1917 2021 104

RHODE ISLAND MEDICAL JOURNAL

ZOOM – It's a Match!

Virtual National Match Day is largest on record

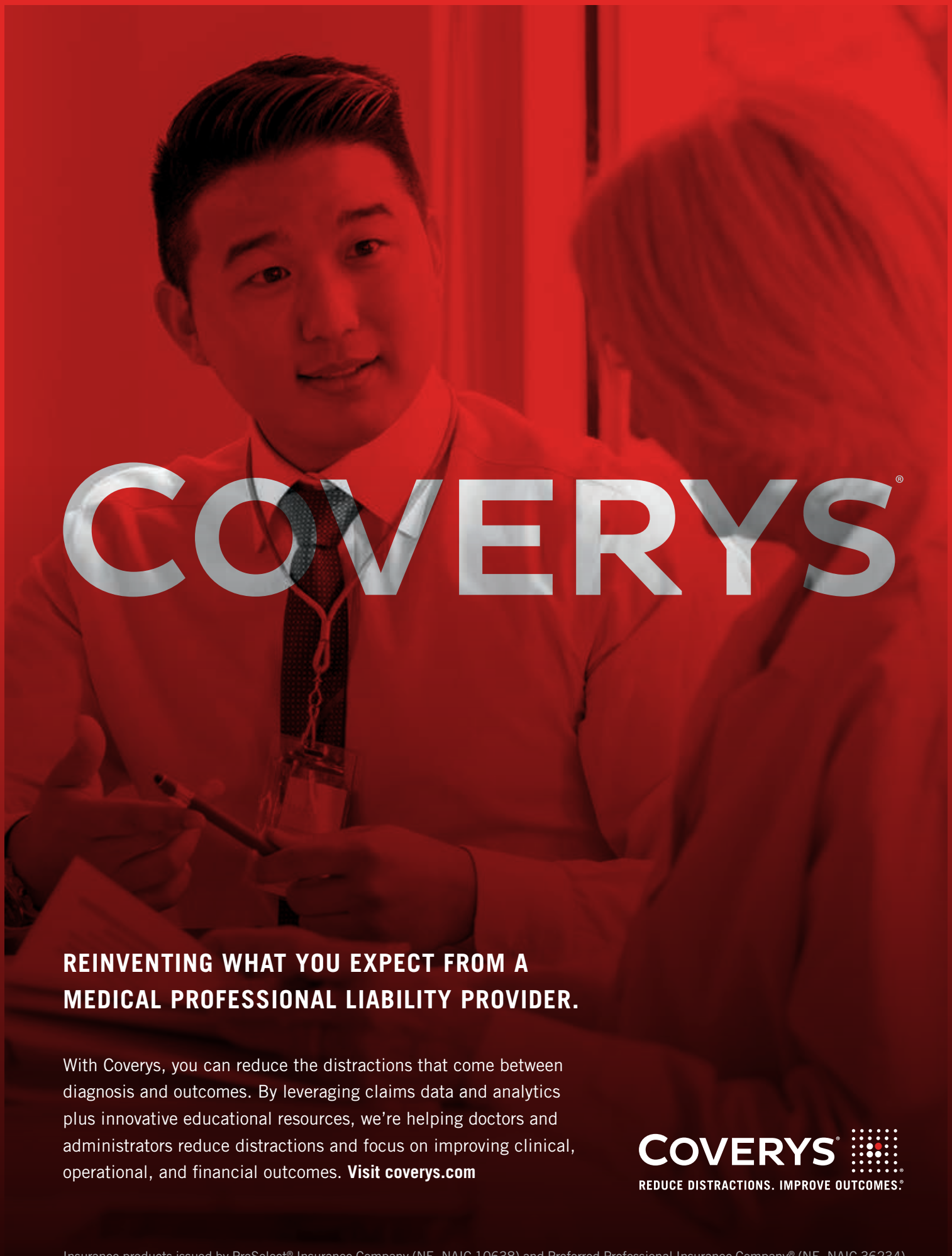
See page 75

SPECIAL SECTION, PART II

BIOMEDICAL/TRANSLATIONAL RESEARCH *in* RI

GUEST EDITORS: JAMES PADBURY, MD; BONGSUP CHO, PhD

APRIL 2021 VOLUME 104 • NUMBER 3 ISSN 2327-2228



REINVENTING WHAT YOU EXPECT FROM A MEDICAL PROFESSIONAL LIABILITY PROVIDER.

With Coverys, you can reduce the distractions that come between diagnosis and outcomes. By leveraging claims data and analytics plus innovative educational resources, we're helping doctors and administrators reduce distractions and focus on improving clinical, operational, and financial outcomes. **Visit coverys.com**

COVERYS®

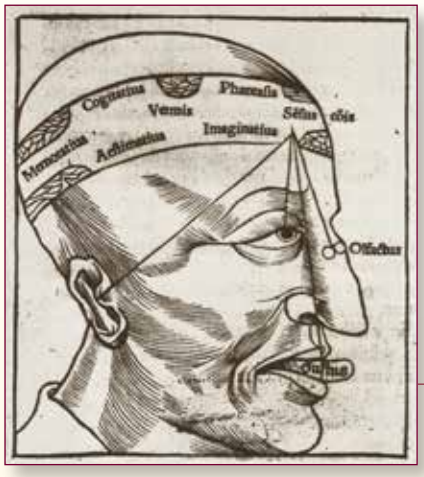
REDUCE DISTRACTIONS. IMPROVE OUTCOMES.®

RHODE ISLAND
MEDICAL JOURNAL


James F. Padbury, MD


Bongsup Cho, PhD

RHODE ISLAND
MEDICAL JOURNAL



RHODE ISLAND MEDICAL JOURNAL

IN THE NEWS

PEOPLE/PLACES

APRIL 2021
VOLUME 104 • NUMBER 3

RHODE ISLAND MEDICAL JOURNAL

RHODE ISLAND MEDICAL JOURNAL (USPS 464-820), a monthly publication, is owned and published by the Rhode Island Medical Society, 405 Promenade Street, Suite A, Providence RI 02908, 401-331-3207. All rights reserved. ISSN 2327-2228. Published articles represent opinions of the authors and do not necessarily reflect the official policy of the Rhode Island Medical Society, unless clearly specified. Advertisements do not imply sponsorship or endorsement by the Rhode Island Medical Society.

IMAGES IN MEDICINE

CASE REPORT

CONTRIBUTIONS

PUBLIC HEALTH

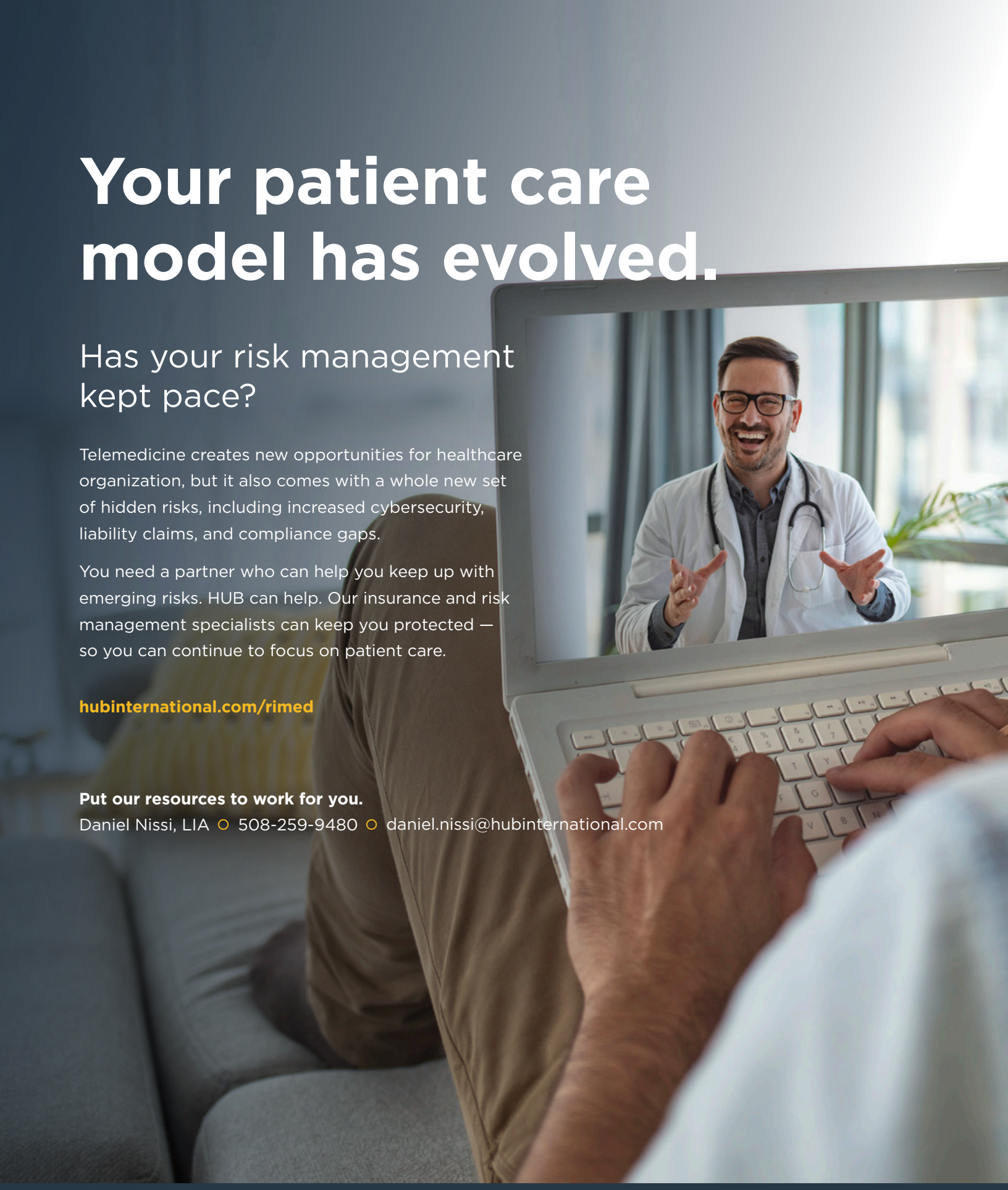
Your patient care model has evolved.

Has your risk management kept pace?

Telemedicine creates new opportunities for healthcare organization, but it also comes with a whole new set of hidden risks, including increased cybersecurity, liability claims, and compliance gaps.

You need a partner who can help you keep up with emerging risks. HUB can help. Our insurance and risk management specialists can keep you protected — so you can continue to focus on patient care.

hubinternational.com/rimed



Put our resources to work for you.

Daniel Nissi, LIA ○ 508-259-9480 ○ daniel.nissi@hubinternational.com

HUB

Risk & Insurance | Employee Benefits | Retirement & Private Wealth

[*Editor's Note: The following commentary was written by the late Stanley M. Aronson, MD, founding dean of the Alpert Medical School of Brown University, who served as Editor-in-Chief of the* Rhode Island Medical Journal *for more than a decade.*]

Searching for a Lost Cousin during the Depression and War Years

Tribute to an Israeli physician

STANLEY M. ARONSON, MD

If they achieved little else, the Depression years of the 20th Century left us with enduring memories. Those early Depression years witnessed bank failures, families evicted from their homes for failure to pay rent, soup kitchens on major street corners and ill-clad men wandering the streets at midday seeking itinerant employment. But there was also a fragile sense of hope that the recent election of President Franklin D. Roosevelt might counteract the economic and emotional despondency which gripped the nation in 1932.

In the Brooklyn tenement where I lived as a teenager, we learned the principles and exigencies of food shortages the hard way. And yet I also vividly recall that there were always two small tin boxes on our kitchen table, somewhere near the salt cellar. One can bore the name Palestine in pale blue letters and the other was nameless. Every week we would deposit into each can the few coins that the family could spare. The money in the named receptacle was then forwarded to the Jewish National Fund to support the development of the Land of Israel, and the other was to support my mother's brother in Czernowitz, Romania, particularly his ailing wife and son, my cousin Hugo.

During the 1930s my mother would go to the local post office each month to purchase postal money orders, which were then faithfully mailed to the old country. And each month we received word from Europe of Cousin Hugo's educational progress, how well he did and finally, in 1936, when he was admitted to medical school in the city of Cluj, in northern Romania.

September 1939: War breaks out in Europe

When war arrived in Europe on the first day of September 1939, my family lost contact with Hugo and his family. The years that followed were years of silence and increasing anguish that Hugo and his family had become victims of the Romanian fascist government. And when Germany invaded the Soviet Union in the summer of 1941, occupying Romania in the process, we were convinced that Hugo and his family had been consumed by the spreading Holocaust.

In the early spring of 1946, when I was returning from the Army, I received a call from my mother excitedly exclaiming, "Hugo is alive!" The family gathered to review a brief and cryptic letter that my mother had received, postmarked from Turkey, written by Hugo and with little information as to where he had been during the seven terrible years of silence, how he managed to get to Turkey, where he was currently living or whether his parents were yet alive. The family had no way of communicating with him and the weeks that followed were weeks of anguish.

Months passed with no further word from Hugo and during that interval we learned from other sources that Hugo's family back in Czernowitz were all victims of the Holocaust. Hugo's letter, by then a precious family document, was read and reread during the months of silence. Early in 1947 we finally received word from Hugo, now postmarked from the Palestinian Mandate, indicating that Hugo had managed to travel through Syria and French-held Lebanon, to cross into British-controlled Palestine. He reported that he was in reasonably good health but had no possessions except for a very precious document that he had preserved in a waterproof container bound to his chest. It was, of course, his diploma from the university in Cluj, indicating that he was the possessor of the M.D. degree.

In the early spring of 1946, when I was returning from the Army, I received a call from my mother excitedly exclaiming, "Hugo is alive!"

Long years' flight to freedom

Where was he from 1939 to '47? From Cluj he traveled by foot to Moldavia in the east, found his way into the Ukraine, which was overrun by advancing German troops in 1941, and joined

the refugee masses all attempting to survive. His newly developed medical skills probably kept him alive in the vast refugee gatherings of the southern Ukraine, and when the war ended he found his way to northern Turkey across the Black Sea. By 1947 he survived yet another trek, into British Palestine.

In the years that followed, Hugo joined the Israeli Defense Force serving honorably, then married a refugee from Austria, established a family-oriented practice of medicine in the city of Gedera and enlarged his family with the births of two sons.

Hugo Hassner never aspired to achieve academic recognition in Israel. He practiced his medical art with a sense of humility and commitment, never joining any of the medical faculties or the staffs of any of the impressive hospitals of his nation. Yet within Gedera he was revered as a devoted practitioner of medicine who spoke a badly accented but earnest Hebrew. One of his sons joined the Israeli diplomatic corps and the other became a physician in the field of endocrinology.

My mother, who died in 1963, was never well enough to make the trip to Israel, but she received an abundance of letters from her nephew, Hugo, always beginning with the tender words, "Liebe Tante Lena."

My daughter, Sarah, received her M.D. degree in 1987 and after a year of medical internship in Connecticut, resolved to practice in Israel for two years. One of her first actions, of course, was to visit my cousin Hugo. They spent much time together and shared many family stories, both happy and sad.

I visited Israel for the first time in 1989, eagerly anticipating a visit with Hugo. But coronary disease has neither sentiment nor respect for hallowed memory and Hugo died before we met. I am heartened by the reality that Hugo's life was fulfilled and that he and Sarah, after more than half a century, reunited the family. ❖

New Rules for Patient Data Sharing Risk Harm to our Most Vulnerable

JESSICA J. POURIAN, MD; DANIEL COGHLIN, MD

KEYWORDS: 21st Century Cures Act, data sharing, adolescent health, confidentiality, health data

Starting this April, patients will be able to access their electronic medical records (EMR) through online patient portals soon after their providers finish their notes. This immediate access will be rolled out as part of the 21st Century Cures Act, a 2016 law passed with broad bipartisan support, which included significant changes for health data sharing. Though some practices have historically allowed patients to see lab results and certain notes, the Cures Act will roll out data access on an unprecedented scale, everywhere. Under the new law, "information blocking," a practice where a provider prevents or discourages access to health information, becomes illegal.

Giving patients ownership of their data is a noble goal – studies show that patients who are more engaged with their care have improved adherence to medications and better patient-provider communication.[1] Facilitating more patient-provider interactions through online portals has been shown to help address health disparities, especially in patients of color, and to improve patient satisfaction.[2,3] This is particularly important given that we are in the midst of the COVID-19 pandemic, where telemedicine is increasingly used to manage patient care.

Adolescent data/privacy concerns

However, the new law lacks important nuance on who can access what data and what they can do with it. The Cures Act makes no distinction between adult and pediatric patients, leaving teens in a dangerous grey area. State laws vary dramatically regarding parental access to adolescent data, including whether minors have a right to full confidentiality regarding sexually transmitted infection (STI) screening.[4] In Rhode Island, minors have a right to confidentiality for STI and pregnancy screening. By default, healthcare data will be accessible to the patient themselves as well as anyone who legally acts on their behalf, such as a caregiver or parent. While a parent accessing the data for the well-child visit of their three-year-old makes sense, the possibility for parents to intrude on the physician-patient relationship for their adolescent children may carry a risk of significant harm. The guarantee of confidentiality has been shown repeatedly to be one of the most important factors for adolescents seeking healthcare. If teenage patients cannot trust their providers to keep issues of sexual health or substance use – risky behaviors which all peak during adolescence – confidential from their parents, we risk them not disclosing anything at all.[5] This withholding could have lifelong consequences – a simple chlamydia infection, for example, can lead to permanent infertility if left untreated.[6] And accidental disclosure for sensitive issues such as gender identity or sexual orientation may cause serious harm to the patient.[7]

We began piloting a note sharing throughout our academic medical center at the end of 2020 in anticipation of the coming changes this spring. Within a month of rollout, we learned that some protected adolescent behavioral health notes were accessed by parents. Upon further investigation, it became clear that many pediatric charts listed the parents' phone numbers and email addresses as the patients' contact information, which provided parents with enough information to obtain access to their adolescent children's portals. With our system sharing notes by default for thousands of kids (in compliance with the impending changes of The Cures Act), it was impossible to distinguish which notes were being sent to the teen versus the parent. As a result, our hospital reached the difficult decision to inactivate all adolescent portal accounts prior to the onset of the Cures Act enforcement date and then offer teens the option to re-enroll in person. This approach provides confirmation that the patient's phone number and email address are the ones linked to their electronic health information moving forward. This effort has been an enormous logistical challenge. Our institution's vulnerability to adolescent confidentiality is likely far from unique; we suspect countless other offices and clinics will discover analogous threats as they conform to the information-blocking statutes.

Additional concerns

Adolescents are not the only population at risk from data oversharing. Children in foster care may suddenly find that an estranged biological parent has their new address and healthcare information. Victims of domestic abuse – both children and adults – may face retaliation at home if their abuser sees that violence was discussed in a clinic note. With the Cures Act, all an individual needs is a password to get instant access to extremely sensitive and confidential data.

This is to say nothing of the other elephant in the room – the security risk of a data breach considering the coming EMR integration with third-party applications, which will become more prevalent under the Cures Act. Nationally, there have been repeated data breaches by careless companies and concerted efforts by hackers to access healthcare data. The Cures Act will enable a tremendous flow of health data, yet it provides no regulation for third parties. Mobile app companies have already demonstrated that they need more oversight: it is estimated that 79% of popular health apps routinely share user data, often without informing the patient.[8] The FDA has not provided any regulations surrounding cybersecurity of healthcare data, and the Health Insurance Portability and Accountability Act of 1996 (HIPAA) protections do not apply to third party applications – once that data is out, the patient no longer owns it.

The current wording of the law allows doctors to block release of a specific note or datapoint only if it "prevents harm." However, this vague wording leaves interpretation up to individual institutions and practitioners, for whom values and incentives may differ. Hospitals may face fines in the millions for instances of information blocking, potentially making it challenging for physicians to advocate for a patient's privacy on a note-by-note level if hospital policy dictates otherwise. As a result, physicians may self-censor in their notes or water down their conclusions to avoid offending patients in an attempt to preserve the physician-patient relationship.[9,10] Worries over data sharing may also cause providers to take even longer to write their notes – in institutions where note sharing has already begun, 37% of physicians report spending more time on documentation than before.[11]

Challenges concerning data privacy within electronic medical records are not new, but the advent the 21st Century Cures Act may bring these difficulties to the forefront of medicine. HIPAA is not enough – we need clearer protections on a national level for our most vulnerable patient populations. National medical societies should move urgently to publish guidance and lobby Congress for patient privacy rights, both for specifics on information blocking and for what third-party apps are permitted to do with health data. We also desperately need technical solutions from our EMR vendors that will enable providers to safeguard patient information without overwhelming us with additional documentation, which contributes disproportionately to physician burnout.[12]

As physicians, we must take care of our patients both in the exam room and in cyberspace. If we cannot remain a trusted, confidential resource, we risk harming our most vulnerable patients. ❖

References

1. Dendere R, Slade C, Burton-Jones A, Sullivan C, Staib A, Janda M. Patient portals facilitating engagement with inpatient electronic medical records:A systematic review. J Med Internet Res. 2019;21(4).
2. Gerard HC. The Importance of Visit Notes on Patient Portals for Engaging Less Educated or Nonwhite Patients: Survey Study. J Med Internet Res. 2018;20(5):191.
3. Walker J, Leveille S. OpenNotes After 7 Years: Patient Experiences With Ongoing Access to Their Clinicians' Outpatient Visit Notes. J Med Internet Res. 2019;21(5).
4. Guttmacher Institute. An Overview of Consent to Reproductive Health Services by Young People. Published October 2020. Accessed October 11, 2020. https://www.guttmacher.org/state-policy/explore/overview-minors-consent-law#
5. Ford CA, English A. Limiting confidentiality of adolescent health services: What are the risks? J Am Med Assoc. 2002;288(6):752-753.
6. Murray PJ, Braverman PK, Adelman WP, et al. Screening for nonviral sexually transmitted infections in adolescents and young adults. Pediatrics. 2014;134(1):302-311.
7. McGeough BL, Sterzing PR. A Systematic Review of Family Victimization Experiences Among Sexual Minority Youth. J Prim Prev. 2018;39(5):491-528.
8. Grundy Q, Chiu K, Held F, Continella A, Bero L, Holz R. Data sharing practices of medicine-related apps and the mobile ecosystem: Traffic, content, and network analysis. BMJ. 2019;364:920.
9. Blease C, O'Neill S, Walker J, Hagglund M. Sharing notes with mental health patients: balancing risks with respect. The Lancet Psychiatry. 2020;7(11):924-925.
10. Dobscha S, Denneson L. VA mental health clinician experiences and attitudes toward OpenNotes. Gen Hosp Psychiatry. 2016;38:89-93.
11. DesRoches C, Leveille SB. The Views and Experiences of Clinicians Sharing Medical Record Notes With Patients. JAMA Netw. 2020;3(3).
12. Ehrenfeld JM, Wanderer JP. Technology as friend or foe? Do electronic health records increase burnout? Curr Opin Anaesthesiol. 2018;31(3):357-360.

Authors

Jessica J. Pourian, MD, PGY-1, Department of Pediatrics, Warren Alpert Medical School of Brown University, Providence, RI.

Daniel Coghlin, MD, Associate Professor, Clinician Educator, Department of Pediatrics, Warren Alpert Medical School of Brown University, Providence, RI.

Correspondence

Jessica J. Pourian, MD
Department of Pediatrics
593 Eddy St.
Providence, RI 02903
jessica_pourian@brown.edu

Cognitive Sinks & the Bermuda Triangle of fMRI Cognitive Studies

JOSEPH H. FRIEDMAN, MD

(POSTER PRESENTATION, 2021 WORLD CONGRESS OF SPECIAL HONORED GUESTS: INVITED, HELD VIRTUALLY DUE TO COVID-19.)

Cognitive sinks (CS) have attracted increasing amounts of attention since the earliest medical and scientific publications.[1,2] However, the topic has developed an inertia of its own as neuropsychiatry and neuropsychology have expanded, to cover topics that were initially deemed "fringe" but have become more mainstream as their importance has become more clearly defined. Cognitive sinks are people who, without drugs or physical contact, reduce the intelligence of those around them simply through bidirectional written or verbal communication. This is not a voluntary or controllable effect. It occurs passively and only as a result of communication. Typically, the involved party is unaware of his/her effect on others and the effect appears to be variably perceived by the affected. Equally interesting is that this effect violates the second law of intellectual thermodynamics, the conservation of mass intellect. In a group that includes a cognitive sink, the mean IQ of the group declines, as some suffer a decline which lasts for a variable period of time, probably dependent on duration and severity of exposure.[3-6] The conundrum caused by this violation of 150 years of neuropsychology research findings has yet to be explained.

METHODS

Only right-handed volunteers over 5′ tall were allowed to participate. Five patients identified as likely cognitive sinks by the investigator in the course of normal clinic evaluations were asked to volunteer and then confirmed as CS using validated scales.[10-14] Healthy age-matched controls (HC) were recruited from an undisclosed location. This protocol was approved by Flexible IRB, Inc. Subjects and controls provided informed consent.

fMRI was obtained at baseline on each subject, along with the Neurostat psychological/intelligence battery. One HC was randomly assigned to 1 CS and met in a soundproof room. They were encouraged to talk to each other and given a list of topics to consider if conversation flagged. The session was considered complete when each participant had been recorded in a conversation for 30 minutes. Within 5 minutes of ending the session, both subjects had a repeat fMRI, and given the same verbal and logical test questions as at baseline.

RESULTS

fMRI and cognitive testing revealed no differences at baseline between the two groups, both in voxel-to-voxel comparisons as well as in volumes predefined to include 1,000 voxels (see supplemental tables). After 1 hour of conversation, there were differences only in a region forming a triangle, bridging Brodmann's regions 39, 41 and 44, encompassing Wernicke's and Broca's areas, plus the insular cortex.

A human head in profile with lines from the ear, the eye, nose, and tongue to a point on the forehead; a band around the head labels the areas of the brain that are vital to the memory, imagination, cognition and the senses.

[NATIONAL LIBRARY OF MEDICINE, ARS MEMORATIVA GUILELMI LEPOREI AVALLONENSIS, L. IV VERSO; HTTP://RESOURCE.NLM.NIH.GOV/101435889.]

Patterns of network coherence showed insufficient activity in the region described to even attempt a comparison between baseline and follow-up in the subjects. Oxygen extraction imaging techniques showed a marked reduction ($p<00001$) in blood flow to this region as well, post exposure. Interestingly, the findings on both sides were symmetric (axis of symmetry coefficient $K=10^{-5}$). Activity in these was stable in the cognitive sinks, indicating no change in blood flow as a result of the conversations. Measures of brain activity during arithmetic, geometric, memory and language tasks all showed reduced activation measures compared to baseline in the subjects. "Super-fast" neuropsychological testing (Neurostat testing) before and after the conversations, administered within 5 minutes of the completion of the fMRI, showed a decline in measures of generalized intellectual function, which was compatible with an equal reduction in each of the basic 5 neuropsychological domains.

Repeat testing the next day revealed a return to baseline in all subjects.

DISCUSSION

In this pilot study we demonstrated that intelligence, as measured by Neurostat testing and self-report, suffered as a result of the intervention (structured conversation with the cognitive sink), and that a change in brain functioning, measured by various fMRI parameters, was evident in a restricted region of the brain, termed "the Bermuda triangle," since brain activity, as measured by fMRI, was indistinguishable from background "noise." This is a considered a "dead zone," in fMRI parlance. Of note is that brain function, as measured by the very same measures used to document the change, all returned to baseline by the next day.

These findings have implications for understanding brain physiology, as well as for the interpretation of fMRI. In terms of physiology, they violate Lashley's law of "mass action" but support, albeit in a modified manner, the concept of "equipotentiality," theories based on ablation studies in which the volume of neuronal tissue removed rather than location, determine intelligence changes, as measurable in non-humans. These results confirm the isolated reports of physiological declines associated with exposure to cognitive sinks. Further studies are needed to confirm these preliminary ones, but unique ethical concerns need to be addressed. ❖

References

References are available from the author on special request.

Financial disclosure

Supported by grants from the Defense Advanced Research Projects Agency (DARPA).

Acknowledgment

The above is validated as an April Fool's Day production of Joseph H. Friedman, MD.

Author

Joseph H. Friedman, MD, is Editor-in-chief Emeritus of the *Rhode Island Medical Journal,* Professor and the Chief of the Division of Movement Disorders, Department of Neurology at the Alpert Medical School of Brown University, chief of Butler Hospital's Movement Disorders Program and first recipient of the Stanley Aronson Chair in Neurodegenerative Disorders.

'Man Therapy' website addresses suicide risk in men

Program introduced in Washington County

"According to science, men have feelings, too." Or so says Dr. Rich Mahogany, Man Therapy's (www.ManTherapy.org) fictional therapist, who uses humor and "manspeak" to tackle the age-old stigma that gets in the way of many men talking honestly about their emotions and mental health.

As part of our Zero Suicide efforts, *Healthy Bodies Healthy Minds Washington County* is bringing Man Therapy™ to men in our community. Our goal is to help reduce suicide risk and improve overall mental health among our men. This initiative comes at a particularly critical time. The mental health impacts of the COVID pandemic include well-documented increases in mortality from drug overdose and suicide, with working aged men at particularly high risk.[1]

Man Therapy helps to reshape conversations and tackle issues (like depression, divorce, substance abuse, and even suicidal thoughts) head on, the way a man would do it. Man Therapy provides men, as well as the people who care about them, a place to go online and learn more about men's mental health, complete a "20-point head inspection," and consider a wide array of actions that can put them on the path to mental wellness.

Since "Men can't fix their mental health with duct tape!", we encourage healthcare providers to promote this new, free and anonymous resource among their patients and colleagues. Learn more at www.mantherapy.org. To stay updated about our campaign in Washington County or get involved, follow us on Facebook @ManTherapyWashington County and Twitter @ManTherapyWC or email us at mantherapyWC@gmail.com.

Sincerely,
Robert Harrison, Jr., MD
Project Director, Washington County Zero Suicide Program
Healthy Bodies, Healthy Minds Washington County,
the region's Healthy Equity Zone

Reference

1. Hallowell, BD et al. (2020). Accidental Drug Overdose Deaths in Rhode Island: January 1, 2016–July 31, 2020. RIMJ 103(10): 62-65.

AMA statement on CMS decision to update Medicare payments for administrating COVID-19 vaccine

"The Biden administration acted promptly in updating the Medicare payment rate for COVID-19 vaccine administration. The updated rate reflects new information about the costs involved in administering the vaccine for different types of providers and suppliers, and the additional resources necessary to ensure the vaccine is administered safely and appropriately."

"The American Medical Association and the AMA/Specialty Society RVS Update Committee (RUC) met early with the Biden transition team, Congress, and the Centers for Medicare & Medicaid Services and advocated for an increase payment for the administration of these life-saving vaccines for Medicare patients, while ensuring there were no out-of-pocket costs for patients. The additional resources will increase the number of clinicians who can administer the vaccine."

"This has been a trying time for physician practices, and we thank the administration for acknowledging the challenges of practicing medicine during a pandemic."

Susan R. Bailey, MD
President, American Medical Association

Translational Research: The Time is Now

JAMES F. PADBURY, MD
BONGSUP P. CHO, PhD
GUEST EDITORS

The National Institutes of Health (NIH) Roadmap identified the need to develop new research pathways and inter- and cross-disciplinary research teams to accelerate clinical research and solve enigmatic problems.[1] This critical need has been intensified by advances in genome science and transformational improvements in technology over the years. Whole-genome DNA sequencing of humans and model organisms is not only realistically possible and economically feasible, but it is also widespread. The opportunity has emerged to use cell and molecular techniques to decipher the "secrets of the genome" and initiate therapies based on a wide array of "omics" platforms. Breakthroughs in gene editing and gene therapy are changing the landscape of cancer, genetic, and metabolic disorders. Nonetheless, many clinicians do not yet recognize this as part of their "core business." Likewise, many basic scientists lack the clinical insights of their medical colleagues. This is due to traditional, if not parochial, disciplinary barriers. Still, for the most part, it is due to lack of knowledge and awareness of new developments in rapidly evolving scientific trajectories. Many new therapeutic options in medicine will derive from a new generation of clinical researchers having a facility with the lexicon of cell and molecular biology, genomics, next-generation sequencing, semantic data-mining, large datasets, informatics tools, and an ability to conduct extensive clinical research initiatives employing integrated, federated databases.

The past decades have been associated with changes in society and the public's interface with the healthcare system. With increasing income inequality and economic uncertainties, access to healthcare has become ever more fragmented. Disruptions in access to care and preventive services have led to a worsening of long-standing healthcare problems. In addition, racial, ethnic, socio-economic and geographic differences across our community are increasingly associated with significant health disparities. Both the opioid epidemic and the COVID-19 pandemic, while sparing no racial or ethnic group, have had a disparate impact on minority and rural populations. Notably, the effect of behavioral and mental health problems on individuals and populations' overall health has become increasingly recognized. These are challenges that affect the healthcare systems and the people in all domiciles of the United States. However, the impact of each varies by region, race, income, and historical factors. Recognition of these factors' interplay with the extraordinary breakthroughs in clinical and basic science is among the challenges faced by clinical and translational research programs. Whether it is through efforts to bring discoveries from the "bench to the bedside," to effectively testing new clinical applications, or to generalize advances to broader populations, the clinical and translational research enterprise needs to address health disparities head-on to improve health across the translational research continuum and to serve our communities.

In the previous issue of the Journal, we presented contributions from "basic science" biomedical-oriented Institutional Development Award (IDeA) programs in Rhode Island. In this issue we highlight programs for their "clinical" and "translational" impact on research and research opportunities. **ADAM CZYNSKI** et al describe studies to develop systematic approaches to the care of infants with Neonatal Opiate Withdrawal Syndrome (NOWS). **TRACI GREEN** et al provide an overview of the COBRE on Opioid and Overdoses, a collaborative research-based center addressing the opioid crisis in Rhode Island. **PETER MONTI** et al describe the Center for Addiction and Disease Risk Exacerbation (CADRE), a COBRE that is establishing a thematically linked, state-of-the-art, multidisciplinary Center investigating mechanisms whereby substance use increases risk for or exacerbates chronic disease. **SUNIL SHAW**'s overview of the COBRE for Perinatal Biology (CPB) describes their scientific focus on perinatal diseases such as preeclampsia and preterm birth, as well as more broadly on cardiopulmonary development and reproductive biology. **JEROME SANES** presents a description of the COBRE Center for Central Nervous System Function: Progress and Perspectives. **VALERIE ZABALA** has provided an overview of the Advance Clinical and Translational Research (Advance-CTR) award's efforts to bridge translational research gaps by creating a statewide hub to coordinate and leverage existing research resources and provide new career development support and funding for academic researchers, particularly junior investigators.

As we noted in our first Edition, our goals are to enhance understanding of these dynamic programs among the clinical, biomedical, and scientific research community and drive usage of the extraordinary resources that have been made available through the IDeA programs. We are fortunate to have been awarded this endowment of resources and are using them to strengthen our region's biomedical enterprise.

Reference

1. Zerhouni E. Medicine. The NIH Roadmap. Science. 2003 Oct 3;302:63-72.

Guest Editors

James F. Padbury, MD, Principal Investigator of Advance-CTR, William and Mary Oh - William and Elsa Zopfi Professor of Pediatrics for Perinatal Research, Brown University, Providence, RI.

Bongsup P. Cho, PhD, Professor of Pharmacy, University of Rhode Island, Program Director of Rhode Island IDeA Network of Biomedical Research Excellence (RI-INBRE), Kingston, RI.

Correspondence

James F. Padbury, MD
james_padbury@brown.edu

The Time is NOW: Filling the Gaps in Treatment of Opioid-Exposed Infants: A Prospective, Pragmatic, Randomized Control Drug Trial

ADAM J. CZYNSKI, DO; ABBOT R. LAPTOOK, MD

ABSTRACT

The opioid epidemic has reached into all aspects of life in the United States. The epidemic has crossed racial, economic, social, and generational barriers. This epidemic also impacts infants. Fetal exposure to opioids can produce a withdrawal effect in newborns, referred to as Neonatal Opioid Withdrawal Syndrome (NOWS). NOWS treatment lacks a standard approach, with prominent variation across the United States. Furthermore, many treatment strategies for NOWS are not evidence-based but reflect anecdotal experience. Variable approaches to NOWS treatment contribute to more extended hospital stays and greater postnatal opioid exposure. The most prolonged period of NOWS treatment occurs during the weaning phase. This paper describes the first prospective randomized control trial to address systematized weaning of opioids for infants with NOWS.

KEYWORDS: Neonatal Opioid Withdrawal Syndrome, Neonatal Abstinence Syndrome, Substance Use Disorder, Opioids

INTRODUCTION

The opioid epidemic in the United States has affected all aspects of our society, including pregnant patients and their newborns. The incidence of maternal opioid use in the United States has increased substantially since 2000,[1] affecting both rural and urban communities.[2] The rise in opioid use is not just in illicit substances, but in prescription opioids, and a subsequent surge in medication-assisted treatment.[3] The increased incidence of opioid use in pregnancy has contributed to an increase in Neonatal Opioid Withdrawal Syndrome (NOWS), the clinical syndrome that reflects the signs of opioid withdrawal in newborns. The National Institutes of Health (NIH) has developed an aggressive research strategy to make headway in the epidemic under the initiative's umbrella, Helping to End Addiction Long-Term (HEAL).[4] HEAL is a trans-agency national initiative to address the opioid public health crisis. In 2019, the Health Care Cost and Utilization Project by the Agency for Healthcare Research and Quality (AHRQ)[5,6] reported rates of NOWS from < 3.2 to > 10.9 newborns per 1000 births. NOWS rates vary by region within the United States.[2] The rates are particularly high across the Northeast and the Appalachian states. The states most affected are West Virginia, Vermont, and Kentucky, where rates are 48.1, 28.0, and 22.9 per 1000 live births.[2] While NOWS initial focus was on newborn hospitalization, there is now growing recognition that NOWS effects extend beyond the neonatal period and impact developmental outcomes.[7,8] Also, infants with NOWS have increased hospital readmission rates than infants without opioid exposure (46.3/1000 vs. 25.6/1000 live births in 2016.[9] Hospital readmission reflects higher rates of failure to thrive, seizures, and child abuse. This article will focus on the neonatal aspects of opioid withdrawal to identify gaps in treatment approaches and a recently initiated clinical trial to fill these gaps.

