Post−Surgical Artifact Correction in MR Imaging by Deep Neural Networks

****WINNER** Innovation Category for 2023 Lifespan Research Day**

Research Category: Innovation

Primary Research Location: Brown University

Funded By: NIH (NIAMS R01−AR065462, NIGMS P30 GM122732)

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Abstract

Background: Quantitative magnetic resonance imaging (qMRI) non−invasively measures soft tissue structural properties. However, anterior cruciate ligament (ACL) surgery can leave metal particles in the joint, producing magnetic susceptibility artifacts that distort regions of MR images. As a result, both morphological and signal−based measures of the complete ROI are not always possible. The objective of our study was to train a deep−learning model to correct simulated magnetic susceptibility artifacts observed post−ACL surgery. It was hypothesized that the signal intensity obtained from the deep learning corrected artifact regions would not be significantly different from the ground truth.

Methods: Data were collected from constructive interference in steady state (CISS) MRI scans acquired from 120 patients in two IRB−approved clinical trials who underwent ACL surgery and had both the surgical and contralateral limb imaged at multiple time points post−surgery. Simulated artifacts were generated and inserted into surgical limb MR images without prior artifacts (n=1720). Four models were evaluated: a shallow dense network, a deep dense network, a convolutional neural network (CNN). Model performance was evaluated using a two−sided paired t−test on the signal intensity (SI) values in the image regions where artifacts were corrected.

Results: The deep dense network demonstrated the smallest paired percent difference of 14.82% between artifact region ground truth and predicted signal intensity. All other models resulted in significantly different signal intensities in the artifact regions. The findings of the present study offer preliminary evidence that deep learning may be used to correct non−implant metal susceptibility artifacts resulting from surgical instrument wear particles.

Conclusion: Future work will confirm whether the model generalizes to non−simulated artifacts. Nevertheless, reconstructing artifact occluded ROIs may still increase segmentation accuracy for obtaining morphological measures. These artifacts' occluded regions may potentially be reconstructed post−acquisition with reasonable fidelity via deep learning.

Clinical Implications: The metal wear particles from tools used during ACL surgery may obstruct the view of the ACL. These findings are significant as they suggest that with further training and improvements of the deep neural networks, the findings may be used as a tool in the post−processing of MR images to provide a clear picture of the healing ACL.

Transfer Learning Boosts Performance of Deep Learning Model Prediction of In−hospital Mortality in Patients Treated with Extracorporeal Membrane Oxygenation

2023 Lifespan Research Day Abstract Submission Contest

Research Category: Innovation
Primary Research Location: Ocean State Research Institute, Rhode Island Hospital
Funded By: CPVB COBRE, Francis Family Foundation

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Abstract

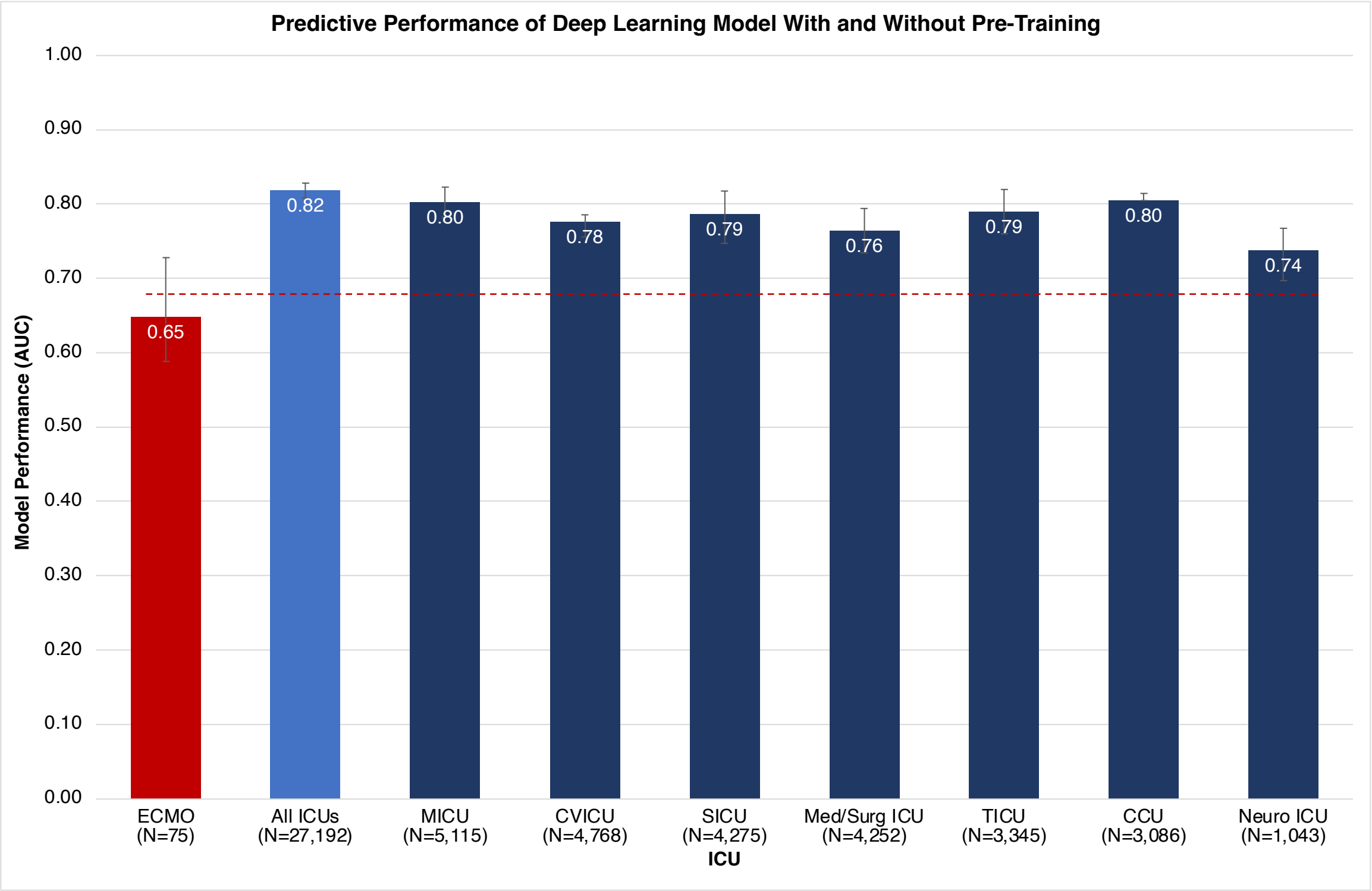
Background: The application of deep learning − a powerful but data−intensive subset of machine learning − to smaller cohorts including extracorporeal membrane oxygenation (ECMO) datasets is challenging. Transfer learning can boost the performance of deep learning models trained on smaller datasets by pre−training on related larger datasets. We applied transfer learning to a large intensive care unit (ICU) dataset to predict in−hospital mortality in a small cohort of patients treated with ECMO.

Methods: We applied an unsupervised deep learning autoencoder to routinely collected electronic health record data within the Medical Information Mart for Intensive Care (MIMIC) IV database to predict in−hospital mortality in subjects treated with ECMO 24 hours prior to death. Model performance was assessed with and without pre−training on data for subjects admitted to any or select ICUs not treated with ECMO.

Results: The study dataset included 27,192 subjects admitted to one of seven ICUs between 2008 and 2019, including 4,768 (17.5%) subjects admitted to the to the cardiovascular ICU (CVICU) and 3,086 (11.3%) to the coronary care unit (CCU). Seventy five (0.3%) subjects were treated with ECMO. In−hospital mortality in subjects not treated with ECMO was 16.1% and 57.3% in subjects treated with ECMO. The model performed poorly at predicting in−hospital mortality in subjects treated with ECMO without pre−training, AUC 0.65 (95% CI 0.59−0.73) (Figure 1). However, pre−training on data from any subjects admitted to the ICU not treated with ECMO significantly improved model performance, AUC 0.82 (95% CI 0.81−0.83). Pre−training on smaller cohorts of subjects not treated with ECMO in the CVICU and CCU resulted in similar strong performances, 0.78 (95% CI 0.76−0.79) and 0.80 (95% CI 0.80−0.81) respectively, while pre−training on a cohort of patients in the neurosurgery ICU resulted in only a minor performance bump.

Conclusion: A transfer learning model performed well at predicting in−hospital mortality in a small cohort of patients treated with ECMO after first pre−training on a larger cohort of ICU patients not treated with ECMO.

Clinical Implications: Transfer learning allows pre−trained deep learning models to be applied to smaller clinical datasets, including datasets of patients undergoing rare or highly specialized treatments, resulting in better overall performance.


