THESIS PROJECT PORTFOLIO

Differentiating Acute Otitis Media (AOM) from Otitis Media with Effusion (OME) Using Autofluorescence of NADPH in Neutrophils

(Technical Report)

An Analysis of Racial Bias in Pulse Oximetry, and its Impact on Patients with Marginalized Racial Identities During the COVID-19 Pandemic

(STS Research Paper)

An Undergraduate Thesis

Presented to the Faculty of the School of Engineering and Applied Science

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In Fulfillment of the Requirements for the Degree

Bachelor of Science, School of Engineering

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Department of Biomedical Engineering

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The National Society of Professional Engineers' (NSPE) code of ethics states that "... the services provided by engineers require honesty, impartiality, fairness, and equity, and must be dedicated to the protection of public health, safety, and welfare[1]." These words reflect the importance of ethical responsibility in engineering practice. At the core of engineering thinking is the design process, an iterative and complex problem-solving method. As a biomedical engineer, it is important to understand how to employ the design process for beneficial impact on a real, diverse, holistic society.

While these thesis and technical topics are not overtly related or "coupled", they are mutually linked to the process of engineering design through the lens of equity and justice. The Otitis Media technical project, still in technological stages of proof of concept, will be further developed into a product that will ideally be accessible to any patient. It will ideally be a device that will not discriminate on the basis of a patient's identity, but instead will only assess their true physical condition. These design goals correlate closely with a goal to disrupt normalized deviance of racial biases and inequity in medical devices and standards. Said normalized deviance is directly related to the thesis problem of racial biases in pulse oximetry, and their potential connection to health inequity during the COVID-19 pandemic.

The technical topic revolves around Otitis Media, or inflammation of the middle ear typically caused by the presence of fluid due to improper eustachian drainage[2]. Otitis Media with Effusion (OME) is simply the presence of fluid (effusion) in the middle ear, while Acute Otitis Media (AOM) is the presence of infected fluid in the middle ear. 2.2 million cases of AOM occur annually among children, costing $4 billion per year due to unnecessary procedures, over-prescriptions of antibiotics, and loss of hearing[3]. Ideally, clinicians will be able to accurately distinguish between OME and AOM, which requires antibiotic treatment. However, it

is currently difficult for clinicians to differentiate between them. Specifically, diagnoses by general practitioners and primary care providers are unreliable ~27% of the time due to the unoptimized diagnosis techniques and subjective diagnosis criteria[4]. A feasible approach to Otitis Media diagnosis is through evaluation of middle ear effusion contents. In infected effusion, it is logical that there is a corresponding immune response and therefore neutrophils present. NADPH is present in neutrophils responding to infection[5]. Therefore, the goal of the technical project is to develop a successful proof of concept for detecting NADPH as a surrogate measure of neutrophils in the middle ear, thereby indicating if infected fluid is in the space and enabling a physician to make a correct diagnosis.

The separate thesis topic analyzed the research question: What is the significance of disparity in pulse oximetry and how might it contribute to COVID-10 health inequity for BIPOC patients? A variety of commonly-used medical devices and health standards harbor racial biases, and therefore create a limitation of medical practice for provision of a consistent standard of care for patients with diverse ethnic and racial identities. These disparities are often products of normalized deviance, a problem framework that revolves around the development of tolerance for lower-than quality standards created by exposure to these lowered standards over time. This framework can be applied when investigating inequities and biases associated with medical devices and standards of medical care in the United States. These disparities do not allow for compliance with medical standards and codes of ethics, and therefore they must be mitigated by equitable engineering design solutions. Inaccurate device functionality and inconsistent medical treatment when applied to patients who identify as Black, Indigenous, and/or People of Color (BIPOC) cyclically contribute to the normalized deviance of systemic racism in the US medical system.

The nature of racial disparity in medical devices can be represented by the case of pulse oximetry and its impact on COVID-19 health equity for BIPOC patients. BIPOC patients have been identified as at higher risk for getting sick and dying from COVID-19, and factors such as limited access to healthcare, underlying medical conditions, and education, income, and wealth gaps have been identified as potential contributors to this problem[6]. Analysis of the thesis topic is an examination of racial bias in pulse oximetry as a potential additional contributing factor to COVID-19 health inequity.

It is a professional and personal goal to always practice engineering in a way that is compassionate, inclusive, and accessible, and that considers all aspects of patient identity when designing a device or system. I would like to thank my technical project partners: Megan Talarek and Esha Tulsian, my mentors and advisors: Dr. William Guilford, Dr. Brian Helmke, Dr. Kent Wayland, and Professor Adarsh Ramakrishnan, and my peers: Piper O'Donnell, Raina Mourad, and Emily Boland for helping me discover a passion for engineering design through the lens of equity and justice.

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By
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On my honor as a University Student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments.

Signature ABoitnott MTalarek Date 5/11/22
Abigail Boitnott, Megan Talarek

Approved _____ Date May 11, 2022
William Guilford, Department of Biomedical Engineering

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Abstract

Ideally, clinicians will be able to accurately distinguish between Otitis Media with Effusion (OME) and Acute Otitis Media (AOM), which requires antibiotic treatment. However, it is currently difficult for clinicians to differentiate between them. Specifically, diagnoses by general practitioners are unreliable about 27% of the time due to unoptimized diagnosis techniques and subjective diagnosis criteria[1]. Additionally, ~2.2 million cases of AOM occur annually among children, amounting to a direct cost of $4 billion each year due to unnecessary removal of adenoids or tonsils, antibiotic over-prescription, and hearing loss[2]. AOM is an infection of the middle ear fluid behind the tympanic membrane (TM). OME is a condition commonly confused with AOM in which there is fluid present behind the TM that is not infected with bacterias that cause AOM[3]. The high rate of misdiagnosis between AOM and OME can be attributed to current clinical diagnostic methods of visual observation and tympanometry. The goal of this project is to detect infection indirectly by measuring NADPH concentration as an indicator of neutrophil accumulation in response to infection, and therefore develop a proof of concept detection method to be further adapted for implementation in an otoscopic medical device. It resulted in detection of NADPH down to a concentration of ~0.01mM, and a discovery that the relationship between the concentration of NADPH and its fluorescence voltage output is logarithmic. Future development of a device that employs this diagnostic method will help reduce the 27% rate of misdiagnosis, and therefore decrease the annual $4 billion cost associated with AOM. Improved diagnostic accuracy will also increase patient and parent comfort and confidence in their physician.

Introduction

Otitis Media and NADPH

Acute Otitis Media (AOM) is an infection of the middle ear fluid behind the tympanic membrane (TM). It accumulates ~2.2 million cases annually in pediatric patients, and is diagnosed in 80%-90% of children before school age (~5yo)[4]. It is a painful condition that, if left untreated, can lead to development of meningitis, permanent hearing loss, and other more serious conditions[5]. Otitis Media with Effusion (OME) is a condition commonly confused with AOM in which there is fluid present behind the TM, but it is not infected with *Haemophilus influenzae, Moraxella catarrhalis,* or *Streptococcus pneumoniae* - bacterias that cause AOM. On average, AOM is misdiagnosed about 27% of the time by general practitioners and primary care providers, however, among otolaryngologists, misdiagnosis only occurs about 10% of the time[1]. Misdiagnosis of inflammatory ear conditions leads to over- and/or underprescription of antibiotics; another problem that has consumed countless resources for the medical community. In the western world, AOM accounts for the most antibiotics prescriptions[6]. Unstable doctor-patient relationships, pressure from patients, and physician's lack of confidence contribute to increased use of antibiotics. Overprescription of antibiotics can lead to a patient developing resistant bacteria and later make it difficult to treat if AOM reoccurs.

The high rate of misdiagnosis between AOM and OME can be attributed to the method of clinical assessment used to determine presence or absence of infected effusion (fluid) in the middle ear space. In contemporary practice, clinicians use one or a combination of multiple methods for analysis of the TM and contents of the middle ear canal. The provider will use an otoscope either with or without a pneumatic attachment to observe the visual properties of the TM, specifically looking for signs of inflammation such as redness, swelling, presence of a "pus drum" (obvious infected purulence behind the TM), and vasculature (hyperemia). If the provider is using a pneumatic otoscope, they will completely occlude the canal creating a vacuum, and will then use the pneumatic attachment to pump a puff of air into the space while looking through the otoscope to assess rigidity of the TM. This technique assumes that an infected

ear will have little to no tympanic movement due to the pressure exerted by fluid present behind the TM. This technique does not assess the actual contents of the middle ear fluid in any way. A similar technique, tympanometry, is also commonly used when conducting a diagnostic ear exam for Otitis Media. To diagnose with tympanometry, clinicians evaluate TM response to changes in outer ear pressure using a tympanometer which generates a compliance response curve for the patient's TM called a tympanogram. A mostly flat curve indicates little to no movement of the TM, and suggests that there is fluid exerting positive pressure behind the TM in the middle ear, thereby hindering its compliance[7]. This technique also does not assess the actual contents of middle ear effusion. While these diagnostic methods are legitimate for analysis of the elasticity and appearance of the TM, they do not assess the presence or absence of infected fluid in the middle ear space, instead relying on inferences that are only likely to be correct when made by seasoned otolaryngologists. In order to analyze the characteristics of middle ear effusion, a diagnostic method is proposed to assess patient infection status by detecting nicotinamide adenine dinucleotide phosphate (NADPH) as a surrogate measure of neutrophils in the middle ear, thereby indicating if infected fluid is in the space and enabling a physician to make a correct diagnosis.

NADPH, the reduced form of NADP, is a cofactor that donates electrons and hydrogens to reactions catalyzed by some enzymes. It is produced from the pentose phosphate pathway and oxidizes to form[8] NADP+. A primary function of NADPH is the donation of electrons to reduce oxidized compounds in redox reactions such as reductive biosynthesis, detoxification, oxidative defense, and reactive oxygen species (ROS) generation[9,10]. It is also commonly involved in anabolic pathways to create large molecules[9].

