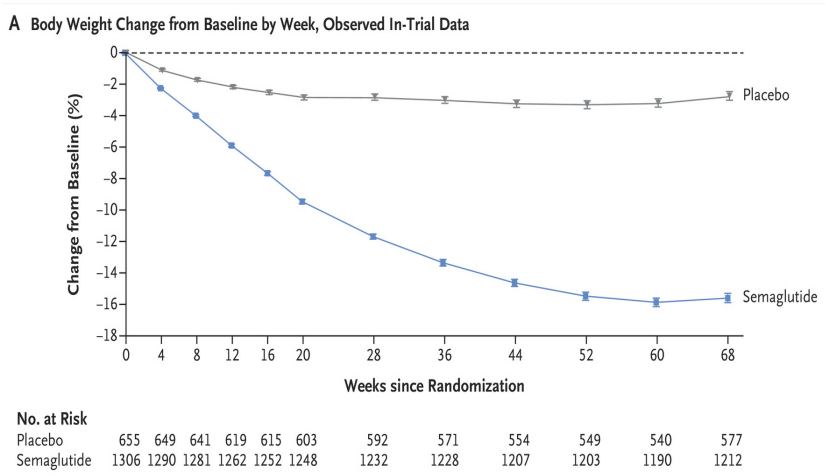

Figure 2: In this study, the experimental group taking semaglutide appears to have had a 16% decrease in body weight compared to a 2% decrease in body weight in the control group. (Wilding et al., 2021)

to medications like TZDs and sulfonylureas which are known to cause weight gain (Inzucchi, 2002). The weight-loss potential of semaglutide is particularly attractive for many patients since obesity and diabetes are closely related (Bhupathiraju and Hu, 2016). The mechanism for GLP-1 receptor agonists' appetite suppression has to do with their "uptake into specific brain regions and interaction with CNS neural circuits involved in the homeostatic or hedonic regulation of energy household and food intake" (Nauck et al., 2021).

Another study found that "Weight loss with semaglutide was accompanied by greater improvements than placebo with respect to cardiometabolic risk factors" and "that semaglutide led to [a] greater reduction in fat mass than lean body mass" (Wilding et al., 2021). There is also evidence that GLP-1 receptor agonists are "anti-inflammatory and anti-atherosclerotic," meaning that they could reduce plaque buildup in arteries (Nauck et al., 2021). These cardiovascular benefits further underscore the pharmacological potential of GLP-1 receptor agonists.

The discovery of GLP-1 receptor agonists has further expanded the landscape of diabetes treatments.

It is important to note that there are differences between drugs in the GLP-1 receptor agonists class regarding their efficacy and duration of action. Notably, semaglutide and dulaglutide have much longer half-lives compared to liraglutide, and thus, their administration schedules also differ (Nauck et al., 2021). In the United States, the semaglutide medications Ozempic and Wegovy are given as once-a-week injections, with up to 2.0 mg doses for Ozempic and up to 2.4 mg doses for Wegovy (Frías et al., 2021; Wilding et al., 2021). The dosage difference between the two drugs is important when considering off-label use, the use of a medication for a purpose that is not indicated.

Although GLP-1 receptor agonists like semaglutide are incredibly promising because of their ability to target many

components of type 2 diabetes, they come with their own side effects. For example, one article notes that "mild to moderate nausea and vomiting" were some of the gastrointestinal side effects experienced by patients, resulting in some patients discontinuing their treatment (Singh et al., 2022). Online discussions of Ozempic and Wegovy by celebrities and social media influencers often lack this context which can create the narrative that these medications will be the holy grail for individuals with type 2 diabetes and/or obesity. In weight-loss discourse, for example, it is often overlooked that during clinical trials for Wegovy, participants were asked to perform physical exercise and were advised to make dietary changes (Wilding et al., 2021). Thus, lifestyle adjustments are an important factor for the weight loss observed in studies about semaglutide's efficacy. Simply taking the drug alone without exercise and dietary changes may not provide the weight loss that is desired. When influencers tout the benefits of Ozempic and Wegovy, they face the risk of giving their audiences false expectations for semaglutide, leading individuals to seek out these medications inappropriately. With a shortage of semaglutide-based medications, this behavior can prevent those who rely on this drug from accessing it (Blum, 2023). Any decision to begin or discontinue a treatment plan should be made with a physician who can explain the drug's mechanism of action, provide realistic expectations, and discuss any adverse effects.

When influencers tout the benefits of Ozempic and Wegovy, they face the risk of giving their audiences false expectations for semaglutide, leading individuals to seek out these medications inappropriately.

The adverse effects and risks associated with semaglutide is further compounded by the steep cost of these treatments. Without insurance, taking semaglutide medications for a year can cost patients over $10,000 (Blum, 2023). Ensuring that insurance companies provide fair and adequate access to these medications for patients that need them should be pursued via legislation that limits prices. The price of Ozempic and Wegovy are extremely important factors that patients need to be aware of, especially given that diabetes is an already expensive chronic condition that requires multiple concurrent treatments.

The development of new medications is an exciting prospect, especially for patients who are not responding adequately to existing treatments. However, patients must be informed of the nuanced risks and costs associated with the drug to ensure that misconceptions are not spread. There is an ever growing need for effective online medical communication which should involve clinicians and healthcare governing bodies that can provide the necessary context about novel drugs. GLP-1 agonists like semaglutide offer a promising new avenue for patients to manage type 2 diabetes and obesity, conditions that play a large role in cardiovascular disease risk. With time, these medications will hopefully become more accessible to patients with the condition. ❧

AUTHOR BIO

Srinivas is a second year majoring in Anthropology & Human Biology and Chemistry. His interests are in endocrinology and pharmacology.

Edited by Zuha Jaffar, Neha Bajaj, and Dr. Muhammed Azeem

Placed by Neha Bajaj

REFERENCES

Adult Obesity Facts. (2022, May 17). Centers for Disease Control and Prevention. https://www.cdc.gov/obesity/data/adult.html

Bhupathiraju, S. N., & Hu, F. B. (2016). Epidemiology of Obesity and Diabetes and Their Cardiovascular Complications. Circulation Research, 118(11), 1723–1735. https://doi.org/10.1161/CIRCRESAHA.115.306825

Blum, D. (2023, July 24). What Is Ozempic and Why Is It Getting So Much Attention? The New York Times. https://www.nytimes.com/2022/11/22/well/ozempic-diabetes-weight-loss.html

Davies, M., Pieber, T. R., Hartoft-Nielsen, M.-L., Hansen, O. K. H., Jabbour, S., & Rosenstock, J. (2017). Effect of Oral Semaglutide Compared With Placebo and Subcutaneous Semaglutide on Glycemic Control in Patients With Type 2 Diabetes: A Randomized Clinical Trial. JAMA, 318(15), 1460–1470. https://doi.org/10.1001/jama.2017.14752

Diabetes Quick Facts. (2023, April 4). Centers for Disease Control and Prevention. https://www.cdc.gov/diabetes/basics/quick-facts.html

Frías, J. P., Auerbach, P., Bajaj, H. S., Fukushima, Y., Lingvay, I., Macura, S., Søndergaard, A. L., Tankova, T. I., Tentolouris, N., & Buse, J. B. (2021). Efficacy and safety of once-weekly semaglutide 2.0 mg versus 1.0 mg in patients with type 2 diabetes (SUSTAIN FORTE): A double-blind, randomised, phase 3B trial. The Lancet Diabetes & Endocrinology, 9(9), 563–574. https://doi.org/10.1016/S2213-8587(21)00174-1

Inzucchi, S. E. (2002). Oral Antihyperglycemic Therapy for Type 2 Diabetes: Scientific Review. JAMA, 287(3), 360–372. https://doi.org/10.1001/jama.287.3.360

Kahn, S. E., Cooper, M. E., & Del Prato, S. (2014). Pathophysiology and treatment of type 2 diabetes: Perspectives on the past, present, and future. The Lancet, 383(9922), 1068–1083. https://doi.org/10.1016/S0140-6736(13)62154-6

Medications Containing Semaglutide Marketed for Type 2 Diabetes or Weight Loss. (2023, May 31). Food and Drug Administration. https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/medications-containing-semaglutide-marketed-type-2-diabetes-or-weight-loss

Nauck, M. A., Quast, D. R., Wefers, J., & Meier, J. J. (2021). GLP-1 receptor agonists in the treatment of type 2 diabetes—State-of-the-art. Molecular Metabolism, 46, 101102. https://doi.org/10.1016/j.molmet.2020.101102

Singh, G., Krauthamer, M., & Bjalme-Evans, M. (2022a). Wegovy (Semaglutide): A New Weight Loss Drug for Chronic Weight Management. Journal of Investigative Medicine, 70(1), 5–13. https://doi.org/10.1136/jim-2021-001952https://doi.org/10.1056/NEJMoa2032183

Zhao, J. Z., Weinhandl, E. D., Carlson, A. M., & Peter, W. L. S. (2022). Hypoglycemia Risk With SGLT2 Inhibitors or Glucagon-Like Peptide 1 Receptor Agonists Versus Sulfonylureas Among Medicare Insured Adults With CKD in the United States. Kidney Medicine, 4(8). https://doi.org/10.1016/j.xkme.2022.100510

IMAGE REFERENCES

Holst, J. J. (2007). The Physiology of Glucagon-like Peptide 1. Physiological Reviews, 87(4), 1409–1439. https://doi.org/10.1152/physrev.00034.2006

Wilding, J. P. H., Batterham, R. L., Calanna, S., Davies, M., Van Gaal, L. F., Lingvay, I., McGowan, B. M., Rosenstock, J., Tran, M. T. D., Wadden, T. A., Wharton, S., Yokote, K., Zeuthen, N., & Kushner, R. F. (2021). Once-Weekly Semaglutide in Adults with Overweight or Obesity. New England Journal of Medicine, 384(11), 989–1002. https://doi.org/10.1056/NEJMoa2032183

Effects of glaucoma-caused vision loss on Asian populations

ASHLEY ZHU
Staff Writer

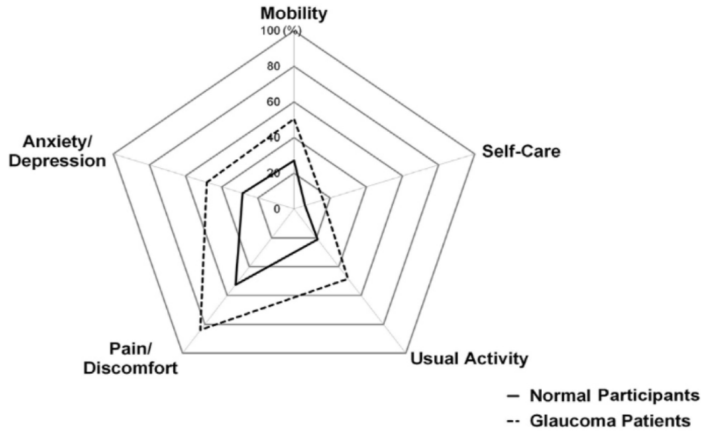

Figure 1. Prevalence of impaired health-related quality of life versus glaucoma patients. Glaucoma patient reported significantly higher impariment in health-related qualties of life measures (Park et al., 2015).

An estimated 12.3% of existing blindness of the world has resulted from glaucoma, a term that describes the general loss of function of the optic nerve. In particular, primary angle-closure glaucoma disproportionately affects Asians — especially in countries showing higher rates of aging populations. Glaucoma-induced visual impairments affect peripheral vision and are associated with decline in physical and social functioning, bodily pain, mental health and higher rates of falls with injuries sustained. While a number of studies have already been conducted on Western populations, there is a greater need to focus glaucoma studies on Asian populations in order to improve treatment plans and outcomes in response to the increasingly high prevalence of glaucoma within aging Asian populations.

Glaucoma-induced visual impairments are often associated with marked declines in physical health, social functioning and mental health with higher rates of falls with injury and a general decline in health-related quality of life (Park, 2015).

Glaucoma, a disease encompassing irreversible damage to optic disc morphology, is a leading cause of vision impairment with 12.3% of existing blindness of the world resulting from glaucoma (Park, 2015). Glaucoma damages the optic nerve and retinal nerve fiber layer, leading to peripheral and central visual field defects, as well as elevated intraocular pressure (IOP). Increased IOP is important because it is the only modifiable risk factor and a crucial determinant of disease progression (Wagner, 2022). Elevated IOP is generally caused by inadequate drainage of the aqueous humor, the transparent fluid that fills the eye, leading to irreversible death of retinal and optic nerve cells (Wagner, 2022). However, even IOP is not fully accurate in predicting glaucoma because one-third of patients with glaucoma have normal IOPs (Wagner, 2022).

Glaucoma-induced visual impairments are also often associated with marked declines in physical health, social functioning and mental health, with higher rates of falls with injury and a general decline in health-related quality of life (Park, 2015). Because glaucoma is an age-related process that is very common in elderly populations and with aging populations rapidly growing globally, glaucoma-caused vision loss is a major public health concern that needs to be at the forefront of geriatric healthcare. With increasing life expectancies and increasing incidences of glaucoma, 112 million people are expected to be affected by 2040 (Wagner, 2022).

Asian populations have a high predisposition to glaucoma — though they may not have the highest incidence compared to other racial groups, their rapidly increasing and aging populations position them to be a highly affected group in the future. Primary open angle glaucoma (POAG) is the most common type of glaucoma. Based on current studies, POAG prevalence in Asian pop-

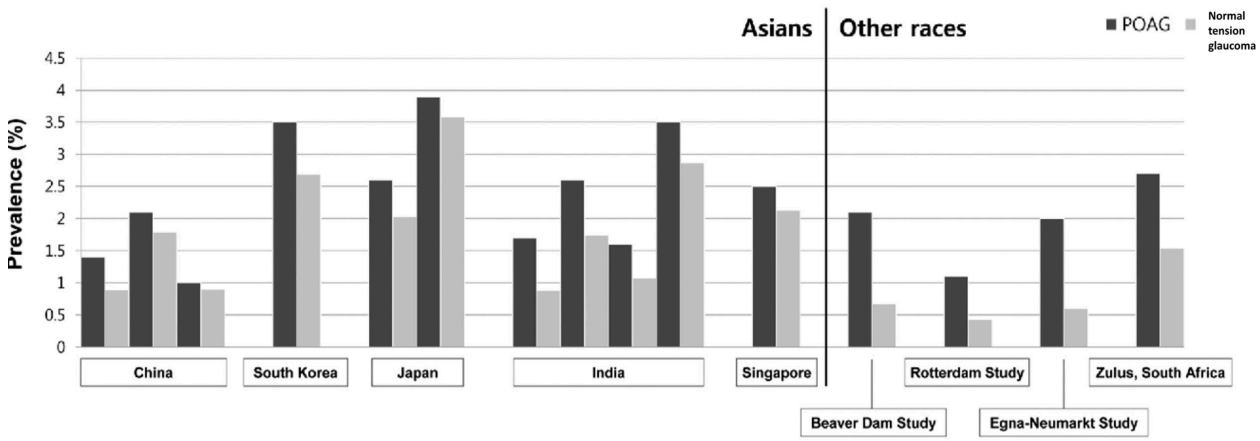

Figure 2. The proportion of normal tension glaucoma and POAG ini Asian populations compared to other races (Cho, 2014). The proportion of NTG in Asians is higher findings of glaucoma in Asians compared with other races. Each bar represents a different study conducted on a given population.

ulations is projected to increase significantly in South and Central Asia — from 17 million in 2016 to 23 million in 2040 (Belamkar, 2022). Already, the prevalence of glaucoma in Korean populations is one of the highest in the world (Park, 2015). China and India are also predicted to have one of the highest total glaucoma cases in the world, including POAG and primary angle closure glaucoma (Belamkar, 2022). Despite such a high prevalence in East and South Asian countries, most academic literature has centered around Western and developed countries, which poses a key problem: there are drastic differences between racial groups in regards to risk, potential mechanistic pathways and lifestyle (Belamkar, 2022). Thus, research studying glaucoma in Asian populations is imperative to more effectively treat individuals of Asian descent, who are generally more predisposed to developing the disease. Findings from current literature are not well synthesized to properly evaluate the specific characteristics and treatment options available to Asian populations and its ethnic subgroups (Belamkar, 2022).

A number of different reasons why glaucoma is so prevalent in Asians have been postulated. The fact that the prevalence of POAG in the urban population is more than double that in the rural population (Cho, 2014) may be due to an aging population, as mentioned before, or increased access to primary care and glaucoma screening in urban areas. However, more study is necessary to confirm this hypothesis. The Beijing Eye Study conducted in adult Chinese populations found that glaucoma progression was significantly more likely in patients with a larger optic cup — the size of the depression in the middle of the nerve when viewed from the front of the eye (Wang, 2012). Diabetes and hypertension increase the risk for glaucoma in Asians, as well as obstructive sleep apnea and hypopnea syndrome, which are all trends also observed in Caucasian populations (Belamkar, 2022).

With increasing life expectancies and increasing incidences of glaucoma, 112 million people are expected to be affected by 2040 (Wagner, 2022).

The heritability of glaucoma has been emphasized in Asian population glaucoma studies, with many genes identified in its pathogenesis. One Chinese study found that approximately 80% of phenotypic variations in optic disc were genetic, with heritability for cup disc and cup-to-disc ratio — factors the Beijing Eye Study found to correlate with glaucoma incidence — to have high correlation coefficients (Belamkar, 2022). Recent genome-wide association studies (GWAS) have also identified several single nucleotide polymorphisms at a number of different loci to be associated with POAG, including CAV1/CAV2, which have been postulated to influence several signaling pathways involved in glaucoma pathogenesis (Abu-Amero, 2012). Additionally, many loci seem to be ethnic-

ity-specific: for example CAV1/CAV2 do not seem to contribute to POAG in the Middle East (Abu-Amero, 2012). It should be noted that specific disease-causing genes seem to account for less than 10% of POAG cases in the general population, prompting the idea that glaucoma is a polygenic disease and that gene-environment interactions are very important (Abu-Amero, 2012). With the advent of GWAS, a large number of single nucleotide polymorphisms have been linked to POAG, but the clinical applicability of these discoveries is still somewhat limited — the development of therapeutic agents to target these genetic markers will be an even more extended process, especially to those that are specific to a certain race or ethnicity (Abu-Amero, 2012). These genetic links, however, are very helpful to broaden our current understanding of glaucoma and provide a foundation for future diagnostic and therapeutic efforts.

Like all diseases, glaucoma diagnosis and treatment is a multifactorial ailment influenced by a variety of environmental, genetic, and political factors.

Because POAG is largely asymptomatic, with large numbers of people who have undiagnosed disease, how healthcare systems manage a patient with glaucoma in Asia is a significant consideration. Reduction of IOP with medical therapy is very effective in preventing the onset of POAG; however, the cost of such therapy is too high in developing countries and is oftentimes infeasible to maintain in the long run (Yip, 2006). Most trials were performed on Western populations, so the generalizability of results is very limited, especially when considering costs. Nevertheless, laser or surgical peripheral iridotomy — the creation of a microscopic hole in the iris that provides an alternative pathway for aqueous flow, thus reducing IOP — remains the most popular treatment for angle closure, a symptom that often leads to glaucoma (Yip, 2006). In developing countries, where treatment centers are oftentimes very far away from the patient, experts advise that all eyes with angle closure require a peripheral iridotomy to protect from an acute angle-closure glaucoma, which can be sudden and unpredictable (Yip, 2006). Laser iridoplasty — placing burns to the iris and causing contracting of the iris away from the anterior chamber angle — is also an option, but limited capacity prevents extensive use in developing countries (Yip, 2006). Finally, surgery carries a much greater risk than use of a laser, but is a considerable option: lens extraction is an alternative for treatment of angle closure, as well as trabeculectomy, which involves creating a new pathway for aqueous fluid to be drained (Yip, 2006).

In addition to all of the issues mentioned above, there is a current trend for the migration of doctors and nurses to richer countries — the U.S., U.K. and Canada — further increasing the glaucoma doctor demand in Asian countries (Thomas, 2006). Additionally, efficiency of the provision of healthcare varies considerably between different Asian nations; for example, China's cataract surgery rate is only 500 CSR (expressed in case per million year), compared to Australia's 6300 and India's 3100 (Thomas, 2006). Like all diseases, glaucoma diagnosis and treatment is a multifactorial ailment influenced by a variety of environmental, genetic and political factors. However, with existing medical technology and the synergistic cooperation of government, non-governmental organizations and healthcare systems, the prevention of POAG is an immediately achievable goal that could afford a huge step in worldwide blindness prevention. ❧

AUTHOR BIO

Ashley is a third year majoring in Biology. Her interests are maternal health and the intersection of journalism and medicine.

Edited by Claire Qu, Lianna Levine, and Dr. Kim Tran

Placed by Lianna Levine

REFERENCES

Abu-Amero, K., Kondkar, A.A., Chalam, K.V. (2015). An Updated Review on the Genetics of Primary Open Angle Glaucoma. Int. J. Mol. Sci., 16(12), 28886-28911; https://doi.org/10.3390/ijms161226135

Belamkar, A., Harris, A., Oddone, F., Verticchio Vercellin, A., Fabczak-Kubicka, A., & Siesky, B. (2022). Asian Race and Primary Open-Angle Glaucoma: Where Do We Stand?. Journal of clinical medicine, 11(9), 2486. https://doi.org/10.3390/jcm11092486

Foster, P.J., Thomas, R. (2006). Glaucoma Care in Developing Countries of Asia. In: Grehn, F., Stamper, R. (eds) Glaucoma. Essentials in Ophthalmology. Springer, Berlin, Heidelberg . https://doi.org/10.1007/3-540-34773-9_7

Hyun-kyung Cho, Changwon Kee (2014). Population-based glaucoma prevalence studies in Asians. Survey of Ophthalmology. Volume 59, Issue 4, Pages 434-447, ISSN 0039-6257. https://doi.org/10.1016/j.survophthal.2013.09.003.

Sangshin Park, Young Lim Kho, Hyo-Jin Kim, JiHyun Kim, Eun-Hee Lee. Impact of Glaucoma on Quality of Life and Activities of Daily Living. Hong Kong Journal of Occupational Therapy, Volume 25, 2015, Pages 39-44, ISSN 1569-1861. https://doi.org/10.1016/j.hkjot.2015.04.002.

Wagner, I. V., Stewart, M. W., & Dorairaj, S. K. (2022). Updates on the Diagnosis and Management of Glaucoma. Mayo Clinic proceedings. Innovations, quality & outcomes, 6(6), 618–635. https://doi.org/10.1016/j.mayocpiqo.2022.09.007

Wang, Y. X., Hu, L. N., Yang, H., Jonas, J. B., & Xu, L. (2012). Frequency and associated factors of structural progression of open-angle glaucoma in the Beijing Eye Study. The British journal of ophthalmology, 96(6), 811–815. https://doi.org/10.1136/bjophthalmol-2011-301224

Yip, J. L., & Foster, P. J. (2006). How to manage a patient with glaucoma in Asia. Community eye health, 19(59),

IMAGE REFERENCES

Cho, H., & Kee, C. (2014). Population-based glaucoma prevalence studies in Asians. Survey of ophthalmology, 59 4, 434-47. https://doi.org/10.1016/j.survophthal.2013.09.003

Sangshin Park, Young Lim Kho, Hyo-Jin Kim, JiHyun Kim, Eun-Hee Lee. Impact of Glaucoma on Quality of Life and Activities of Daily Living. Hong Kong Journal of Occupational Therapy, Volume 25, 2015, Pages 39-44, ISSN 1569-1861. https://doi.org/10.1016/j.hkjot.2015.04.002.

