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HMSR

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HMSR

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Dear readers,

We are delighted to present the sixth issue of the Harvard Medical Review (HMSR), Harvard Medical School's student-run medical journal dedicated to showcasing important issues facing health and medicine. We are proud of the work, collaboration, and commitment that HMSR members have put into making this issue possible. In our pages, our authors explore a wide array of topics ranging from race-based disparities in healthcare to a physician's role in gun violence.

This past year, we have striven to increase the quality of our work through recruiting more members onto our editorial team. In this same vein, we are excited to introduce a broader array of voices and enhance HMSR's visibility through working with those from other institutions. Looking forward, we hope to continue introducing new backgrounds and perspectives while delivering the same professional-quality journal.

The work that HMSR does would not be possible without the dedication and support from the board of faculty, strategic, and alumni advisors, as well as Gina Vild and the Office of Communications and External Relations. We would also like to thank our editorial team, including our Associate Editors, who diligently ensure the scholarly excellence of our work.

We are very excited and proud to present our newest issue and to share scholarly work with you. Enjoy!

Sincerely,

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

The articles represent the views and opinions of the original authors and does not necessarily represent the views or opinions of the Harvard Medical Student Review or Harvard Medical School.

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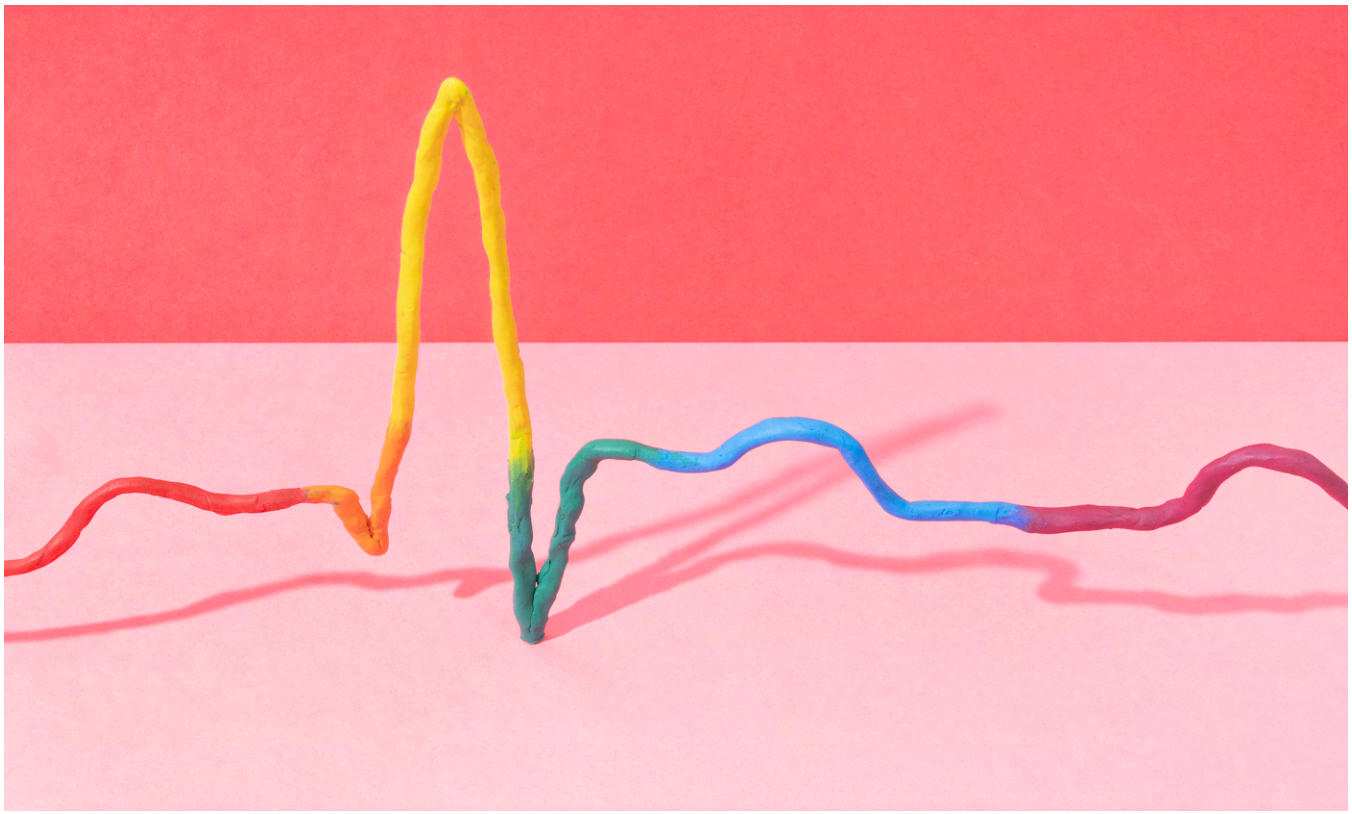

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Addressing Pervasive Homophobia in Medical Education

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Public opinion around LGBTQ issues in the United States has progressed rapidly over the last few decades.[1] This shift has occurred faster than it has for race, disability, and even elder bias. In fact, support for marriage equality and equal adoption opportunity doubled in just one decade. As of 2014, a majority of Americans reported support for anti-discrimination laws for gay and lesbian workers.[1] As early as 1990, less than 30% of Americans viewed marriage equality and same-sex adoption favorably, but as of 2014 greater than 50% viewed marriage equality favorably and greater than 60% viewed same-sex adoption favorably.[1] While this overall trend is beneficial to LGBTQ Americans, we cannot ignore pockets of extreme bias that continue to persist and remain in the shadows.

I am a 25-year-old gay medical student in the Deep South. My medical school sits in the middle of a county that, in many ways, has remained in those "shadows". Our county made national news in the Spring of 2019 for attempting to pass what came to be known as "The Anti-Gay Resolution." This resolution decreed that LGBTQ people in our county were unwelcome to live, own businesses, or raise families. Although a resolution of this nature would not hold legal standing, it had the potential to impact the health and well-being of the entire LGBTQ+ community. Luckily, after

months of protests and divisive rhetoric at County Council Town Halls, this resolution was removed with a 6-5 vote.[2,3] In the end, our efforts brought the LGBTQ community closer together than ever before. However, the necessity of public uprising to prevent its passage lingers as evidence of stigma and discrimination.

The persistence of homophobia is not isolated from medical education, nor from within the walls of clinic. I have seen the impact of discrimination on my role as a medical student and future physician. I have also experienced the impact of homophobia as a community member in the Deep South. Despite my own personal efforts to support equitable healthcare for people who identify as LGBTQ+, I have repeatedly observed discriminatory behavior. During one particularly grueling week, I witnessed physicians: 1) mock pronouns in the EMR; 2) state that a 16-year-old's bisexual identity would "deflower" the innocence of his peers; 3) assume gay patients were HIV-positive; and 4) refer to LGBTQ+ as "LGB...ABCDEFG or whatever." This type of behavior directly impacts patient outcomes.[4] Additionally, this has a dual impact on my personal identity. This environment is not a place where I can freely be my whole self: a gay man *and* a medical student.

Being a gay man and a medical student are two critical parts of my identity. However, for most people, my sexuality is invisible. I have the privilege of concealing or revealing my identity to avoid the microaggressions and macroaggressions others with visible identities experience daily in clinic. Attendings often meet me and see a young, white male, assuming that I share their conservative ideology. The privilege of my worn identity – including my ability to "pass" as heterosexual - also opens up the opportunity for unfiltered homophobic or transphobic remarks that expect to meet agreeable ears. In these situations, I am faced with another internal struggle: Do I speak up to defend my identity and risk the assessment that I am being "unprofessional"? If I do not speak up, am I failing LGBTQ+ students who will follow me? If I do not perform perfectly today, will I contribute to this physician's biases?

When LGBTQ+ students face such unnecessary encounters, it is disruptive to our education. It causes internal conflict, raises our awareness of stereotype threat, and hurts our performance.[5,6,7] The experience of increased performance anxiety is all too common for LGBTQ+ students as well as for many populations who have experienced oppression, including racial and ethnic minorities and people with disabilities.[5] Just as the HRC survey[8] revealed, LGBTQ+ people who fear discrimination report negative impacts on productivity, satisfaction, and wellbeing. These impacts are pervasive, and they noted that upward of 35% of LGBTQ+ professionals lie about their personal life at work. Medical schools and clinical learning environments alike are not immune to these forces.

Bias and discrimination are common experiences among various LGBTQ+ medical professionals, and in many ways we are still waiting for medical education to catch up to public opinion.[7,8,9,10,11] Students, residents, and attending physicians alike report experiencing similar hardships throughout their careers and report these hardships as perceived barriers to success.[9] Almost a third of sexual minority medical students conceal their sexual and gender identity, and this is often rooted in the threat of discrimination.[7] In fact, first-year medical students self-identifying as a sexual minority have higher risk of depressive symptoms, anxiety symptoms, low self-rated health, and increased incidence of social stressors such as harassment.[6] Beyond medicine, the need to conceal sexual and gender identity at work persists across America.

I have personally found the fears of those surveyed to be validated through my own experiences. The classroom is often the equivalent of my workplace, and as the only LGBTQ+ student in my class I am constantly aware of my identity. For example, once a classmate told me they did not "support my lifestyle choices" and that any family other than "the traditional family" was less-than-ideal. Another classmate consistently used the expression "that's gay as AIDS" for months until being confronted.

Witnessing homophobia from physicians and colleagues alike led me to feel deep discomfort in coming out to medical professionals involved in my personal care. This fear was validated when I attempted to establish care with a local physician. They asked me for my sexual orientation, but immediately followed up with "you're not gay are you?" before I could answer. When I told them I was gay, their first words were "Okay, we will add HIV testing to your bloodwork for today" before taking any further sexual history. My frustration only worsens as I study for examinations, reading practice questions on the most popular online study programs that link homosexuality to HIV, Kaposi Sarcoma, Pneumocystis pneumonia, and even spousal abuse. I have never once read a vignette that includes a homosexual couple without linking their identity to disease.

I reflect on these experiences often and I recognize that the presence and persistence of homophobia has been unnecessary and disruptive to my education. I am constantly managing these delicate scenarios when my sole focus should be on learning medicine. I love myself and am proud of my identity. However, the prejudice I experience has an impact on my happiness. It steals my peace. It robs me of my focus.

These trends in the classroom, in clinic, and at home only reinforce sexuality stereotypes. This leads to minimization and invalidation of the sexualities of providers, students, and patients alike.

In adding my voice to what many braver and bolder students and physicians before me have expressed and advocated, I hope to remind my colleagues about the opportunity we have as the next generation of physicians to change medical culture for the better. This will require creating an inclusive culture that values diversity in all forms to advance health equity. I suggest the following as first steps in that process.

First, increase the number of LGBTQ+ medical students and faculty, and ensure that they are celebrated and valued. While Harvard recently announced an incoming M1-class that is 15% self-identified as LGBTQ+, this is not the reality nationwide.[6] While New England and West Coast medical centers have relatively high LGBTQ+ matriculation compared to national demographics, many other institutions such as my own, have a much lower rate.

Second, as medical schools become increasingly – and necessarily – diverse to meet the needs of all of our communities, it is all-the-more essential to create spaces that support all learners, including LGBTQ+ students. To this end, medical schools can ensure that there is some form of allied organization designated for fostering acceptance between LGBTQ+ students and their peers. There is a protective role in having these organizations.[10] Whether they are independent or part of a larger organization such as the Medical Student Pride Alliance (MSPA), such places are needed. We have a new MSPA chapter at my medical school, creating a more official voice that is linked to the medical school and creating a safer space for learning and growth. Additionally, allied faculty and students can demonstrate support. Simple actions such as wearing an allyship pin, putting up welcome or safe-space signage, or having a pride flag in an office window can make a big difference.

Third, all members of a learning community should engage in ongoing training around the social determinants of health. This should include but not be limited to implicit bias training. Oftentimes discussing LGBTQ+ mistreatment in medicine alongside racism, xenophobia, sexism, and other forms of discrimination only occurs in the context of implicit bias training. In isolation, implicit bias training may obscure other necessary actions that provide long-lasting cultural improvements.[12] Medical schools need to expand training about the social determinants of health and the impacts of mistreatment of communities within the medical environment, and these training sessions must be mandatory and interactive.[4,6,13]

The steps I have laid out above can be used to mitigate homophobia at any medical school or other clinical learning setting. Though I am under no illusion that homophobia will be resolved any time soon, I plan to return to the South someday.

I believe there is still hope in the "shadows" where homophobia and other blatant forms of discrimination persist. There is hope because there is work to be done.

In anticipation that my story and my call to action resonate with medical educators across the country, I repeat the demands of community activists and LGBTQ physicians alike: we must be treated fairly, we must be respected, and we must be included in institutional leadership. Together, let us build a truly inclusive medical culture.

ACKNOWLEDGMENT: I extend my gratitude to Dr. Ann Blair Kennedy LMT, DrPH and Dr. Julie Linton MD for their constant support and guidance. Their leadership in the field of medical education keeps me hopeful for a brighter future. I also thank Dr. Chase Anderson MD for encouraging me to find my voice.

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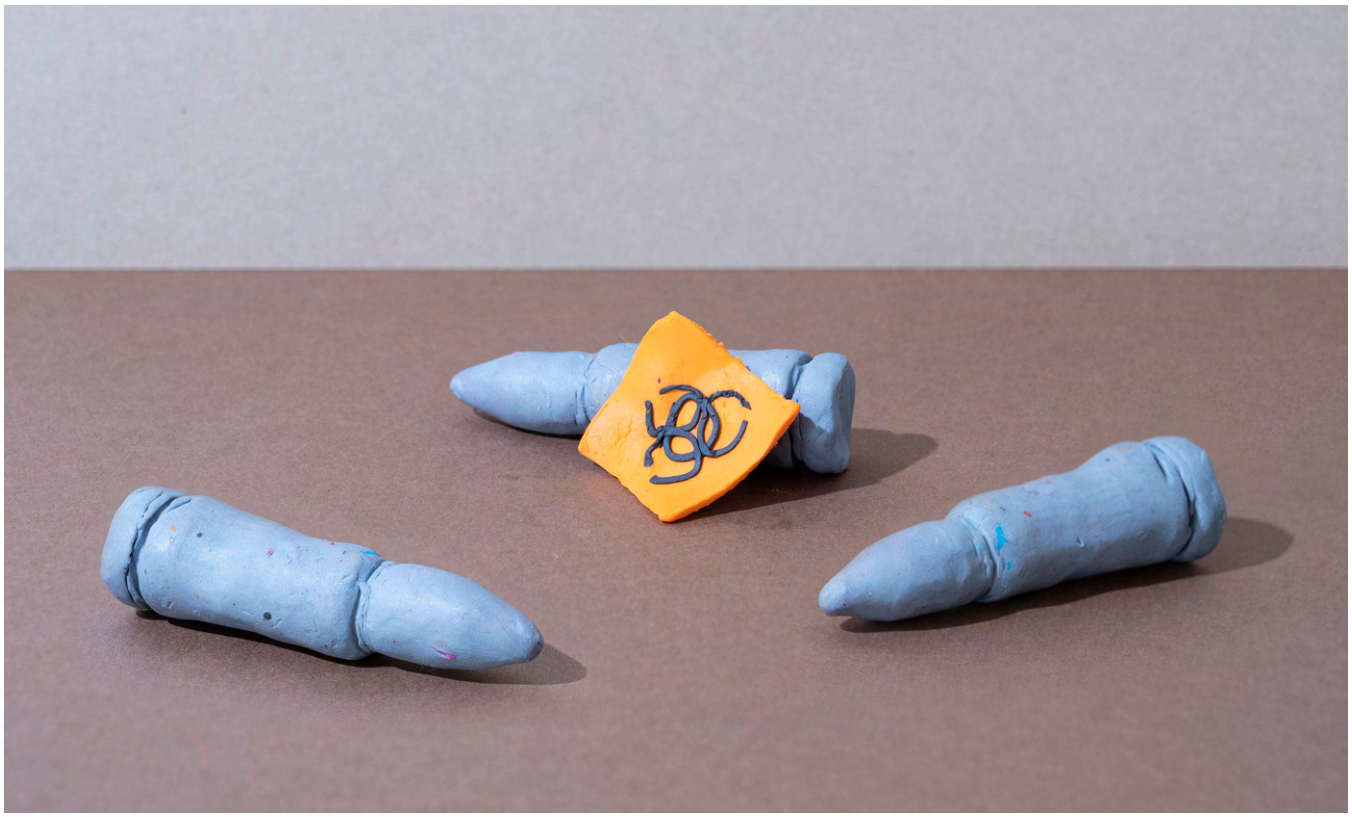

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Gun Violence is Every Doctors' Lane: Ways Healthcare Providers Can Protect Public Health

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The following describes a personal experience from my hometown regarding physician standing in gun violence. The brief history of the physicians' quest to establish credibility on gun violence is reviewed. In addition, the myriad ways in which violence affects all healthcare providers is discussed. In particular, three interventions are examined for their evidence: safe storage counseling, violence intervention programs, and extreme risk protection orders/risk assessments. To act on these evidence-based interventions and save lives, all healthcare providers need legitimacy to counsel their patients on firearm use.