Predictive Performance of Deep Learning Model With and Without Pre-Training
Model Performance (AUC)
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
0.65
0.82
0.80
0.78
0.79
0.76
0.79
0.80
0.74
ECMO (N=75)
All ICUs (N=27,192)
MICU (N=5,115)
CVICU (N=4,768)
SICU (N=4,275)
Med/Surg ICU (N=4,252)
TICU (N=3,345)
CCU (N=3,086)
Neuro ICU (N=1,043)
ICU

Bridging the Literacy Gap for Surgical Consents: An AI−Human Expert Collaborative Approach

2023 Lifespan Research Day Abstract Submission Contest

Research Category: Innovation
Primary Research Location: Rhode Island Hospital
Funded By: N/A

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Abstract

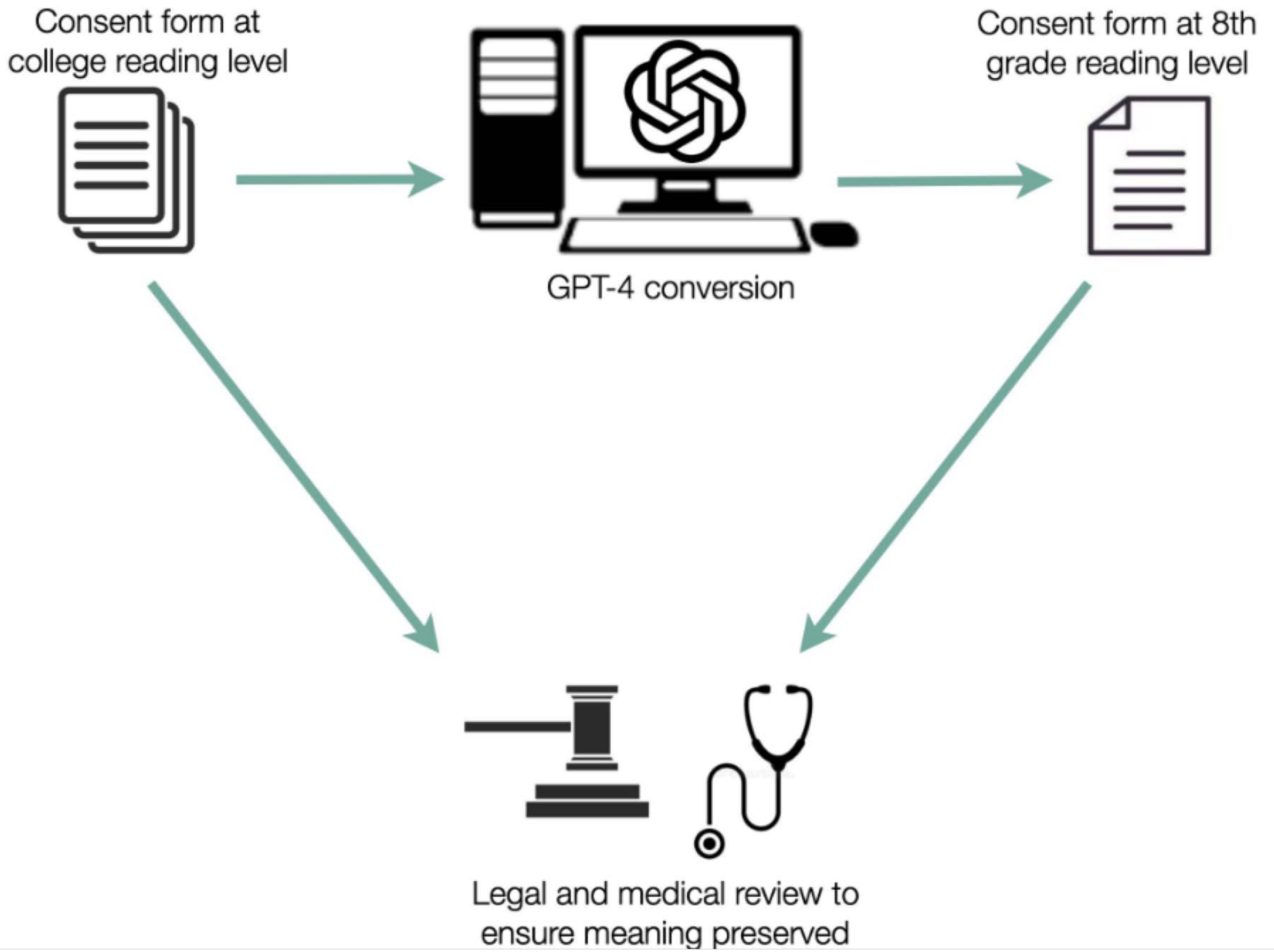
Background: Despite the importance of informed consent in healthcare, the readability and specificity of consent forms often impedes patients' comprehension. Health literacy is linked to patient outcomes, making it essential to address these issues. This study investigates the use of GPT−4 to simplify surgical consent forms and introduces an AI−human expert collaborative approach to validate content appropriateness.

Methods: Consent forms from multiple institutions were assessed for readability and simplified using GPT−4, with pre− and post−simplification readability metrics compared using nonparametric tests. Independent reviews by medical authors and a malpractice defense attorney were conducted. Finally, GPT−4's potential for generating de novo procedure−specific consent forms was assessed, with forms evaluated using a validated 8−item rubric and expert subspecialty surgeon review.

Results: Analysis of 15 academic medical centers' consent forms revealed significant reductions in average reading time, word rarity, and passive sentence frequency (all $P<0.05$) following GPT−4−faciliated simplification. Readability improved from an average college freshman to an 8th−grade level ($P=0.004$), matching the average American's reading level. Medical and legal sufficiency consistency was confirmed. GPT−4 generated procedure−specific consent forms for five varied surgical procedures at an average 6th−grade reading level. These forms received perfect scores on a standardized consent form rubric and withstood scrutiny upon expert subspeciality surgeon review

Conclusion: This study demonstrates the first AI−human expert collaboration to enhance surgical consent forms, significantly improving readability without sacrificing clinical detail. Our framework could be extended to other patient communication materials, emphasizing clear communication and mitigating disparities related to health literacy barriers.

Clinical Implications: Ensuring AI technologies are safely incorporated into clinical practice is crucial to reach a wide range of patients, including the most vulnerable.


Consent form at college reading level
GPT-4 conversion
Consent form at 8th grade reading level
Legal and medical review to ensure meaning preserved

COVID−19 Data Analysis: Harnessing Artificial Intelligence, IoT, and Social Network Analysis to Combat the Global Pandemic and its Societal Impact

2023 Lifespan Research Day Abstract Submission Contest

Research Category: Clinical & Translational, Innovation

Primary Research Location: Bryant University

Funded By: Department of Mathematics and Computer Science, Mercy College, Dobbs Ferry, NY, USA.

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Abstract

Background: This study intends to analyze COVID−19 data and examine how it affects social life in people. The study includes a variety of COVID−19 data analysis topics, such as the cooperative use of AI, ML, deep learning, and the Internet of Things (IoT) in the COVID−19 eradication effort. Additionally, the project investigates how artificial intelligence and Internet of Things (IoT) techniques might be used to forecast, identify, and diagnose patients with the novel coronavirus. Using social network analysis and sentiment analysis techniques, the project will also look into how false information, corrupted data, and conspiracy theories are spread on social media sites like Twitter. Existing approaches are assessed through a thorough comparative examination. In the end, the study will offer various data analysis methods, identify areas for future research, and offer broad guidelines for successfully controlling the coronavirus and adjusting to the shifting work and living circumstances.

Methods: The study used a thorough and methodical way to look into several COVID−19 data analysis issues. The survey report starts out by introducing the novel virus and exploring the historical background of earlier pandemics. The research also examines the function of social media and online activism in the communication of COVID−19−related information. The study primarily looks at how social media sites affect the propagation of false information and fabricated virus−related data. The project also examines the application of machine learning, artificial intelligence, and Internet of Things (IoT) strategies to attack COVID−19.

Results: The comprehensive survey on COVID−19 data analysis yielded significant findings across various research areas. Firstly, the study highlighted the emergence of the novel coronavirus and provided insights into previous pandemics of the last century, establishing a contextual foundation for understanding the current crisis. The role of social media platforms in the dissemination of information related to COVID−19 was thoroughly examined. It was observed that social media played a crucial role in the spread of fake news and manipulated results concerning the virus. The study delved into the application of artificial intelligence (AI), machine learning (ML), and Internet of Things (IoT) techniques in the fight against COVID−19. AI techniques also demonstrated promise in detecting, predicting, and diagnosing COVID−19 infections.

Conclusion: This research offers a thorough analysis of the COVID−19 epidemic, covering a variety of topics. The study also covers how to analyze data linked to the epidemic and how to fight it using AI, ML, IoT, social media, and social network analysis. The authors give future prospects for research as well as a taxonomy of disciplines and how they are used in COVID−19 data processing.