Declined Religiosity in Neurodegradation

Daniel Sung
Staff Writer

Religious belief has become an integral aspect of people's lives, leading to careful consideration in medicine from varying patient beliefs and experiences. The progression of neurodegenerative disease imparts detrimental effects on specific regions of the brain that are associated with religiosity, which represents religious thought, behavior, and beliefs. Historically, research that examines the brain and religion has had difficulty securing funding and publishing due to hesitancy surrounding the validity of results clearly showing the link between health and religion. However, modern key discoveries have been made that further the understanding of religiosity and neurodegeneration. Currently, there is no universally accepted method for measuring and determining religiosity levels; however, many of the conducted studies utilize reliable scale methods for respondents to self-report their religious beliefs and behaviors. Neurodegenerative diseases, such as Parkinson's Disease and hippocampal-targeting diseases, show trends of decreased religiosity for patients compared to control-matched groups and can potentially be used as a predictive factor for diagnosing neurodegenerative disease. Special cases of selective neurodegeneration have shown opposing effects, such as hyper-religiosity.

To examine the connection between the brain and religion, a study examined the neural activity of 30 healthy subjects – 15 committed Christians and 15 non-believers — using functional magnetic resonance imaging (fMRI) to study the neural correlates in religious belief (Harris et al., 2009). To determine their religious beliefs, participants indicated "belief" or "non-belief" to statements such as "Jesus Christ performed the miracles attributed to him in the Bible", and "Alexander the Great was a very famous military leader". At the same time, their neural signal changes were studied. Study results found that religious and non-religious thinking engage the broad regions of the frontal, parietal, and medial temporal lobes differently. However, the neural response from both study groups was content-independent for statements they found true, signifying a similar neural response regardless of whether the statement was religious or non-religious. More specifically, the medial prefrontal cortex showed an increased response when participants responded "belief" whereas the anterior insula showed increased activity when participants responded "non-belief". Figure 1 further shows the different regions engaged in stimuli from the statements (Figure 1).

Although there is no specific brain region for religious belief, neuroimaging can discriminate between belief and nonbelief using areas associated with self-representation and reward. For example, there are similar responses in both the Christian and non-believer groups to blasphemous statements (statements

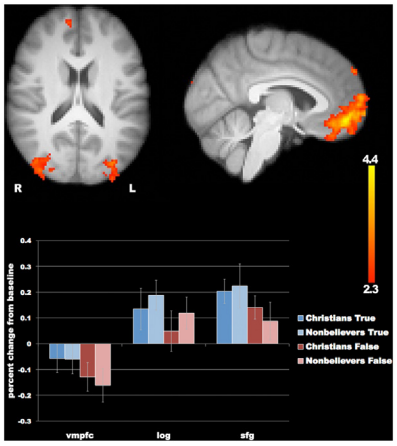

Figure 1. Greater activity in the ventromedial prefrontal cortex, lateral occipital cortex, and superior frontal gyrus was seen for belief rather than disbelief. (Harris et al., 2009)

that contradict a subject's set of beliefs) since rejecting statements is rewarding This leads to increased activity and signals in the ventromedial prefrontal cortex, lateral occipital cortex, and superior frontal gyrus when participants responded that statements are true rather than not true.

As religiosity uses the activation of various parts of the brain, neurodegenerative diseases pose a threat to the maintenance of one's religiosity. Specifically, Parkinson's Disease (PD) is a neurodegenerative disease that is progressive and affects the nervous system. There have been correlations between Parkinson's and decreased religiosity levels. A study of 22 male, mid-stage age-matched PD patients aiming to measure "life goals, religiosity, mood, and neuropsychologic function" concluded that PD patients had significantly lower levels of religiosity than the age-matched controls (McNamara et al., 2006). These results may be explained by the prefrontal neuropsychological function rather than age, education, or

mood-related factors. There is less inclination to practice religion in participants with impeded prefrontal neuropsychological function. As a common symptom among PD patients, depression may contribute to these results, as the emotional and mental toll that patients experience may lead to a declined inclination for religion. Religiosity can lead to feelings of hope and optimism, but harsh symptoms PD patients endure can negatively influence religious fervor, leading to a more negative outlook on life. Dopamine levels, which are decreased in Parkinson's, could also be an explanation since dopamine is important in motivational support for religious practices. The areas of the brain that Parkinson's Disease damages could be key role players in the motivation and inclination to practice religion.

Religiosity can lead to feelings of hope and optimism, but harsh symptoms PD patients endure can negatively influence religious fervor, leading to a more negative outlook on life.

The damage Parkinson's Disease has on the brain is further evidenced through a study, in which patients with left-onset (right forebrain disease) show a more severe inability to activate and think of religious concepts in comparison to the controls. In an evaluative priming test, respondents were evaluated on how quickly they could respond to religious phrases and statements. The study further connects the inability to the "dopaminergic dysfunction in right-sided striatal-prefrontal networks" (Butler et al., 2009). The dopaminergic networks in right-sided striatal-prefrontal networks are vital for the activation of religious concepts, which can explain the decreased religiosity seen in patients with decreased religiosity. In comparison to the control group, patients with PD were slower in responding to the stimuli. The inability to automatically think of religion makes PD patients less intrinsically religious compared to their controls.

Moreover, further studies have shown that decreased religiosity could be used as a predictive factor for PD diagnosis. In a longitudinal study led by Abidemi Otaiku, there was an examination of collected data "from the English Longitudinal Study of Aging (ELSA) from July 2010 through to July 2019, and the Midlife in the United States (MIDUS) study from January 1995 through to June 2014" (Otaiku et al., 2022). Throughout the time, patients from ELSA conducted follow-up interviews every two years while patients from MIDUS had follow-up interviews every 9-10 years. The interviews were designed to assess the respondent's religious devotion through a four-point scale, in which 1 meant very important while 4 meant not at all important. The patients who considered religion to be "not at all important" were seen to have a tenfold risk of developing PD. A key finding was the dose-response relationship; as religiosity decreased in the subject, the risk of developing PD increased. Even after adjusting for the differing sociodemographic factors among the subjects like health, lifestyle, and religious practice, the finding was still consistent. Additionally, individuals who valued spirituality but not religion as much also had a higher risk of developing PD. In the ten years before the baseline was established, patients displaying decreased religiosity showed increased risks for developing PD. If there was higher religiosity in the patient, there were decreased risks of developing PD.

The inability to automatically think of religion makes PD patients less intrinsically religious compared to their controls.

Religion has further shown negative effects for hippocampal targeting neurodegenerative diseases. A study by Amy Owen examined the hippocampal atrophy in 268 religious older adults through high-resolution MRI. The baseline that was set for the study was "1) frequency of public worship, (2) frequency of private religious activity (prayer, meditation, or Bible study), (3) religious group membership. Religious factors assessed at baseline and annually included (4) born-again status and (5) life-changing religious experiences" (Owen et al., 2011). The study found that the frequency of religious practice did not correlate with the prediction for atrophy severity in the patients. Figure 2 shows the differences in hippocampal volume from different groups (Figure 2).

A major finding was that

	Left Hippocampus			Right Hippocampus		
	b	(SE)	β	*b*	(SE)	β
Intercept	0.45	(0.53)		0.48	(0.53)	
Religion/Spirituality						
Born-again[a] (new)	−0.05	(0.12)	0.03	−0.21	(0.12)	−0.12
LCRE[b] (baseline)	−0.45***	(0.12)	−0.22	−0.32	(0.13)	−0.16
LCRE[b] (new)	−0.01	(0.12)	−0.01	−0.15	(0.12)	−0.08
Born-again[a] (baseline)	−0.15*	(0.08)	−0.16	−0.15*	(0.08)	−0.16
Catholic	−0.22*	(0.11)	−0.13	−0.12	(0.11)	−0.07
Other	0.06	(0.12)	0.04	−0.05	(0.12)	−0.03
None	−0.28*	(0.12)	−0.13	−0.20	(0.12)	−0.10
Private practice	0.02	(0.02)	0.06	0.03	(0.02)	0.11
Public worship	−0.002	(0.02)	0.01	0.001	(0.02)	0.001
Covariates						
Depression status	−0.09	(0.09)	0.09	−0.08	(0.09)	0.08
Social support	0.01	(0.01)	0.09	0.01	(0.01)	0.09
Stress	0.01	(0.01)	0.03	0.003	(0.01)	0.02
Total brain size	0.0001	(0.001)	0.03	0.001	(0.001)	0.004
Age	−0.01*	(0.004)	−0.16	−0.01	(0.004)	−0.18
Duration in study	0.001	(0.02)	0.01	−0.01	(0.02)	0.02
Sex (female)	0.10	(0.08)	0.10	0.04	(0.08)	0.04
Race (White)	−0.004	(0.08)	−0.01	0.04	(0.08)	0.03
Education	−0.001	(0.01)	−0.01	0.004	(0.01)	0.02

*$p<.05$, ** $p<.01$,
***$p<.001$.
[a]Born-again labels refer to Protestants reporting born-again status.
[b]Life-changing Religious Experience.
doi:10.1371/journal.pone.0017006.t002

Figure 2. Regression Analysis to see varying religious factors and covariates that impact changes in hippocampal volume. A sample size of 268 patients. Looks at both the left and right hippocampal changes. (Owen et al., 2011)

there was greater hippocampal atrophy seen in born-again Protestants, Catholics, and patients with no religious affiliation in comparison to non-born-again Protestants. To further explain, there are religious aspects that have a positive mental impact, but there are other religious factors that can lead to increased cumulative stress on the brain. For example, being a part of a religious minority could be a cause of increased stress, which has been displayed in studies showing associations with stress and atrophy. The increased stress on the brain makes neuronal death, dendritic retraction, and decreased neurogenesis possible, leading to higher atrophy levels seen in the subjects. Furthermore, the atrophy could not be explained by the acute stress levels, further pointing to the possibility that the main source of atrophy is more cumulative stress. Another key finding was that increased atrophy was seen in the subjects who experienced life-changing religious experiences. Life-changing religious experiences can potentially contribute to the overall atrophy in the brain because these experiences could lead to doubts about past experiences or incite major changes in one's life. The study reveals how hippocampal volume could be uniquely affected by certain religious factors and experiences, leading to varying atrophy results.

Another area of the religious effects on neurodegeneration is religious dogmatism seen in patients with selective neurodegeneration. Religious dogmatism is defined to be hyper-religiosity or increased belief in religion compared to prior diagnosis. Patients express their religious beliefs as fact, without considering the perspective of others. Religious dogmatism has been associated with the limbic and paralimbic regions of the brain, including the temporal and orbitofrontal cortex. These regions are targeted by the frontotemporal lobar degenerative disorders. A study analyzing a large cohort of 1607 patients classified into four different groups – Alzheimer's Disease (AD), Behavioral Variant Frontotemporal Dementia (bvFTD), Semantic Variant Primary Progressive Aphasia (svPPA), and Normal Controls (NC) — measured the rates of religious dogmatism and mental rigidity (the inability to yield to other viewpoints). The results of the study found that the groups of bvFTD and svPPA had significantly higher rates of religious dogmatism than AD and NC patients. This is connected to associated higher rates of mental rigidity, potentially through the effects in the neural systems that involve cognitive flexibility. PD patients with higher rates of mental rigidity will be less likely to yield to other's beliefs leading to hyper-religiosity. This study shows novel examples of patients with increased religiosity due to selective neurodegeneration.

With religion being an integral part of the culture, it is vital to understand the linkage between religion and neurodegeneration in better predicting neurodegenerative disease diagnoses. Neurodegeneration not only negatively affects religiosity in patients with Parkinson's but also in patients with hippocampal atrophy. Selective neurodegeneration leads to damage of specific brain regions that lead to decreased religiosity. However, there are even cases when selective neurodegeneration leads to hyper-religiosity or increased belief due to high mental rigidity. With further funding into the research of the intersection of neurodegeneration and religion, more operationalization of concepts can be made in two areas that did not mix. ❧

AUTHOR BIO

Daniel Sung is a second year studying Chemistry and Film & Media. His research interests are neurodegenerative diseases and rural healthcare accessibility.

Edited by Justin Hahm, Claire Qu and Dr. Jonathan K. Crane

Placed by Claire Qu

REFERENCES

Block, N., Perry, D., Sturm, V., Miller, Z., & Miller, B. (2013). Religious dogmatism in neurodegenerative disease. Alzheimer's & Dementia, 9(4), P750. https://doi.org/10.1016/j.jalz.2013.05.1517

Butler, P. M., McNamara, P., & Durso, R. (2010). Deficits in the automatic activation of religious concepts in patients with Parkinson's disease. Journal of the International Neuropsychological Society : JINS, 16(2), 252–261. https://doi.org/10.1017/S1355617709991202

de Diego-Cordero, R., Martos-Lorite, I., & Vega-Escaño, J. (2022). Spiritual Dimension in Neurological and Neurodegenerative Diseases: A Systematic Mapping Review. Journal of Religion and Health. https://doi.org/10.1007/s10943-022-01683-6

Grafman, J., Cristofori, I., Zhong, W., & Bulbulia, J. (2020). The Neural Basis of Religious Cognition. Current Directions in Psychological Science, 29(2), 126-133. https://doi.org/10.1177/0963721419898183

Harris, S., Kaplan, J. T., Curiel, A., Bookheimer, S. Y., Iacoboni, M., & Cohen, M. S. (2009). The Neural Correlates of Religious and Nonreligious Belief. PLoS ONE, 4(10), e7272. https://doi.org/10.1371/journal.pone.0007272

Ludden, D. (2020, February 15). This is your brain on religion. Psychology Today. https://www.psychologytoday.com/us/blog/talking-apes/202002/is-your-brain-religion

Malmir, M., Khanahmadi, M., & Farhud, D. (2017). Dogmatism and Happiness. Iranian Journal of Public Health, 46(3), 326–332. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5395528/

McNamara, P., Durso, R., & Brown, A. (2006). Religiosity in patients with Parkinson's disease. Neuropsychiatric Disease and Treatment, 2(3), 341–348. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2671825/

Otaiku, A. I. (2022). Religiosity and Risk of Parkinson's Disease in England and the USA. Journal of Religion and Health. https://doi.org/10.1007/s10943-022-01603-8

Owen, A. D., Hayward, R. D., Koenig, H. G., Steffens, D. C., & Payne, M. E. (2011). Religious Factors and Hippocampal Atrophy in Late Life. PLoS ONE, 6(3), e17006. https://doi.org/10.1371/journal.pone.0017006

Sayadmansour A. (2014). Neurotheology: The relationship between brain and religion. Iranian journal of neurology, 13(1), 52–55.

IMAGE REFERENCES

Harris, S. (2009). Belief minus disbelief (Both Categories; Both Groups). PLOS ONE. Retrieved November 25, 2023, from https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0007272.

Owen, A. D. (2011). Regression Analyses of Religious Factors and Changes in Hippocampal Volume (N=268). PLOS ONE. Retrieved November 25, 2023, from https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0017006.

Opvee, a newly approved drug to combat opioid overdoses in emergency settings

EMMA KINGWELL
Secretary

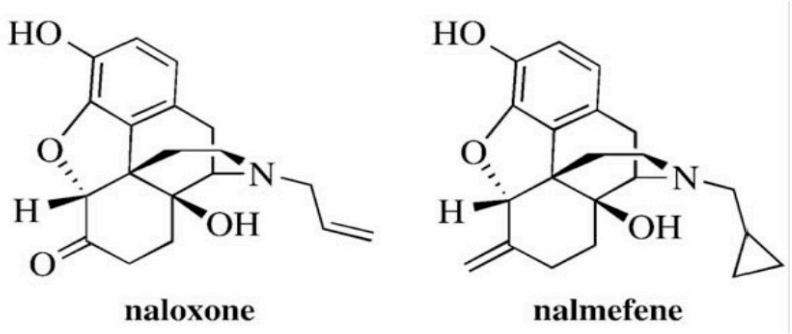

Figure 1. Although Naloxone (left) and Nalmefene (right) have similar structures, their differences give rise to different effectiveness. Nalmefene's structure is designed to have efficient opioid receptor binding, optimized bioavailability, and less of a risk for liver toxicity. (Pettinati et al., 2013)

The Federal Drug Administration (FDA) has recently approved a new nasal spray drug, nalmefene, to combat acute opioid overdoses. Nalmefene, also known as Opvee, is often compared to naloxone (Narcan), which is commonly used by first responders in emergency medical services. While Opvee and Narcan have similar applications, indications, and pharmacodynamics, it is important to understand the differences which will determine when and how the drug will be applied. As Opvee is still new, there is much contention comparing effectiveness and potential adverse effects of both Opvee and Narcan. However, since Opvee provides a second opportunity for potential overdose reversal and is just as, if not more effective than Narcan, it should soon be incorporated into emergency medicine practices across the country.

The opioid epidemic in the United States started in the 1900s and has since escalated into a full-blown public health emergency.

The opioid epidemic in the United States started in the 1900s and has since escalated into a full-blown public health emergency. This epidemic has incurred staggering costs, exceeding one trillion dollars from 2001 to 2017, and has claimed thousands of lives (Britch et al., 2022). The primary drugs behind this epidemic include prescription opioids such as oxycodone, heroin, and synthetic opioids such as fentanyl. Opioid overdoses present a narrow window for effective reversal and treatment which highlights the importance of accessible and efficient interventions such as Opvee and Narcan.

Although it has only been approved recently, Nalmefene is not a new drug and has been extensively studied in the past. The FDA approved a parenteral formulation of Nalmefene, a non-orally administered version of the drug, in 1995 to treat opioid overdoses, but it was withdrawn from the market in 2008 for commercial reasons rather than safety or efficacy concerns. The now-approved version of Nalmefene, which is indicated for adults and pediatric patients above 12 years old, is a 2.7 mg-dose nasal spray that can reverse opioid overdose effects for as long as eight hours after the first dose is administered. Now, Opvee is backed by a $10.8 million federally funded contract from the Biomedical Advanced Research and Development Authority (BARDA) and is also supported by a $7.4 million U01 "grand opportunities in medications development" grant from the National Institute on Drug Abuse (NIDA). Opvee's funding was granted priority review designation, which "expedites the development of drugs that have the potential to provide a significant improvement in the safety or effectiveness of the treatment, diagnosis, or prevention of a serious condition" (Valentino, 2023).

Nalmefene is a pure opiate antagonist which blocks opioid transmembrane neurotransmitter receptors in the central or peripheral nervous system (Theriot et al., 2022). There are three types of opiate receptors, namely, μ-opioid receptor (MOR), δ-opioid receptor (DOR), and κ-opioid receptor (KOR), which all have similar primary structures, function, and intracellular signaling mechanisms, and Nalmefene has antagonistic activity against all three of them (Feng et al., 2012). By blocking these opi-

oid receptors, Nalmefene can prevent respiratory depression, which is common in opioid overdoses. The FDA recognizes that Nalmefene can also reverse not only respiratory depression but also sedation and hypotension. Nevertheless, it may lead to opioid withdrawal symptoms including body aches, tachycardia, fever, runny nose, sneezing, and sweating.

One of the key distinctions between Narcan and Opvee is their efficacy against high-potency opioids, such as fentanyl and its analogs. Naloxone has a shorter half-life of 80 minutes and a duration of action of 60 to 90 minutes, necessitating higher doses and potentially leading to a higher incidence of opioid withdrawal symptoms. On the other hand, Opvee has a longer elimination half-life that ranges from 8 to 11 hours and a longer duration of action of one to four hours and therefore just as effectively reverses opioid signs and symptoms (Edinoff et al., 2021). In a study comparing the receptor pharmacology of GSK121498, a novel opiate receptor antagonist, in comparison to naltrexone, naloxone, 6-β-naltrexol, and nalmefene, researchers found that Nalmefene was about 8.6 times more potent than Naloxone (Kelly et al., 2015). However, it is worth noting that Opvee has a slower absorption rate when administered intranasally. Nonetheless, Opvee is generally considered safe and well-tolerated.

Opvee's recent approval by the FDA on May 22, 2023, marked a significant milestone in the fight against opioid overdoses. This approval granted Opvee the distinction of being the first Nalmefene hydrochloride nasal spray available for healthcare and community use. The FDA's decision has been framed as an opportunity to place a new prescription opioid reversal option in the hands of communities, harm reduction groups, and emergency responders. Opvee's efficacy in reversing the effects of respiratory depression, sedation, and hypotension is a critical factor in its approval. The FDA further expedited the development and review of Opvee by granting it priority review designation, recognizing its potential to significantly improve the safety and effectiveness of treating opioid overdoses (FDA, 2023).

Although the drug has been approved for use, there is still a transition to applications in emergency medicine, where it is most needed.

However, it is also crucial to note the presence of conflicting opinions in the scientific community. For example, some studies have argued that high-dose opioid antagonists are not necessary and found that most overdoses are reversed with standard doses (Lemen et al., 2023). Additionally, adverse effects such as allergic reactions have been observed after administration of strong opioid antagonists. To date, there have been no studies focused solely on Opvee's adverse effects.

Although the drug has been approved for use, there is still a transition to applications in emergency medicine, where it is most needed. While there may be concerns about potential adverse side effects compared to Narcan, the consequences of untreated opioid overdoses far outweigh these concerns. Implementing Opvee in the field can save countless lives, especially when considering the narrow treatment window for opioid overdoses. Some regions, such as Missouri, have already approved use of Narcan alternatives for first responders as early as July of 2023 (Wilson, 2023). As Opvee is integrated in emergency medical services, steps must also be taken towards increasing the accessibility.

Addressing the social determinants of health, including accessibility, is crucial to ensure that life-saving medications like Opvee are readily available, especially with the increasing rate of opioid overdoses. In a 2019 study done by Singh et al., the researchers compared disparities in terms of the opioid epidemic's effects between different groups and found that a lack of education and poor working and economic opportunities contribute to the epidemic. The data show increasing trends in drug overdose mortality among all major racial/ethnic groups with mortality rates being the highest among non-Hispanic whites and the lowest among Asian/Pacific Islanders (APIs); an annual rate of increase in drug mortality rates of 6.7% in women vs. 6.1% in men; a markedly upward trend in drug overdose mortality among children and adolescents compared to other age groups; and rapid increases in drug over-

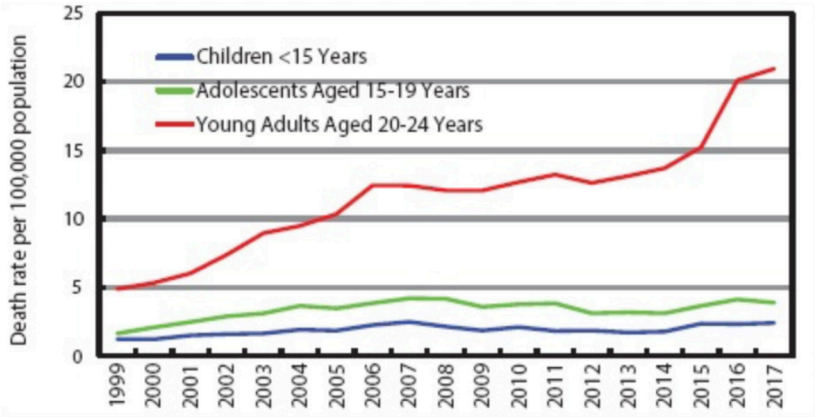

Figure 2. The rates of drug overdose mortality have been increasing since 1999 in the United States. Although the overall mortality rate has increased, the death rate among young adults aged 20-24 has quadrupled from 1999 to 2017, so it is crucial to have adequate emergency response options against overdoses. (Singh et al., 2019)

dose mortality in both metropolitan/urban and non-metropolitan/rural areas of the US. Beyond the overall rise in the therapeutic use, abuse, and nonmedical use of opioids in the US, several additional factors have been correlated as determinants of drug overdose mortality and prevalence of prescription opioids, including increased availability of and access to prescription opioids, low social capital, area poverty rate, unemployment rate, lack of economic opportunities, and racial/ethnic composition have been correlated as determinants of drug overdose mortality and prevalence of prescription opioids (Singh et al., 2019). Therefore, accessibility and education key ethical issues that must be addressed in terms of justice and equity in health care. Cost-effective strategies must be developed to bridge gaps in accessibility and provide an interim solution for managing opioid overdoses in emergency situations. One example of an initiative is 'Take-home naloxone' (THN) programs involving the provision of emergency naloxone kits to non-medical individuals, along with comprehensive training in basic overdose management, naloxone administration, and after-care (Strang et al., 2019). The idea of these kits are rooted in the idea of community-based Naloxone,which can be provided for emergency use for individuals at high risk, patients enrolled in treatment programs, and active drug users. A London survey of opioid users estimated that roughly two thirds of witnessed overdose deaths could have been prevented by THN, and about 90% of the survey respondents would have used the kit and medication if it had been available (Strang et al., 1999). By incorporating Nalmefene into such programs that educate the general public, we can better combat the opioid epidemic and improve patient outcomes.