Recently, the Freeholders of Cape May County, New Jersey passed a gun sanctuary resolution. Gun sanctuaries either symbolically condemn state gun regulations or direct police to disobey related state laws. The Cape May County resolution was a reaction to evidence-based gun reform (background checks, extreme risk protection orders, and magazine capacity limits) passed by the New Jersey

State Legislature. As a Cape May County native who has published on gun violence previously, I drafted an op-ed opposing my county's stance. Unfortunately, I received a rejection from a regional newspaper because I lacked "standing" on gun violence. As a local rising fourth year medical student applying into emergency medicine, I thought my standing was self-evident. The news was disheartening, but not shocking (although the piece was eventually published in another outlet).[1]

Unfortunately, many Americans agree with my regional newspaper about the role of physicians in gun reform. The most egregious example is the 2011 Florida Firearm Owners' Privacy Act, known as the "Gag Rule", which prevented physicians from asking screening questions related to firearm ownership and safety.[2] The law was eventually overturned, but doctors struggled to re-establish their legitimacy on this issue. As firearm violence rates continued to rise, physicians increased their presence in the public sphere.[3] In 2018, after the American College of Physicians published a position paper regarding gun violence[4], the National Rifle Association tweeted, "tell self-important anti-gun doctors to stay in their lane."[5] A social media movement, dubbed "This is Our Lane", led by doctors and nurses began telling stories of life-changing patients. Unfortunately, controversy regarding the role of doctors in gun violence reform remains unsettled.

Nearly all healthcare professionals are affected by gun violence. Trauma and plastic surgeons evaluating patients after firearm injuries must recognize their patients are at increased risk for repeat gun violence.[6] Psychiatrists, primary care providers, and emergency medicine physicians seeing suicidal patients must be conscious that owning a firearm increases risk of suicide by at least two-fold.[7,8] Pediatricians and obstetricians counseling families must acknowledge gun ownership significantly increases the risk of accidental deaths among youth.[9]

As providers we recognize that our patients' health is influenced by gun reform. Unintentional injuries, suicides and homicides are leading causes of death in Americans aged 1 year old to 44 years old.[10] Approximately 37,000 of these annual deaths are from gun violence.[11] There are evidence-based screening techniques and interventions that nearly all healthcare providers can apply to reduce deaths. In particular, there are three specific areas where healthcare providers play a role in decreasing violence: safe firearm storage counseling, post-incident violence prevention programs, and risk assessments/extreme risk protection order (ERPO) laws.

Evidence suggests physician directed safe storage training is successful. In one trial, 137 pediatric practices were randomly assigned to office-based intervention or an educational handout. The intervention arm displayed a 10% increase in safe firearm storage compared to a 12% decrease in the control group.[12] Another randomized study of 1,223 patients in which physician-directed counseling was compared to an educational brochure demonstrated a 25% increase in safe storage habits.[13] Conversely, a public health campaign directed via television and radio announcements did not show an effect.[14] When physicians play an active role in gun safety conversations, patients and their families are safer.

Second, healthcare worker directed violence intervention programs have shown promise although more research is needed to ensure the data correspond to morbidity or mortality benefits. The Boston Violence Intervention Advocacy Program (VIAP) matches each violence victim with family crisis support experts and violence intervention advocates. In a survey of twenty program participants, all reported positive experiences and felt networked to the support services they needed.[15] An Oakland hospital program focuses on bedside counseling of teenagers who are victims of violence. To study this program, 112 participants were selected in a case-control study and the results showed a significant decrease in criminal justice involvement over the following 6 months.[16]

Lastly, physicians play an important role in risk assessments and by extension, some ERPO laws. Promising early data has led to increased efforts to better train physicians for this role.[17] In one nonrandomized study of 106 families with adolescents suffering from major depressive disorders, clinician-directed firearm counseling resulted in 27% of families removing guns from their homes.[18] Before exploring the interaction of ERPO laws and physician directed

risk assessments, it is important to define ERPO policies. They allow family or household members, law enforcement, and, less commonly healthcare professionals to petition courts to temporarily remove access to firearms from people who are thought to pose an imminent risk to themselves or others.[16] While many states do not authorize healthcare providers as formal petitioners, providers may still use risk assessment techniques to inform family about serving as ERPO petitioners. Families and patients trust their physicians, and often present to their doctors for guidance in times of crisis. Moreover, these laws are effective at saving lives, likely more so than some medical interventions.[19] In a study of Connecticut citizens for whom ERPO laws were applied, researchers found 1 suicide death was averted for every 10 to 20 temporary firearm removals.[20] In Indiana, a quasi-experimental design using state-level data evidenced a 7.5% reduction in firearm-related suicides.[21]

Healthcare providers have unique evidence-based skills at their disposal that can save lives. To achieve these gains, healthcare providers require legitimacy to have active conversations about gun safety. Physicians are guardians of public health – legislators and pro-gun advocacy leaders that demand physicians "stay in their lane" undermine this critical role. Now more than ever, we must continue to establish credibility in the gun violence sphere through evidence-based, socially sensitive care and advocacy.

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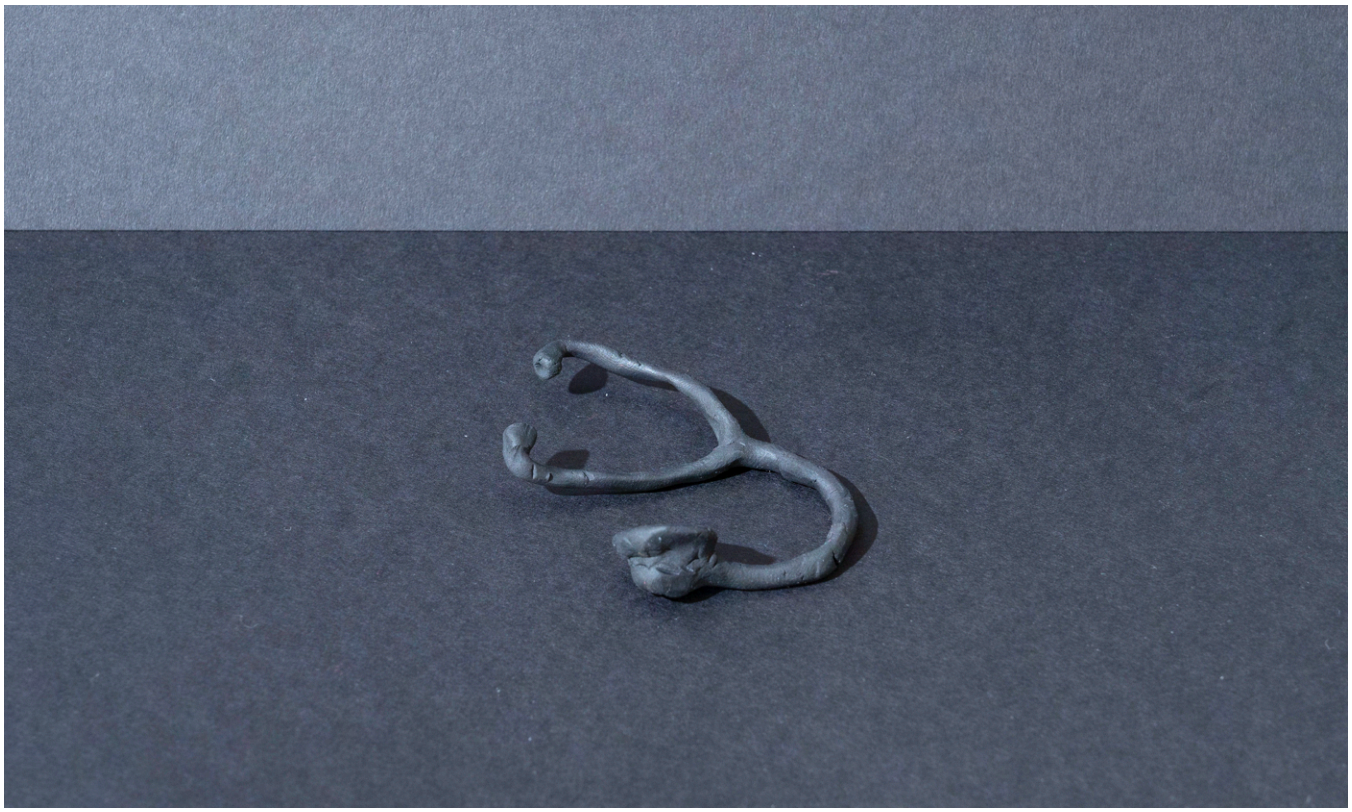

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Race and Medicine: Black People Are Not Born Sick

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Last fall my white professor, Dr. L was lecturing my second-year medical school class on the logistics of pulmonary function tests (PFTs). PFTs are a common clinical tool used to assess lung capacity, as well as diagnose and monitor pulmonary disease. He started off by listing the factors needed to determine a reference value to compare a patient, "age, height, gender and… race." Estimated glomerular filtration rate, an indicator for kidney health, is also computed based on whether you are African American. I wondered to myself why we are so often told to calculate race into medicine. Dr. L probed further by challenging our class on how to consider the impact of race, suggesting—as all great teachers do—that it may be time to reevaluate the status quo. I took this prompt personally. As a black woman who is training to be a physician, I have an investment in distinguishing evidence-based research from mere correlation or worse, sloppy assumption.

The idea that black people have deficient lungs may have first been hypothesized by Thomas Jefferson, the founder of the university I currently attend, in his Notes on the State of Virginia [1]. Anti-abolitionists would cite these notes as justification for the hardships that Blacks were forced to endure. Samuel Cartwright, plantation physician, was motivated to develop his own spirometer and quantified

the black lung deficiency to be 20% compared to Whites [2]. In 1865 after the Civil War, Benjamin

Gould conducted a study on anthropometrical data of black and white soldiers, which he wrote about in Investigations in the Military and Anthropological Statistics of American Soldiers [3]. Without accounting for the bleak living conditions of the then-emancipated slaves, Gould arrived at the same conclusion as Cartwright. The ideas set in motion by Jefferson and Cartwright, and further supported by Gould became the framework for clinician handbooks by 1922 [4], and that framework is still used today.

The race science that Thomas Jefferson perpetuated may no longer be formally taught in medical curricula, but society did not escape unscathed. The subtleties of racism today are baked into institutions and societal structures, including social determinants of health (SDH). SDH describe the complex relationship between health and the environment in which we live, work and play. Experts estimate that SDH contribute anywhere between 40%-80% to health outcomes [5,6]. Race and race-related SDH are different, though. Black people are not born sick. While much emphasis is placed on genetic causes for certain disease prevalence seen among black patients, fewer than 0.5% of black deaths can be attributed to hereditary conditions like sickle cell anemia [7]. In my attempt to answer Dr. L's prompt, it did not take long to reflect on the historical, political and environmental injustices imposed on low-income communities, which are not coincidentally largely communities of color. For example, nearly 68% of Blacks and 40% of Latinos live within 30 miles of polluting power plants [8-10].

Here is my answer: there are two main flaws with race-based PFTs. First, there are few comprehensive answers in the literature to explain the differences we do observe between the races. The authors of the Human Genome Project recommended that "in the interpretation of racial differences, all conceptually relevant factors should be considered [11]." These conditions have not been satisfied.

The PFT race correction factors that are used in the U.S are derived from the National Health and Nutrition Survey III. For this national study, PFTs were conducted on a random sample of asymptomatic and non-smoking individuals and included people from various races [12,13]. The authors concluded that African-Americans have a lower average Forced Expiratory Volume, but only half of these racial differences observed could be explained by sitting height, leaving the other half to be explored. In a systematic review, Dr. Lundy Braun, author of Programming Race into the Machine, found that most articles that have emerged since 1922 examining race and lung function fail to account for socioeconomic status. While some articles offer anthropometric, environmental and social factors towards explaining the racial differences in the discussion section, nearly 25% of articles cite no reason at all [14].

Second, we fail to accurately and consistently define race and lack language to capture entire populations. "Latino" is considered an ethnicity, not a race category in the U.S census, and so our fastest growing demographic demonstrates wide variation and uncertainty in identifying as either black or white [15]. Race no longer signifies common origins and should not be used as a vague proxy for genetic homogeneity. The use of race for predictive analytics has been mediocre at best; however, collecting racial data retrospectively is indeed imperative. For example, health equity experts have been pleading with health institutions to track racial and ethnic information of Covid-19 patients with the hopes of concentrating and funneling resources and prevention efforts where they are needed—in vulnerable communities of color. The trends we observe help highlight the stark disparities in housing practices, education attainment, and differences in time to treatment and quality of treatment. This data is needed to inform public policy and help reverse systems of structural inequities. Rather than address the systemic issues that lead to these outcomes, we quite literally calculate race into the diagnosis—further perpetuating structural and institutional racism.

Fast forward a couple months from that PFT lecture and this pandemic is unveiling society's gross shortcomings— black people are dying at higher rates than their representation, disparities that are entirely preventable [16]. Just one hundred years ago, activists such as W.E.B. Du Bois fought to convince the white medical professional community about what we now know as SDH: "The high infant mortality of Philadelphia today is not a Negro affair, but an index of social condition." UVA professors and I are finding ourselves making that exact same argument today.

In medical school, SDH topics are often relegated to stand-alone classes, deemphasizing the intimate connection between social condition and health. High rates of type two diabetes among black patients should be spoken about in the same breath as food deserts. Environmental factors, such as exclusionary zoning practices should be spoken about in the same breath as PFTs. It is not enough to offer differences in health trends and then move on unquestioned and unchallenged.

University test writers: if race is used as an identifier in a clinical vignette, include information on the patient's social context. Curriculum committee: survey lecture presentations to ensure race is not purported to be a biological entity. When we teach medical students the perfect science of medicine, we simply cannot divorce from our imperfect world. We must prompt them to ask why they see disparities to avoid the dangerous assumptions of the past and pathologizing race. Only then can we identify the root causes and attempt to mitigate the inequities we see today.