Clinical Implications:

Including nutrition in a Lifestyle Medicine Clinical elective improves nutrition knowledge of medical students

2023 Lifespan Research Day Abstract Submission Contest

Research Category: Innovation
Primary Research Location: Lifespan Women's Medicine Collaborative
Funded By: none

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Abstract

Background: The traditional medical school education does not include nutrition but may include optional lectures that pertain to nutrition. However, it can be difficult to find the time to provide in−person nutrition lectures. In addition, learning cannot be measured if the lecture is not required. The objective of this Lifestyle Medicine clinical elective for 3rd and 4th year WAMS students is to 1. test if on−line nutrition lectures with pre− and post−testing will show improvement in scores which could be used for assessing learning; and 2. provide an in−person session with a dietitian to promote further understanding of nutrition concepts, when to refer to a dietitian and the role of dietitians in clinical management of chronic diseases.

Methods: Three nutrition lectures were developed and recorded by a PhD dietitian who has lectured in the WAMS for more than 20 years. Students viewed the videos at their convenience while completing the clinical elective. The topics were: Nutrients v Food, Food and Weight management, and Food Insecurity and the Role of the Physician. Each unit has pre−and post−tests using the same questions to evaluate learning from the lecture videos. In addition, students have a separate session with a clinical dietitian to provide time for questions and discussion on nutrition concepts.

Results: Twenty−four students have completed the nutrition modules as of August 2023. Results are in the Table. The individual session with Lifestyle Medicine dietitian had no testing associated with it.

Conclusion: Based on the test scores, an on−line nutrition course that includes recorded videos and pre−and post−testing can lead to an increase in learning nutrition concepts and how to incorporate this into their future clinical practice.

Clinical Implications: Through the completion of the nutrition modules and separate session with dietitian, medical students have shown proficiency in understanding the basics of nutrition, the various recommended dietary lifestyle changes for chronic disease prevention and language of helping to incorporate this information into the clinical setting. These modules also fill clear gaps in medical education where nutrition is often presented through biochemistry and without clinical applications.

Unit	Pre score	Post score	P=
Nutrients v Food	20.9±9.1	46.7±3.7	<0.00001
Food and Weight management	29.4±8.6	48.0±3.4	<0.00001
Food Insecurity and the Role of the Physician	31.6±9.4	48.9±9.7	<0.00001

Identification of significant gene expression changes in multiple perturbation experiments using knockoffs

2023 Lifespan Research Day Abstract Submission Contest

Research Category: Innovation
Primary Research Location: Bryant University and UMass Amherst
Funded By: NSF TRIPODS

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Abstract

Background: Large−scale multiple perturbation experiments have the potential to reveal a more detailed understanding of the molecular pathways that respond to genetic and environmental changes. A key question in these studies is which gene expression changes are important for the response to the perturbation. This problem is challenging because (i) the functional form of the nonlinear relationship between gene expression and the perturbation is unknown and (ii) identification of the most important genes is a high−dimensional variable selection problem. (This paper has been published on Briefings in Bioinformatics in 2023. The journal impact factor is 13.997 and it ranks #1 out of 57 mathematics and computational biology journals)

Methods: We present here a method based on the model−X knockoffs framework and Deep Neural Networks to identify significant gene expression changes in multiple perturbation experiments. We apply this approach to the Library of Integrated Network−Based Cellular Signature data sets which is a National Institutes of Health Common Fund program that catalogs how human cells globally respond to chemical, genetic and disease perturbations.

Results: We identified important genes whose expression is directly modulated in response to perturbation with anthracycline, vorinostat, trichostatin−a, geldanamycin and sirolimus.

Conclusion: We compare the set of important genes that respond to these small molecules to identify co−responsive pathways. Identification of which genes respond to specific perturbation stressors can provide better understanding of the underlying mechanisms of disease and advance the identification of new drug targets.

Clinical Implications: We compared the set of important genes that respond to vorinostat, geldanamycin, sirolimus, trichostatin−a, wortmannin and anthracycline to elucidate the response gene network and identify co−responsive pathways.

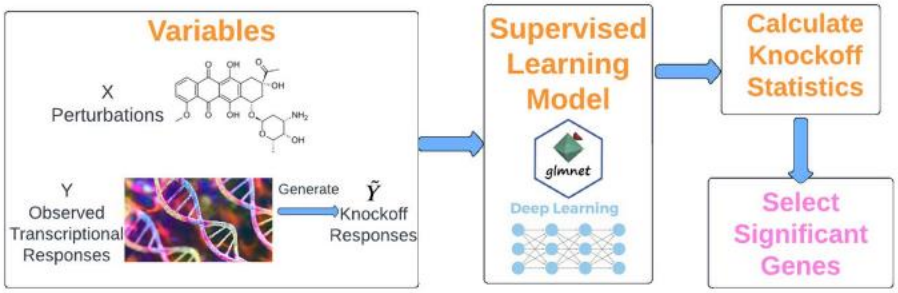

Figure 1. Flow chart of the model-Y knockoffs methodology.

Distal−less homeobox 5 (DLX5) knockdown inhibits Osteoarthritis pathway networks while inciting cartilage repair networks in mesenchymal lineage cells

2023 Lifespan Research Day Abstract Submission Contest

Research Category: Clinical & Translational, Innovation

Primary Research Location: Dept of Orthopaedics, Brown University/RI Hospital, Providence, RI, USA

Funded By: NIH NIAMS grant R21AR077326 and a Pilot Project from NIH NIGMS parent grant P20GM104937

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Abstract

Background: Knee Osteoarthritis (OA) is a leading cause of disability and functional impairment in the United States. As the articular cartilage is regularly exposed to biomechanical forces from joint impact, focal cartilage are common. There is a need to develop effective strategies to restore damaged cartilage tissue. Bone−marrow−derived mesenchymal stromal cells (BM−MSCs) have been extensively researched in preclinical models of cartilage restoration. However, BM−MSCs have certain limitations. During late−stage chondrogenesis, BM−MSCs exhibit increased gene expression of common cartilage hypertrophy−ossification markers. DLX5, a bone−morphogenic protein 2 (BMP−2) inducible transcription factor and hypertrophy markers, is significantly upregulated in BM−MSCs and in the chondrocytes isolated from OA patients. The objective of this study is to investigate the therapeutic efficacy of using DLX5 knock−down BM−MSCs as a cell based therapy for attenuating OA.

Methods: BM−MSCs were stabilized with pRetro−E2−SV40 to ensure phenotypic stability during culture expansion. DLX5 knock−down was performed using lentivirus bearing shDLX5. DLX5 knockdown was confirmed by westernblot. RNAseq was performed and the resulting large data set was analyzed using ingenuity pathway analysis (IPA) software to determine affected gene networks. shDLX5 cells, non−targeting controls (NTC) or saline were administered via intraarticular injection into the knees of athymic rats following medial meniscus destabilization by partial tearing. Knees were isolated for histological analysis using Toluidine Blue stain 48 days post−injury.

Results: DLX5 knockdown(Fig.1A) does not affect the viability of the cells(Fig.1B). RNAseq analysis of these cells revealed that DLX5 knockdown inhibits osteoarthritits pathway and activated woundhealing pathways(Fig.2). DLX5 knockdown BM−MSCs significantly promoted the cartilage repair in the rats in vivo as compared to NTC and saline controls(Fig.3).

Conclusion: We investigated the therapeutic capability of using DLX5 knockdown BM−MSCs for cartilage injury repair and OA prevention. BM−MSCs did not show significant cell death upon DLX5 knockdown. Further, RNAseq suggested vital changes in the gene expression of DLX5 knockdown cells indicating the inhibition of OA pathway and the activation of cartilage injury repair pathways. Our in−vivo study demonstrates that DLX5 knockdown BM−MSC treatment results in significantly improved cartilage health.

Clinical Implications: These findings suggest that DLX5 is a potential theraputic target for stimulating cartilage repair and post−traumatic OA prevention.