Addressing the social determinants of health, including accessibility, is crucial to ensure that life-saving medications like Opvee are readily available, especially with the increasing rate of opioid overdoses.

While drug approval is a slow process, so is policy change. Although the FDA has approved Opvee, Opvee's accessibility and full integration into emergency medicine protocols are incomplete and crucial to addressing disparities in, and the progression of, the opioid epidemic. Although accessibility is a challenge, low-cost, creative solutions are needed to offer new opportunities to educate and combat the climbing opioid death rates. ❧

AUTHOR BIO

Emma is a second-year majoring in chemistry. She is interested in emergency medicine and cardiology and plans on attending medical school after college.

Edited by Siya Malhotra, Advaita Krishnan and Dr. Joseph Petrosino

Placed by Advaita Krishnan

REFERENCES

Bethesda (2020). LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. *National Institute of Diabetes and Digestive and Kidney Diseases*. https://www.ncbi.nlm.nih.gov/books/NBK548295/

Britch, S. C., Walsh, S. L. (2022). Treatment of opioid overdose: current approaches and recent advances. *Psychopharmacology* 239, 2063-2081. https://doi.org/10.1007/s00213-022-06125-5

Edinoff, A. N., Nix, C. A., Reed, T. D., Bozner, E. M., Alvarez, M. R., Fuller, M. C., Anwar, F., Cornett, E. M., Kaye, A. M., Kaye, A. D. (2021). Pharmacologic and Clinical Considerations of Nalmefene, a Long Duration Opioid Antagonist, in Opioid Overdose. *Psychiatry Int.* 2(4), 365-378. https://doi.org/10.3390/psychiatryint2040028

FDA Approves Prescription Nasal Spray to Reverse Opioid Overdose. *U.S. Food and Drug Administration*, 2023. https://www.fda.gov/news-events/press-announcements/fda-approves-prescription-nasal-spray-reverse-opioid-overdose

Feng, Y., He, X., Yang, Y., Chao, D., Lazarus, L. H., Xia, Y. (2012). Current Research on Opioid Receptor Function. *Current Drug Targets*, Vol. 13, Issue 2. https://doi.org/10.2174%2F138945012799201612

Glass, P. S., A., Jhaveri, R. M., Smith, L. R. (1994). Comparison of Potency and Duration of Action of Nalmefene and Naloxone. *Anesthesia & Analgesia* 78(3):p 536-541. https://doi.org/10.1213/00000539-199403000-00021

Kelly, E., Mundell, S. J., Sava, A., Roth, A. L., Felici, A., Maltby, K., Nathan, P. J., Bullmore, E. T., Henderson, G. (2015). The opioid receptor pharmacology of GSK1521498 compared to other ligands with differential effects on compulsive reward-related behaviors. *Psychopharmacology* 232, 305-314. https://doi.org/10.1007/s00213-014-3666-3

Lemen, P. M., Garrett, D. P., Thompson, E., Aho, M., Vasquez, C., Park, J. N. (2023). High-Dose Naloxone Formulations Are Not as Essential as We Thought. medRxiv. https://doi.org/10.1101/2023.08.07.23293781

Singh, G. K., Kim, I. E., Girmay, M., Perry, C., Daus, G. P., Vedamuthu, I. P., De Los Reyes, A. A., Ramey, C. T., Martin, E. K., Allender, M. (2019). Opioid epidemic in the United States: Empirical trends, and a literature review of social determinants and epidemiological, pain management, and treatment patterns. *International Journal of Maternal and Child Health and Aids* Vol. 8 No. 2. https://doi.org/10.21106/ijma.284

Skolnick, P. (2021). Treatment of overdose in the synthetic opioid era. *Pharmacology & Therapeutics* Vol. 223. https://doi.org/10.1016/j.pharmthera.2021.108019

Strang, J., McDonald, R., Campbell, G., Degenhardt, L., Nielsen, S., Ritter, A., Dale, O. (2019). Take-Home Naloxone for the Emergency Interim Management of Opioid Overdose: The Public Health Application of an Emergency Medicine. *Drugs* 79, 1395-1418. https://doi.org/10.1007/s40265-019-01154-5

Strang, J., Powis, B., Best, D., Vingoe, L., Griffiths, P., Taylor, C., Welch, S., Gossop, M. (2002). Preventing opiate overdose fatalities with take-home naloxone: pre-launch study of possible impact and acceptability. *Addiction* Vol. 94, Issue 2. https://doi.org/10.1046/j.1360-0443.1999.9421993.x

Theriot, J., Sabir, S., Azadfard, M. (2023). Opioid Antagonists. *National Library of Medicine*. https://www.ncbi.nlm.nih.gov/books/NBK537079/

Valentino, T. (2023). New Opioid Overdose Reversal Nasal Spray Receives FDA Approval. *Addiction Professional*. https://www.hmpgloballearningnetwork.com/site/ap/news/new-opioid-overdose-reversal-nasal-spray-receives-fda-approval

Wang, D. S., Sternback, G., Varon, J. (1998). Nalmefene: a long-acting opioid antagonist. Clinical applications in emergency medicine. *The Journal of Emergency Medicine*, Volume 16, Issue 3. https://doi.org/10.1016/S0736-4679(98)00019-5.

Wilson, J. (2023). Mo. Senate bill provision allows first responders to use Narcan alternatives. *St. Joseph News-Press*. https://www.ems1.com/politics/articles/mo-senate-bill-provision-allows-first-responders-to-use-narcan-alternatives-vKFM3nizMBRZcTZb/

IMAGE REFERENCES

Pettinati, H. M., Dundon, W. D., Lopez, M. J. C. (2013). Naltrexone and Opioid Antagonists for Alcohol Dependence. Interventions for Addiction. *Comprehensive Addictive Behaviors and Disorders* Vol. 3. https://doi.org/10.1016/B978-0-12-398338-1.00039-7

Singh, G. K., Kim, I. E., Girmay, M., Perry, C., Daus, G. P., Vedamuthu, I. P., De Los Reyes, A. A., Ramey, C. T., Martin, E. K., Allender, M. (2019). Opioid epidemic in the United States: Empirical trends, and a literature review of social determinants and epidemiological, pain management, and treatment patterns. *International Journal of Maternal and Child Health and Aids* Vol. 8 No. 2. https://doi.org/10.21106/ijma.284

Applications of chaos theory in predicting arrhythmia

AMELIA DASARI
Staff Writer

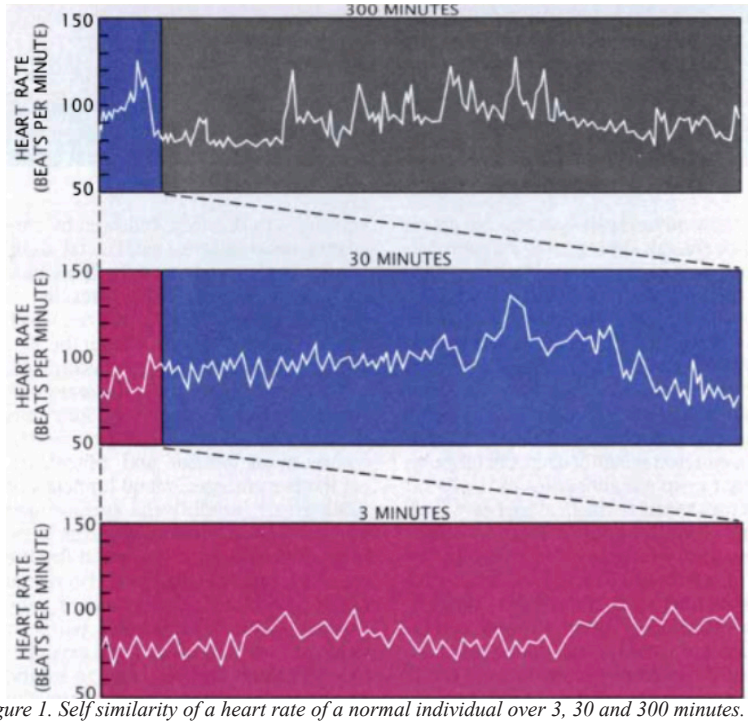

Figure 1. Self similarity of a heart rate of a normal individual over 3, 30 and 300 minutes. (Goldberger et al., 1990)

The human heart beats around 2 to 3 billion times throughout life, driven by the pacemaker cells in the right atrium's sinoatrial node (SAN). The SAN, an electrical oscillator, dictates the heart's rhythm, known as "sinus rhythm," which has an inherent variability with activities like breathing, relaxation, stress, or danger. Heart rate variability (HRV) results from the interplay between the sympathetic (fight or flight) and parasympathetic (rest and digest) nervous systems, maintaining a healthy balance.

Disruptions in this balance due to aging, lifestyle, or heart disease can lead to arrhythmias. Arrhythmias range from mild to serious conditions like atrial fibrillation, bradycardia, and tachycardia. Sustained ventricular tachycardia (rapid heartbeat) which can cause ventricular fibrillation (chaotic heartbeat) is one of the leading causes of Sudden Cardiac Death (SCD) (Ludhwani, 2023). Mortality can be prevented with intervention using defibrillators within 10 minutes of the onset of VF though every passing minute can lead to the failure of an organ and decrease the chances. But underlying such interventions is a timely identification of VT/VF using mathematical models of heart rate rhythms. While wearables like smartwatches and devices like auto-defibrillators can detect VT/VF using statistical techniques, the detection happens after the onset of symptoms. Understanding why a tachycardia degenerates into fibrillation and SCD and detecting triggers for the degeneration remains a challenge. In this paper, we'll review how modeling the dynamics of our heart not as a well-behaved linear system where its response is proportional to the input stimuli, but as a dynamical chaotic system to study HRV using non-linear chaos theory techniques may help us predict the likelihood of fibrillation and SCD.

Modeling the dynamics of our heart as a dynamical chaotic system may help us predict the likelihood of fibrillation and SCD.

The first noted example of chaos theory in natural phenomena was in the 1880s when mathematician and theoretical physicist Henri Poincaré was studying the motion of an asteroid under gravitational pull from Jupiter and the sun - the n-body problem in physics which uses math to predict the motion of a group of celestial objects that interact gravitationally. While he couldn't solve the problem, he discovered that even minute changes in the initial conditions could produce unpredictable, large changes in the resulting orbit of an asteroid thus making the prediction of the motion of an asteroid almost impossible (Oestreicher, 2007). Edward Lorenz found the exact same sensitivity to initial conditions while building climate models to predict weather conditions at MIT in the

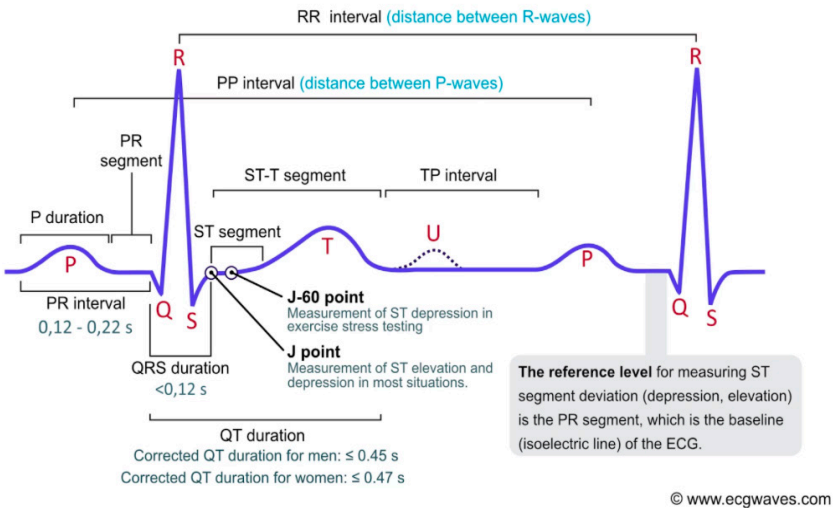

Figure 2. An ECG curve with its most common waveforms, T, P, and S. (ECG and Echo, 2023)

60s leading to his very famous chaos theory prediction that a butterfly flapping its wings in New Mexico may eventually cause a hurricane in Asia. Lorenz presented his models of chaotic systems in 1972 and the computer graphic of his chaotic system was the first representation of what's known as an "attractor" - a specific set of values towards which a system evolves (Oestreicher, 2007). Chaos theory was born and over time, as computing power grew, the theory disseminated into the medical field in the early 90s, when scientists like Goldberger observed that the characteristics of chaos theory and non-linear dynamics might underlie some of the unique features seen in biology like the fractal characteristics of a temporal heart rate pattern - the pattern over a 300 minute interval looks similar to a pattern over a 3 minute time scale (Figure 1).

Abnormalities in heart waves signify electrical depolarization, causing excessive contractions. Depolarization unfolds sequentially in the heart's chambers: first the atrium, then the septum, and finally, the ventricles. Traditionally, physiologists, since the 1970s, used statistical metrics for rhythm or HRV abnormalities. Metrics, categorized into time and frequency domains, include SDNN for overall HRV and RMSSD for short-term HRV. Frequency domain metrics, like LF and HF, represent sympathetic and parasympathetic activities. The LF/HF ratio indicates autonomic balance. While these metrics offer insights into autonomic activity, they aren't standalone arrhythmia diagnostic tools. Algorithms have been designed with predefined rules to classify arrhythmias - for eg: the lack of QRS complex, S-T segments or T-waves could indicate VF. Machine learning models like SVMs, neural networks, or decision trees have also been trained to recognize patterns and classify arrhythmias but they still use traditional HRV linear metrics as their feature set.

Though widely used in smartwatches and defibrillator monitors, these algorithms are post-condition. VF onset hampers effective blood pumping, leading to organ failure within

DFA (α1)	Deceased			Alive			Mean Difference (Dead vs Alive)		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random	95% CI
1.1.1 Myocardial Infraction									
Makikallio 1999	0.9	0.26	72	1.07	0.25	87	8.20%	-0.17	[-0.25, -0.09]
Huikuri 2000	0.67	0.19	114	0.83	0.2	332	11.10%	-0.16	[-0.20, -0.12]
Tapanainen 2002	0.76	0.33	49	1.02	0.3	648	7.20%	-0.26	[-0.36, -0.16]
Peltola 2004 (MI Group)	0.71	0.33	42	0.89	0.36	42	4.50%	-0.18	[-0.33, -0.03]
Subtotal (95% CI)			**277**			**1109**	**31%**	**-0.18**	**[-0.22, -0.14]**
1.1.2 Left Ventricular Dysfunction									
Perkiomaki 2001	0.68	0.24	11	0.98	0.32	41	3.60%	-0.3	[-0.47, -0.13]
Makikallio 2001	0.84	0.19	210	0.91	0.21	289	11.40%	-0.07	[-0.11, -0.03]
Perkiomaki 2003	0.71	0.264	70	0.998	0.293	24	5.10%	-0.29	[-0.42, -0.16]
Maestri 2007	1.08	0.23	75	1.18	0.24	125	9.20%	-0.1	[-0.17, -0.03]
Subtotal (95% CI)			**366**			**479**	**29.40%**	-0.16	**[-0.26, -0.07]**
1.1.3 Non-Cardiac									
Makikallio 2001	0.956	0.19	100	1.14	0.17	161	10.80%	-0.18	[-0.23, -0.14]
Peltola 2004 (Healthy group)	0.83	0.27	42	0.96	0.19	42	6.90%	-0.13	[-0.23, -0.03]
Makikallio 2004	1.06	0.24	33	1.2	0.18	51	7.20%	-0.14	[-0.24, -0.04]
Stein 2010	0.97	0.21	49	1.11	0.2	97	8.90%	-0.14	[-0.21, -0.07]
Chiang 2016	0.89	0.2	14	1.18	0.29	120	5.90%	-0.29	[-0.41, -0.17]
Subtotal (95% CI)			**238**			**471**	**39.60%**	-0.17	**[-0.21, -0.13]**
Total (95% CI)			**881**			**2059**	**100%**	-0.17	[-0.21, -0.13]

Figure 3. α1 in the deceased group was significantly lower than the alive group (pooled mean difference −0.17, 95% CI [−0.21, −0.13]) (n = 2940, p < 0.00001). α1 was significantly different between the alive and deceased groups for all three subgroups—MI , LV Dysfunction, and NC subgroups. (Sen, 2018)

	Unadjusted Association			Association Adjusted for All Risk Variables		
	Relative Risk	95% CI	p Value	Relative Risk	95% CI	p Value
All-cause mortality						
Short-term fractal exponent ($\alpha_1 < 1.0$)	1.7	(1.4–1.9)	< 0.001	1.4	(1.1–1.7)	< 0.01
SDNN (<120 ms)	1.3	(1.1–1.6)	< 0.01	1.1	(0.9–1.3)	NS
Power-law ($\beta < -1.5$)	1.8	(1.4–1.9)	< 0.001	1.6	(1.3–1.9)	< 0.001
Cardiac death						
Short-term fractal exponent ($\alpha_1 < 1.0$)	2.5	(1.9–3.2)	< 0.001	2.1	(1.5–2.9)	< 0.001
SDNN (<120 ms)	1.4	(1.1–1.8)	< 0.05	0.9	(0.6–1.2)	NS
Power-law ($\beta < -1.5$)	2.3	(1.7–3.1)	< 0.001	1.7	(1.3–2.5)	< 0.001
Sudden cardiac death						
Short-term fractal exponent ($\alpha_1 < 1.0$)	4.1	(2.5–6.6)	< 0.001	4.3	(2.0–9.2)	< 0.001
SDNN (<120 ms)	1.6	(1.1–2.4)	< 0.05	1.1	(0.6–2.1)	NS
Power-law ($\beta < -1.5$)	2.2	(1.5–3.1)	< 0.001	1.9	(0.9–4.0)	NS
Autopsy-verified sudden cardiac death						
Short-term fractal exponent ($\alpha_1 < 1.0$)	4.5	(2.4–8.4)	< 0.001	4.9	(1.8–13.4)	< 0.01
SDNN (<120 ms)	1.6	(0.9–2.7)	NS	1.3	(0.5–3.2)	NS
Power-law ($\beta < -1.5$)	2.8	(1.7–4.4)	< 0.001	2.8	(1.2–6.7)	< 0.05

Figure 4. Traditional diagnostic metrics like SDNN (Standard Deviation of the R-R intervals (See Figure 2)) show no statistical significance (NS) for cardiac death making them useless to predict SCD (Mäkikallio et al., 2001)

10 minutes without treatment. Early detection, crucial for intervention, involves research on signals preceding deadly arrhythmias and SCD. Detecting imminent VF minutes before occurrence allows timely interventions. And a lot of these attempts also involve nonlinear or fractal HRV metrics.

This plot can show a system's evolution and a wealth of physiological information of the cardiovascular system (Wang, 2022).

Some of the early fractal dynamic metrics of HRV involved using the power law to compute the fractal dimension of a heart signal () using frequency domain measurements. This was based on the observation that some self similar fractals can be modeled using a power function f(x) = x-. Scaling such a function leads to a self similar function: f(cx) = c-f(x). Computation of for the heart rate function was computationally intensive and required a huge amount of data and the best fit was observed only for very low frequency measurements only. This led to a technique called Detrended Fluctuation Analysis (DFA), where the RR interval data is a) converted to spreads around the mean, b) divided into smaller parts based on a scale (for ex. 10 points per part). A linear fit slope is computed for each part and the root and a RMS is calculated for each part (detrending) and averaged over all parts. This is then repeated for multiple scales (10, 100, 1000, and so on) and finally the best linear fit is computed for the log average RMS vs log scale (assuming RMS and scale have a power law relationship and the slope of log RMS vs log scale is the fractal dimension) (Goldberger, 2002). A review of all HRV fractal measure studies done in 2018 by Sen shows that efficacy of a fractal measure like DFA as a prognostic measure even in free running conditions (Figure 3).

A similar study done by Mäkikallio and used by Sen above involving 325 elderly in Finland back in 2001 had predicted the same results (Figure 4). But one more observation from Mäkikallio was that traditional HRV diagnostic metrics like SDNN for cardiac deaths show no statistical significance ($p \sim 0.05$) implying the fractal metrics have a more predictive power.

There have been other non-linear metrics that have been developed over the last two decades like multiscale entropy (which assesses the regularity and ordering of the signals over multiple scales) and symbolic dynamics (again measures variability of patterns) which have been shown to outperform traditional statistical measure for predicting SCD. (Gazzetti, 2005)

Another well-studied nonlinear technique used to study chaos is a Poincaré Plot (Figure 5). It can be used to assess the dynamics of HRV by a representation of the values of each pair of R-R intervals into a simplified phase space where a point's x value

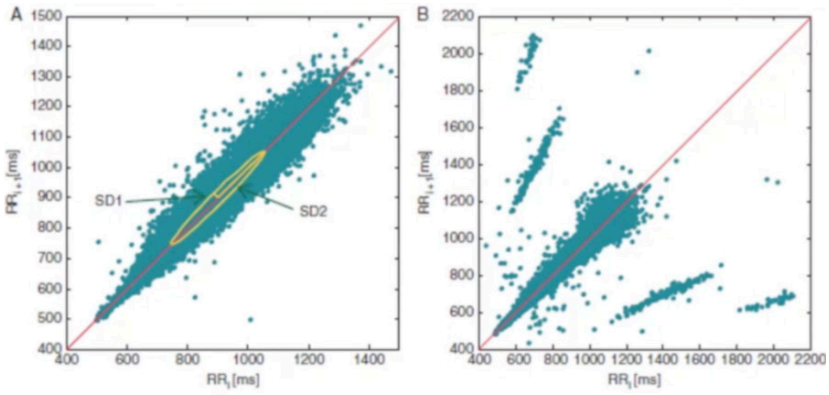

Figure 5. A standard Poincaré plot of the RR intervals for a healthy heart (left) and an unhealthy one (right) (Wang, 2022).

denotes the current R-R interval time and the y value denotes the previous value. This plot can show a system's evolution and a wealth of physiological information of the cardiovascular system (Wang, 2022). As in any chaotic system, the future state of a system depends on the previous state and that's the underlying principle. If the relationship between one heartbeat interval and the next is deterministic, the Poincaré plot may exhibit structure reflecting the underlying dependence of the present state on previous state(s) as seen in Figure 5 (left) where the Poincaré plot of healthy human is an approximate ellipse. If the relationship between the current heart state and the previous state is random, then the Poincaré plot yields a formless group of points as in the right half of Figure 5 showing that the heart rate has bifurcated into a chaotic arrhythmic system

An electrocardiogram (ECG) can record and visualize this heartbeat rhythm, which can then be used for "detecting cardiovascular diseases and also examining breathing patterns and mental stress" (Gupta, 2020).

There has been research done to design automated algorithms using Poincare plots features - like detecting the ellipse pattern and measuring its major and minor axes - to predict fibrillation without the need for any human intervention and any specific threshold (Park et al., 2009).

There are also numerous studies involving the use of the nonlinear/chaos metrics combined with traditional time and frequency domain measures like SDNN to build and train machine learning or deep learning models to analyze heart rate signals and predict arrhythmias and SCDs (Benitez & Duque, 2017), (Fujita et al., 2016) and (Ebrahimzadeh et al., 2014)

Overall, non-linear/chaos metrics have been proven to be better at predicting SCD but the enthusiasm has faded over recent years. And the reason for this is that most of these techniques - a) need long term measurements, b) are restricted to centers with advanced knowledge in engineering and/or computer science, c) not reproducible easily, d) are sensitive to adjustable parameters and preprocessing/denoising steps and e) difficult to explain and understand from a physiological/biochemical perspective. But we now have entered an era of wearable technology like smart watches and large public datasets like AllofUs from NIH, MVP (Million Veteran Program) or private datasets like Epic and Cerner. Some of these are considering incorporating wearable device data in their datasets and this data set will also include other clinically relevant information like genetic information and biochemical biomarkers from blood tests. This golden era of wearables and data collection will make it possible to now have continuous long term measurements available to now apply the non-linear techniques and then correlate them to not just SCD but other biochemical markers and even genetic information.