BACKGROUND

A recent Journal of Pediatrics editorial emphasized the rapid rise of NOWS in the United States. It provided a framework to target research initiatives and care delivery innovations for these infants.[10] Research and quality improvement initiatives should be safe, effective, patient-centered, equitable, and achieve the goals of limiting ongoing infant opioid exposure, minimizing family separation, and reducing healthcare expenditures. To date, there is a lack of randomized clinical trials that rigorously evaluate aspects of NOWS treatment.[11]

Quality improvement (QI) methods to standardize NOWS treatment have been successful in reducing the length of therapy (LOT) and hospital stays among affected infants.[12,13] There is the acceptance that initial care should be individualized, supportive and non-pharmacologic. This has been the focus of many QI initiatives.[3] These measures include minimizing environmental stimuli,[14] encouraging breastfeeding, and providing on-demand nutrition. If non-pharmacologic strategies cannot control NOWS signs, pharmacological therapy is indicated. The pharmacological treatment uses opioid replacement to control NOWS signs to avoid severe central nervous system dysfunction. In contrast to QI initiatives addressing non-pharmacologic strategies, limited randomized clinical trials guide NOWS pharmacologic treatment.

Pharmacologic treatment traditionally begins once an infant has reached a predetermined threshold using a NOWS

assessment tool. There are many different NOWS assessment tools; the original and gold standard is the Finnegan Neonatal Abstinence Scoring System (FNASS).[15] Irrespective of the assessment tool, once a child crosses the treatment threshold, opioid replacement therapy (ORT) occurs in three phases: initiation, stabilization, and weaning. Initiation is the start of ORT, stabilization is the interval of time where no further escalations in dose are needed, and weaning consists of serial reductions in ORT and/or lengthening the time interval between doses.

Medical professionals generally agree on ORT phases, but they do not agree on a standard of care for pharmacologic treatment of NOWS.[16] Clinical teams may use different drugs as first-line agents (morphine, methadone, or buprenorphine) and second-line agents (phenobarbital or clonidine), with limited data to guide either. To date, there have been five trials that have enrolled a total of 345 infants.[12-16] Three trials were terminated early due to slow recruitment.[17-19] These trials compared morphine to another medication for NOWS treatment (phenobarbital, methadone, or buprenorphine). The inclusion of morphine in each arm reflects that morphine has been used most widely for ORT. This was further supported by data from the ACT NOWS Current Experience, a retrospective chart review conducted among the IDeA States Pediatric Clinical Trials Network (ISPCTN) and Neonatal Research Network (NRN) indicated that morphine was the first-line drug for ORT in 86% of NOWS infants and represented one of the few aspects of care without variation.[20] The ACT NOWS Current experience data affirms the historical use of morphine and reflects limited high-quality data to effect change in treatment.

Of the three phases of opioid replacement therapy, the weaning phase is the longest and contributes to the greatest variation on length of hospitalization. Like other aspects of NOWS care, there is no standardized approach to weaning ORT. A review of practice guidelines from over 20 centers in the ISPCTN and NRN affirm the weaning decrements' variability. Centers most often wean ORT by a percentage reduction of the stabilization dose, varying from 10% to 15%; some centers even reduce by 20%. Although a standard of care for weaning morphine does not exist, the plurality of existing clinical trials used 10% reductions of the stabilizing dose.[17-19,21,22] The interval between dosage weans also varies by center and ranges from every 12 to 48 hours. This facet of weaning was absent from the prior trials and remained a significant gap in previous studies' interpretation.

The weaning phase of ORT has the greatest variation and thus shortening the weaning phase has the greatest potential to impact healthcare costs. Based on data from the ACT NOWS Current Experience, the average LOS for pharmacologically treated infants is 14.6 days. A treatment reduction of 2.0 days represents a14% reduction in treatment duration and has the potential to reduce healthcare costs by more than $15.7 million per year. Potential cost savings would be even greater for hospitals that care for NOWS infants in NICUs or special care nurseries. Unfortunately, there are no randomized trials to inform clinicians of potentially better regimens to wean morphine or methadone.

OPPORTUNITY FOR AN INTERVENTION

The absence of a well-studied weaning strategy contributes to wide practice variation adding to LOS and costs. Since clinical teams want to minimize NOWS signs' recurrence as drug treatment is reduced, and a state of inertia is often perpetuated whereby clinical consensus drives decisions rather than an evidence-based protocol. It is easy for clinical teams to adopt a "let's wait another day" mentality. Given the potential to reduce healthcare costs with a systematic weaning strategy, investigators at Women & Infants Hospital of Rhode Island are leading a large multicenter randomized trial to develop an evidence-based weaning strategy. The trial's hypothesis is that among infants receiving an opioid (defined as morphine or methadone) as the primary treatment for NOWS, a rapid-wean intervention (15% reduction from stabilization dose) will reduce the days of opioid therapy from the first weaning dose to the cessation of opioid, compared to a slow-wean intervention (10% reduction from stabilization dose). This trial will be a pragmatic, randomized, blinded trial. It will compare what is used by most centers (10% decrements from the stabilization dose) with an emerging practice of faster weaning (15% decrements from the stabilization dose). The following is an overview of this clinical trial's essential elements, which began recruitment in September of 2020.

INCLUSION CRITERIA

The study has both site-level and patient-level inclusion and exclusion criteria. Site- inclusion criteria are that the hospital provides pharmacologic treatment to at least 12 opioid-exposed infants each year, uses a scoring system to assess for signs of NOWS, and the primary opioid replacement therapy is either morphine or methadone. Site-level exclusion criteria are discharging more than 10% of infants from the hospital on opioid replacement therapy.

Infant-level inclusion criteria are gestational age ≥ 36 weeks, receiving scheduled pharmacological therapy with morphine or methadone as the primary drug treatment for NOWS secondary to maternal opioid use, and tolerating enteral feeds and medications by mouth. Infant-level exclusion criteria are major birth defects, surgery, hypoxic-ischemic encephalopathy, seizures, treatment with opioids for reasons other than NOWS, respiratory support greater than 72 hours, use of other opioids for NOWS, and/or weaning before randomization.

PRAGMATIC FEATURES

This is a pragmatic, randomized, blinded trial of opioid weaning; **Figure 1** illustrates when the study interventions will occur during the hospitalization.

The treatment of NOWS has regional, state, and center differences. With such variation, this trial purposely incorporated pragmatic components into the design. A practical design's benefits are to gain acceptance among participating centers and allow center-specific management practices for NOWS treatment after birth and before randomization. The protocol-directed elements are limited to direct care management after randomization during the weaning phase. Pragmatic features may include the following practices:

- Location of care for the infant (mother-baby unit, Neonatal Intensive Care Unit (NICU) or Pediatric floor, etc.).
- Monitoring frequency of vital signs and the use of cardiopulmonary monitors.
- Agreement to optimize non-pharmacologic treatment based on choice from a protocol-provided standardized bundle.
- Use of breast milk and breastfeeding.
- Scoring assessments of NOWS signs.
- Scoring criteria to initiate ORT and thresholds for weaning vs. escalation of study drug.
- Choice of opioid (morphine or methadone) as the primary treatment and dosing to initiate pharmacological therapy.
- Initiation and dosing adjustment of the second- and third-line drugs for NOWS signs (e.g., phenobarbital, clonidine) if NOWS signs are not adequately controlled with ORT.
- Duration of stabilization whereby the clinical team determines the interval over which no further drug dosage changes are needed to control NOWS signs before weaning is initiated.

The pragmatic components will hopefully bolster recruitment and center engagement. To account for the pragmatic elements in the data analysis, randomization will be stratified by center.

STUDY INTERVENTION

Infants will be randomized to either a rapid-wean intervention arm (15% reduction from stabilization) or a slow-wean intervention arm (10% reduction from stabilization) whenever the clinical team weans the opioid (**Figure 2; Table 1**). The clinical team will discontinue ORT when the infant can tolerate 25% or 20% of the stabilization dose without NOWS signs in the rapid- and slow-wean arms, respectively.

There are eight weans or dose levels for the rapid- and slow-wean intervention arms, each representing the amount of opioid the clinical team will administer. Infants in the rapid-wean intervention arm will undergo 5 study drug weans followed by three placebo levels. Infants in the slow-wean

Figure 1. Timing of Study Intervention in Relationship to Hospital Stay

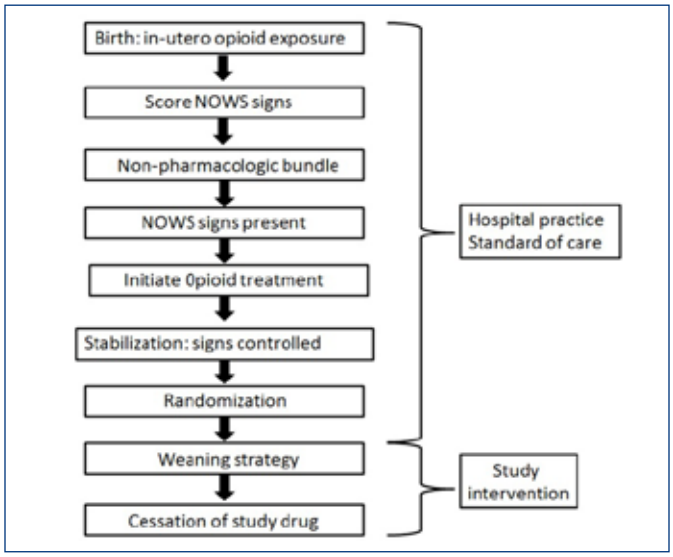


Figure 2. Overview of the Study Intervention

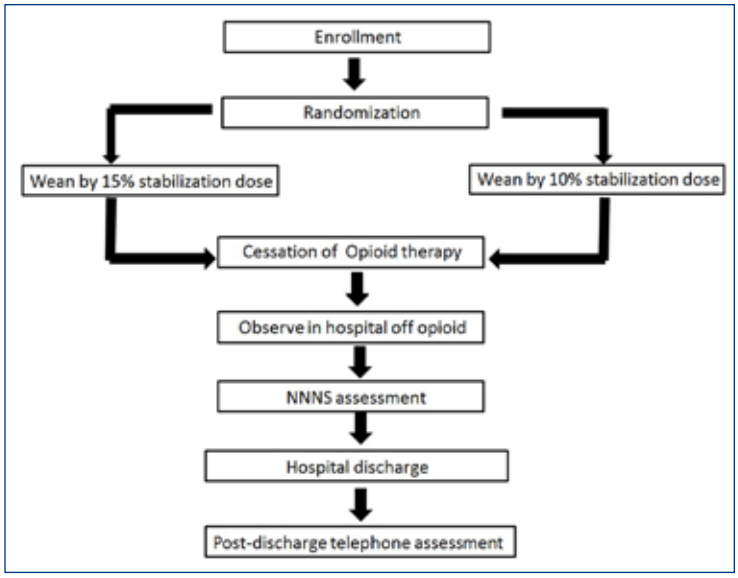


Table 1. Dose Levels of the Rapid-Wean and Slow-Wean Interventions

Dose	Rapid wean: 15% of stabilization dose	Slow wean: 10% of stabilization dose
Stabilization Dose	100%	100%
Dose Level A	85%	90%
Dose Level B	70%	80%
Dose Level C	55%	70%
Dose Level D	40%	60%
Dose Level E	25%	50%
Dose Level F	Placebo	40%
Dose Level G	Placebo	30%
Dose Level H	Placebo	20%

arm will undergo 8 study drug steps and no placebo levels. The rapid-wean intervention arm requires three placebo levels to maintain the blind. If opioid escalation does not occur, the infant will receive eight dose levels over 8 study days. However, if there are escalations, the clinical team will need to repeat the prior higher dose level (escalation), and there will be eight dose levels but more than 8 study days.

The trial has specific elements that centers must declare as part of the weaning intervention. Centers can choose which opioid, morphine, or methadone they plan to administer and at which frequency. Centers that choose morphine will need to select a dosing frequency of either every 3 hours or every 4 hours. Centers that choose methadone will need to select a dosing frequency of either 8 or 12 hours.

The clinical team will use hospital-specific assessment tools to determine the severity of NOWS signs, and infants with NOWS will be scored with these tools every 3 to 4 hours. Based on the assessment scores and as directed by center practices, infants who reach a threshold for escalation during the weaning phase will resume the previous dose level. To avoid the inertia among clinical centers when weaning drug ORT, centers will need to either wean or escalate every 24 hours. Centers are free to wean more rapidly and can escalate before 24 hours if center guideline criteria are met. Should a patient not reach center thresholds for escalation, the protocol will direct them to wean the infant. In situations where an infant is approaching the end of 24 hours and the team is concerned by a pattern of scores, the clinical team can monitor the infant beyond the 24-hour window until the concerning pattern dictates an escalation or a wean. This extended period can continue for 12 hours before it meets the criteria for a protocol violation. Hospitals do not need to use the entire 12-hour period to either wean or escalate if the infant completes the requirements before 12 hours.

STUDY OUTCOME

This study has a single primary outcome and multiple secondary outcomes. The primary outcome will be the number of days of opioid treatment (used as primary treatment), including escalation, resumption, and spot treatment, from the first weaning dose to opioid cessation. The primary outcome will be assessed by analyzing data from all infants undergoing rapid-wean compared to slow-wean with morphine or methadone. Days of opioid treatment is a single outcome that will be a function of a) the weaning algorithm and b) the extent of recurrence of NOWS signs. The use of hospital guidelines combined with study protocol guidelines will ensure that NOWS signs deemed clinically meaningful result in appropriate treatment of the infant. The trial's secondary outcomes will focus on 1) additional measures of efficacy, 2) safety, and 3) 18 months follow-up.

STATISTICAL ANALYSIS PLAN PRIMARY OUTCOME

This is an intention-to-treat trial, and the outcome of the primary hypothesis will determine intervention differences of two means by analyzing the average number of days of opioid treatment from the first weaning dose to the cessation of opioid therapy. The study is powered to enroll 502 infants with 251 infants to each arm, irrespective of the proportion of infants treated with morphine or methadone. The projected recruitment window is 3.3 years, with 25 centers enrolling. At present, 20 centers are participating, and additional centers are being evaluated for participation (**Figure 3**).

Figure 3. Map of ISPCTN, NRN, and Other Sites

CONCLUSION

When non-pharmacological therapy is inadequate to control NOWS signs, pharmacologic treatment is used. Unfortunately, there are heterogeneous practices in all aspects of pharmacological therapy. This proposed study is a pragmatic trial powered to detect a two-day difference in the LOT between a rapid- and a slow-wean intervention. Hospitals will be able to use either morphine or methadone with the knowledge that we may find a positive treatment effect for both, one, or neither drug. The speed that infants can be successfully weaned without recurrence of NOWS signs is unknown. If successful, this clinical trial will limit ongoing opioid exposure for infants, minimize separation of the family, and reduce healthcare expenditures.

References

1. Patrick SW, Schumacher RE, Benneyworth BD, Krans EE, McAllister JM, Davis MM. Neonatal abstinence syndrome and associated health care expenditures: United States, 2000-2009. JAMA. 2012;307(18):1934-40.
2. Patrick SW, Davis MM, Lehman CU, Cooper WO. Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States 2009 to 2012. J Perinatol. 2015;35(8):667.

3. McQueen K, Murphy-Oikonen J. Neonatal Abstinence Syndrome. N Engl J Med. 2016;375(25):2468-79.
4. National Institute of Child HEAL Initiative. NIH HEAL Initiative Research Plan 2020 [Available from: https://heal.nih.gov/about/research-plan.
5. H-CUP Healthcare Cost and Utilization Project. Trends in Neonatal Abstinence Syndrome Births in the United States Updated: January 18, 2018 2018. Available from: https://hcup-us.ahrq.gov/reports/Trends_NeonatalAbstinenceSyndrome_Births_UnitedStates.pdf
6. Agency for Healthcare Research and Quality. Number of Newborns with Neonatal Abstinence Syndrome Continued To Increase Through 2016. 2019. Available from: https://www.ahrq.gov/data/infographics/neonatal-abstinence-syndrome-2016.html.
7. Czynski AJ, Davis JM, Dansereau LM, Engelhardt B, Marro P, Bogen DL, et al. Neurodevelopmental Outcomes of Neonates Randomized to Morphine or Methadone for Treatment of Neonatal Abstinence Syndrome. J Pediatr. 2020;219:146-51 e1.
8. Iannery T, Davis JM, Czynski AJ, Dansereau LM, Oliveira EL, Camardo SA, et al. Neonatal Abstinence Syndrome Severity Index Predicts 18-Month Neurodevelopmental Outcome in Neonates Randomized to Morphine or Methadone. J Pediatr. 2020;227:101-7 e1.
9. Gaither J. E-PAS2020:1175.2.2020: Pediatric Academic Society. 2020. [cited 2021].
10. Patrick SW. The Triple Aim for Neonatal Abstinence Syndrome. J Pediatr. 2015;167(6):1189-91.
11. Wachman EM, Schiff DM, Silverstein M. Neonatal Abstinence Syndrome: Advances in Diagnosis and Treatment. JAMA. 2018;319(13):1362-74.
12. Walsh MC, Crowley M, Wexelblatt S, Ford S, Kuhnell P, Kaplan HC, et al. Ohio Perinatal Quality Collaborative Improves Care of Neonatal Narcotic Abstinence Syndrome. Pediatrics. 2018;141(4).
13. Grossman MR, Berkwitt AK, Osborn RR, Xu Y, Esserman DA, Shapiro ED, et al. An Initiative to Improve the Quality of Care of Infants With Neonatal Abstinence Syndrome. Pediatrics. 2017;139(6).
14. Holmes AV, Atwood EC, Whalen B, Beliveau J, Jarvis JD, Matulis JC, et al. Rooming-In to Treat Neonatal Abstinence Syndrome: Improved Family-Centered Care at Lower Cost. Pediatrics. 2016;137(6).
15. Finnegan LP, Connaughton JF, Jr., Kron RE, Emich JP. Neonatal abstinence syndrome: assessment and management. Addict Dis. 1975;2(1-2):141-58.
16. Patrick SW, Kaplan HC, Passarella M, Davis MM, Lorch SA. Variation in treatment of neonatal abstinence syndrome in US children's hospitals, 2004-2011. J Perinatol. 2014;34(11):867-72.
17. Davis JM, Shenberger J, Terrin N, Breeze JL, Hudak M, Wachman EM, et al. Comparison of Safety and Efficacy of Methadone vs Morphine for Treatment of Neonatal Abstinence Syndrome: A Randomized Clinical Trial. JAMA Pediatr. 2018;172(8):741-8.
18. Kraft WK, Adeniyi-Jones SC, Chervoneva I, Greenspan JS, Abatemarco D, Kaltenbach K, et al. Buprenorphine for the Treatment of the Neonatal Abstinence Syndrome. N Engl J Med. 2017;376(24):2341-8.
19. Brown MS, Hayes MJ, Thornton LM. Methadone versus morphine for treatment of neonatal abstinence syndrome: a prospective randomized clinical trial. J Perinatol. 2015;35(4):278-83.
20. Young LW, Hu Z, Annett RD, Das A, Fuller JF, Higgins RD, et al. Site-Level Variation in the Characteristics and Care of Infants With Neonatal Opioid Withdrawal. Pediatrics. 2021;147(1).
21. Jackson L, Ting A, McKay S, Galea P, Skeoch C. A randomised controlled trial of morphine versus phenobarbitone for neonatal abstinence syndrome. Arch Dis Child Fetal Neonatal Ed. 2004;89(4):F300-4.
22. Nayeri F, Sheikh M, Kalani M, Niknafs P, Shariat M, Dalili H, et al. Phenobarbital versus morphine in the management of neonatal abstinence syndrome, a randomized control trial. BMC Pediatr. 2015;15:57.

Acknowledgments

The project, Data Coordinating and Operations Center for the ECHO IDeA States Pediatric Clinical Trials Network, was approved by the central IRB at the University of Arkansas for Medical Sciences, under the NIH PTE Federal Award number 2U24OD024957; subcontracted with the University of Arkansas, Award number 54005.

Authors

Adam J. Czynski, DO, Department of Pediatrics, Women and Infants Hospital, Brown University; COBRE on Opioids and Overdose, Rhode Island Hospital, Providence, RI.

Abbot R. Laptook, MD, Department of Pediatrics, Women and Infants Hospital, Brown University, Providence, RI.

Correspondence

Adam J. Czynski, DO
101 Dudley Street
Providence RI 02905
aczynski@wihri.org

COBRE on Opioid and Overdose: A Collaborative Research-Based Center Addressing the Crises in Rhode Island and Beyond

TRACI C. GREEN, PhD, MSc; ELIANA KAPLOWITZ, BA; KIRSTEN LANGDON, PhD; JACLYN M.W. HUGHTO, PhD, MPH; WILLIAM C. GOEDEL, PhD; ADAM J. CZYNSKI, DO; GAYLE FRASER, BS; JOSIAH RICH, MD, MPH

ABSTRACT

Overdose deaths across the country have spiked since the onset of the COVID-19 pandemic. It is crucial now, more than ever, to address the continuing and worsening, complex and dynamic opioid and overdose epidemics. In 2018, The Center of Biomedical Research Excellence (COBRE) on Opioids and Overdose, based at Rhode Island Hospital, launched with three major goals: 1) establish a center of scientific excellence on opioids and overdose; 2) train the next generation of scientists to become independent investigators and address the opioid and overdose crises; and 3) contribute to the scientific progress and solutions to combat these epidemics. To date, we have made substantial progress. While the opioid and overdose crises continue to evolve, the COBRE on Opioid and Overdose and its team of investigators are well poised to address the daunting task of understanding and meaningfully addressing these deadly epidemics, with the ultimate goal of saving lives.

KEYWORDS: opioid, overdose, fentanyl, prison, jail

INTRODUCTION

Preliminary data from 2020 suggests that there has been a 30% increase in overdose deaths in Rhode Island. Despite a gradual decline in overdose deaths over the prior four years, 2020 marks, by far, the worst year yet.[1,2] This alarming trend is not unique to Rhode Island. Overdose deaths across the country have spiked since the onset of the COVID-19 pandemic.[3] The horror of the pandemic has diverted attention away from the worsening overdose crisis, which was the leading cause of accidental death nationally before the pandemic. It is crucial now, more than ever, to address the continuing and worsening opioid and overdose epidemics. One thing is quite clear – the opioid and overdose epidemics are very complex and dynamic and demand extensive attention to address them effectively.

A majority of the overdose deaths in the country are opioid-related.[5] The current opioid epidemic in the United States started in the mid-1990s when pharmaceutical companies began heavily marketing their opioid medications to physicians eager for pain management solutions.[6] The first wave of the opioid crisis in the United States was defined by physicians over-prescribing opioids and was marked with a steady increase in overdose deaths.[7] By 2010, the prescription opioid crisis had evolved into an illicit heroin epidemic as opioid dependence became more common, resulting in higher demand for a more consistent pill supply than was affordable or accessible.[8] The impact of increased demand for heroin has most recently led to increased production of more powerful synthetic opioids, notably fentanyl and its related analogs. Illicit fentanyl and synthetic compounds are between 50 and 100 times more potent than heroin and have a more rapid onset of action, making them far more deadly for people without adequate tolerance or unintentionally consuming fentanyl,[9] for example, when it contaminated cocaine. In 2018, over 70% of Rhode Island's 308 overdose deaths involved fentanyl.[5] Further, with increases in fentanyl presence in the illicit drug supply and increases in polysubstance use in Rhode Island, there has also been a recent surge in overdoses involving stimulants (e.g., cocaine and methamphetamine) alone and together with opioids,[5] underscoring the need for interdisciplinary research and programming to address the opioid and overdose epidemics.

THE COBRE ON OPIOIDS AND OVERDOSE

In 2018, The Center of Biomedical Research Excellence (COBRE) on Opioids and Overdose launched with three major goals: 1) establish a center of scientific excellence on opioids and overdose; 2) train the next generation of scientists to become independent investigators and address the opioid and overdose crises; and 3) contribute to the scientific progress and solutions to combat these epidemics. To date, we have made progress on all three fronts.

The COBRE on Opioids and Overdose, based at Rhode Island Hospital (RIH), is the first center of its kind to address the opioid and overdose epidemics collaboratively. The center is funded with a five-year, Phase 1 grant from the National Institute of General Medical Sciences (NIGMS) and is currently in its third year (P20GM125507). The COBRE is an innovative, multidisciplinary research center that brings together dedicated investigators and utilizes a comprehensive approach to understand and develop solutions to the opioid and overdose crises. There is a tremendous need, especially considering the COVID-19 pandemic, for a greater scientific understanding of the mechanisms underpinning opioid use disorder and overdose and developing effective interventions to address them.

Structures and Cores

The COBRE's director Josiah Rich, MD, MPH, and deputy director Traci C. Green, PhD, MSc, are both expert advisors to the Governor's Overdose Prevention and Intervention Task Force with over 40 years of combined research experience on people with opioid use disorder and other substance use disorders. Over the past two years, they have spearheaded the Center's mission to bring together experts from across the state to provide mentorship to junior investigators committed to addressing the opioid epidemic that is devastating Rhode Island. The COBRE's External Advisory Committee, NIGMS, and RIH have provided an open and encouraging environment that has allowed the Center to fund new, creative and innovative ways to address the epidemic by partnering with local organizations such as the Rhode Island Communities for Addiction Recovery Efforts (RICARES), the Rhode Island School of Design (RISD) and the Providence/Boston Center for AIDS Research (CFAR).

Within short order, the COBRE on Opioids and Overdose has proven to be extraordinarily successful. Since its inception in 2018, it has supported over 35 Investigators, 9 Pilot Projects, 4 Research Projects, and 3 Research 'Cores' (see **Table 1**). Additionally, 40 publications have received COBRE support, 21 of which have been published by COBRE Junior Investigators, Pilot Project Awardees, and COBRE Graduates; 22 scientific presentations have been given, and 16 applications have been submitted for funding outside the COBRE funding mechanism. Additionally, two Research Project Leaders have graduated from the COBRE and received independent funding. The COBRE on Opioids and Overdose has worked exceptionally hard to establish a presence in Rhode Island and beyond through cutting-edge research and innovative projects showcased on the COBRE website, along with a successful 2020, week-long, virtual symposium jointly hosted with the University of Nebraska's Rural Drug Addiction Research COBRE Center and the West Virginia Clinical and Translational Science Institute with over 400 attendees. Social media posts and YouTube channel platforms are further leveraged to amplify the COBRE reach and elevate the contributions to science and community through short, engaging videos.

Table 1. COBRE on Opioids and Overdose Research Projects and Pilot Projects

Research Project	Neonatal Abstinence Syndrome (NAS): Fetus to First Years	Adam Czynski, DO	9/1/18–present
Research Project	CoMBAT Opioid Use Disorder: A Pilot RCT of a Combined Medication and Behavioral Activation Treatment for People Living with Opioid use Disorder	Jaclyn White Hughto, PhD, MPH	5/1/19–present
Research Project (proposed)	Estimating the Causal Effects of Residential Eviction on Substance Use Treatment Outcomes	William C. Goedel, PhD	3/1/21–present
Pilot Project	Unintentional Fatal Opioid Overdose in Women: Toxicologic and Pharmacologic Sex Differences in Cause of Death	Rachel S. Wightman, MD	11/1/20–present
Pilot Project	Evaluation of a Nonopioid Recovery Pathway After Percutaneous Nephrolithotomy	David Sobel, MD	12/1/20–present
Pilot Project	Trauma and Stressor-Related Disorders Among Layperson Opioid Overdose Responders	Brendan Jacka, PhD	12/1/20–present
Pilot Project	Buprenorphine with Additional Rx Exposure (B-WARE)	Steven Kogut, PhD	12/1/20–present
Pilot Project	Development of a Text Message Delivered Intervention to Promote Engagement in Medication Assisted Treatment among the Criminal Justice-Involved Population	Kirsten Langdon, PhD	4/1/20–present
Pilot Project	Co-Occurrence of Post-traumatic Stress Disorder and Opioid Use Outcomes among Community Individuals	Nicole Weiss, PhD	12/1/19–present
Mini-Pilot Project	Factors Associated with Establishment of Emergency Department-Initiated Buprenorphine Induction for Opioid Use Disorder in Rural New England.	Noah Rosenberg, MD	1/16/20–1/15/21
Graduate–Research Project	Informed Opioid Prescribing for Acute Musculoskeletal Pain After Motor Vehicle Collision: A Support Tool for Assessing Risks and Benefits of Analgesic Medications Before Prescribing (STAAMP).	Francesca Beaudoin, PhD, MD	9/1/18- 2/28/20
Graduate–Research Project	Contingency Management in Combination with MAT for Opioid Use Disorder	Sara Becker, PhD	9/1/18–11/14/18
Former Pilot Project Awardee	Use of Non-opioid and Non-drug Treatments for Chronic Pain: Trends and Relationship with Opioid Prescribing and Outcomes in the Rhode Island All Payer Claims Database	Patience Moyo, PhD	1/1/19–12/31/20
Former Pilot Project Awardee	Monitoring Newborn Sleep to Improve Treatment and Outcomes from Opioid Exposure	Amy Salisbury, PhD	3/1/20–7/1/20

Administrative Core

The COBRE is led by an Administrative Core with an oversight structure and has three scientific Cores to support Rhode Island-based investigators. This Administrative Core, responsible for the general management of the COBRE, oversees three committees (Executive Committee, Internal Advisory Committee, and External Advisory Committee) that provide integral feedback on the center's progress and ensure the program is meeting the guidelines and missions of NIH, NIGMS, RIH, and the COBRE. The Executive Committee plays an essential role in monitoring the COBRE's Research Cores' productivity and finances and facilitates additional mentorship for the Research and Pilot Project Leaders. The Internal Advisory Committee provides feedback specifically on COBRE projects' development and provides mentorship to junior investigators. Lastly, the External Advisory Committee conducts an annual evaluation on the progress of the Project Leaders, the mentorship program's effectiveness, and the usefulness of the Core services. The External Advisory Committee's Year 2 annual evaluation was overwhelmingly positive and stated that they "were highly impressed with the progress the investigators are making and how successful they have been in publishing and writing grants." In addition to overseeing these feedback-providing committees, the Administrative Core also leads several working groups, including the Medication for Opioid Use Disorder in Corrections Working Group. This working group is in the process of developing a comprehensive website that streamlines up-to-date data on medication for opioid use disorder in correctional settings nationally (see The Prison Opioid Project on www.opioidcobre.org). In addition to the Administrative Core, the three research 'Cores' collaborate closely and play an essential role in supporting Rhode Island-based investigators with services that assist them in refining research methods, increase their network of collaborators, assist with grant and manuscript development and provide additional resources as needed.

Data and Research Methods (DRM) Core

The Data and Research Methods (DRM) Core, led by Dr. Brandon Marshall at Brown University's School of Public Health, assists COBRE Project Leaders and Pilot Project Investigators with methodological, analytic, and data-related support. This Core has focused on supporting junior investigators and pilot applicants during the past two years by providing workshops on innovative research methods. The DRM Core has done a remarkable job supporting junior investigators by reviewing and assisting in analytical plans revisions. Additionally, the DRM Core has also organized and hosted a series of talks focused on innovative research and methods, as well as co-sponsored a Community Overdose Data Workshop with the Brown School of Public Health that focused on using novel analytic methods, such as machine learning and predictive analytics, to better implement interventions to prevent fatal overdoses. Notably, the DRM Core has provided analytic support for the publication of seven new manuscripts published in prestigious journals, including The Lancet and Addiction.

Special Populations (SP) Core

The Special Populations (SP) Core, led by Drs. Curt Beckwith and Tim Flanigan located at The Miriam Hospital, supports investigators and researchers in addressing practical challenges posed when conducting opioid and overdose research with vulnerable and underserved populations. This Core supports the COBRE's mission by building an infrastructure to recruit and retain vulnerable individuals as participants in research studies, build capacity in the ethical conduct of research, and promote research among populations most impacted by opioids and overdose. The SP Core has provided mentorship on research protocol design, study development, institutional review board applications, and study recruitment materials. The SP Core also works to develop training modules (seminars, webinars, and course curriculum) to promote clinical and translational research among populations most impacted by opioids and overdose. Notably, the SP Core recently created a multi-disciplinary continuing education harm reduction module targeting community health providers.

The SP Core has successfully established a Community Advisory Board (CAB). The CAB was developed and expanded by reaching out to community partners to identify individuals interested in bettering overdose-related research. Through these efforts, the CAB successfully recruited 42 members throughout the five initial meetings. Members of the CAB include people who are in recovery from opioid use disorder; people living with HIV; people who are homeless; people with a history of incarceration; people who use drugs; people with a history of sex work; recovery and harm reduction advocates; and people of diverse gender identities, races and ethnicities, sexual orientation, and ages. The CAB diversity is essential to the Core's work to support investigators in researching vulnerable populations. The CAB is committed to ensuring low-barrier access to the meetings and partners with recovery and harm reduction specialists to determine meeting locations. Additionally, transportation and meals are provided at every meeting. The CAB meetings have addressed a spectrum of concerns and community needs, from initial discussions around the role of CABs in supporting research to reviewing intervention content to providing feedback to Junior Investigators on their methods such as recruitment and reimbursement. A discussion-based CAB meeting about stigma and discrimination, facilitated by a community member, helped the SP Core identify the need for further research and developed a call for pilot programs specifically focused on the impact of stigma on recovery.

Translational and Transformative Research (T2) Core

The Translational and Transformative Research (T2) Core led by Drs. Traci C. Green and Susan Ramsey is dedicated to providing expert support in translating innovative findings to transform the care of addiction and overdose. The urgency of the opioid crisis in our state calls for innovative research and interventions and necessitates rapid dissemination of said research. The goal of the T2 Core is to establish a hub of translational and transformative resources to support junior investigators as they bridge research from theory and bench to bedside, from bedside to neighborhood, and from the community to policy change, to transform the care of opioid use disorder and the prevention of overdose. Due to the challenges posed by COVID-19, the T2 Core met with investigators. It helped them revise their protocols to maximize productivity, minimize study delays, and continue to pursue the aims of the studies. Additionally, the COBRE recently partnered with RIH to establish a buprenorphine hotline that can be used to access low barrier buprenorphine during the pandemic. To increase the hotline's reach, the T2 Core assisted in the development and distribution of materials regarding the hotline in the community. In addition, T2 Core members have engaged in community outreach activities to increase hotline traffic, including placing phone calls to patients who have been recently seen in local emergency departments for an opioid-related cause.

In fall 2019, the T2 Core hosted a successful Hackathon event. Teams of community members, students, and professionals were charged with developing innovative "hacks" or solutions to combat the opioid epidemic. The participants were encouraged to collaborate to address one or more topics: a community strategy for opioid overdose, healthcare solutions to opioid overdose, or policy solutions to opioid overdose. The three winning teams created high impact projects that continue to garner community and professional development opportunities (see YouTube Channel on www.opioidcobre.org). As a result of the hackathon, these projects received COBRE funding and became feasibility projects under the COBRE to further develop their innovations.

The COBRE on Opioids and Overdoses is not only committed to mentorship and collaboration among its investigators, but it also has been dedicated to institutional and organizational partnerships. In September 2019, the COBRE on Opioids and Overdose and the Rural Drug Addiction Research (RDAR) COBRE at the University of Nebraska – Lincoln began small efforts to collaborate to increase access to research around substance use and addiction science more broadly. This started with brief phone calls between center PIs and administrators, a site visit and quickly expanded to a fully realized partnership as synergies emerged across almost all programming areas. Our early goal of sharing more information across centers has grown into a valuable collaboration that includes hosting joint seminars, events, workshops, training, and conference symposiums. We built on the existing resources and expertise that each of our COBREs provides to further increase our efficiencies and capacities at both institutions. This successful collaboration with the RDAR COBRE has piloted efforts to grow our successful COBRE collaboration with other substance use focused centers across the US in the coming years.

CONCLUSION

Although Rhode Island is the smallest state, it has been disproportionally impacted by the opioid and overdose crises. However, it has made a substantial impact. In 2017, the state government initiated the Governor Raimondo's Overdose Prevention and Intervention Task Force. Three COBRE Leaders serve as the Task Force's Expert Advisors. Additionally, the Rhode Island Department of Corrections initiated the first-ever statewide comprehensive program for medication for opioid use disorder in a correctional setting. This program has led the charge to provide people who are incarcerated access to the gold-standard treatment for opioid use disorder in a correctional setting. While the opioid and overdose crises continue to evolve, the COBRE on Opioid and Overdose and its team of investigators are well poised to address the daunting task of understanding and meaningfully to address these deadly epidemics to save lives.