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Mental Health Referrals in Physician Aid in Dying Laws

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Abstract

Physician aid in dying (PAD) is a practice that has grown in prevalence in the United States in recent years. In fact, of the ten U.S. jurisdictions that now allow capable terminally ill adults to obtain and self-administer medication meant to hasten death, six enacted their respective PAD statutes between 2015 and 2019, with several other states considering bills on this issue. Most jurisdictions that allow PAD have statutory requirements that set forth the steps and criteria for individuals to receive PAD medication. Comparing the different statutes, it is clear that the language used to describe mental health referrals differs between states. One state's protocol requires every patient to meet with a mental health professional at least once, whereas others require referrals under certain circumstances—such as when there are indications of a mental disorder, psychiatric or psychological disorder or depression causing impaired judgment. Additionally, when such a referral is made, the role of the mental health professional is to evaluate an individual in order to confirm eligibility, rather than to provide supportive counseling. With this being said, only one state requires that patients be informed of the availability of supportive counseling. This article examines the PAD statutes' provisions related to mental health referrals in the United States; proposes adopting the same statutory language regarding mental health referrals; and recommends adding guidance for early, continuous supportive counseling for qualified terminally ill patients requesting a medication to hasten their death.

TERMINOLOGY

In the United States, physician aid in dying (PAD) is an end-of-life treatment that allows an individual with a terminal illness to hasten their death through the voluntary self-administration of lethal medication prescribed by a physician at the patient's request.[1] Other terms frequently used to describe PAD include medical aid in dying, aid in dying, physician-assisted death, death with dignity, and physician-assisted suicide.[2] Importantly, in the U.S., these terms are distinct from euthanasia, which refers to the active administration of a lethal drug by someone other than the patient. Euthanasia is illegal in the United States.

TIMELINE OF PAD IN THE UNITED STATES

In 1994, Oregon became the first state to legalize PAD when its citizens' initiative, the Oregon Death with Dignity Act (DWDA), was passed by Oregon voters by a margin of 51% in favor and 49% opposed.[3] The law did not go into effect immediately due to a legal injunction.

In 1997, the U.S. Supreme Court rendered its landmark decisions in *Vacco v. Quill* and *Washington v. Glucksberg*, two cases that challenged the constitutionality of New York's and Washington's statutes prohibiting PAD.[4],[5] In upholding the laws, the Supreme Court held that there is no fundamental constitutional right to die. Therefore, the individual states could enact legislation permitting or prohibiting PAD as long as the state law was rationally related to legitimate government interests.[4],[5]

Shortly thereafter, in October 1997, the Oregon DWDA went into effect.[6] In the years that followed, proponents attempted to pass PAD statutes in other states as well. In 2008, Washington voters approved the Washington Death with Dignity Act, which went into effect in 2009.[7] Later that year, PAD became legal in Montana by a Montana Supreme Court decision.[8]

Since then, six other states and the District of Columbia have passed PAD laws: Vermont's Patient Choice and Control at End of Life Act (PCEOL) (2013);[9] California's End of Life Option Act (ELOA) (2015);[10] Colorado's End-of-Life-Options Act (2016);[11] the District of Columbia Death with Dignity Act (2016);[12] Hawaii's Our Care, Our Choice Act (OCOCA) (2018);[13] New Jersey's Medical Aid in Dying for Terminally Ill Act (2019);[14] and the Maine Death with Dignity Act (2019).[15] **(Figure 1).**

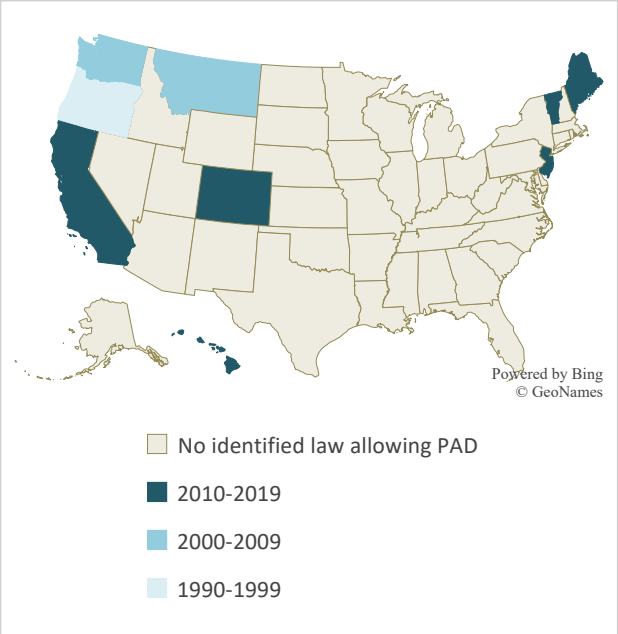

Figure 1 Legalization of Physician Aid in Dying by Decade. [District of Columbia not pictured.]

STATUTORY SAFEGUARDS

In her concurrence in *Glucksberg*, Justice O'Connor stated that one of the most challenging tasks in drafting PAD legislation would be "crafting appropriate procedures for safeguarding ... liberty interests[.]"[5] This task, she found, is best left to the "laboratory of the States."[5] Consequently, each state's approach to physician aid in dying may be guided by a unique set of factors, including public and physician attitudes, societal debate, research data from preceding PAD states, reasoned legislative deliberation, and a "principled desire to protect individuals at the most vulnerable moments of their lives."[2],[16],[17] Research shows that public attitudes on PAD can be rooted in "cultural, religious and spiritual traditions and historical experience," which can vary across states.[2]

Since its implementation, the Oregon DWDA has been adopted or used as a starting point for states to craft their own PAD safeguards and procedures.[18] The statutory construction of each statute is similar, with technical and substantive

changes varying state by state. Using the Oregon DWDA as a reference, the law requires the person to be (1) at least eighteen years of age, (2) a resident of the state, (3) capable of making and communicating their own health care decisions, and (4) diagnosed with a terminal illness that will lead to death within six months.[6] The individual is required to meet with an attending physician and a consulting physician—each with designated responsibilities—and, in some cases, is referred to a mental health professional who determines whether the individual is capable of making an informed decision and does not have impaired judgment.[6] The language used to describe referrals varies by state, but includes the terms "assessment," "counseling," and "evaluation."

There are many additional safeguards and procedures outlined in the statutes, such as that the individual is informed of feasible alternatives—including comfort care, hospice and palliative care, and pain control.[9],[10], [11], [13],[14],[15]

REFERRALS TO MENTAL HEALTH PROFESSIONALS

The states and the District of Columbia agree that if a mental health referral is made, the patient may not receive the prescription until the mental health professional confirms the patient's eligibility.[18] [19] However, there is interstate variability in the statutory constriction of these provisions, which may hold important implications for patient care and may contribute to health disparities."[17]

The four DWDA jurisdictions—Oregon, Washington, District of Columbia, and Maine—require a "counseling" referral to confirm that the patient is capable and not suffering from impaired judgment if, "in the opinion of the attending physician or the consulting physician, a patient may be suffering from a psychiatric or psychological disorder or depression causing impaired judgement[.]"[6],[18] It has been reported that Oregon wrote this safeguard into the law to ensure that an individual is competent and their request for PAD is not stemming from a treatable mental illness.[19] California uses a similar protocol for confirming a patient's capacity; however, the ELOA revises the statutory language to instead require referrals if "there are indications of a mental disorder[.]"[10]

Vermont, Colorado, and New Jersey also require referrals on a case-by-case basis. However, these states simply require referrals if either the attending physician or the consulting physician believes the patient may not be capable of making an informed decision.[9],[11],[14] Their statutes omit any explicit reference used by other jurisdictions related to a "*mental disorder*" or a "*psychiatric or psychological disorder or depression.*" Some have argued that these less-specific referral requirements are superior because they allow physicians to observe the patient's functioning relative to the capacity standards without searching for a specific mental disorder.[18]

Notably, the legislative history of Vermont's Patient Choice at End of Life Act reflects that when the bill was introduced in 2013, it required referrals if, in either physician's opinion, the individual "may be suffering from a mental disorder or disease, including depression, causing impaired judgment."[20] However, this language was removed from the bill during legislative deliberation.[9],[20]

Unlike the other eight physician aid in dying statutes, Hawaii's OCOCA makes referrals mandatory for *every* patient that makes a request for the medication—not just when there are indications of a mental disorder or psychiatric or psychological disorder or depression causing impaired judgment.[13] This decision came after a long, ongoing debate over whether states should require a referral for every patient.[18],[19] Some argue that a mandatory referral requirement may create an unnecessary burden—both on the patient and the mental health professionals—and delays the process.[21],[22] Some also worry that the mental health professionals' ethical and moral views on PAD may influence their assessments.[19] Others argue it is necessary to ensure that each individual is properly assessed to confirm that their request for medication is not rooted in a disorder or condition that can be treated.[23]

Additionally, mental health professionals in Hawaii are required to confirm whether the patient is "suffering from undertreatment or non-treatment of depression or other conditions which may interfere with the patient's ability to make an informed decision[.]"[13] The "*undertreatment or non-treatment*" language may be in response to historical concerns that some psychiatrists believed that the presence of a mood disorder should automatically result in a finding of incapacity to consent to PAD.[23] By focusing on the level of treatment of depression or other conditions, Hawaii seeks to avoid any presumptions that the mere presence of a condition precludes the evaluator from finding that the patient is capable and has the ability to make an informed decision.[13]

CONTINUOUS SUPPORTIVE CARE SAFEGUARDS

While there is some interstate variability regarding the mental health referral criteria, these safeguards aim to ensure that a patient is competent and not requesting PAD because of a treatable mental illness.[19] Thus, under these statutes, the mental health professional's role, if called upon, is to evaluate an individual to confirm eligibility for physician aid in dying medication, rather than to provide supportive counseling.[18] For this reason, among others, the majority of patients are not referred for a mental health assessment in most states. In Oregon and Washington, for example, less than 5% of patients are referred for assessments.[16]

Of the nine physician aid in dying statutes, only the District of Columbia DWDA contains a supplemental safeguard to ensure that patients are made aware of supportive counseling options.[12] Specifically, in D.C., attending physicians are required to "[i]nform the patient of the availability of supportive counseling to address the range of possible psychological and emotional stress involved with the end stages of life[.]"[12] The Council of the District of Columbia Committee on Health and Human Services explains that this substantive change was made to address concerns raised by members of the community over the possibility of coercion or undue influence on vulnerable individuals.[24] This allows a mental health professional to explore the emotional distress and responses commonly experienced by patients as they approach the end of life and not just focus their evaluation on assessing whether the patient is capable of making an informed decision. Additionally, this opens the door for a mental health professional-patient relationship that can continue even after the individual is prescribed PAD medication.

Similarly, although California's ELOA does not have a supportive counseling safeguard, some California health care systems, such as the University of California Los Angeles (UCLA), have implemented internal policies that provide continuous support for a collaborative consultation with a psychologist or social worker.[25]

FURTHER CONSIDERATIONS

There is still much debate over whether mandatory or case-by-case mental health referrals are better safeguards for patients requesting PAD medication, and it is important to conduct further investigation to answer this question. Additionally, the efficacy of the various evidence-based psychotherapies for terminally ill patients should be further explored in the context of PAD, with special attention given to their effectiveness on different cultures and groups of terminally ill patients, including those with terminal illnesses outside of cancer.[26],[27]

CONCLUSIONS AND RECOMMENDATIONS

In an attempt to prevent ambiguity which could lead to health disparities, this article recommends that future PAD legislation use the same language when addressing mental health referrals. It further recommends that PAD statutes include a recommendation regarding early, continuous supportive counseling for all patients. As seen in the District of Columbia, states can do this by making it the physician's responsibility to inform all patients of the availability of supportive counseling to address the range of possible

psychological and emotional stress involved with the end stages of life.[12] This takes into consideration the modern framework that interactions between practitioners and patients should be dialogues occurring over multiple meetings, rather than one-time and one-way interactions.[18] Moreover, continuous supportive care would also help ensure that care is directed to the day-to-day life and morale of patients and not only focused on whether the patient meets certain criteria to determine eligibility for PAD.[28]

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POTENTIAL CONFLICTS OF INTEEST:

None.

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What's in the Cauldron: Witches, Folk Remedies, and their Contributions to Modern Medicine

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Disease is a part of the human condition and before the rigor of the scientific process and peer review, healers had to work with anecdotal folk remedies and word of mouth medicines. These folk remedies were often known by women and shaman who, throughout time, passed on their esoteric knowledge. Some of these remedies, like excretions from toads, Hemlock, Yew, and Foxglove have persisted for centuries and were used for a wide range of ailments. In modern days, with the use of the scientific process and peer review, these plants form the foundation of many medications. This demonstrates the benefit that can be gained with the investigation of folk medicine.

INTRODUCTION

In the fourth act of Macbeth, the Bard introduces us to the Weyward Sisters (1). These sisters established the stereotypical image of a witch. In the play, before the witches even have a chance to speak, Shakespeare sets them up with a prop. The sisters

were to be in "a cave. In the middle, a boiling cauldron." It is the contents of that cauldron that are the subject of our investigation.

These witches mix a peculiar concoction, poison excretions of a toad, root of hemlock, slips of yew, and other unsavory items. For what purpose are they creating this potion? It is surely for some evil design, yet, in literature, witches are also shown making medicines and healing salves. Some of the ingredients in the Weyward Sister's brew are used in modern medicines (2). In Shakespeare's time, before medical schools and licensed physicians, women labeled as "witches" often had knowledge of the healing arts. There is benefit to be gained by investigating and studying these folk medicines with rigorous scientific inquiry

TOAD SWELTERED VENOM

The Wayward Sisters threw a toad, chosen for its particularly poisonous secretions, into their potion. Oddly enough, practices mirroring this exist today. The Giant Monkey Frog, *Phyllomedusa bicolor,* is found in rainforests of South America. It produces a whitish secretion from its skin, called Kambo, which is used in a shaman ritual of the same name (3). In this traditional healing ritual, a shaman burns a patient with a sharp stick and then applies the Kambo to the lesions (4). Kambo isn't restricted to tribal shamans. It is occasionally used in Brazil at clinics run by "holistic and medical therapists" (3). These therapists and their patients have reported incredible benefits from Kambo. Claiming that it heals headaches, gastritis, diabetes, depression, epilepsy, cirrhosis, cancer, and AIDS. The National Sanitary Surveillance Agency of Brazil, as well as other academic scientific institutions have not found any evidence to validate these claims (3), and any benefits from the treatment are ascribed to a placebo effect (5).

Most scientific examination has shown Kambo to be dangerous. The amphibious secretions contain bioactive peptides which cause predators to feel nauseated and regurgitate the frogs. These peptides contain excitatory and opiate-like neuropeptides which cause effects such as tachycardia, dizziness, nausea, and vomiting (3). Hypotensive effects have also been observed which have led to cardiac arrhythmia and sudden death (6). Despite the claims of holistic medical practitioners and its generational use by shamans, it seems that Kambo is not an effective or safe medical therapy. Researchers do suggest that the secretions of the *Phyllomedusa* species could be used for anti-microbial drugs, however, further research and testing is required (3).

Although Kambo has no medical benefit, the idea of using secretions from amphibians has yielded beneficial medical applications, but only once such applications have been thoroughly vetted through academic research. In South America some poison-dark frogs of the family *Dendrobatidae* have secretions containing alkaloids that work as a nicotinic acetylcholine receptor inhibitor. Researchers have tested these secretions to help treat movement disorders, seizures, or autosomal dominant nocturnal frontal lobe epilepsy (7). Other researchers have discovered toxins that act as protease inhibitors (8) which they propose could manage HIV, hepatitis, and even some cancers.

Toads from the genus *Bufo* produce protective secretions that contain alkaloids, steroids, and bufadienolides. The main reason for the secretions is a defense against predators, however, these secretions also protect the toads against pathological microorganisms in their wet environments. This helps insulate the toads against disease as they dwell in habitats where other creatures would fall sick (9). Studies have shown the secretions to have diverse antimicrobial effects against *Staphylococcus aureus, Escherichia coli,* and other gram-negative and gram-positive bacteria (10). Anti-viral effects are seen in some of these secretions, most notably from the *Bufo andrewsi* in Asia. Secretions from this toad even inhibit recombinant HIV reverse transcriptase (11). The potential for toad secretions in medicine is staggering since the toxins differ slightly between species leaving many potential medicines to be discovered. Some researchers point out the lamentable fact that the habitats of these toads are being destroyed, thus robbing humanity of a potential solution to diseases that are becoming ever increasingly resistant to established treatments (9).