In summary, the heart is a complex non-linear dynamic system where small changes in the initial conditions of the system can lead to large and unpredictable changes like arrhythmias. Traditional diagnostic metrics fail to correctly predict SCD due to arrhythmia and are mostly ineffective. The metrics derived by assuming that chaos theory applies to the heart have been proven to be effective in predicting SCD, but their widespread usage is hindered due to an inherent computational complexity and lack of data needed to perform such analysis. It is this author's opinion that we are entering a golden age of wearable, heart monitoring devices which also have the ability to perform computationally intensive tasks. This will likely lead to a resurgence of the study of HRV using non-linear techniques to not just predict the likelihood of an SCD but also correlate these metrics to other genetic, medical conditions to enable a holistic treatment. ❧

AUTHOR BIO

Amelia is a second year majoring in neuroscience & behavioral biology. Her interests are neuroscience and neurodegenerative diseases.

Edited by Aastha Bansal, Claire Zegger, and Dr. Tyler Cymet

Placed by Claire Zegger

REFERENCES

Benitez, R. U., & Duque, A. (2017). Sudden Cardiac Death Prediction Based On a Nonlinear Estimation. In IFMBE proceedings. https://doi.org/10.1007/978-981-10-4086-3_122

Bin Wang, Dewen Liu, Xin Gao, Yunlei Luo, "Three-Dimensional Poincaré Plot Analysis for Heart Rate Variability", Complexity, vol. 2022, Article ID 3880047, 9 pages, 2022. https://doi.org/10.1155/2022/3880047

Choi, B. (2018). Heart beat interval estimation algorithm for low sampling frequency electrocardiogram signal. The Transactions of the Korean Institute of Electrical Engineers, 67(7), 898–902.

Claus D Wagner, Pontus B Persson, Chaos in the cardiovascular system: an update, Cardiovascular Research, Volume 40, Issue 2, November 1998, Pages 257–264, https://doi.org/10.1016/S0008-6363(98)00251-X

Ebrahimzadeh, E., Pooyan, M., & Bijar, A. (2014). A Novel Approach to Predict Sudden Cardiac Death (SCD) Using Nonlinear and Time-Frequency Analyses from HRV Signals. NLM. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3913584/

Fujita, H., Acharya, U. R., Sudarshan, V. K., Ghista, D. N., Sree, S. V., Eugene, L. W. J., & Koh, J. E. W. (2016). Sudden cardiac death (SCD) prediction based on nonlinear heart rate variability features and SCD index. Applied Soft Computing, 43, 510–519. https://doi.org/10.1016/j.asoc.2016.02.049

Goldberger, A. L., Rigney, D. R., & West, B. J. (1990). Science in Pictures: Chaos and Fractals in Human Physiology. Scientific American, 262(2), 42–49. https://doi.org/10.1038/scientificamerican0290-42

Goldberger, Ary L. et al. (2002). Fractal Dynamics in Physiology: Alterations with Disease and Aging. Proceedings of the National Academy of Sciences of the United States of America, 99(1), 2466–2472. http://www.ncbi.nlm.nih.gov/pmc/marticles/PMC128562/

Gupta, V., Mittal, M. & Mittal, V. Chaos Theory: An Emerging Tool for Arrhythmia Detection. Sens Imaging 21, 10 (2020). https://doi.org/10.1007/s11220-020-0272-9

Gupta, V., & Mittal, M. (2020). Chaos theory and ARTFA: Emerging tools for interpreting ECG signals to diagnose cardiac arrhythmias. https://doi.org/10.1007/s11277-021-08411-5

Kranjec, J. (2014). Non-contact heart rate and heart rate variability measurements: A review. Journal of Biomedical Signal Processing and Control, 13, 102–112.10.1016/j.bspc.2014.03.004

Ludhwani, D. (2023, August 8). Ventricular fibrillation. StatPearls - NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK537120/

Mäkikallio, T. H., Huikuri, H. V., Mäkikallio, A., Sourander, L., Mitrani, R. D., Castellanos, A., & Myerburg, R. J. (2001). Prediction of sudden cardiac death by fractal analysis of heart rate variability in elderly subjects. Journal of the American College of Cardiology, 37(5), 1395–1402. https://doi.org/10.1016/s0735-1097(01)01171-8

Oestreicher, C. (2007). A history of chaos theory. Dialogues in Clinical Neuroscience, 9(3), 279–289. https://doi.org/10.31887/dcns.2007.9.3/coestreicher

Qu Z. (2011). Chaos in the genesis and maintenance of cardiac arrhythmias. Progress in biophysics and molecular biology, 105(3), 247–257. https://doi.org/10.1016/j.pbiomolbio.2010.11.001

Savi, M. A. (2005 Apr-June). Chaos and Order in Biomedical Rhythms. Journal of the Brazilian Society of Mechanical Science and Engineering. Vol. XXVII, No. 2, 157-169. 10.1590/S1678-58782005000200008

Sen, J., & McGill, D. (2018). Fractal analysis of heart rate variability as a predictor of mortality: A systematic review and meta-analysis. Chaos, 28(7). https://doi.org/10.1063/1.5038818

Sharma, V (2009). Deterministic chaos and fractal complexity in the dynamics of cardiovascular behavior: perspectives on a new frontier. Division of Pharmacology and Toxicology, Faculty of Pharmaceutical Sciences, University of British Columbia. 10.2174/1874192400903010110

S. R. F. S. M. Gois and M. A. Savi, "An analysis of heart rhythm dynamics using a three-coupled oscillator model," Chaos, Solitons and Fractals, vol. 41, no. 5, pp. 2553–2565, 2009. https://doi.org/10.1016/j.chaos.2008.09.040

Tahmineh Azizi, "On the fractal geometry of different heart rhythms, Chaos, Solitons & Fractals": X, Volume 9, 2022, 100085, ISSN 2590-0544, https://doi.org/10.1016/j.csfx.2022.100085.

Valderrábano, M. (2022). The future of antiarrhythmic drug therapy: Will drugs be entirely replaced by procedures? Methodist DeBakey Cardiovascular Journal, 18(5), 58–63. https://doi.org/10.14797/mdcvj.1185

Weiss, J. N., Garfinkel, A., Karagueuzian, H. S., Qu, Z., & Chen, P. S. (1999). Chaos and the transition to ventricular fibrillation. Circulation, 99(21), 2819–2826. https://doi.org/10.1161/01.cir.99.21.2819

W. Thanom and R. N. K. Loh, "Nonlinear control of heartbeat models," Journal on Systemics, Cybernetics and Informatics, vol. 9, no. 1, pp. 21–27, 2009.

IMAGE REFERENCES

Bin Wang, Dewen Liu, Xin Gao, Yunlei Luo, "Three-Dimensional Poincaré Plot Analysis for Heart Rate Variability", Complexity, vol. 2022, Article ID 3880047, 9 pages, 2022. https://doi.org/10.1155/2022/3880047

ECG interpretation: Characteristics of the normal ECG (P-wave, QRS complex, St Segment, T-wave). ECG & ECHO. (2023, June 25). https://ecg-waves.com/topic/ecg-normal-p-wave-qrs-complex-st-segment-t-wave-j-point/

Sharma, V (2009). Deterministic chaos and fractal complexity in the dynamics of cardiovascular behavior: perspectives on a new frontier. Division of Pharmacology and Toxicology, Faculty of Pharmaceutical Sciences, University of British Columbia. 10.2174/1874192400903010110

Pig organs and alternate technologies for human transplant

UMA OBALAPURAM
Staff Writer

In the United States, more than 100,000 people are currently on the organ transplant list waiting for a life-saving organ. Every 10 minutes, another person is added to this endless list (Organ Donation Statistics 2023). This creates a growing concern in American healthcare today about the increasing lack of organs to match current demand (Figure 1).

The average patient waits three to five years for a kidney transplant (Transplant Waiting List 2023). Recently, however, researchers have been developing an alternative - using animal, particularly pig, organs. In fact, earlier this year, researchers at NYU Langone Transplant Institute transplanted a pig kidney into a brain-dead human recipient; the organ was still viable after 32 days, the longest time a pig kidney has stayed viable in a human. Pig organ transplants rely on complex physiological features that allow them to work in humans, but these porcine organs also introduce ethical and medical concerns which has left the medical community to continue considering alternative solutions.

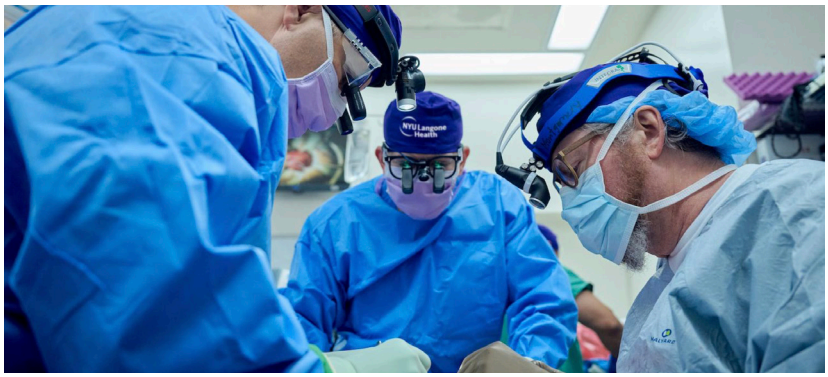

Figure 2. An image of the surgeons actually xenotransplanting the pig kidney into the human patient. (NYU, 2023)

Xenotransplantation is the transplant of animal tissues or organs into a different species. Xenotransplantation often occurs in science laboratories, where human cells, samples, or tumors are xenografted into research model organisms, like mice or zebrafish (the process of transplant is called xenotransplantation, the actual cells or tissues once in the source are called the xenograft). Xenotransplantation was first tested for its viability using non-human primates (NHP). After having NHPs with the xenotransplanted organs live for more than a year, humans started testing this theory in brain-dead patients (Adams 2023). After testing the viability of pig organs in brain-dead human patients, the next step will likely be to see how pig organs fare in living human patients, and for how long they are viable. In the instances from NYU's 2023 study, this involved taking kidneys from a pig and transplanting them into a human source, where they remained functional for over a month (NYU 1 2023).

Xenotransplantation is the transplant of animal tissues or organs into a different species.

The surgical team used a pig kidney that had been genetically modified to knock out alpha-gal, a signaling protein responsible for a rapid antibody-mediated rejection of pig organs by the human. In addition to this, the pig's

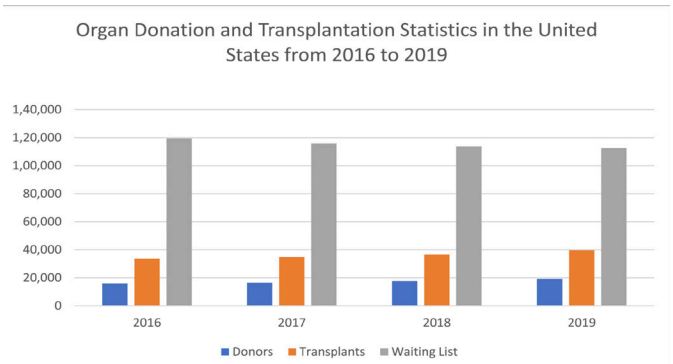

Figure 1. A graphic showing organ transplant data from 2016-2019 in the US (Shinkar 2022).

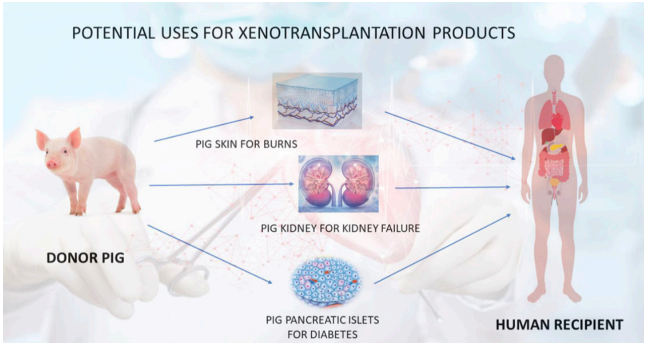

Figure 3. Many potential uses for xenotransplantation, particularly from donor pigs. (FDA 2022)

thymus - one of the organs responsible for training a pig's immune defenses - was transferred along with the organ to prevent complex and new immune responses in the human body. The thymus is where T-cells mature and by transplanting it with the organ, it is less likely for the pig organ to be rejected by the human body. Normal urine production is a marker of a healthy kidney and creatinine is a waste product created by kidney filtration. After the organ was transplanted, the human patient showed normal urine production and creatinine levels, and did not show any other signs of rejection (NYU 2 2023).

A natural question would be why pig organs? Would it not make more sense to use organs from a more closely related species to humans, like monkeys or great apes? To consider an animal for human transplant, a several standards should first be met: the animal should have compatible anatomy and physiology to humans, there should be little to no risk of cross-species infections that could danger the patient, there should be little to no immunological barriers between species that could cause rejection, the donor animal should be easy to sustain and breed, and have multiple offspring per pregnancy, and the species used should have minimal ethical controversy (Levy 2000). NHPs are the most physiologically and anatomically similar to humans. However, they do not fulfill the second condition as many deadly human diseases, such as HIV and Herpes species, originated as monkey vectors that transfected humans. Many infectious diseases in monkeys still exist that could transfect humans and become potentially lethal if NHP organs were used for xenotransplantation. Unlike these NHPs, pigs meet most of these standards. They are anatomical and physiologically similar to humans, there is little risk of transfection, and they are easy to breed and sustain (Levy 2000). In addition, pigs and humans share important similarities in their anatomy and genetic composition like metabolic rates and similar organ sizes, making them ideal candidates for organ transfer (Bourret, 2016). Though they are currently the best option, the use of pig organs for xenotransplantation still faces immunological barriers and raises major ethical concerns.

Is it morally right to raise these pigs for slaughter to extend human lives?

One of the biggest ethical concerns to consider is the life and value of each pig. While these pigs could provide organs that can save thousands of lives a year, is it justified to raise an animal only to kill it to harvest its organs? The pig used for xenotransplantation would likely have to be genetically modified to block out alpha-gal and any other immunological mechanisms that could cause rejection of the organ in the human body. However, this would likely leave the pig vulnerable to many diseases it would normally be able to fight off. In addition, these pigs would have a decreased quality of life, especially without key immune system defenses. Is it morally right to raise these pigs for slaughter to extend human lives? These are just a few questions researchers and lawmakers must consider as pig organs become a more viable solution for organ transplant.

Another dilemma to consider is how these pigs should be treated in various legal scenarios. In the US, there are different sets of laws that apply to various species of animals, which are different from human laws (i.e. in cases of organ donation, what is considered "proper" or humane treatment, etc.). Would these pigs, who are being raised for the purpose of human organ donation, be subjected to human laws or pig laws? This is another consideration that scientists and lawmakers take into account to ensure that these pigs not only

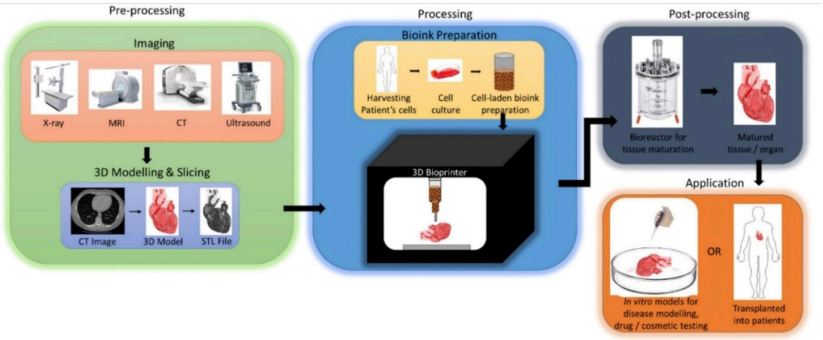

Figure 4. A visual to show the process of 3D bioprinting organs as a viable solution for organ transplant. (Shinkar 2022)

have a good life, but also that their organs remain in optimal condition for xenotransplantation.

One could argue that there is a danger associated with using organs from pigs: the lack of understanding of pig-specific diseases. It might be possible for human recipients to contract a disease that usually affects pigs, which could act as a catalyst for a public health crisis, such as a pandemic. Some examples of such transfections from pigs to humans in the past include swine influenza and Porcine endogenous retrovirus. These cross-species infections are especially dangerous as humans are not adapted to fight these illnesses. As a result, these infections are more deadly to humans, like in the case of COVID-19. Though there are examples of pig to human transfections in the past, most researchers believe that this type of transfection is unlikely, since pigs and humans have lived in close proximity for millenia and pigs are a common food source for humans (Boneva 2001). Thus, scientists believe that the potential risks of using pig organs outweigh the benefits and thus, using pig organs would be a much safer alternative compared to those of other, similarly sized organisms.

Though these organs would save the lives of many humans, there are other options besides harvesting organs from pigs – like organoids. Organoids are organs grown in vitro primarily to isolate individual organs and study how they behave in the body. These organoids can be grown in the lab setting using a patient's pluripotent stem cells (PSC). While they are primarily used in vitro as a means of studying the specific organ they form, there have been instances where they have worked in vivo. For example, iPSC retinal cells were transplanted into humans with macular degeneration (Reza 2021). There have also been recent studies showing that liver organoids can work as functional organs in mice (Reza 2021). Though this solution is unorthodox and still requires much testing, it is a viable solution that does not sacrifice pigs for the sake of their organs.

"In the past, 3D bioprinting has been used to create skin grafts, livers, hearts, and vasculature" (Shinkar et al, 2022)

Another alternative approach to using pig organs for transplants would be to 3D print organs, also known as 3D bioprinting. This is a multi-step process that is being explored currently. First, a 3D model of the organ is made with internal and external microstructure of the desired organ. Second, cells from a patient or donor are collected to create the organ; these cells are then combined with bioinks, made from hydrogels and cellular biomaterials. Once these supplies are gathered, the actual organ can be printed. In the past, 3D bioprinting has been used to create skin grafts, livers, hearts, and vasculature (Shinkar et al, 2022). Though 3D bioprinting is still being developed to use across a larger variety of applications and needs to be further perfected before implementing it as a full scale solution, it has promising implications for the future of organ transplants.

Saving human lives and doing it in a humane manner is the crux of the ongoing issue of organ transplantation. Understanding how xenotransplantation works and the importance of using pig organs is key to having a more nuanced understanding of this dilemma. Though the advent of xenotransplantation came about to save human lives, that does not mean a pig or non-human primate's life is any more expendable. The true solution to the issue of organ transplant is investing time and resources into developing alternative methods, like organoids or 3D printed or-

gans. Though it may be unpleasant, it seems that pig organs may be the best solution the medical field can provide for patients in need of organ transplants for the time being. ❧

AUTHOR BIO

Uma is a fourth year majoring in biology with a minor in religion. Her interests are in organ translants and healthcare access.

Edited by Claire Qu, Justin Hahm, and Dr. Kim Tram

Placed by Justin Hahm

REFERENCES

Research, C. for B. E. and. (2022, September 26). Xenotransplantation. FDA; FDA. https://www.fda.gov/vaccines-blood-biologics/xenotransplantation

Pig Kidney Xenotransplantation Performing Optimally After 32 Days in Human Body. (2023). NYU Langone News. Retrieved September 23, 2023, from https://nyulangone.org/news/pig-kidney-xenotransplantation-performing-optimally-after-32-days-human-body

Progress in Xenotransplantation Opens Door to New Supply of Critically Needed Organs. (2023). NYU Langone News. Retrieved October 9, 2023, from https://nyulangone.org/news/progress-xenotransplantation-opens-door-new-supply-critically-needed-organs

Transplant Waiting List. (2023). Retrieved October 18, 2023, from https://www.kidneyfund.org/kidney-donation-and-transplant/transplant-waiting-list

Adams, A., Cendales, L. C., Cooper, D. K. C., Cozzi, E., Gill, J., Judd, E., Katz, E., Kirk, A. D., Fishman, J. A., Reese, P. P., Wall, A., & Markmann, J. F. (2023). American Society of Transplant Surgeons-American Society of Transplantation report of FDA meeting on regulatory expectations for xenotransplantation products. American Journal of Transplantation, 23(9), 1290–1299. https://doi.org/10.1016/j.ajt.2023.05.010

Bobier, C., Rodger, D., Hurst, D. J., & Omelianchuk, A. (2023). In defense of xenotransplantation research: Because of, not in spite of, animal welfare concerns. Xenotransplantation, 30(1), e12791. https://doi.org/10.1111/xen.12791

Boneva, R. S., Folks, T. M., & Chapman, L. E. (2001). Infectious Disease Issues in Xenotransplantation. Clinical Microbiology Reviews, 14(1), 1–14. https://doi.org/10.1128/CMR.14.1.1-14.2001

Bourret, Rodolphe, et al. (2016). Human–Animal Chimeras: Ethical Issues about Farming Chimeric Animals Bearing Human Organs - Stem Cell Research & Therapy. BioMed Central, BioMed Central https://stemcellres.biomedcentral.com/articles/10.1186/s13287-016-0345-9.

Chan, J. C. Y., Chaban, R., Chang, S. H., Angel, L. F., Montgomery, R. A., & Pierson, R. N. (2023). Future of Lung Transplantation: Xenotransplantation and Bioengineering Lungs. Clinics in Chest Medicine, 44(1), 201–214. https://doi.org/10.1016/j.ccm.2022.11.003

Levy, M. F. (2000). Animal organs for human transplantation: How close are we? Proceedings (Baylor University. Medical Center), 13(1), 3–6.

Mohd Zailani, M. F., Hamdan, M. N., & Mohd Yusof, A. N. (2023). Human–Pig Chimeric Organ in Organ Transplantation from Islamic Bioethics Perspectives. Asian Bioethics Review, 15(2), 181–188. https://doi.org/10.1007/s41649-022-00233-2

Organ Donation Statistics | organdonor.gov. (n.d.). Retrieved September 23, 2023, from https://www.organdonor.gov/learn/organ-donation-statistics

Reza, Hasan Al, et al. (2021). Organoid Transplant Approaches for the Liver. Wiley Online Library, John Wiley & Sons, Ltd. https://onlinelibrary.wiley.com/doi/10.1111/tri.14128.

Shinkar, K., & Rhode, K. (2022). Could 3D extrusion bioprinting serve to be a real alternative to organ transplantation in the future? Annals of 3D Printed Medicine, 7, 100066. https://doi.org/10.1016/j.stlm.2022.100066

IMAGE REFERENCES

Shinkar, K., & Rhode, K. (2022). Could 3D extrusion bioprinting serve to be a real alternative to organ transplantation in the future? Annals of 3D Printed Medicine, 7, 100066. https://doi.org/10.1016/j.stlm.2022.100066

Pig Kidney Xenotransplantation Performing Optimally After 32 Days in Human Body. (n.d.). NYU Langone News. Retrieved September 23, 2023, from https://nyulangone.org/news/pig-kidney-xenotransplantation-performing-optimally-after-32-days-human-body

Research, C. for B. E. and. (2022, September 26). Xenotransplantation. FDA; FDA. https://www.fda.gov/vaccines-blood-biologics/xenotransplantation

Special Feature:

Maternal Health

From crisis to care: Identifying disparities in black maternal health

DOREEN OKEH
Staff Writer

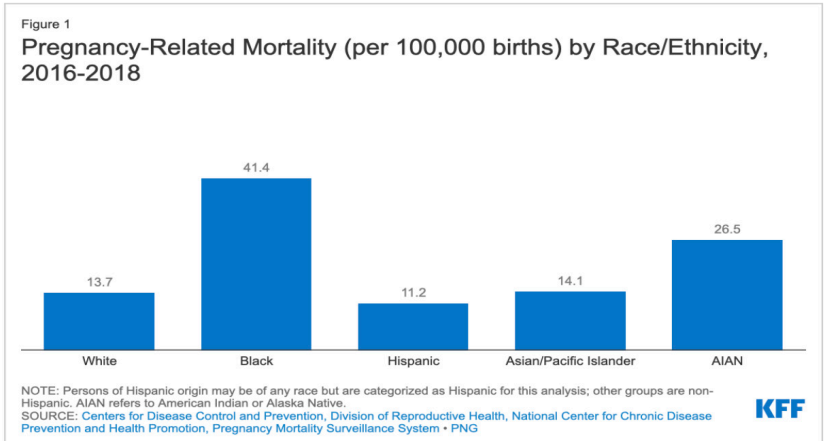

Figure 1. Both Black and American Indian/Alaska Native women experience prengnancy-related morality rates around three times and two times larger, respectively, than those of white women. (41.6 and 26.5 compared to 13.7 per 100,000 live births). (CDC, 2022)

Maternal mortality is a prevalent issue in the United States of America, and minorities and community members from low-income communities are disproportionately at risk of mortality following childbirth. Black women make up 13% of the American population, yet are four to five times more likely to die in childbirth than their Caucasian counterparts (Petersen, 2019). With 43.5 maternal deaths per 100,000 live births, regions of the United States with high concentrations of poverty-stricken Black women have alarming maternal death rates (Howell, 2018). Pregnancy-related death is defined as "the death of a woman during or within 1 year of pregnancy that was caused by a pregnancy complication, a chain of events initiated by pregnancy, or the aggravation of an unrelated condition by the physiologic effects of pregnancy" (Creanga, 2014). Pregnant minority women are predisposed to maternal mortality at higher rates than their white counterparts, which can be combated by understanding the existing barriers preventing the advancement of health outcomes in both mothers and their babies.