References

1. Drug Overdose Deaths: Department of Health. Accessed December 2, 2020. https://health.ri.gov/data/drugoverdoses/
2. RI.gov: Rhode Island Government. Accessed January 14, 2021. https://www.ri.gov/press/view/39687
3. Ahmad F. Provisional Drug Overdose Data. National Center for Health Statisitics. Published January 7, 2021. Accessed January 14, 2021. https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm
4. Schiller EY, Goyal A, Mechanic OJ. Opioid Overdose. In: *StatPearls*. StatPearls Publishing; 2020. Accessed January 19, 2021. http://www.ncbi.nlm.nih.gov/books/NBK470415/
5. O'Donnell J, Gladden RM, Mattson CL, Hunter CT, Davis NL. Vital Signs: Characteristics of Drug Overdose Deaths Involving Opioids and Stimulants – 24 States and the District of Columbia, January–June 2019. *MMWR Morb Mortal Wkly Rep*. 2020;69(35):1189-1197. doi:10.15585/mmwr.mm6935a1
6. DeWeerdt S. Tracing the US opioid crisis to its roots. *Nature*. 2019;573(7773):S10-S12. doi:10.1038/d41586-019-02686-2
7. Paulozzi L, Jones CM, Mack K, Rudd R. Vital Signs: Overdoses of Prescription Opioid Pain Relievers – United States, 1999-2008. Accessed January 14, 2021. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6043a4.htm
8. Ciccarone D. The triple wave epidemic: Supply and demand drivers of the US opioid overdose crisis. *Int J Drug Policy*. 2019;71:183-188. doi:10.1016/j.drugpo.2019.01.010
9. Han Y, Yan W, Zheng Y, Khan MZ, Yuan K, Lu L. The rising crisis of illicit fentanyl use, overdose, and potential therapeutic strategies. Transl Psychiatry. 2019;9. doi:10.1038/s41398-019-0625-0

Acknowledgment

This work was supported by P20GM125507 from the NIGMS of the NIH. Dr. Langdon was supported by K23 DA046482 from NIDA of the NIH. Dr. Rich has been supported by the Providence/Boston Center for AIDS Research (CFAR) P30AI042853 from the NIH.

Authors

Traci C. Green, PhD, MSc, Department of Emergency Medicine, Alpert School of Brown University; The Opioid Policy Research Collaborative, The Heller School of Social Policy and Management at Brandeis University; Department of Epidemiology, Brown University School of Public Health; The COBRE on Opioids and Overdose, Rhode Island Hospital.

Eliana Kaplowitz, BA, The Center for Health and Justice Transformation, The Miriam Hospital; The COBRE on Opioids and Overdose, Rhode Island Hospital.

Kirsten Langdon, PhD, Department of Psychiatry, Rhode Island Hospital; Department of Psychiatry and Human Behavior, Alpert Medical School of Brown University; The COBRE on Opioids and Overdose, Rhode Island Hospital.

Jaclyn M.W. Hughto, PhD, MPH, Departments of Behavioral and Social Sciences and Epidemiology, Brown School of Public Health; Center for Health Promotion and Health Equity, Brown University; The COBRE on Opioids and Overdose, Rhode Island Hospital.

William C. Goedel, PhD, Department of Epidemiology, Brown School of Public Health; The COBRE on Opioids and Overdose, Rhode Island Hospital.

Adam J. Czynski, DO, Department of Pediatrics, Alpert Medical School of Brown University; Department of Pediatrics, Women & Infants Hospital; The COBRE on Opioids and Overdose, Rhode Island Hospital.

Gayle Fraser, BS, The COBRE on Opioids and Overdose, Rhode Island Hospital.

Josiah Rich, MD, MPH, Departments of Medicine and Epidemiology, Brown University; The Center for Health and Justice Transformation, The Miriam Hospital; The COBRE on Opioids and Overdose, Rhode Island Hospital.

Disclaimer

The views expressed herein are those of the authors and do not necessarily reflect those of the funders, or Rhode Island Hospital, Brown University or The Miriam Hospital.

Correspondence

Traci C. Green, PhD, MSc
COBRE on Opioids and Overdose
Rhode Island Hospital, Suite 213
1125 N Main Street
Providence, RI 02906
401-444-3845
traci.c.green@gmail.com

Brown University COBRE Center for Addiction and Disease Risk Exacerbation

PETER M. MONTI, PhD; JENNIFER W. TIDEY, PhD; JASJIT S. AHLUWALIA, MD

ABSTRACT

The Center for Addiction and Disease Risk Exacerbation (CADRE) is a COBRE establishing a thematically linked, state-of-the-art, multidisciplinary Center investigating mechanisms where-by substance use (SU) increases the risk for or exacerbates chronic disease. It does so by employing a combination of behavioral and physiological laboratory-based approaches across several substances and across several diseases. COBRE projects investigate mechanisms underlying effects of opioids, cannabis, tobacco, and alcohol on risks for and progression of SU-related disease. Though linkages between SU and disease are well documented, physiological mechanisms underlying such associations are poorly understood, mainly because published studies use cross-sectional designs that do not allow for causal interpretations. Mechanisms studied in CADRE projects include systemic inflammation, immune system dysregulation, high blood pressure, pulmonary effects, and carcinogen exposure. A Clinical Laboratory Core provides infrastructure, resources, and scientific expertise and a center-wide database of risk factors associated with the development of SU and chronic disease.

KEYWORDS: substance use, chronic disease, mechanisms, interdisciplinary, early career faculty

INTRODUCTION

The Brown University Center for Alcohol and Addiction Studies has established the Center for Addiction and Disease Risk Exacerbation (CADRE), a COBRE funded by the National Institute of General Medical Sciences (NIGMS) in August 2019. The CADRE is led by Peter M. Monti, PhD, Director of the Brown University Center for Alcohol and Addiction Studies and Professor of Behavioral and Social Sciences (BSS), by Jasjit S. Ahluwalia, MD, Professor of BSS and Professor of Medicine, and by Jennifer W. Tidey, PhD, Professor of BSS and Associate Dean for Research at the Brown School of Public Health. Together these three constitute the CADRE's Executive Committee, which has the formal charge of internal governance of the Center.

The primary goal of this Center is to establish a thematically linked, state-of-the-art, multi-disciplinary center to investigate the mechanisms by which substance use increases the risk for or exacerbates chronic disease. More specifically, our CADRE investigates the biobehavioral mechanisms whereby substance use impacts disease. It does so by employing a combination of behavioral and physiological laboratory-based approaches and across several substances of abuse and several chronic diseases. Our overarching goal in establishing this Center is to create a vehicle that will support the emerging careers of promising early-career interdisciplinary faculty, and in so doing, enhance their competitiveness for external independent funding. The ultimate goal is to improve the lives of those living with substance use disorders (SUDs).

ASSOCIATIONS BETWEEN SUBSTANCE USE AND MAJOR MEDICAL ILLNESSES

Substance use negatively affects the risk, management, progression, and outcomes of chronic disease and contributes to socio-economic and racial/ethnic disparities. Prevalence rates of medical conditions among patients with versus those without SUDs support this thesis. Furthermore, risks of disease or disease progression are exacerbated among those otherwise at risk or who already have chronic medical conditions, such as people living with HIV (PLWH) and people living with chronic pain.[1-3] For example, among sexual minority men who have sex with men, alcohol contributes to the fact that they are more severely affected by HIV than any other group in the United States. Further, among HIV-positive smokers, tobacco accounts for more deaths than HIV.

Though linkages between substance use and disease are well documented, physiological mechanisms underlying such associations are poorly understood and underappreciated, mainly because the literature is based on studies that use cross-sectional designs that do not allow for causal interpretations. For example, as pointed out by Bahorik and colleagues,[4] documented relationships between pain and illicit opioid use may evolve because patients who are prescribed pain medication later migrate to illicit opioid use, or patients misuse illicit opioids instead of using pain medications, or both. Studies using experimental designs are needed to understand the biobehavioral mechanisms that link substance use and chronic disease and inform the development of

targeted prevention and intervention efforts to reduce risks.

Unfortunately, experimental research in this area is relatively nascent. A review by Bachi et al[5] characterizes the effects of SUDs on the organism as "accelerated aging", which occurs when biological aging (i.e., wear and tear on one's organs) outpaces chronological age. Factors by which SUDs contribute to accelerated aging include effects of drugs on the brain (brain dopamine, cerebrovascular pathology, neuroinflammation, enhanced stress sensitivity), other physiological effects of drugs (on cardiovascular, pulmonary, metabolic, immune, and circadian health), and effects of drugs on behavior and social functioning (poor nutrition, poor sleep patterns, lack of physical activity, stigmatization, impaired access to healthcare, low family/community support, poverty, infectious diseases and involvement in the criminal justice system).[5]

Clearly, this is a vast area of research. Fortunately, pathophysiological processes underlying these factors are beginning to be identified. One major pathway is the promotion of oxidative stress by drugs and alcohol, leading to cellular damage, tissue injury, and inflammation. Exposure to toxic substances promotes inflammation in the gut, liver, brain, and other organs. Inflammation in combination with increased oxidation may be especially damaging.[6] Oxidation, inflammation and stress hormone exposure also accelerate telomere shortening[7] and stem cell decline,[8] diminishing resilience and regeneration capacity. When chronically present, oxidative stress and inflammation lead to pathologies such as diabetes, cancer, cardiovascular disease, and neurodegenerative diseases.[9]

A basic tenant of the CADRE is that investigating systems and pathways involved in associations between substance use and chronic disease, and intervening to prevent these associations, requires multidisciplinary, multilevel approaches, which bring together behavioral scientists, clinical researchers, physicians, and basic scientists who conduct basic biology, prevention and intervention studies, as well as lab-based human behavioral studies. CADRE studies are especially attentive to the many biological and socio-environmental factors that contribute to racial and ethnic disparities. Our interdisciplinary multilevel approach, focused on related questions using shared resources and learning experiences, not only is poised to contribute new knowledge but importantly serves as the nexus and path toward independence for the next generation of CADRE scientists. The research projects and pilot studies comprising our CADRE investigate mechanisms underlying the effects of opioids, cannabis, tobacco, and alcohol on risks for SUD-related disease progression. Mechanisms studied in the initially funded four CADRE research projects include systemic inflammation, immune system dysregulation, high blood pressure, pulmonary effects, and carcinogen exposure. CADRE studies are serviced by an Administrative Core and a Clinical Laboratory Core.

ADMINISTRATIVE CORE

Peter M. Monti, PhD, CADRE PI, is Brown University's Distinguished Professor of Alcohol and Addiction Studies and Director of the Center for Alcohol and Addiction Studies (CAAS). He founded and is currently Deputy Director of Brown University's Alcohol Research Center on HIV and is PI of CAAS's Alcohol T32 Postdoctoral Training Program. His research interests span understanding the biobehavioral mechanisms involved in behavior change and addiction treatment intervention, and he is particularly interested in the relationship between alcohol and HIV. Jasjit S. Ahluwalia, MD, MPH, MS, Deputy Director, and Core Leader, is a physician and population health/public health scientist. He has been a practicing physician, faculty member, department chair, and Associate Dean. He has served as PI of an NIH Center of Excellence on Minority Health and Health Disparities and as Associate Director of the University of Minnesota's CTSA grant, directing education, training, and career development. He most recently served as a School of Public Health Dean. His primary research has focused on nicotine addiction and smoking cessation in African-American smokers.

The Administrative Core provides an organizational structure for the CADRE, state-of-the-art mentoring for CADRE Project Leaders (PLs) and Pilot PLs, a Pilot Project Program, supports diversity and health disparities work, and leads CADRE's evaluation effort. The Core creates an environment that promotes and encourages scientific exchange and innovation in the realm of substance use and chronic disease. Core personnel work with PLs to prepare competitive grant proposals and peer-reviewed manuscripts emanating from CADRE-sponsored research. The Core brings nationally-known distinguished scholars to the Brown campus each year to present to the extended academic community.

By its nature, COBRE's operate such that once a PL obtains an independent research grant, e.g., an R01, she/he "rotates off" salary funding from the COBRE grant. Thus, an important task of the Executive Committee is to solicit and organize the selection of replacement PLs. This is done in consultation with a distinguished External Advisory Committee.

CLINICAL LABORATORY CORE

Jennifer W. Tidey, PhD, lead, the Clinical Laboratory Core, Associate Dean for Research at the Brown School of Public Health, Associate Director of CAAS's Drug Abuse T32 Training Program, and Director of the CAAS Laboratory. Dr. Tidey is a translational addictions scientist who focuses on developing and testing interactive models of biological, social, and environmental variables to understand the etiology and persistence of SUDs. Her work has assessed the behavioral, subjective, and physiological effects of opioids, psychomotor stimulants, alcohol, and nicotine/tobacco,

in studies based on conditioning and behavioral economic theories of addiction. Her work spans multiple intervention development stages – from basic science, to intervention generation, and pilot testing, to traditional efficacy testing, to policy-informed research.

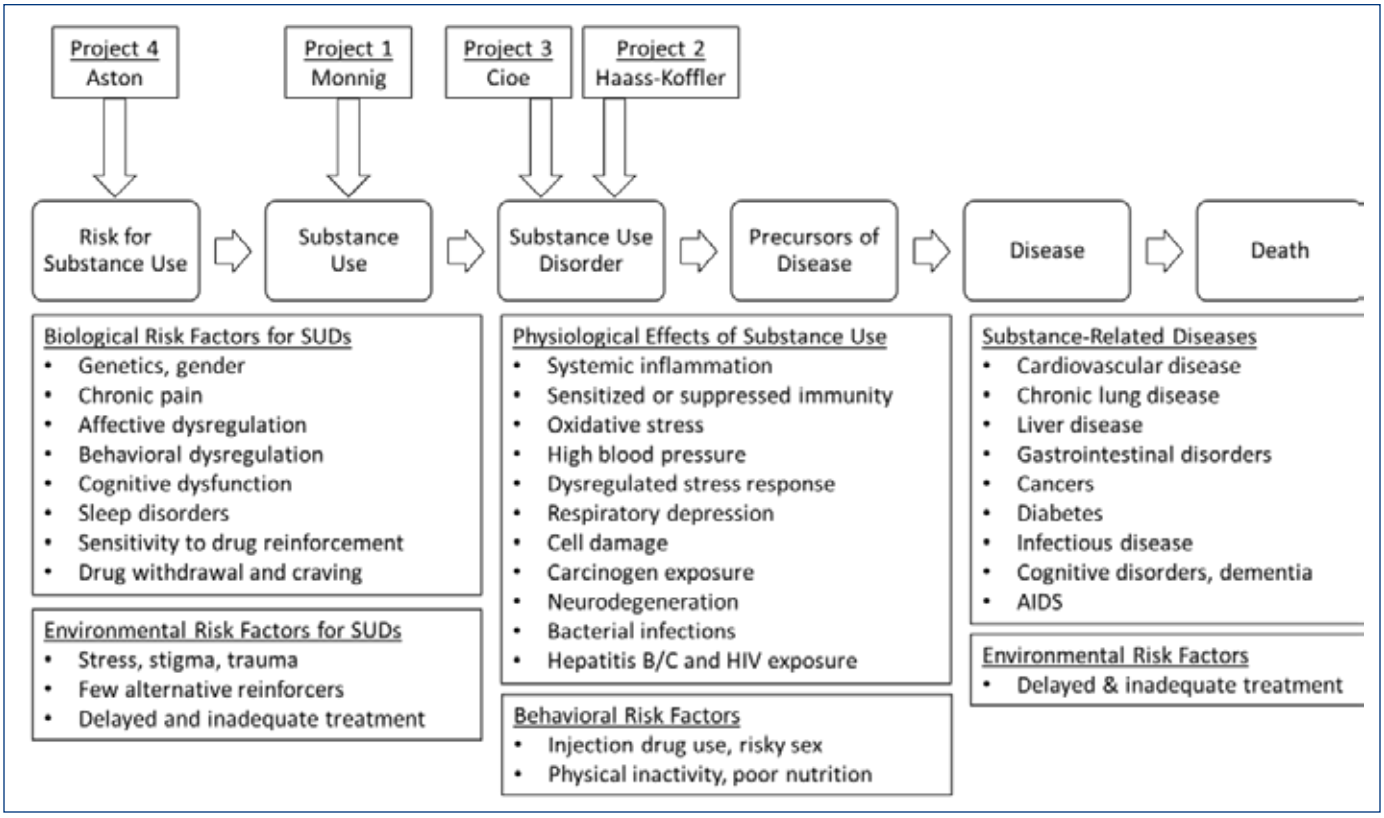
The Clinical Laboratory Core facilitates the goals of the major projects and pilot projects and benefits the broader Brown community, by providing infrastructure, resources, and scientific expertise, in the service of developing and sustaining a multi-disciplinary center. It maximizes CADRE's efficiency and cost-effectiveness by creating linkages between CADRE's Research Projects and other COBREs. Additionally, it is creating a center-wide data base of risk factors associated with development and progression of SUDs and chronic disease available to CADRE PLs and others engaged in research consistent with CADRE's mission. This center-wide database consists of biopsychosocial assessments collected across projects to allow for the formulation and testing of multi-causal models of relationships between SUDs and chronic disease. Further, through NIGMS funding, supplemented by institutional funds, we have made significant renovations to the CAAS Laboratory and purchased major state-of-the-science equipment to meet the ever-growing needs and technical capability of the CADRE.

CADRE RESEARCH PROJECTS

CADRE originally consisted of four thematically and technically linked research projects (RPs) led by an interdisciplinary group of early-career faculty. These RPs and their relationship to biological risk factors, physiological effects, and substance-related diseases are depicted in **Figure 1.**

Mollie Monnig, PhD, Research PL, is a clinical psychologist and Assistant Professor of BSS at CAAS. Dr. Monnig's primary research objective is to advance understanding of alcohol's effects on the gut-brain axis in the context of HIV. In her CADRE project, Dr. Monnig is examining acute neural and immune effects of alcohol in PLWH. Given the dearth of experimental research on alcohol use in PLWH, it is not known whether alcohol exacerbates immune dysfunction in this population. Monnig examines whether alcohol stimulates acute inflammatory responses along the gut-brain axis and compares alcohol's effects on immune biomarkers and neurobiological outcomes in PLWH and healthy controls. This multidisciplinary framework will enable the detection of temporally related changes through measurement of plasma biomarkers of microbial translocation and immune activation and MRI measures of neurometabolic, white matter diffusivity, and extracellular water, consistent with alcohol-induced inflammation in the peripheral immune system and brain.

Figure 1. CADRE conceptual model indicating biopsychosocial mechanisms underlying the linkages between substance use and chronic disease, and where the aims of the initial CADRE research and pilot projects fit on this continuum.



Elizabeth Aston, PhD, Research PL, received a PhD in Neuroscience from Wake Forest School of Medicine and is currently an Assistant Professor of BSS at CAAS. Dr. Aston's primary research objective is to examine predictors of cannabis use disorder severity among regular marijuana users and the relative reinforcing value of marijuana using a behavioral economic marijuana purchase task. In her CADRE project, Dr. Aston examines the effects of cannabis on rheumatoid arthritis pain, affect, and inflammation and investigates whether the effects of cannabis on pain and affect are mediated via the effects of cannabis on inflammatory biomarkers. As such, her study is motivated by a looming concern that some analgesic pharmacotherapy classes have limited efficacy in pain treatment and, in the case of opioids, have significant abuse liability.

Patricia Cioe, PhD, an Assistant Professor of BSS at CAAS with a background in nursing research, was part of the original CADRE application and had proposed in her CADRE project to examine the effects of electronic nicotine delivery systems (ENDS) in PLWH, who are not motivated to quit smoking. PLWH have increased cardiovascular disease rates, pulmonary disease, infection and lung cancer relative to the general population. Outcomes were to include smoking as well as effects on biomarkers of cardiac disease, pulmonary disease, and carcinogen exposure. Dr. Cioe rotated off the CADRE once her U01 was funded to conduct a similar (though more extensive) study to that proposed for the CADRE.

Carolina Haass-Koffler, PharmD, is an Assistant Professor of Psychiatry and Human Behavior and BSS at CAAS and came to CADRE with a strong background in pharmacology and neuroscience. Dr. Haass-Koffler is a translational investigator who integrates preclinical and clinical research to examine the biobehavioral mechanisms of addiction toward developing novel medications. For her CADRE project, Dr. Haass-Koffler proposed translating a validated preclinical paradigm (yohimbine-induced stress) to human laboratory research and pairing it with a human laboratory paradigm (cue reactivity) to investigate whether the anti-stress hormone, oxytocin, reduces opioid craving during stress induction. Dr. Haass-Koffler rotated off the CADRE as a PL once an R01 was recently awarded to her by NIAAA. However, as described below, CADRE has funded a pilot study of reduced scope to the initially proposed research.

Hayley Treloar Padovano, PhD, pending PL, is a clinical psychologist and Assistant Professor of Psychiatry and Human Behavior and BSS at CAAS. Dr. Treloar Padovano's research program's long-term goal is to develop more effective interventions to promote alcohol abstinence and prevent relapse in AALD patients. For her CADRE project, Dr. Treloar has recently proposed to examine alcohol-associated liver disease (AALD) and drinking in patients suffering from AALD. She proposes a prospective, two-arm intervention study comparing patients with AALD/AUD vs. those with AUD only. Ecological momentary assessment and a human laboratory paradigm will assess biomarkers of inflammation and immune response and behavioral AUD endophenotypes in the setting of a brief motivational intervention targeting drinking. This project has received approval from CADRE's External Advisory Board and is in the final stages of NIGMS approval.

CADRE PILOT PROJECTS

Carolina Haass-Koffler, PharmD, is examining the initial efficacy of oxytocin as a potential pharmacotherapy for opioid use disorder, as described above.

Mollie Monnig, PhD, is examining participants' experiences and substance use behavior during the Coronavirus pandemic in the context of a community/longitudinal survey. As Dr. Monnig is a CADRE PL, her pilot study is funded with institutional funds rather than by NIGMS.

A third pending pilot project has been approved internally and is awaiting final approval from NIGMS.

SUMMARY

As shown in the above-listed projects, our CADRE has been very productive during its initial 18 months. Indeed, we have published 22 manuscripts to date. We are fortunate to have excellent, interdisciplinary PLs and an impressive pipeline for future potential early career applicants. Two of our original PLs have "graduated," and the remaining PLs have R01s in various stages of submission. We have two replacement PL's pending NIGMS approval. Through our Laboratory Core, the provision of resources and expertise is a highly sought-after feature of CADRE, one which already is in high demand by non-CADRE faculty. Given the innovative theme of the CADRE, biopsychosocial mechanisms linking SUDs and chronic illness, and the prevalence of substance use and chronic disease, scientific contributions emanating from CADRE should be of high public health significance and therefore should accelerate the careers of our faculty. We anxiously await our initial studies' results and look forward to sharing them with the scientific community.

References

1. Dahlman D, Berge J, Nilsson AC, et al. Opioid and amphetamine dependence is associate with Methicillin-resistant Staphylococcus aureus (MRSA): An epidemiological register study with 73,201 Swedish in- and outpatients 1997-2013. *Infect Dis* (Lond), 2017. **49**(2):120-127.
2. Justice AC, McGinnis KA, Tate JP, et al. Risk of mortality and physiologic injury evident with lower alcohol exposure among HIV-infected compared with uninfected men. *Drug Alcohol Depend*, 2016. **161**:95-103.
3. Reddy KP, Parker RA, Losina E, et al. Impact of cigarette smoking and smoking cessation on life expectancy among people with HIV: A US-based modeling study. *J Infect Dis*, 2016. **214**(11):1672-1681.

4. Bahorik AL, Satre DD, Kline-Simon AH, et al. Alcohol, cannabis, and opioid use disorders, and disease burden in an integrated health care system. *J Addict Med*, 2017. **11**(1):3-9.
5. Bachi K, Sierra S, Volkow ND, et al. Is biological aging accelerated in drug addiction? *Curr Opin Behav Sci*, 2017. **13**:34-39.
6. Rawdin BJ, Melon SH, Dhabhar FS, et al. Dysregulated relationship of inflammation and oxidative stress in major depression. *Brain Behav Immun*, 2013. **31**:143-52.
7. Lindqvist D, Epel ES, Mellon SH, et al. Psychiatric disorders and leukocyte telomere length: Underlying mechanisms linking mental illness with cellular aging. *Neurosci Biobehav Rev*, 2015. **55**:333-64.
8. Molofsky AV, Slutsky SG, Joseph NM, et al. Increasing p16INK4a expression decreases forebrain progenitors and neurogenesis during ageing. *Nature*, 2006. **443**(7110):448-52.
9. Sena LA, Chandel NS. Physiological roles of mitochondrial reactive oxygen species. *Mol Cell*, 2012. **48**(2):158-67.

Acknowledgments

The authors thank Donna Kaplan, MBA, CADRE Project Manager, for her work extracting elements of this report from our original COBRE application. Thanks also go to the original Project Leaders who made our COBRE application competitive: Elizabeth Aston, PhD; Patricia Cioe, PhD; Carolina L. Haass-Koffler, PharmD and Mollie Monnig, PhD. Drs. Monti, Tidey and Ahluwalia are supported, in part, by the National Institute of General Medical Sciences (NIGMS), Center of Biomedical Research Excellence (COBRE, P20 GM 130414).

Authors

Peter M. Monti, PhD, Distinguished Professor of Alcohol and Addiction Studies and Director, Center for Alcohol and Addiction Studies and Center for Addiction and Disease Risk Exacerbation, Brown University School of Public Health.

Jennifer W. Tidey, PhD, Professor of Behavioral and Social Sciences, Center for Alcohol and Addiction Studies and Associate Dean for Research, Brown University School of Public Health.

Jasjit S. Ahluwalia, MD, Professor of Behavioral and Social Sciences and Professor of Medicine, Center for Alcohol and Addiction Studies, Brown University School of Public Health and Alpert Medical School.

Disclaimer

The views expressed herein are those of the authors and do not necessarily reflect the views of the National Institute of General Medical Sciences.

Correspondence

Peter M. Monti, PhD
Center for Alcohol and Addiction Studies
Brown University School of Public Health
Box G – S121-5
Providence, RI 02912
401-863-6661
Peter_monti@brown.edu

The Center of Biomedical Research Excellence (COBRE) for Perinatal Biology – Accomplishments, Impact, and Long-term Results

SUNIL K. SHAW, PhD

ABSTRACT

The COBRE for Perinatal Biology (CPB) was the third grant in Rhode Island to be funded by the COBRE mechanism. The CPB was based at Women & Infants Hospital, and housed in the Kilguss Research Institute, in the Jewelry District in Providence. The scientific focus of the CPB was on perinatal diseases such as preeclampsia and preterm birth, as well as more broadly on cardiopulmonary development and reproductive biology. Over the course of three phases and 17 years, the CPB funded 22 projects. CPB investigators, in turn, generated over $27.5 million in independent funding from federal and non-federal sources. Besides providing scientific and career mentorship to new investigators in Rhode Island, the CPB established a Research Core. The Kilguss Research Core remains active and flourishing and provides advanced imaging, molecular biology and flow cytometry abilities to researchers at Women & Infants as well as the greater Rhode Island scientific community.

KEYWORDS: cardiopulmonary development, reproductive biology, perinatal biology, mentoring

INTRODUCTION

Congress established the Institutional Development Award (IDeA) program to promote research in states that historically had low success rates in National Institutes of Health (NIH) funding. The Centers of Biomedical Research Excellence (COBRE) funding mechanism was designed by the NIH in response to support the development of cutting-edge research centers in IDeA states.[1] Women & Infants Hospital is the primary provider of tertiary perinatal services in Southeastern New England. The Hospital maintains accredited residency and subspecialty training programs in obstetrics and gynecology, pediatrics, and developmental pathology. Hospital leadership recognized that preeminent basic research programs always accompany clinical excellence at leading hospitals in the US. Matching the Hospital's clinical expertise with the funding opportunity led to the award for the COBRE for Perinatal Biology (CPB) in 2003. The COBRE's scientific focus was on basic research on pregnancy and development, and translational research on therapeutic strategies to treat their associated diseases. The CPB was the anchoring award for the newly opened Kilguss Research Institute at Women & Infants. Over the next 17 years, the COBRE founded a Center for Perinatal Biology, mentored new investigators, and established a Research Core.

PHASE I (2003–2008)

Directed by James Padbury, and with Surendra Sharma as Deputy Director, the first phase of the CPB supported four major projects and five smaller pilot projects (**Table 1**). During this period, COBRE investigators published 47 publications in peer-reviewed journals, and seven went on to achieve independent funding. Additionally, the CPB established a Research Core focusing on developing molecular biology, histology, and imaging instrumentation and techniques for the Kilguss Institute. The author of this article was recruited as Associate Director for the Research Core during Phase I and provided a technical focus on microscopy and live-cell imaging.

Research Project I was led by Lazaros Kochilas, "Role of p57KIP2 in Cardiomyocyte Differentiation". This project focused on this cyclin-dependent kinase inhibitor, also known as CDKN1C, and the differentiation of ventricular myocytes. The project proposed to study p57KIP2 physiologic expression and over-expression in murine and zebrafish models of heart development. The project's significance lies in the potential role for this protein in dilated cardiomyopathy, ventricular hypertrophy and translationally in cardiac regeneration. Dr. Kochilas is now a full professor at Emory University in Atlanta, and is the Medical Director of Cardiac Clinical Research.

Yi-Tang Don Tseng led Project II, "Signaling Pathways Regulating Cardiomyocyte Proliferation". This project focused on the β1-adrenergic receptor, phosphoinositide 3- kinase and extracellular signal-related kinases and cardiac growth regulation during gestation and postnatal development in a mouse model. Translational aspects lay in the potential for reinitiating cardiomyocyte differential proliferation in adults after damage.

Project III was led by Juan Esteban, "Mechanotransduction and lung alveolar differentiation". This project focused on intra-uterine fetal breathing movement, mechanosensing via EGFR and subsequent differentiation of type II lung epithelial cells in a murine model. Translational aspects lay in potential therapies for pulmonary complications in premature infants with underdeveloped lungs.

Table 1. COBRE for Perinatal Biology Investigators and Projects

Phase I			
Project I	Lazaros Kochilas, MD	2003-2008	Role of p57KIP2 in Ventricular Cardiomyocyte Differentiation
Project II	Yi-Tang Tseng, PhD	2003-2008	Signaling Pathways Regulating Cardiomyocyte Proliferation
Project III	Juan Sanchez-Esteban, MD	2003-2008	Mechanotransduction and Lung Alveolar Differentiation
Project IV	Monique DePaepe, MD	2003-2008	Role of Fas -Mediated Apoptosis in Perinatal Lung Remodeling
Pilot I	Ting C. Zhao, MD, PhD	2004-2008	Transcriptional Regulation of the β1AR by c-Myc
Pilot II	Zhongbin Lai, MD, PhD	2006-2008	Genetic Mouse Models of Preeclampsia
Pilot III	Edward Chien, MD	2006-2008	Biomechanical Molecular Events in Cervical Remodeling
Pilot IV	Mary Hixson, PhD	2006-2008	Examination of Neonatal Stress Response Genes following intrauterine MEHP-Induced Testicular Injury
Pilot V	Jonathan Kurtis, MD, PhD	2006-2008	Mechanism of Schistosome-Associated Trophoblast Injury

Phase II			
Project I	Joseph Bliss, MD, PhD	2008-2013	Neonatal Candidiasis and Immune Compromise during Development
Project II	Jared Robins, MD	2008-2013	Programming Trophoblast Differentiation and Invasion by Multiple Oxygen Pathways
Project III	Ting Zhao	2008-2009	The role of PI3 kinase in myocardial remodeling and regeneration
Project IV	Carmen Marsit, PhD	2008-2012	Epigenetic Alterations as Markers of the Intrauterine Environment
Pilot I	Satyan Kalkunte, PhD	2008-2012	Novel Animal Models of Preeclampsia
Pilot I	Shibin Cheng, MD	2012-2013	Novel Animal Models of Preeclampsia
Pilot II	Sunil Shaw, PhD	2009-2013	Uterine NK Cell Homing from the Peripheral Circulation
Pilot III	Beatrice Lechner, MD	2011-2013	The Role of Biglycan and Decorin in Preterm Birth
Pilot IV	Peng Zhang, PhD	2011-2013	Reactivation of Fetal/Early Postnatal MicroRNA Program in Adult Cardiac Fibroblasts during Cardiac Remodeling
Pilot V	Eric Morrow, MD, PhD	2011-2013	Trafficking Mechanisms and Axonal Growth in Embryonic and Perinatal Development

Phase III			
Pilot I	Yi-Tang Tseng, PhD	2015-2019	A novel PRKAG2 mutation- an early-onset hypertrophic cardiomyopathy phenotype and treatment
Pilot II	Joseph Bliss, MD, PhD	2015-2020	Contribution of Galectin-3 to Host Defense against Neonatal Candidiasis
Pilot III	Tanbir Najrana, PhD	2015-2020	Role of mechanical stretch induced EV-miRNA in lung development
Pilot IV	Martin Keszler, MD	2015-2020	NIPPV vs. CPAP at equal mean airway pressure
Pilot V	Jin O-Uchi, PhD	2016-2017	Role of mitochondrial calcium and ROS in the early postnatal cardiac development

Dr. Esteban is now Associate Professor of Pediatrics at Brown University/Women & Infants.

Project IV was led by Monique DePaepe, "Role of Fas-mediated Apoptosis in Perinatal Lung Remodeling". This project focused on testing if apoptosis of alveolar type II cells was necessary for lung development and differentiation in a murine model. Translational aspects lay in potential therapies for bronchopulmonary dysplasia in newborns. Dr. DePaepe is now Professor of Pathology and Laboratory Medicine at Brown University/Women & Infants.

Pilot I was led by Ting Zhao, "Transcriptional Regulation of the β1AR by c-Myc". This project focused on myocardial ischemic injury and β1AR and PI3K signaling roles in recovery. Dr. Zhao is now Associate Professor of Surgery at Boston University.

Pilot II was led by Zhongbin Lai, "Genetic Mouse Models of Preeclampsia". In this project, IL-10 knockout mice treated with preeclampsia serum were established as an animal model of preeclampsia. The generation of an animal model for this human disease has already led to a better understanding of this disease and more effective therapies for treatment and diagnosis.

Pilot III was led by Edward Chien, "Biomechanical molecular events in cervical remodeling". This project focused on cervical ripening and its role in preterm birth, and glycosaminoglycan changes associated with it in a rat model. Dr. Chien is at Cleveland Clinic in Ohio, at the Women's Health Institute.

Pilot IV was led by Mary Hixson, "Examination of Neonatal Stress Response Genes following intrauterine MEHP-Induced Testicular Injury". This project focused on the effect of phthalates on male germline cells during development. Dr. Hixson is a Senior Toxicologist at Gradient Corporation in Boston.

Pilot V was led by Jonathan Kurtis, "Mechanism of Schistosome-associated trophoblast injury". This project focused on the effect of Schistosoma antigens on primary human trophoblasts in vitro. Dr. Kurtis is now Professor and Chair of the Department of Pathology and Laboratory Medicine at Brown University and Director of the Lifespan Center for International Health Research.

PHASE II (2008–2013)

During Phase II, a new round of four major and five pilot projects was initiated. During this period, COBRE investigators published 156 articles in peer-reviewed journals, and 9 went on to achieve independent funding. The Research Core expanded its user base and added expertise in microscopy to include live-cell imaging.

Project I was led by Joseph Bliss, "Neonatal Candidiasis and Immune Compromise during Development". The focus of this project was on developing a model for *Candida albicans* infections in neonatal mice. Translational aspects lay in understanding mechanisms of disease in and identifying potential therapies for the most common fungal infection in premature and term neonates. Dr. Bliss is now Professor of Pediatrics and Director of the Fellowship Program in Neonatal and Perinatal Medicine at Brown University.

Jared Robins led Project II, "Programming Trophoblast Differentiation and Invasion by Multiple Oxygen Pathways". This project focused on the role of hypoxia during remodeling of placental and uterine vasculature by trophoblasts. Dr. Robins is now Associate Professor of Obstetrics and Gynecology and Chief of the Division of Reproductive Endocrinology and Infertility at Northwestern University.

Project III was led by Ting Zhao, "The role of PI3 kinase in myocardial remodeling and regeneration". This project

focused on myocyte proliferation and hyperplasia and the effect of PI3 kinase. Dr. Zhao is now a Professor of Surgery at Boston University.

Project IV was led by Carmen Marsit, "Epigenetic Alterations as Markers of the Intrauterine Environment". This project focused on DNA methylation analysis of placental tissue as a marker of environmental toxicants. Dr. Marsit is now Professor of Environmental Health at the Rollins School of Public Health, Emory University.

Pilot I was initially led by Satyan Kalkunte, "Novel Animal Models of Preeclampsia". This project identified that misfolding of the serum protein transthyretin contributed to preeclampsia. After Dr. Kalkunte entered a job in industry, the project was led by Dr. Shibin Cheng. Dr. Cheng is now Associate Professor of Pediatrics at Brown University/Women & Infants.

Pilot II was led by the author, "Uterine NK Cell Homing from the Peripheral Circulation". This project focused on adhesion molecules expressed by Natural Killer cells, and their migration from the peripheral circulation into the uterus during early pregnancy.

Pilot III was led by Beatrice Lechner, "The roles of Biglycan and Decorin in Preterm Birth". This project's focus was the small chondroitin sulfate/dermatan sulfate proteoglycans that are necessary for structural integrity of the fetal membranes, and testing if their loss led to premature membrane rupture and preterm birth. Dr. Lechner is an Associate Professor of Pediatrics at Brown University/Women & Infants.

Peng Zheng led Pilot IV, "Reactivation of Fetal/Early Postnatal MicroRNA Program in Adult Cardiac Fibroblasts during Cardiac Remodeling". The focus of this project was to examine the role of microRNAs in fetal and adult heart function. Dr. Zhang is an Assistant Professor of Medicine at Lifespan/Brown University.