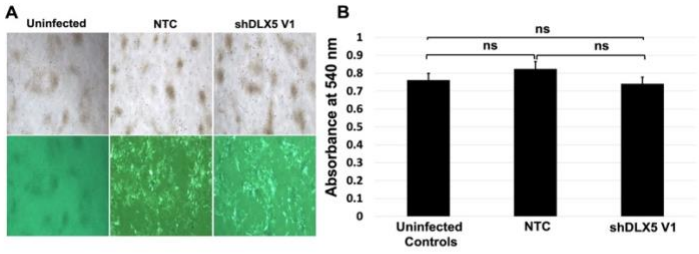

Fig - 1: DLX5 knockdown does not affect viability of the cells. **(A)** The knock down of DLX5 in phase contrast as well as fluorescent images. **(B)** Cell viability at passage #17 was analyzed using MTT cell viability assay kit. ns = not significant

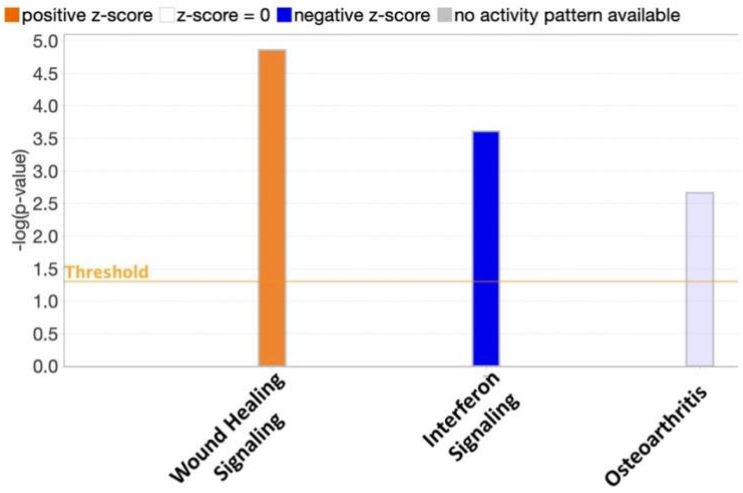

Fig - 2: DLX5 knockdown modulates cell signaling network in BM-MSCs. The wound healing pathway (Orange) is upregulated, and the Osteoarthritis pathway (Blue) is inhibited

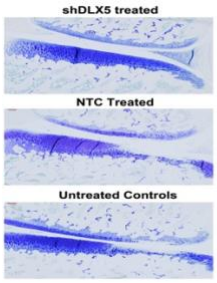

Fig - 3: DLX5 knockdown BM-MSCs injection results in better cartilage profile in rats. Representative images of knee cartilage histology stained with Toluidine Blue at 6 weeks post surgery of shDLX5-BM-MSC treated, non-targetting control (NTC)-BM-MSC treated and untreated animals is shown. Scale bar = 100 uM

Stability and Motif Analysis of RNA−Seq Reads from Covid−19 Patients

2023 Lifespan Research Day Abstract Submission Contest

Research Category: Innovation
Primary Research Location: Rhode Island Hospital
Funded By: Surgical Research Department

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Abstract

Background: Sequencing (RNA−seq) has been increasingly incorporated in many research aspects ranging from analyzing the transcriptome to elucidate pathogenesis of certain diseases and evaluating potential treatment approaches. This technology can also identify novel diagnostic targets to be used with common laboratory tools such as PCR. In order to ensure efficacy of the target, we hypothesize that these targets are more stable than other RNA segments.

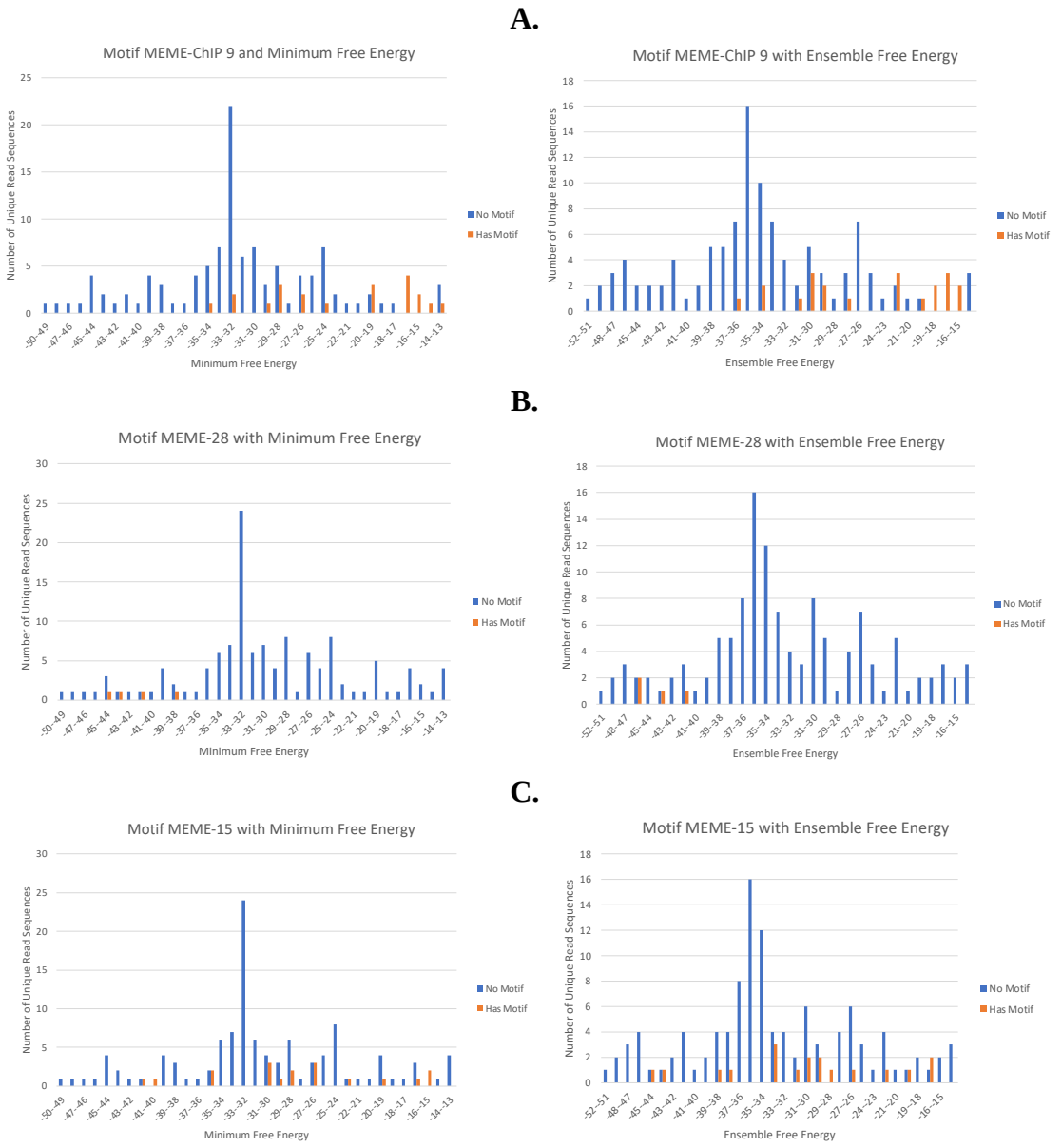
Methods: In this study, we present an analysis of the stability of targets to diagnose COVID−19. RNAfold from the ViennaRNA Package was used to predict the minimum free energy of the secondary structure of RNA−Seq read sequences. It was also used to calculate the minimum free energy value of the structures and ensemble free energy values to compare stability between different read sequences. Energy parameters for calculations were set at 37°C. Different statistical tools were used to assess the stability or instability of a secondary structure in addition to RNAfold.

Results: Of the 676 reads that aligned to COVID−19, there were 137 unique sequences. Among all the unique read sequences, the average minimum free energy (MFE) in kcal/mol was −30.46 and the average ensemble free energy (EFE) in kcal/mol was −32.94. Motif effect analysis on energy revealed potential destabilizing and stabilizing values. Within the N gene, we found that reads from different regions also differed in stability. Our motif analysis demonstrated 7 motifs that corresponded to destabilization of the RNA and a single motif that corresponded to stabilization of the RNA.

Conclusion: Our results demonstrated that the stability of reads from different genes varied. RNA structure stability in addition to levels of gene expression contribute to the presence of this RNA and its potential as a diagnostic target. We have also identified motifs that impact stability.

Clinical Implications: Whether a secondary structure is stable or not can be used for evaluating the diagnostic target should be used in clinical laboratory settings. If the gene is expressed at a high level and the target is stable, this makes for an ideal RNA sequenced to be used in a PCR.

Attachment for Table or Figure (Limit 1 tab of fig per submission)



Examples of motif effects on energy. **A.** The motif which we discovered and labeled MEME-ChIP 9 may destabilize RNA sequence reads. (Right) This motif may increase the minimum free energy. (Left) This motif may increase the ensemble free energy. **B.** The motif which we discovered and labeled MEME-28 may stabilize RNA sequence reads. (Right) This motif may decrease the minimum free energy. (Left) This motif may decrease the ensemble free energy. **C.** The motif which we discovered and labeled MEME-15 may not have an effect on RNA sequence read stability. (Right) This motif does not seem to affect the minimum free energy. (Left) This motif does not seem to affect the ensemble free energy.