These amphibious secretions may have seemed demonic and strange back in Shakespeare's day. However, their benefits, when used properly, have been demonstrated by modern scientific inquiry.

ROOT OF HEMLOCK

Hemlock, or *Conium maculatum* (12), is a flowering plant that works on the nervous system, often resulting in death. Hemlock's most famous use is in the concoction Socrates self-administered for his execution (13). This plant is found to contain alkaloids, flavonoids, coumarins, polyacetylenes, and other bioactive compounds (14). At doses higher than 10–20 mg/kg Hemlock is deadly, and its toxicity follows a serious course of symptoms. Starting with weakness in the lower extremities which slowly progresses to the upper extremities, and eventual death by asphyxiation due to paralysis of the diaphragm. Other symptoms include fixed pupils, weak pulse, salivation, loss of urinary control, and nausea (14). Victims remain conscious during most of this, as displayed in the death of Socrates who, after ingesting hemlock, taught the onlooking crowd until he could no longer breathe and died (Brickhouse and Smith).

Doses lower than 10 mg/kg have shown beneficial pharmacological effects. In ancient Greece and Arabia, it was used as an anesthetic and for spasmodic disorders (14). Some, lesser scientific and outdated homeopathic studies are still being cited which propose Hemlock as a treatment for breathing problems, teething in babies, anxiety, Parkinson's, and more (15). This is terrifying and dangerous advice because of the deadly nature of Hemlock.

Stricter, more recent research has attempted to find pharmacologic value despite the danger Hemlock poses. It has been evaluated in rats as a potential medication for pain and nervousness. The researchers compared it against morphine and indomethacin, but it wasn't found to be any more efficacious than existing drugs. Because of this and its narrow therapeutic index, it was deemed inferior to existing analgesics (16).

Hemlock is a teratogen and studies of hemlock ingestion in maternal pigs showed an increase in cleft palates in the offspring (17). Additional studies of farm animals display other effects of Hemlock's teratogenicity. Goats showed cleft palates as well as spinal deformations. Calves had gross skeletal malformations. Chicks and infant rats had deformities of their toes. All these creatures showed decreased fetal movements in utero (14). Because of its deleterious effects on fetal growth and movement Hemlock was used, along with other herbs, as an abortifacient during the 19th century (18). Due to its unimpressive efficacy, along with its dangerous nature, it isn't recommended as a modern medical treatment. Nobody should ingest hemlock for purposes medical or otherwise.

SLIPS OF YEW

Yew is a plant of the genus *Taxus*. The trees can grow 80 feet tall and their wood is hard and fine-grained. This wood was often used for longbows, as popularized by Robin Hood (19). The bark and the leaves contain bioactive substances including cardiotoxic taxine alkaloids which are calcium channel antagonists. Ingestion of small doses usually causes gastrointestinal discomfort and even vomiting. High doses can cause cardiac side effects such as ventricular conduction problems with subsequent arrhythmia, with one documented case eventually progressing to irreversible cardiogenic shock and eventually death (20). It should be noted that this kind of fatal poisoning is rare. This case happened in 1987 and the woman ingested 150 yew leaves (21). Most people don't go around eating any tree leaves, let alone 150.

In 1960 the National Cancer Institute, or NCI, hired botanists in the United States Department of Agriculture to submit plant samples that were screened for cytotoxicity. In 1962, Arthur S. Barclay submitted a sample of 200 different plants, one of which was a slip of bark from the Pacific Yew Tree or *Taxus brevifoila*. In 1964, the NCI found that extracts of yew bark could kill cancer cells. They had found what they were searching for, a natural source of cytotoxic material (22). They began isolating the cytotoxic compound from these Taxus trees and in 1971 the drug, Taxol, was developed, which showed moderate efficacy against tumors (23).

Over time Taxol was shown to be most effective against ovarian and breast tumors and is a standard of care today. Taxol works by inhibiting progression from the metaphase stage of cell division. As microtubules develop, the energy from GTP hydrolysis compacts the alpha and beta subunits of the tubulin complex that makes up the microtubules. This compaction builds tension so that once the microtubule stops growing it will depolymerize. This depolymerization is necessary when the cell needs to breakdown mitotic spindles and progress to anaphase (24). Taxol effectively cancels the impact of GTP hydrolysis by preventing the compaction of the alpha and beta subunits. Without this compaction there is no tension and the microtubules are unable to depolymerize, thus freezing the cell in metaphase. When the cell progression halts it eventually reverts to G_0 phase or apoptosis effectively silencing or killing the cancerous cells (25).

While Taxol is highly effective in its treatment, problems arose with production. The main concern was the environmental impact of harvesting enough bark needed to treat the abundance of cancer in the United States. Roughly 60 pounds of yew tree bark is needed to produce enough Taxol to treat the average cancer patient. The average yew tree produces 12.5 pounds of bark a year (26). Therefore, about 4.8 trees are required to treat one person. This highlights the moral dilemma of creating life-saving drugs at the expense of whole forests of yew trees. In 1990 the Pacific Yew Tree was declared endangered and in 1992 the Pacific Yew Act was passed, protecting trees from being over-harvested (27). Luckily, a breakthrough came in 1993 when a pathway to create synthetic Taxol was discovered (28), and one year later synthesis of Taxol from other plants was also discovered (23).

It is interesting to note that out of all the plant samples obtained by the NCI only the yew tree provided what they were looking for, a cytotoxic compound (22). One must wonder what other possible medicinal properties exist in the hundreds of samples harvested from different plants. If one were to test for other properties beyond cytotoxicity what else could be discovered? Further research should be done with preference given to plants that have anecdotal medical benefits.

FOXGLOVE

Digitalis lanata, or Foxglove, is a beautiful flowering plant that has a multitude of names; Fairy Caps, Fairy Thimbles, Dead Man's Bells, and Witches Gloves. While Foxglove wasn't mentioned by the Weyward Sisters as part of their concoction, the story of its discovery warrants it a place in this discussion. In 1775 a physician named Dr. William Withering was looking for a treatment for "dropsy", now called edema. Dr. Withering heard of a cure for dropsy that "had long been kept secret by an old woman in Shropshire, who had sometimes made cures after the more regular practitioners had failed" (29).

Dr. Withering interviewed the woman and observed the effects of her medicine. He noted that it provided the desired diuretic effect, along with occasional adverse symptoms of extreme vomiting. Dr. Withering studied the potion, which was made of about 20 different herbs, and was able to pinpoint the diuretic down to Foxglove which he began administering to his patients. After 10 years of experimentation Dr. Withering published the results and proper usage of Foxglove and it was accepted into medical practice (29).

In 1930 British physician Dr. Sidney Smith isolated Digoxin from the Foxglove leaves and demonstrated its impact on the body, not as a diuretic, but by increasing cardiac myocyte contractility (30). Two years later it was accepted for regulated distribution in the medical field and it remains a viable option for treating variable heart conditions (31). Digoxin is a cardiotonic glycoside that increases myocardial force of contraction by reversibly inhibiting the Na-K ATPase pump. It can be used for rate control in atrial arrhythmia by slowing conduction through the atrioventricular node. Its more common use is for systolic heart failure; however, it should be noted that while Digoxin is used to treat heart failure it does not decrease mortality (32).

While the use of Digoxin has begun to wane in favor of safer, more effective drugs, it was an especially useful method of treatment for many years

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CONCLUSION

In Many medical advancements can be made by examining what is "in the cauldron". Witches and shaman, with their concoctions and folk remedies, have treated illness and ailments for thousands of years. The historical concoctions created in their cauldrons have greatly influenced the modern medical field. From the disgusting excretions of amphibians, roots of the Hemlock, bark of the Yew, and beautiful petals of Foxglove, we have taken what once seen as sorcery and turned it into medicine. Some of these remedies went thousands of years without an understanding of how they worked, only that they worked. Without the "witches" who used them, we may have never known or discovered their usefulness.

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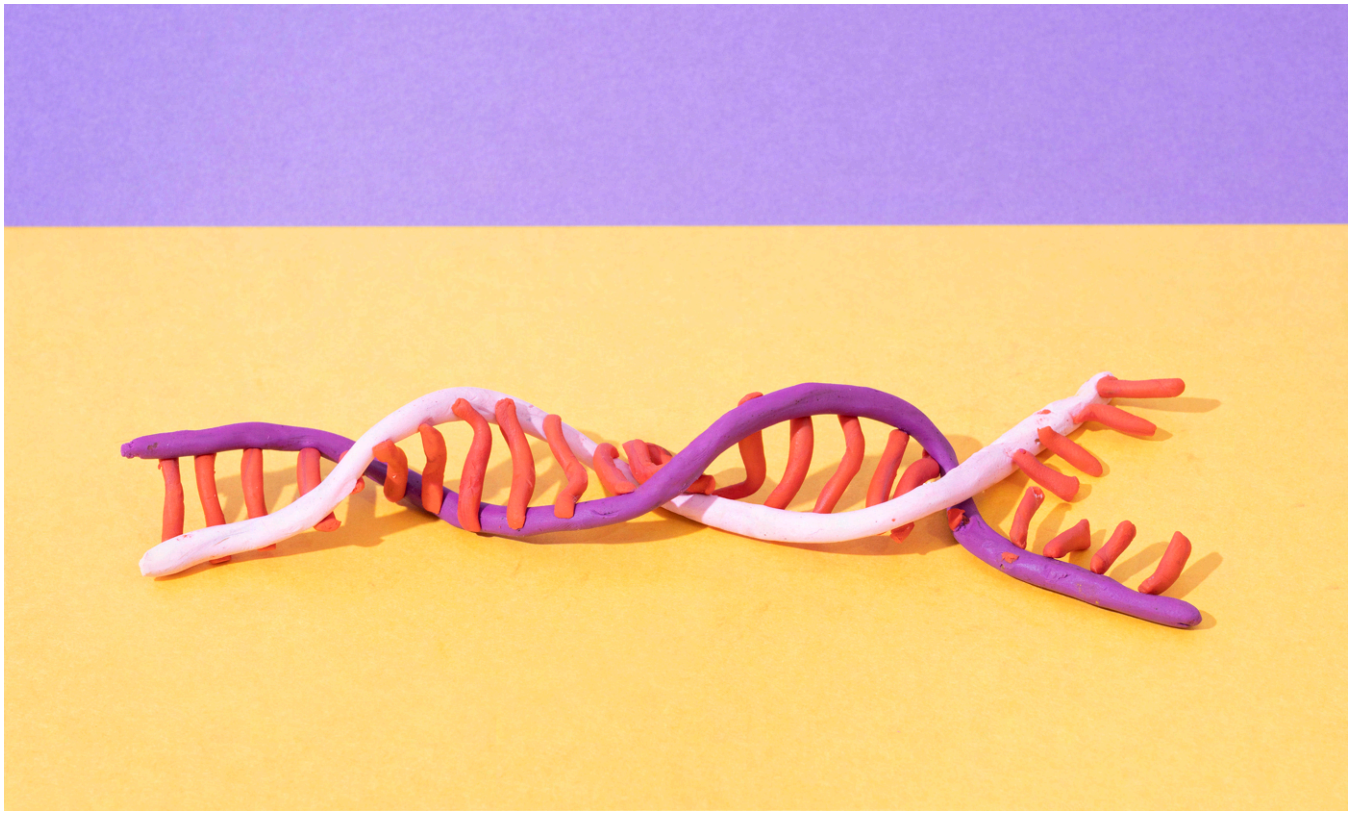

Clay illustration by Lily Offit; Photographed by Ben Denzer

The Danger of Genetic Risk Scores for Worsening Race-Based Disparities in Healthcare

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Over the last twenty years, there has been an explosion of new technological advancements in sequencing the human genome. It originally cost $2.7 billion dollars to sequence the first human genome, but now, human sequencing costs have dropped to below $1000 per person.[1] During this period, there also have been many advancements in our understanding of the genetics underpinning common, non-communicable disorders such as diabetes, coronary artery disease, and depression.[2] We now know that these common diseases often have a genetic contribution from thousands of genetic variants throughout the genome, each of which confer a small effect on disease risk. The cumulative sum of these genetic variants (known as polygenic risk scores) have been shown to have a significant effect on disease risk, similar to the effects of rare Mendelian disorders.[3]

In the last ten years, research groups and genetic companies have been creating personalized polygenic risk scores with the goal of predicting an individual's susceptibility to chronic diseases. These scores have shown promise in predicting the onset and severity of future diseases before the emergence

of symptoms or traditional risk factors.[4] With these scores, clinicians have the potential to more effectively target intervention (i.e. reducing LDL cholesterol with statins in patients with high polygenic risk for coronary artery disease[5]) and prevention (i.e. early mammogram screening for patients with high polygenic risk for breast cancer).[6]

A significant concern about personalized polygenic risk scores is that they have been developed, optimized, and validated in white individuals with European ancestry. As a result, personalized genetic risk scores have not been as validated in non-white demographics.[7] In fact, these risk scores have poorer performance in non-white groups and may misrepresent their genetic risk for diseases.[7] African descent populations, which have the most health disparities worldwide, are expected to benefit the least from personalized genetic risk score assessments.[7]

In this paper, I will discuss the reasons why there are differences in clinical polygenic risk score efficacy between different demographics, the potential danger in worsening race-based disparities in healthcare, and methods to improve parity of polygenic risk prediction.

Differences in Clinical Efficacy of Polygenic Risk Scores Between Demographics

In *Low Representation of Non-White Groups in Genetic Databases*

There are several steps needed to calculate an individual's personalized genetic risk score for a specific disease.[8] First, you need an ancestry-specific genome-wide association study (GWAS) that identifies the disease risk for each genetic locus (or single nucleotide polymorphism [SNP]). Then you would need an unbiased reference population of genomes for that same ancestry. To calculate an individual's polygenic risk score, one sums the cumulative effect of SNPs calculated from GWAS and compares this number to the population reference. This score is often referred to as a percentile (i.e. in the top fifth percentile of genetic risk).