When infection is detected by the body in the middle ear space, an innate immune response takes place; neutrophils are considered the first line of this host immune response against invading pathogens[11]. They are primarily attracted to sites of inflammation by chemotactic factors such as C5a, a complement-activated chemoattractant[12,13]. In AOM, neutrophils are also recruited by IL-17A proteins specifically responding to *Streptococcus pneumoniae*[14]. Neutrophils have a high concentration of NADPH, the substrate of the oxidase responsible for the "respiratory burst" of innate immune response release of ROS in activated neutrophils[15–18,41] . When neutrophils are recruited and then activated by pro-inflammatory stimuli, they use NADPH oxidation to donate electrons to make superoxide. Neutrophil activation causes an emergency response to foreign pathogens in the system, and therefore NADPH concentrations can be used as an indicator for infection. To elaborate, NADPH oxidase (NOX) is a membrane-bound enzyme that faces the extracellular space, and is dormant until activated by stimuli (such as bacteria). Once activated, NOX is used as a reaction catalyst to transfer electrons from NADPH to generate ROS. NADPH's role in neutrophil immune response begins with the stimulation the neutrophil by bacterial detection. This leads to NOX2 activation which then catalyzes oxygen reduction with 1 electron sent from NADPH resulting in production of superoxide. Neutrophils then engulf bacteria in phagosomes and release superoxide into the phagosomes through activated NOX2. The superoxide dismutates to hydrogen peroxide which is then used by myeloperoxidase (MPO) to make additional ROS and hypochlorous acid (HOCl) to kill bacteria. NADPH is also integral to the formation of neutrophil extracellular traps (NETs), as ROS generated by NOX2 is used to stimulated MPO which then mediates activation of neutrophil elastase (NE), a product that drives chromatin decondensation by processing histones. This sparks the release of NETs that then capture pathogens, degrade bacterial toxic factors, and kill bacteria[15–19].

Fluorescence

This project relies on autofluorescence of NADPH as a means to detect neutrophil content in middle ear effusion. When light of a certain wavelength is absorbed by a solution or tissue, endogenous fluorophores are excited and emit light of a longer wavelength[20]. Molecules have unique fluorescence spectra based on their electron distribution in the ground state[21]. When a susceptible molecule is excited

with a specific wavelength of light their energy state increases to a higher level spurred by the energy absorbed from the light. After excitation, the molecule falls back down to lower energy states in a process known as vibrational relaxation. This process occurs at a slower rate than excitation, and allows the molecule to approach the energy level at which it will fluoresce. As the molecule continues to fall in energy level, it emits a photon at a wavelength unique to its composition. Once it has emitted, the molecule returns to ground state, again at a slower rate than previous steps of the fluorescence process[22]. NADPH specifically is excited with ~360nm wavelength light, resulting in fluorescent emission at ~450nm.

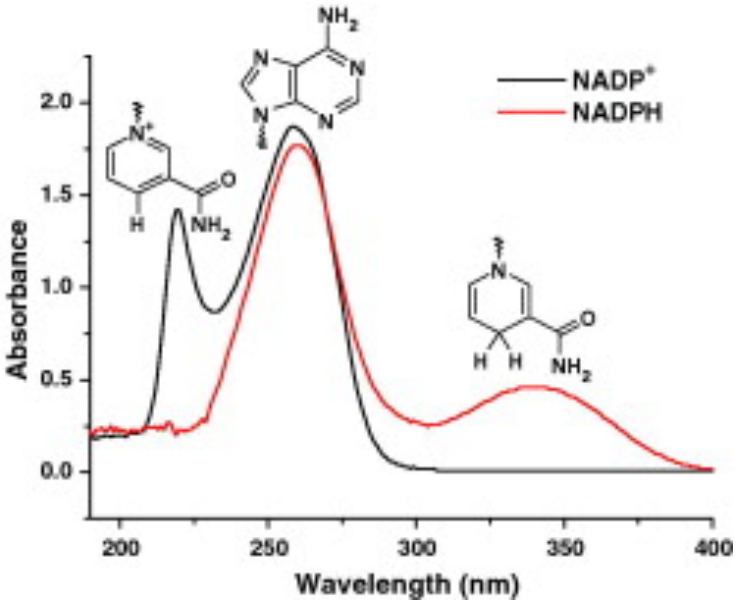


Figure 1: NADPH Fluorescence Spectrum[23]

Prior Art

With regards to previous innovation for diagnosis of OM, there are many existing technologies that attempt to evaluate patients' middle ear status. The most commonly used diagnostic tools are visible light otomicroscopy and pneumatic otoscopy (tympanometry), however these have contributed to the 27% rate of misdiagnosis for OM, as they do not assess the specific molecular contents of effusion, require physician training and practice for accurate usage, and possess limitations in their diagnostic certainty[1]. A number of techniques have been developed to improve diagnosis; they can be subdivided based on their method/mechanism of action into *imaging technologies* and *bioengineering tools*[24].

Recent advances in middle ear imaging modalities use acoustics, radiology, visible light techniques, and near infrared techniques to improve visualization on the middle ear. Acoustic techniques include high frequency ultrasound (HFUS), spectral gradient acoustic reflectometry (SGAR), and transmastoid ultrasound[24]. While HFUS allows for visualization of the middle ear anatomy, it has not been tested *in vivo*, and may not translate through thicker soft tissue. HFUS also only analyzes anatomy, and not the molecule contents of effusion[25]. Similarly, SGAR uses sonar waves to assess presence of effusion, however it can not detect progression or clearance of effusion nor can it differentiate if effusion is infected[26]. Finally, transmastoid ultrasound detects effusion via the mastoid air system, but can not determine if effusion is infected[27].

To continue, the primary radiology-based technique preceding the project is synchrotron radiation phase-contrast imaging (SR-PCI). This method involves phase-shifted beam interference to visualize middle ear anatomy with improved contrast for soft tissue compared to its competitors (absorption contrast micro-CT), however, it does not image for effusion specifically, and presents standard health risks associated with radiative imaging modalities[28]. The project addresses the limitations of these technologies by evaluating the molecular NADPH content of effusion as opposed to simply assessing middle ear anatomy or the mere presence/absence of effusion. The device eventually developed from the project will

also have low health risks associated with its usage as the patient will be exposed to 360nm light for a few seconds at most for fluorescence data to be collected and converted to a readable output.

Visible light and near-infrared techniques include multicolor reflectance imaging, narrow band imaging (NBI), anti-confocal middle ear assessment, and optical coherence tomography (OCT)[24]. Multicolor reflectance imaging uses RGB narrow-band reflectance imaging to visualize middle ear tissue structure, however it is very susceptible to patient movement and image distortion, and does not evaluate effusion contents[29]. Similarly, NBI uses visible light to penetrate tissue at varying depths to indicate hypervascular areas and can identify diseased tissue, however it is a poor diagnostic for AOM because diseased tissue does not necessarily mean there is infected effusion present[30]. Anti-confocal middle ear assessment uses near infrared spectroscopy to analyze inflammatory blood content of middle ear, however it does not precisely evaluate effusion, and has not been tested *in vivo*[31]. In similar fashion, OCT uses near infrared spectroscopy to evaluate TM thickness and displacement as an indication of infected effusion. This technique has had notable success in visualization of middle ear biofilm structure and combined assessment of TM thickness, however it can not image through the ossicles, is uncomfortable for patients as it requires an ear canal seal for data collection, and is inefficient with a long image processing time[32–34]. The project builds on these light-based techniques and addresses their limitations by specifically evaluating the molecular NADPH content of effusion, and the eventual device being minimally invasive and comfortable for the patient to endure.

Bioengineering tools for diagnosis of OM use computerized software to develop an AI training algorithm for diagnosis of OM based on otoscopic images of the TM. The software uses an image database of over 200 TM images that have been diagnosed as AOM or OME, and virtually segments the TM into regions for evaluation of color and shape. The technique claims to have a diagnostic accuracy of >90%, however, it is difficult to be sure that the training images have been given the correct label diagnoses, as they were not confirmed with physical extraction and assessment of effusion contents[35]. This technique is also used for detection of ventilation tubes in the TM, however this function is excessive, as tubes are visible using normal otoscopic evaluation[36]. Additionally, because it involves the use of remote software, bioengineering techniques are susceptible to error due to failed network connection and algorithm errors, and are only as good as the image database used to train them. Overall, bioengineering tools depend on images that may already be misdiagnosed and therefore labeled incorrectly, and pose additional challenges for troubleshooting based on their remote nature. The project addresses these limitations by making a primary diagnosis based on the molecular NADPH content of effusion, and is not dependent on a separate collection of data or images for analysis. It also does not require the use of complex software and AI algorithms to function correctly, and can therefore be easily assessed for sources of failure if it is operating incorrectly.

Materials & Methods

Instrument Design

In order to detect infection indirectly by measuring NADPH concentration as an indicator of neutrophil accumulation, the project team created a proof of concept instrument to be used in experimental trials. Light from a ~360nm LED illuminator (M365L3, ThorLabs) is collimated and passes through the first lens (125mm focal length) of a beam reducer. The light continues to the dichroic mirror (#34-725, Edmund Optics) where it is reflected through another lens (25mm focal length) into the NADPH-concentrated solution sample, contained in a cuvette in a custom-designed holder. The light emitted from the excited sample (~460nm) is directed back through the previous lens and dichroic mirror and then through another lens (25mm focal length). An emission filter (452nm, #86-351, Edmund Optics) is secured

flush to the detecting face of a photomultiplier tube detector (PMT) (Hamamatsu H10721-110, Edmund Optics) to reduce background light.

The PMT is used to detect the emitted ~450nm NADPH fluorescence, but has current as an output. Therefore, the project team designed and built a transimpedance amplifier circuit to convert current to voltage allowing us to measure the fluorescent output in millivolts (mV) using a multimeter (Figure 2). The optical component of the instrument was contained within a box with a blackened interior during experimental trials to reduce background light, and its completed form is shown in Figure 3. In experiments, the project team loaded NADPH solutions of varying concentrations into an empty cuvette, and then enclosed the experiment in the dark box before beginning each trial. The emitted signal was detected by the PMT and then converted to a voltage output by the transimpedance amplifier that was recorded for later data analysis.

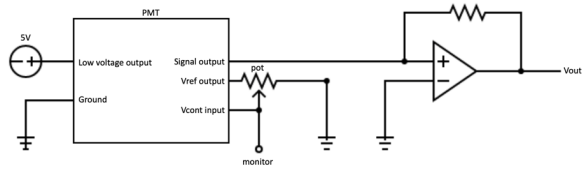


Figure 2A: Electrical diagram.