Safety Profile of Silver Carboxylate as an Antimicrobial Coating: Viability and Mechanism in Human Cells

2023 Lifespan Research Day Abstract Submission Contest

Research Category: Clinical & Translational, Innovation
Primary Research Location: CORO West, Orthopaedic suite 402F
Funded By: NIH R03, CARTD

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Abstract

Background: The growing burden of antibiotic resistant pathogens warrants rapid attention to developing novel antimicrobial modalities. This is coupled with the heavy cost incurred upon hospitals and patients due to chronic surgical site infections, with 300k–500k cases occurring annually in the US and a monetary cost of upwards of $1.5B. The aim of this project is to analyze the cytotoxic effect of a novel antimicrobial, silver carboxylate, on human cells involved in surgical wounds. Silver carboxylate may provide an improvement to antibiotics in that silver induces bacterial death in a multimodal fashion, and the organic moiety improves entry of the silver ion into bacterial cells. We are specifically investigating the apoptotic versus necrotic mechanism with the goal of inhibiting apoptosis and improving human cell viability while promoting microbial death.

Methods: Human osteoblasts, endothelial cells, skeletal muscle cells, and keratinocytes were exposed to silver carboxylate in increasing multiples of the MIC for 24 hours. Silver carboxylate was delivered in a novel TiO_2–PDMS matrix to induce controlled release. Cell viability and apoptosis/necrosis were measured using specific fluorescent markers and fluorometry.

Results: The 1x MIC of silver carboxylate was shown to not impact cell viability, whereas the 10x–150x conditions did result in increased cell death. Preliminary mechanistic results suggest a 39% increase in apoptosis from the 1x MIC to the 10x MIC in skeletal muscle cells. The 1x MIC did not induce a statistically significant level of apoptosis.

Conclusion: Silver carboxylate does not impact human cell viability at the 1x MIC, and may induce an apoptotic–like mechanism of cell death in human cells above a 1x concentration. Further work is necessary to improve the power of the conclusion and further characterize results using flow cytometry.

Clinical Implications: Understanding the mechanism of cell death is critical because an apoptotic mechanism can be inhibited, resulting in improved cellular viability. Silver carboxylate in the TiO_2–PDMS matrix is being studied for application as a novel antimicrobial coating for surgically implanted materials, to mitigate the risk of chronic bacterial seeding post–operatively. This innovative biomaterial may also have beneficial synergistic effects when used conjunctively with current antibiotics.

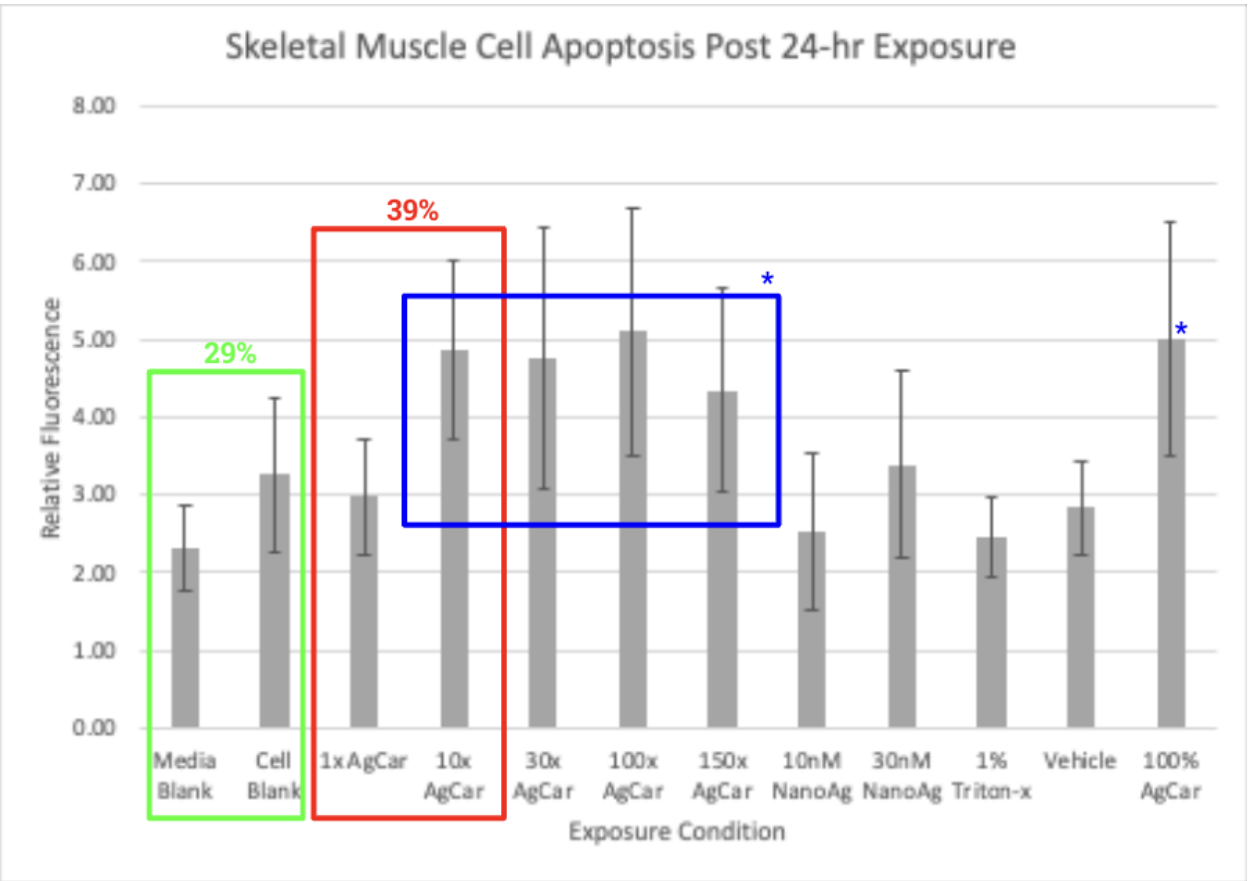

Figure 1. Levels of apoptosis in skeletal muscle cells after 24hr condition exposure. Statistically significant increase in apoptosis seen between the 1x and higher AgCar concentrations as well as the media and cell blanks. N=24

Using Outcomes Data to Drive Innovation in a Virtual Adolescent Partial Hospitalization Program

2023 Lifespan Research Day Abstract Submission Contest

Research Category: Clinical & Translational, Innovation
Primary Research Location: Bradley Hospital
Funded By: Bradley Hospital

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Gabrielle Beaudoin, Bradley Hospital. Dept of Psychiatry & Human Behavior
Marissa Marcus, Bradley Hospital. Dept of Psychiatry & Human Behavior

Abstract

Background: In a time of unprecedented mental health care demands, partial hospitalization programs (PHPs) are crucial to the overall continuum of care. PHPs are intensive programs that fill the gap between inpatient and outpatient services. They are more comprehensive than weekly outpatient care but allow for the development of coping skills within community environments rather than in a more restrictive environment (Vlavianos & McCarthy, 2022). Lifespan has been at the forefront of this model of care for several decades by providing partial levels of care to children, adolescents and adults (e.g., Musella et al., 2016; Musella & Hedrick, 2019; Zimmerman et al., 2023). During the COVID−19 pandemic, many of these programs were adapted for telehealth, leading to innovative models of care beyond the pandemic. This presentation aims to present research on the effectiveness of the Bradley REACH virtual PHP on adolescent psychosocial functioning compared to in−person programs.

Methods: Adolescents ages 12−18 participating in Bradley's in−person (N = 243) and virtual (N = 119) PHPs completed questionnaires at admission and discharge. Therapies were the same aside from treatment modality. The battery of outcome measures included the Difficulties in Emotion Regulation Scale, the Family Assessment Device, and the Youth Outcomes Questionnaire.

Results: Repeated measures ANOVAs demonstrated significant improvement in adolescent emotion regulation, family discord, intrapersonal distress, interpersonal difficulties, suicidal ideation, self−injurious behaviors, somatic problems, oppositional behaviors, and substance use in both the virtual and in−person PHPs from admission to discharge. Somatic symptoms improved more in the virtual PHP compared to the in−person PHP. All other treatment outcomes were the same across programs.

Conclusion: Data from Bradley Hospital's virtual and in−person adolescent PHPs suggests virtual treatment is feasible and effective for teens and their families. These results have propelled exciting opportunities to develop this evidence−driven care model to increase access to care in Rhode Island and beyond.

Clinical Implications: Virtual partial programming is an evidence−based and inventive approach to meeting the needs of the community and expanding access to mental health services for a variety of populations. This data provides evidence that supports the scaling process for Bradley REACH and other virtual mental health services.

Plasma Progerin in Patients With Hutchinson− Gilford Progeria Syndrome: Immunoassay Development and Clinical Evaluation

2023 Lifespan Research Day Abstract Submission Contest

Research Category: Clinical & Translational, Innovation
Primary Research Location: Rhode Island Hospital and Boston Children's Hospital
Funded By: The Progeria Research Foundation

Author(s):

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Abstract

Background: Hutchinson–Gilford progeria syndrome (HGPS) is an ultra–rare, fatal, premature aging disease caused by the toxic protein, progerin. Circulating progerin has not been previously detected, precluding research using readily available biological samples. This study aimed to develop a plasma progerin assay to evaluate progerin's quantity, response to progerin–targeted therapy, and relationship to patient survival.