Pregnant minority women are predisposed to maternal mortality at higher rates than their white counterparts.

Additionally, health disparities encompass variations in health outcomes across different racial groups. These differences arise from various factors, including health literacy, racial considerations, access to medical information, and socioeconomic status. All in all, health disparities begin to manifest as inequalities in the ease of access of healthcare facilities and services (Howell, 2018). Socioeconomic and related disparities due to income create a gap in the affordability of essential services and vaccinations for pregnant African-American women. Furthermore, the quality of service is also determined by insurance coverage. Additional important issues driving disparity include medical mistrust between Black patients and their primary care providers, higher morbidity rates, and most prominently, dangerously low vaccination rates among pregnant women.

Structural racism against Black women serves as a powerful social determinant of maternal health, which deepens the pre-existing roots of oppression against Black women navigating the healthcare world. Additional health disparities, such as health literacy and geographical limitations, have also had detrimental effects on the quality of care received by pregnant minority women. I think I get this following sentence, but it is unclear; may want to break into two sentences? While maternal mortality remains a global issue primarily in lesser-developed countries, the United States conveys a disproportionate amount of deaths in comparison to the access to medication, materials, and able healthcare workers to achieve health equity and lower the maternal mortality ratio (Murray, 2019).

Three leading underlying causes of pregnancy-related death accounted for 72.1% of all pregnancy-related deaths. Most responsible for pregnancy-related deaths are (1) hemorrhage and cardiovascular and coronary conditions. These are responsible for

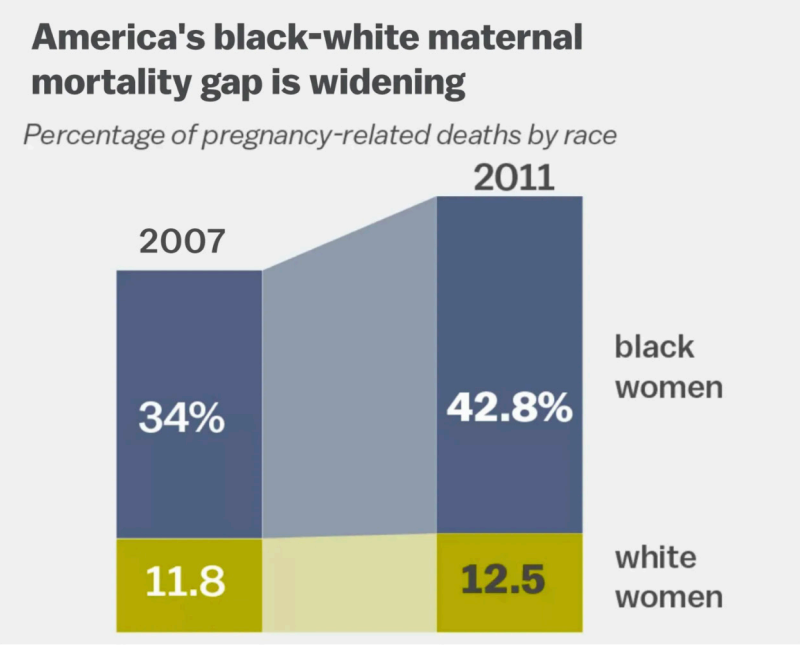

Figure 2. In the United States, Black mothers face a 3.5-fold increased risk of perishing during childbirth compared to their white counterparts. The pregnancy-related morality rate stands at 40 per 100,000 live births for Black women while it remains at 12 per 100,000 for white women (Frostenson, 2017).

a combined 28.0 percent of total deaths. (2) Infection and cardiomyopathy are responsible for 21.4% of deaths. (3) Embolism falls third at 8.4%, preeclampsia and eclampsia at 7.4%, and mental health conditions at 7.0% (CDC, 2018).

Black women dwelling in low-income communities are dying in their attempts to bring life into the world. Socioeconomic disparities due to income and educational gaps widen the margin in the affordability of essential services for pregnant Black women. Among the higher percentage of Black women facing complications during pregnancy, the specific health issues contributing to these challenges can be identified as hemorrhage and preeclampsia. This holds true even for women who do not have preexisting conditions like chronic hypertension, asthma, or infections. (Howell, 2019).

Within the past decade, developed countries have seen a 3.1% decline in the annual assessment of the maternal mortality ratio; however, the United States displayed an increase of 1.7% (Grant, 2016). Though it leads the globe in various sectors and is as top-ranked in development as other first-world countries are, the U.S. continues to its downward slide in maternal health.

The responsibility for the country's low vaccination rates is attributed to African-American and Hispanic women. Within minority health care and maternal health, minority patients, including African-American and Hispanic women, frequently encounter heightened rates of birth complications, negative outcomes, and fatalities in comparison to their white counterparts. This disparity emphasizes the urgent need to address maternal health inequities, ensuring that interventions and support systems are in place to mitigate the risks faced by minority women during pregnancy and childbirth.

In America, the gap is ever-widening: pregnancy-related deaths of Black women increased from 34% to 42.8% in a four-year span whereas that of white women went from 11.8% to 12.5% (CDC, 2017).

In gynecological health, statistics for Black women in 2015 were also alarming (Committee on Health Care for Underserved Women). Approximately 12% of Black women experienced infertility within the past couple of years, 11/1000 pregnancies resulted in fetal death, and 13/5000 of those resulted in maternal death (Belluz, 2017). The infant mortality rates were more than double in the black community in comparison to those of Asian, White, and Hispanic communities. Maternal death rates of Black/African women were more than three times as high as the demographic with the second-highest rate (Collier, 2019).

Additional health disparities, such as in health literacy and limitations have also had detrimental effects on the quality of care received by pregnant minority women. Social determinants, like poverty, employment, housing, and access to education,all impact the health of a community (Olivero, 2012). In 2012, nearly half of the teen pregnancies in the state of Connecticut were that of Hispanic mothers. They were also more likely to face unemployment, poverty, and housing problems in their region of Connecticut. In cases where the mother and daughter are

both teenage mothers, it is more likely that they lived in the same environment for the duration of their adolescent and/or adult life, therefore making nearly inevitable the same roadblocks of inaccessibility to care, medical mistrust of their healthcare providers, and not keeping up with vaccinations, equally affecting both generations. Overall, access to and lack of information about vaccines act to impede the uptake of antenatal immunizations beneficial to both the mother and the infant.

... lack of information about vaccines act to impede the uptake of antenatal immunizations beneficial to both the mother and the infant.

Current approaches to addressing maternal mortality and morbidity include the integration of educational resources on antenatal care into under-resourced communities with high minority populations, distribution of information on vaccine education, proper nutrition and exercise regimens, and how to assess if a woman is entering pregnancy with a predisposition to diseases like hypertension. These efforts serve to educate Black women who are or intend to be pregnant and are also for the advancement of achieving health equity for all pregnant minority women and informing them on steps they can take to ensure positive pregnancy outcomes.

Recommendations resulting from research are presenting said work at conferences regarding maternal health, informing its audience of the overwhelming presence of health disparity. This research is also incredibly important to educate members of the public on how Black women are at the forefront of risk, and that disproportionate causes of death among Black women might reflect differences in access to care, quality of care, and prevalence of chronic diseases. Both addressing and mitigating the current disparities among Black women is not only critical for the well-being of pregnant minority women but also of vital importance to the general public and the future of healthcare and medicine for generations to come. By rectifying these inequities, we can improve healthcare outcomes and ensure that healthcare is equitable, accessible, and of high quality, setting a more just standard for healthcare for the greater good. ❧

AUTHOR BIO

Doreen Okeh is a junior at Emory, double-majoring in Human Health and Sociology on the pre-law track. Okeh explores the issue of medical mistrust in the Black community and seeks ways to bridge the gap between Emory healthcare and its surrounding communities.

Edited by Siya Malhotra, Samir Lohana, and Dr. Arri Eisen

Placed by Samir Lohana

REFERENCES

Carvalho, K. (2022). A Systematic Policy Review of Black Maternal Health-Related Policies Proposed Federally and in Massachusetts: 2010–2020. Frontiers, [Link](http://A Systematic Policy Review of Black Maternal Health-Related Policies Proposed Federally and in Massachusetts: 2010–2020).

Centers for Disease Control and Prevention. (2020). Improving pregnancy outcomes for African American women. Centers for Disease Control and Prevention. [Link](insert link).

Centers for Disease Control and Prevention. (2019). Racial and ethnic disparities continue in pregnancy-related deaths. Centers for Disease Control and Prevention. [Link](insert link).

Centers for Disease Control and Prevention. (2020). Health Equity Considerations and Racial and Ethnic Minority Groups. [Link](insert link).

Collier, A. Y., & Molina, R. L. (2019). Maternal Mortality in the United States: Updates on Trends, Causes, and Solutions. NeoReviews, 20(10), e561–e574. DOI.

Creanga, A. A., Berg, C. J., Ko, J. Y., Farr, S. L., Tong, V. T., Bruce, F. C., & Callaghan, W. M. (2014). Maternal mortality and morbidity in the United States: where are we now?. Journal of Women's Health (2002), 23(1), 3–9. DOI.

Creanga, A. A., Bateman, B. T., Kuklina, E. V., & Callaghan, W. M. (2014). Racial and ethnic disparities in severe maternal morbidity: a multistate analysis, 2008-2010. American Journal of Obstetrics and Gynecology, 210(5), 435.e1–435.e4358. DOI.

Howell, E. A. (2018). Reducing Disparities in Severe Maternal Morbidity and Mortality. Clinical Obstetrics and Gynecology, 61(2), 387–399. DOI.

Howell, E. A., Janevic, T., Blum, J., Zeitlin, J., Egorova, N. N., Balbierz, A., & Hebert, P. L. (2020). Double Disadvantage in Delivery Hospital for Black and Hispanic Women and High-Risk Infants. Maternal and Child Health Journal, 24(6), 687–693. DOI.

Joia Crear-Perry, Rosaly Correa-de-Araujo, Tamara Lewis Johnson, Monica R. McLemore, Elizabeth Neilson, and Maeve Wallace. Journal of Women's Health, Feb 2021, 230-235. DOI.

Kozhimannil, K. B., Vogelsang, C. A., Hardeman, R. R., & Prasad, S. (2016). Disrupting the Pathways of Social Determinants of Health: Doula Support during Pregnancy and Childbirth. Journal of the American Board of Family Medicine: JABFM, 29(3), 308–317. DOI.

Mehta, P. K., Kieltyka, L., Bachhuber, M. A., Smiles, D., Wallace, M., Zapata, A., & Gee, R. E. (2020). Racial Inequities in Preventable Pregnancy-Related Deaths in Louisiana, 2011-2016. Obstetrics and Gynecology, 135(2), 276–283. DOI.

Minehart, R. D., Jackson, J., & Daly, J. (2020). Racial Differences in Pregnancy-Related Morbidity and Mortality.

Murray, Donna, R. N. (2021). Chances of Dying in Pregnancy and Childbirth Around the World. Verywell Family.

Petersen EE, Davis NL, Goodman D, et al. (2019). Racial/Ethnic Disparities in Pregnancy-Related Deaths — United States, 2007–2016. MMWR Morb Mortal Wkly Rep, 68, 762–765. [DOI](http://dx.doi.org/10.15585/mmwr.mm6835a3external icon).

Saluja, B., & Bryant, Z. (2021). How Implicit Bias Contributes to Racial Disparities in Maternal Morbidity and Mortality in the United States. Journal of Women's Health (2002), 30(2), 270–273. DOI.

Taylor, J. K. (2020). Structural Racism and Maternal Health Among Black Women. The Journal of Law, Medicine & Ethics, 48(3), 506–517. DOI.

Thiel de Bocanegra, H., Braughton, M., Bradsberry, M., Howell, M., Logan, J., & Schwarz, E. B. (2017). Racial and ethnic disparities in postpartum care and contraception in California's Medicaid program. American Journal of Obstetrics and Gynecology, 217(1), 47.e1–47.e7. DOI.

Tucker, M. J., Berg, C. J., Callaghan, W. M., & Hsia J. (2007).

IMAGE REFERENCES

CDC. (2022). Racial Disparities in Maternal and Infant Health: Current Status and Efforts to Address Them. KFF. Retrieved October 17, 2023, from https://www.kff.org/racial-equity-and-health-policy/issue-brief/racial-disparities-in-maternal-and-infant-health-current-status-and-efforts-to-address-them/

Frostenson, S. (2017). Pregnancy Mortality Surveillance System. Vox. Retrieved October 17, 2023, from https://www.vox.com/health-care/2017/7/3/15886892/black-white-moms-die-childbirth-north-carolina-less

Navigating challenges in fetal alcohol spectrum disorder (FASD) prevention: From screening methods to supportive interventions and stigma reduction

JULIA BRACCI
Staff Writer

Fetal Alcohol Spectrum Disorder (FASD) refers to a range of physical, cognitive, and behavioral conditions resulting from alcohol exposure during prenatal development that persist for a lifetime (National Institutes of Health, 2022). Currently, alcohol exposure during pregnancy is the leading preventable cause of congenital anomalies and neurodevelopmental disabilities in the United States, affecting 1% to 5% of U.S. first graders (National Institutes of Health, 2022). In addition to the developmental disabilities faced by children with FASD, the consequences of the stigma associated with FASD further impedes mothers' ability to receive proper support for themselves and their children. FASD poses challenges due to gaps in prenatal healthcare interventions and screening methods for maternal alcohol use. The prevalence of FASD is marked by significant socioeconomic and racial disparities (Luong et al., 2017). Educational barriers, along with pregnancy unawareness, further contribute to the prevalence of FASD. There exists an increasing demand for evidence-based alcohol screening and intervention approaches within prenatal care settings, as well as for initiatives that reduce the stigma surrounding FASD.

Pregnancy unawareness and lack of education as risk factors for FASD

A significant hurdle in prevention of FASD is the unawareness of a pregnancy during its early stages. Surprisingly, many mothers whose children are affected by FASD don't have an alcohol use disorder; instead, they were unaware of their pregnancy when they consumed alcohol (Abadir et al., 2016). One of the three most predictive maternal risk variables for FASD in a representative Midwestern US community is late recognition of pregnancy (May, 2014). This indicates that many cases of fetal alcohol exposure occur prior to pregnancy awareness. Pregnancy unawareness is a significant risk for FASD as alcohol during the early stages of gestation is linked to more severe cognitive abnormalities (Dejong et al., 2019).

Racial and socioeconomic disparities in FASD are prominent, and are likely due to social and structural determinants of health. Black infants have been reported to have a 7-fold higher risk of FASD than white infants (Oh et al., 2023). Education level has been identified as a determinant that may be strongly associated with FASD: Pregnant women who did not graduate from high school reported a lower prevalence of alcohol screening (53.5%) compared with women who graduated from high school (83.4%) (Luong et al., 2017). These disparities may be due to inequities in prenatal services (Singal et al., 2019). Improving equitable access to maternal health services is a key step in mitigating disparities in FASD outcomes.

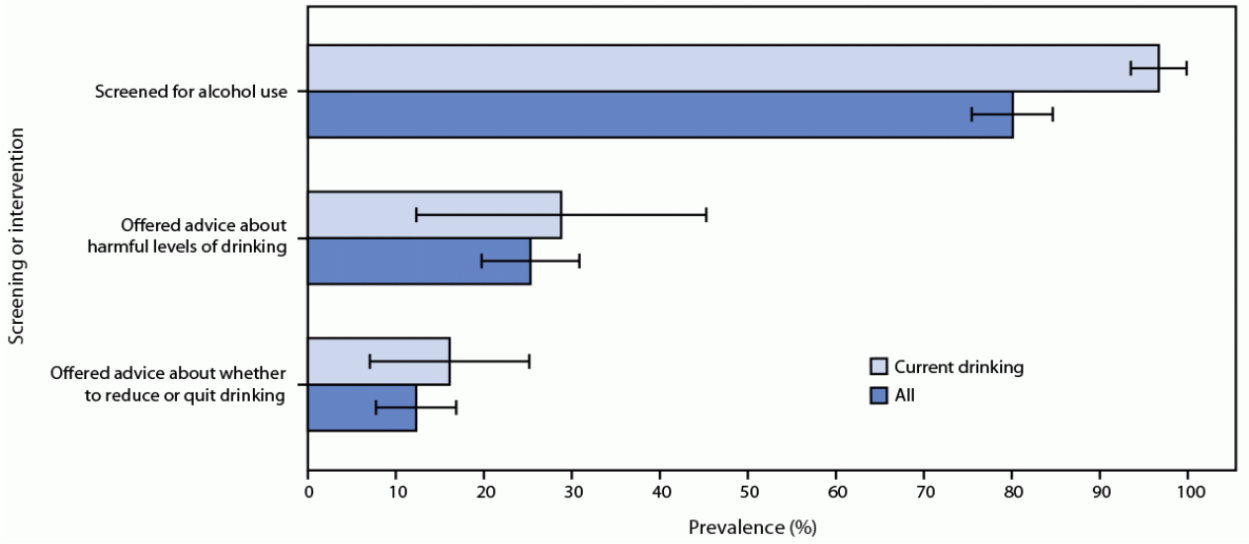

Figure 1: Prevalence of age-standardized alcohol screening and brief intervention among pregnant persons in 23 states and the District of Columbia, 2017 and 2019 (Luong et al., 2019)

Imperfections in maternal alcohol screening methods

The recommenations from the US Surgeon General and Secretary of the Department of Health and Human Services stress the importance of abstinence from alcohol both before conception and during pregnancy (Chang, 2001). Despite these recommendations, alcohol consumption during pregnancy is common and rising. According to a study conducted from 2018 to 2020, 13.5% of pregnant women reported current drinking, with 5.2% reporting binge drinking, representing a 2-percentage point increase from 2015 to 2017 (Denny et al., 2019). This alarming rise in alcohol consumption during pregnancy highlights the urgent need for effective prevention and clinical intervention methods during the prenatal period.

A challenge lies in the limitations of alcohol screening tests. Methods like blood, urine, and breath tests can be useful in detecting alcohol consumption, however no marker has the diagnostic sensitivity necessary to be considered a biomarker for prenatal alcohol use (Bearer et al., 2004). Consequently, prenatal care providers often rely on maternal self-report to assess alcohol consumption during pregnancy.

Many common self-report screening tools widely used by primary care clinicians to assess alcohol consumption during pregnancy have imperfections. For example, the CAGE questionnaire, constituting 58.6% of screening methods, has been found to inaccurately detect alcohol misuse in prenatal women (Dhalla et al., 2007). A study assessing the sensitivity, specificity, and predictive value of brief alcohol screening questionnaires in identifying problem drinking during pregnancy revealed the CAGE tests demonstrated poor performance in these measures (Green, 2023). This lack of effectiveness may be attributed to pregnant women's reluctance to provide accurate responses to alcohol screening questions due to social desirability bias. Additionally, the CAGE questionnaire assesses lifetime alcohol-related issues rather than current ones which is less relevant to assessing recent prenatal alcohol consumption (Dhalla et al., 2007).

The US Preventive Services Task Force (USPSTF) recommendation statement suggests employing concise screening tools like the abbreviated Alcohol Use Disorders Identification Test–Consumption (AUDIT-C) and the Single Alcohol Screening Question (SASQ). AUDIT-C and SASQ, result in adequate sensitivity, and specificity in identifying excessive drinking behavior in adults and pregnant women (US Preventive Services Task Force, 2018; Burns, 2010). Despite the availability of more comprehensive testing strategies, very few providers use tools specifically tailored to pregnancy, fewer than half feel confident in their screening and brief intervention abilities, and only two-thirds use evidence-based tools recommended by the USPSTF (Green et al., 2019). This gap in implementation highlights a crucial need for increased awareness among healthcare professionals regarding the effectiveness of evidence-based screening tools, such as AUDIT-C and SASQ. Notably, beneficial universal screening includes those that help classify individuals into different risk categories: low-risk women should receive brief advice, those with moderate risk should be offered a brief intervention, and high-risk individuals should be referred to specialized care (Wright et al., 2016).

Inadequacies in interventions for women who report alcohol use during pregnancy

Equally important to screening is providing intervention and resources for pregnant women who engage in prenatal alcohol consumption. According to the USPSTF, when pregnant women screen positive on a brief screening instrument, clinicians should provide a form of counseling intervention (US Preventive Services Task Force, 2018). Despite the importance of advice and intervention regarding alcohol consumption, many women go without this care. According to the CDC, in 2017 and 2019, only 16% of pregnant women who had self-reported consuming alcohol in the past 30 days received advice from a healthcare provider to either quit or reduce their alcohol intake (Figure 1). In addition only about a quarter of expectant individuals who underwent alcohol screening received guidance from a healthcare professional regarding the potential harm of alcohol consumption (Figure 1). Even when pregnant women self-report alcohol consumption, there is a pervasive deficiency in the commitment of healthcare providers to deliver interventions and support.

Improving screening and intervention methods for alcohol use during pregnancy

The Massachusetts ASAP program improves both screening and intervention rates for prenatal alcohol use. This program uses the "ASAP chart checklist" to determine whether a woman has been screened for alcohol use, identify any associated risk factors, and respond accordingly (Figure 2). The ASAP program provides prenatal caregivers a suggested approach for delivering brief interventions and offering educational materials regarding prenatal alcohol consumption (Figure 2). The implementation of the ASAP Project resulted in 95% of pregnant women being screened for alcohol use and 77% screening positive for at least one risk factor recieved a brief intervention during a routine office visit (Kennedy et al., 2004). This program is inno-

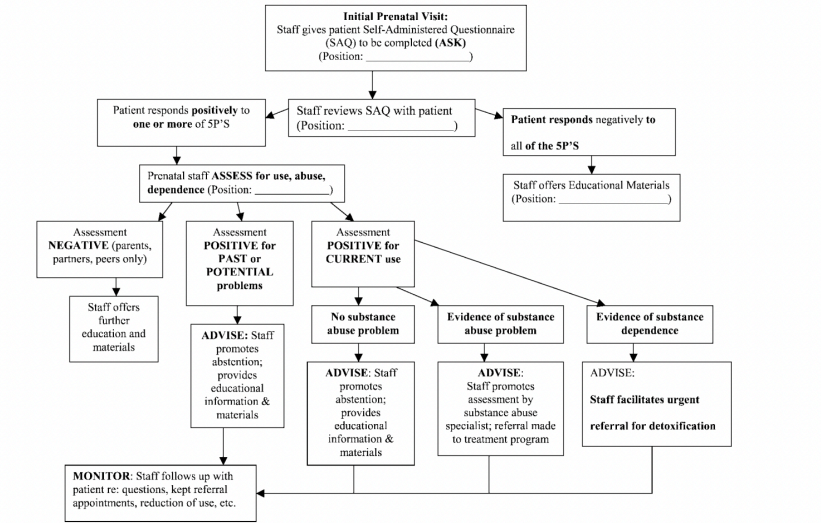

Figure 2: Massachusetts ASAP office protocol flow chart made to screen for prenatal alcohol usage, initiate intervention, educate, and refer pregnant women for additional assessments or treatment (Kennedy et al., 2004)

vative as it establishes guidelines that motivate healthcare workers to actively screen for alcohol misuse and provide interventions for prenatal patients who may otherwise be dismissed.