The main reason why polygenic risk scores perform better in white groups is that this demographic is the best represented in genetic databases. Approximately 80% of all individuals in GWAS databases are whites of European descent.[9] Since 2010, the recruitment of white Europeans in genetic databases has skyrocketed whereas the fraction of non-white groups have remain relatively stagnant (Figure 1).[9] This stagnation is caused by several different factors ranging from lagging diversity in the scientific community, limited engagement with volunteer participants from minority backgrounds, preference of researchers to study European ancestry cohorts, challenges in publication, and analytic challenges.[10]

As a result, for white individuals with European ancestry, there have been a greater number of genetic loci identified as significantly associated with disease, greater accuracy in calculating the genome-wide polygenic risk score, and a more reliable population reference cohort for comparison.[11] Conversely, for the same reasons, there have been fewer discoveries of genetic variants significantly associated with disease in African and East Asian populations.[11] The predictive accuracy of polygenic risk scores is also significantly worse in East Asian and African populations compared to Europeans (Figure 2).[7]

Complicated Gene-Environment Interactions

Most common non-communicable diseases are influenced by both genes and environment. Environmental pressures have led to selective selection of specific genes, such as the sickle cell trait to protect against malaria. However, it is currently unknown what extent environmental pressures played in the up or down regulation of genetic variants at the genome-wide level. This is an important consideration because GWAS calculations and polygenic risk score estimates assume that all causal genetic loci have the same effect across populations.[8]

Certain traits such as height and weight are heavily influenced by genetics, but also significantly affected by access to food and resources.[12] This makes it difficult to disentangle which part of someone's trait is caused by the environment and which is caused by genetics.[12] The complexity of cultural factors with biology can also play a huge role in disease susceptibility. For example, the differences in alcohol use disorder between Asians and Europeans is partially explained by genetic risk scores, but also

have a significant contribution from availability to alcohol and differences in alcohol metabolism.[13]

Certain genetic data banks such as the UK Biobank addressed this challenge of gene-environment interactions by recruiting many healthy people (around 500,000) from Britain and cataloguing many different types of sociodemographic information such as income and housing.[14] However, white Europeans comprise most of this genetic data bank and minority groups are poorly represented.[14]

Poor Generalizability in Different Ethnic Groups

One possibility is to use white European cohorts as reference populations or polygenic risk calculations for everyone, regardless of demographic. However, polygenic risk scores have been shown to have poor generalizability across different populations. Martin et al. evaluated the performance of polygenic risk scores derived from white European GWAS data across 17 anthropometric and blood-panel traits and found that the prediction accuracy is far worse for non-European white groups.[7] The prediction drop-off was 1.6 fold in Hispanics, 2.0 fold in East Asians, and 4.5 fold in Africans.[7]

Danger in Worsening Race-Based Healthcare Disparities

Limited Access to Genetic Risk Scores and Healthcare Guidance

Commercial deployment of polygenic risk scores in their current state has the potential to worsen race-based healthcare disparities. The demographic with the greatest access to genetic risk scores are white individuals. Carroll et al. studied the consumer behavior of approximately 57,000 people at Kaiser Parmenente and found that white individuals were more likely to receive direct-to-consumer genetic testing, clinician-ordered testing, and research-related testing.[15] Among those who received a genetic test and received a notification about a potential genetic abnormality, Hispanic, Black, and Asian individuals were less likely to speak to a medical professional for healthcare guidance and/or understand the meaning of the abnormal results.[16]

Different Benefits from Genetic Risk Score Prediction

At present, clinical application of polygenic risk scores are less useful in minority populations such as those from African descent. Martin et al. studied the polygenic risk prediction in African-descent individuals and found that the prediction accuracy is barely above random chance.[7] Conversely, the prediction accuracy is much stronger for white individuals with British ancestry (Figure 3).[7] Current clinical use of polygenic risk scores is problematic because they will only meaningfully benefit white individuals. African descent populations, which already experience the most disparities in healthcare worldwide, will marginally benefit, if at all.

Methods to Improve Parity of Polygenic Risk Score Prediction

Increase Diversity and Representation in Genetic Databases

There are a couple solutions to address this concern of disparities in polygenic risk score prediction. The most obvious solution is to increase the number of underrepresented groups in genetic databases. Some initiatives with this goal include the All of Us Research Program and the Population Architecture using Genomics and Epidemiology Consortium.[17] The All of Us Research Program, for example, is an NIH sponsored genetic database recruiting over 1,000,000 people with goals to represent a diversity of races, ethnicities, sexes, genders and sexual orientations. Participants who volunteer in this program will also get information about their health and have full access to their own information and records.[17] This latter point is especially important given the pernicious history of medical exploitation of minority groups. A large diverse data bank can help identify more genetic variants associated with disease, uncover new disease biology, and improve genetic risk prediction.

Other countries are also spurring new initiatives to increase the number of underrepresented individuals in genetic data banks. For example, the Human Hereditary and Health in Africa Initiative has invested more than $200 million for genomics research in Africa.[18] Similarly, China and Japan are creating large national biobanks in order to build more accurate ancestry-derived genome wide association studies for various diseases.

Increase Analytical Tools to Improve Accuracy in Different Populations

In addition to recruitment of a diversity of individuals in genetic databases, there needs to be greater effort in methods development to improve polygenic risk score predictions for different ancestry groups.[10] Several different research groups have started to tackle this challenge.[10] Grinde et al. used ancestry-derived meta-analyses to weight genetic loci to improve polygenic prediction accuracy.[19] Similarly Marquez-Luna et al. developed a new tool called MultiPred that creates multi-ethnic polygenic risk scores derived from European and non-European ancestry groups.[20] It is critical that these novel analytic tools become open sourced to facilitate widespread adoption.

FURTHER CONSIDERATIONS

There is still much debate over whether mandatory or case-by-case mental health referrals are better safeguards for patients requesting PAD medication, and it is important to conduct further investigation to answer this question. Additionally, the efficacy of the various evidence-based psychotherapies for terminally ill patients should be further explored in the context of PAD, with special attention given to their effectiveness on different cultures and groups of terminally ill patients, including those with terminal illnesses outside of cancer. [(26),(27)]

CONCLUSION

Polygenic risk scores have tremendous potential in improving diagnostic prediction of disease and guiding treatment management. Because genetic studies have predominated in white European groups in the last twenty years, polygenic risk score prediction is well-characterized and optimized for these groups. Unfortunately, non-white individuals will benefit the least from polygenic risk scores if they were clinically deployed today. It is essential that we increase diversity in genetic databases, and we develop new tools to improve polygenic prediction in underrepresented groups. Otherwise, we will worsen race-based disparities in healthcare.

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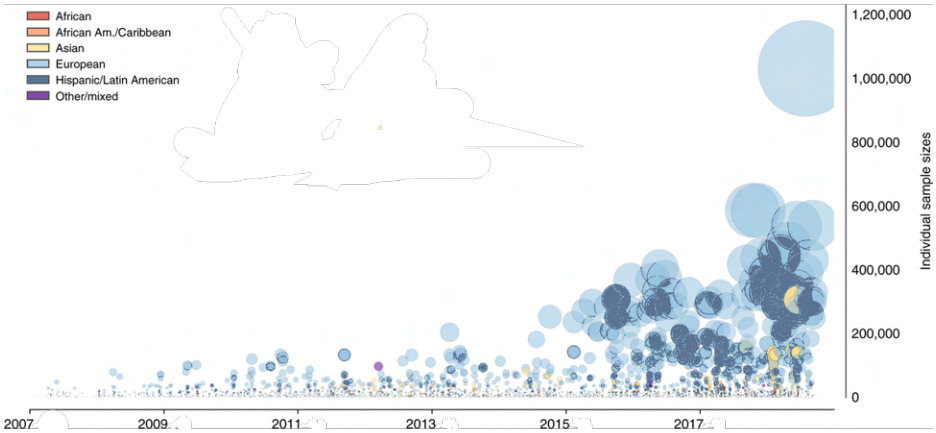

Figure 1. Non-white individuals are poorly represented in genetic databases. Inclusion of non-white groups have stagnated in the last five years. Adapted from Mills et al.[9]

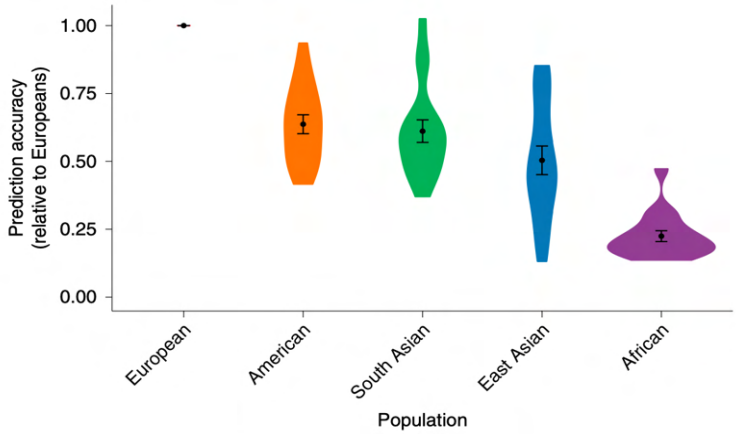

Figure 2. The predictive accuracy of polygenic risk scores across 17 anthropomorphic and blood panel traits is worse in non-white demographics. Adapted from Martin et al.[7]

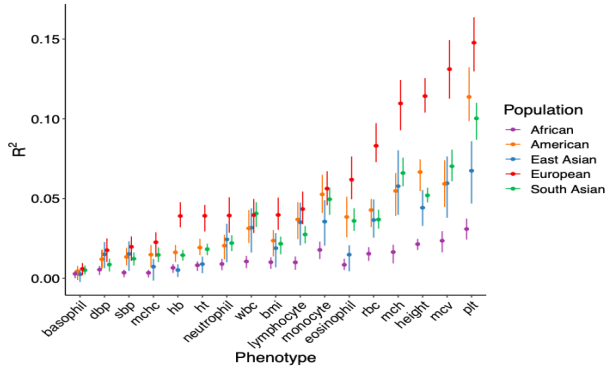

Figure 3. The only demographic that will meaningfully benefit from accurate polygenic risk score prediction are white individuals with European ancestry. The predictive accuracy for those from African ancestry are barely better than random chance. Adapted from Martin et al.[7]

Clay illustration by Lily Offit; Photographed by Ben Denzer

Reducing Childhood Respiratory Infections through Interventions in Indoor Household Air Pollution in Rural Underdeveloped Countries

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Abstract

Introduction: Acute lower respiratory infections (ALRIs) are a major cause of mortality in young children, especially for those living in rural areas of underdeveloped nations. A major risk factor for lower respiratory infections is indoor household air pollution. A common source of this pollution in rural areas of underdeveloped nations is cooking. This review sets out to assess interventions related to cooking to see if they provide any long-term clinically important outcomes.

Methods: A literature review using PubMed in July 2019 using terms relating to childhood pneumonia and air pollution. Full-text reports for relevant studies were included in this review.

Results: Interventions for the reduction of indoor air pollution generally fell into one of three categories, i) switching from polluting fuels to cleaner fuel types, ii) alternative-cooking devices, and iii) behavioral modifications. Findings regarding the use of clean fuel over biomass fuels and alternative-cooking devices were controversial. Behavioral modifications were more consistent in findings of decreased respiratory infections.

Conclusion: It was concluded that interventions for indoor household air pollution, and in particular, behavioral modifications, have the potential to provide significant reductions in ALRI in young children. However, more research is needed to elucidate how best to enact interventions in rural areas of underdeveloped nations.

INTRODUCTION

Pneumonia and other lower respiratory infections have consistently been a major cause of mortality in young children, especially for those living in rural areas of underdeveloped nations.[1-7] One risk factor for lower respiratory infection is indoor household air pollution. Many rural homes in developing countries rely on burning biomass fuels to cook,[8] a source that has been shown to cause higher rates of household air pollution,[5,9] particularly, increased rates of carbon monoxide and nitrogen dioxide.[10] According to the World Health Organization (WHO), about 3 billion people, mostly in living in low to middle-income earning countries, still cook using solid fuels or kerosene in either open fires or inefficient stoves.[11] The risk for childhood pneumonia approximately doubles with exposure to household air pollution, and furthermore is responsible for 45% of pneumonia-related deaths in children under 5 years old.[11] WHO also states that acute lower respiratory infection (ALRI) is the leading cause of death in children under five years old.[12]

As substances found in biomass fuel smoke have been associated with deteriorated lung function,[13] it is not surprising that many studies have found a relationship between household air pollution and respiratory infection.[10,14-16] Specifically, a cohort study in rural India that followed infants from birth until 6 months of age demonstrated a 34% increase of respiratory illness in children exposed to biomass fuel smoke,[15] and a systematic review found a significantly elevated risk of respiratory infection with exposure to biomass combustion in children living in rural areas.[17]

If interventional studies show that decreased household air pollution reduces the risk of pneumonia, as other studies and trend analysis have shown,[1-7] they have the potential to lower child mortality. This review sets out to assess interventions related to cooking to see if they provide any long-term clinically important outcomes in rural settings.

METHODS

We conducted a literature review using PubMed in July 2019 using terms relating to childhood pneumonia and air pollution. We identified keywords and subject headings relating to each of these concepts; terms included 'Childhood Pneumonia', 'pneumonia [MeSH]', 'Respiratory Tract Diseases [MeSH]', 'acute lower respiratory infection', 'air pollution, indoor [MeSH]', 'household biomass fuel', 'rural population [MeSH]', 'developing countries [MeSH]', 'rural community', 'infant [MeSH]' and 'childhood'. Terms were combined using "OR" and "AND" to create specific searches. The 'published after' option was applied to include only studies published in the last 15 years. We identified 682 articles from this search strategy as potential relevant articles. After screening titles and abstracts for relevance to the topic and a rural study location, we identified 19 relevant studies. We obtained full-text reports for these studies. Eventually, 17 studies were included in this review.

RESULTS

Researchers and medical professionals have taken various approaches to address the use of interventions for decreasing indoor household air pollution (IHAP) such as the use of alternative fuel types for cooking, improved cooking appliances, and assessing behavioural interventions. Results are summarized below by the intervention approach.

Alternative Cooking Fuels

A meta-analysis conducted by Bruce et al[18] compared health outcomes including childhood pneumonia in homes that used solid fuels (biomass fuels, which include wood, dung, crop residues, coal, and charcoal) to homes that used other fuel types. The study included data on children up to 59 months, and reported odds ratios for all ALRI's, all non-fatal ALRI's, severe ALRI's and fatal ALRI's. Odds ratios were 1.73, 1.56, 2.04 and 2.80 respectively. As the homes using biomass fuels had greater odds ratios for pneumonia-related outcomes, the authors concluded that reducing HAP could significantly reduce the risk of childhood mortality and that one way to do this is by implementing the use of cleaner fuels. Furthermore, as the meta-analysis was conducted using a database with surveys from 155 different countries, the results from this study may be extrapolated beyond a specific developing country and instead be applicable to developing nations in general. The data, however, is potentially limited by the individual quality of the surveys obtained.

A cross-sectional study conducted using data from a National Health Survey in Nepal found that acute respiratory infection was 1.79 times higher in children living in homes that used solid fuels than children living in homes using cleaner fuels (eg. liquefied petroleum gas, kerosene, electricity, ethanol).[19] The results from a meta-analysis reported a similar risk estimate of a 1.8 times increase in pneumonia in children under 5 living in homes where they were exposed to unprocessed solid fuels.[20] Both of these increases were less than that reported by Po, FitzGerald, and Carlsten[17] who found that children in homes where biomass fuels were used for cooking were 3 times more likely to develop acute respiratory infection (ARI) than children in homes that used clean fuels.

A study conducted in Shanxi province, China, investigated the use of cleaner fuels including liquefied petroleum gas (LPG), kerosene and electricity for cooking and heating purposes.[5] The authors found that the use of clean fuels as opposed to coal could decrease chronic respiratory illness in children by 9%. Furthermore, the use of a mix of clean and biomass fuel types, such as using both LPG and polluting fuels, was found to decrease risk of ARI by 5% in comparison to homes using only polluting fuels.[21] Another study reported that using a mix of two polluting fuels, specifically cow dung and wood, resulted in a greater incidence or ARI's in children than using wood only.[22]

Niessen et al[23] used demographic information from 40 countries with high mortality rates to assess various methods of decreasing pneumonia in children under 5. Interventions included two cooking alterations, i) the use of cleaner fuels for cooking and ii) improved combustion ventilation in biomass stoves; the latter will be addressed in the following section. The authors reported that burning of solid fuel contributes to 30% of the childhood pneumonia burden, however in comparison to other interventions such as vaccinations, nutritional interventions, etc. cooking interventions were less cost-effective.

In contrast to the previous research, a study conducted on children in rural Southern Ecuador found that when controlling for confounders, the only respiratory symptoms significantly associated with biomass fuel use for cooking, in comparison to homes that used clean fuels, was earache.[6] Furthermore, a systematic review conducted using data on children under five from low and middle-income countries reported no significant association between the use of solid fuels and pneumonia in young children.[24] A similar lack of association was found by Asante et al,[25] who reported no significant relationship between burning firewood to cook with respiratory symptoms in children.