Pilot V was led by Eric Morrow, "Trafficking Mechanisms and Axonal Growth in Embryonic and Perinatal Development". This project focused on endosomal Na+/H+ exchanger 6 (NHE6), and its role in reduced branching in axonal and dendritic branching in an autism-type disorder. Dr. Morrow is now the Mencoff Family Associate Professor of Biology, Associate Professor of Neuroscience, Associate Professor of Psychiatry and Human Behavior at Brown University.

PHASE III (2015–2020)

Phase III of the CPB was initially led by James Padbury, who stepped down to lead the Advance-CTR Award. The project was then led by Surendra Sharma, who later stepped down to lead the COBRE for Reproductive Health. For its last three years, CPB has been led by Sunil Shaw, the author. During this phase, only pilot projects were permitted, and five were funded, resulting in 15 peer-reviewed publications. During this period, the Research Core transitioned to a fee-for-use shared equipment model and significantly widened its user base. Phase III ended in 2020, and is currently in no-cost extension.

Pilot I was led by Don Tseng, "A novel PRKAG2 mutation – an early-onset hypertrophic cardiomyopathy phenotype and treatment". This project focused on a functional mutation within the γ2-subunit isoform of 5′-AMP-activated protein kinase (AMPK), which resulted in hypertrophy that was reversed with rapamycin.

Pilot II was led by Joseph Bliss, "Contribution of Galectin-3 to Host Defense against Neonatal Candidiasis". The project's focus was on the S-type lectin receptor, Galectin-3, and its role in defense against the fungal pathogens *C. albicans* and *parapsilosis*.

Tanbir Najrana led Pilot III, "Role of mechanical stretch induced EV-miRNA in lung development". This project focused on microRNAs expressed in lung extracellular vesicles, and their role in differentiation of epithelial cells. Dr. Najrana is an Investigator in Pathology and Laboratory Medicine at Lifespan/Brown University.

Pilot IV was led by Martin Keszler, "NIPPV vs. CPAP at equal mean airway pressure". This project compared two ventilation methods, continuous positive airway pressure (CPAP) and noninvasive positive pressure ventilation (NIPPV). Dr. Keszler is a Professor of Pediatrics at Brown University/Women & Infants.

Pilot V was led by Jin O-Uchi, "Role of mitochondrial calcium and ROS in early postnatal cardiac development". This project focused on calcium signaling and reactive oxygen species in cardiomyocytes. Dr. O-Uchi is Assistant Professor of Medicine in Cardiology at the University of Minnesota.

KILGUSS RESEARCH CORE

The Research Core for the CPB remains active and provides advanced imaging and molecular biology capabilities to researchers at Women & Infants Hospital, Brown University, and affiliated institutions. Academic researchers are billed at uniform rates for equipment maintenance and supplies. The Core also serves researchers from for-profit laboratories. Core staff provides training and consultation in experimental design, data interpretation and analysis, and presentation. The Kilguss Research Core offers several unique capabilities that are not widely available in Rhode Island. A detailed listing of core equipment is available at coresri.org, and equipment may be scheduled on a web-based service, facilitating billing and use by researchers outside the Kilguss Institute.

CONCLUSION

Over 3 phases spanning 17 years, the COBRE for Perinatal Biology has supported a cadre of researchers and projects in the fields of reproductive biology, development, and perinatal diseases such as preeclampsia and preterm birth. It has left a lasting positive impact on junior investigators' careers and helped develop basic and translational research in Perinatal Biology at Women & Infants Hospital and throughout the state of Rhode Island. COBRE and INBRE grants have provided an important boost to research and continue to play a critical role in building a scientific workforce that will continue to enhance the local economy on a sustainable and long-term basis.

References

1. https://grants.nih.gov/grants/guide/pa-files/par-19-313.html

Acknowledgment

This report was supported by an Institutional Development Award (IDeA) from the National Institute of General Medical Sciences of the National Institutes of Health under grant number P30GM114750.

Author

Sunil K. Shaw, PhD, Program Director, COBRE for Perinatal Biology, Kilguss Research Institute, Women & Infants Hospital, Providence, RI; Department of Pediatrics, Alpert Medical School of Brown University.

Correspondence

Sunil K. Shaw, PhD
Women & Infants Hospital
Kilguss-210, 101 Dudley Street, Providence RI 02905
401-430-8005
Sunil_Shaw@brown.edu

Rhode Island COBRE Center for Central Nervous System Function: Progress and Perspectives

JEROME N. SANES, PhD

ABSTRACT

The Center of Biomedical Research Excellence (COBRE) Center for Central Nervous System Function (CCNSF) was funded in 2013 by the National Institute for General Medical Sciences to establish a collaborative environment for basic and applied research in higher nervous system function with humans and experimental animal model systems. Since its inception, the COBRE CCNSF has funded junior faculty investigators as Project and Pilot Project Leaders and one established investigator on projects investigating fundamental properties of nervous system function using a range of tools spanning molecular genetics, neurophysiology, invasive and non-invasive brain stimulation, behavior and neuroimaging. The Administrative Core facilitates all Center activities with a focus on career development, grant proposal submission, and deployment of technology developed by our research cores. The Design and Analysis Core aims to provide principled study design expertise, statistical modeling, machine learning, inference, and computation. The Behavior and Neuroimaging Core provides project-specific collaboration and support to COBRE scientists to promote the acquisition of high quality behavioral, physiological, neuroimaging and neurostimulation data, to ensure the integrity of the data collection infrastructure and to help implement robust data processing and visualization pipelines. While the cores principally serve Center scientists, our Center and the core resources have availability to all Rhode Island researchers.

KEYWORDS: neural function, neural recording, neuroimaging, behavior, core services

INTRODUCTION

Higher brain function often refers to the general ability to plan, organize, and select behaviors in a goal-directed manner.[1-5] Deficits in higher brain function are common in both neurological and psychiatric disorders. They can result in a wide range of higher-order behavioral deficits, including an inability to plan a purposeful sequence of actions, a failure to inhibit inappropriate or detrimental responses, and difficulty initiating or flexibly shifting to novel responses as task demands change.[2,6-8] These high-level deficits can occur following a stroke, brain damage, or neurological diseases, including Alzheimer's disease[9] and Parkinson's disease.[10] Moreover, many psychiatric disorders result in high-level cognitive deficits, such as schizophrenia[11] and attention-deficit hyperactivity disorder.[12]

The American Psychiatric Association's definition of dementia (DSM IV) includes executive dysfunction (synonymous with deficiencies in high-level brain function).[13] However, specific diagnosis and clinical assessment remain difficult. The limited understanding of the neural systems' specific organizations mediating high-level function and its underlying mechanisms may contribute to this problem. For example, the Research Council of the American Neuropsychiatric Association conducted a comprehensive, clinically-oriented review of research from 1966 to 2002 on higher brain function. It concluded that a lack of basic knowledge into its mechanisms, functional organization and diversity remained a persistent obstacle to clinical assessment and treatment.[14] Since that time, the basic mechanisms of attention, decision, and action have received growing interest, and these have formed the core of our COBRE project.

Integration of psychophysics, genetic tools, and neuroimaging represents a fundamental approach to address clinically significant gaps in the basic understanding of high-brain function. A significant obstacle to understanding higher brain function arises from uncertainty about how defining its major components, some of which – attention, decisions and action – we focused upon in Phase 1 of our COBRE project. Functional neuroimaging methods can measure the impact of a particular cognitive manipulation on activation in a specific brain region. Therefore, differences in developmental and adult-level attention, decision and action functions may be indexed by changes in activation in different brain regions or networks. Second, functional neuroimaging, neural recording, and intracranial stimulation can reveal how brain areas interact during the elaboration of these key processes. Attention and decision-making often operate through top-down modulation of ongoing processing, such as in the primary visual cortex or lateral temporal cortex. The impact of these top-down modulatory effects on local processing is difficult to assess using behavioral measures alone. However, functional MRI, source localized EEG, and combined neural recording and intracortical stimulation,

coupled with contemporary analysis methods, can permit measurement of local changes in targeted regions, such as the primary visual cortex, due to top-down modulation. This offers a means of studying the mechanisms and dynamics of top- down control. Finally, the ability to precisely localize higher brain function to neocortical and subcortical sites using functional neuroimaging permits more specific predictions regarding the impact of neurological and psychiatric disorders on higher brain function and the potential effects of behavioral and pharmacological interventions on these deficits. Integrating genetic analysis provides the opportunity to probe how genetic variations shift the parameters of these various components of higher brain function, which is essential for understanding variability across natural human populations.

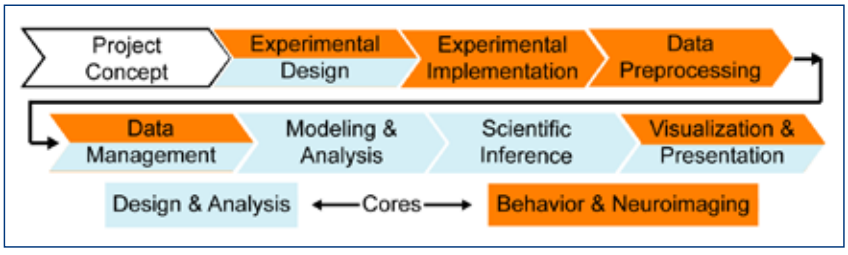
ORGANIZATION OF THE COBRE CCNS

When we considered applying to the National Institute for General Medical Sciences (NIGMS) for COBRE funding, Brown University had significant research activities concerned with higher central nervous system function. Nevertheless, we believed that Brown and its affiliated hospitals and the larger Rhode Island community, could benefit by establishing a research center focused on nervous system function especially that related to cognition in health and brain disorders. We, therefore, proposed establishing a Center for Central Nervous System Function (CCNSF) to develop infrastructure in two domains: faculty researchers, particularly junior investigators, who would serve as Project Leaders (PL) and Pilot Project Leaders (PPL), and research cores, designed to facilitate the development of the research programs of PLs and PPLs.

Like all COBRE Centers, we established the obligatory Administrative Core. This core, with input from our Internal Advisory and External Advisory Committees, aims to support the scientific, technical and mentoring goals of our COBRE Center by providing leadership and an administrative structure to facilitate and coordinate the activities of the leaders of each research project, the overall Principal Investigator, the Deputy, and Associate Directors, positions held respectively by David Sheinberg (professor, Department of Neuroscience) and John Davenport (Managing Director, Carney Institute for Brain Science). The Administrative Core, among other functions, provides administrative support for the Principal Investigator and all PLs, PPLs, and Core Directors, collection and maintenance of financial records for all projects and cores; prepares the annual Progress Report; coordinate activities of the Internal Advisory Committee, the University Advisory Committee, and the External Advisory Committee in their roles of mentoring and evaluating the research and personnel in each project and core; organizes the COBRE Center's internal meetings, and assists in data dissemination and sharing. Additional activities may include interactions with relevant departments and programs in faculty searches, external seminar series, and internal journal clubs. Indeed, we have used COBRE funds for the recruitment of one PL (T. Desrochers) and have made commitments to two incoming tenure-track faculty, pending NIGMS approval.

For the initial four years of Phase 1, we had a single research core, the Design and Analysis Core (DAC), and this core has continued into Phase 2. Applied scientists from Brown's Department of Biostatistics, Division of Applied Mathematics, and the Department of Computer Science have directed the DAC. The primary purpose of the DAC concerned developing novel analytic tools for designing experiments and analyzing data, all in the service of the specific experiments proposed and implemented by PLs and PPLs. This core had more of a research-slanted focus compared to the typical service-related emphasis of COBRE research cores, aiming to develop collaborations with PLs and PPLs. We expected that the DAC would also provide more prosaic statistical and data science queries related to experimental design and data analysis implements. The core has succeeded in generating many original publications, more than 10 during Phase 1, and DAC staff have provided valuable consulting services to our PLs and PPLs. As Phase 1 progressed, and particularly due to input from PLs and PPLs, we recognized a need to enhance services related to implementation of research, especially for developing best practices to conduct experiments using structural MRI, task-based and resting state functional MRI, diffusion imaging, transcranial magnetic stimulation, transcranial direct-current and transcranial alternating-current stimulation, galvanic skin response, electroencephalography, and eye tracking. Clearly, the complexity of these techniques and the challenges of mastering the infrastructure required for effective and efficient deployment of them can significantly impede research progress, especially in the case of relatively junior investigators. Therefore, we created the Behavior and Neuroimaging Core (BNC) to provide ongoing expert support, training, assistance, and advice to

Figure 1. Project flow. PL or PPL brings a concept to DAC (light blue shading) and BNC (orange shading), which initiates a series of sequential steps from experimental design to final realization. Boxes with both orange and blue coloring indicate a cooperation between the two research cores.



the COBRE PIs and PPLs in the practical aspects of data collection, data management, and data processing.

Together, the DAC and BNC have provided support and assistance to COBRE PLs and PPLs and their research teams to promote and facilitate the acquisition of high-quality research data and facilitate analysis of COBRE research data through deployment of tools, analysis platforms, and training. **Figure 1** illustrates the typical flow for research projects from project inception through its completion. One notes that the DAC and BNC have overlapping and non-overlapping functions.

RESEARCH ACTIVITIES OF THE COBRE CCNSF

Since the inception of our COBRE in 2013, we have supported 11 PLs, eight in Phase 1, with two of these PLs spanning Phase 1 and Phase 2 and three solely in Phase 2. We will soon recruit at least two new PLs to "replace" PLs who will rotate off COBRE support. In the final years of Phase 2, we may recruit up to three other PLs for the total of 13 to 16 PLs who have or will have benefitted from COBRE support. **Table 1** lists Phase 1 and Phase 2 supported PLs, along with their primary academic department, their project title and their support term. The PLs have come from Brown University's Division of Biology and Medicine (MCB, Neuroscience, Neurosurgery), Arts and Sciences (CLPS), and School of Public Health (Biostatistics). All but W. Asaad and M. Worden had tenure-track appointments, with Neurosurgery (W. Asaad) not having tenure-track options and M. Worden serving in the research track. Most of the PLs conducted research with humans, spanning systems and cognitive neuroscience questions and addressing a wide range of questions from basic visual processing (M. Worden) to brain mechanisms of social interactions (O. FeldmanHall). Two PLs (W. Asaad and T. Desrochers) used non-human primates to investigate fundamental questions about learning, decision-making and mental sequences. Two PLs used other model systems (rodents and Drosophila) to investigate fundamental mechanisms underlying developmental disorders (E. Morrow) and the molecular genetics and neural circuit dynamics mediating reward behavior (K. Kaun).

Along with the eight awarded pilot projects (not listed), whose leaders had primary appointments in several different departments and Brown University divisions, including Neuroscience, CLPS, Psychiatry, and Behavioral and Social Sciences, the unifying theme of all projects and pilot projects concerned revealing brain mechanisms of higher central nervous system function in health and disease. The project led by K. Kaun exemplifies our approach. She uses fruit flies as a model system and employs standard and novel methods spanning behavioral analysis, neural circuit recording, and molecular genetics to learn basic reward mechanisms. For her COBRE project, Prof. Kaun proposed investigating a glutamate-dopamine feedback circuit responsible for reward prediction and the localization of dopamine-2 like receptors (D2Rs) within this circuit in Drosophila. She hypothesized that feedback from glutamate neurons would result in a sparse representation of reward dopamine neurons in-memory expression and that D2R localization in these dopamine neurons would change during memory consolidation. One aim focused on testing whether a mushroom body (a major component of the fruit fly's brain) γ5β'2 glutamate to dopamine connection is required for memory expression. A second aim proposed to develop a new tool for in vivo localization of D2Rs within this circuit. Other projects funded by our COBRE had similar focused and important goals.

Not listed in Table 1 are the genders of the Project Leaders: seven women and four men; the Pilot Project Leaders were roughly equally split between men and women. Following NIGMS's emphasis on building capacity, especially for junior investigators, all but Prof. Jones had junior investigator

Table 1. Project Leaders of the COBRE CCNSF

	Department*	Project Title	Tenure
Morrow, E.	MCB	Genetic-imaging study of obsessive compulsive behavior in autism	2013–2015
Amso, D.	CLPS	Development of vision and attention in typical and ASD individuals	2013–2016
Worden, M.	Neuroscience	Conflict adaptation and selective attention	2013–2017
Asaad, W.	Neurosurgery	Cortical-subcortical interactions in attention and learning	2013–2018
Song, J-H.	CLPS	Target selection for visually guided actions	2013–2018
Kaun, K.	Neuroscience	Microcircuits for reward driven decisions in Drosophila	2015–2018
Desrochers, T.	Neuroscience	The neural basis of sequence monitoring in human and nonhuman primates	2017–2021
Shenhav, A.	CLPS	Mechanisms of cognitive interference from value-based choice conflict	2017–2021
FeldmanHall, O.	CLPS	The neural and affective mechanisms of socially risky learning	2018–2021
Eloyan, A.	Biostatistics	Quantitative methods for brain connectivity network estimation and interference in functional magnetic resonance imaging	2018–2021
Jones, S.	Neuroscience	The causal role of neocortical beta events in human sensory perception	2018–2021

* MCB: Molecular Biology, Cell Biology and Biochemistry; CLPS: Cognitive, Linguistic and Psychological Sciences

status when COBRE support began. Prof. Jones was included in Phase 2, since she proposed to extend her computational-driven work into empirically based data collection related to predictions of her computational models. Similarly, we considered all Pilot Project Leaders as junior investigators since none had received an R01 or equivalent grant when starting their pilot project, though one Pilot Project Leader had a K99/R00 grant, which NIGMS consider as a research project grant.

OUTCOMES OF COBRE CCNSF

Our PLs and PPLs and research core members have been particularly productive in garnering external research funds, publishing peer-reviewed papers, and advancing their careers at Brown (and unfortunately for us, also elsewhere via recruitment), while also receiving professional recognition. Collectively and to date, our cohort of faculty researchers have published nearly 90 peer-reviewed papers supported by COBRE funds, including many in well-respected journals such as *Annals of Neurology, Cell Reports, Current Biology, eLife, Genetics, Journal of Neuroscience. Nature*, *Nature Communications*, *Nature Human Behaviour, Nature Reviews Neuroscience, Neural Computation, NeuroImage Neuron, PLoS Computational Biology, PLoS Genetics, PNAS,* and *Psychological Review*, among others. As a group, the PLs and PPLs have successfully leveraged their COBRE support to garner more than $22 million in external research support, mostly from the NIH, but also from the NSF and other Federal agencies as well as from private foundations (e.g., Simons Foundation). As our Phase 2 PLs and PPLs progress in their research, we expect additional grant awards; indeed, one of our PLs has received promising news of both an NIH and an NSF award, thereby increasing, by about $3 million, the total grant awards of our COBRE cohort. Our COBRE supposed PLs have also received recognition for their outstanding work by being awarded tenure (Amso, Kaun, Morrow, Song) at Brown. In contrast, those supported in Phase 2 have made excellent progress toward tenure. For a loss to Brown but their benefit, some PLs and PPLs have been recruited to other institutions, even though Brown made competitive counteroffers. Some of our PLs have received national recognition, such as a PECASE award (E. Morrow) and field-specific young investigator citations (O. FeldmanHall and A. Shenhav). Taken together, our research cohort has made outstanding progress using the standard metrics of scientific achievement.

THE FUTURE OF THE COBRE CCNSF

As we reach the mid-point of the Phase 2 funding period, we have accelerated our Phase 3 application plans. To this end, we have identified a small cohort of PLs to "replace" graduating PLs for at least two years of project-level funding, using the faculty recruitment mechanisms provided by the COBRE program. Since Phase 3 COBRE grants provide only for pilot projects and cores, we have continued our outreach to inform department chairs and center and institute directors that we will have research funds for larger-scale pilot projects. We have also undertaken a review of our research cores' effectiveness, as we position them for the Phase 3 application. First, we have opened our cores to the entire Brown community, including Brown-affiliated hospitals and, with time, the whole Rhode Island scientific community, with an aim to demonstrate usage and need. Second, we have begun discussing how to leverage expertise in other COBRE Centers that use similar or related methodologies employed by our CCNSF researchers. Along these lines, we note that many NIGMS-funded IDeA programs have data handling capabilities, sometimes in the form of cores. We endorse efforts to coordinate data science expertise across the many COBRE and other IDeA supported programs (INBRE and CTR). The objective is to seek partners related to leveraging resources, especially financial ones and to demonstrate to the staff of NIGMS's Division for Research Capacity Building that the funds devoted to Rhode Island are being used well. Regarding the future of our research cores, in recognition that Phase 3 cores should focus on developing sustainability, we will refocus the DAC more toward service and less toward creating novel statistical approaches. Recall that, at the end of Phase 1, we split our DAC into two cores, one to develop theoretical approaches for experimental design and data analysis, the original main feature of the DAC, and the BNC to serve the practical needs of our COBRE cohort for experimental implementation. We now believe that we should reintegrate these two cores while maintaining efforts on developing novel statistical tools and integrating, but to integrate these efforts with those of other COBRE and other IDeA programs in Rhode Island.

We close with gratitude toward NIGMS for providing generous funds to foster the careers of many junior investigators in Rhode Island by providing direct support to their research endeavors and supporting research cores that have served our COBRE cohort.

References

1. Norman DA, Shallice T. Attention to action: Willed and automatic control of behaviour. In: Consciousness and self-regulation: Advances in research and theory, Vol. 4 1986 (Davidson R, Schwartz G, Shapiro D, eds), pp 1-18. New York: Plenum.
2. Stuss DT, Benson DF. The frontal lobes and control of cognition and memory. 1987 In: The Frontal Lobes Revisited (Perecman E, ed), pp 141-158. New York: The IRBN Press
3. Miller E, Cohen JD. An integrative theory of prefrontal cortex function. Annual Review of Neuroscience. 2001;24:202.
4. Badre D, Wagner AD. Selection, integration, and conflict monitoring; assessing the nature and generality of prefrontal cognitive control mechanisms. Neuron. 2004; 41:473-487.
5. Bunge SA. How we use rules to select actions: a review of evidence from cognitive neuroscience. Cogn Affect Behavior Neuroscience. 2004;4:564-579.

6. Duncan J. Disorganization of behavior after frontal lobe damage. Cognitive Neuropsychology. 1986;3:271-303.
7. Shallice T, Burgess PW. Deficits in strategy application following frontal lobe damage in man. Brain. 1991;114:727-741.
8. Schwartz MF, Montgomery MW, Buxbaum LJ, Less SS, Carew TG, Coslett HB, Ferraro M, Fitzpatrick-De Salme EJ, Hart T, Mayer NH. Naturalistic action impairment in closed head injury. Neuropsychology. 1998;12:13-28.
9. Binetti G, Magni E, Padovani A, Cappa SF, Bianchetti A, Trabucchi M. Executive dysfunction in early Alzheimer's disease. Journal of Neurology, Neurosurgery, and Psychiatry. 1996;60:91-93.
10. Cools R, Barker RA, Sahakian BJ, Robbins TW. Mechanisms of cognitive set flexibility in Parkinson's disease. Brain. 2001;124:2503-2512.
11. Carter CS, Perlstein W, Ganguli R, Brar J, Mintun M, Cohen JD. Functional hypofrontality and working memory dysfunction in schizophrenia. American Journal of Psychiatry. 1998;155: 1285-1287.
12. Lovejoy DW, Ball JD, Keats M, Stutts ML, Spain EH, Janda L, Janusz J. Neuropsychological performance of adults with attention deficit hyperactivity disorder (ADHD): diagnostic classification estimates for measures of frontal lobe/executive functioning. Journal of International Neuropsychological Society. 1999;5:222-233.
13. Association Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. 1994 Washington, DC: American Psychiatric Association.
14. Royall DR, Lauterbach EC, Cummings JL, Reeve A, Rummans TA, Kaufer DI, LaFrance WC, Jr., Coffey CE. Executive control function: a review of its promise and challenges for clinical research. A report from the Committee on Research of the American Neuropsychiatric Association. Journal of Neuropsychiatry and Clinical Neuroscience. 2002;14:377-405.

Acknowledgments

Supported by an Institutional Development Award (IDeA) from the National Institute of General Medical Sciences of the National Institutes of Health under grant number P20GM103645. We acknowledge the meritorious work of all the COBRE Project Leaders, Pilot Project Leaders, Mentors, and members of our Internal and External Advisory Committees who have provided fundamental skills, knowledge and advice to build our COBRE Center. Special thanks go to Diane Lipscombe, Director of the Carney Institute for Brain Science, who has provided key guidance throughout our COBRE progress.

Author

Jerome N. Sanes, PhD, Department of Neuroscience and Carney Institute for Brain Science, Brown University, Providence, RI; Center for Neurorestoration and Neurotechnology, Providence Veterans Affairs Medical Center, Providence, RI.

Correspondence

Jerome N. Sanes
Department of Neuroscience
185 Meeting Street, Box GL-N
Brown University
Providence, RI 02912
Jerome_Sanes@Brown.edu
https://www.brown.edu/carney/centers-initiatives/cobre-center-central-nervous-system-function

Advance-CTR: Statewide Infrastructure to Improve Health in Rhode Island through Clinical and Translational Research

VALERIE ZABALA, PhD; GABRIELLE STRANIERI, BA; HEATHER FOURNIER, MA; EDWARD HAWROT, PhD; JAMES PADBURY, MD

ABSTRACT

The universities, hospitals, government agencies, and community organizations in Rhode Island (RI) are well-positioned to bridge gaps between basic and clinical science. RI's manageable size, population demographics, and organizational structure present opportunities to test and implement impactful, transformative clinical and translational research. However, the state's resources had not been optimally coordinated to develop a multi-institutional, clinical and translational research infrastructure to improve clinical practice effectiveness and impact health care in RI. The objective of Advance Clinical and Translational Research (Advance-CTR) is to bridge these gaps by creating a statewide hub to coordinate and leverage existing research resources and provide new career development support and funding for academic researchers, particularly junior investigators. Research support offerings are responsive to a wide variety of needs and readily available via a service request form on AdvanceCTR.org, the first of its kind on a statewide level.

KEYWORDS: institutional development award, clinical and translational research, junior investigator funding, research services hub, NIGMS

INTRODUCTION

In 2016, Advance-CTR was created as a statewide network of academic and hospital partners, funded (U54GM115677) through the Institutional Development Award Program Infrastructure for Clinical and Translational Research (IDeA-CTR) established by the National Institute of General Medical Sciences (NIGMS). The IDeA-CTR program has three aims to ultimately address state health needs, particularly within medically underserved communities: (1) provide infrastructure and resources for clinical and translational research, (2) develop competitive clinical and translational research programs, and (3) promote clinical and translational research collaborations.1 Advance-CTR offers complimentary research resources and services to investigators and provides statewide awards programs aimed toward junior investigators that offer career development and mentoring. Requests for applications for awards and announcements for professional development opportunities and training are listed on AdvanceCTR.org and promoted in the Advance-CTR weekly newsletter. Using an online form, researchers can request guidance from experts to design and conduct clinical trials and observational research, use health care databases, apply advanced methods for statistical analysis, and engage research participants.

Following receipt of its award, Advance-CTR first sought to identify barriers to clinical and translational research in Rhode Island (RI) through a survey of investigators across our statewide partner network.2 Prominently, investigators identified the absence of pilot funding for broad clinical research, the lack of accessible biostatistics support, limited biomedical informatics expertise, and the challenge of sufficient protected research time as major obstacles (**Figure 1**). The survey found limited general awareness of the availability of the state's Core research services and instrumentation. Respondents also reported a lack of in-patient research facilities, general clinical research infrastructure, NIH-funded clinical research mentors, and programmatic support for clinical and translational research. In response to the needs assessment survey results, the Awards and Service Cores of Advance-CTR created resources, increased communication between its partner institutions, and enhanced pre-existing resources. Each partner site was provided a customized report highlighting results specific to their institution.

Most recently, RI's most vulnerable populations have been highly affected by the COVID-19 pandemic. Partnerships between the academic medical centers, the Department of Health, and the state government have led to early, robust participation in national medication, vaccine, and plasma-based clinical trials. Advance-CTR has sponsored supplemental applications to address the impact of COVID-19 on harm prevention organizations, the creation of a regional biobank that collaborates with the national IDeA-CTR consortium, participation in the National COVID Cohort Collaborative (N3C) data registry (ncats.nih.gov/n3c), and implementation of a National Institutes of Health (NIH) Rapid Acceleration of Diagnostics-Underserved Populations (RADx-UP) initiative aimed at addressing the disproportionate impact of COVID-19 on the Latinx community in RI (3U54AG063546-02S2). Advance-CTR will continue to support research responsiveness to emerging RI health concerns through its services and partnerships.

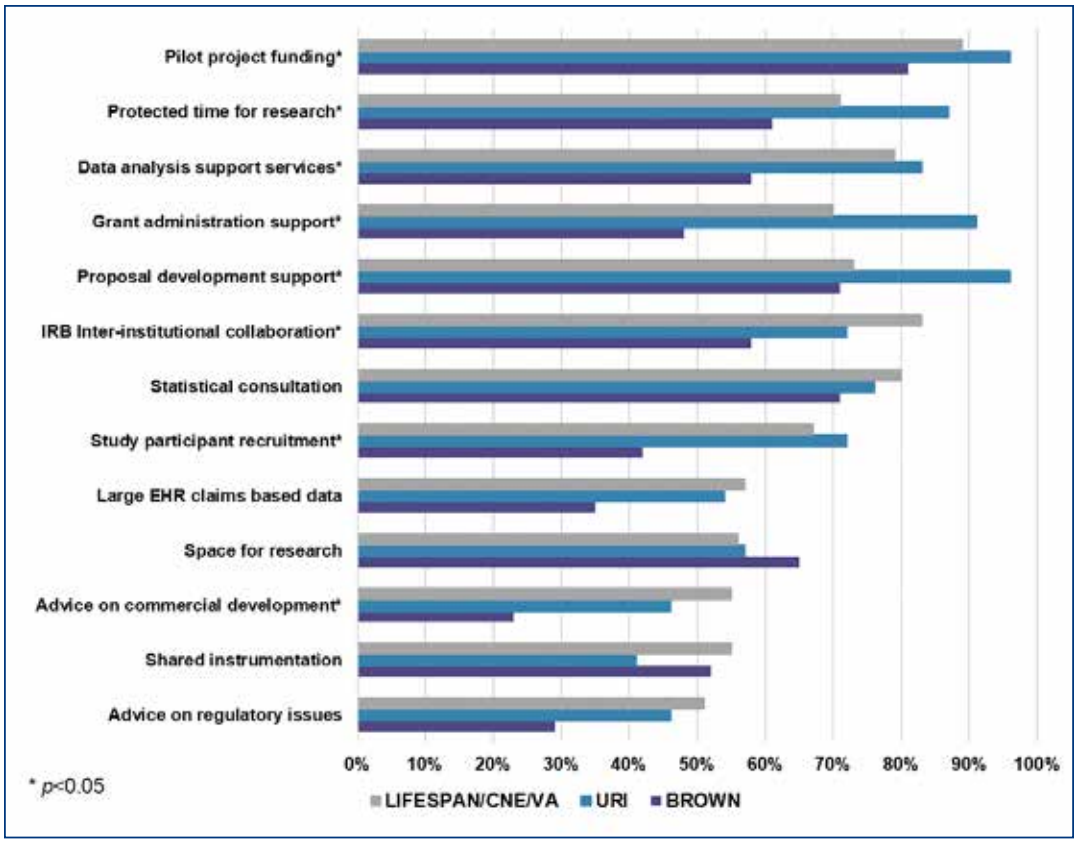


Figure 1. RI Investigator Needs Assessment Results (2017). Investigators (n = 171) indicated the most critical barriers to clinical and translational research. Respondents chose their primary affiliation from three options: Lifespan, Care New England or the VA Providence Healthcare System (Lifespan/CNE/VA; grey bars), University of Rhode Island (URI; blue bars), and Brown University (Brown; purple bars).

ADVANCE-CTR PARTNERS

The Advance-CTR partnership includes Brown University, the University of Rhode Island (URI), three academic health systems (Lifespan, Care New England, and VA Providence Healthcare System), and the RI Quality Institute (RIQI). These partners contribute expertise in biological, clinical, public health, pharmacy, nursing, population, and community-engaged research, and undergraduate, graduate, and professional school education. Combined, the three healthcare systems provide care to over 75% of the state's population, facilitating population-based and clinical research. RIQI is home to the state's health information exchange, CurrentCareTm. The RI Department of Health, RI Public Health Institute, and Brown University's Swearer Center also serve as key collaborators. The culture of collaboration across RI has been strengthened by the inter-institutional and intra-IDeA program cooperation across the Centers for Biomedical Research Excellence (COBRE), IDeA Network of Biomedical Research Excellence (INBRE), Environmental Influences on Child Health Outcome (ECHO) and CTR awards. This is reflected by open access to CTR resources, prioritization of services, recurring PI meetings, shared sponsorship of statewide symposia, and collaboration on newly identified initiatives to expand our network's capabilities.

ORGANIZATIONAL STRUCTURE

The organizational structure of Advance-CTR is shown in **Figure 2**. Oversight is provided by two support Cores: a centralized Administrative Core and a Tracking and Evaluation Core. Three Service Cores provide support to RI investigators: Clinical Research Design, Epidemiology, and Biostatistics; Biomedical Informatics and Cyberinfrastructure Enhancement; and Clinical Research Resources and Facilities. Advance-CTR's two Award Cores provide funding to foster new collaborations among early-career investigators new to clinical and translational research: Pilot Projects Program and Professional Development. Core Directors direct the implementation and progress of their respective cores, participate in Advance-CTR's Operations Committee, and coordinate inter-Core collaborations (**Table 1**). Core-specific Steering Committees provide the knowledge and experience necessary to offer guidance on initiatives and issues. In the Award Cores, these committees also provide crucial input as the "Study Section" for the application review process.

The Administrative Core provides centralized leadership, governance, financial management, organizational structure, and advisory support to develop, maintain, and enhance the Advance-CTR activities. The Administrative Core leads the development, coordination, and implementation of new strategic initiatives to enable highly efficient operational integration across the Cores. In addition to administering

Figure 2. Organizational Structure of Advance-CTR.
The two centralized Administrative and Tracking and Evaluation Cores (grey circles) support two Award Cores (blue circles) and three Service Cores (purple circles).

Table 1. Advance-CTR Core Directors

Name	Core	Home Institution
Elizabeth S. Chen, PhD, FACMI *Director*	Biomedical Informatics and Cyberinfrastructure Enhancement	Brown University
Christopher H. Schmid, PhD *Director*	Clinical Research Design, Epidemiology and Biostatistics	The School of Public Health, Brown University
Jason T. Machan, SCM, PhD *Co-Director*	Clinical Research Design, Epidemiology and Biostatistics	Rhode Island Hospital (Lifespan)
Bharat Ramratnam, MD *Director*	Clinical Research Resources and Facilities	Lifespan
Sharon Rounds, MD *Director*	Pilot Projects Program	Brown University
Michelle Lally, MD, MSc *Co-Director*	Pilot Projects Program	VA Providence Healthcare System
Ira B. Wilson, MD, MSc, FACP *Director*	Professional Development	The School of Public Health, Brown University
Stephen Kogut, PhD, MBA *Director*	Tracking and Evaluation	The College of Pharmacy, University of Rhode Island
Anthony Hayward, MD, PhD *Co-Director*	Tracking and Evaluation	Brown University

the business, financial, communication, and program management functions, this Core develops comprehensive written policies and standard operating procedures that support effective organization and governance. The Administrative Core fosters the growth and long-term sustainability of Advance-CTR to support clinical and translational research investigators' retention in RI.

The Tracking and Evaluation (T&E) Core supports tracking, evaluation, planning, needs assessment, and data dissemination. The T&E Core implements a participatory evaluation model that relies upon collaboration with Core directors in adapting evaluation plans to the evolving array of programs and services. Key Performance Indicators track output and outcome measures of CTR-related infrastructure, resources, and activity. The T&E Core monitors achievement of short- and long-term overall and specific Core goals and promotes quality improvement through outcomes-based feedback to the Operations Committee and each Core Director. The T&E Core led the statewide needs assessment and collection of baseline data addressing clinical and translational investigators' needs and created the focus for evaluation planning by stakeholder groups.[2] This was followed by a participatory Group Concept Mapping (GCM) study involving investigators and research administrators from each of the partner institutions to prioritize efforts to enhance the quality and quantity of clinical and translational research in RI.[3] Results of this statewide GCM study have been shared across the CTR/CTSA Evaluators collaborative and were presented at the 2018 meeting of the American Evaluation Association.[4] The T&E Core conducted a subsequent GCM study with Brown University's Swearer Center and its community partners to identify leading health priorities from the communities' perspective.

The Clinical Research Design, Epidemiology, and Biostatistics Core provides services, resources, education, mentoring, and tools to support clinical and translational research. Through their distributed "storefront model," the Core offers drop-in sessions and service consultations, resulting in >500 consultations to date to faculty at all career levels across our partner institutions. The Core supports investigators in study design, data collection, management, analysis, interpretation, and presentation using procedures that ensure quality control and reproducibility of analyses. They support a full range of quantitative, qualitative, survey, and mixed methods research designs. The Core has developed its seminar series, mini-symposia, and training materials in study design, epidemiology, and biostatistics for clinical investigators, and as well as training in statistical collaboration and consultation by Core statistical staff and student consultants. To increase

accessibility, all resources are available on the Advance-CTR website, shared broadly on the national IDeA-CTR website, CTRnet.org, and the DIAMOND™ web portal hosted by CLIC at the University of Rochester (https://clic-ctsa.org/diamond).