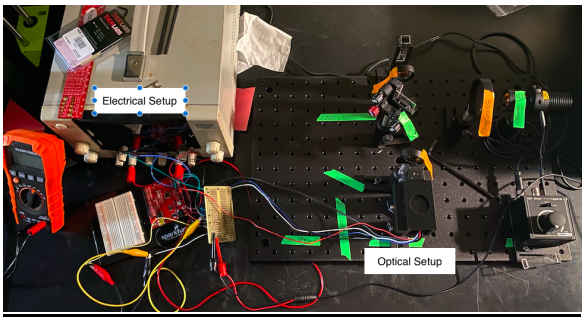


Figure 2B: Instrument overview image.

Figure 2: Instrument Electrical Component

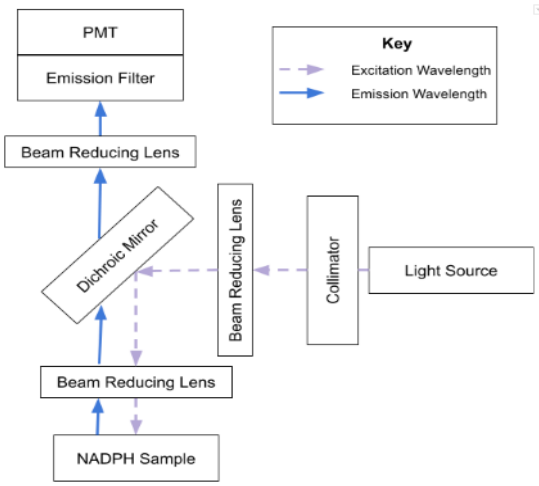


Figure 3: Instrument Optical Component Diagram

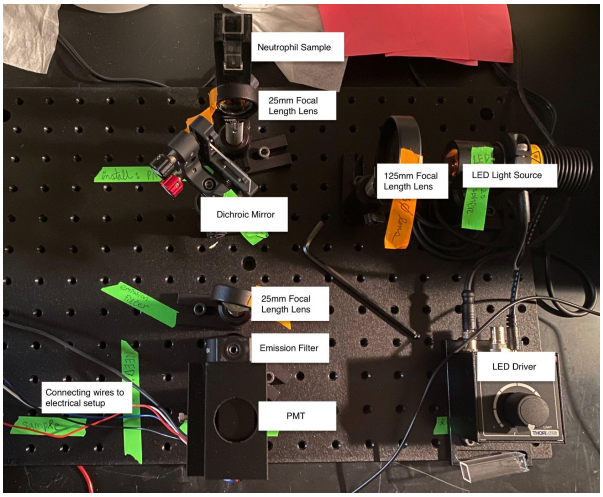


Figure 4: Instrument Optical Component Image

Pre-NADPH Integration Experiment

For the first round of experimentation, the project team conducted trials with an empty cuvette to determine the background noise and level of gain saturation based on the LED driver setting and the transimpedance amplifier adjustable gain level. The project team recorded the transimpedance amplifier output voltage as a function of LED light output level over a wide range of gain values. These data were

recorded and analyzed to determine the ideal parameters for gain and LED setting. In Figure 5, the data is plotted as output voltage (mV) versus light output level over four different gain values. The project team analyzed this figure to find the settings where the PMT is sensitive to light, indicated by a visible range in y-values, while ensuring the PMT is not saturated, indicated by a high output voltage plateau in the y-values. Based on these requirements, the project team knew that the 0.936V gain value was not appropriate since it is saturating the PMT while the 0.320V and 0.006V gain values were not appropriate since the PMT is not sensitive enough at this level. The project team determined that a gain of 0.611V and a light output level of 3 were the ideal settings for the PMT to be both sensitive and not saturated.

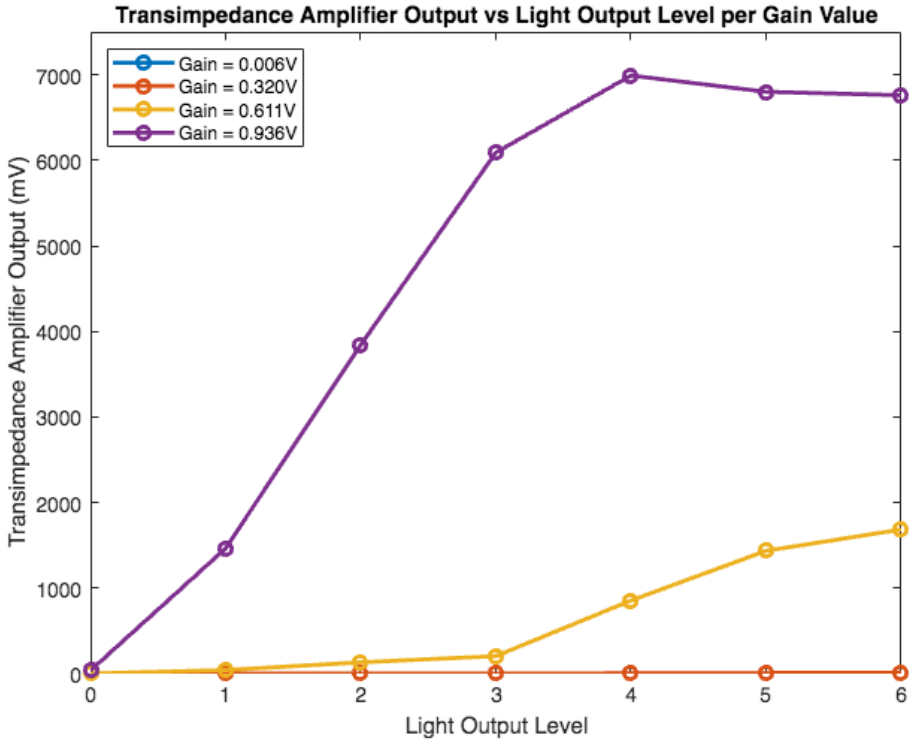


Figure 5: Output Voltage (mV) vs Light Output Level per Gain Value (V)
This plot shows the voltage output recorded across various LED Driver Light Output Levels for various gain values. Using this plot, the project team was able to determine which Gain value and Light Output Level to use for future experimental trials to ensure the setup is both sensitive (wide range of voltage output values) while not saturating the PMT with light (maximum voltage output of ~7000mV).

NADPH Integration Experiments

In order to determine the target concentration for NADPH in solution, the project team reviewed the literature to estimate how much NADPH is present in infected effusion. The total concentration of NADP in hyman normal lymphocytes was found to be 14.5±3.9 pmol/10 million cells[37]. This concentration was divided by the volume of one neutrophil to yield NADPH concentration of a neutrophil[38]: $\frac{14.5*10^{-9}mmol}{10{,}000{,}000\ cells} * \frac{1\ neutrophil}{500*10^{-15}\ L} = 0.0029mM\ NADPH$. Given that there are $2.11*10^6 \pm 7.91*10^5$ neutrophils in 1 ml of purulent (infected) effusion[39], the estimated concentration for NADPH in a suspension of neutrophils adjusting for the volume fraction of cells is approximately: $\frac{500*10^{-15}L*2110000\ neutrophils}{0.001L} = 3.06 * 10^{-6}mM.$ Once the target concentration was found, 2 stock solutions of NADPH were created with concentrations of ~30mM and ~15mM respectively. These concentrations were tested to determine if the instrument can detect NADPH at high levels of concentration. The transimpedance amplifier output voltage was measured

(mV) for two experimental controls (empty cuvette and a cuvette filled with deionized water) and the two NADPH solutions (30mM and 15mM). When comparing the voltage output of the NADPH trials to the control trials in Figure 6, a large increase in output voltage was found after introducing the NADPH indicating that the instrument is detecting NADPH at high concentrations. It was also determined that the output voltage measured for both the 30mM and 15mM solutions were approximately the same, leading to the conclusion that the PMT is saturated at this high level of concentration and the stock solutions must be diluted repeatedly before seeing a relevant change in light detection.

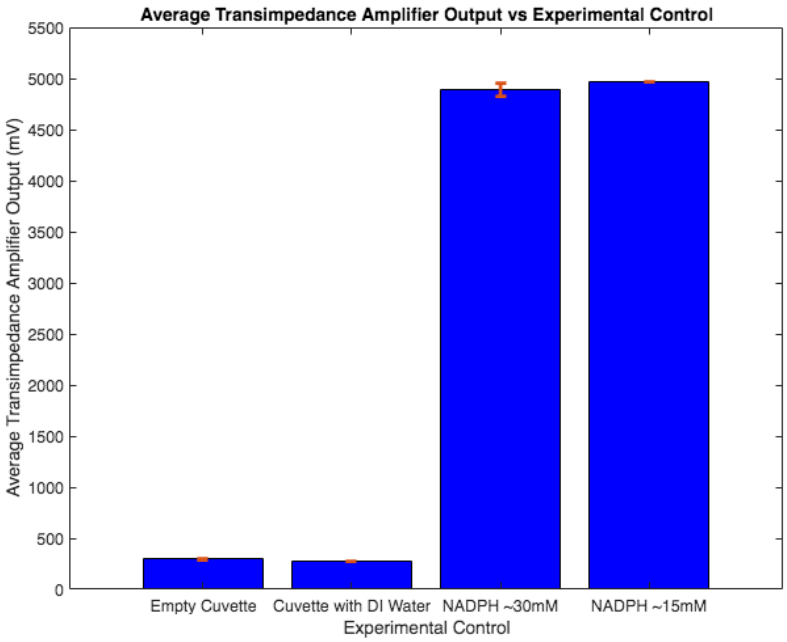


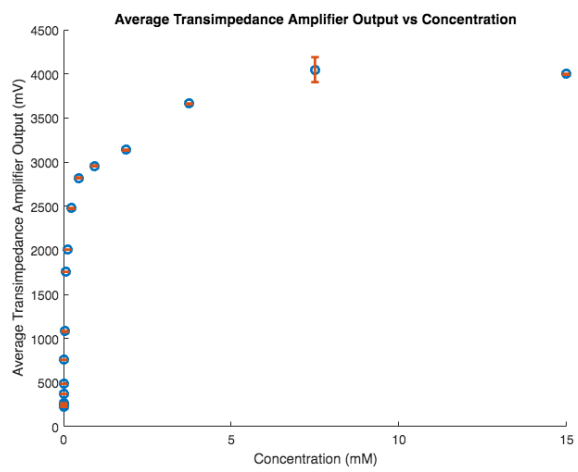
Figure 6: Average Output Voltage (mV) per Experimental Control
To determine if the optical setup is functioning properly and can detect NADPH, the transimpedance amplifier output voltage was measured (mV) detected for an empty cuvette, a cuvette filled with DI water, a NADPH solution of concentration ~30mM, and a diluted NADPH solution of concentration ~15mM. The spike in voltage output when comparing the control values to the NADPH values shows that the optical setup is functioning correctly by fluorescing and detecting the NADPH solution.