Overall, the use of cleaner fuels for decreasing childhood LRTI is controversial; while

many studies found reduced childhood morbidity/mortality when using cleaner fuels (kerosine, electricity, gas) over solid fuels (wood, dung, crop residues, coal, and charcoal) for cooking,[5,17,18,19,20,,21,22,23] a handful found a lack thereof.[6,24,25] Furthermore, there is a lack of case-control studies on the effects alternative fuel use for decreasing child respiratory illness, and thus the results are primarily limited to those of cross-sectional and other observational research. As such, randomized case-control designs would prove particularly useful in clarifying the efficacy of alternative fuel types for decreasing childhood LRTI while simultaneously minimizing concerns over confounding factors and assessing uptake/compliance for these fuel types of families living in rural, developing nations.

Alternative Cooking Devices

A randomized controlled trial (RESPIRE) was conducted in a rural Guatemalan community to assess whether the use of a chimney stove compared to the traditional wood fire stove would reduce pneumonia in children under 18 months.[26] Houses were randomly assigned to continue using the traditional stove or receive a chimney stove intervention. Homes were visited weekly by fieldworkers to assess for respiratory infection, and sick infants were referred to physicians blinded to intervention status. The chimney stove resulted in significant reductions in severe physician-diagnosed pneumonia, severe field-worker assessed pneumonia and severe RSV-negative pneumonia, but not the baseline incidence of pneumonia.

Mortimer et al[27] investigated the use of a cleaner biomass-fuelled stove through a randomized controlled trial in Malawi. The intervention stoves in this study had solar panels that powered fans that improved combustion efficacy, whereas the control group used traditional open fires. The intervention ultimately yielded no significant decrease in pneumonia or severe pneumonia episodes in the young children occupying these homes.

Another randomized controlled trial investigated the use of multi-pot wood-burning stoves compared to traditional open fires in homes with children under four belonging to communities in the Purepecha region of Mexico.[28] Children received monthly visits from nurses for 10 months and information was collected on children presenting with symptoms to identify upper and lower respiratory tract infections (URI and LRI, respectively). Although the study did not find a difference in the incidence of infection between the control and intervention group, the intervention group children had significantly lower durations of infection.

A cross-sectional study investigated the cost-effectiveness of two cooking interventions for child pneumonia.[23] The first involved cleaner fuels and was described previously, however, the authors also investigated the use of high-quality biomass stove with better combustion efficacy. The study authors found the use of the improved combustion stove tended to be less cost-effective than other interventions in most countries.

Thakur et al[29] conducted a meta-analysis to assess the impact of various adjustments to biomass cookstoves such as using improved combustion centres and adding chimneys. They found that although improved cookstoves resulted in reductions in negative respiratory outcomes in women, the adjustments had no significant effect on the incidence of lower ARI's or severe pneumonia in children. It should be noted, however, that the children in this study were up to 14 years old, and thus results may have varied if investigation focused on children under five like the studies previously discussed.

Overall, the results of studies evaluating the use of alternative cooking devices for decreasing childhood LRTI were largely inconsistent, ranging from interventions showing decreases in severe pneumonias,[26] to interventions showing no significant effect in children at all.[29] The inconsistency of results was to be expected, due to the heterogeneity of approaches taken to alter cooking devices. While some of these alterations showed important clinical reductions in illness, more research would be useful to further confirm intervention efficacy, particularly in comparison to

other methods of pollution reduction such as the use of alternative fuel-type, in a case-controlled manner.

Behavioural Interventions

A few studies have investigated the role of behavioural interventions for decreasing respiratory infection in children, including an observational case-control study that was performed in Bhaktapur, Nepal.[30] Children aged 2-35 months were included. Those with ALRI were matched with healthy controls. Analysis was performed to assess potential contributors, including environmental factors of having the child in the kitchen while cooking, having only a door or window open while cooking but not both, and having a small-sized kitchen. Homes that had children in the kitchen while cooking at a frequency reported as 'all the time' had an odds ratio of 1.60 for ALRI when compared to homes that never had the child present while cooking. It is notable that this odds ratio was computed using a model adjusted for factors such as parental occupation and mother's education, thus reducing potential for confounding related to socioeconomic status. Further, a significant association was found for kitchen size, as small or very small kitchens were associated with increased ALRI risk in comparison to medium or large-sized kitchens giving an odds ratio of 1.45. However, these results were computed with an unadjusted model.

Another study that investigated the influence of having children present while cooking found similar results.[22] In this study, the fuel type and whether children were present or absent during cooking were considered together. The researchers found that the greatest risk of childhood ARI occurred in homes using biomass fuels and had children in the kitchen while cooking, followed by biomass fuel use without children present, then homes using fossil fuels with children in the kitchen and finally homes using fossil fuels without children present.

Finally, a study conducted by Naz, Page, and Agho[31] additionally found important effects of children being away from the kitchen while stoves were being used. Although this study looked at mortality in children under five as opposed to specific respiratory outcomes, it is notable that increased mortality was associated with the lack of a separate kitchen for cooking.

Overall, behavioural interventions in rural homes demonstrated important effects on childhood respiratory illnesses. Important associations between behavioural intervention and childhood respiratory illness was discovered for each of the aforementioned studies, making the results relatively consistent. However, the quantity of research in this area is lacking. There are also limits in the capacity to discern causality from these studies, and more randomized control studies would be useful. More research assessing the practicality and uptake of behavioural interventions in families would provide useful information as to whether these interventions may be recommended in clinical practice.

CONCLUSIONS

The current study reviewed various cooking-related interventions taken to decrease childhood respiratory illness in developing countries. Findings regarding the use of clean fuel over biomass fuels were controversial. While most studies found significant associations between the use of biomass fuels and respiratory infection, a handful of studies found a lack thereof. Notably, however, no studies found increased risk while using cleaner fuels and thus it seems that homes adopt no risk of harm with use. Although the current review does not assess the feasibility of interventions, the recommendation of clean fuel use in clinical practice may be warranted. As for stove-related alterations, effects were largely dependent on the specific intervention used; while the chimney stove intervention in the RESPIRE trial decreased severe pneumonia, the stoves used by Mortimer et al[27] with improved combustion efficacy had no significant effect on childhood respiratory infections. While less research has investigated the use of behavioural interventions, removing children from the kitchen while cooking was consistently associated with decreased respiratory infections. Behavioural interventions, such as this, require no implementation fees, maintenance costs or training

and thus may be of particularly important use in decreasing respiratory infection in children.

Given the current body of research on the use of interventions for decreasing biomass fuel exposure, two interventions may be of particular importance. Firstly, it may be recommended that families use cleaner fuel types instead of solid fuels for cooking; these fuel types often demonstrated promising decreases in childhood LRTI, but in the cases where they demonstrated no benefit, they neither demonstrated harm. Secondly, it may be recommended that children be removed from the kitchen while families cook whenever possible, in order to decrease their exposure to fumes. Similarly to the approach of using cleaner fuels, despite the fact that this behavioural modification requires further research to confirm it's efficacy, adapting it currently is unlikely to cause harm. Although more research is necessary to further develop effective and confirm useful interventions, healthcare workers should consider recommending these interventions to families living in rural homes in developing countries in an effort to reduce harm.

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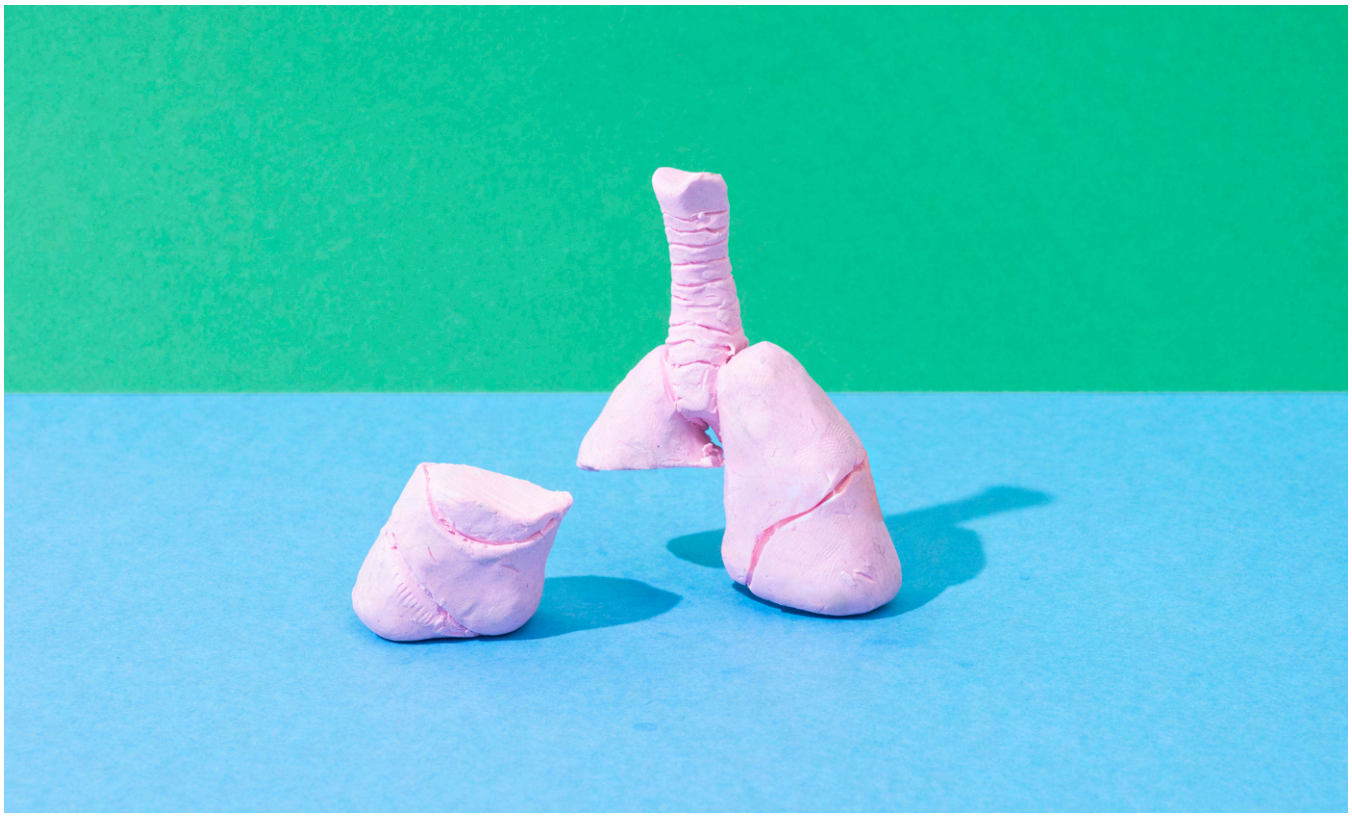

Clay illustration by Lily Offit; Photographed by Ben Denzer

Too Loose, Too Tight, But Never Just Right: Adhesions, Aspirations, and Atelectasis

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INTRODUCTION

I have my own version of Bobby's death tie: 3 inch wedges[1]. I thought to myself that morning as I turned around to slip the beeper into my bag, that there was no way we could get paged this early, on the second day after group borborygmi. Yet, the death wedges prevailed, and, though not pleased at the thought of missing pathology (why couldn't it be biochem!), I ran[2] to the Brigham to meet my first patient.

CLINICAL BACKGROUND

The decedent was a 72-year-old obese female. Her past medical history was significant for Parkinson's disease, an umbilical hernia, and a hiatal hernia. The hiatal hernia had been treated with a laparoscopic type III mesh placement as

[1] Surprisingly, not death for my ankle: I have yet to put myself in a walking boot wearing heels. Sneakers, on the other hand...

[2] Yes, in those wedges. A benefit of training as a figure skater!

well as a Nissen fundoplication on September 6, 2016.

The patient presented to Faulkner hospital on September 18, 2016, with sharp and crampy abdominal pain. She was found to have a ventral hernia, which was confirmed by CT. CT also revealed findings concerning for strangulation. The patient underwent emergent laparotomy to reduce and repair the hernia. The surgery and recovery were uneventful until post-op day 1, September 19, 2016, when the patient went into respiratory arrest. The code team arrived and had difficulty intubating, as the patient had two prominent upper canines that blocked the passage of the tube. After the tube was placed, the patient's oxygen saturation remained between 85-88%. The decision was made to re-intubate. During the process of re-intubation, the patient entered pulseless electrical activity and fluid could be seen in the back of the oropharynx. The reintubation was completed and the patient's oxygen saturation climbed to 94%; however, she had persistent arrhythmia and could not be resuscitated. She expired at 5:19 PM on September 19, 2016. Consent for an unrestricted autopsy at Brigham and Women's Hospital was given by the decedent's daughter. The goals of the autopsy were to elucidate the reason for the respiratory arrest. Possibilities included, but were not limited to, a pulmonary embolism from a deep vein thrombus, or a myocardial infarction.

GROSS PATHOLOGY

At autopsy, the patient was identified by a hospital ID bracelet on the left wrist and an ID tag attached to the right great toe. External examination of the patient revealed a female with grey hair, brown eyes with arcus senilis, and 0.5 cm pupils bilaterally. There was a plethora of evidence of medical intervention, including the following: two sets of electrical pads, one attached to her left anterior chest wall and upper back, and the other attached to her left superior abdomen; an endotracheal tube; access lines on the dorsal left hand and left chin; a bandage in the antecubital fossa; EKG pads on the right shoulder, right and left superior chest, right superior abdomen, left central abdomen, bilateral thighs, and bilateral ankles; a midline, 8.5 cm stapled incision site that was well-approximated, clean, and dry; laparoscopy port sites on the superior midline abdominal wall (0.7 cm), upper right abdominal wall (1.9 and 1.3 cm), left abdominal side wall (0.9 cm), and left anterior abdominal wall (1.2 and 0.8 cm). Further external examination revealed two abrasions near the xyphoid process (4.6 and 3.2 cm), ecchymoses bilaterally on the anterior thighs. Also noted was a 10.5 x 0.6 cm white fibrotic region of the skin on the right superior buttock.

After the organ block was removed, the thoracic cavity was examined and determined to be unremarkable. The thoracic cavity contained small lungs with increased weight (right lung 620 g, nl 360-570 g; left lung 540 g, nl 325-480 g). No pulmonary emboli were seen in the main pulmonary artery or the arteries of the left and right lungs. There was no grossly evident obstructing material or mucous in the lumina. The mucosa itself was uniform and hyperemic. The right lung was adhered to the diaphragm and esophagus at the esophageal hiatus, and there was significant fibrosis surrounding the adhesions. After sectioning, the lungs were dark red and non-crepitant, but no areas of consolidation were found. The bronchiolar tree was attenuated at the periphery. There was 150 mL of serosanguinous pleural fluid in the right pleural cavity and no fluid found in the left pleural cavity. The trachea was patent and showed no signs of upper airway obstruction. There were petechiae (up to 0.2 cm) present on the larynx between the true and false vocal folds and inferior to the true vocal folds. The thyroid gland (28.5 g, nl 30-70 g) was small but otherwise unremarkable.

Apart from its smallness (230 g, nl 250-300 g), the examination of the heart proved to be unremarkable. The ventricles were unremarkable, and no areas of recent or remote myocardial infarction were seen upon sectioning of the ventricles or triphenyltetrazolium chloride stain. The tricuspid, pulmonary, mitral, and aortic valves were unremarkable. The coronary vessels were patent, and there was no atherosclerosis of the aortic root. Dissection and sectioning of the coronary arteries

revealed no thrombi. The aortic arch contained no atherosclerosis.

Next, we progressed to the abdomen. There was no ascites noted. The esophagus and stomach were adhered to the diaphragm at the esophageal hiatus. The stomach was fully expanded with air. Inside the stomach were 5 undigested pills, and another 2 undigested pills in the proximal duodenum. Each of the pills was 0.5 cm in diameter, orange-yellow, and had a 'T' inscribed on one surface. A google search[3] revealed a match with 325-mg enteric-coated aspirin tablets, which had previously been prescribed to the patient. According to the medical record, the patient was not taking these pills in the hospital. The pyloric sphincter was thickened (0.7 cm in greatest wall thickness. The examination of the small and large bowel demonstrated fecal contents, and there were no obstructions or ischemic segments of intestine identified. The appendix (8.1 cm in length x 0.6 cm in diameter) was present and unremarkable in appearance. The liver (1150 g, nl 1200-1400), was slightly small and showed evidence of autolytic changes. The gallbladder was not present. The pancreas and the spleen (75 g, nl 110-170) were both soft and cohesive consistent with early autolysis.