Methods: Biological samples were collected by The Progeria Research Foundation Cell and Tissue Bank from a nonHGPS cohort cross–sectionally and a HGPS cohort longitudinally. HGPS donations occurred at baseline and intermittently while treated with farnesylation inhibitors lonafarnib ± pravastatin and zoledronate, within 3 sequential open label clinical trials at Boston Children's Hospital totaling up to 13 years of treatment. An ultrasensitive single molecule counting progerin immunoassay was developed. Intra–and inter–patient group statistics were descriptive. The relationship between progerin and survival was assessed using joint modeling with time–dependent slopes parameterization.

Results: Study was originally published as 'Plasma Progerin in Patients With Hutchinson–Gilford Progeria Syndrome: Immunoassay Development and Clinical Evaluation'. Circulation. 2023;147(23), Gordon, et al. Mean plasma progerin in nonHGPS participants (N=69) was 351±251pg/mL, and in drug–naïve participants with HGPS (N=74) was 33,261±12,346 pg/mL, reflecting a 95–fold increase ($p<0.0001$). Lonafarnib treatment resulted in an average per–visit progerin decrease from baseline of between 35–62% (all $p<0.005$); effects were not augmented with pravastatin and zoledronate. Progerin levels fell within 4 months of therapy and remained lower for up to 10 years. The magnitude of progerin decrease positively associated with patient survival ($p<0.0001$). For any given decrease in progerin, life expectancy incrementally increased with longer treatment duration.

Conclusion: A sensitive, quantitative immunoassay for progerin was developed and used to demonstrate high progerin levels in HGPS plasma that decreased with lonafarnib therapy. The extent of improved survival was associated with both the magnitude of progerin decrease and duration at lower levels. Thus, plasma progerin is a biomarker for HGPS and its reduction enables short and long–term assessment of progerin–targeted treatment efficacy.

Clinical Implications: The quantitative relationship between plasma progerin and HGPS patient survival solidifies the clinical relevance of progerin measurement and its potential for use as a clinical treatment trial outcome measure.

Comparing wrist acrigraphy to a novel wearable (Actigpatch): Nonparametric activity estimation

2023 Lifespan Research Day Abstract Submission Contest

Research Category: Basic Science, Innovation

Primary Research Location: COBRE Center for Sleep and Circadian Rhythms in Child and Adolescent Mental Health

Funded By: R01AA025593, P20GM139743. Actigpatches provided by Circadian Positioning Systems

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Abstract

Background: Wrist actigraphy is a standard for monitoring sleep in the field; however, data quality is reduced if participants remove the device. The Actigpatch is a novel, adhesive water−resistant wearable that we have previously demonstrated as comparable to wrist actigraphy for traditional sleep−wake estimation. Here we compare assessment of nonparametric activity indexes.

Methods: While following fixed schedules, 39 participants simultaneously wore the Micro Motionlogger actigraph (Ambulatory Monitoring Inc., Ardley, NY) on their non−dominant wrist and the Actigpatch (Circadian Positioning Systems, Newport, RI) over the triceps of their dominant arm. Our analyses included 35 participants (21F; 32.9±13.2yrs) who contributed =four nights of data (range: 4−14 [mean: 10] nights). After matching devices' tri−axial actimetry in one−minute epochs, we derived key non−parametric parameters of diurnal activity and calculated intraclass correlations to measure agreement. The non−parametric parameters include interdaily stability (IS), intradaily variability (IV), timing of the five hours of lowest activity (L5onset) and ten hours of highest activity (M10onset), and overall relative amplitude (RA).

Results: We observed agreement ranging from good for IS (ICC=0.77 [95%CI=0.59;0.88]; [all mean differences are patch−watch] mean difference=−0.21) to poor for IV (ICC=0.43 [0.12;0.67]; mean difference=0.29). ICC showed good agreement for M10onset (ICC=0.82 [0.67; 0.90]; mean difference=−37min) and excellent agreement for L5onset (ICC=0.91 [0.82;0.95]; mean difference=−2min). Finally, we identified good agreement when estimating the activity relative amplitude (RA ICC=0.86 [0.75; 0.93]; mean difference=0.03). An example of excellent agreement was manifested in the close estimation of L5onset (patch mean=1:04am, SD=70min; watch mean=1:06am, SD=68min).

Conclusion: Adding to our prior evidence that these two devices offer similar sleep−wake estimation using traditional algorithms, the present data indicate the Actigpatch offers good agreement to the Motionlogger for nonparametric analyses of IS, activity timing, and RA. Agreement was not as good for IV, with the Actigpatch showing more intradaily variability than the watch, perhaps due to the triceps placement. Because the Actigpatch is unobtrusive, water−resistant, and can be worn continuously for three weeks, it has potential benefits for studies of individuals who struggle with adherence to wearing wrist worn devices.

Clinical Implications:

Center of Biomedical Research Excellence (COBRE) Center for Sleep and Circadian Rhythms in Child and Adolescent Mental Health: Pediatric Biopsychology Core (PBC)

2023 Lifespan Research Day Abstract Submission Contest

Research Category: Innovation
Primary Research Location: 1 Hoppin St, Providence, RI 02903
Funded By: COBRE

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Abstract

Background: Aim 1: The primary aim of the Center is to select, mentor, and provide career advancement to junior investigators as RPLs and in a Pilot Project Program. Aim 2: The second aim of the Center is to institute CORE facilities that will sustain the infrastructure required to build a Center of Biomedical Excellence in sleep, circadian rhythms, and pediatric mental health. Aim 3: The final aim of the Center is to recruit faculty with expertise in sleep and circadian science in the context of pediatric mental health to augment the Center's academic and mentoring capacity.

Methods: The PBC is structured to support pediatric mental health assessment; provide consultation for collection, maintenance, and analysis of such data, including use of technology–based resources; and provide resources and consultation for collection, storage, and processing biospecimens. Listed below highlights our services provided to date: 1. REDCap Project Setup 2. Assisted with using EMR for recruitment 3. Provided information for IRB guidelines and ethical use of EMR in research 4. Created materials for guiding the use of reference managers 5. IRB Project Setup and Management for Project Leaders 6. IRB and REDCap Training for Research Assistants 7. Technology Consults– LifeData EMA Set Up, Sleep Diary EMA 8. DNA preparation, collection, extraction, and quantification training for RAs 9. Transitioned several of our clinical research programs to using new diagnostic interview 10. DIAMOND Interview Assessment training with Dr. David Tolin 11. Developed Diagnostic Interview Data Collection in REDCap 12. Consultation on storage and processing of biosamples through utilization of new COBRE equipment 13. Consultations for data analysis components of new projects

Results: To include future steps, available equipment, consultations, and other support provided to researchers at Lifespan.

Conclusion: The PBC is an important resource to support clinical research of sleep and adolescent mental health care within Lifespan.

Clinical Implications: Advancing research in the integration of sleep and child and adolescent mental health care to explore areas critical to improving the wellbeing of children and adolescents.

Identification and Mitigation of Bias in Multi−Modal Pulmonary Embolism Data to Improve Survival Analysis Prediction

2023 Lifespan Research Day Abstract Submission Contest

Research Category: Innovation

Primary Research Location: Rhode Island Hospital

Funded By: 701 1893 Diagnostic Imaging Research

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Abstract

Background: Bias in healthcare unfairly impacts lower socioeconomic populations and can be baked into predictive modeling datasets, especially in multimodal datasets where different biases can pool together. Our purpose is to develop a model that debiases multimodal Pulmonary Embolism (PE) datasets and to improve survival prediction (SP) over the current clinical standard of Pulmonary Embolism Severity Index (PESI).

Methods: 918 PE patients with 3978 CTPA images and 918 clinical reports were collected from 3 institutions including race, ethnicity, gender, survival time−to−event labels, and the 11 PESI variables. We extracted text and image features from clinical notes and scans. We then developed 3 SP modules with a baseline and debiased version; each module based on either PESI variables, clinical text features, or imaging features. For a multimodal prediction, the 3 SPs were integrated using CoxPH. Debiasing used disentanglement learning to measure and mitigate bias. We ran experiments to compare PESI predictions against our debiased multimodal SP model, debiasing and evaluating 1 population bias factor: race (White or not White), Ethnicity (Latino or not Latino), or Gender (Male or Female). Concordance(c)−index was used to measure accuracy of SP, with higher c−indexes meaning better predictions.

Results: Compared to PESI, our debiased multimodal SP had higher and more consistent c−indexes with lower biases across race, ethnicity, and gender experiments. The Latino PESI c−index was 0.481, significantly lower than the non−Latino PESI c−index of 0.687, indicating PESI's poor prognosis for Latino populations. After ethnicity debiasing, the debiased SP Latino c−index was 0.731 and 0.723 for non−Latino populations. Similarly with gender disentanglement, we observed a female PESI c−index of 0.529 and male PESI c−index of 0.739. Gender debiased SP had a female c−index of 0.763 and a male c−index of 0.785.