After determining that the instrument design can detect NADPH at high concentrations, the team wanted to find the relationship between NADPH concentration and the transimpedance amplifier output voltage. Based on the last experiment of NADPH integration, it is known that the PMT is saturated at values above 15mM so experimentation began with the 15mM stock solution and apply 2-fold dilutions to the stock solution until the instrument can no longer detect the NADPH in solution. The first experimental trial started with analysis of the 15mM stock solution and then progressed to 2-fold serial dilutions of the NADPH solution in a cuvette. At each concentration, the gain was recorded to ensure that it was ~0.611, the output voltage was recorded before turning on the LED, for a measured noise level to normalize the data, and when the LED was turned on, producing five trials at each concentration level. The team ensured that the LED was only on for a short period of time since the NADPH can photobleach which could lead to a lower concentration over time[40]. Sample dilutions and recordings of the voltage output were recorded until the output plateaued. The point was assumed to be the point at which the instrument saturated with background noise with no NADPH being detected. Lastly, these values were measured for an empty cuvette and a cuvette filled with deionized water, to act as a control. For the second experimental trial, the experimental method was adjusted to only include a decreased range of concentration values, and to make the NADPH solutions by direct dilution from the stock rather than serial dilution. Then the same measurements were recorded over a reduced range of concentrations and for the two controls.

Results

For the analysis of data, there were two main goals: first, to determine the relationship between the transimpedance amplifier output voltage and NADPH concentration, and second, to gain information on the baseline noise level of the instrument. First, the team plotted the raw data with the output voltage on the y-axis and the NADPH concentration on the x-axis (Figure 7A). The team noticed that the shape of the curve appeared to be a logarithmic relationship between the variables and decided to apply a log-transform on the x-axis data (Figure 7B). By applying the log-transform, the plot turned into a more linear line that was determined would be easier to analyze. The team started by performing a linear regression on the linear portion of the plot and found that the relationship is in fact logarithmic. To confirm this is a proper fit, the root mean square error (RMSE) was calculated for the linear regression to be ~136.91mV. By normalizing this RMSE value to the dataset by using the equation *Normalized RMSE = RMSE/(maximum data point - minimum data point)*, it can be concluded the linear regression is a good fit because the adjusted RMSE value was ~0.038 on a scale from 0 to 1. Next, it was determined which data points show a statistically significant increase in output voltage when compared to the control of a cuvette filled with deionized water by performing an independent two sample t-test for each data point. It was found that the data point with the first significant increase in output voltage was at a concentration of ~0.00183mM. Based on this information, it was determined that the baseline noise level was the average of the output voltages of concentrations lower than ~0.00183mM, which was ~240.39mV. Using the baseline noise level and the linear regression equation, the team was able to determine the noise equivalent concentration to be ~0.004mM by plugging the baseline noise level (*~240.39mV*) into the linear regression equation (*y=1172.0*log(x)+3031.2*) and solving for the concentration, *x*. The noise equivalent concentration tells us the limit of NADPH detection.

For the second experimental trial analysis, the same approach was followed with a few modifications to adjust for the change in concentration range. First, the raw data (Figure 8A) and the log-transformed data (Figure 8B) were plotted, then the linear region was analyzed with a linear regression. The team noticed that the two highest concentration points had a lot of noise, indicated by the large error bars, and that the PMT was near saturation. Excluding these two points, it was found that the relationship between the output voltage and NADPH concentration is logarithmic (*y=798.3*log(x)+1725.5*) and calculated a RMSE value of 90.12mV. The normalized RMSE value was calculated to be 0.043 on a scale from 0 to 1, indicating that both datasets and linear regressions are approximately equally fitted. . Lastly, the baseline noise level was calculated to be ~178.5mV and the noise equivalent concentration to be ~0.0115mM.



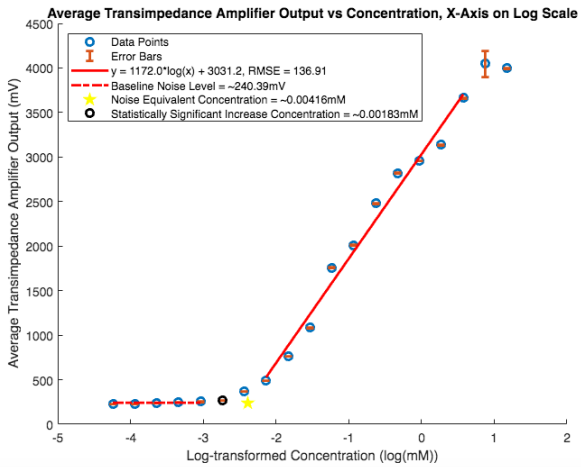
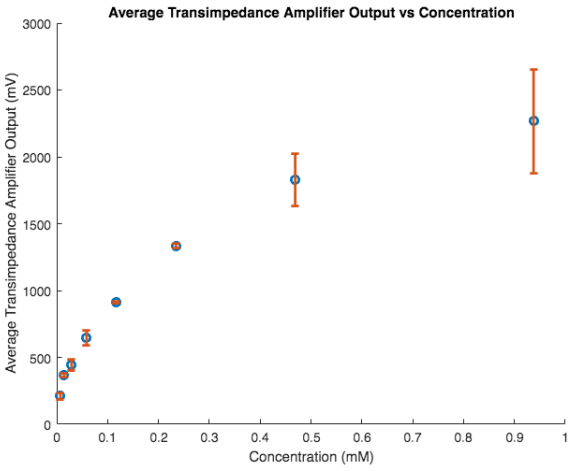


Figure 7A: Output Voltage (mV) vs Concentration (mM) **Figure 7B:** Output Voltage (mV) vs Log-Transformed Concentration (log(mM))

Figure 7: Trial #1, Average Transimpedance Amplifier Output Voltage (mV) vs Concentration (mM)

To determine the relationship between the Transimpedance Amplifier Output Voltage and the NADPH concentration as well as the baseline noise level of the instrument design, the output voltage (mV) was measured across a range of concentration values. The raw data of output voltage versus concentration is plotted in Figure 7A and the log-transformed data of output voltage versus the log of concentration is plotted in Figure 7B.



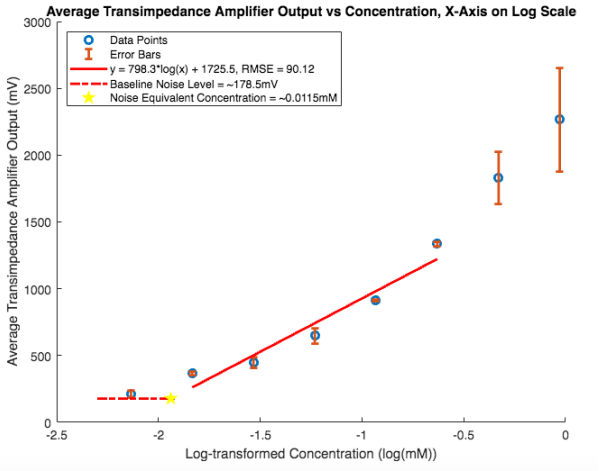


Figure 8A: Output Voltage (mV) vs Concentration (mM) **Figure 8B:** Output Voltage (mV) vs Log-Transformed Concentration (log(mM))

Figure 8: Trial #2, Average Transimpedance Amplifier Output Voltage (mV) vs Concentration (mM)

To determine the relationship between the Transimpedance Amplifier Output Voltage and the NADPH concentration as well as the baseline noise level of the instrument design, the output voltage (mV) was measured across a range of concentration values. The raw data of output voltage versus concentration is plotted in Figure 8A and the log-transformed data of output voltage versus the log of concentration is plotted in Figure 8B.

Discussion

Overview

The goal of this project was to develop a proof of concept method for detection of AOM infection by measuring NADPH concentration as an indicator of neutrophil accumulation. This new diagnostic method will help decrease the ~27% rate of AOM misdiagnosis for general practitioners and primary care physicians, and will therefore reduce the annual $4 billion cost associated with unnecessary antibiotic prescription, surgical procedures, and patient hearing loss. Above all else, this method of detection will

help to increase patient and parent comfort in the clinic, and confidence in their physician, therefore creating a more beneficial clinical experience with reliable diagnosis. The major findings are successful proof of concept in the fluorescence-based detection of NADPH in solution down to a concentration of ~0.01mM, and the determination of a logarithmic relationship between NADPH concentration and fluorescence voltage output.

Impact

The otoscopic device eventually developed from the team's method of detection will have a significant impact on the differential diagnosis of AOM and OME, and will help ensure that patients receive appropriate treatment once their condition has been accurately diagnosed. Improvement from the 27% misdiagnosis rate will help reduce the $4 billion annual cost associated with AOM treatment methods such as antibiotic prescription, surgical removal of adenoids or tonsils, and eventual loss of hearing with recurrence. Knowing that they will receive an accurate diagnosis, pediatric patients and their parents will feel more comfortable in clinical settings, and more confident in their physician to provide them with accurate diagnosis. Patients will also experience more physical comfort by benefitting from appropriate treatment methods, as opposed to not receiving necessary treatment based on incorrect diagnosis that creates more potential for painful recurrence of AOM.

Marketability

The potential market for the eventual device derived from this project is very promising. The Otoscopes Global Market is projected to reach $198.1 million by 2026. Additionally, the device would be marketable in a variety of clinical settings as it could be adapted not only for use by primary care physicians and general practitioners, but also for specialty use in otolaryngology clinics. The method of detection itself also holds potential for adaptation to diagnose infections in other areas of the body such as through the nose and mouth, and an adjustment of the specific excitation wavelength and specific emission wavelength for detection could allow this method to be applied to detection of other molecular compounds responding to infections outside of AOM, or other types of ear infections such as Otitis Externa. Given the fact that >80% of children experience an ear infection before the age of five[4], and that it is a condition that is very painful and can lead to later complications, most pediatric patients and their parents would likely be very interested in a more reliable method for detection and accurate diagnosis of infection.