There was minimal atherosclerosis present in the abdominal aorta near the bifurcation into the common iliac arteries. The right and left renal arteries were patent. The kidneys (right 65 g, left 70, g, nl 115-155) were small, and both contained cortical retention cysts. The cut surfaces of the kidneys demonstrated intact corticomedullary junctions. The adrenal glands (right 9.4 g, left 13.5 g, nl 5-6 g) were large but otherwise unremarkable. The ureters were patent. The bladder had a white mucosal surfaces and a pink glistening peritoneal surfaces. The uterus and ovaries were unremarkable. The great saphenous veins were patent bilaterally, and there was no evidence of thrombosis.

The brain (1110 g, nl 1200-1300 g) and spinal cord were removed and sent to Neuropathology to examine due to her Parkinson's disease. The findings were not pertinent to the cause and manner of death, which was the focus of this autopsy.

Taken together, the gross autopsy suggests that the cause of death in this patient, a 72-year-old woman status post ventral and hiatal hernia repair surgeries, was most likely an acute post-operative aspiration event, which was exacerbated by atelectasis, post-surgical adhesions between the esophagus, diaphragm, and right lung, and an enlarged and dilated stomach and a right pleural effusion, all of which led to respiratory distress that was complicated by a difficult intubation. In addition, there was evidence of gastroparesis and ileus, given the 7 undigested pills present in the patient's stomach and proximal ileum. There was no indication of myocardial infarction, no gross or microscopic evidence of pulmonary emboli, upper airway obstruction, or coronary artery thrombi.

MICROSCOPIC PATHOLOGY

A thorough examination of the ventricles of the heart revealed no signs of ischemia. No thrombi were seen in the coronary arteries. There was mild atherosclerosis with 10% mural compromise.

A histological examination of the lungs revealed vascular congestion and focal extravasation of red blood cells into alveoli, which is consistent with sudden death and resuscitation efforts. Rare bone marrow emboli were seen bilaterally in small vessels. There were rare, scattered foci of bacteria, squamous debris, and polarizable material in the alveoli, consistent with aspiration. There was no reaction around these foci of aspiration, suggesting that the aspiration event occurred either shortly pre-mortem or in the peri-mortem period. The large bronchi exhibit focal acute and chronic inflammation. There were no signs of aspiration in the trachea. The larynx exhibited subepithelial hemorrhage.

The muscular hypertrophy of the pylorus was confirmed histologically with trichrome

[3] Dr. Google comin' in clutch.

staining. There was also evidence of submucosal chronic inflammation.

Microscopic investigation of the esophagus and paraesophageal soft tissue found extensive hemorrhage, fibrosis, and granulation tissue, all of which are consistent with a healing surgical site. There was no evidence of infection.

Examination of the kidneys microscopically showed congestion in small vessels. The spleen also had signs of congestion, but there were no other pathological abnormalities noticed. The liver was devoid of pathological abnormalities.

CLINICAL-PATHOLOGICAL CORRELATIONS

Unlike in the third portion of our course, cancer is not the answer; instead, the answer is everything hernia.

Twelve days before presenting for her final hospital admittance, the decedent underwent emergent repair for a hiatal hernia. This was not our patient's first hernia: she had previously presented with an umbilical hernia, which reveals general muscle weakness; additionally, the patient was well over the age of 50 and was obese, both of which are risk factors for hiatal hernias. A Nissen fundoplication with a laparoscopic type III mesh placement was performed to correct the defect and prevent a further hiatal hernia; however, this measure may have been a cause in her demise. Nissen fundoplications have been known to cause "gas-bloat syndrome," which comprises a variable and not clearly defined set of complaints and which is assumed to result from an inability to vent gas from the stomach into the esophagus (Richter, 2013). This, along with difficulties in tube placement, may have contributed to the distended stomach filled with air noted in the gross pathological portion of the autopsy. Some gas-bloat syndrome patients also have issues with delayed gastric emptying, which would be consistent with the undigested pills in the patient's stomach and proximal duodenum. The thickened pyloric sphincter also contributes to this difficulty in gastric emptying.

Fibrotic adhesions were found between the esophagus, the diaphragm, and the right lung. These are most likely a direct result of the Nissen fundoplication surgery, and this reduced the ability of the right lung to expand and of the diaphragm to maintain its full range of motion, decreasing the maximal volume of the lungs further.

The adhesions and the gas-bloat syndrome symptoms may have led to increased difficulty of passages of boluses through the gastrointestinal tract. That, combined with the increased age, the size of the patient, and her past multiple pregnancies, leading to weakness of the abdominal wall, aided in the formation of her ventral hernia. This was the cause of her abdominal pains, which caused her to present to the hospital on September 6, 2016.

The patient then underwent an emergent surgery to repair the ventral hernia due to findings concerning for strangulation. Atelectasis, a partial collapse of a lung, is a common complication during surgery ("What Causes Atelectasis?", 2012). In the gross examination of the lungs, the bronchi were found to be attenuated at the periphery, a finding that is consistent with atelectatic lungs. Furthermore, the pleural effusion noted in the right lung supports the clinical diagnosis of post-surgical atelectasis and would further reduce the expansion potential of the lung. This is consistent with the results of the gross pathological examination of the lungs, which revealed that the lungs were both smaller and heavier than normal limits. A pleural effusion was also noted in the autopsy; pleural effusions due to regional inflammation after surgery are a common complication in older patients (Lawrence et al, 1996).

Aspiration can occur in patients recovering from anesthesia. Anesthesia can weaken the autonomic regulation of the pharynx; because of this, aspiration events have happened, although they are not exceedingly common (Asai, 2004).

The polarizable material found in the microscopic pathology of the lung, combined with the squamous debris and scattered foci of bacteria, point to aspiration of the contents of the stomach, which, as we will recall, contained five undigested

pills. Additionally, the lack of inflammation or reaction around the aspirated foci point to this event as the cause of death, as it must have occurred in the immediate pre-mortem period. The aspiration event is the likely cause of death, especially considering the exclusion of myocardial infarction from the triphenyltetrazolium chloride stain and physical examination as well as the lack of evidence of deep vein thrombi.

SUMMARY OF CAUSE OF DEATH

The reduced size of her lungs, from the atelectasis, pleural effusion, and adhesions, all of which resulted from her previous surgical repair for her hiatal hernia, were implicated in the immediate events leading to the patient's expiration. Due to a thickened pyloric sphincter and delayed gastric emptying from the Nissen fundoplication, the patient was unable to digest pills taken preceding her hospital visit. The patient underwent an aspiration event the morning after her ventral hernia repair. This, combined with the already decreased lung volume, led to the respiratory arrest. The intubation most likely reached the stomach on first effort due to the excessive amount of air present. The patient then entered pulseless electrical activity due to her hypoxia, and she expired.

THE MORE YOU KNOW

While complications from hernia repair led to our patient's ultimate expiration, she avoided an issue that plagues mesh hernia repairs: infection. Mesh-related infections in hernia repairs have a reported incidence of between 1%-8% (Falagas and Kasiakou, 2005). Indeed, nosocomial infection is the fourth leading cause of death for American hospital patients with 2 million cases annually (Wenzel, 2007). Out of these, 60-70% are associated with an implantation of a medical device (Bryers, 2008). One of the main culprits of the infections associated with implantation of devices such as mesh during hernia repair or orthopaedic replacements is biofilm formation (Choi et al, 2012). My brief foray into materials science[4] and surgical research was focused on this field; we engineered a patch derived from organic collagen and seeded with human mesenchymal stem cells to, among other aims, thwart biofilm formation on two fronts. Firstly, the alginate portion of patch would degrade over time, decreasing the nutrient source and surface area for biofilm formation. Additionally, the human mesenchymal stem cells seeded upon the patch promote neovascularization, which allows for greater immune system recruitment and destruction of biofilms (Ayala et al, 2015). Biofilms are cool, bacteria are cool, and the way that bacteria have evolved to work together is incredible, kinda spooky, and has important implications on the evolutionary history of multicellularity as well as potential clinical applications.

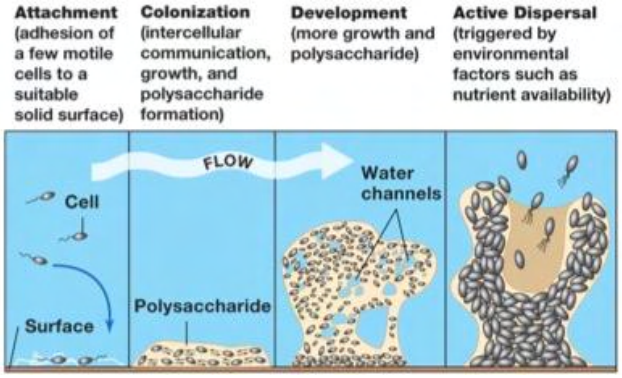
Let's back up a second - what exactly are biofilms? Biofilm, a term coined in 1978 though the discovery of these structures' existence dates back to the 17th century (Banthia et al, 2011), refers generally to a multicellular community of microorganisms encased within an extracellular matrix, invariably involving multiple species (Lopez et al, 2010). This extracellular matrix protects the encased bacteria from antibiotics and other methods of destruction, and in these states biofilms and their biological components can persist in the body for long periods of time. These films are present almost everywhere, from our teeth in the form of dental plaques to ships and pipes and even in geothermal vents.

Though Antoine van Leeuwenhoek first noted the existence of biofilms in 1684, prior to 1978 the main research focus on bacteria was in planktonic (single and free-floating) form. This was due to the assumption that this was the natural state of most bacteria (Branda et al, 2005). However, in a groundbreaking Scientific American paper in 1978, Costerton et al asserted that most bacteria in natural environments adopt a sessile, multicellular form via a bacterial glycocalyx that

[4] In this, I discovered that I will not be a materials scientist, and I also reaffirmed that bacteria and evolution are mind-blowingly cool. All in all, a productive experience.

allow the cells to stick to each other and anchor themselves in a film (Costerton et al, 1978).

Biofilm formation has now been studied in the lab through the development of techniques conducive to their growth, such as flow cells, liquid-air interfaces, and submerged films, and several general stages of biofilm formation have been identified (Branda et al, 2005)[5]. Initiation happens when microorganisms interact with a surface and each other. Once a critical mass has been reached, the biofilm maturation process begins with the production of an encasing extracellular matrix. Different species or mixes of species produce different extracellular components - Other maturation events include the formation of "persister" cells, which are dormant cells that are essentially invulnerable (metabolically inactive, exhibiting multidrug resistance) and are important to the survival of biofilms (Lewis, 2008). Despite the generality of these steps, biofilms can be incredibly diverse. Even small changes in the surrounding environment can lead to significant differences in the extracellular makeup of a biofilm and its architecture (Branda et al, 2005).



A diagram of biofilm formation, maturation, and dispersal (taken from the Microbiology, Immunology, and Molecular Genetics 301 class study guide at Michigan State University)

Biofilms have several ways of causing problems medically. Due to their enclosed structure and a social evolution between the component species, the communities are able to recycle nutrients and persist for long periods of time (Boyle et al, 2013). Diffusion of small molecules and antibiotics are slowed through the extracellular matrix encapsulating the biofilm, rendering the films largely resistant to antibiotics. Furthermore, the sequestering and cooperation between different bacterial species in a confined space leads to increased conjugation and antibiotic resistance. The "slime" of biofilms was thought to protect against immune cell penetrance, but recent studies have shown that the interaction between leukocytes (neutrophils, peripheral blood mononuclear cells, etc) and biofilms may actually promote and stabilize biofilm formation by stimulating the production of various cytokines (Walker et al, 2005; Chandra et al, 2007). Additionally, biofilms undergo repeated cycles of formation, maturation, and release, whereby the bacterial community can perpetuate itself by forming a new biofilm. Finally, biofilms contain within them "persister cells." These cells, making up approximately 1% of the exponentially replicating cells during the formation of the biofilm but coming to play a much larger role in the later life of the biofilm, are in a state of dormancy and are almost impossible to kill. While not outright resistant to antibiotics, they are able to modulate their phenotypes to tolerate antimicrobial agents without undergoing genetic changes (Wood et al, 2016). The main model in the formation of these persister cells are toxin-antitoxin pairs which cause the cell to go into dormancy and protect itself by diminishing translation and the ability of cells to respond to stress. It is now thought that persister cells are the reason biofilms are so deadly to humans (Wood et al, 2016).

The formation of biofilms is an evolutionarily ancient and conserved process that is currently poorly understood. While there is a general understanding of how biofilms form and the evolutionary pressures that forced them to do so - sequestering of nutrients, efficacy of division of metabolic labor, increased protection from the exterior environment - this grey area between cell

[5]In one of the best-titled articles of all time, "Biofilms: The Matrix Revisited"

independence and multicellularity could hold the key to understanding how complex organisms such as ourselves evolved. How do these different species of cells contact one another? How do they maintain a balance between dependence and independence? The answer, other than evolution being incredibly complex and cool, is the concept of quorum sensing.

Quorum sensing is the regulation of gene expression in response to fluctuations in cell-population density. Certain bacteria with the capacity to perform quorum sensing release signaling molecules called "autoinducers," such as acetylated homoserine lactones for gram-negative bacteria and processed oligo-peptides for gram-positive bacteria (Bryers, 2008). These molecules increase in concentration as a function of cell density. There is some threshold of minimal detection at which point the autoinducers cause genetic alterations. These genetic alterations induce a whole host of collaborative phenotypes, from symbiosis, conjugation, and competence to the production of virulence factors, antibiotic production, and motility. Just like everything else that is associated with biofilms, there is plenty of variation present in quorum sensing pathways. For example, some pathways have the ability to severely downregulate polymer production whereas other systems continuously secrete polymer. Evolutionary models have demonstrated that this, again, is due to the exquisite diversity in the composition of species contained within biofilms. If dispersal is necessary to access more nutrients (species are not able to recycle nutrients or are outcompeting crucial components of their ecosystem), the bacteria associated with these types of biofilms have evolved the ability to downregulate extracellular polymer production through quorum sensing. However, the energy expended in maintaining these pathways is not favorable in microorganisms present in chronic biofilm plaques, in which the strains involved can sustain stable nutrient equilibria (Nadell et al, 2008). Quorum sensing has been shown to be effective not only within a particular species but also across species and in some cases has been shown to elicit responses from host organisms (Miller and Bassler, 2001). This may hold a clue in the first steps of multicellular development and evolution. Not only that, but blocking autoinducers may be a way to prevent biofilm formation, disrupt this "social" behavior, and force microbes to exist in planktonic form, whereby they are susceptible/more reachable by antibiotics (Boyle et al, 2013).

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Clay illustration by Lily Offit; Photographed by Ben Denzer

Advancing Preclinical Medical Education through High Fidelity Simulation and Standardized Patient Families

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Abstract

Introduction: Simulated patient encounters in preclinical medical education are being implemented at various medical schools throughout the United States. In this study, we aimed to evaluate the perceived effectiveness of early preclinical simulations on medical students' education.

Methods: Two classes of osteopathic medical students, class of 2019 and class of 2020, participated in two simulated clinical experiences using high-fidelity patient mannequins and standardized family members during their second year of medical school. These same students, who are now completing their clinical rotations, completed a survey to assess if the experience with a simulated patient/family

Results: A total of 379 students were emailed a survey. Out of 379 total students, 122 surveys were completed (59 from the Class of 2019, 63 from the Class of 2020). The overall response rate was 32%. A majority of the respondents responded positively, with 63% of students stating in their free responses that the simulated patient encounters were experiences that improved their ability to interact professionally and appropriately with patients and family members. P-values between the classes for each survey question was greater than 0.05, indicating that there were no statistically significant differences between the classes of 2019 and 2020 in their survey responses.