Conclusion: Our results demonstrate that debiasing population bias in multimodal datasets is possible and improves SP. The debiased multimodal SP was more accurate and equitable for populations relative to the PESI standard.

Clinical Implications: Our work demonstrates a method to minimize population biases in multimodal datasets while producing a debiasing SP model that is more equitable and accurate than the current clinical standard of PESI. We offer an improvement in equity.

Table1: Performance of PESI Survival Prediction and Debiased Survival Prediction across the three different population bias groups using C-Index. The larger C-Index value means better survival prediction performance, and the lower bias is fairer.

Methods		**Race**				**Ethnicity**				**Gender**			
	Modal	Overall	White	Not White	Bias	Overall	Latino	Not Latino	Bias	Overall	Male	Female	Bias
	PESI	0.669	0.654	0.697	0.043	0.682	0.481	0.687	0.207	0.631	0.739	0.529	0.210
Debiased SP	Imaging	0.673	0.671	0.578	0.092	0.640	0.692	0.635	0.058	0.635	0.727	0.607	0.120
	Text	0.687	0.679	0.730	0.051	0.714	0.731	0.716	0.014	0.770	0.750	0.813	0.064
	Variable	0.706	0.687	0.784	0.096	0.655	0.538	0.666	0.128	0.615	0.587	0.625	0.038
	Multimodal	0.739	0.735	0.734	0.001	0.733	0.731	0.723	0.008	0.766	0.785	0.763	0.023

Assessing the acceptability of a mindful eating mobile app for adolescents

2023 Lifespan Research Day Abstract Submission Contest

Research Category: Clinical & Translational, Innovation
Primary Research Location: Hasbro Children's Hospital
Funded By: Children's Miracle Network

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Abstract

Background: Mindful eating can decrease maladaptive eating, and may be a good adjuvant to weight management interventions. Mobile health (mHealth) interventions are viable for youth behavior change and there is scarce literature on their use. The Unified Theory of Acceptance and Use of Technology (UTAUT) integrates key predictive constructs for the behavioral intention to use technology. The study's aim was to assess adolescent perceptions of an mHealth mindful eating intervention, as part of a study to develop a mHealth mindful eating intervention for adolescents.

Methods: 25 youth with overweight/obesity were recruited at a weight management clinic. Mean age 14.6y ± 1.5y; BMI 36.4 ± 7.8 kg/m2; 60% male; 57% Hispanic, 20% AA. Participants viewed videos from a mindful eating phone app. They completed a semi−structured interview and a survey based on UTAUT constructs (Table 1). Survey data was analyzed to examine internal validity. Bayesian principal component analysis was used to inform interpretation. A Framework Analysis approach was used to analyze the interview data.

Results: 96% of participants answered 'agree'/'strongly agree' to the statement 'Using a mindful eating app will help me develop a healthier relationship with food,' and 80% answered 'agree'/ 'strongly agree' to the statement 'I will use a mindful eating app if I have access to it.' Most weights were large (.. > 0.5) except for facilitating conditions (.. = 0.01), which all teens endorsed (Table 1). The association with behavioral intention was positive (.. ^ = 0.15, 95% CI [0.07, 0.23]). Reliability was acceptable (0.70). Inductive codes included attitude, flexibility and overall perception. Deductive codes included easy to understand, educational, appealing, engaging. Results pointed to app features that adolescents consider important additions, including closed captions, a colorful interface, text reminders, and gamification. Interview responses supported the findings from the survey in that participants were overall receptive to a mindful eating app.

Conclusion: Survey data showed internal consistency reliability and concurrent validity. Qualitative data supported the findings from the UTAUT−based survey.

Clinical Implications: Use of a mindful eating app for adolescents is acceptable and feasible. Future directions include pilot testing the mindful eating app in adolescents with overweight/obesity.

Construct	Loading	Average (1-5)	Statements
Performance Expectancy	0.73 [0.34, 1.12]	4.20 [3.45, 4.70]	Using a mindful eating app will help me develop a healthier relationship with food
Performance Expectancy	0.23 [-0.19, 0.65]	4.29 [3.55, 4.75]	Using a mindful eating app will improve my chances of eating healthier
Performance Expectancy	0.69 [0.31, 1.14]	3.94 [3.16, 4.53]	Using a mindful eating app will help me be healthier overall
Effort Expectancy	0.24 [-0.19, 0.65]	3.47 [2.67, 4.18]	Learning how to use a mindful eating app will be easy for me
Effort Expectancy	0.43 [0.01, 0.83]	3.81 [3.02, 4.44]	I will find a mindful eating app easy to understand, use and navigate
Social Influence	0.76 [0.38, 1.17]	4.67 [4.06, 4.94]	My parents will think it is a good idea for me to use a mindful eating app
Social Influence	0.57 [0.15, 1]	3.94 [3.16, 4.53]	Other people who are important to me will think it is a good idea to me to use a mindful eating app
Facilitating Conditions	0.01 [-0.43, 0.42]	4.80 [4.26, 4.98]	I have what I need (smartphone, time, skills) to be able to use a mindful eating app
Attitudes Toward Technology	0.51 [0.14, 0.97]	4.58 [3.94, 4.91]	Using a mindful eating app is a good idea to help me eat healthy
Self Efficacy	0.66 [0.25, 1.14]	3.86 [3.06, 4.47]	I am confident that I will be able to use a mindful eating app
Anxiety	-0.69 [-1.16, -0.29]	2.27 [1.62, 3.07]	I think using a mindful eating app could make me worry or hurt my feelings
	Reliability	**Concurrent validity**	
Estimate	0.70 [0.50, 0.85]	0.15 [0.07, 0.23]	I will use a mindful eating app if I have access to it
		0.19 [0.11, 0.27]	I will participate if there is a study to use a mindful eating app for teens

Note: reported are the estimates and 98% CI. A more conservative 98% CI was selected because we had performed an interim analysis to be consistent with the alpha spending approach.

Characterizing the Antimicrobial Profile of Silver Carboxylate in Methicillin−Resistant S. aureus MW2/VRS1 − Derived Persister Cells

2023 Lifespan Research Day Abstract Submission Contest

Research Category: Basic Science, Innovation

Primary Research Location: Providence, RI

Funded By: P20GM103430/ P20GM121344, NIAIG R03AI159776, NIH/NIAID R25, NIH/NIAID R25AI140490

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Abstract

Background: Due to the misuse of antibiotics, surgical site infections (SSIs) by antimicrobial−resistant (AMR) pathogens are an increasing threat to the US healthcare system. Furthermore, the stagnant discovery of new antibiotics requires the development of novel approaches to combat these infections. Thus, research has turned to organometallics as a possible solution, specifically silver due to its multimodal bactericidal properties. To harness silver's capabilities, we have developed a silver carboxylate (AgCar) compound released via a titanium dioxide−PDMS matrix. In this study, we assess AgCar's ability to induce reactive oxygen species (ROS) release and peroxidase (POD) activity in Methicillin−Resistant S. aureus (MRSA) strains MW2 and VRS1 persister cells.

Methods: To generate persister cells, MRSA MW2 and VRS1 strains were grown to stationary phase overnight, then exposed to 20X and 4X antibiotic MIC respectively, to ensure the formation of persister cells. For ROS and POD assays, MW2/VRS1 persister cells were placed in 96−well plates and exposed to a gradient of AgCar from 1x to 150x for 6 hours. The levels of ROS and POD were assessed by the manufacturer's protocol for each of the respective kits. 10nm and 30nm nano−silver will serve as a positive control, and 1% triton X and titanium dioxide−PDMS matrix will serve as negative controls. Replicates of n=12 were done for each condition.

Results: When compared to untreated persister cells, MRSA MW2 persister cells treated with 30X−150X silver carboxylate demonstrated a statistically significant fold change increase in ROS release (100%−fold change, $P<0.05$), while VRS1 persister cells did not show statistically significant fold change in ROS release when treated with 1X−150X silver carboxylate. Peroxidase activity was not significantly different between treated and untreated persister cells.

Conclusion: Silver carboxylase demonstrates the potential for combating MRSA persister cells by inducing ROS stress without allowing bacteria to respond with appropriate antioxidant enzymes such as peroxidase. However, further research into the bactericidal mechanisms of silver carboxylase is required.

Clinical Implications: If properly harnessed, AgCar's multimodal antimicrobial capabilities have the potential to be an essential tool against AMR pathogens, especially when used synergistically with existing drugs.