The Biomedical Informatics and Cyberinfrastructure Enhancement Core contributes to professional development in biomedical informatics through its consultation program, educational programs, workshops, and other engagement activities that enhance collaborative interactions within RI and across the IDeA network. The Core has implemented widely used standards-based tools, such as OHDSIOMOP and i2b2/SHRINE, to support multi-purpose cohort identification and studies using electronic health record (EHR) data from our affiliates. They enable widespread use of the state's designated health information exchange (HIE), CurrentCare™. The Core also secured access to the HealthFacts RI, an all-payer claims database (APCD) for clinical and translational research. They developed the first statewide instance of REDCap and directed an Advance-CTR award program to fund projects using Big Data. This Core will host the IDeA-CTR Network Biomedical Informatics Consortium's Coalition that builds collaborations across each of the CTR award programs on a national level.

The Clinical Research Resources and Facilities (CRC) Core provides services, resources, and professional development opportunities to support clinical and translational research. This Core is an easily accessible center that provides investigators with a space to perform study visits and trained Research Nurses and Coordinators to perform study measures and phlebotomy. The Core provides expertise in clinical trial study design and budget development, resources for biospecimen processing and storage, and support for IRB applications, particularly for junior investigators. The Core supports the education and certification of research personnel at each of our partner sites, including training for Good Clinical Practice (GCP) and Public Responsibility in Medicine and Research (PRIM&R), and professional certification in Clinical Research by the Society of Clinical Research Associates (SOCRA).

The Pilot Projects Program (PPP) Core addresses the identified statewide gaps in pilot funding to support clinical and translational research investigators to ultimately impact state health priorities. Special consideration is given to community-engaged projects that address health disparities and other research priorities. The PPP Core has significantly enhanced the quality and quantity of clinical and translational research in RI by awarding 33 Pilot Projects spanning the T0 to T4 research spectrum and by developing multi-disciplinary research collaborations among co-PIs across the state. This Core has received proposals from 454 unique applicants across our statewide consortium. The 59 awarded investigators have subsequently received 26 independent, extramural awards. The PPP Core coordinates the annual statewide Emerging Areas of Research Symposia, which brings together all RI IDeA program staff and faculty.

The Professional Development (PD) Core offers training opportunities that promote the career development of clinical and translational research investigators. These opportunities include a monthly trans-institutional seminar series where investigators present their research-in-progress and receive feedback from peers and Advance-CTR leadership. A two-year Mentored Research Award program has funded 11 scholars, and to date, 10 have received extramural funding. This Core provides partner-wide, web-based training in interdisciplinary clinical and translational research-oriented topics (e.g., team science), and in-person and web-based training focused on the commercialization of research findings. The PD Core sponsored faculty from each of our partner organizations to become qualified to implement the evidence-based curriculum for mentor training developed by the National Research Mentor Network (NRMN) and the Center for the Improvement of the Mentored Experience (CIMER). To date, 8 trainers have applied this curriculum to train 105 RI faculty to become more effective research mentors to junior faculty. In partnership with the Brown Division of BioMed, the PD Core supported Advance-K's creation, a formally structured, year-long, intensive program to guide selected early-career faculty to prepare and submit individual career development awards. This program was formed specifically to address the challenges of clinician scientists' ability to secure release time and obtain the mentorship needed to develop career development plans and awards.

LEADERSHIP AND SHARED GOVERNANCE

The PD/PI of Advance-CTR and the chair of the Operations Committee is James Padbury, MD. With Program Coordinator Edward Hawrot, PhD, he co-leads a centralized Administrative Core that provides an integrated and efficient structure for program management. The Administrative Core includes a Director and a dedicated Manager for the Award Cores, the Service Cores, Communications, and Data Management. This administrative structure provides close integration across the multi-institutional Cores, assurance of best practices with and between administrative functions, and balance across our network of partners. Advance-CTR is advised by highly engaged Operations, Steering, Internal, and External Advisory Committees, with oversight and guidance provided by key stakeholders from our partner sites. The leadership approach is based on institutional integration and balance, representing every stakeholder in our network. The Operations Committee oversees Core management and productivity; allocation of resources, educational initiatives, and training programs; supports projects at individual institutions; contributes to building and space decisions, the distribution of infrastructure resources, and decision-making

for program evaluation. The Steering Committee assures accountability for operations, coordination, resource management, data tracking, and program effectiveness across the Advance-CTR partner institutions. The Internal Advisory Committee includes leaders from partner institutions and community representatives who contribute to the strategic vision and allocation of Advance-CTR resources. The External Advisory Committee advises Advance-CTR leadership, providing formal recommendations and support.

HIGHLIGHTS AND ACCOMPLISHMENTS

In response to investigator needs and keeping with the health priorities of RI, Advance-CTR funded 53 awards to projects that span the translational research spectrum. Funded projects address top RI health concerns, including mental health disorders among adults, children, and adolescents, and research on opioid use at the individual, patient, and community level. Advance-CTR gives priority consideration to projects that address community health priorities, are conducted in communities, and employ community partners. Awarded research has utilized computational approaches across various areas: in health services, analytical decision support, and machine learning approaches to sophisticated diagnostic algorithms. In the past 4.5 years, 42 investigators supported by Advance-CTR (awardees and direct service users) have generated 61 extramural grants totaling $14.3M for a return on investment of 3 to 1. Additionally, Advance-CTR Core Directors and investigators have received supplemental awards for Alzheimer's Disease Risk Assessment, participation in the N3C CTSA/CTR COVID-19 Data Registry, and in the RADx-UP consortium.

The Service Cores continue to meet investigators' needs through complimentary service consultations, original seminars and symposia, and resource creation. There is a particularly high demand for consultations in biostatistics, research design, and qualitative methods. In response, the Biostatistics Core has provided 639 consultations to 295 unique investigators as of December 31, 2020. Likewise, the Cores have provided individual and group training for NVivo qualitative software, which was previously unavailable on a statewide level, as well as consults for survey creation, design, and analysis. The Biostatistics and Biomedical Informatics Cores have led a joint effort to provide REDCap assistance to investigators. In contrast, the CRC Core has supported costly clinical research certification training to administrators at its hospital partners. One of the most impactful services that Cores have provided is its matchmaking of early-career investigators with mentors and faculty experts at different institutions. The Service Cores have facilitated dozens of cross-institutional collaborations between investigators of diverse disciplines that have yielded extramural funding, publications, and ongoing partnerships.

SUMMARY

Advance-CTR leverages resources to establish clinical and translational programs that were either not previously available or siloed within single partners with a statewide consortium of partners. Notably, Advance-CTR introduced pilot, career development, and big data awards along with faculty development programs. Advance-CTR has created three consultative Service Cores, all of which were previously limited in availability at the statewide level. As a result, Advance-CTR serves as a research hub and training umbrella for the entire RI clinical and translation research investigator community. Advance-CTR aims to enhance patient-centered research and accelerate health discoveries that benefit RI's communities, and impact the state's leading health needs.

References

1. Institutional Development Award Program Infrastructure for Clinical and Translational Research (IDeA-CTR). National Institute of General Medical Sciences website. www.nigms.nih.gov/Research/DRCB/IDeA/Pages/IDeA-CTR.aspx; January 2021.
2. Willey C, Fede J, Stevenson J, Hayward A, Kogut S, Fournier H, Padbury J. Clinical and Translational Research in Rhode Island: Results of a Needs Assessment Survey. RI Med J (2013). 2018 Feb 2;101(1):21-25.
3. Fede J, Kogut S, Hayward A, Stevenson J, Willey-Temkin C, Fournier H, Padbury J. (2021). Improving the Quality and Quantity of Clinical and Translational Research Statewide: An Application of Group Concept Mapping. J Clin Transl Res. 2021 Jan;1-30. doi:10.1017/cts.2020.572.
4. Fede J, Kogut S, Stevenson J, Hayward A, Willey C. Increasing the Quality and Quantity of CTR in RI: Comparing Views of Program Leadership and the Local Research Community. American Evaluation Association 2018 Conference. November 2, 2018; Cleveland, OH.

Acknowledgments

Research and activities reported in this publication were supported by an Institutional Development Award (IDeA) from the National Institute of General Medical Sciences of the National Institutes of Health under award number U54GM115677.

Authors

Valerie Zabala, PhD; Project Manager, Advance-CTR, Brown University, Providence, RI.

Gabrielle Stranieri, BA; Communication Manager, Advance-CTR, Brown University, Providence, RI.

Heather Fournier, MA; Administrative Director, Advance-CTR, Brown University, Providence, RI.

Edward Hawrot, PhD; Program Coordinator, Advance-CTR; Alva O. Way Professor of Medical Science, Senior Associate Dean for the Program in Biology, Brown University, Providence, RI.

James Padbury, MD; Principal Investigator, Advance-CTR; William and Mary Oh - William and Elsa Zopfi Professor of Pediatrics for Perinatal Research, Brown University, Providence, RI.

Correspondence

James Padbury, MD; Principal Investigator, Advance-CTR
Brown University, Division of Biology and Medicine
233 Richmond Street
Providence, RI 02912
james_padbury@brown.edu

Spontaneous Pneumomediastinum in a Healthy 25-Year-Old Male

JULIE WOODSIDE, PA-C; RICHARD V. MORGERA, MD

CASE PRESENTATION

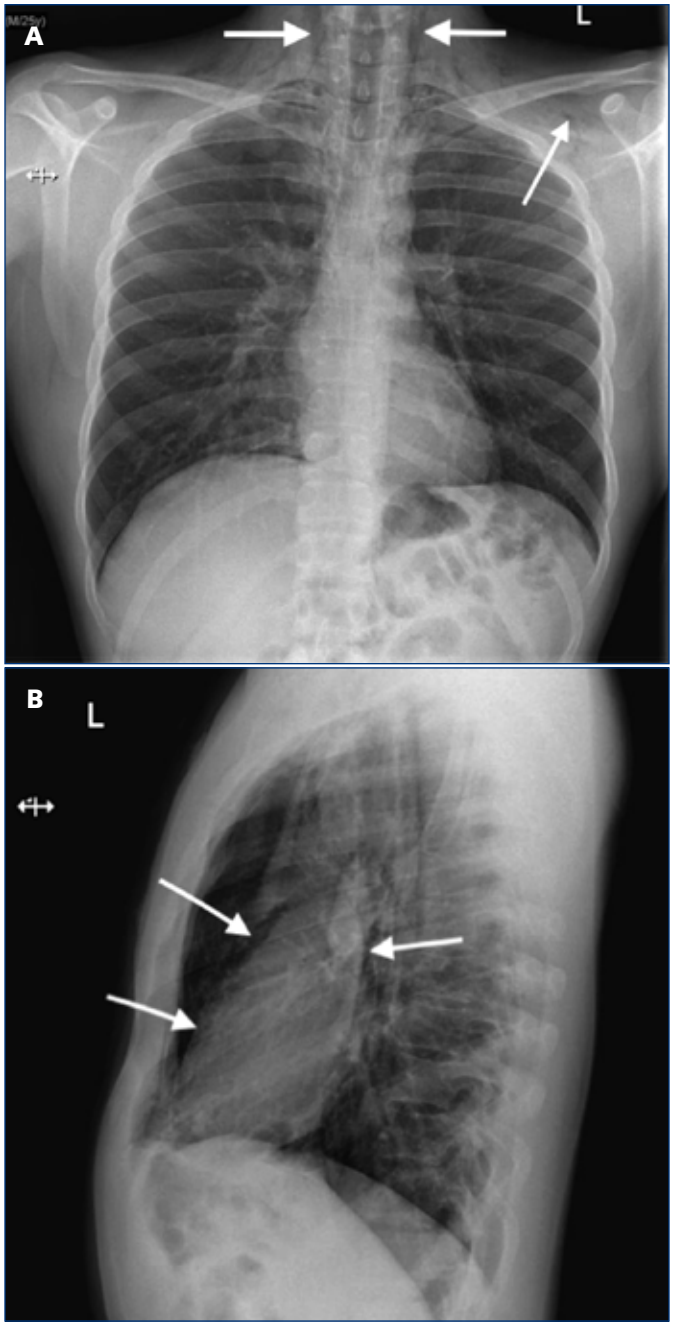
A 25-year-old man with no significant past medical history presented to an urgent care clinic with four days of an abnormal sensation of throat and neck swelling ("as if I had been punched in the throat"), chest pain, pain with deep inspiraton, fatigue, and a feeling of generalized anxiety. The symptoms appeared worsened at night when recumbent. The patient denied fever, chills, cough, headache or heart palpitations. He denied exposure to COVID-19, but had a PCR test the day prior with results pending at time of presentation. The patient denied any recent trauma. He reported occasional alcohol and marijuana use but denied tobacco use.

Physical examination showed a well appearing, well-groomed, anxious young male in no acute respiratory distress. Oxygen saturation was 98% on room air and the patient was afebrile. Pulse was 110 bpm, and blood pressure was 128/84 mm Hg. HEENT exam revealed the posterior pharynx to be clear with no oral swelling. The neck was without lymphadenopathy. Palpation of the thyroid did not show enlargement, but crepitations around the anterior neck and supraclavicular region were present, consistent with subcutaneous emphysema. Lung sounds were clear. The remainder of the patient's exam was within normal limits.

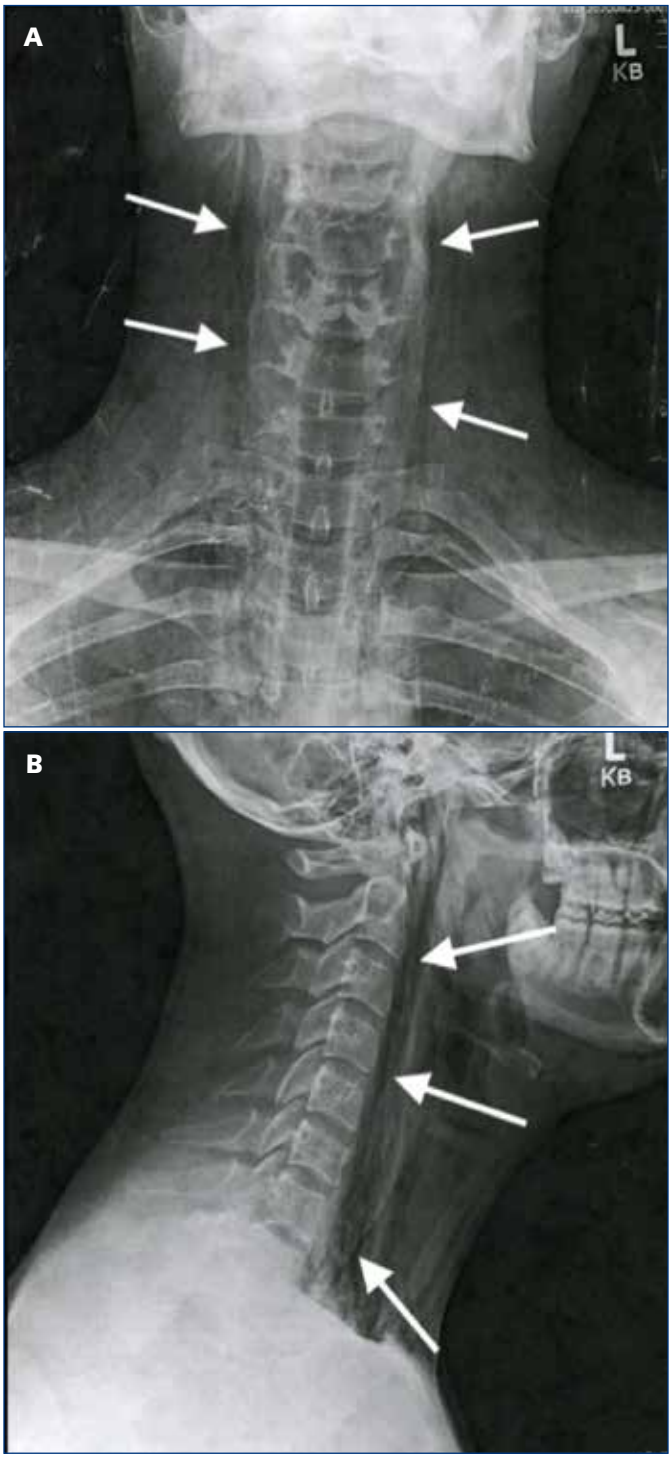
Radiographic imaging was obtained including chest and neck soft tissue views. Chest X-ray (**Figures 1A, 1B**) showed free air tracking up towards the cervical region, concerning for pneumomediastinum. Neck views (**Figures 2A, 2B),** showed extensive gas throughout the soft tissues of the anterior neck. Additional history revealed that the patient smoked marijuana four days prior and often "rips from the bong" with deep inspirations. EKG was obtained with normal findings. The underlying etiology of his pneumomediastinum was speculated to be his recent marijuana smoking as described previously. The patient was transferred to the emergency department and was offered admission to the hospital, but he declined. He was given strict instructions to not smoke, avoid flying, diving, hiking and Valsalva maneuvers. Return precautions were discussed. He was instructed to follow up in one week with a chest X-ray and to establish care with a PCP.

Patient did return for a chest X-ray one week later showing resolution of the pneumomediastinum. (**Figures 3A, 3B**).

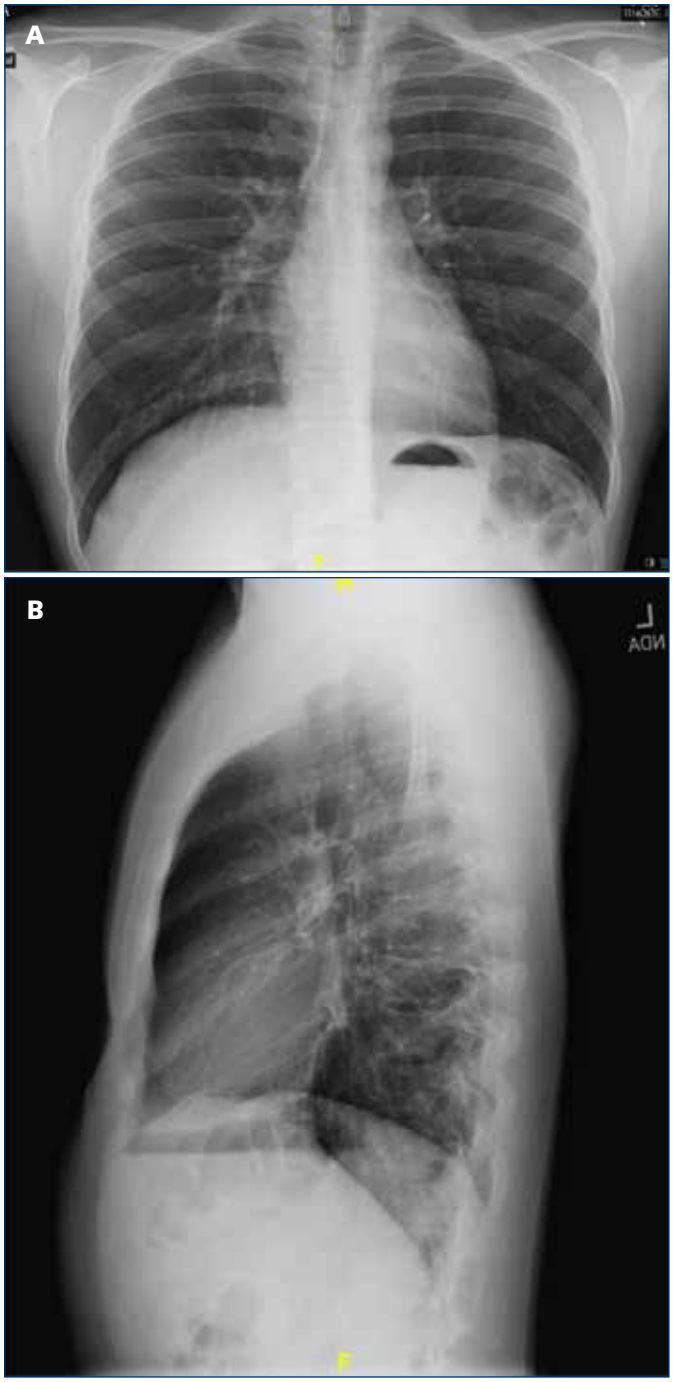
Figures 1A, 1B. Chest X-rays showing subcutaneous emphysema, pneumomediastinum



Figures 2A, 2B. Neck X-rays (AP, Lateral) showing subcutaneous emphysema



Figures 3A, 3B. Chest X-rays one week after ED visit showing resolution of pneumomediastinum



DISCUSSION

Spontaneous pneumomediastinum (SPM) is an uncommon problem, primarily seen in young men, and defined as the presence of free air in the mediastinum in the absence of trauma, recent surgical procedure, mechanical ventilation or obvious inciting factor. SPM can be caused by asthma exacerbation, sporting events, Valsalva maneuvers, emesis, smoking, vaping, excessive coughing, and drug use. It can also occur in pregnant women as a result of/or during labor.[1] The triad of symptoms that young males generally present with include dyspnea, chest pain and subcutaneous emphysema. Pneumomediastinum was first described by Laennec in 1819, describing the condition as a result of trauma, and Hamman reported atraumatic spontaneous pneumomediastinum over a century later. SPM in the setting of marijuana use was first described in 1972.[2]

In this case, it was suspected the patient's spontaneous pneumomediastinum occurred due to barotrauma while smoking marijuana; in particular, taking deep inspirations from a bong followed by breath holding. The act of deep inspiration followed by a forced apnea resulting in a closed glottis after each inhalation and/or inhalation through a high-resistance smoking apparatus are both thought to produce a decrease in intrathoracic pressure, an increase in the intra-alveolar air volume causing rupture of the alveoli and dissection of the air from the pulmonary interstitium to the mediastinum, neck, and, at times, the pericardium(the Macklin effect).[1,3,4] Pneumothorax can occur at times if the intrathoracic pressure fails to fully decompress from the air dissecting into the subcutaneous tissue. Secondary pneumomediastinum, on the other hand, occurs as a result of trauma (blunt/penetrating), head and neck surgical procedures or mechanical ventilation.

A thorough physical exam, a high index of suspicion and radiologic imaging are crucial in diagnosing SPM. X-ray often confirms the presence of subcutaneous emphysema, but a CT Scan may be needed in equivocal plain x-ray findings, to identify underlying pulmonary pathology and to exclude pneumopericardium. Acute myocardial infarction, pulmonary embolism, cardiac tamponade, aortic dissection, Boerhaave syndrome, and other critical diagnoses with similar presenting symptoms must be ruled out.

Treatment of SPM is conservative including pain control, avoiding excessive physical and aggravating activities, and the administration of oxygen (in some cases) to increase gas absorption and hasten resolution.[5] In most cases resolution of symptoms is noted within a few days, but follow up including repeat radiographs are indicated. Risk of recurrence is very low.

References

1. Weiss ZF, Gore S, Foderaro A. Pneumomediastinum in marijuana users: a retrospective review of 14 cases. *BMJ Open Resp Res*. 2019;6:e000391. doi:10.1136/bmjresp-2018-000391.
2. Koullias GJ, Korkolis DP, Wang XJ, Hammond GL. Current assessment and management of spontaneous pneumomediastinum: experience in 24 adult patients. *Eur J Cardiothorac Surg*. 2004 May. 25:852-855. https://doi.org/10.1016/j.ejcts.2004.01.042.
3. Hazouard E, Koninck JC, Attucci S, Fauchier-Rolland F, Brunereau L, Diot P. Pneumorachis and pneumomediastinum caused by repeated Müller's maneuvers: complications of marijuana smoking. *Ann Emerg Med*. December 2001;38:694- 697. https://doi.org/10.1067/mem.2001.118016.
4. Rajendran T, Shaikh O, Kumbhar U, Balasubramanian G, Bhattarai S. Spontaneous pneumomediastinum in a young adult: a rare presentation. *Cureus*. 2020 May;12(5):e8306. doi:10.7759/cureus.8306.
5. Takada K, Matsumoto S, Hiramatsu T, Kojima E, Shizu M, Okachi S, Ninomiya K, Morioka H. Spontaneous pneumomediastinum: an algorithm for diagnosis and management. *Ther Adv Respir Dis*. 2009 Dec;3(6):301-307. doi:10.1177/1753465809350888.

Authors

Julie Woodside, PA-C, South County Hospital Express Care, Department of Emergency Medicine, Lifespan Physician Group, Newport Orthopedics.

Richard V. Morgera, MD, South County Hospital Express Care, Department of Emergency Medicine, Clinical Assistant Professor. Alpert Medical School of Brown University, Providence, RI.

Disclosures

The authors have none to declare.

Correspondence

Julie Woodside, PA-C
Newport Orthopedics
19 Friendship Street, Suite 130
Newport, RI 02840
401-845-1474
woodside.julie@gmail.com

Pneumomediastinum in a Patient with Cannabinoid Hyperemesis Syndrome

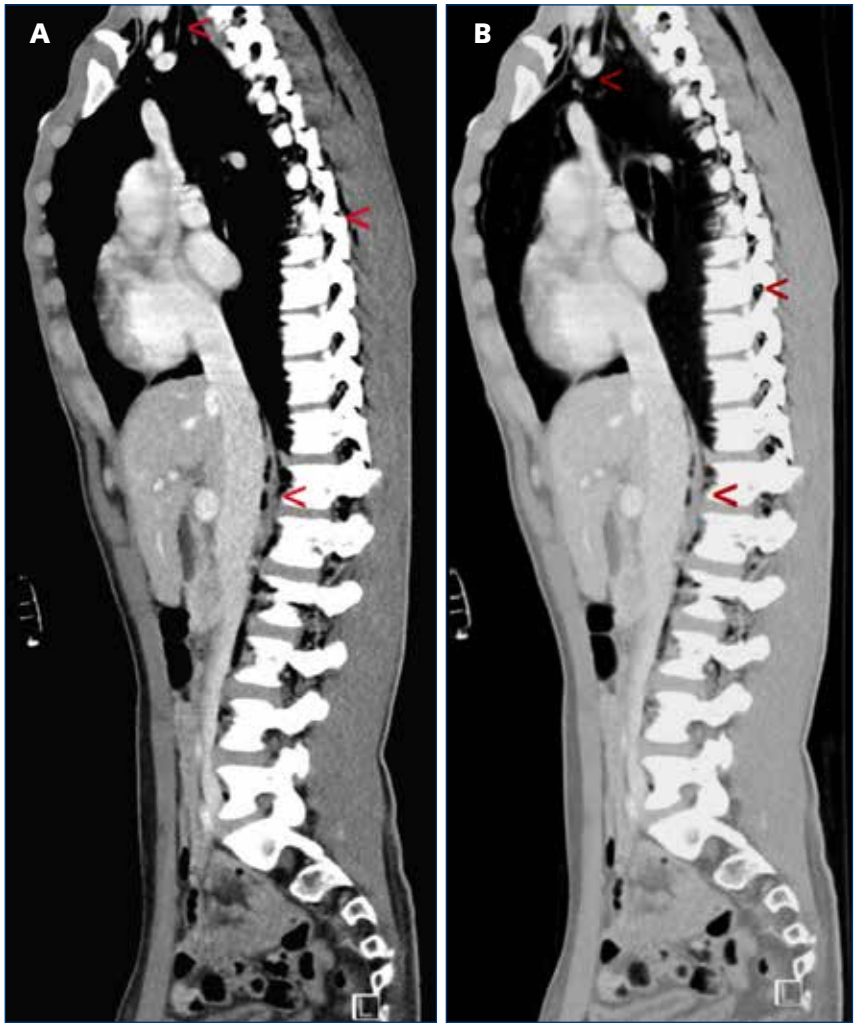
MARC J. VECCHIO, MD; WILLIAM D. BINDER, MD, FACEP

CASE PRESENTATION

A 23-year-old man with a past medical history of cannabinoid hyperemesis syndrome presented to the emergency department with 1 week of nausea, emesis and poor oral intake. Prior to presentation, the patient had been treated in the emergency department several times for intractable vomiting. The patient reported he was a daily long-term user of marijuana cigarettes.

On presentation, the patient was afebrile with a pulse of 117 beats per minute, respirations of 20 per minute, blood pressure of 111/79 and oxygen saturation of 99% on room air. Physical examination revealed a thin man with eructation and subcutaneous crepitation over the neck and thorax. Lung sounds were clear to auscultation bilaterally. Laboratory testing revealed a pH of 7.26, anion gap of 33, blood-urea nitrogen of 107 mg/dL and a newly elevated creatinine of 13.01 mg/dL. Notably, the patient had normal labs with a creatinine of 0.84 mg/dL during a similar presentation for intractable vomiting one month prior to presentation. Chest X-ray showed evidence of subcutaneous gas and pneumomediastinum. Computed tomography (CT) of the chest and abdomen with intravenous contrast revealed pneumomediastinum and pneumoretroperitoneum with extension into the spinal canal (**Figure 1**). Repeat CT imaging of the chest with oral contrast was performed and did not show extraluminal oral contrast extravasation into the mediastinum. The patient was evaluated by cardiothoracic surgery, who recommended conservative management with close monitoring of symptoms. Urinalysis demonstrated muddy brown casts and renal tubular epithelial cells, suggesting pre-renal azotemia secondary to volume depletion. Treatment with 3 days of intravenous fluids and anti-emetics resulted in normalization of the patient's creatinine (**Figure 2**). The patient was subsequently discharged without further complication.

Figure 1. (A) Red arrows illustrating extensive pneumomediastinum and pneumoretroperitoneum; (B) illustrating air extending into the neck and spinal canal.



Two months after discharge, the patient presented with a subsequent episode of intractable vomiting from cannabinoid hyperemesis syndrome. CT of the chest with intravenous contrast revealed complete resolution of the patient's prior findings of pneumomediastinum and pneumoretroperitoneum.

Figure 2. Laboratory evaluation revealing patient's basic metabolic panel prior to, during and following presentation for cannabinoid hyperemesis syndrome.

	1 Month prior to presentation	Presentation	1 week after discharge
Sodium	144 mEq/L	152 mEq/L	136 mEq/L
Potassium	3.7 mEq/L	4.7 mEq/L	3.2 mEq/L
Chloride	111 mEq/L	102 mEq/L	101 mEq/L
Bicarbonate	21 mEq/L	17 mEq/L	28 mEq/L
BUN	14 mg/dL	107 mg/dL	10 mg/dL
Creatinine	0.84 mg/dL	13.01 mg/dL	0.87 mg/dL

DISCUSSION

Definitive diagnosis of cannabinoid hyperemesis syndrome (CHS) has proven to be challenging, as there is no standardized diagnostic criteria. This is likely due to the elusive nature of the syndrome's pathophysiology. It has been hypothesized to involve a complex interaction between the endogenous CB_1 and CB_2 cannabinoid receptors (with CB_1 responsible for the majority of deleterious clinical effects) and tetrahydrocannabinol (THC) in marijuana.[1,2] In an effort to increase the sensitivity for diagnosis, a recent systematic review evaluated several case reports to determine which symptoms were most frequently encountered in patients with CHS. The symptoms with the highest sensitivity included severe nausea and vomiting in a cyclical pattern over several months, a minimum of weekly cannabis use for longer than 1 year, symptom relief with hot baths or showers and resolution of symptoms after cessation of cannabis use.[3] There is a male predominance and episodes usually last 1–2 days, but can extend up to 10 days.[4] While the symptoms of CHS may appear benign, intractable vomiting from CHS can result in severe complications including acute renal failure, esophageal perforation, severe electrolyte derangement, pneumomediastinum, and death.[5,6] While our patient did not end up having esophageal perforation, his acute renal failure, electrolyte derangements and pneumomediastinum demonstrate the potential life-threatening complications of CHS. This case illustrates the importance of monitoring for these complications in patients who present with intractable vomiting as a manifestation of CHS.

References

1. Galli JA, Sawaya RA, Friedenberg FK. Cannabinoid hyperemesis syndrome. Curr Drug Abuse Rev. 2011;4(4):241-249.
2. DeVuono MV, Parker LA. Cannabinoid Hyperemesis Syndrome: A Review of Potential Mechanisms. Cannabis and Cannabinoid Research. 2020;5:1132-144.
3. Sorensen CJ, DeSanto K, Borgelt L, Phillips KT, Monte AA. Cannabinoid Hyperemesis Syndrome: Diagnosis, Pathophysiology, and Treatment – a Systematic Review. J Med Toxicol. 2017;13(1):71-87.
4. Lapoint J, Meyer S, Yu CK, Koenig KL, et al. Cannabinoid Hyperemesis Syndrome: Public Health Implications and a Novel Model Treatment Guideline. West J Emerg Med. 2018;19:380-386.
5. Gajendran M, Sifuentes J, Bashashati M, McCallum R. Cannabinoid hyperemesis syndrome: definition, pathophysiology, clinical spectrum, insights into acute and long-term management. Journal of Investigative Medicine. 2020;68:1309-1316.
6. Nourbakhsh M, Miller A, Gofton J, Jones G, Adeagbo B. Cannabinoid Hyperemesis Syndrome: Reports of Fatal Cases. J Forensic Sci. 2019;64(1):270-274.

Authors

Marc J. Vecchio, MD, Department of Medicine, Warren Alpert Medical School of Brown University, Providence, RI.

William D. Binder, MD, FACEP, Department of Emergency Medicine, Warren Alpert Medical School of Brown University, Providence, RI.

Correspondence

Marc J. Vecchio, MD
Rhode Island Hospital
593 Eddy St.
Providence, RI 02903
401-444-4000
mvecchio@lifespan.org

Chin Numbness as a Presenting Symptom of Malignancy

CHRISTIAN E. BUSTAMANTE, MD; KYLE DENISON MARTIN, DO, MPH, DTM&H; EMILY COLYER, DO

ABSTRACT

Numb Chin Syndrome (NCS) is a sensory neuropathy that was first described in the early 1800s. It has various etiologies, most commonly benign local pathology. However, NCS has been documented as the primary presenting symptom of systemic malignancy, most commonly breast cancer.[1] This is the case of a young male who presented to the emergency department with complaints of a numb chin and was ultimately found to have invasive neoplastic lesions in the right tonsillar and mandibular regions of the face arising from metastatic large B-cell lymphoma.

KEYWORDS: facial paresthesia, Numb Chin Syndrome, neuropathy, lymphoma, malignancy

ABBREVIATIONS: NCS – Numb Chin Syndrome

INTRODUCTION

Isolated symptoms of a numb chin can have various etiologies and origins. (**Table 1**) In many cases, it involves manifestations of maxillofacial pathology including dental infections and anatomical variances that lead to the compression of nerves innervating the mandible.[1] Interestingly, numb chin can also be a presenting symptom for an underlying malignancy with metastasis to the mental nerve.[2] In the presenting case, the patient's chin paresthesia was found to be the initial symptom for underlying lymphoma.

Table 1. Differential Diagnosis for Chin Numbness

ACUTE
Dental infection (gingivitis, abscess)
Bone infection (osteomyelitis)
Ill-fitting dentures or implants
Trauma from recent dental extraction or mandibular surgery
Malignancy (typically metastatic disease)
CHRONIC
Diabetes mellitus
Multiple sclerosis
Benign tumor
Prior radiation therapy to region

CASE REPORT

A 31-year-old male with no past medical history presented to the emergency department for evaluation of chin numbness. He complained that for 2 weeks he had a constant, progressively worsening numb sensation over his right chin spreading into his right lower anterior teeth. He denied any trauma, signs of infection, or recent dental surgery.

On review of systems, he endorsed mild abdominal cramping with normal stools for the past month. He became concerned when he queried the Internet regarding his symptoms of a numb chin and subsequently came across research literature associating his presentation with malignancy of the colon. His concern was further supported by a family history of colon cancer on his mother's side at the age of 48.

Abdominal and neurological exam were benign other than mild decreased sensation of the right mandible in the V3 distribution. There was no evidence of dental infection, soft tissue swelling or tonsillar mass.

Although the chief complaint and physical exam indicated maxillofacial pathology, the patient's primary concern was for malignancy due to a strong family history of colon cancer. As such, a CT scan of the abdomen and pelvis was performed. This showed an ileocecal lesion with some surrounding adenopathy and omental caking, concerning for malignancy. Blood work demonstrated a leukocytosis of 17K with abnormal lymphocytes.

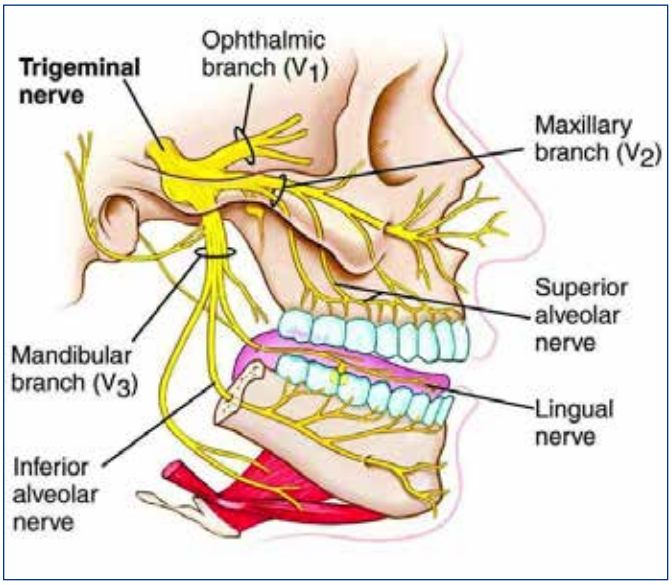
He was admitted to the hospital for gastroenterology, oncology and surgical evaluation. The patient had a colonoscopy performed on hospital day 1, which revealed a 6–7 cm mass in the cecum noted to be polypoid, firm and infiltrative with 60% luminal involvement. Pathology evaluation of biopsies from the mass ultimately found cells concerning for lymphoma. The patient had a bone marrow biopsy on hospital day 2 which showed high-grade large B-Cell lymphoma. PET scan performed on hospital day 3 revealed marked abnormal FDG activity within the abdomen: terminal ileum, peritoneal and omental surfaces. PET scan also showed significant uptake in the right tonsillar region concerning for metastasis into facial structures. MRI was subsequently performed demonstrating a 3.7 x 3.2 cm mass in the right maxillary sinus with local invasion. This mass lesion was found to be the cause of the chin numbness. The patient was discharged on hospital day 5 with a plan to start Modified McGrath Chemotherapy Regimen.