Combating the stigma attached to FASD

In cases of FASD, ensuring that both the parents and child can receive proper care is challenging due to obstacles such as the stigmatization of FASD, which affects both the child and their parents. In a study where 43% of infants tested positive for illicit substances, only 11% of mothers reported drug usage (Huestis & Choo, 2002). On an individual level, fear of losing custody may lead many pregnant mothers to not disclose their substance use to their healthcare provider (Huestis & Choo, 2002). Mothers of children with FASD may also suffer from anxiety regarding possible stigmatization and guilt associated with personal responsibility attached to causing FASD in one's child. (Roozen et al., 2022). Self-blame has been shown to negatively impact parent-child relationships and contribute to the difficulties of a child living with FASD (Roozen et al., 2022). In addition, social judgment and isolation after childbirth may negatively impact the experience of raising a child with FASD (Roozen et al., 2022). The perspective that mothers of children with FASD are less deserving of support is evidenced by the lack of FASD philanthropic support; in one survey, participants reported that they were less likely to allocate money to programs supporting mothers of children with FASD compared to programs supporting mental illness, substance use disorder, and incarceration (Roozen et al., 2022). Future focus and priority should revolve around establishing comprehensive support systems for mothers and eliminating the stigma associated with their situations.

Conclusion

FASD, a preventable disorder, has far-reaching consequences for both children and their parents. The widespread necessity for robust screening, brief intervention, and referral to treatment resources during prenatal care checkups is imperative. Programs such as the Massachusetts ASAP program do a good job at enforcing screening and intervention protocols that do not always occur during prenatal checkups (Kennedy et al., 2004). There is a demand to assess the effectiveness of existing screening methods for alcohol exposure in pregnant women. Most protocols used to detect alcohol exposure are designed for normal adults and implemented onto pregnant women (Dhalla et al., 2007; Green et al., 2019). The circumstance in which a mother may use substances or respond to self-reports differ from that of a typical adult, signifying the necessity for alcohol screening methods tailored specifically to pregnant women.

Furthermore, to effectively reduce the prevalence of pregnancy unawareness and its impact, it is beneficial to ensure universal access to contraception methods for individuals with limited resources. Increasing funding for resources such as planned parenthood that work to increase family planning and birth control efforts may help decrease the likelihood of fetal alcohol exposure associated with unwanted, and/or unknown pregnancy (Planned Parenthood, 2023). Furthermore, as important as the prevention of FASD, is the support of children affected by FASD and their mothers. Programs such as United Circle of Hope work to reduce the stigma of FASD through providing mothers of children with FASD a platform to share their story, amplifying their voices (FASD United, 2023). Understanding the lived experiences of mothers of children with FASD, can help alter demonizing perceptions of such individuals, and help garner public support and acceptance. ❧

REFERENCES

Abadir AM, Ickowicz A. (2016) Fetal alcohol spectrum disorder: reconsidering blame. CMAJ, 188(3), 171-172. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4754173/

Anderson BL, Dang EP, Floyd RL, Sokol R, Mahoney J, Schulkin J. Knowledge, opinions, and practice patterns of obstetrician-gynecologists regarding their patients' use of alcohol. (2010). Addict Med. 4(2):114-21. doi: 10.1097/ADM.0b013e3181b95015. PMID: 21769028.

Bearer CF, Stoler JM, Cook JD, Carpenter SJ.(2004-2005). Biomarkers of alcohol use in pregnancy. Alcohol Res Health, 28(1), 38-43. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6601656/

Burns, E., Gray, R. and Smith, L.A. (2010), Brief screening questionnaires to identify problem drinking during pregnancy: a systematic review. Addiction, 105: 601-614. https://doi.org/10.1111/j.1360-0443.2009.02842.x

Chang G. (2001). Alcohol-screening instruments for pregnant women. Alcohol Res Health, 25(3, 204-9. https://pubmed.ncbi.nlm.nih.gov/11810959/

Dehlendorf C, Rodriguez M, Levy K, Borrero S, Steinauer J (2010). Disparities in family planning. American Journal of Obstetrics and Gynecology, 202(3), 214-220, https://doi.org/10.1016/j.ajog.2009.08.022.

Dejong K, Olyaei A, Lo, J.O. (2019). Alcohol Use in Pregnancy. Clin Obstet Gynecol, 62(1), 142-155. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7061927/

Denny, C. H., Acero, C. S., Naimi, T. S., & Kim, S. Y. (2019). Consumption of alcohol beverages and binge drinking among pregnant women aged 18–44 years — United States, 2015–2017. MMWR Morbidity and Mortality Weekly Report, 68(16), 365–368. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6483284/

Dhalla S, Kopec JA. (2017) The CAGE questionnaire for alcohol misuse: a review of reliability and validity studies. Clin Invest Med, 30(1), 33-41. https://cimonline.ca/index.php/cim/article/view/447/554

FASD United. (2023). Stamp out the stigma. https://fasdunited.org/stamp-out-stigma/#:~:text=The%20Circle%20of%20Hope%20peer,and%20helps%20to%20prevent%20FASD

Green C, George N, Park Y, Denny CH, Weber MK, Meaney-Delman D, et al. (2019). Screening and Brief Interventions for Alcohol Use During Pregnancy: Practices Among US Primary Care Clinicians, DocStyles. Prev Chronic Dis 2023;20:220226. DOI: https://www.cdc.gov/pcd/issues/2023/22_0226.htm

Drollinger, T., Comer, L. B., & Warrington, P. T. (2006). Development and validation of the active empathetic listening scale. Psychology & Marketing, 23(2), 161-180. https://doi.org/10.1002/mar.20105

Huestis, M. and Choo, R. (2002). Drug abuse's smallest victims: in utero drug exposure. Forensic Science International, 128(1-2), 20-30. https://doi.org/10.1016/S0379-0738(02)00160-3

Kennedy C, Finkelstein N, Hutchins E, Mahoney J. (2004). Improving screening for alcohol use during pregnancy: the Massachusetts ASAP program. Matern Child Health 8(3), 137-47. https://pubmed.ncbi.nlm.nih.gov/15503394/

Koehlmoos, T. P., Lee, E., Wisdahl, J., & Donaldson, T. (2023). Fetal Alcohol Spectrum Disorders Prevention and Clinical Guidelines Research-Workshop Report. BMC Proceedings, 17(S12). https://doi.org/10.1186/s12919-023-00272-z

Luong J, Board A, Gosdin L, Dunkley J, Thierry JM, Pitasi M, Kim SY. Alcohol Use, Screening, and Brief Intervention Among Pregnant Persons - 24 U.S. Jurisdictions. (2017 and 2019). MMWR Morb Mortal Wkly Rep, 72(3), 55-62. https://www.cdc.gov/mmwr/volumes/72/wr/mm7203a2.htm

May PA, Baete A, Russo J, Elliott AJ, Blankenship J, Kalberg WO, Buckley D, Brooks M, Hasken J, Abdul-Rahman O, Adam MP, Robinson LK, Manning M, Hoyme HE. (2014). Prevalence and characteristics of fetal alcohol spectrum disorders. Pediatrics. 134(5):855-66. doi: 10.1542/peds.2013-3319. PMID: 25349310; PMCID: PMC4210790.

Medical University of South Carolina (n.d,) About Urine Ethyl Glucuronide (EtG) Testing. https://medicine.musc.edu/departments/psychiatry/divisions-and-programs/programs/clinical-neurobiology-lab/heavy-alcohol-testing/etg#:~:text=EtG%20can%20be%20found%20in,if%20the%20drinking%20is%20heavier

US Preventive Services Task Force. Screening and Behavioral Counseling Interventions to Reduce Unhealthy Alcohol Use in Adolescents and Adults. (2018). US Preventive Services Task Force Recommendation Statement. JAMA. 320(18):1899–1909. doi:10.1001/jama.2018.16789

Roozen, S., Stutterheim, S., Bos, A.. et al. (2022). Understanding the Social Stigma of Fetal Alcohol Spectrum Disorders: From Theory to Interventions. Found Sci, 27, 753–771. https://doi.org/10.1007/s10699-020-09676-y

Shukla L, Sharma P, Ganesha S, Ghadigaonkar D, Thomas E, Kandasamy A, Murthy P, Benegal V. (2017). Value of Ethyl Glucuronide and Ethyl Sulfate in Serum as Biomarkers of Alcohol Consumption. Indian J Psychol Med, 39(4), 481-487. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5559998/

Singal D, Brownell M, Wall-Wieler E, Chateau D, Hanlon-Dearman A, Longstaffe S, Roos LL. (2019).Prenatal care of women who give birth to children with fetal alcohol spectrum disorder in a universal health care system: a case-control study using linked administrative data. CMAJ Open. 11;7(1), E63-E72 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6404961/

Tricia E. Wright, Mishka Terplan, Steven J. Ondersma, Cheryl Boyce, Kimberly Yonkers, Grace Chang, Andreea A. Creanga. (2016). The role of screening, brief intervention, and referral to treatment in the perinatal period. American Journal of Obstetrics and Gynecology, 215(5), 539-547,https://doi.org/10.1016/j.ajog.2016.06.038.

U.S. Department of Health and Human Services. (n.d.). Fetal Alcohol Spectrum Disorders. National Institute on Alcohol Abuse and Alcoholism. https://www.niaaa.nih.gov/research/fetal-alcohol-spectrum-disorders#:~:text=Recent%20 prevalence%20studies%20estimate%20that,by%20alcohol%20use%20during%20pregn ancy

US Preventive Services Task Force. Screening and Behavioral Counseling Interventions to Reduce Unhealthy Alcohol Use in Adolescents and Adults: US Preventive Services Task Force Recommendation Statement. JAMA. 2018;320(18):1899–1909. doi:10.1001/jama.2018.16789. https://jamanetwork.com/journals/jama/fullarticle/2714537

IMAGE REFERENCES

Kennedy C, Finkelstein N, Hutchins E, Mahoney J. (2004). Improving screening for alcohol use during pregnancy: the Massachusetts ASAP program. Matern Child Health 8(3), 137-47. https://pubmed.ncbi.nlm.nih.gov/15503394/

Luong J, Board A, Gosdin L, Dunkley J, Thierry JM, Pitasi M, Kim SY. Alcohol Use, Screening, and Brief Intervention Among Pregnant Persons - 24 U.S. Jurisdictions. (2017 and 2019). MMWR Morb Mortal Wkly Rep, 72(3), 55-62. https://www.cdc.gov/mmwr/volumes/72/wr/mm7203a2.htm

AUTHOR BIO

Julia is a third-year majoring in Human Health. Her interests include public health, maternal health, mental health, substance abuse, and immunology.

Edited by Claire Zegger, Christina Fu, and Dr. Sarah Turbow

Placed by Christina Fu

Unshackling women: Labor, delivery, and postpartum realities for incarcerated women in the U.S.

ISABELLE SHUB
Staff Writer

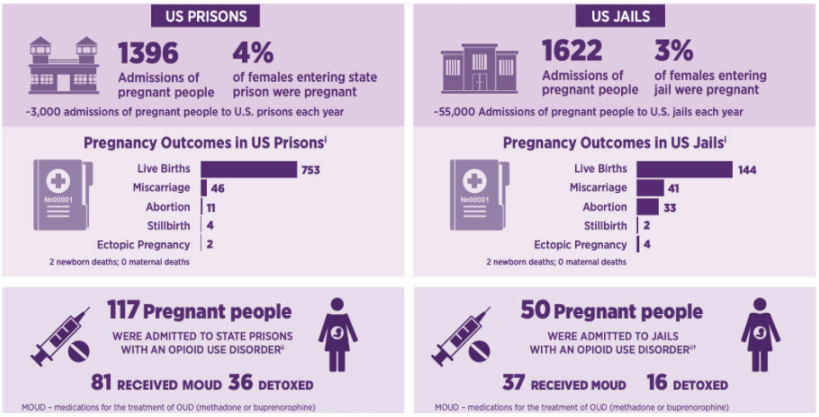

Figure 1. "Incarcerated Pregnant People in a 12 Month Period:" A 2016-2017 study of pregnancy outcomes on 57% of all female inmates in US prison. (ARRWIP, 2017)

"I felt like a farm animal," cried Michele Adana after having her hands and feet shackled to the bed for 30 hours of labor (Anderson, 2021). Ms. Adana's maltreatment has become the standard among 55,000 pregnant inmates in the United States (Dufresne, 2023). Shackles, a "mechanical device that limits inmate's movement and may include handcuffs, ankle cuffs, belly chains, or soft restraints," is used to minimize the theoretical risk of inmate escape or harm during childbirth (Palmer et al., 2018). In reality, shackles increase birth complications and pregnancy risk two-fold; compounding upon the other unique challenges incarcerated women face navigating prenatal and postpartum care (Friedman et al., 2020). The American College of Obstetricians and Gynecologists (ACOG), American Medical Association, American Public Health Association, and American Civil Liberties Union (ACLU) have all condemned shackling during pregnancy and established prison-specific recommendations for incarcerated mothers (ACLU). The shackling of pregnant inmates is an outcome of a system that does not protect women.

Since 1980, prisons have experienced a 500% uptick in female inmates, with 55,000 inmates per year pregnant upon admission.

The physical and emotional detriment of shackling during pregnancy has significant implications on maternal health and fetal development. Outcomes related to pain management, cervical dilation, and delivery safety can be reduced by walking around during pregnancy. This, however, is not possible with shackles (ACOG). Shackling a prenatal inmate increases fall complications as their ability to break the fall and protect the fetus becomes limited (Ferszt, 2018, ACOG). During labor, reduced mobility of the pregnant person during childbirth makes it significantly more difficult for the physician to maneuver the child and increases the physician's reaction time when performing necessary assessments (ACOG, ACLU, 2012). The shackles themselves cause bruising and bleeding on wrists and ankles, as well as leaving the infant vulnerable to preterm birth and decreased birth weight (Friedman et al., 2023). Additionally, the mother's first moments with their child – skin-to-skin contact and breastfeeding – are restricted by shackles (Hayes et al., 2020). The accumulation of physical and psychological stress caused by the shackles constitutes a traumatic birth which perpetuates the transmission of trauma from mother to infant. Traumatic births are marked by increased maternal cortisol levels which can alter fetal development and affect maternal physical and mental health (Evans, 2015). Essentially, shackles strip away a mother's reproductive autonomy by removing all sacredness and tenderness from the birthing process.

Despite state, federal, and international laws prohibiting the use of shackling during childbirth, shackling of pregnant inmates is commonplace in American prisons. Estelle vs. Gamble, a 1976 Supreme Court Case, was crucial in improving healthcare conditions for inmates, ruling that indifference

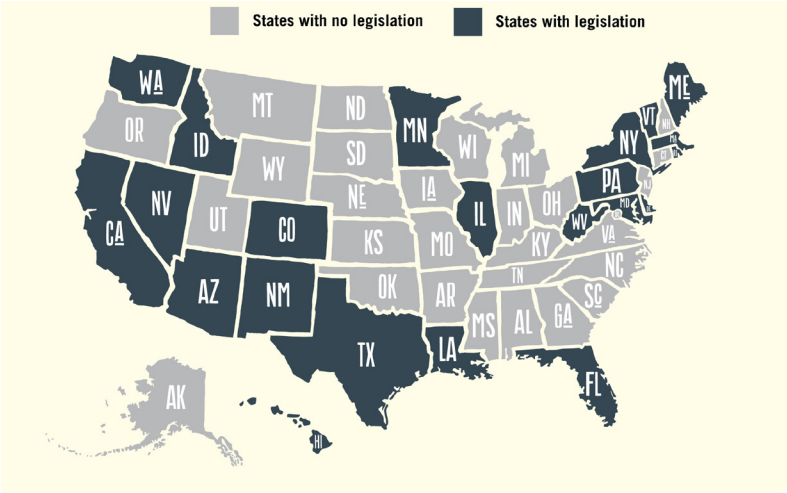

Figure 2: Anti-Shackling Laws by State. As a general trend, more coastal and typically democratic-leaning states tend to have anti-shackling legislatio (Ferszt et al., 2018)

to healthcare contradicted the 8th Amendment and constituted "cruel and unusual punishment" (Allen et al., 2010). Currently, 36 states have passed legislation outlawing the use of shackles during labor (Dufresne, 2023, Incarcerated Women and Shackling Laws, 2021). Nonetheless, 82.9% of US prison nurses reported witnessing shackle use during childbirth despite only 9% ever feeling concerned for their own safety (Goshin et al., 2019). The enactment of federal laws does not ensure compliance, especially in circumstances where hospital norms and physician opinions contradict explicit policies (Goshin et al., 2019). Disregarding anti-shackling regulations is the antithesis of reproductive justice; though reproductive rights exist on paper, they are not protecting America's most vulnerable constituents.

A dearth of understanding of the specific and complex needs of women throughout the prison system leaves incarcerated women particularly vulnerable. The recent focus on mass incarceration as "solely a male problem" excludes the reproductive injustice women face (Hayes et al., 2020). Since 1980, prisons have experienced a 500% uptick in female inmates, with 55,000 inmates per year pregnant upon admission (Dufresne, 2023). The geography of prisons does not reflect these numbers: there are more male prisons than female prisons. As a result, women are forced further away from their families, which complicates infant placement after release (Bergh et al., 2011). Even before the child is born, incarcerated women face unique challenges navigating pregnancy care, such as pregnancy testing, abortion counseling, HIV treatment, adequate food and rest, postpartum contraception, privacy, and transparency regarding postpartum infant care (Friedman et al., 2020). Given that female inmates are three times more likely to have experienced physical or sexual abuse than male inmates, they are at a greater risk of entering prison with STDs, HIV, bloodborne illnesses, mental illness, and addiction. Up to 90% of female prisoners report mental health distress – significantly more than their male counterparts (Bergh, 2011). The subset of medical and social needs of incarcerated women are pushing up against a system that was not created to serve them. In particular, female inmates of color bear the heaviest load of injustice as they face higher rates of incarceration. Half of all female inmates are African American and two-thirds are women of color (Clarke et al., 2013). African American women have much higher rates of maternal mortality, a result of embedded racism in the healthcare and criminal justice system. Because pregnant women are victims to a system not designed to protect them, shackling becomes a hasty solution to a systemic problem.

Once the baby is delivered, an incarcerated mother faces a new set of challenges in forming a strong bond with her infant. Prison nurseries provide the postpartum mother with opportunities to live with her child; the underlying structure of the US prison system, however, does not allow for their widespread use. After a traumatic and shackled birth, mothers experience significant difficulty connecting with their infant, given that they are usually separated within 24 hours of delivery (Hayes et al., 2020). The United States is among a tiny list of countries – Liberia, Bahamas, Suri-

Mothers receive a variety of services including parenting classes, discharge counseling and crisis intervention.

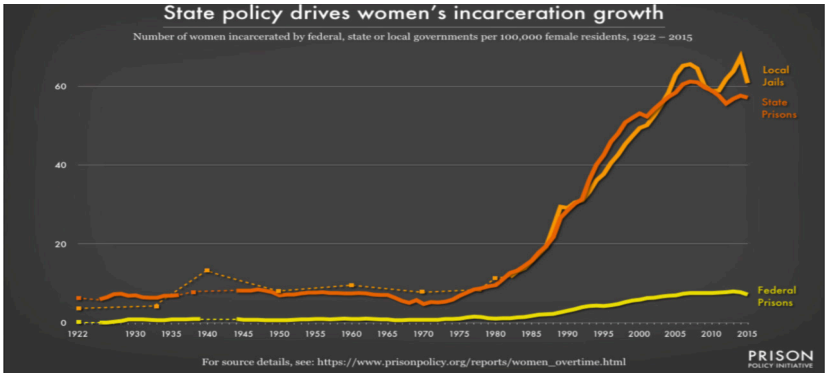

Figure 3. "State policy drives women's incarceration growth". Rise in female inmates in US prisons over the last 100 years (Prisn Policy, 2018).

name – that tolerate separating children from inmate mothers immediately after birth (Warner, 2015). Without prison nurseries, incarcerated mothers must decide between placing their child with family, up for adoption, or into the foster care system. This can be incredibly difficult due to the short timeline of the Adoption and Safe Families Act, which requires the child be put up for adoption if the mother has at least a 15-month sentence. Though placing the child with their family seems like an effective alternative, only 37% of incarcerated women report feeling comfortable or able to place the child with their father (Warner, 2015). In contrast to incarcerated men, incarcerated women are five times more likely to place their child in the foster care system (Warner, 2015). Prison nurseries would allow the mother to spend up to 18 months with their child. The Bedford Hills Correctional Facility Prison Nursery Program, the oldest US prison nursery, is a model for the program. Mothers receive a variety of services including parenting classes, discharge counseling and crisis intervention. Effective at reducing recidivism rates and increasing mother-child attachment, prison nurseries still function in the confines of prison and cannot free the mother from the psychological distress inherent to the place. Given the limited number of female prisons, prison nurseries are even more limited with only eight states offering their services (Kennedy et al., 2020).

A systemic eradication of shackling pregnant women during childbirth and the integration of prison nurseries is crucial for the health and safety of incarcerated women and their children in the United States. The prison backdrop limits the mother's autonomy to create a warm environment for the infant while they have to balance their role as inmate and mother (Kennedy et al., 2020). Many organizations scattered around the United States have stepped up to fight for the rights of incarcerated women. Motherhood Beyond Bars in Georgia and Women and Infants at Risk in Michigan offer comprehensive support for incarcerated mothers through advocacy and programming. Both Washington and Minnesota have passed laws to extend doula support to incarcerated women given their proven efficacy in reducing mortality (Friedman, 2020).

Steady progress through grassroots efforts have been helpful, yet a societal responsibility to ensure reproductive freedom for incarcerated women still remains. Advocacy from physicians and reproductive justice supporters is crucial in passing legislation protecting female inmates – as well as women before they are incarcerated. Further, given the intersectionality of reproductive justice during incarceration with a myriad of factors — racism, sexism, socioeconomic status, demographics, homophobia, classism, ableism, environmental racism — the efforts of all women, individuals, and communities are crucial in the fight. ❧

AUTHOR BIO

Isabelle Shub is a sophomore studying Psychology. She is particularly interested in issues pertaining to Reproductive Justice and Women's Rights.

Edited by Madeline Proctor, Ankitha Kumar, and Dr. Subhadra Shashidharan

Placed by Ankitha Kumar

REFERENCES

ACLU Briefing Paper: The Shackling of Pregnant Women & Girls in U.S. Prisons, Jails & Youth Detention Centers. (2012, October 12). ACLU. Retrieved September 23, 2023, from https://www.aclu.org/wp-content/uploads/legal-documents/anti-shackling_briefing_paper_stand_alone.pdf

Anderson, E. (2021). Childbirth in Chains: Why the Shackling of Incarcerated Pregnant Women is Unconstitutional. University of Cincinnati Law Review. https://uclawreview.org/2021/04/23/childbirth-in-chains-why-the-shackling-of-incarcerated-pregnant-women-is-unconstitutional/#_ftn1

Bergh, B. J. van D., Gatherer, A., Fraser, A., & Moller, L. (2011). Imprisonment and women's health: concerns about gender sensitivity, human rights and public health. Bulletin of the World Health Organization, 89(9), 689-694. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3165969/

Clarke, J. G., & Simon, R. E. (2013). Shackling and Separation: Motherhood in Prison. AMA Journal of Ethics, 15(9), 779-785. https://journalofethics.ama-assn.org/article/shackling-and-separation-motherhood-prison/2013-09

Dufresne, L. (2023). Pregnant Prisoners in Shackles. Voices in Bioethics, 9. https://journals.library.columbia.edu/index.php/bioethics/article/view/11638

Evans, L., Myers, M., & Monk, C. (2008). Pregnant women's cortisol is elevated with anxiety and depression — but only when comorbid. Archives of women's mental health vol, 11(3), 239-248. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4471957/

Ferszt, G. G., Palmer, M., & McGrane, C. (2018). Where Does Your State Stand on Shackling of Pregnant Incarcerated Women? Nursing for Women's Health, 22(1), 17-23.