Conclusion

Completion of this project has resulted in successful proof of concept for detection of AOM infection indirectly by measuring NADPH concentration as an indicator of neutrophil accumulation down to concentration of ~0.01mM. While this concentration is still much greater than the target concentration of ~0.003uM, the simple detection of NADPH through fluorescent emission is a major accomplishment to the goals of this project. This project has also resulted in the determination of a logarithmic relationship between the concentration of NADPH in solution and fluorescence voltage output picked up by the PMT, an important finding as it was previously unknown. These findings will be helpful to future iterations of the project, as they will be used to make further improvements to the detection capabilities of the instrument.

The primary limit on the sensitivity of this instrument is the background signal from the excitation light. In the future, the team would like the instrument to be improved for better reduction of background signal. This could be accomplished by creating a structure to enclose the optical pathway since much of the noise is from scattered excitation light. The project should also continue on to the design and implementation of a phantom model to mimic the TM and middle ear space that would be the environment for the diagnostic instrument. This will also raise the new challenge of determining the level of penetration of light through the TM itself, and if the detector will be able to pick up on the NADPH emission light,

which will likely be at a very low intensity level. Finally, the project should be improved by repeating the same methods and trials as have been done this year, but with a neutrophil-concentrated sample instead of NADPH as a surrogate measure. Using real neutrophils will better mimic the conditions of infected middle ear effusion that has garnered an immune response. By making the necessary improvements, and continuing to optimize the experimental parameters and technical components of the detection instrument, this project can develop into a diagnostic device with potential to save billions of dollars and change Otitis Media diagnosis, and patients' experiences with it, for the better.

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Supplementary Information

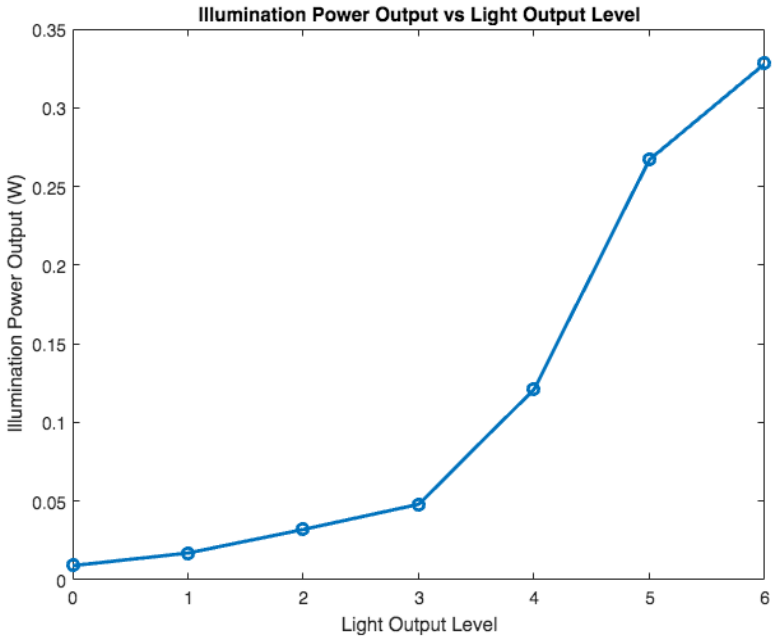

Figure S1: Illumination Power Output (W) vs Light Output Level
This plot shows the Illumination Power Output recorded across various LED Driver Light Output Levels. Using this plot, the project team was able to determine the relationship between the level set on the LED driver and the amount of light actually emitted to ensure the LED driver was working properly.

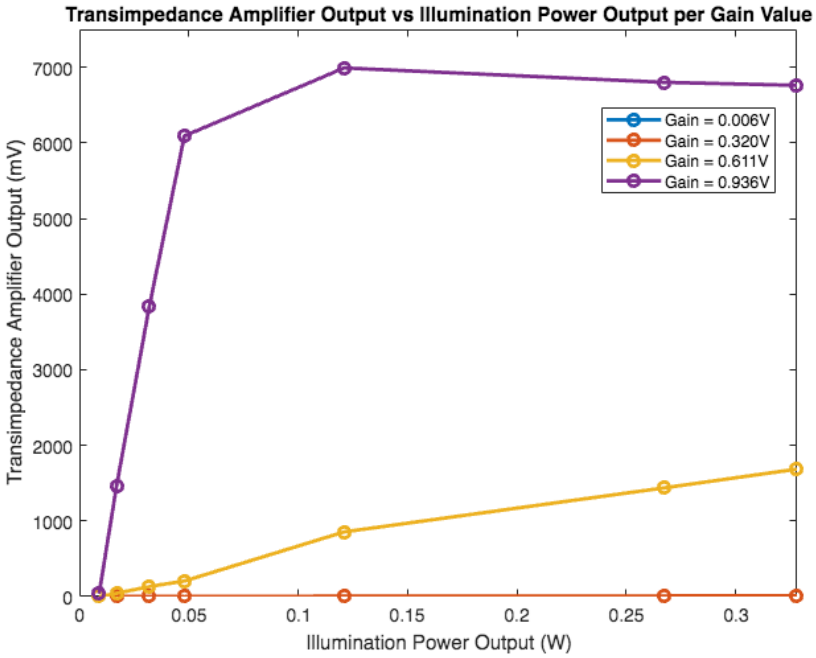

Figure S2: Output Voltage (mV) vs Illumination Power Output (W) per Gain Value (V)
By combining the information in Figure 5 and Figure S1, a plot of Output Voltage (mV) versus Illumination Power Output (W) was created to ensure the proper gain value and light output level was selected for experimentation.

AN ANALYSIS OF RACIAL BIAS IN PULSE OXIMETRY, AND ITS IMPACT ON PATIENTS WITH MARGINALIZED RACIAL IDENTITIES DURING THE COVID-19 PANDEMIC

A Research Paper

In STS 4600

Presented to

The Faculty of the

School of Engineering and Applied Science

University of Virginia

In Partial Fulfillment of the Requirements for the Degree

Bachelor of Science in Biomedical Engineering

By

Abigail Boitnott

April 18, 2022

On my honor as a University student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments.

Signed:  Date: 5/13/22

Approved:  Date: May 12, 2022

Kent Wayland, Department of Engineering & Society

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Signed: _____ Date: _____

Approved: _____Date:_____

Kent Wayland, Lecturer, Department of Engineering & Society

Introduction: Biomedical engineers (BMEs) are responsible for bridging the gap between engineering and medicine to enhance health care ("BMES," n.d.). This purpose is one that reflects the magnitude of biomedical engineering and its impact on health-based quality of life in modern society. The field of medicine as a whole places great emphasis on fair and just treatment supported by scientific research and administered to the best abilities of physicians and healthcare professionals, as is evident in different iterations of the Hippocratic Oath (Hulkower). Additionally, the American Medical Association (AMA) Code of Ethics includes a statement that physicians shall seek changes to circumstances that are contrary to the best interests of the patient/s ("Various Physicians Oaths," n.d.). More specifically, the BME Code of Ethics states that BMEs must "use their knowledge, skills, and abilities to enhance the safety, health, and welfare of the public… [and] regard responsibility toward and rights and rights of patients… [and] comply fully with legal, ethical, institutional, governmental, and other applicable research guidelines respecting the rights of… [the] general public" ("ECC," n.d.). Therefore, just as it is the responsibility of medical professionals to provide excellent standards of care for all patients, it is the responsibility of BMEs, as members of the medical field, to design and develop technologies and devices that embody these standards, and eliminate or mitigate racial disparities and biases in their design's technological functions.

A variety of commonly-used medical devices and health standards harbor racial biases, and therefore create a limitation of medical practice for provision of a consistent standard of care for patients with diverse ethnic and racial identities. These disparities are often products of normalized deviance. Normalized deviance is a problem framework that revolves around the development of tolerance for lower-than quality standards created by exposure to these lowered

standards over time. This framework can be applied when investigating inequities and biases associated with medical devices and standards of medical care in the United States. These disparities do not allow for compliance with medical standards and codes of ethics, and therefore they must be mitigated by equitable and inclusive engineering design solutions. The vast majority of US medical technologies and standards are designed for and tested on populations that are overwhelmingly white, and are not representative of the diverse population of US society. This leads to inaccurate device functionality and inconsistent medical treatment when applied to patients who identify as Black, Indigenous, and/or People of Color (BIPOC) and therefore cyclically contributes to the normalized deviance of systemic racism in the US medical system.

The nature of racial disparity in medical devices can be represented by the case of pulse oximetry and its impact on COVID-19 health equity for BIPOC patients. Health equity is defined by the CDC as: "when all members of society enjoy a fair and just opportunity to be as healthy as possible" (CDC, "Health Equity"). It is considered a standard of public health, and has gained recent attention for its absence in COVID-19 pandemic response. BIPOC patients have been identified as at higher risk for getting sick and dying from COVID-19, and factors such as limited access to healthcare, underlying medical conditions, and education, income, and wealth gaps have been identified as potential contributors to this problem (CDC, "Community, Work, and School"). Analysis of this thesis topic will examine racial bias of pulse oximetry as a potential additional contributing factor to COVID-19 health inequity.

Research Question and Methods: In an attempt to evaluate the thesis topic, literary analysis was performed with the research question of: What is the significance of disparity in pulse oximetry and how might it contribute to COVID-10 health inequity for BIPOC patients?

Literature sources include peer-reviewed scholarly articles, news and social media sources, blogs, podcasts, and government agencies/institutions. Additional sources were explored to provide a more holistic qualitative analysis of the societal contribution to the problem, the public response to it, and the importance for its mitigation. Additional quantitative data was collected from literature to incorporate numerical representations of the magnitude and severity of the problem. A potential solution for mitigation was also examined in order to understand current scientific and engineering efforts addressing the problem. A holistic review and comparison of the data resulted in both quantitative and qualitative representations of the impacts of pulse oximetry-based medical racial disparities on BIPOC living in the US, and its potential contribution to BIPOC COVID-19 health inequity.

Discussion: Throughout US history, the medical field has suffered the effects of systemic racism, defined as "the complex interaction of culture, policy and institutions that holds in place outcomes we see in our lives… [it] is naming the process of white supremacy" ("Systemic Racism: What Does It Mean and How Can You Help Dismantle It," n.d.). Unacceptable standards of care for BIPOC patients have existed since the country's founding, causing loss of life for these marginalized populations. Contributing factors to medical racism in the US are the societal atmosphere created by historic racial inferiority theories and stereotypes, historical enslavement of Black people, and biased educational processes. These have ultimately contributed to a trend of scientific and medical abuse towards marginalized racial groups (Byrd & Clayton, 2001).