Complete resolution of the patient's chin numbness was noted after four cycles of chemotherapy.

DISCUSSION

Numb Chin Syndrome, although rare, is a well-documented presentation of systemic malignancy. It is characterized by sensory neuropathies presenting with numbness of the chin in the distribution of the mental nerve and mandibular division of the trigeminal nerve.[2] (**Figure 2**) It is thought to be due to invasion of neoplasm into local tissue surrounding the mental nerve or even involving the nerve itself.[1,2] The PET scan in this case supports this theory as it showed highly suspicious activity for metastatic malignancy in the right facial structures. Interestingly, cases have been identified where no local mandibular metastasis was noted, making its presentation perplexing. Though it is nonspecific to any malignancy, NCS has been more frequently associated with metastatic lymphoma and breast cancer, the latter being most common.[1,3] Other cancers with high metastatic potential have also been described in the setting of NCS.[2,4] Its presentation is many times the first identifiable symptom and manifestation of an underlying malignancy.[1-5] CT imaging of the maxillofacial region should be considered as well as additional imaging based upon patient presentation. In this case, it was fortunate that the underlying malignancy was found on CT of the abdomen and pelvis. This led to further imaging and identification of the maxillofacial lesion causing the patient's symptoms.

Figure 2. The Mandibular Branch (V3) of the Trigeminal Nerve



CONCLUSION

Although Numb Chin Syndrome presents more frequently in the setting of dental abscesses, gingivitis, local trauma and benign tumors, it is imperative that emergency medicine physicians understand that this presentation could have a more significant life-threatening origin, such as metastatic disease.

References

1. Baskaran, Ramesh Kapa, et al. Numb Chin Syndrome – a Reflection of Systemic Malignancy. *World Journal of Surgical Oncology*, BioMed Central, 9 Aug. 2006.
2. Assaf AT, Jürgens TP, Benecke AW, Riecke B, et al. Numb chin syndrome: a rare and often overlooked symptom. *J Oral Facial Pain Headache.* 2014 Winter;28(1):80-90.
3. Chapa NJ. Numb chin syndrome: a signal of underlying concern. *J Dent Hyg*. 2014 Dec;88(6):348-52.
4. Tejani N, Cooper A, Rezo A, Pranavan G, Yip D. Numb chin syndrome: a case series of a clinical syndrome associated with malignancy. *J Med Imaging Radiat Oncol*. 2014 Dec;58(6):700-5.
5. Lata J, Kumar P. Numb chin syndrome: a case report and review of the literature. *Indian J Dent Res*. 2010 Jan-Mar;21(1):135-7.

Authors

Christian E. Bustamante, MD, Emergency Medicine Resident, Kent Hospital, Warwick, RI.

Kyle Denison Martin, DO, MPH, DTM&H, Academic Faculty, Department of Emergency Medicine, Kent Hospital, Warwick, RI.

Emily Colyer, DO, Clinical Faculty, Department of Emergency Medicine, Kent Hospital, Warwick, RI.

Correspondence

Christian Bustamante, MD
Division of Emergency Medicine
Kent Hospital
455 Toll Gate Road, Warwick, RI 02886
CBustamante@KentRI.org

Characterizing the Symptoms of Patients with Persistent Post-Treatment Lyme Symptoms: A Survey of Patients at a Lyme Disease Clinic in Rhode Island

SARA E. VARGAS, PhD; MEGHAN McCARTHY, ScB; MATTHEW BOUDREAU, BA; DYLAN CANFIELD, BA; REBECCA REECE, MD; TIMOTHY FLANIGAN, MD

ABSTRACT

BACKGROUND: 10–20% of individuals diagnosed with Lyme disease develop chronic symptoms after antibiotic treatment.

METHODS: A convenience sample of adults with self-reported, persistent post-Lyme treatment symptoms seeking treatment at the Lifespan Lyme Disease Center in Rhode Island completed a demographic and medical survey, the Patient Reported Outcomes Measurement Information System (PROMIS)-29 v2.0, and other short-form PROMIS measures of cognitive function, sleep disturbance, and fatigue.

RESULTS: Compared to average standardized scale scores (T=50; SD=10), participants had mild impairments in physical (T=41) and social (T=42) functioning, mild symptoms of depression (T=56), anxiety (T=60), and sleep disturbance (T=57), and moderate pain interference (T=62), and fatigue (T=65). Participants reported greater symptoms than some other clinical samples including those with cancer and chronic pain. Post-hoc analyses revealed that women reported higher levels of fatigue than men.

CONCLUSIONS: People with persistent post-Lyme treatment symptoms report debilitating symptoms and functional impairments which must be considered in clinical care.

KEYWORDS: Lyme disease, chronic disease, patient-reported outcomes, quality of life

ABBREVIATIONS: α – Cronbach's alpha;
PROMIS – Patient-Reported Outcomes Measurement Information System;
PTLDS – post-treatment Lyme disease syndrome

BACKGROUND

Lyme is the most common vector-borne disease in the United States with an estimated 300,000 new cases each year, and Northeastern states, including Rhode Island, have particularly high rates of Lyme infection.[1] Among those who do undergo recommended antibiotic treatment for acute symptoms (e.g., distinct skin rash, fever, headache, muscle and joint aches), an estimated 10-20% develop symptoms of persistent fatigue, pain, and impaired cognitive functioning that persist more than 6 months post-treatment in the absence of continued clinical findings such as a rash.[2]

These persistent symptoms, known as post-treatment Lyme disease syndrome, or PTLDS, are distinct from the acute phase of Lyme disease and medically unexplained. The Infectious Diseases Society of America has proposed inclusion criteria for the diagnosis of PTLDS including a previous diagnosis of Lyme, stabilization of symptoms after antibiotic treatment, and relapsing symptoms of fatigue, musculoskeletal pain, or complaints of cognitive difficulties that persist for at least 6 months after completing antibiotic treatment. Risk factors for PTLDS have been identified (e.g., having more severe symptoms and being diagnosed at a later date),[3] but the etiology and pathophysiology are not well understood.[4] These persistent symptoms overlap with many other conditions including chronic fatigue syndrome and Epstein-Barr virus infection, which can lead to extensive diagnostic workups and may complicate and delay diagnosis causing confusion and uncertainty in the patient.[5] Limited understanding and support for PTLDS in the medical support may lead to conflict and strained communications between patients and providers, and patients have reported feeling dismissed and frustrated.[6]

At the same time, patients may be experiencing significant morbidity[6] and may report declines in functioning commensurate with patients with congestive heart failure.[7] Some patients with post-treatment Lyme disease symptoms feel hopeless about ever returning to their baseline (pre-Lyme) level of functioning.[6] Clinical trials have failed to demonstrate benefits of continued antibiotics for persistent symptoms[8], thus, clinical care for PTLDS generally consists of symptom management.[4]

Study Aims

The search is underway to develop appropriate diagnostic tests and treatments for PTLDS; but, in the meantime, patients are suffering with debilitating symptoms. The current proposal aims to explore the constellation and severity of these persistent, post-treatment Lyme disease symptoms. Our work can contribute to a better understanding of the types and severity of symptoms experienced by patients who reported having post-treatment Lyme disease symptoms.

METHODS

Setting and Sample

Patients were approached by a study team member during routine care at the hospital-affiliated, outpatient Lifespan Lyme Disease Center. Patients were eligible if they self-reported 1) being 18 years of age or older, 2) being a patient at the Center, and 3) self-reporting a history of Lyme disease with persistent symptoms that were present at least 6 months post-treatment and believed to be related to their Lyme diagnosis as based on the inclusion criteria proposed by the Infectious Diseases Society of America.[9]

Study Procedures

Patients were approached and provided with a brief description of the study. Interested patients were asked to self-report whether they met eligibility criteria. Eligible patients were then provided with a one-page patient information letter (written in English) that described the study purpose and procedures and elements of informed consent (e.g., voluntary nature of the study) and the survey packet. No identifying information was collected. Participants were compensated with a $10 gift card once they completed the surveys. All procedures were deemed to be exempt from federal regulation by the Lifespan Institutional Review Board Reference 207117 45CFR 46.101(2).

Measures

Surveys included a brief demographic and medical history survey that included gender and time since onset of symptoms.[4,10]

Symptoms were measured using the Patient-Reported Outcomes Measurement Information System (PROMIS®) and Cronbach's alpha (α) was calculated for each scale using the current sample:

1. PROMIS-29 Profile v2.0 assessed physical function (4 items; α=.913), anxiety (4 items; α=.922), depression (4 items; α=.931), fatigue (4 items; α=.950), sleep disturbance (4 items; α=.795), ability to participate in social roles and activities (4 items; α=.952), and pain interference (4 items; α=.974) and pain intensity (1 item),[11]
2. Neuro-QOL Item Bank v2.0 – Cognitive Function – Short Form assessed cognitive abilities such as attention, and concentration (8 items; α=.952),[12]
3. PROMIS Item Bank v1.0 – Fatigue – Short Form 7a measured additional fatigue-related concepts (7 items; α=.804),[13] and
4. PROMIS Item Bank v1.0 – Sleep-Related Impairment – Short Form 8a measured additional sleep-related concepts (8 items; α=.901).[14]

All PROMIS® measures use a 7-day recall period and relevant 5-point Likert scales (e.g., 1=never, 2=rarely, 3=sometimes, 4=often, 5=always). For each scale, scores are summed and converted to a standardized T-score with using conversion tables available in the scoring instructions at the PROMIS website. The standardized average was 50 with a standard deviation of 10. Higher scores mean more of the concept that is being measured. Here, higher scores on the physical function, social roles, and cognitive function (sub) scales indicate less functional impairment (i.e., better functioning) with standard benchmarks for mild (T = 40–45), moderate (T = 30–40), or severe (T < 30) impairment. Higher scores on the anxiety, depression, fatigue, seep disturbance, pain interference, and pain intensity indicate greater severity of symptoms with standard benchmarks for mild (T = 55–60), moderate (T= 60–70), and severe (T > 70) symptoms. Possible ranges for total raw (sub)scale scores were 4–20 for the subscales of the PROMIS-29 measure (with the exception of pain intensity which consists of a single item rated on an 11-point Likert scale from 0 for 'no pain' to 10 for 'worst pain imaginable'), 8–40 for the 8-item cognitive function and sleep-related impairment short forms, and 7–35 for the 7-item fatigue short form.

Data Analysis

Raw data was entered in IBM SPSS Statistics 20 and scale scores were calculated per PROMIS scoring instructions. Cronbach's alpha (α) was calculated to measure internal consistency for each scale within the current sample. Frequencies and percentages were calculated for all demographic and medical variables, and means and standard deviations were calculated for all (sub)scale scores. Pearson correlations were calculated between all (sub)scales. PROMIS Raw scale scores were converted to T-scores using the PROMIS T-score conversion tables to allow for comparison between our sample, the reference sample on which the scores were normalized, and other patient groups that have been assessed using PROMIS scales. Finally, average (sub)scale scores were compared by gender (male or female), age group (18–30, 31–50, 51–70), and time since onset of post-treatment Lyme disease symptoms (<1 year, 1–3 years, 4+ years) utilizing analysis of variance.

RESULTS

Fifty-two (N=52) patients provided demographic and medical history information (see **Table 1**) and completed PROMIS® measures. All PROMIS (sub)scales were significantly correlated, most at the .01 p-value level. Patients in this sample reported symptoms that were generally 0.5-1.0 standard deviations more severe and impaired than not only the PROMIS reference sample, but also clinical samples including those with cancer and chronic pain (see **Table 2**).

Compared to the reference sample (T=50; SD=10), patients with persistent symptoms had mild impairment in physical (T=41) and social (T=42) functioning, mild symptoms of depression (T=56), anxiety (T=60), and sleep disturbance (T=57), and moderate symptoms of pain interference (T=62), and fatigue (T=65).

Table 1. Demographic and Medical Variables (n=52)

	n (%)
Gender	
Male	23 (44.2)
Female	29 (55.8)
Age (years)	
18–30	12 (23.1)
31–50	16 (30.7)
51–70	24 (46.2)
Time Since Onset of Symptoms	
Less than 6 months	4 (7.7)
6–12 months	8 (15.4)
1–3 years	20 (38.5)
4–10 years	8 (15.4)
More than 10 years	12 (23.1)
Positive Lyme Serology	49 (96.1)
Immunoglobulin M antibodies	14 (27.5)
Immunoglobulin G antibodies	16 (31.4)
Not Sure	29 (56.9)
Co-Morbid Conditions (current or past)	
Lyme Rash	21 (45.7)
Bell's Palsy	8 (18.6)
Arthritis	33 (70.2)
Heart Disease	7 (16.3)
Neurological Disease	19 (44.2)

Table 2. PROMIS® (sub)scale means (standard deviations [SDs]) and T-scores for the study sample, as well as T-scores for the reference sample and other published samples of patients with chronic health conditions

	Study Sample		T-scores for Reference and Other Published Samples			
	Study Sample Mean (SD)	Study Sample T-scores	Reference Sample	Neuro-Endocrine Tumors (26)	Systemic Scleroderma (27)	Musculo-Skeletal Pain (28)
Physical Function	13.92 (4.22)	41	50	45	47	41
Anxiety	10.81 (4.42)	60	50	54	50	52
Depression	9.40 (4.62)	56	50	52	49	50
Fatiguea	15.90 (3.90)	65	50	55	52	54
Sleep Disturbancea	13.53 (3.34)	57	50	52	52	52
Social Roles	10.94 (4.40)	42	50	46	48	45
Pain Interference	13.06 (4.94)	62	50	52	55	61
Pain Intensity	5.63 (2.44)	N/A	N/A	N/A	N/A	N/A
Cognitive Function	24.52 (8.46)	40	50	N/A	N/A	N/A
Fatigue SF-7ab	24.71 (4.64)	63	50	N/A	N/A	N/A
Sleep SF-8a	26.77 (6.80)	62	50	N/A	N/A	N/A

[a] n=51; [b] n=48

There were no significant or trending differences in average (sub)scale scores by age, but there were differences in subgroup comparisons. Specifically, women reported greater levels of fatigue than men on both the fatigue subscale of the PROMIS-29 (mean = 17.36 [SD = 2.45] versus 14.13 [4.60]; $F[1,49]=10.24$, $p<.01$) and the PROMIS Fatigue-SF 7a (26.21 [4.29] versus 22.60 [4.36]; $F[1,46]=8.18$, $p<.01$). Scales scores also varied by time since onset of post-treatment Lyme disease symptoms such that those who reported such symptoms for <1 year had the greatest average total scores for fatigue and sleep disturbance (see **Table 3**). No other significant differences were found.

DISCUSSION

Relevant patient-reported outcomes were assessed among individuals with self-reported post-treatment Lyme disease symptoms who were seeking care at The Lifespan Lyme Disease Center in Rhode Island. Fatigue and pain were the most highly endorsed symptoms, though the patients in this sample reported symptoms and functional impairments that were more severe than both the general population and other severely and chronically ill groups of patients such as cancer and chronic pain.[15-17] Though the mean anxiety score was relatively low, that translated to a relatively high anxiety T-score, suggesting that anxiety levels endorsed in this group were quite a bit higher than the comparison groups.

Differences in symptoms scale scores were examined by gender, age group, and time since the onset of the post-treatment Lyme disease symptoms. Significant differences emerged in terms of fatigue and sleep disturbance such that women reported greater levels of a fatigue, and those who had been diagnosed for the shortest amount of time (less than 1 year) reported the greatest levels of fatigue and sleep disturbance. Gender differences are in line with other evidence that suggests that fatigue is more commonly reported by women than men.[18] In terms of the duration of symptoms, it is not uncommon to see fluctuations in symptoms over the course of an illness. For example, many patients with chronic fatigue syndrome – a condition that is similar to post-treatment Lyme disease syndrome – report fluctuating symptom severity and lower prevalence of fatigue over time.[19]

Table 3. Subgroup comparisons of average PROMIS® (sub)scale scores between participants identifying as male or female, and time since onset of symptoms (<1 year, 1–3 years, 4+ years)

	Grouping Variable	Levels	Mean (SD)	F Statistic (df)	P Value	Observed Power
PROMIS-29 Fatigue	Gender	Male Female	14.13 (4.60) 17.36 (2.45)	10.24 (1,49)	.002	0.88
	Time Since Onset	<1 year 1–3 years 4+ years	17.36 (3.38) 14.35 (4.57) 16.65 (2.96)	2.94 (2,48)	.063	0.55
PROMIS-29 Sleep Disturbance	Gender	Male Female	12.96 (3.25) 14.00 (3.40)	1.24 (1,49)	.272	0.19
	Time Since Onset	<1 year 1–3 years 4+ years	15.58 (2.81) 12.15 (3.52) 13.68 (2.85)	4.56 (2,48)	.015	0.75
PROMIS-SF Fatigue	Gender	Male Female	22.60 (4.36) 26.21 (4.29)	8.18 (1,46)	.006	0.80
	Time Since Onset	<1 year 1–3 years 4+ years	27.50 (4.40) 22.94 (5.13) 24.90 (3.65)	3.46 (2,45)	.040	0.62
PROMIS-SF Sleep-Related Impairment	Gender	Male Female	24.78 (7.48) 28.34 (5.86)	3.71 (1,50)	.060	0.47
	Time Since Onset	<1 year 1–3 years 4+ years	30.92 (5.82) 23.45 (7.69) 27.60 (4.71)	5.63 (2,49)	.006	0.84

LIMITATIONS

The study limitations should be considered when interpreting these findings. This study consisted of a small convenience sample of patients who – in the absence of diagnostic testing for PTLDS – self-identified as having post-treatment symptoms associated with Lyme diseases. Of note, 96% did report having a positive Lyme serology. Additionally, scale comparisons by gender, age, and time since onset of symptoms were underpowered and should be considered exploratory analyses only. Given that the diagnosis and treatment of post-treatment Lyme disease syndrome or chronic Lyme can be contested among medical professionals and confusing for patients, our sample may have included a relatively heterogenous sample. Future studies should consider the feasibility of confirming diagnosis per medical record.

IMPLICATIONS FOR CLINICAL PRACTICE

The symptoms endorsed by the participants in this study including fatigue, pain, sleep disruption, and issues with cognitive function are similar to those seen in conditions such as chronic fatigue syndrome.[5] Without any clear diagnostic testing for these three conditions with similar clinical presentations, consideration of a PTLDS diagnosis will rely on the collection of medical history information pertaining to Lyme disease. Relevant medical history includes whether and when the participant had any symptoms of Lyme disease (e.g., characteristic Lyme rash), has had a prior positive Lyme serology, and if the participant received treatment for diagnosed or presumed Lyme infection. Additionally, clinicians should consider that patient characteristics may affect their symptom profile. For example, while limited in scope, this study replicates previous findings[18] that women report higher levels of fatigue than men, which may influence diagnostic and treatment considerations.

IMPLICATIONS FOR FUTURE RESEARCH

Prospective studies that begin following patients around the onset of symptoms, assess pre-morbid functioning as close in time to the onset of symptoms as possible, and monitor symptoms across months or years are warranted. To our knowledge one such study exists to date, but only followed patients out 6 months after acute Lyme infection.[4] These prospective studies should assess symptoms in concert with disease-specific events (e.g., biomedical or other treatments), comorbid medical conditions and treatments, and other life events. In addition to long-term symptom monitoring, previous work has suggested diurnal fluctuations in symptoms such as fatigue.[20] Future studies should employ methods intended to take frequent, real-world assessments of symptoms such as ecological momentary assessment and actigraphy.

CONCLUSIONS

While many patients recover from acute Lyme infection after antibiotic treatment, there is a sizeable group of patients who continue to experience symptoms including fatigue, pain, and cognitive disruptions for months or years after initial treatment.[2] These patients report severe morbidity, with life-changing disruptions to their physical, cognitive, emotional, and social functioning.[6-8] With little known pathophysiology,[4] and no diagnostic testing for post-treatment Lyme disease symptoms,[5] accurate diagnosis and assessment and management of symptoms is critical to improving daily functioning and quality of life. Identifying the most disabling, persistent Lyme symptoms will also aid in assessing the effects of therapeutic interventions or symptom management approaches. This work contributes to efforts to better understand persistent symptoms following Lyme diagnosis and treatment and suggests a number of clinical and research questions to be addressed in future studies.

References

1. Centers for Disease Control and Prevention. How many people get Lyme disease? Available from: cdc.gov/lyme/stats/humancases.html. Accessed March 30, 2020.
2. Marques A. Chronic Lyme disease: A review. *Infect Dis Clin North Am*. 2008;22(2):341-360.
3. Aucott JN. Posttreatment Lyme disease syndrome. *Infect Dis Clin North Am*. 2015;29(2):309-323.
4. Aucott JN, Rebman AW, Crowder LA, Kortte KB. Post-treatment Lyme disease syndrome symptomatology and the impact on life functioning: Is there something here? *Qual Life Res*. 2013;22(1):75-84.
5. Ljostad U, Mygland A. Chronic Lyme; diagnostic and therapeutic challenges. *Acta Neurol Scand*. 2013;196:38-47.
6. Ali A, Vitulano L, Lee R, Weiss TR, Colson ER. Experiences of patients identifying with chronic Lyme disease in the healthcare system: A qualitative study. *BMC Fam Pract*. 2014;15:79.
7. Johnson L, Wilcox S, Mankoff J, Stricker RB. Severity of chronic Lyme disease compared to other chronic conditions: A quality of life survey. *PeerJ*. 2014;2:e322.
8. Klempner MS, Hu LT, Evans J, Schmid CH, Johnson GM, Trevino RP, Norton D, Levy L, Wall D, McCall J, Kosinski M, Weinstein A. Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. *N Engl J Med*. 2001;345(2):85-92.
9. Wormser GP, Dattwyler RJ, Shapiro ED, Halperin JJ, Steere AC, Klempner MS, Krause PJ, Bakken JS, Strle F, Stanek G, Bockenstedt L, Fish D, Dumler JS, Nadelman RB. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis*. 2006;43(9):1089–1134.
10. Rebman AW, Soloski MJ, Aucott JN. Sex and gender impact Lyme disease immunopathology, diagnosis and treatment. In: Klein, S., Roberts, C. (Eds). *Sex and Gender Differences in Infection and Treatments for Infectious Diseases*. 2015; Springer.
11. Craig BM, Reeve BB, Brown PM, Cella D, Hays RD, Lipscomb J, Simon Pickard A, Revicki DA. US valuation of health outcomes measured using the PROMIS-29. *Value Health*. 2014;17(8):846-853.
12. Cella D, Lai JS, Nowinski CJ, Victorson D, Peterman A, Miller D, Bethoux F, Heinemann A, Rubin S, Cavazos JE, Reder AT, Sufit R, Simuni T, Holmes GL, Siderowf A, Wojna V, Bode R, McKinney N, Podrabsky T, Wortman K, Choi S, Gershon R, Rothrock N, Moy C. Neuro-QOL: Brief measures of health-related quality of life for clinical research in neurology. *Neurology*. 2012;78(23):1860-1867.
13. Cella D, Lai JS, Jensen SE, Christodoulou C, Junghaenel DU, Reeve BB, Stone AA. PROMIS Fatigue Item Bank had clinical validity across diverse chronic conditions. *J Clin Epidemiol*. 2016;73:128-134.
14. Buysse DJ, Yu L, Moul DE, Germain A, Stover A, Dodds NE, Johnston KL, Shablesky-Cade MA, Pilkonis PA. Development and validation of patient-reported outcome measures for sleep disturbance and sleep-related impairments. *Sleep*. 2010;33(6):781-792.
15. Beaumont JL, Cella D, Phan AT, Choi S, Liu Z, Yao JC. Comparison of health-related quality of life in patients with neuroendocrine tumors with quality of life in the general US population. *Pancreas*. 2012;41(3):461-466.
16. Deyo RA, Katrina R, Buckley DI, Michaels L, Kobus A, Eckstrom E, Forro V, Morris C. Performance of a Patient Reported Outcomes Measurement Information System (PROMIS) Short Form in older adults with chronic musculoskeletal pain. *Pain Med*. 2016;17(2):314-324.
17. Hinchcliff M, Beaumont JL, Thavarajah K, Varga J, Chung A, Podlusky S, Carns M, Chang RW, Cella, D. (2011). Validity of two new patient-reported outcome measures in systemic sclerosis: Patient-Reported Outcomes Measurement Information System 29-item Health Profile and Functional Assessment of Chronic Illness Therapy-Dyspnea short form. *Arthritis Care Res*. 2011;63(11):1620-1628.
18. Bensing JM, Hulsman RL, Schreurs KM. Gender differences in fatigue: Biopsychosocial factors relating to fatigue in men and women. *Med Care*. 1999;37(10):1078-1083.
19. Chu L, Valencia IJ, Garvert DW, Montoya JG. Onset patterns and course of myalgic encephalomyelitis/chronic fatigue syndrome. *Front Pediatr*. 2019;7:12.
20. Powell DJH, Liossi C, Schlotz W, Moss-Morris R. Tracking daily fatigue fluctuations in multiple sclerosis: Ecological momentary assessment provides unique insights. *J Behav Med*. 2017;40(5):772-783.

Acknowledgments

This project was funded by departmental funds (Timothy Flanigan). Matthew Boudreau is now working for the Rhode Island Department of Health. Rebecca Reece is now an Assistant Professor at West Virginia University, Section of Infectious Diseases. Portions of this manuscript were presented at a poster session at the 2019 Society of Behavioral Medicine conference in Washington, DC.

Authors

Sara E. Vargas, PhD, Research Scientist, Center for Behavioral and Preventive Medicine, The Miriam Hospital, Providence, RI; Assistant Professor (Research), Department of Psychiatry and Human Behavior, Warren Alpert Medical School of Brown University, Providence, RI.

Meghan McCarthy, ScB, Research Assistant, Division of Infectious Disease, The Miriam Hospital, Providence, RI.

Matthew Boudreau, BA, Research Assistant, Division of Infectious Disease, The Miriam Hospital, Providence, RI.

Dylan Canfield, BA, Research Assistant, Division of Infectious Disease, The Miriam Hospital, Providence, RI.

Rebecca Reece, MD, Infectious Disease Fellow, Rhode Island Hospital and The Miriam Hospital, Providence, RI; Assistant Professor of Medicine, Warren Alpert Medical School of Brown University, Providence, RI.

Timothy Flanigan, MD, Infectious Disease Physician, Rhode Island Hospital and The Miriam Hospital, Providence, RI; Dean's Professor of Medical Science, Professor of Medicine, and Professor of Health Services, Policy, and Practice, Warren Alpert Medical School of Brown University, Providence, RI.

Disclosures

Ethics approval and consent to participate: This study was exempted for ethical review by The Miriam Hospital Institutional Review Board (Board Reference # 207117 45CFR 46.101(2)).

Availability of data and material: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

Funding: This study was funded by departmental funds provided by Dr. T. Flanigan (co-author). Dr. Flanigan assisted in the study design and interpretation of findings.

Correspondence

Sara Vargas, PhD
Centers for Behavioral and Preventive Medicine
Suite 3.09, 164 Summit Avenue
Providence, RI 02906
svargas@lifespan.org

How to Build It So They'll Come: Faculty Opinion on Faculty Development

JENNIFER JEREMIAH, MD; KELLY McGARRY, MD; JOAO FILIPE MONTEIRO, PhD; DOMINICK TAMMARO, MD

ABSTRACT

BACKGROUND: Residents report low satisfaction with faculty evaluation and feedback. To improve skills, successful faculty development interventions must be accessible and acceptable.

METHODS: A faculty development survey was administered to 145 specialty and non-specialty Internal Medicine faculty at the Warren Alpert Medical School of Brown University, Providence, RI. Analyses assessed demographics, opinion regarding evaluation and feedback and interest in faculty development.

RESULTS: Only 70% of faculty were satisfied with their evaluation ability and only 59% were satisfied with their feedback skills. Despite this, 32% had limited interest in faculty development. Non-specialty faculty were more interested than subspecialty faculty, p-value=0.02. Faculty preferred short electronic audio slideshows and 38% reported participation barriers.

CONCLUSIONS: Although faculty report evaluation and feedback are important skills, not all were satisfied with their abilities. Subspecialty faculty were less interested than non-specialty in faculty development. Our findings suggest that more effective ways to engage faculty in the process of faculty development are needed.

KEYWORDS: post-graduate, evaluation, feedback, medical education research

INTRODUCTION

Graduate Medical Education (GME) programs rely on faculty to mentor, teach, supervise, evaluate, and guide trainees in their progression from students to independent practitioners. Regular feedback tied to evaluation of educational goals is essential to promote trainee success. Nevertheless, learners report receiving inadequate evaluation and feedback. The annual Accreditation Council for Graduate Medical Education (ACGME) Resident Survey consistently demonstrates low resident satisfaction with feedback after assignments.[1] Trainees across all levels of medical education frequently identify feedback from faculty as inadequate, and they typically desire more feedback than they receive.[2] Furthermore, faculty cite multiple challenges to providing high-quality feedback, including lack of time, lack of recognition and reward for teaching, inadequate opportunity for direct observation, suboptimal learner insight, and discomfort with providing constructive criticism to residents.[3,4] A separate survey of 478 medical educators from 110 teaching hospitals and community practices found high rates of self-reported lack of training in teaching skills, providing feedback, assessment, and mentoring.[5] The need for skill development in the delivery of feedback has been identified in prior needs assessment studies.[6]

To be successful, faculty development must meet the perceived needs of the faculty and respond to faculty sources of motivation. Programs that conduct and respond to a needs assessment of the faculty will be more likely to succeed.[7] There is no one size fits all.

To address trainee dissatisfaction with feedback and improve faculty skills through targeted faculty development, we assessed our faculty's participation in teaching activities, comfort with evaluating and providing feedback to learners, desire for faculty development activities in evaluating and providing feedback to residents, and preference for the mode of faculty development delivery. In addition, we assessed whether faculty characteristics were related to perceived faculty development needs and desire for development activities.

METHODS

Study Design

A web-based survey tool which allows for the anonymous collection of data, REDCap, was used to assess faculty development needs and desires. The survey was developed by a focus group at the Warren Alpert Medical School of Brown University consisting of three internal medicine faculty and a biostatistician.

The survey was given to faculty who were identified through our evaluation system (e-value). Prior to the dissemination of the survey to faculty, it was reviewed and approved by the Institutional Review Board (IRB) at Rhode Island Hospital.

Participant selection

Internal Medicine teaching faculty from three institutions at the Warren Alpert Medical School of Brown University

were surveyed via REDCap between January 29 and April 13, 2018. Two hundred and fifty-one faculty in the internal medicine training program responsible for teaching residents and completing evaluations during the 2018 academic year were included. Incomplete responses were excluded.

Survey instrument, administration, and data collection

The survey consisted of 15 multiple choice questions. We assessed the participants' demographics, including gender, years in practice, subspecialty or non-specialty, and teaching setting. Respondents were categorized into two groups based on their divisions: subspecialty (cardiology, endocrinology, gastroenterology, hematology/oncology, nephrology, infectious diseases, pulmonary critical care, and rheumatology) or non-specialty (primary care, general internal medicine, geriatrics, palliative care, and hospital medicine). Years of experience were categorized into 4 groups: 1 to 5, 6–10, 11–20, and ≥21 years.

Faculty were asked about interest in and barriers to participating in faculty development sessions targeted to evaluation and feedback, their satisfaction with their ability to evaluate and provide feedback, willingness to be observed and provided feedback about their skills, and what types of faculty development activities they desired.

The number of learners taught by each faculty member were grouped into 1–5 and 6–10 learners. Weekly teaching hours by the faculty was classified as 1 to 5, 6 to 10, and more than 10 hours per week. Participants were asked to rate on a 1 to 5 Likert scale the extent to which they agreed with several statements about feedback to learners. Responses were coded as "Agree" if they responded "Agree" or "Strongly agree," all other responses were coded as "Disagree." Faculty were asked to give their preferred methods for faculty development from a list of choices, which included teaching tweets, half-day workshops outside of work week, half-day workshops during work week, webinars, ongoing longitudinal series, online self-directed modules, and short electronic audio slide shows.

Analysis

Analyses were performed using SAS[1] software Version 9.3 of the SAS System for Windows, copyright © 2019 SAS Institute Inc. Chi-square and Fisher exact tests were performed to describe demographics, current participation in teaching activities, opinions regarding evaluation and feedback of learners, and desire for faculty development in the evaluation and feedback of residents and to compare subspecialty and non-specialty groups on these variables.

RESULTS

One hundred and forty-five of the 251 teaching faculty completed the survey with a 58% response rate. More respondents were male (59%) than female, and the majority taught

Table 1. Demographics of respondents

	n (%)
Gender	
Female	52 (40.0)
Male	76 (58.5)
Prefer not to answer	2 (1.5)
Specialty division	83 (63.4)
Years after completing training in the area of practice	
1–5 years ago	29 (25.7)
6–10 years ago	18 (15.9)
11–20 years ago	34 (30.1)
21-–6 years ago	32 (28.3)
Number of learners taught	
1–5 learners	109 (85.2)
6–10 learners	19 (14.8)
Weekly hours of teaching	
1 to 5 hours per week	58 (44.6)
6 to 10 hours per week	26 (20.0)
More than 10 hours per week	46 (35.4)
Teaching setting	
Inpatient	31 (24.0)
Outpatient	17 (13.2)
Both inpatient and outpatient	81 (62.8)

Table 2. Respondent Survey Responses

	n (%)
Interested in being observed while teaching and receiving feedback	
Yes	58 (44.6)
No	32 (24.6)
Not sure	40 (30.8)
Interested in faculty development sessions designed to improve your ability to evaluate and give feedback to residents	
Yes	89 (67.9)
No	16 (12.2)
Not sure	26 (19.9)
There are barriers perceiving to participating in faculty development sessions	46 (35.7)
Type of barriers perceiving to participating in faculty development sessions	
Time	125 (95.4)
Travel	2 (1.5)
Other	4 (3.1)
Faculty development activities have participated in during the last 2 years	
None	47 (39.8)
1–3	44 (37.3)
4–5	9 (7.6)
More than 5	13 (11.0)
Don't know	5 (4.2)
Evaluating and giving feedback to learners is an important part as an educator	126 (98.4)
Satisfied with the ability to evaluate the performance of the resident	91 (70.0)
Satisfied with the ability to provide effective feedback to the residents	77 (59.2)

in both the inpatient and outpatient setting (63%). A majority of respondents were subspecialty faculty (63%). Forty-five percent taught less than 5 hours per week and 35% more than 10 hours per week. Fifty-nine percent completed training in their area of practice more than 10 years ago (**Table 1**).

An overwhelming majority (98%) of those surveyed felt that evaluating and providing feedback was an important part of their job, yet 30% of faculty were not satisfied with their ability to evaluate residents and 41% were not satisfied with their ability to provide feedback (**Table 2**). Gender, time from training, or whether subspecialty or non-specialty physician did not affect satisfaction with evaluation skills.

Forty percent had not attended any faculty development sessions in the last two years and 37% had attended 1–3 sessions. Among those dissatisfied with their ability to evaluate resident performance or provide feedback, 26% and 37%, respectively, didn't attend any faculty development activities during the last two years. Most reported that time was the greatest barrier to participating in faculty development, with a small percent citing the need to travel as a deterrent (**Table 2**).

Significantly more male than female faculty were not interested in faculty development to improve their ability to evaluate and provide feedback (42% vs. 15%, p-value= 0.0008). Subspecialty faculty reported less interest in faculty development, when compared with non-specialty, (61% vs. 79%, p-value=0.02). While not statistically significant, faculty more than 21 years from training reported less interest (56%) in faculty development, when compared with 79% in 1–5, 67% in 6–10, 68% in 11–20 years ago, with p-value=0.09.

Choice of faculty development activities in desired order was electronic audio slide shows (46%), online self-directed modules (45%), ongoing longitudinal series (34%), webinars (31%), half day workshop during work week 929%), half day workshop outside of work week (14%) and teaching tweets (11%). There were no significant differences in the choice of faculty development by gender, specialty, or time from completion of training.

Significantly fewer subspecialty faculty compared with non-specialty faculty were interested in being observed and provided with feedback on their skills (41% vs. 50%, p-value =0.013). Interest in being observed was not influenced by gender or time from completion of training.

DISCUSSION

To provide learners with important formative feedback to succeed and professionally develop, faculty must be skilled in evaluation and feedback. While faculty agree that providing feedback is an important part of their role as educators, we found that 30% of our faculty were dissatisfied with their ability to evaluate residents and 41% were dissatisfied with their ability to provide feedback. Satisfaction rate was not affected by gender, time from training, or whether the physician was a subspecialist or non-specialist.

Male faculty and subspecialty faculty reported less interest in participating in faculty development. This is particularly notable because the majority of teachers are male and specialty-identified. Further investigation as to why these differences exist might provide insight regarding ways to increase interest, particularly since these subsets represent the majority of teaching faculty at many institutions.[8]

Time was the most commonly endorsed barrier to participation. Fewer than half of our faculty, despite their dissatisfaction with their ability to assess and provide feedback, had attended any faculty development sessions in the last two years. Given limited non-clinical time, it is not surprising that faculty want efficient faculty development sessions. To meet this need, innovative methods for faculty development that allow asynchronous learning at a time convenient to the faculty member should be considered. Future studies ought to be performed to determine the effectiveness of these methods. Being observed and receiving feedback is an effective technique to improve skills and is a requirement for trainees in competency-based medical education. The value of direct observation should not just be limited to trainees. Direct observation of faculty members can improve their teaching skills.[9] Nevertheless, interest in being observed was not universal. Generalist faculty were significantly more interested than subspecialty faculty. A focus on the formative and context-specific nature of the activity might increase interest. Further examining the differences between the subspecialty and non-specialty faculty might be important in future studies since program directors need to ensure that all faculty members have the desire and the skills to evaluate and give feedback to trainees.