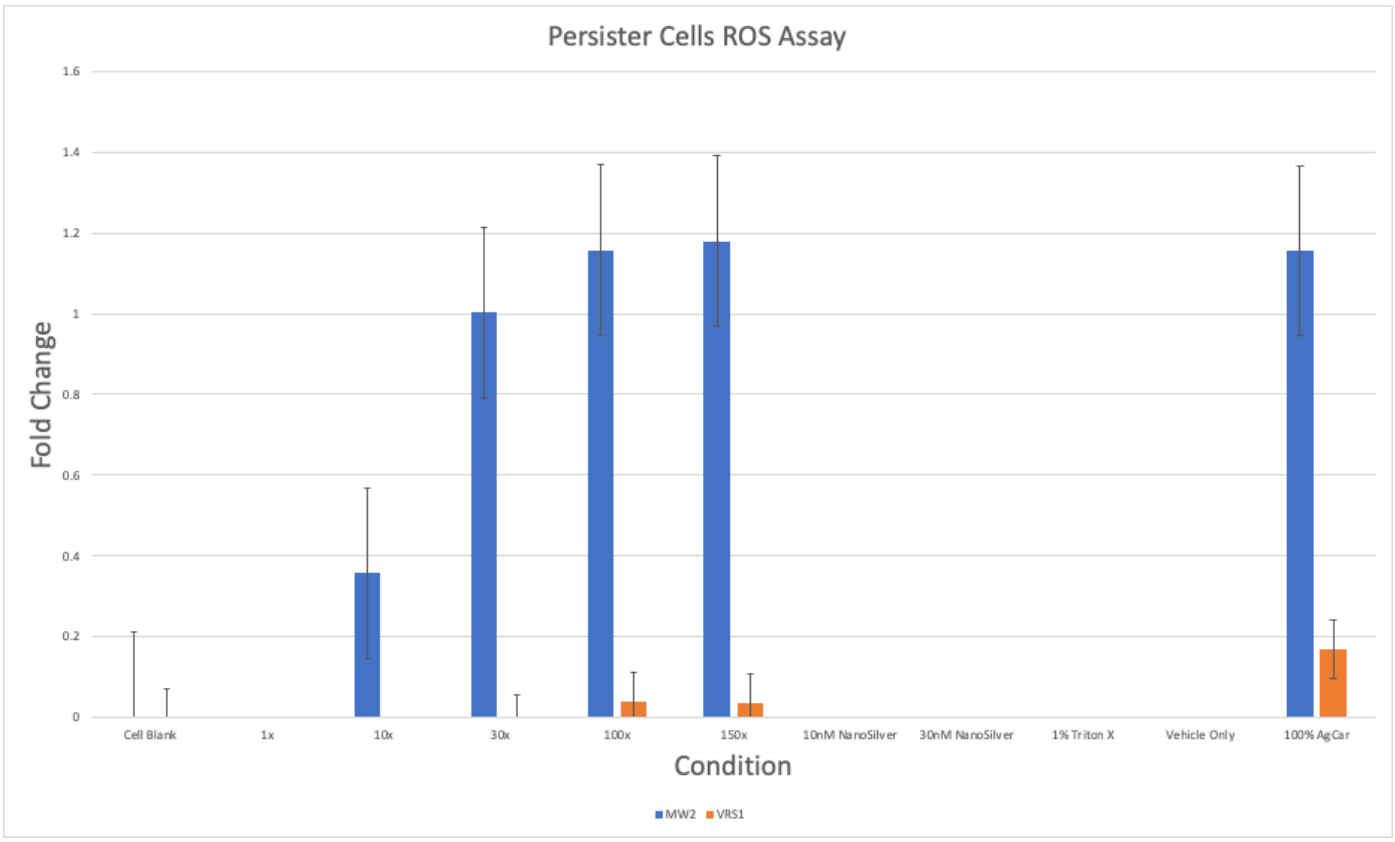

Figure 1. Fold change of ROS presence in persister cells of MRSA strains MW2 and VRS1.

Silver Carboxylate Antibiotic−Independent Antimicrobial: Exploration of Potential Solutions for the Post−Antibiotic Era

2023 Lifespan Research Day Abstract Submission Contest

Research Category: Clinical & Translational, Innovation

Primary Research Location: The Diane N. Weiss Center for Orthopaedic Trauma Research, Brown University

Funded By: P20GM103430/ P20GM121344, NIAIG R03AI159776, NIH/NIAID R25, NIH/NIAID 5R25AI140490 & T35 HL094308

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Abstract

Background: Antibiotic resistance has been steadily rising due to increased use of synthetic antibiotics, lack of novel antibiotics, and poor stewardship, leading to a perilous 'post−antibiotic era.' Prompt innovation is crucial to avoid millions of deaths from antibiotic−resistant infections by 2050. Organometallics offer a potential solution, and our group has developed a silver carboxylate (AgCar) compound with distinct bactericidal mechanisms. This study presents an overview of the release pharmacokinetics of AgCar in Titanium dioxide−polydimethylsiloxane (TiO2−PDMS) matrix, its safety concerning human−derived cell lines, antimicrobial efficacy, biofilm dysregulation, and impact on the viability of persister cells.

Methods: Antimicrobial efficacy was evaluated using Vancomycin−Resistant Enterococcus faecalis, Methicillin−sensitive Staphylococcus aureus, and Methicillin−resistant Staphylococcus aureus strains MW2 and VRS1 on 96−well plates and PEEK implants. Bacteria were exposed to varying concentrations of silver carboxylate, 'last resort' antibiotics, nanoparticle silver, colloidal silver, and controls, for 24 hours. The safety assessment of silver carboxylate on human−derived cell lines [osteoblasts, keratinocytes, and skeletal muscle cells (SKMs)] involved subjecting the cells to the same antimicrobial conditions, and cell viability was assessed using MTT assay. Each condition was replicated n=15, and biofilm imaging was performed using confocal microscopy.

Results: 10X minimal inhibitory concentration (MIC) demonstrated consistent, significantly greater elution than 1X at 96 hours, with sustained persister cell killing over 72 hours. Concentrations above 10X MIC improved biofilm eradication. 1X MIC showed comparable or lower cytotoxicity compared to crude silver and 'last resort' antibiotics, especially in SKMs. 10X exhibited increased cytotoxicity across all cell lines. Silver carboxylate outperformed most last resort antibiotics at 1X and 10X MIC against all tested pathogens. At 10X MIC, it effectively dispersed and neutralized biofilms.

Conclusion: Our study revealed that 1X silver carboxylate demonstrated comparable or lower cytotoxicity to crude silver formulations and tested antibiotics. 10X silver carboxylate showed higher antimicrobial efficacy in bacteria, persister cells and biofilms, however it also exhibited significant cytotoxicity across human lines.

Clinical Implications: Silver carboxylate in TiO2−PDMS matrix shows promise as a novel antimicrobial coating for surgical implants, potentially reducing the risk of post−operative bacterial infections. Our data suggests that this innovative biomaterial could be a viable alternative; however, further investigation into cytotoxicity is necessary.

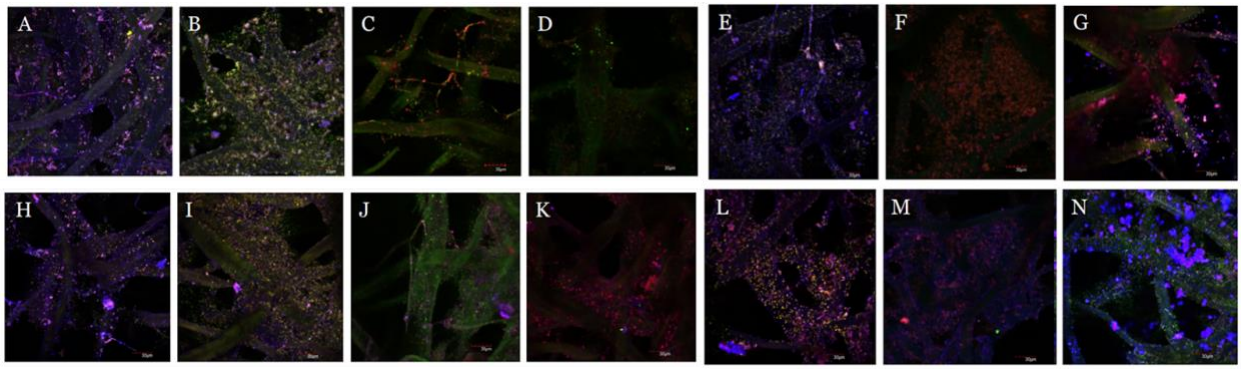

Figure 1: Biofilm Images of MRSA MW2 and VRS1 in response to silver carboxylate treatment: A, B, C, D, E, F, and G show confocal images of biofilms for MW2. Image A is an untreated biofilm, and Images B, C, D, and E were treated with 1x, 10x, 30x, and 300x AgCar, respectively. Image F was a positive control treated with 100% AgCar, Image G was treated with vehicle only. All biofilms were stained with SYPRO, TOTO-1, and Concanavalin A (594).