Friedman, S. H., Kaempf, A., & Kauffman, S. (2023). The Realities of Pregnancy and Mothering While Incarcerated. The Journal of the American Academy of Psychiatry and Law, 51(3).

Goshin, L., Sissoko, G., Neumann, G., Sufrin, C., & Byrnes, L. (2019). Perinatal Nurses' Experiences With and Knowledge of the Care of Incarcerated Women During Pregnancy and the Postpartum Period. Journal of obstetric, gynecologic, and neonatal nursing, 48(1), 27-26. https://pubmed.ncbi.nlm.nih.gov/30528303/

Hayes, C. M., Sufrin, C., & Perritt, J. (2020). Reproductive Justice Disrupted: Mass Incarceration as a Driver of Reproductive Oppression. American Journal of Public Health, 110(1), 21-24. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6987912/

Incarcerated women and shackling state laws . Washington, DC. (2021). American College of Obstetricians and Gynecologists . Retrieved October 1, 2023, from https://www.acog.org/-/media/project/acog/acogorg/files/advocacy/policy-priorities/incarcerated-women-shackling_state-policies.pdf

Kennedy, S. C., Mennicke, A. M., & Allen, C. (2020). 'I took care of my kids': mothering while incarcerated. Health Justice, 8(12). https://journals.scholarsportal.info/pdf/21947899/v8inone/nfp_tcomkmwi.xml_en

Mendiola-Martinez v. Arpaio, 1 U.S. ___ (9th Cir. Feb. 11, 2016). https://www.govinfo.gov/content/pkg/USCOURTS-ca9-14-15189/pdf/USCOURTS-ca9-14-15189-0.pdf

Warner, J. (2015). Infants in Orange: An International Model-Based Approach Prison Nurseries. Hastings Women's

IMAGE REFERENCES

Ferszt, G. G., Palmer, M., & McGrane, C. (2018). Where Does Your State Stand on Shackling of Pregnant Incarcerated Women? Nursing for Women's Health, 22(1), 17-23.

Incarcerated Pregnant People in a 12 Month Period [Infographic]. (2017). Advocacy and Research on Reproductive Wellness of Incarcerated People. https://arrwip.org/projects/pregnancy-in-prison-statistics-pips-project/

State policy drives women's incarceration growth [Chart]. (2018). Prison Policy Initiative. https://www.prisonpolicy.org/reports/women_overtime.html

Addressing medical non-adherence: The micro and macro levels of prescription drug treatment

ALISSA DURAKOVIC

First-Year Liaison

VIVEK RAO

First-Year Liaison

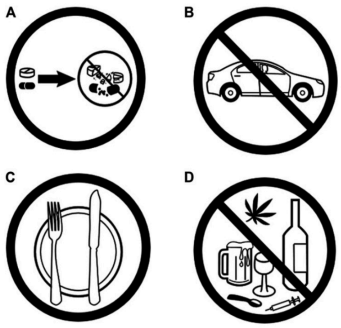

Figure 1: Sample of an effective pictogram. (A) Do not crush; (B) Do not drive; (C) Take with food; (D) Do not take with alcohol or drug (Merks et al., 2021).

Medical nonadherence is a growing threat to America's current healthcare system. Defined as patients not following treatment plans (typically regarding prescription medication) laid out by their doctors, medical nonadherence puts thousands in danger every year. It is said that "nonadherence can account for up to 50% of treatment failures, around 125,000 deaths, and up to 25% of hospitalizations each year in the United States" (Kim et al., 2018). This poses a significant question: what leads patients to medical nonadherence and how can this be addressed? Nonadherence stems from various sources, such as lack of access to information and failure to properly communicate with patients. Lack of access to information is a large-scale issue that is best addressed by policy, such as the recent FDA proposal requiring a one-page fact sheet on every prescription drug. On the other hand, effective connection with the patient requires facilitating a strong patient-physician relationship where the patient's background is taken into consideration. Thus, to truly address this complex problem, it must be analyzed from these two perspectives.

An increase in access to quality information can potentially improve medical adherence rates.

Medical information is one of the greatest factors that affects non-adherence, with many patients not having a proper understanding of the relevant medical information about their conditions and treatments. This is defined as health literacy, or the "degree to which individuals have the ability to find, understand, and use information and services to inform health-related decisions" (Health Literacy, 2022). Over a third of Americans (77 million) indicate that they would have trouble understanding and following basic medical information such as immunization schedules or instructions on prescription drugs (Kutner et al., 2006). This indicates that an increase in access to quality information can potentially improve adherence rates, this information limiting misunderstandings and unintentional non-adherence, while also reaffirming those who may be hesitant with evidence on efficacy and common side effects (Jimmy and Jose, 2011).

However, current approaches to medical education often ignore the health literacy level of the average American. While the FDA requires that specific high-potent drugs have some sort of medication guide, there is no regulation that requires information on all prescription drugs. While the private industry attempts to fill this gap with informational leaflets provided through Consumer Medical Information (CMI), these leaflets are not regulated whatsoever. Consequently, these guides only meet basic information requirements about 70% of the time, presenting information with small text, lengthy documents, and heavy jargon. As such, a survey evaluating the accessibility of a CMI for three common prescription drugs indicated that on average only 38% of participants indicated that they would be likely to actually read the CMI (Aker et

al., 2013). Thus, more streamlined and accessible medication guides are needed.

Fortunately, the FDA has recently proposed the incorporation of a new guide, Patient Medical Information (PMI), which would be attached to all prescription drugs. If properly executed, this new PMI would be a significant step towards a more health-literate society, decreasing medical non-adherence. The PMI is a single-page document that would be created by the manufacturer of the drug and reviewed by the FDA. This guide would be attached to each prescription drug sold, offering consistent formal health education that is not only accessible but also credible. It would include 4 key components: [Drug name] is, Important Safety Information, Common Side Effects, and Directions for Use. Moreover, unlike the CMI, the PMI incorporates the findings of past work done on creating accessible and inviting medical information. Indeed, the guidelines require all text to be greater than 10 font, use conversational language, and incorporate all text into the four main headings. Studies evaluating the accessibility of the PMI and the CMI report that PMI participants scored on average 36.7% higher than the CMI participants on comprehension tests and almost double the percentage of participants indicating they would likely read the PMI rather than the CMI (Aker et al., 2013). In other words, these interventions take into account important nuances about how medical information is best shared, which could potentially increase national adherence rates.

However, this new proposal is not sufficient on its own to truly address medical non-adherence. For instance, some of the guidelines are rather vague. The proposal repeatedly mentions that the text in the guides should be "clear and concise" without any definition of what that entails. The proposal would benefit from a more rigid mechanism, such as a limiting sentence length (8-10 words) which has a strong correlation with comprehension (Badarudeen & Sabharwal, 2010). Additionally, the proposal specifically prohibits the use of pictograms, explaining that cultural differences make the images hard to interpret, and the additional cost is not warranted. However, a recent review indicates that, when combined with written explanations, pictograms can convey information more effectively for those who struggle with general literacy, even considering cultural differences (Sedeh et al., 2022).

We cannot expect people to trust the guidance of our healthcare system if they feel it has left them behind.

Another hurdle for disseminating medical information and reducing non-adherence is the rapid growth of misinformation which seems to be primarily spread through social media. The most effective way to combat this misinformation, however, is by providing more accurate information from credible institutions. This responsibility falls on more than just the FDA, it is important for other reputable health institutions, such as the AMA, nationwide hospitals, and the CDC to consistently share content and view social media as a powerful tool that can advance medical information (Chen & Weng, 2021).

Furthermore, limited knowledge of one's condition fosters non-adherence as it can cause a breakdown in communication between patient and physician, leading patients to distrust or feel disconnected from healthcare providers. In an investigation of patient distrust in pharmaceutical companies, it was found that patients who had not heard of their condition prior to diagnosis were one of the top three groups who declared distrust. Receiving a diagnosis is a stressful situation for any patient, especially if said patient lacks an understanding of the pathology of their condition. It has long been known that "difficulties in the effective delivery of health care can arise from problems in communication between patient and provider rather than from any failing in the technical aspects of medical care." Hence, it is essential that healthcare providers create a space for patients that allows for open inquiry and discussion of concerns—in relation to both their condition and treatment plan (Teutsch, 2023). Medicine has been, in recent decades, moving from blind following of physician recommendations "toward shared decision-making" (Teutsch, 2023). Patients value agency in their treatment plans more now than they have previously, meaning they need more space in the conversation if an effective plan is to be established.

Additionally, the identities of

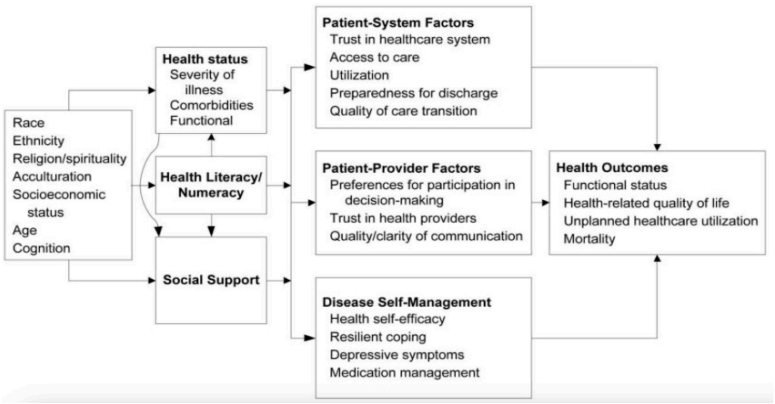

Figure 2: A conceptual framework of factors influencing the patient-physician relationship used in a Vanderbilt Inpatient Cohort Study. (Meyers et al., 2014)

patients prove a significant factor in analyzing distrust. The same study found that women also expressed high levels of distrust and were "more reluctant to join drug trials than men" (Pahus et al., 2023). Furthermore, a 2019 survey of gender bias in healthcare found that 20% of female participants have felt that their symptoms were dismissed by a healthcare provider and 17% felt they were treated differently because of their gender, compared to "14% and 6% of men, respectively" (Paulsen, 2020). It was found that "compared with male patients, women who present with the same condition may not receive the same evidence-based care" (Paulsen, 2020). If women do not feel secure in their treatment plan or that their concerns have been properly addressed, distrust begins to develop. We cannot expect people to trust the guidance of our healthcare system if they feel it has left them behind.

A look into clinical trial practices provides some insight into this disparity. Recruitment bias, which refers to how narrow eligibility (based on identity, location, etc.) for clinical trials can skew which populations are represented, leading to less comprehensive treatment options for those who are not represented. Due to variable hormone levels and the fact that women are capable of child-bearing, women have often been left out of clinical trials—researchers fearing they could not control these variable levels and adverse side effects to fetuses—leading to less comprehensive care options. If women do not feel they can voice their concerns to physicians who listen and pharmaceutical research continues to leave them behind, distrust and subpar treatment will only continue.

Rural populations also report higher levels of distrust, mostly specifically those who misuse drugs. In a qualitative study of this population, participants reported "breaches of trust by healthcare providers, often involving law enforcement and Emergency Medical Services, that dissuaded them from accessing medical care" (Ellis et al., 2020), including disclosure of protected health information to law enforcement and forced medical procedures. Moreover, those who use drugs, whether prescription or not, are often at higher risk for various infections. However, these individuals use primary care less and Emergency Medical Services more than those who do not use prescription drugs—indicating a reluctance to use medical care unless absolutely necessary, specifically due "to anticipation of stigma or mistreatment"(Ellis et al., 2020). This isolation from healthcare not only fosters further distrust but also puts these patients at higher risk for complications and non-adherence.

The question becomes: how can physicians work to build trust with their patients? A key step seems to be making space in the office for patients to voice their concerns and ask questions of a non-judgmental physician. For "a successful and humanistic encounter at an office visit, one needs to be sure that the patient's…concerns have been… specifically solicited and addressed…the clinician must gain an understanding of the patient's perspective on his or her illness" (Teutsch, 2003). Ultimately, if physicians do not make the effort to understand their patients, create welcoming spaces, and strive for meaningful connections they risk the health of their patients.

However, this is not an all-encompassing solution. Many still lack access to comprehensive healthcare (e.g. those without insurance), meaning many will not make it to the office in the first place. Steps must be taken to engage with these groups and bridge healthcare disparities if significant change is to be made. The issue with this is that what these steps are is not

is to be made. The issue with this is that what these steps are is not entirely clear. However, working to improve accessibility seems to be a good first step. Establishing a multilingual healthcare system could become a priority or growing telehealth could become a focus to increase the flexibility and accessibility of primary care. Addressing systemic issues in the healthcare system is no easy feat but progress is possible.

The current limitations of healthcare must be acknowledged, both in reference to issues in prescription drug treatment and the patient-physician relationship. ***On the macro level, health literacy is a powerful tool that can allow us to address non-adherence. While current proposals show promise, much work must be done by reputable institutions to combat medical misinformation and reduce the clinical and economic implications of non-adherence. On the micro level, medical education must emphasize compassion, integrity, and clear communication as necessary skills in being a physician.*** There must be emphasis on the point that being a good doctor goes beyond excellent technical skills. Being a good doctor requires emotional intelligence, openness, and empathy. In making accessibility a priority, thousands of lives can be saved every year. Through addressing the roots of non-adherence, providing better care—for everyone—can become more of a reality. ❧

AUTHOR BIO

Alissa is a first year studying Computer Science and Human Health. She is interested in exploring the intersection of technology and healthcare, advances and issues in women's healthcare, and the accessibiity and of health education.

AUTHOR BIO

Vivek is a first year studying Neuroscience & Behavioral Biology. He is interested in epigenetics and oncology.

Edited by Joseph Park Madeline Proctor, and Dr. Muhammad Azeem

Placed by Madeline Proctor

REFERENCES

Aker J, Beck M, Papay JI, Cantu T, Ellis M, Keravich D, Bibeau K. Consumers Better Understand and Prefer Simplified Written Drug Information: An Evaluation of 2 Novel Formats Versus the Current CMI. Ther Innov Regul Sci. 2013 Jan;47(1):125-132. doi: 10.1177/0092861512462371. PMID: 30227488.

Badarudeen, S., & Sabharwal, S. (2010). Assessing Readability of Patient Education Materials: Current Role in Orthopaedics. *Clinical Orthopaedics and Related Research*, 468(10), 2572–2580. doi:10.1007/s11999–010–1380–y.

Chen J, Wang Y. Social Media Use for Health Purposes: Systematic Review. J Med Internet Res. 2021 May 12;23(5):e17917. doi: 10.2196/17917. PMID: 33978589; PMCID: PMC8156131.

Dean, L. T., Moss, S. L., McCarthy, A. M., & Armstrong, K. (2017, December). Healthcare system distrust, physician trust, and patient discordance with adjuvant breast cancer treatment recommendations. *PubMed*.

Ellis, K., Walters, S., Friedman, S. R., Ouellet, L. J., Ezell, J., Rosentel, K., & Pho, M. T. (2020, November 10). Breaching trust: A qualitative study of healthcare experiences of people who use drugs in a rural setting. *PubMed Central (PMC)*. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8022503/

Health literacy. Health Resources and Services Administration. (n.d.). https://www.hrsa.gov/about/organization/bureaus/ohe/health-literacy#:~:text=Personal%20health%20literacy%20is%20the,actions%20for%20themselves%20and%20others.

Jimmy B, Jose J. Patient medication adherence: measures in daily practice. Oman Med J. 2011 May;26(3):155-9. doi: 10.5001/omj.2011.38. PMID: 22043406; PMCID: PMC3191684.

Kim, J., Combs, K., Downs, J., & Tillmann III, F. (2018, January 19). Medication adherence: The elephant in the room. *U.S. Pharmacist – The Leading Journal in Pharmacy*. https://www.uspharmacist.com/article/medication-adherence-the-elephant-in-the-room#:~:text=Nonadherence%20can%20account%20for%20up,chronic%20medications%20is%20around%2050%25

Kish-Doto, J., Scales, M., Eguino-Medina, P., et al. (2014). Preferences for Patient Medication Information: What Do Patients Want? *Journal of Health Communication: International Perspectives*, 19, 77–88. doi:10.1080/10810730.2014.946114.

Kools, M., Ruiter, R. A., van de Wiel, M. W. J., et al. (2007). The Effects of Headings in Information Mapping on Search Speed and Evaluation of a Brief Health Education Text. *Journal of Information Science*, 34(6), 833–844. doi:10.1177/0165551508089719.

Kutner et al., (2006, September 6). The Health Literacy of America's Adults: Results from the 2003 National Assessment of Adult Literacy. National Center for Education Statistics (NCES) Home Page, a part of the U.S. Department of Education. https://nces.ed.gov/pubsearch/pubsinfo.asp?pubid=2006483

Meyers AG, Salanitro A, Wallston KA, Cawthon C, Vasilevskis EE, Goggins KM, Kripalani S. Determinants of health after hospital discharge: rationale and design of the Vanderbilt Inpatient Cohort Study (VICS). *BMC Health Serv Res*, 14, 10. doi: 10.1186/1472-6963-14-10.

Pahus, L., Suehs, C. M., Halimi, L., Bourdin, A., Chanez, P., Jaffuel, D., Marciano, J., Gamez, A., Vachier, I., & Molinari, N. (2020, August 13). Patient distrust in pharmaceutical companies: An explanation for women under-representation in respiratory clinical trials? *BioMed Central*. https://bmcmedethics.biomedcentral.com/articles/10.1186/s12910-020-00509-y#citeas

Pearson, S. D., & Raeke, L. H. (2000, July). Patients' trust in physicians: Many theories, few measures, and little data. *PubMed Central (PMC)*. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1495476/

Raynor, D. K., & Dickinson, D. (2009). Key Principles to Guide Development of Consumer Medicine Information—Content Analysis of Information Design Texts. *The Annals of Pharmacotherapy*, 43(4), 700–706. doi:10.1345/aph.1L522.

Sedeh, F. B., Arvid Simon Henning, M., Mortensen, O. S., Jemec, G. B. E., & Ibler, K. S. (2022). Communicating with patients through pictograms and pictures - a scoping review. *J Dermatolog Treat*, 33(6), 2730-2737. doi:10.1080/09546634.2022.2068790. Epub 2022 Jun 10. PMID: 35440279.

IMAGE REFERENCES

Merks, P., Cameron, J., Bilmin, K., Świeczkowski, D., Chmielewska-Ignatowicz, T., Harężlak, T., Białoszewska, K., Sola, K. F., Jaguszewski, M. J., & Vaillancourt, R. (2021). Medication Adherence and the Role of Pictograms in Medication Counselling of Chronic Patients: a Review. Frontiers in pharmacology, 12, 582200. https://doi.org/10.3389/fphar.2021.582200

Meyers AG, Salanitro A, Wallston KA, Cawthon C, Vasilevskis EE, Goggins KM, Kripalani S. Determinants of health after hospital discharge: rationale and design of the Vanderbilt Inpatient Cohort Study (VICS). *BMC Health Serv Res*, 14, 10. doi: 10.1186/1472-6963-14-10.
articles/10.1186/s12910-020-00509-y#citeas)

Envisioning a brighter future: The effectiveness of AI-enabled techniques for cataract screenings in Nepal

MATHIEU RIHET
First Year Liaison

SARA GARG
First Year Liaison

Fifty-one percent of global blindness in low-income countries is accounted for by a screenable and treatable disease: cataracts. While healthcare has become increasingly globalized, the distribution of resources is still heavily skewed, often disproportionately placing a cataract burden on people with lower socioeconomic statuses (Fang et al., 2022). This is largely due to a reliance on analysis by retina specialists and trained human graders, who are often scarce at an international scale (Balyen & Peto, 2019). This problem is especially prevalent in South Asia, where income levels and access to cataract screenings are low while incidence of vision impairment is high. In fact, out of the 52.90% of visually impaired patients among a study of 1,960 older adults in Nepal, 68.07% of visual impairment (including 43.33% of blindness) was caused by cataracts (Thapa et al., 2018). Artificial Intelligence (AI) offers a solution with telediagnosis made possible through Convolutional Neural Networks (CNNs). These machine learning (ML) methods are highly accurate, with an average of 94.8% sensitivity and 96.0% specificity in cataract diagnosis (Cheung, 2022). Moreover, they can be utilized to foster greater access to diagnosis and treatment due to economic efficiency. However, AI, especially CNNs, often draw on "black box" algorithms, in which the human perspective can only see the inputs and outputs of the AI but not the methodology used to reach its conclusion. As CNN software tries to take the shortest possible route to diagnosis, oftentimes, it links socioeconomic background or external factors to diagnosis, as seen through international case studies. Overall, regarding cataract screening in Nepal, AI is promising as current innovations work to create more diverse datasets to reduce bias and increase accuracy, making them a more economical and accessible tool to eye camps with the potential to aid global cataract screening.

At the surface level, ML methods appear highly accurate and efficient. Literature reviewing the efficacy of ML methods to screen for various ocular diseases, such as glaucoma and diabetic retinopathy, reveals a high accuracy of these methods — seen in particular with one model that offered a sensitivity of 95.6% and specificity of 92.0% (Lokman & Tunde, 2019). In recent years, this approach has targeted cataracts. One potential cataract screening model for implementation used 37,638

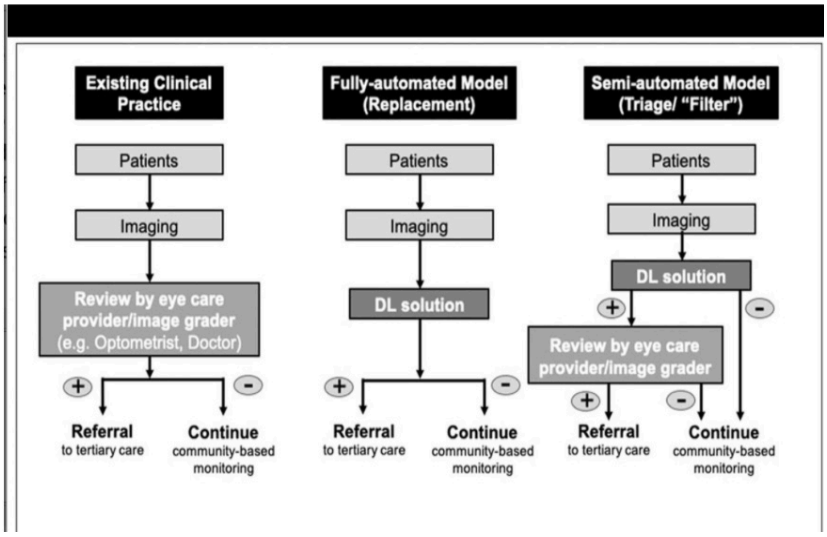

Figure 1. Illustration of the process of AI-enabled diagnosis using a deep-learning (DL) algorithm as compared to traditional methodology. While the total number of steps is similar, the timing and accuracy greatly change in the step post-imaging, illustrating the efficiencies of AI. (Gunasekeran & Wong, 2020)

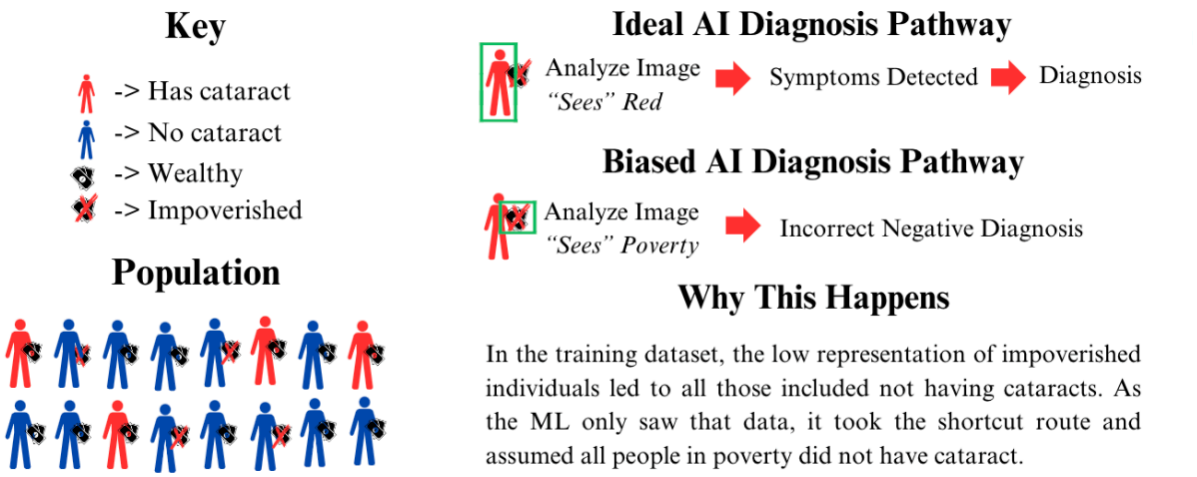

Figure 2. An extreme case study demonstrates how bias in machine learning enabled diagnosis might occur. (Gunasekeran & Wong, 2020)

training images and offered "excellent diagnostic performance" (Ting et al., 2019). Another ML-enabled screening software was tested in Nepal and showed great promise regarding adult cataract diagnosis with 94.8% sensitivity and 96.0% specificity (Cheung, 2022).