Medical Bias against BIPOC

This trend has created a positive feedback loop of marginalized people developing mistrust in the medical system, resulting in low BIPOC participation as testing populations for

clinical research, hindering the system's improvement, thereby leading to more distrust. This vicious cycle has been strengthened by historic injustices such as the Tuskegee Syphilis Study (1932-1972), forced sterilization of >60,000 people, most of them belonging to racial minority groups and/or suffering disabilities (1880s-late 1900s), and landmark cases of racially disparate medical care (Freimuth et al., 2000; Stern; Gamble, 1997). In order to standardize medical care for all, and to restore BIPOC patients' trust in the medical system, these disparities must be examined and mitigated with new technology and medical practices, created and implemented through BME and clinician collaboration.

A primary example of the negative impacts of cyclical systemic racism in the network of US medicine is the health inequity associated with virus severity and mortality rates for BIPOC patients due to COVID-19. A study of such inequity conducted on 77 Chicago Community Areas found that up to 62.8% of COVID-19 related deaths in a ~4 month long period were of Black patients when they make up only ~30% of the Chicago population (Kim; Wendy Bostwick, 2020; "Chicago, Illinois Population 2022 (Demographics, Maps, Graphs)," n.d.). This disproportionate mortality rate was contributed by researchers to social vulnerability and other risk factors such as uneven distribution of resources, social exclusion, poverty, and discrimination. Other statistical analyses have found that BIPOC patients are 0.7-1.5x more likely to test positive for COVID-19, 0.8-3.1x more likely to be hospitalized for COVID-19, and 0.8-2.7x more likely to die of COVID-19 than white, non-Hispanic patients (CDC, "Cases, Data, and Surveillance", 2020). The disparities in these specific data have been attributed to socioeconomic status, access to health care, and exposure to the virus related to occupation. While there is no doubt that there are a myriad of underlying health, socioeconomic, and discrimination-based factors that contribute to the massive health inequity associate with the

COVID-19 pandemic, there are likely additional contributing factors. It is likely that disparate and biased performance of medical devices, such as pulse oximeters, is also a significant contributing factor to this problem.

Pulse Oximetry

The pulse oximeter is an instrument that measures oxygen-blood saturation level (SpO_2) ("Pulse Oximetry | Johns Hopkins Medicine," n.d.). SpO_2 is considered by some to be the '5th' vital sign after temperature, pulse rate, respiration rate, and blood pressure (Johns Hopkins Medicine, 2021; Jubran, 2015). The pulse oximeter was invented by Dr. Takuo Aoyagi, a Japanese Bioengineer, in 1974 as a direct response to the high-altitude hypoxic deaths of many pilots in World War I. It was then modified by its patented inventors, Kenneth A. Hausman and Edwin B. Merrick, whose official application for the device was granted in 1989 (Hausman and Merrick). The technology has been described as "the greatest advance in patient monitoring since echocardiography", and has been attributed to a 90% reduction in anesthesia-related fatalities (Bhattacharya). While it is undoubtedly a technology that was created with the purpose to save lives and provide a higher standard of medical care, pulse oximetry is susceptible to interference when reading through darker skin tones with higher melanin concentrations. This presents the consequence of racial disparities in pulse oximetry readings and is therefore dangerous for BIPOC patients, especially during the COVID-19 pandemic.

Simply, pulse oximetry is a measurement of percentage of hemoglobin molecules that present 'oxygen loading', or binding of O_2. Oxygen-loaded hemoglobin means a patient's blood is more oxygenated, and they will have enough O_2 to allow bodily systems to function properly. SpO_2 is analyzed within the device which is commonly clamped on the patient's finger (Fig. 1): (Baura). It emits red and infrared light through light-emitting diodes (LEDs), oriented towards a

photodiode on the other side of the device across the finger. The instrument records the absorption spectra of each wavelength, which differ significantly for oxygenated and poorly-oxygenated blood (Jubran, 2015). Pulse oximetry racial bias occurs because of overlapping 660nm red light absorption for hemoglobin and melanin. This leads to some BIPOC patients receiving readings that are higher than their actual SpO2 level and can prohibit necessary care to properly oxygenate their blood in a timely fashion (APSF, 2021).

Pulse Oximetry and COVID-19 Health Inequity

The link between racial bias in pulse oximetry and health inequity for BIPOC COVID-19 patients has been examined by researchers since the declaration of a world-wide COVID-19 pandemic in March 2020 (2022, 2022) ("Health Equity Considerations and Racial and Ethnic Minority Groups | CDC," n.d.). One of the reasons that pulse oximetry may be a contributing factor to disproportionate COVID-19 BIPOC patient death is its use in determining the provision of emergency medical intervention.

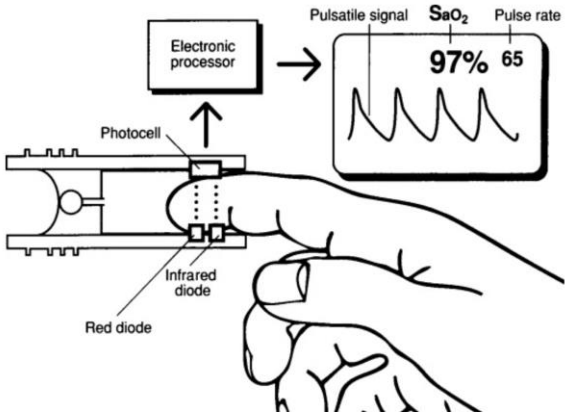

Figure 1: Pulse Oximeter Functional Diagram

Emergency departments and COVID-19 medical units use pulse oximetry along with other technologies to track patients' vital signs and determine if a patient should receive dexamethasone, the only therapy (as of February, 2021) with a proven mortality benefit for treatment of the virus (Group* et al., 2021). Hypoxic patients, those with concerningly low levels of SpO_2, should receive the dexamethasone therapy while normoxic patients (normal SpO_2) should not. Logically, BIPOC COVID-19 patients whose SpO_2 readings record as higher than

their actual physiological levels are at increased risk for being labeled as normoxic, when they are really physically hypoxic, and therefore are less likely to receive much-needed dexamethasone treatment in a timely manner (Otugo, 2022).

Media sources, researchers, and government agencies have also given attention to this serious issue. In January 2021, the British government began investigating the role of racial bias in medical devices such as pulse oximeters, as a response to the disproportionate COVID-19-related death of BIPOC patients (Wilson, 2021). In October 2021, University of Michigan Health Lab's blog published an article analyzing the role of pulse oximeter readings in determining COVID-19 patients' need to undergo extracorporeal membrane oxygenation (ECMO), an advanced form of life support for patients with respiratory failure. The article details researcher findings: a discrepancy between actual SpO_2 levels collected with arterial blood gas evaluations and pulse oximeter SpO_2 readings exists 10% of the time in white patients and 20% of the time in Black patients. This means that Black patients were ~2.5 times more likely to experience occult hypoxemia (extremely low SpO_2 levels that often are used as justification to begin preparing a patient to receive ECMO) due to poor detection of their true SpO_2 content. The article highlighted this discrepancy as a source of worry for physicians, who must decide which patients can receive limited ventilators and lifesaving ECMO care, and implied that it may contribute to higher rates of COVID-19 death for BIPOC patients (Malcom, 2021).

While this problem persists, a more equitable solution to measure SpO_2 may be well on the way thanks to the work of biomedical researchers and engineers in partnership with physicians. A potential solution to the problem of interference of melanin 660nm red light absorbance is to use additional wavelengths that cover a wider range of absorbance in order to decrease error associated with overlapping absorbance wavelengths. One such device that

employs this technique not for the purpose of reducing racial bias, but to visualize more detailed aspects of a patient's oxygenated hemoglobin is the rainbow© Pulse CO-Oximeter by Masimo Corp. (Philips). The rainbow© uses 5-12 waves of light at wavelengths ranging from 500-850nm in an effort to accurately measure patient carboxyhemoglobin (COHb) levels, an indication of the presence of hemoglobin containing carbon monoxide. However, this technique may be refined to help mitigate issues of pulse oximeter racial bias by using alternative wavelengths without melanin absorbance interference to analyze patient SpO_2 levels (Kulcke et al., 2016). However, the fact that this particular technological approach, patented as early as 2014, has not yet been adapted for the purpose of reducing or eliminating racial bias implies that there is an overall societal acceptance of the normalized deviance associated with medical systemic racism (United States Patent No. US10010276B2, 2018). This problem continues, and will require a cohesive effort from patients, BMEs, medical professionals, researchers, and administrative agencies for the design of its solution.

Heightened examination of this problem has led to a call for the FDA to reevaluate the regulations associated with the pulse oximeter's approval (Erin Brodwin and Nicholas St. Fleur Feb. 19 et al., 2021). The FDA released a statement responding to this demand in February 2021. While the statement acknowledges the potential for racial bias in the device, it simply declares that it is actively informing both patients and healthcare providers about the potential limitations and risks of inaccuracy associated with the device (Health, 2021). Instead of stating that the device must be re-examined due to such bias, the FDA uses this statement to re-emphasize the usefulness of the device for estimating blood-oxygen levels, and encourages patients to pay attention to their holistic symptoms when monitoring COVID-19 status. The lack of proper address by this highly-influential regulatory administration again implies the persistence of

normalized deviance of racially biased medical devices, and therefore the normalized deviance of systemic racism on the larger scale of US society. If the need for an engineering solution to pulse oximeter racial bias is not emphasized with greater urgency, countless more lives will be lost, and this broken system will continue to struggle to provide equitable healthcare for all patients, regardless of their racial identity.

Conclusion: In conclusion, the substantial analysis of racial biases associated with pulse oximetry, and its potential contribution to health inequity associated with BIPOC COVID-19 mortality rates is indicative of the magnitude of this problem. It is clear that while pulse oximeter racial bias is not the sole cause of BIPOC COVID-19 health inequity, it is certainly one of many contributing factors that ultimately result in a state of normalized deviance of racial bias in the US medical system. It is promising that technologies for mitigation of this problem exist, and yet also disheartening that they have yet to be adapted for the purpose of providing equitable SpO_2 evaluation for BIPOC patients. This problem must be addressed as soon as possible, as innumerable BIPOC patients around the world have unnecessarily lost their lives to a pandemic with no reasonable end in sight. All patients, regardless of any aspect of their identity, should be guaranteed the best possible medical care. Therefore, it should be a goal of all medical professionals and BMEs to contribute to this human right to quality medical care for the ultimate betterment of society.