Conclusion: This study provides evidence that early simulated patient encounters provide a self-reported experience that improves empathy and communication for the students during their clinical rotations.

INTRODUCTION

Simulated patient encounters in preclinical medical education are being implemented at various medical schools throughout the United States.[1] Osteopathic Medical school education is largely driven by standards created from the National Board of Osteopathic Medical Examiners. A portion of the preclinical standards are based on the humanistic domain of medicine, which includes communication, interpersonal skills, and professionalism. [2] All osteopathic medical students are expected to pass COMLEX-USA Level 2 PE during their third year of medical school. This standardized test assesses whether graduating medical students are proficient in their clinical decision-making skills, and in their ability to communicate effectively with patients and their families as well as the entire healthcare team. According to multiple studies, school-based performance measures during preclinical years are a reliable tool for predicting performance on COMLEX-USA Level 2 PE and rotations. [3, 4] These studies show that experiences during the preclinical years have a notable correlation with future performance.

Medical school curricula are constantly being examined to ensure students can be both successful on these examinations and in their future career as practicing physicians. It has been well established that, "assessments drive teaching and learning." Patient and family surveys routinely find that patients want better communication from their doctors, and simulations are one way to foster this skill. [5, 6]

Simulation encounters occurring during the preclinical years of medical school provide skills that assist in the success of students during their clinical years, such as communication and teamwork[7]. These skills should continue to assist them as resident physicians. One study concluded that resident communication skills training that focused on family system theory resulted in increased confidence and skills for residents, acting as participants, in communicating difficult information to their patients and family members. [8] Family system theory, applied to medicine, is the idea that medical professionals are not only interacting with patients to deliver difficult news, but they also must interact with patients' family members in a family-centered approach.

In the first phase of this study, second year medical students from the Lake Erie College of Osteopathic Medicine in Bradenton, Fl. partnered with RN-BSN nursing students from the State College of Florida, Manatee-Sarasota (SCF) to participate in scenarios involving high-fidelity simulators and standardized patient families. The purpose of these encounters was to foster collaboration and communication skills between members of healthcare staff, as well as communication with patients and their families.

This study was performed to investigate the benefits perceived by clinical students of the early preclinical mannequin simulations with standardized patients as families. The goal of this experience was to prepare students for interactions with actual patients, staff, and family members during their clinical years. [9]

To our knowledge, this is the first study that attempts to analyze how third- and fourth-year medical students compare clinical medicine in their clerkship years with the simulations they experienced in their preclinical years. This study expanded upon our previously published work. [7]

METHODS

Participants: This retrospective, non-experimental, mixed-methods study surveyed 196 students in the LECOM-B Class of 2019 (3rd year students) and 183 students in the class of 2020 (4th year students). All these students participated in two simulated clinical experiences with RN-BSN students, human patient simulators, and standardized patients as family members. The students were scheduled for these experiences once during the fall semester and another during the spring semester of their second year of medical school. The students in the Class of 2019 and 2020 engaged in these encounters during the 2016-2017 and 2017-2018 years, respectively.

Procedure: Students completed the simulated clinical experiences in the Simulator Center

at the SCF. The Simulation Center is set up to reflect an intensive care unit, with nine patient rooms positioned around a large nursing station. The patient rooms contained a hospital bed, cardiac monitor, IV pole with medications hanging and a medical supply cart. A high-fidelity human patient simulator was used. Nursing faculty controlled the mannequin from a remote location. Alterations in vital signs and voice responses were used in the simulation scenario.

Two medical students were paired with one RN-BSN nursing student. The medical students were given a brief bedside report from the nurse on the patient and were then asked to complete a full medical examination of the standardized patient. Upon completion of the physical assessment and huddling with the nurse, they were directed to discuss the status of the patient with two of the patient's family members, who were standardized role-players. The actors were specifically scripted to act out a stressful scenario. Students were expected to follow the SPIKES [10] protocol in relaying difficult news to the patient's portrayed family members.

At the end of the encounter, video debriefing occurred with everyone involved with the medical students, the RN-BSN nursing student, and LECOM-B clinical professors. Throughout the debriefing sessions, students were provided constructive feedback of the encounter. Students were asked specific questions to evaluate areas for improvement and the medical students were asked to reflect on their overall experience. SCF, LECOM-B faculty, and the simulated family members provided written evaluations assessing each student on their patient bedside physical examination, family member encounter, and professionalism. These evaluations were not analyzed for this study, as it was primarily to provide students with immediate feedback and show them areas for improvement. All students were exposed to the same level of acuity in scenarios and the same group of patient families throughout all simulated clinical experiences.

Students in their clinical years, who had previously participated in the simulations, were then surveyed regarding their experiences. A 10-item survey was created using SurveyMonkey®, which was sent to the Classes of 2019 and 2020 on November 1st, 2018. The Class of 2019 submitted responses for the simulation experience, which occurred about 18 to 22 months prior to being surveyed. The Class of 2020 had their simulation approximately 7 to 11 months prior to being surveyed. We had an interest in evaluating differences, if any, between these two classes.

Reminder emails were sent on November 15, 2018, and January 7th, 2019 to encourage completion of the survey. All responses were anonymous and confidential. Seven of the survey items used a 5-point Likert-type scale ranging from five points to one point. Two of the survey questions allowed for written responses. The responses to these open-ended questions were then manually tallied. The study was approved by the Lake Erie College of Osteopathic Medicine's Institutional Review Board, which waived the need for informed consent.

Statistical Analysis: SPSS software (IBM) was used to analyze the data. Responses were compared between the two medical student cohorts using a Mann-Whitney U Test. A non-parametric test was chosen because the data was assumed to not have a normal distribution. The sample means came from the same population. A 2-tailed test was confirmed. Statistical significance was defined as a $P<0.05$.

RESULTS

A total of 379 students were emailed for this study. Out of 379 total students, 122 surveys were completed (59 from the Class of 2019, 63 from the Class of 2020). The overall response rate was 32%. The responses between the two cohorts to all the questions were not statistically significant.

A majority of the respondents from both cohorts (Class of 2019 and Class of 2020) agreed with the survey responses that scored their responses somewhat valuable, valuable, or extremely valuable. The only survey item that didn't receive over 50% positive responses was whether the students would want to repeat the simulated

patient encounters during 3rd year while on rotations. The classes of 2019 and 2020 scored the simulation as being most valuable for their Internal Medicine rotation, with 40.38% and 48.21% responding in the affirmative, respectively.

There were a total of 56 free responses detailing the students' perception of the simulation experience and its impact on their clinical rotations. The overall tone of the response was evaluated. The free responses for both classes were overall positive; however, there were negative free responses (negative responses made up 37% of the free responses). There were 13 negative free responses for the Class of 2019 and there were 8 negatives for the Class of 2020.

One student in the Class of 2020 commented "Very poor translation between the simulation and real-world experiences. Difficult to act "natural" when being recorded and judged on every statement." Some of the students' comments seemed to be contradictory. Another student, who was from the Class of 2019, said "I feel the pattern of two experiences was somewhat contrived, but re-watching video of my own body language was the most helpful." One student noted, "I thought it was a great experience during second year. I feel that during third year I would much rather have the true patient experiences than be taken away from my rotation for a simulation, especially being so far away. I am very happy I had the chance to experience the simulation during 2nd year and would recommend it." A few students agreed that these experiences were helpful, but still not realistic, with comments such as "It's really hard to simulate the same emotions in real life. The actors were good, but it is just not the same. Plus, these situations need to be practiced over and over. I'm not sure it's worth it to do it just one time."

However, other students felt the simulated encounters were not realistic at all, and that these skills must be learned through real life scenarios, making remarks such as "not worth the time" and "practicing on plastic does not help", indicating a minority of the students felt this experience was not valuable to them as future clinicians.

	Survey Item							
1	*At the time you participated, what was your overall impression of the simulation experience at the State College of Florida?*	Extremely valuable	Very valuable	Somewhat valuable	Not so valuable	Not at all valuable	Total Responses	P-value between classes
	2019	10 (16.95)	12 (20.34)	25 (42.37)	12 (20.34)	0 (0.00)	59	**0.25**
	2020	11 (17.46)	19 (30.16)	26 (41.27)	6 (9.52)	1 (1.59)	63	
2	*Was this experience helpful to you during your clinical rotations?*	Extremely helpful	Very helpful	Somewhat helpful	Not so helpful	Not at all helpful	Total Responses	**0.86**
	2019	5 (8.62)	10 (17.24)	22 (37.93)	16 (27.59)	5 (8.62)	58	
	2020	5 (7.94)	10 (15.87)	28 (44.44)	15 (23.81)	5 (7.94)	63	
3	*Was the simulation experience helpful to you in dealing with family members?*	Extremely helpful	Very helpful	Somewhat helpful	Not so helpful	Not at all helpful	Total Responses	**0.42**
	2019	6 (10.17)	12 (20.34)	28 (47.46)	9 (15.25)	4 (6.78)	59	
	2020	4 (6.35)	13 (20.63)	27 (42.86)	15 (23.81)	4 (6.35)	63	
4	*Was the simulation experience helpful to you in your approach to delivering negative news?*	Extremely helpful	Very helpful	Somewhat helpful	Not so helpful	Not at all helpful	Total Responses	**0.33**
	2019	9 (15.25)	14 (23.73)	25 (42.37)	6 (10.17)	5 (8.47)	59	
	2020	6 (9.52)	15 (23.81)	25 (39.68)	12 (19.05)	5 (7.94)	63	
5	*Was the simulation experience helpful in improving your communication skills?*	Extremely effective	Very effective	Somewhat effective	Not so effective	Not at all effective	Total Responses	**0.83**
	2019	5 (8.47)	11 (18.64)	26 (44.07)	12 (20.34)	5 (8.47)	59	
	2020	3 (4.76)	16 (25.40)	27 (42.86)	12 (19.05)	5 (7.94)	63	
6	*Was the simulation helpful in preparing you for interprofessional collaboration?*	Extremely helpful	Very helpful	Somewhat helpful	Not so helpful	Not at all helpful	Total Responses	**0.44**
	2019	4 (6.78)	8 (13.56)	24 (40.68)	17 (28.81)	6 (10.17)	59	
	2020	5 (7.94)	13 (20.63)	24 (38.10)	14 (22.22)	7 (11.11)	63	
7	*Would you recommend this experience to future students?*	Definitely would	Probably Would	Probably Would Not	Definitely would not		Total Responses	**0.11**
	2019	17 (28.81)	20 (30.90)	21 (35.59)	1 (1.69)		59	
	2020	23 (36.51)	28 (44.44)	10 (15.87)	2 (3.17)		63	
8	*Would a similar simulation experience be helpful during on-campus time in year 3?*	Extremely helpful	Very helpful	Somewhat helpful	Not so helpful	Not at all helpful	Total Responses	**0.17**
	2019	3 (5.08)	6 (10.17)	7 (11.86)	23 (38.98)	20 (33.90)	59	
	2020	3 (4.76)	1 (1.59)	6 (9.52)	26 (41.27)	27 (42.86)	63	

Raw dataset showing numbers and (percentages) for each of the surveyed questions.

DISCUSSION

The studies mentioned throughout this paper show that establishing relationships, displaying empathy, and communicating effectively are necessary in order to provide the best care possible. Other studies have shown that clinical performance in the 4th year of medical school affects performance in residency. [11] Therefore, methods to instill and foster these skills should be implemented earlier in medical schools across the country. The NBOME has taken note of the importance of such skills, and therefore now includes a

humanistic domain in the COMLEX-USA Level 2 PE which measures skills in doctor-patient communication, interpersonal skills, and professionalism. [2] Our results show that students find simulated encounters to be beneficial during their clinical rotations. According to the survey responses in this study, simulated encounters were more beneficial for some rotations, like Internal Medicine, rather than other rotations. When asked which rotation benefited the most from these encounters, 44/85 of students selected IM rotations. In reviewing the written responses, many students commented that the simulated encounters were overall helpful to their education, however, the simulations will never be able to replace real clinical encounters. Since the simulated encounters take place during the second year of medical school before clinical encounters, these encounters may help build the foundation for third year medical students and beyond.

The Interprofessional Education Collaborative identifies four core competencies for effective collaboration including: 1) values/ethics, 2) roles/responsibilities, 3) interprofessional communication, and 4) interprofessional teamwork and team-based care [12.] The objectives of implementing the simulated experience were to allow students to improve in each of these four areas. Also, integrating nursing students with medical students earlier in their careers could allow for improved interprofessional healthcare collaboration throughout residency and their careers. Multiple studies have shown the benefits of physicians being able to connect with patients and their families. Duffy et al. demonstrated that "professional conversation between patients and doctors shapes diagnosis, initiates therapy, and establishes a caring relationship". [5] Karkowsky and Chazotte showed that effective communication in a medical setting can improve patient adherence, improve patient outcomes, and lower risk of litigation. [9] Also, Zachariae et al. showed that communication ratings correlated with reduced emotional distress in cancer patients. [13]

Throughout the high-fidelity simulations, the medical students were recorded so that they would be able to review their ability to effectively communicate in difficult scenarios. They were then able to share their opinions of the simulation through a free response question in our survey. The idea of not being able to act "natural" when being video recorded and evaluated was mentioned in several written responses. These comments raise concern that the recordings of students during the simulations could have had an effect on how they delivered the news to the families. However, rewatching video playback of the student' simulation encounter has been shown to be beneficial in clinical research. As noted in M. Bussard's research on nursing students, who were video recorded using high-fidelity mannequins to assess their preclinical judgement, the study found that students can improve their confidence, communication and decision making, and can improve their clinical practice using video recordings. [11] One student in our study voiced that it is hard to treat simulations like real life, and that it may take some time to get used to simulations. Comments like these highlight the need for future studies to evaluate whether simulated encounters improve students' performance in the hospital using objective measures.

The results of this study were based on responses from the students, which may be ineffective at measuring the usefulness of the simulated encounters. Since this survey was voluntary, this study only included self-selected students, rather than all students that participated in the simulated encounters. Students may have answered the survey negatively because the encounter was difficult for them, even though it was useful. For the Class of 2020, at the time of the survey, the students only had about 6 months of rotation experience. Because of this, some of the students may not have had the opportunity or as many opportunities due to the configuration of their rotation schedules (for example, not every student may have had an internal medicine rotation at the time of the survey, which, according to the survey data, was the in which the simulated encounters were most helpful). Additionally, the students' responses to the survey were collected more than 6 months

after the simulated encounters, which may lead to inaccurate recall of the utility of the simulated encounters. The students had limited participation in only two simulated encounters with mannequins (one during each semester in their second year of medical school). Lastly, the response rate was 32% (122/379), which may not fully represent the opinions of all students, however, the results between the two classes were consistent.

Our study measured how the medical students reacted to the training using mannequins and simulated encounters (Kirkpatrick Level 1). Future studies should aim to assess the impact of the simulated encounters by measuring changes in behavior (Kirkpatrick level 3).[14] One possible scenario would be to survey the patients and patients' families of the medical students who *did* have simulated mannequin training, as well as the patients and patients' families of medical students who *did not* have this training. We were unable to do this since all LECOM-Bradenton students receive the same simulated encounters using mannequins. Also, future studies could increase the number of encounters to allow the students to become more familiar with the mannequin technology. It might be beneficial to not have video recorded encounters to better simulate in-hospital rotation experience and allow the students to act more naturally. A longer follow-up study to assess these students' perceptions once they are practicing residents might also be useful information. Future studies should also validate that 3rd and 4th years students that are being surveyed have had the opportunity to implement the skills that are emphasized during the simulation training during first and second year.

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