Faculty development programs targeted towards improving these skills have the potential to combat faculty dissatisfaction and improve resident satisfaction with the feedback they receive, as well as to improve the training received by residents. For faculty development to be successful, faculty must want to participate, have the time to participate, and receive effective training. Creating faculty development that is effective and acceptable to most faculty should be the aim of graduate medical education programs.

Although this study was limited to a single institution and a single specialty, dissatisfaction with feedback is a pervasive issue in medical education. The respondents represented male and female, as well as subspecialty and generalist, faculty with a varied amount of teaching experience, characteristics similar to faculty at many teaching institutions. Although our response rate should be noted as a limitation, there was a wide representation of faculty in terms of time from completion of training, number of learners taught, hours of weekly teaching, and setting for teaching activities. Assessing the needs of diverse faculty may allow for the development of programs that will appeal to the mix of faculty found at most institutions.

CONCLUSION

Our findings suggest that while faculty take their educational roles seriously, not all faculty are confident in their abilities to evaluate and give feedback to learners, and many were not interested in improving their skills through direct observation and evaluation. We need to create effective ways to engage faculty in the process of improving their skills and to overcome barriers to participation in faculty development.

Since this study was performed, three, short electronic audio slide shows titled Faculty Five in Five, which focus on evaluation and feedback skills, have been disseminated to teaching faculty in the Department of Medicine at the Warren Alpert Medical School of Brown University.

References

1. Accreditation Council for Graduate Medical Education (ACGME), ACGME Data Collection System: Resident and fellow survey. http://www.acgme.org/acgmeweb/ DataCollectionSystems/ResidentFellowSurvey.aspx. Accessed: 2018
2. Bing-You R, Hayes V, Varaklis K, Trowbridge R, et al. (2017) Feedback for Learners in Medical Education: What Is Known? A Scoping Review', *Acad Med*. 2017; 92(9): 1346-1354.
3. Steinert Y, Macdonald ME, Boillat M, Elizov M, et al. Faculty development: if you build it, they will come. *Med. Educ 2010;* 44(9): 900-907.
4. Kogen J, Conforti L, Bernabeo E, Durning S, et al. Faculty staff perceptions of feedback to residents after direct observation of clinical skills. *Med. Educ.* 2012; 46(2): 201-215._
5. Houston TK, Ferenchick GS, Clark JM, Bowen J, et al. Faculty development needs. *J Gen Intern Med.* 2004; 19(4): 375–379.
6. Leslie K, Baker L, Egan-Lee E, Esdaile M, et al. Advancing faculty development in medical education: A systematic review. *Acad Med*. 2013; 88(7):1038–1045._
7. Sevkat BO, Dilek A, Nalan SH, Iskender S. A Faculty Development Program Evaluation: From Needs Assessment to Long-Term Effects, of the Teaching Skills Improvement Program. *Teach Learn Med.* 2010; 16(4): 368-375.
8. Association of American Medical Colleges, (AAMC) Faculty Roster, December 31, 2019 snapshot, as of December 31, 2019 655 K Street, NW, Suite 100 Washington, DC, 20001-2399
9. Regan-Smith M, Hirschmann K, Iobst W. Direct Observation of Faculty with Feedback: An Effective Means of Improving Patient-Centered and Learner-Centered Teaching Skills. *Teach and Learn Med.* 2007; 19(3): 278-286.

Acknowledgment

This material was presented as an Abstract: Jeremiah J, McGarry K, Monteiro F, Tammaro T. Faculty Opinion on Faculty Development: How and how much? 2020 Annual Meeting of the Society of General Internal Medicine, Online due to COVID-19.

Authors

Jennifer Jeremiah, MD, Department of Medicine, Rhode Island Hospital and Warren Alpert Medical School of Brown University, Providence, RI.

Kelly McGarry, MD, Department of Medicine, Rhode Island Hospital and Warren Alpert Medical School of Brown University, Providence, RI.

Joao Filipe Monteiro, PhD, Department of Medicine, Rhode Island Hospital and Warren Alpert Medical School of Brown University, Providence, RI.

Dominick Tammaro, MD, Department of Medicine, Rhode Island Hospital and Warren Alpert Medical School of Brown University, Providence, RI.

Disclosures

The author(s)received no financial support for the research, authorship, and/or publication of this article.

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancy, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Correspondence

Jennifer Jeremiah, MD
Warren Alpert Medical School of Brown University
Providence, RI 02905
401-444-4083
Jennifer_jeremiah@brown.edu

The Association between Exercise in the Last Trimester of Pregnancy and Low Infant Birthweight among Rhode Island Mothers, 2016–2018

SCARLETT BERGAM, BA; KARINE MONTEIRO, MPH; MORGAN ORR, MPH; ANNIE GJELSVIK, PhD

INTRODUCTION

Approximately 8% of infants born in the United States are low birthweight (<2,500 grams).[1] Being low birthweight can cause short-term respiratory and gastrointestinal ailments and long-term intellectual deficits.[2] Mothers who are Black, young, low-income, and use substances are most at risk for having a low birthweight infant.[3]

Half of the US pregnant population faces excessive gestational weight gain, correlated with gestational diabetes, preeclampsia, and C-sections.[4] The American College of Obstetrics and Gynecology (ACOG) recommends light to moderate exercise, 150 minutes per week, for pregnant women. White women most commonly meet the recommended prenatal physical activity levels.[5] A physically active pregnancy may be associated with positive epigenetic cardio-metabolic markers in offspring,[6,7] but data is otherwise scarce regarding the effect of physical activity on infant health.[8] The purpose of this study is to examine the association between maternal physical activity during the last three months of pregnancy and low infant birthweight in mothers who gave birth in Rhode Island between 2016–2018. We hypothesize that an active lifestyle in the last trimester will be associated with less low infant birthweight.

METHODS

We analyzed data from the 2016–2018 Rhode Island Pregnancy Risk Assessment Monitoring System (RI PRAMS) dataset. As a collaborative surveillance project of the Centers for Disease Control and Prevention (CDC) and the Rhode Island Department of Health, RI PRAMS collects state-specific, population-based data on maternal behaviors and experiences before, during, and after pregnancy. Mothers delivering low birthweight infants are oversampled to gain adequate data on this high-risk population. The data are weighted to represent the RI PRAMS population.[9]

The RI PRAMS dataset included 3,350 women who recently gave birth in the state of Rhode Island. Respondents eligible for this study included all those with valid response for the exposure (exercise in the last trimester) and the outcome (low infant birthweight). There were zero missing subjects for the outcome, as data was derived from birth certificates. The operational definition of the outcome split infants into low birth weight (<2,500 g) or normal birth weight (>=2,500 g). Exercise in the last three months of pregnancy is operationalized as self-report of whether or not the mother participated in weekly physical activity in the last three months of pregnancy, with two categories grouped into "No" (less than 1 day per week) and "Yes" (including "1 to 2 days per week", "3 to 4 days per week", or "5+ days per week"). We excluded 252 individuals who were marked as "dk" (Don't Know), "blank", "missing", and "told not to exercise". In total, 252/3350 or 7.5% of the eligible population did not have valid information, leaving an analytic sample of 3,098 new mothers.

Among possible covariates, maternal age, race/ethnicity, maternal education, household income, and marital status were demographic variables of interest. Other common covariates such as parity were screened out because of a lack of association in preliminary data. Maternal age was operationalized into "<20", "20–29", and ">29 years old". Maternal Race/Ethnicity included "White, Non-Hispanic"; "Black, Non-Hispanic"; "Other, Non-Hispanic", and "Hispanic". Annual income was stratified into "Less than $24,000", "24,001 to $48,000", "48,001 to 85,000" and "Greater than $85,000". Years of maternal education were split into "Less than", "Equal to", and "Greater than" 12 years. Marital status was self-reported as "Married" or "Unmarried".

We identified smoking in the last three months of pregnancy and maternal BMI as confounders in this study. Based on the literature, we hypothesized that women who are smokers or have higher body mass index (BMI) are less likely to exercise in the last three months of pregnancy.[10,11] Smoking in the last three months of pregnancy was reported as "Yes" or "No". Maternal BMI was a pre-calculated variable derived from height and weight, split into "Underweight" (>18.5), "Normal Weight" (18.5–25), "Overweight" (25–30), and "Obese" (>30).

We used Stata Version 16.0 for all statistical analyses.[12] To describe our data, we determined unweighted frequencies and weighted percentages for low infant birthweight, as well as confounders and demographic characteristics by physical activity status. We used bivariate analysis of the dichotomous exposure variable using complex survey design and weighting for proper representation. We then conducted a logistic regression to model the outcome variable by each covariate. After assessing each covariate, our final model included maternal age, maternal race/ethnicity, income, education level, marital status, smoking status, and BMI, which were correlated with birth weight in the literature and our data.

RESULTS

Overall, 59.9% of Rhode Island women who delivered a live infant between 2016 and 2018 reported exercising in the last three months of pregnancy (**Table 1**). The prevalence of low birthweight is higher among mothers who did not exercise during pregnancy (7%) compared to those who exercised (6%), p-value=0.02.

The maternal exercise rates varied by sub-population. Compared to mothers who exercised, those who did not exercise were more likely to be obese (29%, p<0.01), Hispanic (29%, p<0.01), or over age 30 (56%, p<0.05). Income, education, marital status, and smoking status showed no significant differences in exercise status.

Among new mothers in Rhode Island, adjusting for maternal age, maternal race/ethnicity, income in the last year, years of maternal education, marital status, smoking, and maternal BMI (**Table 2**), those who reported exercising in the last three months of pregnancy have 1.25 (95% CI: 1.08, 1.44) the odds of having a healthy weight infant compared to those who did not exercise in the last three months of pregnancy.

Table 1. Characteristics of postpartum women in Rhode Island by exercise in last trimester of pregnancy, 2016–2018 RI PRAMS

Characteristics	Did not exercise, Weighted % 42% (n=1,344)	Exercised, Weighted % 58% (n=1,754)
Maternal Age*		
<20	3%	5%
20–29	41%	43%
>29	56%	52%
Maternal Race/Ethnicity**		
White, Non-Hispanic	53%	60%
Black, Non-Hispanic	6%	5%
Other, Non-Hispanic	12%	11%
Hispanic	29%	24%
Income		
<$24,000	35%	33%
$24,001 to $48,000	20%	20%
$48,001 to $85,000	18%	18%
>$85,001	27%	30%
Years of Maternal Education		
<12	10%	10%
12	20%	20%
>12	70%	71%
Marital Status		
Married	56%	57%
Unmarried	44%	43%
Smoking in Last 3 Months of Pregnancy	**7%**	**5%**
Maternal Body Mass Index (BMI)**		
Underweight	3%	3%
Normal	40%	51%
Overweight	28%	26%
Obese	29%	20%
Low Infant Birthweight (<2500 g)**	**7%**	**6%**

*(p<0.05), **(p<0.01)

Table 2. Unadjusted and adjusted odds ratios of healthy infant birth weight among women who have recently given birth in Rhode Island, 2016–2018 RI PRAMS

Characteristics	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Maternal Exercise in the Last 3 Months of Pregnancy**		
≤1 day per week	1.00 (ref)	1.00 (ref)
>1 day per week	1.27 (1.12, 1.44)	1.25 (1.08, 1.44)
Maternal Age		
<20	0.75 (0.55, 1.02)	0.85 (0.55, 1.31)
20–29	1.00 (ref)	1.00 (ref)
>29	1.11 (0.98, 1.26)	0.98 (0.83, 1.15)
Maternal Race/Ethnicity*		
White, Non-Hispanic	1.00 (ref)	1.00 (ref)
Black, Non-Hispanic	0.38 (0.30, 0.49)	0.40 (0.30, 0.54)
Other, Non-Hispanic	0.72 (0.59, 0.87)	0.73 (0.58, 0.92)
Hispanic	0.71 (0.61, 0.82)	0.84 (0.68,1.03)
Income		
>24,000	1.00 (ref)	1.00 (ref)
$24,001 to $48,000	1.56 (1.29, 1.87)	1.31 (1.05, 1.64)
$48,001 to $85,000	1.39 (1.16, 1.67)	0.95 (0.73,1.22)
>$85,000	1.78 (1.52, 2.09)	1.03 (0.78, 1.35)
Years of Maternal Education**		
<12	0.70 (0.56, 0.89)	0.67 (0.50, 0.90)
12	1.00 (ref)	1.00 (ref)
>12	1.28 (1.09, 1.49)	1.12 (0.91, 1.39)
Marital Status*		
Married Unmarried	1.00 (ref) 0.65 (0.58, 0.74)	1.00 (ref) 0.82 (0.69, 0.98)
Smoking in Last 3 Months of Pregnancy**		
No	1.00 (ref)	1.00 (ref)
Yes	0.70 (0.59, 0.83)	0.79 (0.64, 0.97)
Maternal Body Mass Index (BMI)		
Underweight	0.35 (0.25, 0.49)	0.40 (0.27, 0.59)
Normal	1.00 (ref)	1.00 (ref)
Overweight	0.93 (0.80, 1.09)	0.98 (0.82, 1.17)
Obese	0.75 (0.64, 0.88)	0.84 (0.70, 1.01)

*(p<0.05), **(p<0.01)

Women who were Hispanic, had less than 12 years of education, smoked in the last trimester of pregnancy, had a preconception BMI <18.5, or who were unmarried had higher odds of having a low birthweight infant ($p<0.05$).

DISCUSSION

According to 2016–2018 RI PRAMS data, women who exercised in the third trimester have a higher odds of giving birth to a healthy birthweight baby. These findings have the potential to encourage health-seeking behaviors in pregnant women in Rhode Island. By identifying existing disparities in maternal exercise, women can work to seek out resources and support in identifying and overcoming barriers to exercise. Although prenatal exercise rates are moderate in Rhode Island, there are inequities in physical activity and infant birthweight for specific demographic groups: in particular, Hispanic, older, and obese women.[13,14] Resources to guide mothers to seek out physically active lifestyles at all stages of pregnancy can now be found in online resources, lowering traditional barriers to in-person fitness training and advice. While individual recommendations should be made by physicians, this study provides another reason to recommend physical activity during pregnancy beyond improved maternal health – there is evidence to suspect improvement to infant health.

LIMITATIONS

Due to the size of the state of Rhode Island and the three-year period of data collection, RI PRAMS 2016–2018 had a sample size of 3,350 women. The variables used in this study had relatively few missing individuals, so the results are liklely not skewed due to this small sample. Furthermore, RI PRAMS data are based on self-report by the survey respondent and are not verified, so they may be subject to recall bias or bias towards the socially-desirable answer. This may lead to over-reporting of exercise in the last trimester of pregnancy. Certain high-risk populations may be under-represented due to non-response or non-coverage bias. However, RI PRAMS oversamples these high-risk groups, such as infants who are born low birthweight, so as to provide comprehensive data for a relatively small sample size.

References

1. FastStats. https://www.cdc.gov/nchs/fastats/birthweight.htm. Published May 28, 2019. Accessed November 21, 2019
2. Hack M, Klein NK, Taylor HG. Long-term developmental outcomes of low birth weight infants. *Future Child*. 1995;5(1): 176-196.
3. Philadelphia TCH of. Low Birthweight. https://www.chop.edu/conditions-diseases/low-birthweight. Published August 23, 2014. Accessed November 21, 2019.
4. Wang J, Wen D, Liu X, Liu Y. Impact of exercise on maternal gestational weight gain. *Medicine (Baltimore)*. 2019;98(27). doi:10.1097/MD.0000000000016199
5. Physical Activity and Exercise During Pregnancy and the Postpartum Period. https://www.acog.org/en/Clinical/Clinical Guidance/Committee Opinion/Articles/2015/12/Physical Activity and Exercise During Pregnancy and the Postpartum Period. Accessed March 20, 2020.
6. Guénard F, Marceau S, Simard S, Kral J, Vohl M-C, Picard M. Epigenetic transmission of cardiometabolic risk in offspring discordant for maternal gestational metabolic fitness | bioRxiv. https://www.biorxiv.org/content/10.1101/435461v1.full. Accessed September 14, 2019.
7. Newton ER, May L. Adaptation of Maternal-Fetal Physiology to Exercise in Pregnancy: The Basis of Guidelines for Physical Activity in Pregnancy. *Clin Med Insights Womens Health*. 2017;10:1179562X17693224. doi:10.1177/1179562X17693224
8. Seneviratne S, Jiang Y, Derraik J. Effects of antenatal exercise in overweight and obese pregnant women on maternal and perinatal outcomes: a randomised controlled trial. BJOG: An International Journal of Obstetrics & Gynaecology. https://obgyn.onlinelibrary.wiley.com/doi/10.1111/1471-0528.13738. Published 2016. Accessed September 14, 2019.
9. Kim H, Monteiro K, Cooper T, Viner-Brown S. 2018 Rhode Island Pregnancy Risk Assessment Monitoring System Data Book. 2018.
10. Bisson M, Alméras N, Plaisance J, et al. Maternal fitness at the onset of the second trimester of pregnancy: correlates and relationship with infant birth weight. *Pediatric Obesity*. 2013;8(6):464-474. doi:10.1111/j.2047-6310.2012.00129.x
11. Fazzi C, Saunders DH, Linton K, Norman JE, Reynolds RM. Sedentary behaviours during pregnancy: a systematic review. *Int J Behav Nutr Phys Act*. 2017;14. doi:10.1186/s12966-017-0485-z
12. *Stata Statistical Software*. College Station, TX: StataCorp LLC; 2019. https://www.stata.com/. Accessed November 21, 2019..
13. McDonald SM, Yeo S, Liu J, Wilcox S, Sui X, Pate RR. Associations between maternal physical activity and fitness during pregnancy and infant birthweight. *Prev Med Rep*. 2018;11:1-6. doi:10.1016/j.pmedr.2018.04.019
14. Saffer H, Dave D, Grossman M, Leung LA. Racial, Ethnic, and Gender Differences in Physical Activity. J Hum Cap. 2013;7 (4):378-410. doi:10.1086/671200

Acknowledgments

The authors would like to thank the RI PRAMS Program coordination team for granting us access to the RI PRAMS Phase 8 2016–2018 dataset.

Authors

Scarlett Bergam, BA, is a Master of Public Health Candidate and Research & Teaching Assistant at the Brown University School of Public Health.

Karine Monteiro, MPH, is the Interim Center for Health Data and Analysis Health Survey Unit Manager at the Rhode Island Department of Health.

Morgan Orr, MPH, is an Epidemiologist and Program Evaluator at the Rhode Island Department of Health.

Annie Gjelsvik, PhD, is the Director of the Master of Public Health Program and Associate Professor of Epidemiology and Pediatrics at the Brown University School of Public Health.

Disclaimer

The views expressed herein are those of the authors and do not necessarily reflect the views of the Rhode Island Department of Health.

Correspondence

Scarlett Bergam
scarlett_bergam@brown.edu

Rhode Island Monthly Vital Statistics Report
Provisional Occurrence Data from the Division of Vital Records

VITAL EVENTS	REPORTING PERIOD		
	OCTOBER 2020	12 MONTHS ENDING WITH OCTOBER 2020	
	Number	Number	Rates
Live Births	923	11,128	10.5*
Deaths	909	11,565	10.9*
Infant Deaths	53	62	5.6#
Neonatal Deaths	3	47	4.2#
Marriages	769	4,896	4.6*
Divorces	197	2,156	2.0*

* Rates per 1,000 estimated population

Rates per 1,000 live births

Underlying Cause of Death Category	REPORTING PERIOD			
	APRIL 2020	12 MONTHS ENDING WITH APRIL 2020		
	Number (a)	Number (a)	Rates (b)	YPLL (c)
Diseases of the Heart	217	2,421	228.5	3,422.0
Malignant Neoplasms	164	2,231	210.6	5151.5
Cerebrovascular Disease	33	452	42.7	500.0
Injuries (Accident/Suicide/Homicide)	74	903	85.2	12,362.5
COPD	43	514	48.5	510.0

(a) Cause of death statistics were derived from the underlying cause of death reported by physicians on death certificates.

(b) Rates per 100,000 estimated population of 1,059,361 for 2019 (www.census.gov)

(c) Years of Potential Life Lost (YPLL).

NOTE: Totals represent vital events, which occurred in Rhode Island for the reporting periods listed above.
Monthly provisional totals should be analyzed with caution because the numbers may be small and subject to seasonal variation.

Working for You: RIMS advocacy activities

March 1, Monday
RIMS Board of Directors meeting: Catherine Cummings, MD, President

Legislative hearings

March 2, Tuesday
RIMS Physician Health Committee (PHC): Herbert Rakatansky, MD, Chair (via teleconference)

RI Health and Privacy Alliance virtual meeting

Legislative hearings

March 3, Wednesday
Conference call with Office of the Health Insurance Commissioner (OHIC) regarding telemedicine legislation

Workers' Compensation Advisory Council

Legislative hearings

March 8, Monday
Zoom Colorectal Cancer Legislation: American Cancer Society

Legislative hearings

March 9, Tuesday
Physician Health Program Governance Committee: Jerry Fingerut, MD, Chair

Meeting with clinical leadership of Tufts Health Plan: Catherine Cummings, MD, RIMS President; Elizabeth Lange, MD, President-Elect; RIMS staff

Vaccine planning discussion with Medicaid Managed Care Organizations (MCOS)

Legislative hearings

March 10, Wednesday
MMJUA Finance Committee: Newell Warde, RIMS Executive Director

RI Department of Health (RIDOH) Board of Medical Licensure and Discipline (BMLD) meeting

Governor's Overdose Intervention and Prevention Task Force: Sarah Fessler, MD, RIMS Past President

Legislative hearings

March 11, Thursday
Legislative hearings

March 12, Friday
Legislative hearings

March 15, Monday
RIMS' Member-only *State House Update*

Monthly meeting with Blue Cross & Blue Shield of Rhode Island (BCBSRI): Catherine Cummings, MD, President

Legislative hearings

March 16, Tuesday
Office of the Health Insurance Commissioner (OHIC) Health Insurance Advisory Council (HIAC) Catherine Cummings, MD, President

RI Health and Privacy Task Force call

Legislative hearings

March 17, Wednesday
RIDOH Primary Care Physician Advisory Committee (PCPAC): Elizabeth Lange, MD, President-elect

Health Professional Student Loan Program: Subcommittee

Legislative hearings

March 18, Thursday
Legislative hearings

MMJUA Board of Directors: Newell Warde, RIMS Executive Director

March 19, Friday
Open Door Health Clinic Tour: Catherine Cummings, MD, President

March 22, Monday
Legislative hearings

March 23, Tuesday
American Medical Association (AMA) Advocacy Resource Center (ARC) regarding Medical Liability

Vaccine planning discussion with Medicaid Managed Care Organizations (MCOS)

Legislative hearings

March 24, Wednesday
Legislative hearings

March 25, Thursday
Diabetes Prevention Programs (DPP) Stakeholder's call

Legislative hearings

March 26, Friday
Legislative hearings

March 29, Monday
Legislative hearings

March 30, Tuesday
Legislative hearings

March 31, Wednesday
Meeting with Senate Leadership: Michael E. Migliori, Chair, RIMS Public Laws Committee

Legislative hearings

RIMS NOTES: *News You Can Use*

Our biweekly e-newsletter is published on alternate Fridays exclusively for RIMS members. Contact Dulce Cosme if you've missed an issue, dcosme@rimed.org.

RIMS CORPORATE AFFILIATES

The Rhode Island Medical Society continues to drive forward into the future with the implementation of various new programs. As such, RIMS is expanded its Affinity Program to allow for more of our colleagues in healthcare and related business to work with our membership. RIMS thanks these participants for their support of our membership.

Contact Marc Bialek for more information: 401-331-3207 or mbialek@rimed.org

Neighborhood Health Plan OF RHODE ISLAND™

www.nhpri.org

Neighborhood Health Plan of Rhode Island is a non-profit HMO founded in 1993 in partnership with Rhode Island's Community Health Centers. Serving over 185,000 members, Neighborhood has doubled in membership, revenue and staff since November 2013. In January 2014, Neighborhood extended its service, benefits and value through the HealthSource RI health insurance exchange, serving 49% the RI exchange market. Neighborhood has been rated by National Committee for Quality Assurance (NCQA) as one of the Top 10 Medicaid health plans in America, every year since ratings began twelve years ago.

RHODE ISLAND PHYSICIANS CORPORATION PRIMARY CARE

www.ripcpc.com

RIPCPC is an independent practice association (IPA) of primary care physicians located throughout the state of Rhode Island. The IPA, originally formed in 1994, represent 150 physicians from Family Practice, Internal Medicine and Pediatrics. RIPCPC also has an affiliation with over 200 specialty-care member physicians. Our PCP's act as primary care providers for over 340,000 patients throughout the state of Rhode Island. The IPA was formed to provide a venue for the smaller independent practices to work together with the ultimate goal of improving quality of care for our patients.

RIMS gratefully acknowledges the practices who participate in our discounted Group Membership Program

ANCHOR MEDICAL ASSOCIATES

AQUIDNECK MEDICAL
Member of University Medicine

THE CENTER FOR orthopaedics INC.

COASTAL MEDICAL
LEADERS IN HEALTHCARE

Ortho Rhode Island

NorthMain Radiation Oncology

Ob-Gyn Associates
A Lifespan Physician Group Practice

Orthopaedic Associates, Inc.

Rhode Island Eye INSTITUTE

RI ENT

SKIN PROS

UEMF
university EMERGENCY MEDICINE foundation

UNIVOTO
University Otolaryngology

Women's Medicine Collaborative
A program of The Miriam Hospital
Lifespan. Delivering health with care.®

For more information about group rates, please contact Marc Bialek, RIMS Director of Member Services

Favorite
Healthcare Staffing

SPRING SPECIAL

10% off any Permanent Placement

Rhode Island's Medical Staffing Experts

Favorite Healthcare Staffing provides a comprehensive range of staffing services at preferred pricing to RIMS members. Call today to see why we are the favorite choice of healthcare professionals and physician practices across the US!

401.354.7115

MedicalStaffing@FavoriteStaffing.com

Favorite Healthcare Staffing is a Valued Sponsor of the Rhode Island Medical Society

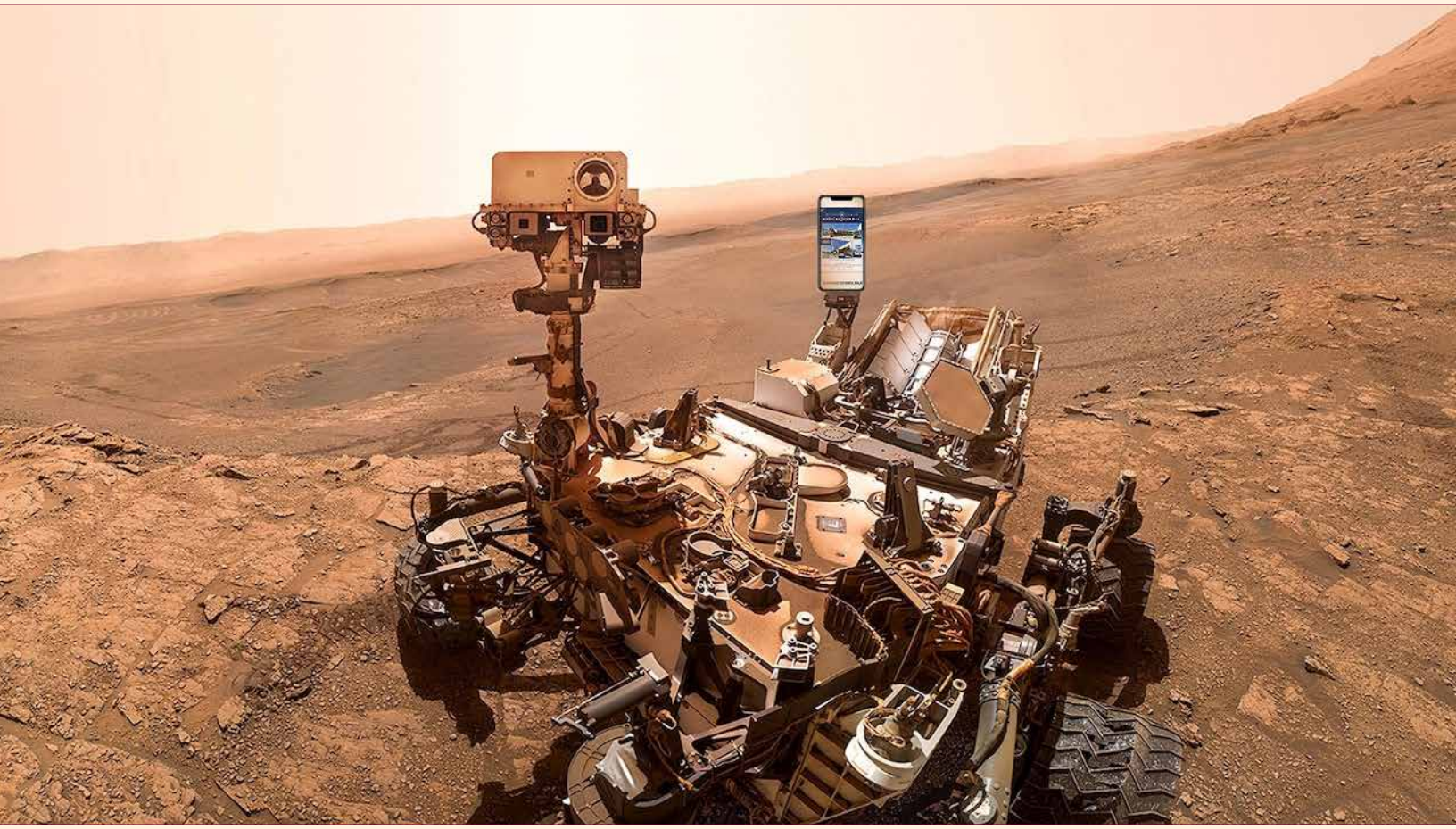
AA / EOE / M / F / V / D

We are read everywhere

In the first three months of 2021, approximately **11,000** readers from **84** countries have viewed articles in the Journal and researched its archives.

Top 10 countries:

1. US
2. Canada
3. UK
4. Australia
5. India
6. China
7. Germany
8. Italy
9. Spain
10. Japan



JEZERO CRATER, MARS

Perseverance, NASA's newest rover, landed on Mars on February 18 after a journey of seven months and more than 300 million miles. Planetary scientists at Brown put the Jezero Crater on NASA's list of possible landing sites, and the ancient lake was ultimately selected. Click this link for Brown feature story on these remarkable scientists: https://www.brown.edu/news/2021-02-18/mars

For a touch of humor on today, April Fool's Day, RIMJ photo-shopped 'Percy' reading the March issue of RIMJ on her iPhone, while continuing her mission to search for signs of ancient microbial life and evidence of Mars' past habitability. Perseverance will leave samples of Martian rock and soil in sealed tubes for pickup by a future mission that will return them to Earth for study.

[IMAGE BY NASA/JPL/MICHAEL RAVINE, MALIN SPCE SCIENCE SYSTEMS, PHOTOSHOPPED BY RIMJ]

Wherever you happen to be quarantining or social distancing, visit the Journal on your mobile device, and send us a photo: **mkorr@rimed.org**.

‘Smart Bandage’ detects, could prevent infections

URI chemical engineering professor embeds nanosensors in microfibers to create ‘smart bandage’

KINGSTON – Bandages are great for covering wounds, but they would be much more useful if they could also detect infections.

By embedding nanosensors in the fibers of a bandage, University of Rhode Island Assistant Professor **DANIEL ROXBURY** and former URI graduate student **MOHAMMAD MOEIN SAFAEE** have created a continuous, noninvasive way to detect and monitor an infection in a wound.

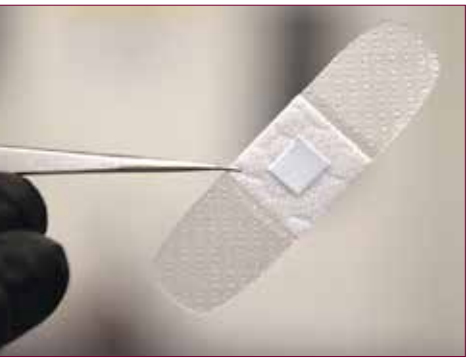
“Single-walled carbon nanotubes within the bandage will be able to identify an infection in the wound by detecting concentrations of hydrogen peroxide,” said Roxbury, a researcher in URI’s College of Engineering.

Until now, the challenge with using nanotubes for this purpose has been immobilizing them in a biocompatible manner such that they stay sensitive to their surroundings, according to Roxbury.

“The microfibers that encapsulate the carbon nanotubes accomplish both of these tasks,” Roxbury said. “The nanotubes do not leach from the material, yet they stay sensitive to hydrogen peroxide within the wounds.”

URI Assistant Professor Daniel Roxbury (left) and former graduate student Mohammad Moein Safaee hold microfibrous materials embedded with carbon nanotube sensors that were produced in Roxbury’s lab. [PHOTOS BY NEGAR RAHMANI]

The “smart bandage” will be monitored by a miniaturized wearable device, which will wirelessly (optically) detect the signal from the carbon nanotubes in the bandage. The signal can then be transmitted to a smartphone-type of device that then automatically alerts the patient or a health care provider.



The smart bandage held by tweezers.

“This device will solely be used for diagnostic purposes,” said Roxbury. “However, the hope is that the device will diagnose an infection at an early stage, necessitating fewer antibiotics and preventing drastic measures, such as limb amputation. We envision this being particularly useful in those with diabetes, where the management of chronic wounds is routine.”

The technology behind the smart bandage is further described in an article published in Advanced Functional Materials. Roxbury, Safaee and URI doctoral student **MITCHELL GRAVELY** authored the article.

Safaee, who completed his doctorate in chemical engineering at URI in December 2020, learned how to create polymeric fibers as an undergraduate student prior to coming to URI.

“Professor Roxbury was very supportive of the idea of designing wearable technologies based on carbon nanotubes and I was excited to take the lead on the project,” said Safaee.

Working in Roxbury’s NanoBio Engineering Laboratory in the Fascitelli Center for Advanced Engineering, Safaee used several advanced technologies to make the bandage a reality.

“We designed and optimized a microfabrication process to precisely place nanosensors inside the individual fibers of a textile,” said Safaee. “We utilized cutting-edge microscopes to study the structure of the materials that we produced. I also utilized a home-built, near-infrared spectrometer to optimize the optical features of the textiles.”

The next stage of the project will involve the verification that the bandages function properly in a petri dish with live cultured cells that would be found in wounds.

“These cells we’ll be using are known as fibroblasts and macrophages (white blood cells) that produce hydrogen peroxide in the presence of pathogenic bacteria,” said Roxbury. “If all goes well, we’ll move to ‘in vivo’ testing in mice. At that point, we would find a collaborator who specializes in these animal wound models.”

Testing has focused on small bandage samples, but the technology can be applied easily to much larger bandages.

“There really is no limitation in terms of the size,” said Roxbury. “In fact, this technology will be most useful in large bandages. Larger bandages can be more of a nuisance to remove and reapply, but our device won’t need to be removed to enable detection.”

While Roxbury moves forward with the project, Safaee has moved to the Massachusetts Institute of Technology for a postdoctoral position.

“I joined the Furst Lab in MIT’s department of chemical engineering to advance and diversify my research in the area of molecular diagnostics and screening technologies,” said Safaee. “I will specifically work on designing high throughput screening technologies based on nanomaterials for point-of-care diagnostics and drug discovery applications.” ❖

New State-run vaccination sites open

Two new State-run sites opened last weekend – in South County, at the Schneider Electric facility, 132 Fairgrounds Road, West Kingston, and in Woonsocket at the old Sears department store at 1500 Diamond Hill Road.

Both of these new sites vaccinated 400 residents with the first dose of the Pfizer vaccine. Officials say they are prepared to administer many more doses per day when the supply comes in. The sites were run with help from the Rhode Island Medical Reserve Corps and hundreds of volunteers.

Both sites will operate from 2 to 6 p.m. Appointments will be available through vaccinateRI.org.

Current Sites

1500 Diamond Hill Road, Woonsocket
132 Fairgrounds Road, West Kingston
1400 West Main Road, Middletown
100 Sockanosset Cross Road, Cranston
Dunkin Donuts Center,
1 La Salle Square, Providence

In addition to these sites, the Rhode Island Dept. of Health (RIDOH) is working to open locations in Westerly, East Providence, and Johnston. As vaccine supplies increase, more appointments will become available at these sites and others. The state currently has the capacity to administer about 100,000 doses, and that number is expected to increase to more than 165,000 doses per week.

Eligibility Timeline

All Rhode Islanders will be eligible to make an appointment to be vaccinated by April 19. The State is currently vaccinating people who are age 64 to 60 and people who are age 64 to 16 with underlying health conditions. Eligibility to the remaining groups is expected by the following dates:

- People age 59 to 50 by April 5
- People age 49 to 40 by April 12
- People age 39 to 16 by April 19

In some of Rhode Island's hardest-hit zip codes in Providence, residents 18 and older already are able to sign up for a vaccine through VaccinatePVD.com or by calling the Providence mayor's office at 401-421-2489. In Pawtucket and Central Falls, all residents 18 or older are eligible for a shot. ❖

A State-run COVID-19 vaccination clinic opened last month at the former Benny's site in Middletown; the first site run by the Federal Emergency Management Agency (FEMA).