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DIFFERENTIATING ACUTE OTITIS MEDIA FROM OTITIS MEDIA WITH EFFUSION USING FLUORESCENCE LIFETIME IMAGING

AN ANALYSIS OF RACIAL BIASES IN MEDICAL DEVICES AND STANDARDS, THEIR IMPACT ON SOCIETY, AND POTENTIAL ENGINEERING APPROACHES FOR MITIGATION

A Thesis Prospectus

In STS 4500

Presented to

The Faculty of the

School of Engineering and Applied Science

University of Virginia

In Partial Fulfillment of the Requirements for the Degree

Bachelor of Science in Biomedical Engineering

By

Abigail Boitnott

October 10, 2021

Technical Team Members: Megan Talarek, Esha Tulsian

On my honor as a University student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments. **X: Abigail Boitnott**

ADVISORS

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Introduction: Biomedical engineers (BMEs) are responsible for bridging the gap between engineering and medicine to enhance health care ("BMES," n.d.). This purpose is one that reflects the magnitude of biomedical engineering and its impact on health-based quality of life in modern society. The field of medicine as a whole places great emphasis on fair and just treatment supported by scientific research and administered to the best abilities of physicians and healthcare professionals, as is evident in different iterations of the Hippocratic Oath ("The History of the Hippocratic Oath: Outdated, Inauthentic, and Yet Still Relevant | Hulkower | Einstein Journal of Biology and Medicine," n.d.). Additionally, the American Medical Association (AMA) Code of Ethics includes a statement that physicians shall seek changes to circumstances that are contrary to the best interests of the patient/s ("Various Physicians Oaths," n.d.). Therefore, just as it is the responsibility of medical professionals to provide excellent standards of care for all patients, it is the responsibility of BMEs, as members of the medical field, to design and develop technologies and devices that embody these standards, and eliminate or mitigate racial disparities and biases in their design's technological functions.

A variety of commonly-used medical devices and health standards harbor racial biases, and therefore create a limitation of medical practice for provision of a consistent standard of care for patients with diverse ethnic and racial identities. These disparities do not allow for compliance with medical standards and codes of ethics, and therefore they must be mitigated by equitable and inclusive engineering design solutions. Additionally, BMEs must seek to optimize devices for their use in diagnosis and treatment, and must therefore incorporate high standards for efficiency, accuracy, and significance of function. Analysis of the technical topic of diagnostic standards of medicine related to Otitis Media will suggest a method of improvement

for its diagnosis primarily in pediatric cases to prevent financial loss currently associated with the condition. This technical topic coupled with the STS topic will provide a large-scale review of the US medical system and its shortcomings. Subsequent analysis of the STS topic will result in increased recognition of bias-based limitations in medicine, and will provide suggested solutions for amelioration of racial inequity in the US medical system.

Technical Topic: Otitis Media is inflammation of the middle ear typically caused by presence of fluid due to improper eustachian drainage ("Ear Infection (Otitis Media): Symptoms, Causes, Prevention & Treatment," n.d.). Otitis Media with Effusion (OME) is simply the presence of fluid (effusion) in the middle ear, while Acute Otitis Media (AOM) is the presence of infected fluid in the middle ear (Guan, Li, & Gan, 2013). These conditions are overwhelmingly prevalent and commonly referred to as "ear infections," despite OME not including infectious effusions. 2.2 million cases of AOM occur annually among US children, costing $4 billion per year due to unnecessary procedures, over-prescription of antibiotics, and loss of hearing (Rosenfeld et al., 2016).

Ideally, clinicians would be able to accurately distinguish between OME and AOM, the latter of which requires antibiotic treatment. However, it is currently difficult for clinicians to differentiate between these conditions. Diagnoses by general practitioners and primary care providers are unreliable about 27% of the time ("Assessing Diagnostic Accuracy and Tympanocentesis Skills in the Management of Otitis Media | Otolaryngology | JAMA Pediatrics | JAMA Network," n.d.).

Present diagnostic methods for Otitis Media primarily include visual observation and tympanometry. To diagnose visually, clinicians use an otoscope to assess a patient's ear for signs of inflammation that could indicate infection such as redness, swelling, an opaque tympanic membrane (TM), and TM bulge indicating pressure exerted on the eardrum by fluid in the middle ear [Dr. Stephen Early, personal communication] ("Ear Infection (Otitis Media): Symptoms, Causes, Prevention & Treatment," n.d.). To diagnose with tympanometry, clinicians evaluate TM response to changes in outer ear pressure using a tympanometer which generates a compliance response curve for the patient's TM called a tympanogram (Fig. 1): ("Understanding and Interpreting a Tympanogram | Epomedicine," n.d.). A mostly flat curve indicates little to no movement of the TM and suggests fluid is exerting positive pressure behind the TM in the middle ear, thereby preventing its compliance (Anwar, Khan, Rehman, Javaid, & Shahabi, 2016). These methods, even when used in tandem with one another, are poor indicators of Otitis Media.

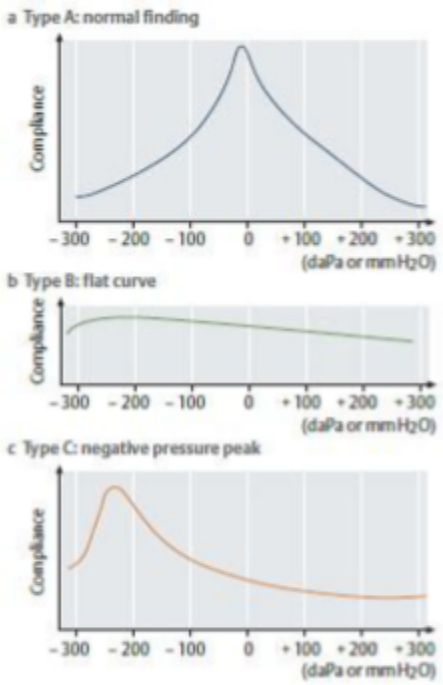

Figure 1: Tympanogram curves

While clinicians may successfully diagnose presence of fluid in the middle ear based on a flattened tympanogram and otoscopic observation of inflammation, they lack any data regarding the content of the effusion and whether it is infected. If infection is in its early stages, or if there is no obvious inflammatory response when visually analyzed, a clinician may assume a case of AOM to be OME, and consequently, may not prescribe a patient necessary antibiotics for AOM

treatment. The converse also results in poor patient outcome; prescription of unneeded antibiotics for a patient with OME may lead to development of antibiotic resistance in addition to unnecessary financial cost associated with such treatment ("A Proposal to Limit Otoscopy to Reduce Unnecessary Use of Antibiotics: A Call for Research: Expert Review of Anti-Infective Therapy: Vol 9, No 2," n.d.). In addition, likelihood of correct diagnosis varies based on the individual assessing the ear. Experienced clinicians specializing in otolaryngology (ENT) are more likely to correctly diagnose Otitis Media than are general practitioners or primary care providers who have less regular exposure to the condition, and less refined diagnostic practice for it (Table 1): ("Diagnostic Accuracy of Otitis Media | American Academy of Pediatrics," n.d.), ("Assessing Diagnostic Accuracy and Tympanocentesis Skills in the Management of Otitis Media | Otolaryngology | JAMA Pediatrics | JAMA Network," n.d.) .

Video Examination No.	Correct Diagnosis	Percentage of Correct Diagnoses Made	
		Pediatricians (n = 524)	ENTs (n = 188)
1	OME	48	88
2	OME	45	69
3	Retracted TM, otherwise normal	56	76
4	AOM	73	76
5	OME	50	79
6	OME	25	48
7	Retracted TM, otherwise normal	46	83
8	OME	48	84
9	Retracted TM, otherwise normal	59	65
	Overall	**50**	**73**

*ENTs indicates board-eligible or board-certified otolaryngologists; OME, otitis media with effusion; and AOM, acute otitis media.

Table 1: Variance in diagnostic accuracy of Otitis Media based on experience

An approach currently used by clinicians to alleviate severe middle ear effusion is surgical perforation of the TM followed by suction evacuation of the effusions and often, insertion of a ventilation tube to prevent early recurrence [Clinical Observation], ("Compositional Difference in Middle Ear Effusion: Mucous Versus Serous - Chung - 2002 -

The Laryngoscope - Wiley Online Library," n.d.). While this solution resolves the condition, at least temporarily, it has both financial and physical costs, as the patient's parents (most cases are pediatric) must pay for surgical intervention, and the patient must heal from the procedure. Some researchers have analyzed the effectiveness of watchful waiting to prevent unnecessary ear tube placement, with one study claiming a 66% success rate of prevention ("Preventing Unnecessary Tympanostomy Tube Placement in Children - ScienceDirect," n.d.). This statistic suggests that some conditions are not severe enough to demand surgical intervention or antibiotic treatment, however the process of watchful waiting implies that a patient will have to cope with persistent symptoms, without a definite diagnosis to indicate if treatment is necessary. A solution to the lack of accurate diagnosis of these conditions is analysis of the contents of the effusion itself, however this is currently not possible with any minimally-invasive technique ("Diagnostic Methods for Acute Otitis Media in 1 to 12 Year Old Children: A Cross Sectional Study in Primary Health Care | BMC Family Practice | Full Text," n.d.). Therefore, the main aim of the technical project is to design a proof of concept otoscopic diagnostic device.

In infected effusion, there is a corresponding immune response with neutrophils (PMNs) present ("Definition of PMN - NCI Dictionary of Cancer Terms - National Cancer Institute," 2011). NADPH is an oxidase present in PMNs responding to infection and can be detected and distinguished from NADH, a similar molecule, through fluorescence lifetime imaging microscopy (FLIM) ("NADPH Oxidase Activation in Neutrophils: Role of the Phosphorylation of Its Subunits - Belambri - 2018 - European Journal of Clinical Investigation - Wiley Online Library," n.d.), ("Separating NADH and NADPH Fluorescence in Live Cells and Tissues Using FLIM | Nature Communications," n.d.), (Bhattacharjee, Datta, Gratton, & Hochbaum, 2017).