Despite the accuracy of ML diagnosis, these methods may overlook subtleties inherent to the disease and diagnosis. Past research on glaucoma, another ophthalmologic condition leading to blindness, found that the algorithm often failed to diagnose patients with multiple illnesses, such as when a patient being screened for glaucoma also had myopia (Lokman & Tunde, 2019). This is not only detrimental to overall accuracy, but also fosters systemic bias against social groups more likely to have multiple diseases. Often, these social groups are those with lower socioeconomic statuses who may not have had the resources to get other diseases diagnosed or treated before arriving in the eye camp. This is exemplified by the correlation between lower vision and ocular health in disadvantaged living situations in England — a correlation likely to hold true in Nepal (Yip et al., 2014).

Moreover, bias in the algorithms, largely due to the under-representation of certain groups in datasets, offers complexity to the question of cataract screening's accuracy. Black-box deep learning methods, often utilized for ML-enabled diagnosis, allow for the analysis of subtle data features, but the algorithm often bypasses this nuanced analysis. This is especially detrimental for minority populations often underrepresented in datasets as seen in Figure 2. In South Asia, cataract data trends likely follow those for access to Cataract Surgical Coverage (CRC), as both require access to resources and ophthalmologic professionals. In a 2017 study, CRC in every country analyzed in South Asia was lower among women than men (Khanna & Murthy). In Nepal specifically, CRC deficiency was greater among illiterate populations (Khanna & Murthy, 2017). Inequities in Nepal appear particularly stark as even in 2016, there were only 3.15 healthcare workers per 1000 population members, a ratio that grew even more skewed during the pandemic (Neupane et al., 2021). Thus, the social determinants of health are seen to profoundly impact routes to cataract treatment globally.

A solution for these potential biases lies in a greater diversity of data collection, primarily focused on training models on representative populations of the groups they will aid. Current data collection methods reflect economic inequities, as seen with only country-wide CRC data being available for countries with lower GDPs. In contrast, wealthier countries had

Out of the 52.90% of visually impaired patients among a study of 1,960 older adults in Nepal, 68.07% of visual impairment (including 43.33% of blindness) was caused by cataracts.

state and regional data (Khanna & Murthy, 2017). While this limits the diversity of datasets, current research is working to address these problems; for example, more ophthalmologic studies have been drawn from more diverse Asian populations instead of US-centered studies (Ruamviboonsuk et al., 2020). This approach will help make cataract screening — in fact, all AI — less prone to bias and make it more ethical to implement AI-centered screenings for cataracts. However, much is yet to be done due to an inability to merge cataract datasets because of the lack of uniformity and quality in any commonly found dataset type (Shweikh, 2022).

A universal objective is to make healthcare accessible to all—to verify AI's broader global impact, it must be explored through an economic lens. Traditional eye camps fall under manual cataract screenings and have seen tremendous growth in sustainability and efficiency in rural areas over the last decade. This progress is mainly due to the Aravind Eye Care System (AECS), operating primarily in India. In 2018-2019, the AECS screened more than 500,000 patients, performing 90,000 cataract-related surgeries through 2,800 eye camps (Natarajan, 2019). Despite these advances, however, the eye camps' international outreach is low—they almost only operate in India, with almost no infrastructure set in other rural countries (Health Market Innovations, 2022). Further critique has been placed on the AECS for unsafe conditions and environments, leaving certain individuals attending eye camps worse than previously unattended. Setting up an eye camp can also be costly and requires volunteer training, which can be extremely time-consuming and inefficient in rural areas (Schehlein, 2021). Despite its promise, this system has many potential flaws that are difficult to address when envisioning a brighter future.

Medical organizations should place more resources into understanding the effectiveness of using AI in healthcare and how its implementation could lead to the globalization of eye care.

However, the technological advances of AI provide an answer to these flaws. Multiple imaging modalities, such as Fundus and slit-lamp images, classify cataracts—a processed diagnosis from a simple picture. These classifications achieved 82.1% and 82.9% true positive rates in training and tests (Wan Zaki et al., 2022). These results are auspicious for such novel technology. AI diagnosis could be a future avenue for eye camp screenings and in-home testing for those with access to internet connection. Some problems were already raised in this research model, such as the extensive time preprocessing a single image takes. Many models were proposed to remedy this problem, all with some drawbacks; the search for the perfect model is still in the early stages of development (Wan Zaki et al., 2022).

A specific investigation on cataract screening access in Nepal has demonstrated the ubiquitous access AI technology can provide (Cheung, 2022). Current initiatives often rely on a single ML model, such as the single deep-learning system implemented to screen for glaucoma, AMD, and DR (Gunasekeran & Wong, 2020). That innovation marked a

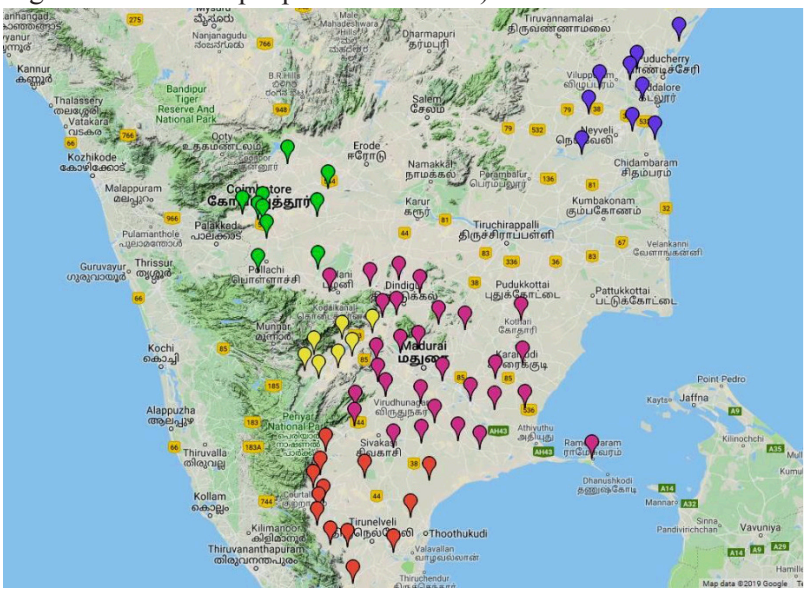

Figure 3. Illustrates the AECS eye camp's outreach in India. The location markers each represent an eye camp location with the different colors corresponding to different regions (Aravind Eye Care).

change to the prevalent forms of ML diagnosis where, in the past, new models were needed for each disease, often impossible for those without the technical experience and again limiting the scope of accessibility in underserved areas such as Nepal. In Nepal, populations in mountainous regions require hours of travel to see a health practitioner, as most hospitals and pharmacies are concentrated in the country's central region (Cheung, 2022). Moreover, the financial barrier imposed by private practice bridges a gap between the rural population of Nepal and its healthcare system; eye specialists are also uncommon in the country. Many eye camps following the AECS model opened in rural areas of Nepal. However, the limitations imposed by this model caused the cataract diagnosis agreement to have a specificity of kappa = 0.623—too low. As a result, one AECS eye camp in Nepal started experimenting with using convoluted neural networks and cataract classification systems to screen their patients.

The base case study processed a sample of 22,805 patients in Nepal attending an AECS eye camp over one year. The machine learning-based camp detected 31 cases of cataracts and 2546 additional non-cataract cases, totaling 2577 correct cases compared to the traditional eye camps. Regarding cost-effectiveness ratios, the average cost per cataract case detected was $23.87, while the conventional eye camps were $45.89—the machine learning camp was almost half as expensive as a traditional eye camp (Cheung, 2022). Every statistic from this case study in Nepal concludes that eye camps incorporating AI are more cost-efficient and precise.

Moreover, future technological advancements offer great potential to further increase access. AI-based automated software being developed uses fundus photography taken using a smartphone-based device and has very high sensitivity for detecting diabetic retinopathy (Ruamviboonsuk et al., 2020). This potential mass screening tool could be applied to cataract screening and help reduce the prevalence of this treatable disease.

In today's globalized world, one can question how the AI camp model in Nepal could be applied to every AECS eye camp. Eye care in South Asian countries is known to be meager; the issue of cataracts remains pervasive. Although AI does carry complication surrounding bias, it is growing more accurate, economically viable, and accessible than traditional methods, making it appear overall effective for future eye camps in Nepal. This case study shines a light on the powers of AI for holistic eye care in rural areas—a clear call to action that medical organizations should place more resources into the effectiveness of AI in healthcare and how it could lead to the globalization of eye care. ❧

AUTHOR BIO

Mathieu Rihet is a first-year student majoring in Applied Mathemtaics & Biomedical Engineering. He is interested in neural prosthetics and their application in underserved countries.

AUTHOR BIO

Sara Garg is a first-year student interested in AI and its applications in healthcare.

Edited by Claire Qu, Justin Hahm, and Dr. Xinhua Chen

Placed by Claire Qu

REFERENCES

Aravind Eye Care System (AECS) | The Center for Health Market Innovations. (n.d.). https://healthmarketinnovations.org/program/aravind-eye-care-system-aecs

Balyen, L., & Peto, T. (2019). Promising Artificial Intelligence-Machine Learning-Deep Learning Algorithms in Ophthalmology. Asia-Pacific Journal of Ophthalmology. https://doi.org/10.22608/apo.2018479

Cheung, R. (n.d.). Effectiveness of machine learning classifiers for cataract Screening - ProQuest. https://www.proquest.com/openview/28b498cb3f0be8a32afd4f07f7d92588/1?pq-origsite=gscholar&cbl=18750&diss=y

Fang, R., Yu, Y., Li, E., Lv, N., Liu, Z., Zhou, H., & Song, X. (2022). Global, regional, national burden and gender disparity of cataract: findings from the global burden of disease study 2019. BMC Public Health, 22(1). https://doi.org/10.1186/s12889-022-14491-0

Gunasekeran, D. V., & Wong, T. Y. (2020a). Artificial Intelligence in Ophthalmology in 2020: a technology on the cusp for translation and implementation. Asia-Pacific Journal of Ophthalmology, 9(2), 61–66. https://doi.org/10.1097/01.apo.0000656984.56467.2c

Gutierrez, L., Lim, J., Foo, L. L., Ng, W. Y., Yip, M., Lim, G., Wong, M. H., Fong, A., Rosman, M., Mehta, J. S., Lin, H., Ting, D. S. J., & Ting, D. S. W. (2022). Application of artificial intelligence in cataract management: current and future directions. Eye And Vision, 9(1). https://doi.org/10.1186/s40662-021-00273-z

Khanna, R. (2016). Inequities in cataract surgical coverage in South Asia. PubMed Central (PMC). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5340111/

Shweikh, Y., Sekimitsu, S., Boland, M. V., & Zebardast, N. (2023). The growing need for ophthalmic data standardization. Ophthalmology Science, 3(1), 100262. https://doi.org/10.1016/j.xops.2022.100262

Thapa, R., Bajimaya, S., Paudyal, G., Khanal, S., Tan, H. S., Thapa, S., & Van Rens, G. H. M. B. (2018). Prevalence and causes of low vision and blindness in an elderly population in Nepal: the Bhaktapur retina study. BMC Ophthalmology, 18(1). https://doi.org/10.1186/s12886-018-0710-9

Ting, D. S. J., Ang, M., Mehta, J. S., & Ting, D. S. W. (2019). Artificial intelligence-assisted telemedicine platform for cataract screening and management: a potential model of care for global eye health. British Journal of Ophthalmology, 103(11), 1537–1538. https://doi.org/10.1136/bjophthalmol-2019-315025

Webmaster. (2011, October 28). Aravind Eye Care System – Social Enterprise Institute at Northeastern University. https://www.northeastern.edu/sei/2011/10/aravind-eye-care-system-case/

Yip, J., Luben, R., Hayat, S., Khawaja, A. P., Broadway, D. C., Wareham, N., Khaw, K., & Foster, P. J. (2013). Area deprivation, individual socioeconomic status and low vision in the EPIC-Norfolk Eye Study. Journal of Epidemiology and Community Health, 68(3), 204–210. https://doi.org/10.1136/jech-2013-203265

IMAGE REFERENCES

Aravind Eye Care. (n.d.). Aravind Eye Care. https://aravind.org/vision-centre/

Gunasekeran, D. V., & Wong, T. Y. (2020b). Artificial Intelligence in Ophthalmology in 2020: a technology on the cusp for translation and implementation. Asia-Pacific Journal of Ophthalmology, 9(2), 61–66. https://doi.org/10.1097/01.apo.0000656984.56467.2c


EUMR

ADVISORY BOARD

ARRI EISEN Ph.D.

Professor of Pedagogy at Emory University

EUMR's primary advisor is Dr. Arri Eisen, professor of pedagogy in biology and at the Center for Ethics at Emory University. After receiving his PhD in biochemistry from University of Washington - Seattle in 1990, he began teaching at Emory and became a teaching coordinator for FIRST, a postdoctoral fellowship in research and teaching that is supported by the National Institutes of Health.

Dr. Eisen aims to engage undergraduate students in the exploration of science and its applications in broad contexts. He has led the Emory-Tibet Science Initiative since 2005, which works with the Dalai Lama to provide a scientific education for Tibetan monks and nuns. He has published a wide variety of academic articles in science, science education, and bioethics.

Emory Undergraduate Medical Review articles are peer-reviewed by medical professionals from more than a dozen leading academic institutions. The Emory Undergradute Medical Review would like to extend its thanks to the following advisors.

MUHAMMAD AZEEM

Medical doctorate in Child Psychiatry at Cornell University

Dr. Azeem's primary clinical and research interests include Autism Spectrum Disorders, ADHD, child and adolescent psychiatry training, global mental health, and looking into innovative ways in reducing seclusions and restraints in inpatient child and adolescent settings.

XINHUA CHEN

Doctorate in biology from the University of Southern California

Dr. Chen is an Assistant Professor at the Harvard School of Medicine. His research in the Department of Gastroenterology focuses on *C. difficile* infection, particularly in children and immunocompromised patients.

SARAH CASTON

Doctorate in Physical Therapy from Emory University

Dr. Caston is an assistant professor in the Division of Physical Therapy in the Department of Rehabilitation Medicine at Emory. Her areas of clinical expertise are in geriatric and neurologic rehabilitation, while her scholarly interests focus on humanities and ethics in rehabilitation, healthcare graduate student well-being, and stories and lived experiences of individuals living with disability.

JOHNATHAN CRANE

Doctorate in religion from the University of Toronto

Dr. Crane serves as the Raymond F. Schinazi Scholar of Bioethics and Jewish Thought at Emory University's Center for Ethics, professor at Emory University School of Medicine, and affiliated faculty in the Department of Religion. As the founder and co-Editor-in-Chief of the *Journal of Jewish Ethics*, he continues to publish research on Judaism, bioethics, and religious ethics.

ADVISORY BOARD

TYLER CYMET

Medical doctorate from Nova Southeastern University College of Osteopathic Medicine

Dr. Cymet is an internist with research interests in joints and the musculoskeletal system. He discovered a new syndrome in 2006 which was named for him called the Erondu-Cymet syndrome. He now serves as the chief of clinical education for the American Association of Colleges of Osteopathic Medicine.

SARAH MITCHELL

Medical doctorate from Creighton University School of Medicine

Dr. Mitchell is a pediatric oncologist at Children's Healthcare of Atlanta and Assistant Professor of Pediatrics in the Emory University School of Medicine. She works as part of a large, multidisciplinary team at the Aflac Cancer and Blood Disorders Center focusing her clinical care on treating children with solid tumors and rare tumors.

SUBADHRA SHASHIDHARAN

Medical doctorate from Bangalore Medical College, India

Dr. Shashidharan is a Pediatric Congenital Cardiothoracic Surgeon at Children's Healthcare of Atlanta and Assistant Professor of Surgery at Emory University School of Medicine. She serves as the Director of Quality for Pediatric Cardiac Surgery at Children's and Director of the Emory Adult Congenital Heart Center. Her clinical interests include neonatal heart surgery and adult congenital cardiac surgery.

SARA TURBOW

Medical doctorate from Emory University

Dr. Turbow's research focuses on care fragmentation, particularly among older adults with Alzheimer's Disease. She practices as a primary care physician at the Grady Primary Care Center. She is also the Associate Program Director for the Public Health and General Preventive Medicine Residency Program in the Department of Family and Preventive Medicine, Division of Preventive Medicine.

JUDY GICHOYA

Medical doctorate from Moi University, Kenya

Dr. Gichoya is an associate professor in the Department of Radiology and Imaging Sciences at Emory University School of Medicine. Dr. Gichoya is a multidisciplinary researcher, trained as both an informatician and an Interventional radiologist. Her research interests lie at the intersection of artificial intelligence, radiology, and racial bias.

JOSEPH PETROSINO

Doctorate in microbiology and immunology from Baylor College of Medicine

Dr. Petrosino is the director of the Alkek Center for Metagenomics and Microbiome Research and Chief Scientific Innovation Officer at Baylor College of Medicine. His research interests are related to metagenomics and genetic interactions between commensal microbiota and the host and how microbially encoded functions influence host health and disease.

KIM TRAN

Medical doctorate from the University of Medicine and Pharmacy at Ho-ChiMinh City, Vietnam and doctorate in Medical Sciences from Hamamatsu University School of Medicine

Dr. Tran is a professor of physiology and pharmacology and director of the PhD program in Biomedical Sciences at Des Moines University. His research interests include cardiovascular pathobiology and therapeutics, especially the role of GPCRs in disorders such as menopause, heart failure and hypertension.

ZANTHIA WILEY

Medical Doctorate from University of Alabama

Dr. Wiley is a co-investigator within the NIH-funded Emory Vaccine and Treatment Evaluation Unit. She has a special interest in addressing health inequities in COVID (and other viral infections) via the promotion of equitable therapeutics and access to vaccination. Dr. Wiley is a member of the Emory Department of Medicine's DEI Council and is passionate about mentorship (particularly of those who are underrepresented in medicine).

Executive Board

ALYSSA CHEN

Editor in Chief

Alyssa is a third year majoring in Biology and minoring in Nutrition Science. She first joined EUMR as a contributing writer and served as treasurer during her sophomore year. She is passionate about acccessible healthcare expansion and lifestyle disease. Outside of EUMR, she enjoys working as an Emory Pre-Health Advising mentor and serves in the Student Government Association.

SHREYA RAMANATHAN

Editor in Chief

Shreya is a third year majoring in Anthropology and Human Biology and South Asian Studies. She first joined EUMR as a freshman liasion and served as Secretary during her sophomore year. She is passionate about addressing gaps in healthcare literacy & accessibility in the US. Outside of EUMR, she works with several free clinics in Georgia & serves on the 68th College Council.

AHONA HAQUE

Treasurer

Ahona is a second year double majoring in Human Health and Business. She is passionate about pursuing a career in healthcare consulting. Since joining EUMR her freshman year, her favorite part about EUMR is the wide variety of topics, ranging from medical breakthroughs to controversies, that are presented by EUMR members.

EMMA KINGWELL

Secretary

Emma is a second year majoring in Chemistry. She previously served as a First-Year Liaison for EUMR. She is interested in emergency medicine and cardiology and is passionate about mentorship. Outside of EUMR, Emma is involved with Emory EMS, the Emory Wheel, and is a Chemistry Learning Assistant.

ZACHARY PAIKIN

Events Chair

Zachary is a second year majoring in Chemistry and Classic Civilization. His interests are in internal medicine, specifically surgical cardiology. Outside of EUMR, he enjoys research in the Raj Lab of the Chemistry Department and volunteers at clinics with Remote Area Medical (RAM).

JOSIE CHEN

Senior Advisor

Josie is a senior studying Human Health. She served as co-EIC in EUMR's previous year. Aside from EUMR, she loves being a part of Emory Planned Parenthood and is passionate about health equity. In her free time, Josie enjoys visiting the beach, baking, and taking care of her pet turtles and betta fish.

MURIEL STATMAN

Senior Advisor

Muriel is a senior majoring in Chemistry and Sociology. She served as co-EIC in EUMR's previous year. She served as a first year liaison during her first year and then a staff writer her second year. Outside of EUMR, she is an Emory Writing Center tutor and a volunteer at the Winship Cancer Institute. Muriel also enjoys going on hikes and practicing yoga.

Editorial Board

Editors

Neha Bajaj

Neha is a third year majoring in Anthropology and Human Biology. Her interests in medicine include cardiology, preventative medicine, and psychology.

Aastha Bansal

Aastha is a fourth year majoring in Neuroscience and Behavioral Biology. She is interested in neurodegenerative diseases, vaccine hesitancy, and healthcare access.

Christina Fu

Christina is a second year majoring in Biology. Her favorite thing about EUMR is being able to engage in a variety of unique, thought-provoking discussions with peers.

Justin Hahm

Justin is a third year double majoring in Economics and Biology. His interests are in autoimmune conditions, controversial big pharma policies, and economic issues regarding healthcare equity.

Zuha Jaffar

Zuha is a third year majoring in Creative Writing. She especially enjoys how EUMR communicates and introduces different facets of medicine.

Advaita Krishnan

Advaita is a third year majoring in Human Health and Philosophy. Her interests are in bioethics and social inequities.

Ankitha Kumar

Ankitha is a third year majoring in Human Health. She is interested in psychiatry, mental illness, and how social structures affect access to mental health resources.

Editorial Board

Editors

LIANNA LEVINE

Lianna is a second year majoring in Biology. Her favorite part of EUMR is meeting driven and hardworking people who are deeply passionate about many different aspects of medicine.

SAMIR LOHANA

Samir is a second year majoring in Quantitative Sciences with a concentration in Neuroscience & Behavioral Biology. His favorite part of EUMR is engaging in medical discussions within a supportive community.

SIYA MALHOTRA

Siya is a fourth year majoring in Biology and minoring in Religion. She loves the emphasis EUMR puts on creativity, perspective, and innovation in the medical field.

JOSEPH PARK

Joseph is a third year majoring in Psychology. His favorite part of EUMR is talking to other students about diverse medical topics.

MADELINE PROCTOR

Madeline is a second year majoring in Psychology, interested in neurodegenerative diseases, neurodevelopmental health, and cardiac health.

CLAIRE QU

Claire is a third year majoring in Biology and minoring in Dance and Movement Studies. Her favorite part of EUMR is reading everyone's interesting articles.

CLAIRE ZEGGER

Claire is a third year majoring in Quantitative Sciences with a concentration in Anthropology. Her interests are in neuroscience and neurodegenerative diseases.

EUMR 2023-2024