Ideally, the proof-of-concept diagnostic device will be able to assess a patient's middle ear effusion using FLIM to quantify NADPH presence and therefore, presence and severity of infection. This will provide the clinician with an accurate diagnosis and ultimately prevent unnecessary financial costs, antibiotic prescriptions, surgical interventions, and prolonged physical discomfort for pediatric patients.

STS Topic: Throughout US history, the medical field has suffered the effects of systemic racism, defined as "the complex interaction of culture, policy and institutions that holds in place outcomes we see in our lives… [it] is naming the process of white supremacy" ("Systemic Racism: What Does It Mean and How Can You Help Dismantle It," n.d.). Unacceptable standards of care for Black, Indigenous, and People of Color (BIPOC) patients have existed since the country's founding, causing loss of life for these marginalized populations. Contributing factors to medical racism in the US are the societal atmosphere created by historic racial inferiority theories and stereotypes, historical enslavement of Black people, and biased educational processes. These have ultimately contributed to a trend of scientific and medical abuse towards marginalized racial groups ("Race, Medicine, and Health Care in the United States: A Historical Survey.," n.d.).

This trend has created a positive feedback loop of marginalized people developing mistrust in the medical system, resulting in low BIPOC participation as testing populations for clinical research, hindering the system's improval, thereby leading to more distrust. This vicious cycle has been strengthened by historic tragedies such as the Tuskegee Syphilis Study

(1932-1972), forced sterilization of >60,000 people, most of them belonging to racial minority groups and/or suffering disabilities (1880s-late 1900s), and landmark cases of racially disparate medical care ("African Americans' Views on Research and the Tuskegee Syphilis Study - ScienceDirect," n.d.), ("Forced Sterilization Policies in the US Targeted Minorities and Those with Disabilities – and Lasted into the 21st Century," n.d.), (Gamble, 1997). In order to standardize medical care for all, and to restore BIPOC patients' trust in the medical system, these disparities must be examined and mitigated with new technology and medical practices, created and implemented through BME and clinician collaboration.

To compound historical unethical practices and experimentations, modern medical racial bias persists in some of the most commonly-used medical devices. One such device is the pulse oximeter, an instrument measuring oxygen-blood saturation level (SpO_2) ("Pulse Oximetry | Johns Hopkins Medicine," n.d.). SpO_2 is considered by some to be the '5th' vital sign after temperature, pulse rate, respiration rate, and blood pressure ("Vital Signs (Body Temperature, Pulse Rate, Respiration Rate, Blood Pressure) | Johns Hopkins Medicine," n.d.), (Jubran, 2015). Pulse oximetry is susceptible to interference when reading through darker skin tones with higher melanin concentrations. This presents the consequence of racial disparities in pulse oximetry readings and is dangerous for BIPOC patients.

Simply, pulse oximetry is a measurement of the percentage of hemoglobin molecules that present 'oxygen loading', or binding of O_2. Oxygen-loaded hemoglobin means a patient's blood is more oxygenated, and they will have enough O_2 to allow bodily systems to function properly. SpO_2 is analyzed within the device which is commonly clamped on the patient's finger (Fig. 2): ("Pulse Oximeter - an Overview | ScienceDirect Topics," n.d.). It emits red and infrared light

through light-emitting diodes (LEDs), oriented towards a photodiode on the other side of the device across the finger. The instrument records the absorption spectra of each wavelength, which differ significantly for oxygenated and poorly-oxygenated blood (Jubran, 2015). Pulse oximetry racial bias occurs because of overlapping 660nm red light absorption for hemoglobin and melanin. This leads to some BIPOC patients receiving readings that are higher than their actual SpO2 level and can prohibit necessary care to properly oxygenate their blood in a timely fashion ("#46 Pulse Oximetry Accuracy and Skin Tone," n.d.). Pulse oximeters of the future need to be redesigned to maintain equitable standards for all people and mitigate fatal errors.

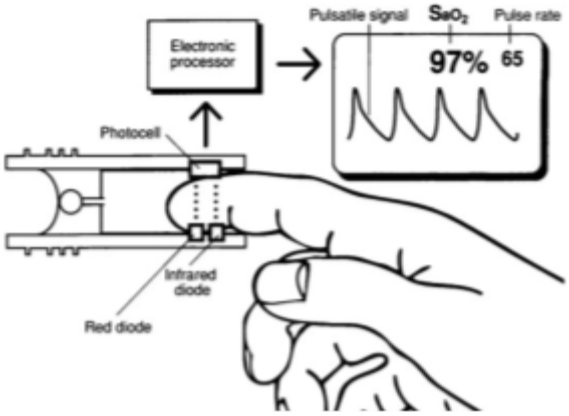

Figure 2: Pulse Oximeter Functional Diagram

Furthermore, racial inequities exist not only in modern medical devices, but also in medical practices and standards of health. An example of this is Body Mass Index (BMI), a numerical system used to diagnose obesity. A patient's BMI is calculated by dividing their weight (kg) / height^2 (m^2), and then categorizing the resulting value as underweight, normal, overweight, or obese (Adults (US), 1998). This standard is incredibly biased towards accuracy for non-hispanic white (NHW) patients, as the cut-scores for each status category were primarily calculated with data from NHW people and were developed in the 1940s ("BMI Is Flawed, Especially for People of Color - The Washington Post," n.d.).

A 2009 study used dual-energy X-ray absorptiometry determination of percentage body fat (DXA-BF%) as a control for evaluation of BMI accuracy in patients of varying races and ethnicities. It found that BMI overestimated the DXA-BF% of Black patients, and also revealed trends in DXA-BF% associated with a patient's race (Fig. 3): ("Body Mass Index Bias in Defining Obesity of Diverse Young Adults: The Training Intervention and Genetics of Exercise Response (TIGER) Study | British Journal of Nutrition | Cambridge Core," n.d.). These data support anecdotal data of Black patients being denied medical treatment for conditions like restrictive eating disorders, because their BMI was above the threshold determined for NHW obesity ("BMI Is Flawed, Especially for People of Color - The Washington Post," n.d.). Additionally, despite having a higher prevalence of obesity, BIPOC patients experience lower rates of treatment and surgical response to the condition than do NHW patients (Byrd, Toth, & Stanford, 2018). These disparities only serve to strengthen the issue of distrust in the medical system among patients with marginalized racial identities, as they are at higher risk for complications associated with obesity and eating disorders due to medical neglect. Bias associated with BMI also contributes to a diminished mental health for BIPOC patients, as their BMI is an overestimation of their true body fat composition, and many societal standards of self-acceptance revolve around body weight and body image ("Mental Health, Family Function and Obesity in African-American Women.," n.d.). Biases in medical standards

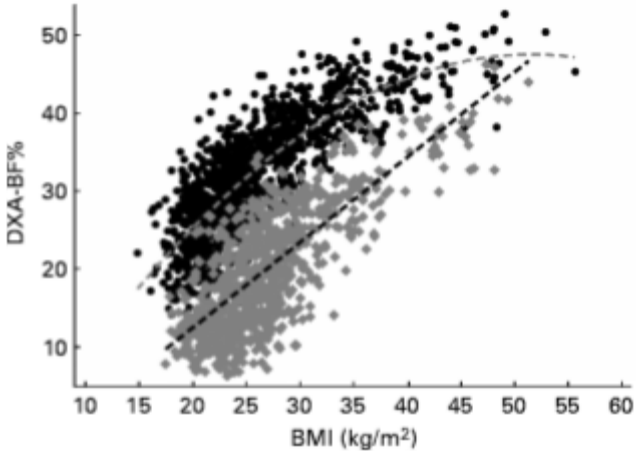

Figure 3: BMI is not an accurate reflection of body fat %

such as BMI contribute to the strengthening of systemic racism and loss of life of BIPOC patients. These standards must be reviewed and revised appropriately.

Research Question and Methods: In an attempt to evaluate racial disparities in medical devices and standards, literary analysis will be performed with the research question of: What is the significance of disparity in the examined medical devices and standards, and how does it impact quality of life for BIPOC patients in the US? Additional data will be collected from literature, and statistical tests for significance will be performed to determine a *P*-value for each instance of bias (Greenland et al., 2016). These findings will then be compared with data from literature for life-expectancy, mental health status, and medical insurance coverage for BIPOC patients that is similarly collected and tested for significance. A holistic review and comparison of the data will result in a quantitative representation of the impacts of medical racial disparities on BIPOC living in the US.

To support independent research and quantitative analysis, it would be beneficial to also conduct interviews with medical professionals and patients with diverse backgrounds regarding their experience with medical racial bias and standards of medical care. Medical professionals include nurses, physicians, medical and nursing students, etc.. They will be asked a group of questions including “Have you observed problems related to racial disparities in medical technology and devices, health standards, or medical practice?”; “To the best of your knowledge, do you recall receiving education regarding bias and inequity in your studies relevant to your position?”; “Does your current position **require** you to participate in any bias-prevention or

equity training to maintain your status?". The group of patients to be interviewed will vary in age from young adults to elderly individuals and will also be varied in biological sex and racial and ethnic identity. This group will be asked a collection of questions including "How often do you go to the doctor?"; "If you've been hospitalized, please describe your experience with 3 words."; "How do you feel when you talk to a medical professional?"; "Have you had any particularly positive or negative experiences?"; "Do you have health insurance/have you ever struggled to afford medical care?". To prevent experimental bias, interviewed patients will not be briefed on the topic of the STS thesis, but will instead be asked their permission to record their answers to a series of questions related to their experience with the medical system. It is of utmost importance to conduct this research with sensitivity and transparency, and with self-recognition of any personal biases, such as inherent white privilege.

Conclusion: In conclusion, the design of an otoscopic device for accurate diagnosis of Otitis Media will contribute to an increased standard of health for all patients, and a lessened waste of resources and finances for medical professionals and patients alike. Additionally, the analysis of racial biases and inequities associated with medical devices and technologies, health standards, and common medical practices will be indicative of the magnitude of the problem and will help identify contributing factors. These factors will be analyzed to design potential solutions for the amelioration of medical racial bias in the analyzed devices and standards. Several potential solutions determined from initial research are: amending testing methods and populations for accurate representation of the true diverse patient population, improving medical education regarding racial biases of both historic and present nature, and suggesting redesigns and new

standards for medical devices and practices. All patients, regardless of any aspect of their identity, should be guaranteed the best possible medical care. Therefore, it should be a goal of all medical professionals and BMEs to contribute to this human right to quality medical care for the ultimate betterment of society.

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