Warren residents Bernard Kwan and Sheila Dai were among the first to be vaccinated at the Middletown site and expressed their gratitude to VA nurses and FEMA for the seamless operation they experienced. [PHOTOS COURTESY OF SHEILA DAI]

Vaccine eligibility expands for Veterans, spouse, caregivers

All Veterans, their spouses and caregivers can get COVID-19 vaccinations from VA under the SAVE LIVES Act signed into law March 24.

Covered individuals can receive a vaccine from VA due to the ongoing COVID-19 public health emergency. Under the bill, covered individuals are:

- Veterans who are not eligible to enroll in the VA health care system
- specified Veterans who are eligible for hospital care, medical services, and nursing home care abroad
- family caregivers approved as providers of personal care services for Veterans under the VA's Program of Comprehensive Assistance for Family Caregivers
- caregivers of Veterans participating in the VA's Program of General Caregiver Support Services
- caregivers of Veterans participating in the VA's Medical Foster Home Program, Bowel and Bladder Program, Home Based Primary Care Program, or Veteran Directed Care Program
- Civilian Health and Medical Programs of the Department of Veterans Affairs recipients
- Veteran spouses

VA must prioritize the vaccination of (1) Veterans enrolled in the VA health care system, (2) Veterans who fail to enroll but receive hospital care and medical services for specified disabilities in their first 12 months of separation from service, and (3) caregivers accompanying such prioritized Veterans. Additionally, vaccines furnished abroad are authorized to be furnished in a geographic location other than a state regardless of whether vaccines are needed for the treatment of Veterans with a service-connected disability. This includes those participating in a VA rehabilitation program. ❖

CDC real-world study confirms protective benefits of mRNA COVID-19 vaccines

Study involved health care personnel, first responders, and essential workers in six states

A new CDC study provides strong evidence that mRNA COVID-19 vaccines are highly effective in preventing SARS-CoV-2 infections in real-world conditions among health care personnel, first responders, and other essential workers. These groups are more likely than the general population to be exposed to the virus because of their occupations.

The study looked at the effectiveness of Pfizer-BioNTech and Moderna mRNA vaccines in preventing SARS-CoV-2 infections among 3,950 study participants in six states over a 13-week period from December 14, 2020 to March 13, 2021.

Results showed that following the second dose of vaccine (the recommended number of doses), risk of infection was reduced by 90 percent two or more weeks after vaccination. Following a single dose of either vaccine, the participants' risk of infection with SARS-CoV-2 was reduced by 80 percent two or more weeks after vaccination.

It takes about two weeks following each dose of vaccine for the body to produce antibodies that protect against infection. As a result, people are considered "partially vaccinated" two weeks after their first dose of mRNA vaccine and "fully vaccinated" two weeks after their second dose. These new vaccine effectiveness findings are consistent with those from Phase 3 clinical trials conducted with the vaccines before they received Emergency Use Authorizations from the Food and Drug Administration. Those clinical trials evaluated vaccine efficacy against COVID-19 disease, while this study evaluated vaccine effectiveness against infection, including infections that did not result in symptoms.

"This study shows that our national vaccination efforts are working. The authorized mRNA COVID-19 vaccines provided early, substantial real-world protection against infection for our nation's health care personnel, first responders, and other frontline essential workers," said CDC Director **ROCHELLE P. WALENSKY, MD, MPH**. "These findings should offer hope to the millions of Americans receiving COVID-19 vaccines each day and to those who will have the opportunity to roll up their sleeves and get vaccinated in the weeks ahead. The authorized vaccines are the key tool that will help bring an end to this devastating pandemic."

One of this study's strengths is its design: participants self-collected nasal swabs each week for RT-PCR laboratory testing, regardless of whether they had developed symptoms of illness. Researchers were able to look for evidence of SARS-CoV-2 infection irrespective of symptoms. A small number (10.7 percent) of infections in this study were asymptomatic (i.e., did not result in symptoms). However, the majority of infections (58 percent) occurred among people whose infections were identified by testing before they developed symptoms or knew they were infected. The study demonstrates that these two mRNA vaccines can reduce the risk of all SARS-CoV-2 infections, not just symptomatic infections.

This is important because preventing both asymptomatic and pre-symptomatic infections among health care workers and other essential workers through vaccination can help prevent the spread of SARS-CoV-2 to those they care for or serve. Findings from this study complement earlier reports that these two mRNA COVID-19 vaccines can reduce both asymptomatic and symptomatic SARS-CoV-2 infections.

This study also provided positive news about partial (one-dose) vaccination. The one-dose VE estimate of this study (80 percent) is consistent with other recent VE studies following the first dose of Pfizer-BioNTech vaccine among health care providers. Studies conducted in the United Kingdom and Israel showed that one dose was about 70 percent and 60 percent effective, respectively, against SARS-CoV-2 infection. The current results provide reassurance that people start to develop protection from the vaccine two weeks after their first dose. The greatest protection was seen among those who had received both recommended doses of the vaccine.

This CDC study was conducted through the HEROES-RECOVER network, a network of prospective cohorts that share a common protocol and methods. This network is part of a vaccine effectiveness surveillance system made possible by federal pandemic flu preparedness funding.

This study is the first of many planned COVID-19 vaccine effectiveness studies CDC is conducting to evaluate the benefits of COVID-19 vaccines in various populations and across different outcomes, such as preventing infections, doctor's visits, hospitalizations, or deaths. Results from these studies assist the medical and public health experts on the Advisory Committee on Immunization Practices and CDC to make important vaccine policy decisions aimed at saving lives. ❖

RIDOH updates monoclonal antibody treatment regimens

The Rhode Island Department of Health (RIDOH) is committed to ensuring timely updates related to the COVID-19 pandemic, including for treatment. Based on new guidance issued by the United States (US) Department of Health and Human Services (HHS), and the sustained increase in COVID-19 variants now circulating in the US that are resistant to bamlanivimab alone, RIDOH no longer recommends the administration of bamlanivimab alone to treat people with COVID-19. HHS stopped the distribution of bamlanivimab alone starting March 24, 2021.

The US Food and Drug Administration recently updated the authorized Fact Sheet for Healthcare Providers for the bamlanivimab emergency use authorization (EUA). This update advises healthcare providers to use alternative authorized monoclonal antibody therapies that are expected to protect against circulating viral variants including bamlanivimab and etesevimab administered together and casirivimab and imdevimab (Regeneron).

RIDOH has updated its healthcare provider page to reflect this change. ❖

WHO calls for further studies, data on origin of SARS-CoV-2 virus, reiterates that all hypotheses remain open

GENEVA, SWITZERLAND – The report of the international team on their Wuhan field visit, from 14 January–10 February 2021, was published on March 30th as WHO Director-General Dr. Tedros Adhanom Ghebreyesus called for further studies.

The report stems from a Member State resolution adopted by consensus at the World Health Assembly in May 2020 and calling on WHO "to identify the zoonotic source of the virus and the route of introduction to the human population, including the possible role of intermediate hosts, including through efforts such as scientific and collaborative field missions."

In remarks to Member States on Tuesday, Dr. Ghebreyesus, who received the full report over the weekend, said it advances our understanding in important ways, while raising questions that will need to be addressed by further studies, as noted in the report. "As far as WHO is concerned, all hypotheses remain on the table. This report is a very important beginning, but it is not the end. We have not yet found the source of the virus, and we must continue to follow the science and leave no stone unturned as we do," he said. "Finding the origin of a virus takes time and we owe it to the world to find the source so we can collectively take steps to reduce the risk of this happening again. No single research trip can provide all the answers."

From the report:

How did the first human SARS-CoV-2 infections occur?

"At this stage, it is not possible to determine precisely how humans in China were initially infected with SARS-CoV-2. However, all available evidence suggests that SARS-CoV-2 has a natural animal origin and is not a manipulated or constructed virus. SARS- CoV-2 virus most probably has its ecological reservoir in bats.

"SARS-CoV, the virus that caused the SARS outbreak in 2003 and probably also had its ecological reservoir in bats, jumped from an animal reservoir (civet cats, a farmed wild animal) to humans and then spread between humans. In a similar way, it is thought that SARS-CoV-2 jumped the species barrier and initially infected humans from another animal host. Since there is usually very limited close contact between humans and bats, it is more likely that transmission of SARS-CoV-2 to humans happened through an intermediate host, that is another animal species more likely to be handled by humans. This intermediate animal host could be a domestic animal, a wild animal, or a domesticated wild animal and, as of yet, has not been identified.

"A number of investigations in the area believed to be the source of the outbreak in China are currently underway or planned. These include investigations of human cases with symptom onset in and around Wuhan in late 2019, environmental sampling from markets and farms in areas where the first human cases were identified, and detailed records on the source and type of wildlife species and farmed animals sold in these markets.

"Until the source of this virus is identified and controlled, there is a risk of reintroduction of the virus into the human population and the risk of new outbreaks like the ones we are currently experiencing."

What is WHO doing to help identify the source of SARS-CoV-2?

WHO continues to collaborate with experts, Member States, and other partners to identify gaps and research priorities for the control of COVID-19, caused by the SARS-CoV-2, including the identification of the source of SARS-CoV-2 in China. WHO also provides advice to countries and individuals on prevention and control measures that are specific to COVID-19.

The report is available on this webpage:
https://www.who.int/health-topics/coronavirus/origins-of-the-virus

WHO team in Wuhan

In July 2020 WHO sent a small team to China to plan a joint study comprising Chinese and independent international scientists. It was agreed that WHO would select the international scientists, who came from around the world: Australia, China, Denmark, Germany, Japan, Kenya, Netherlands, Qatar, the Russian Federation, the United Kingdom, the United States of America and Viet Nam.

The joint international team comprised 17 Chinese and 17 international experts from 10 other countries as well as the World Organization for Animal Health (OIE) and WHO.

Members of the team

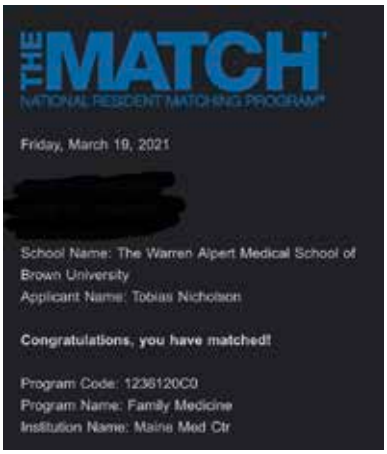
- Prof. Dr. Thea Fisher, MD, DMSc (PhD), Nordsjællands Hospital, Denmark
- Prof. John Watson Public Health England, United Kingdom
- Prof. Dr. Marion Koopmans, DVM PhD, Erasmus MC, Netherlands
- Prof. Dr. Dominic Dwyer, MD Westmead Hospital, Australia
- Vladimir Dedkov, Ph.D Institute Pasteur, Russia
- Dr. Hung Nguyen-Viet, PhD International Livestock Research Institute (ILRI), Vietnam
- PD. Dr. med vet. Fabian Leendertz Robert Koch-Institute, Germany
- Dr. Peter Daszak, Ph.D EcoHealth Alliance, USA
- Dr. Farag El Moubasher, Ph.D Ministry of Public Health, Qatar
- Prof. Dr. Ken Maeda, PhD, DVM National Institute of Infectious Diseases, Japan

The international team also includes five WHO experts led by Dr. Peter Ben Embarek; two Food and Agriculture Organization (FAO) representatives and two World Organisation for Animal Health (OIE) representatives.

Virtual Match Day at Brown

Tobias Nicholson, you have matched with

Maine Medical Center Family Medicine
Family Medicine



Tobias Nicholson, MD-ScM'21, received the email notifications from the Match program and Brown, informing him of his acceptance at the Maine Medical Center in Portland. He is thrilled to be going back to Maine, where he attended Bowdoin College in Brunswick. He told RIMJ the faculty at Maine Med reached out to him via email to offer their congratulations as well. [COURTESY OF TOBIAS NICHOLSON]

Timothy Genovese, MD'21, MPH, matched at the Harvard Spaulding Rehabilitation Hospital for a PM&R residency, affiliated with Harvard Medical School, and the Beth Israel Deaconess Medical Center/Brockton Hospital, where he will do a transitional year. He celebrated with his family in Long Island. [COURTESY OF TIMOTHY GENOVESE]

Catherine Garcia, MD'21, Student Body vice president, matched at the Cedars-Sinai Medical Center in Los Angeles, affiliated with the David Geffen School of Medicine at UCLA, where she will do a residency in neurological surgery. [COURTESY OF CATHERINE GARCIA]

Student Body president **Alec Kinczewski, MD-ScM'21**, (*at right*) matched at the University of Washington Affiliated Hospitals, where he will pursue a residency in psychiatry. He's shown in cover photo with his Corgi, ProZac, in Newport, where his parents and sisters joined him for a celebration. [COURTESY OF ALEC KINCZEWSKI]

Michael S. Woods, MD'21, celebrated Match Day with his family in his apartment in Providence. He matched in the psychiatry residency program at the New York Presbyterian Hospital/Weill Cornell Medical Center in New York City. [COURTESY OF MICHAEL S. WOODS]

Link to Match Day placements:
https://medical.brown.edu/about/facts-and-figures/match-lists/md-2021-match-list

Applicants celebrate the 2021 Main Residency Match, largest on record

WASHINGTON, DC – The National Resident Matching Program® (NRMP®) celebrated Match Day on March 19th with the thousands of applicants and programs participating in the 2021 Main Residency Match®. Results were highly anticipated given the pivot this year to a virtual recruitment season resulting from the COVID-19 pandemic and the effect it might have on the Match.

"The NRMP is honored to have delivered a strong Match to the many applicants pursuing their dreams of medicine. We admire all the Match participants for their hard work and their commitment to train and serve alongside their peers," said Donna L. Lamb, DHSc, MBA, BSN, NRMP President and CEO. "The application and recruitment cycle was upended as a result of the pandemic, yet the results of the Match continue to demonstrate strong and consistent outcomes for participants."

Largest Match on record: outcomes flourish despite pandemic

The 2021 Main Residency Match was the largest in NRMP history. There were 38,106 total positions offered, the most ever, and 35,194 first-year (PGY-1) positions offered, an increase of 928 (2.7%) over 2020. The growth in positions was supported by continued growth in the number of Match-participating programs. A record-high 5,915 programs were part of the Match, 88 more than 2020.

Growth in Match participation drives more PGY-1 placements

The number of applicants who registered for the 2021 Main Residency Match reached an all-time high of 48,700, an increase of 3,741 (8.3%) over 2020, and the largest single-year bump in recorded history. Growth in registration was seen in every applicant group, yielding more PGY-1 matches. Accordingly, concerns about the impact of virtual recruitment on applicants' matching into PGY-1 positions were not realized:

- The number of U.S. MD seniors who submitted rank ordered lists of programs was a record-high 19,866, an increase of 540 (2.8%) over 2020; 18,435 of them matched to first-year positions, an increase of 327 (1.8%) over 2020 and the highest number ever.
- The number of U.S. DO seniors who submitted rank ordered lists of programs was a record-high 7,101, an increase of 520 (7.9%) over 2020; 6,327 of them matched to first-year positions, an increase of 359 (6.0%) over 2020 and the highest number ever.
- The number of U.S. citizen international medical graduates (IMGs) who submitted rank ordered lists of programs was 5,295, an increase of 128 (2.5%) over 2020 and the highest in six years; 3,152 of them matched to first-year positions, a decline of two PGY-1 matched applicants over last year.

Applicants who did not match to a residency position participated in the NRMP Match Week Supplemental Offer and Acceptance Program® (SOAP®) to obtain an unfilled position. This year, 1,892 positions were offered during SOAP. SOAP results will be available in the full Match report published in early May.

Specialty highlights

The results of the Match can indicate the strength or competitiveness of specialties, as measured by the percentage of positions filled overall and the percentage filled by senior students in U.S. medical schools.

PGY-1 specialties with 30 positions or more that filled all available positions were Dermatology, Medicine-Emergency Medicine, Medicine-Pediatrics, Neurological Surgery, Otolaryngology Integrated Plastic Surgery, and Vascular Surgery.

Primary care remains strong. Of the 35,194 first-year positions offered in the 2021 Main Match, 17,649 (49.6%) were in Family Medicine, Internal Medicine, Internal Medicine – Pediatrics, Internal Medicine – Primary, Pediatrics, and Pediatrics – Primary, an increase of 514 positions (3.0%) over the number offered in 2020. Of those offered in 2021,16,860 (95.5%) were filled and 11,013 (65.3%) were filled by U.S. seniors. Although the percent of primary care positions filled by U.S. seniors in 2021 represents a slight (0.3%) decline from the prior year, Family Medicine saw a gain of 63 U.S. MD seniors matched, and Internal Medicine saw a gain of 93 U.S. DO seniors matched in 2021.

Specialties as indicators of workforce supply

Match results may also be a predictor of future physician workforce supply, especially when examining growth in specialties over time. In the last five years, the Main Residency Match has seen sizable increases in the number of positions offered in Neurology (223 positions; 45.3% increase); Family Medicine (1,467 positions; 43.7% increase); Emergency Medicine (793 positions; 38,7% increase); Medicine – Primary (100 positions; 29.3% increase); Psychiatry (412 positions; 27.6% increase); and Internal Medicine (1,791 positions; 24.8% increase). Fills rates for these specialties has exceeded 92 percent for all five years.

In addition to the annual Main Residency Match® for more than 48,000 registrants, the NRMP conducts Fellowship Matches for more than 60 subspecialties through its Specialties Matching Service® (SMS®). ❖

Investigational drug studied at Butler Hospital for AD treatment shows significant results in slowing symptoms

Clinical trial results of donanemab published in New England Journal of Medicine

PROVIDENCE – Clinical trial results announced on March 13th and published in the New England Journal of Medicine (NEJM) indicate that the investigational drug donanemab holds promise as a potential treatment for early Alzheimer's disease (AD).

Eli Lilly and Company, maker of donanemab, announced the study's findings at the International Conference on Alzheimer's & Parkinson Disease 2021 (AD/PD™21), in tandem with the publication of the article in the NEJM. Its phase 2 study of donanemab, called TRAILBLAZER-ALZ, showed that the drug resulted in significant slowing of decline in a composite measure of cognition and daily function in people with early symptomatic AD compared to placebo. The drug works by targeting the amyloid plaque and tau protein build-up in the brain that is associated with the development of Alzheimer's disease and other forms of dementia.

STEPHEN SALLOWAY, MD, MS, director of the Memory and Aging Program and of Neurology at Butler Hospital and the Martin M. Zucker professor of Psychiatry and Human Behavior and professor of Neurology at the Warren Alpert Medical School of Brown University, is a co-author of the NEJM article. He was principal investigator for the TRAILBLAZER study at Butler Hospital and was a lead investigator on the trial.

"This is yet another significant and encouraging milestone in what has proven to be a momentous year in the fight against Alzheimer's disease. In the last twelve months we've seen significant advancements in diagnosing and treating Alzheimer's," Dr. Salloway said.

The TRAILBLAZER-ALZ study was conducted at 61 research sites across the U.S. and Canada, including the two sites in Rhode Island. It utilized new imaging technology, tau Positron Emission Tomograhy (PET) imaging with flortaucipir tracer, that was developed specifically for the detection of tau protein in the brain. These tracers were developed in part at the Memory and Aging Program at Butler Hospital in partnership with the Alzheimer's Disease and Memory Disorders Center at Rhode Island Hospital. Dr. Salloway was a lead study clinician through all phases of the development of the flortaucipir tracer.

"The immediate goal is to provide treatments that will slow cognitive impairment in people experiencing the early stages of Alzheimer's disease. At the same time we're also testing treatments to prevent or delay memory loss in people at risk. We are on the cusp of a watershed moment in Alzheimer's disease treatment that could change the lives of millions of people around the world." Dr. Salloway said. ❖

Heart failure with reduced ejection fraction treatment study funded at VA

PROVIDENCE – Researchers from the VA Providence Healthcare System received funding January 1 to study a treatment for heart failure with reduced ejection fraction (HFrEF). Lead researcher **DR. WEN-CHIH "HANK" WU**, acting chief of the Medicine Service for the VA Providence Healthcare System, and professor of medicine and of epidemiology at Brown University, will research the use of probenecid, a generic, globally available medication for treating gout with minimal side effects, as an outpatient treatment for HFrEF.

"This study is important for Veterans because HFrEF is a common cause for hospital admission and death in the VA Health Care System," said Wu. "While a lot of progress has been made in understanding how the disease works, there is significant progress still to be made in its management and treatment."

The five-year, $2.2 million, VA-funded study will recruit 120 patients to assess whether oral probenecid improves heart function, exercise tolerance and quality of life, versus a placebo.

Previous research with probenecid has shown improvement in the heart's left ventricular function with few adverse effects. The use of probenecid as a treatment for HFrEF was also indirectly supported by a recent retrospective study of approximately 40,000 patients in the Medicare database, which found treatment with probenecid was associated with a nine percent decrease in risk of hospitalization for heart failure.

"Earlier research demonstrated the need for a larger study of longer duration that also evaluates functional and health status outcomes, which is purpose of our study," Wu said. ❖

Rhode Island Hospital memory disorders researcher launches landmark study of brain health following major surgeries

PROVIDENCE – A team at Rhode Island Hospital led by **LORI DAIELLO, PharmD, ScM**, senior research scientist at the Rhode Island Hospital Alzheimer's Disease and Memory Disorders Center (ADMDC), will launch a groundbreaking investigation into brain health after surgery. The 5-year study, Cognitive Recovery After Elective Surgery (CREATES), is funded by a $3.8 million R01 grant from the National Institutes of Health.

Daiello, an Associate Professor of Neurology (Research) and of Health Services, Policy and Practice at Brown University, will lead a team of hospital and university colleagues on the study, which will use a new MRI technique to examine the blood-brain barrier of patients age 65+ before and after surgery to measure their post-operative brain recovery.

According to Daiello, "As we age, more time may be needed to completely recover after surgery. Researchers are increasingly interested in how the body's usual healing and recovery processes after surgery could impact post-operative brain health."

Over the past five decades studies have suggested that some older individuals may experience lingering memory problems after undergoing major surgery with anesthesia, but little is known about why it occurs or even which patients are at greatest risk. Results of recent research suggest that certain types of inflammation after surgery could interfere with the rate of brain recovery.

The CREATES study will expand upon these findings by using a new type of MRI brain imaging technique, recently developed at the University of Southern California, to investigate whether the health of the blood-brain barrier (BBB) is related to the rate of postoperative brain recovery.

CREATES co-investigator, **BRIAN OTT, MD**, added, "Unchecked, we think that BBB dysfunction could increase the risk of certain illnesses, such as Alzheimer's Disease, Therefore, it is important for us to better understand the risk factors that could negatively impact brain recovery in some people who undergo major surgery."

Beginning in Fall 2021, the CREATES project will enroll more than 200 adults, age 65+ who are scheduled for upcoming major elective non-cardiac surgeries at Rhode Island Hospital. Participants will undergo pre- and post-operative brain MRIs, donate blood for genetic and biomarker analysis, and take periodic memory and thinking tests for 18 months following surgery to monitor brain health and cognitive recovery.

Daiello concludes, "The innovative brain imaging technique we'll be utilizing in CREATES will allow us to study pre- and post-operative brain health in an entirely new way. We anticipate that the results of this research will advance our understanding of cognitive aging and ultimately spur development of strategies aimed at improving perioperative brain resilience." ❖

PRoMPT BOLUS study at Hasbro measures potential improvement in children with sepsis

PROVIDENCE – Rhode Island Hospital's Hasbro Children's Hospital Emergency Medicine and pediatric ICU departments will be enrolling its first participants in a new, international pediatric fluid resuscitation clinical research study evaluating the comparison of normal saline and balanced fluids solutions in children with evidence of septic shock.

The study is sponsored by the National Institutes of Health and Children's Hospital of Philadelphia, Philadelphia, Pennsylvania and administered through the Pediatric Emergency Care Research Network (PECARN). Pediatric Emergency Medicine physician **DR. SUSAN DUFFY** and pediatric ICU physician, **DR. RANNA ROZENFELD** will lead the PRoMPT BOLUS study at Hasbro. All children who present to the Hasbro Children's Hospital Emergency Department with sepsis and meeting study criteria will be eligible to participate in this study and will be enrolled, unless opted out prior to visit. All patients enrolled in the study will receive one of the two commonly used IV fluids to treat sepsis along with the best locally available medical care available for their symptoms. Approximately 8,800 patients will be enrolled worldwide on a 1:1 basis to receive either normal saline or balanced fluids intravenous fluid. ❖

URI College of Pharmacy among best in nation in postdoctoral residency placement rate

KINGSTON – The University of Rhode Island College of Pharmacy continues to be a national leader in pharmacy education, most recently placing first in the northeast and no. 8 nationally in postdoctoral residency placement rate for phase 1. A highly competitive second phase for those who have not yet matched is ongoing.

Forty-four members of the class of 2021 have obtained postdoctoral residencies in the first phase of ASHP's highly competitive match program, 79 percent of those applying. The placement rate places URI among the best in the country, well ahead of the 63 percent national average. Only seven of the 143 colleges of pharmacy in the country had a higher average than URI's.

The URI College of Pharmacy has the highest placement rate among pharmacy schools in the northeast, and has placed the most students in residencies for the second straight year.

In addition, 10 members of the URI class of 2021 obtained fellowships or postdoctoral residencies outside of the ASHP match program, and 94 percent of former students from the Class of 2020 obtained second-year postdoctoral residencies, also among the best rate in the country. The two classes are spread out in residencies around the country, in 20 states.

"I continue to be amazed by the significant mark our impressive students are making on the health care community, locally, nationally and globally," URI College of Pharmacy Dean **PAUL LARRAT** said. "It is a credit not just to the high-quality students we continue to attract to URI, but also to our dynamic faculty members who have mentored our students into the pharmacy professionals they've become." ❖

Rhode Island health care providers join nationwide movement to improve older adults' care

Health systems in Rhode Island are recognizing the importance of addressing the health needs of the state's rapidly growing number of older adults by participating in a movement to better identify and address their unique care needs. Currently, nine hospitals, medical practices, convenient care clinics, and/or nursing homes in Rhode Island have joined Age-Friendly Health Systems.

Funded by The John A. Hartford Foundation (JAHF) and led by the Institute for Healthcare Improvement (IHI – in partnership with the American Hospital Association and the Catholic Health Association of the United States – the Age-Friendly Health Systems movement prioritizes what matters most to an older adult.

The COVID-19 pandemic has increased the urgency among health systems to prioritize age-friendly care; from March 2020 through December 2020, 1,671 U.S. health care sites joined the effort, including all approximately 1,100 MinuteClinic locations, the retail medical clinic of CVS Health. This brings the total number of sites to 1,956.

"The rapid growth of the age-friendly care movement means that older adults in Rhode Island have a better chance at receiving high-quality, evidence-based care that is tailored to what matters most to them," said **TERRY FULMER, PHD, RN, FAAN**, president of JAHF. "As COVID-19 has demonstrated, we must prioritize the care of older adults across all care settings to ensure coordinated, evidence-based, age-friendly care is delivered to those who need it most. We are incredibly grateful to IHI, our other partners, and all Age-Friendly Health Systems participants for their work to make health care age-friendly, especially during this terrible pandemic."

Health care treatment decisions that help older adults achieve what matters most to them – like daily walks without pain, having the energy for gardening, or talking with grandchildren while feeling clear-headed – result in healthier aging, according to the movement. When health care providers focus on the 4Ms of age-friendly care for older adults – what Matters, Medication, Mentation (memory and mood), and Mobility – they reduce harm, improve health outcomes, and lower health care costs, according to JAHF and IHI.

"There has never been a more critical time to prioritize adoption of evidence-based care of older adults," said **KEDAR MATE, MD**, president and CEO of IHI. "We are learning and improving care daily through the Age-Friendly Health Systems movement, and that will fortify our health care systems for the future. I am heartened by the increase in Age-Friendly participants and their commitment to better care for older adults."

Participants in the Age-Friendly Health Systems movement in Rhode Island as of Jan. 2021 include:

- Care New England
- Kent Hospital, Warwick
- Primary Care for Older Adults, Warwick
- 7 MinuteClinic locations

To learn more about the movement, visit http://bit.ly/2MGcpLR.

Appointments

Tracey M. Guthrie, MD, named Chair-Elect, American Association of Directors of Psychiatric Residency Training

The American Association of Directors of Psychiatric Residency Training (AADPRT) has elected **TRACEY M. GUTHRIE, MD**, Program Chair-Elect and is in line to be President.

Dr. Guthrie, Butler Hospital Program Director, Adult Psychiatry Residency Program, is an Associate Professor of Psychiatry and Human Behavior and of Medical Science (Clinical) at the Alpert Medical School of Brown University. She is also the Program Director for the Psychiatry Residency Training Program and the Assistant Dean for Diversity in the Division of Biology and Medicine.

She has been actively involved in medical education throughout her career, serving as the Associate Psychiatry Clerkship Director, Specialty Career Advisor for Brown medical students and Director of the Residency Continuity Clinic. Among the numerous honors she has received are the Outstanding Teaching Award in Medical School Education, the Dean's Excellence in Teaching Award and the Outstanding Teaching Award in General Psychiatry. ❖

BCBSRI announces new president and CEO

BCBSRI board selects Martha L. Wofford, group vice president at Denver healthcare company

PROVIDENCE – After a national search, Blue Cross & Blue Shield of Rhode Island (BCBSRI) has announced the appointment of **MARTHA L. WOFFORD**, group vice president at DaVita, Inc. in Denver, Colorado, as the president and CEO of the local, nonprofit health insurer. Wofford will be the eighth president and CEO of the 82-year-old company and the second woman to fill the role. She will join the company in April, succeeding Kim Keck, now president and CEO of the Blue Cross Blue Shield Association.

Wofford, a seasoned healthcare executive, has been with DaVita since 2014, supporting the company's shift to value-based care and taking full financial and clinical accountability for kidney patients. Leading the company's value-based care programs with commercial payers and health systems, Wofford also oversees patient experience and patient education programs at DaVita's 2,800 dialysis clinics nationwide.

Prior to joining DaVita, Wofford worked at Aetna for nearly a decade in various leadership roles. She led the company's effort to deliver simple solutions to help consumers navigate the healthcare system. Wofford joined Aetna in 2005 to help start up the Medicare Advantage and prescription drug plan business; was responsible for Aetna's national direct-to-consumer sales capability; and served as the general manager for the Northeast Region for Aetna's Medicare and consumer segment, with full accountability for more than a billion dollars in P&L.

Wofford was a consultant with Booz Allen Hamilton from 2000 to 2005, focusing on growth strategies in the healthcare and media industries. She served in the Clinton Administration for more than six years in communications and legislative positions in The White House, the U.S. Agency for International Development and the U.S. Environmental Protection Agency.

Wofford received a Master of Business Administration degree from the Kellogg School of Management at Northwestern University, where she focused on strategy and managerial economics, and received a bachelor's degree in history from Swarthmore College.

Wofford serves as executive director of the Aspen Group, a non-partisan group of healthcare leaders dedicated to developing and promoting meaningful solutions that advance the health and healthcare of all Americans. Wofford serves on the Kellogg Alumni Council, and on the Denver Scholarship Foundation board of directors, which provides tools, guidance and financial resources to Denver's public school students to enroll in and graduate from postsecondary institutions of higher education.

"I'm thrilled to be joining Blue Cross & Blue Shield of Rhode Island at this incredibly dynamic time for health and healthcare in our country," Wofford said. "Given our position as the state's largest insurer, we have the opportunity – and the responsibility – to address key longstanding issues like health equity that have been starkly highlighted during the past year. I can't wait to work with Blue Cross' board and leadership, as well as providers, and business and community leaders to realize our vision of passionately leading a state of health and well-being across Rhode Island, for all Rhode Islanders." ❖

Appointments

Star Hampton, MD, named Chief Education Officer at CNE

STAR HAMPTON, MD, has been named Chief Education Officer of Care New England. Dr. Hampton is currently Professor of Obstetrics and Gynecology (Ob/Gyn) and Medical Sciences at The Warren Alpert Medical School of Brown University, and recently completed service to the medical school and the Care New England hospital system as Interim Chair and Chief of the Department of Ob/Gyn.

Dr. Hampton served the medical school as the Ob/Gyn Core Clerkship Director for 9 years, was a former course director for the preclinical Human Growth and Reproduction course, and has been the Vice Chair of Education for the Department of Obstetrics and Gynecology since 2017.

Nationally, Dr. Hampton served as Program Chair of the Association of Professors of Gynecology and Obstetrics (APGO) Faculty Development Seminar for 5 years and was program faculty for their national Clerkship Director School and Transition to Residency School for many years. From 2012–2020 Dr. Hampton was a member and selected Chair of the APGO Undergraduate Medical Education Committee which serves to direct Ob/Gyn learning for all allopathic and osteopathic students across the nation, as well as internationally in some locations.

As Chief Education Officer, Dr. Hampton will work closely as a liaison for educational leadership across CNE Operating Units spanning the undergraduate and graduate medical education continuum. She will work to facilitate consistency across CNE academic programs and develop health system educational goals and priorities. ❖

Linda L. Carpenter, MD, named President-Elect of the Society of Biological Psychiatry

LINDA L. CARPENTER, MD, Chief of the Mood Disorders Program, Butler Hospital, has been elected President-Elect of the Society of Biological Psychiatry. The voting members of the Society recently announced the results of officer election results.

Dr. Carpenter's term as President will be June 2022 to June 2023, followed by a 5-year term as Councilor.

The mission of the Society of Biological Psychiatry is to:

- Promote excellence in research investigating the nature, causes, mechanisms, and treatments of disorders of thought, emotion, and behavior.
- Foster development of investigators in psychiatry.
- Educate clinicians, early career scientists, and educators in psychiatry about the biological underpinnings of psychiatric disorders.
- Disseminate the highest quality knowledge regarding the scientific basis of psychiatry in accessible manner to professionals, trainees, and lay audiences. ❖

James K. Sullivan, MD, PhD, named CMO at CNE Medical Group

JAMES K. SULLIVAN, MD, PhD, has been named Chief Medical Officer of Care New England Medical Group (CNEMG). He is Senior Vice President and Executive Chief of Psychiatry, Care New England; and Clinical Associate Professor of Psychiatry, The Warren Alpert Medical School of Brown University.

In this new role Dr. Sullivan will support clinical operations, quality programs and patient experience initiatives across CNEMG. Dr. Sullivan will also provide clinical and strategic leadership to CNEMG as CNE explores innovative models of care across CNE as well as in the proposed relationship with Lifespan and Brown University. ❖

Recognition

Nikos Tapinos, MD, PhD, earns Bruce M. Selya Award for Excellence in Research

PROVIDENCE – **NIKOS TAPINOS, MD, PhD**, is the recipient of the 2020 Bruce M. Selya Award for Excellence in Research, which recognizes outstanding biomedical research at Lifespan hospitals. Dr. Tapinos is director of Molecular Neuro-Oncology Research at Rhode Island Hospital and an associate professor in the Department of Neurosurgery at The Warren Alpert Medical School of Brown University.

Dr. Tapinos was nominated by Ziya L. Gokaslan, MD, Lifespan neurosurgeon-in-chief, clinical director of the Norman Prince Neurosciences Institute, and professor and chair of neurosurgery at Brown. In his nomination letter, Dr. Gokaslan noted that, "Nikos is one of the most outstanding young researchers in the field of glial cell biology, focusing on mechanisms of epigenetic regulation of sternness and differentiation in peripheral glia (Schwann cells) and human glial cancer (glioblastoma)."

The nomination describes in detail how innovative work in Dr. Tapinos's laboratory has led to a broad array of advancements in the highly complex science of treating certain tumors. Intellectual property developed from his work includes drug delivery methods, techniques to lure migrating tumor cells towards targeted regions in the brain, development of novel antibodies for cancer therapy, development of RNA therapeutics against eRNA targets in glioblastoma and the identification of drugs now in preparation for human clinical trials.

Dr. Tapinos is published widely in his field, including seminal papers in such noted journals as Science, Nature Medicine and the Proceedings of the National Academy of Sciences of the United States of America (PNAS), describing a non-immune mediated demyelination pathway in the Peripheral Nervous System and characterizing how Leprosy bacteria bind, invade and highjack the signaling network of human Schwann cells.

Dr. Tapinos's notable research grant awards include a current $4 million, four-year grant from the Alpert Foundation for which he is co-Primary Investigator, supporting, "Investigation of the role of epigenetics in adult and pediatric malignant glioma."

He has been an invited presenter nationally and internationally, and maintains memberships in prominent professional associations, including the Society for Neuroscience, the American Society for Neurochemistry, the Society of Neuro-Oncology and Sigma Xi Scientific Research Honor Society.

Dr. Gokaslan also makes note of Dr. Tapinos's role in fostering the careers of promising young scholars, serving as a mentor to dozens of undergraduates, postdoctoral fellows and medical students; and as thesis advisor to numerous PhD, master's and undergraduate honors students.

After completing his MD and PhD in molecular biology at the University of Athens, Greece, Dr. Tapinos completed his postdoctoral fellowship at the Laboratory of Bacterial Pathogenesis and Immunology at The Rockefeller University, New York, NY, which is where, he says on his website, he was introduced to the field of molecular neuroscience.

Dr. Gokaslan concludes in his letter, "I find Dr. Tapinos to be one of the most creative, innovative young researchers in the United States and we are fortunate to have recruited him to Lifespan and Brown…He is one of my finest colleagues - an outstanding researcher and a terrific mentor. I expect that soon he will cement his worldwide reputation as a creative leader in the fields of glial cell biology and neuro-oncology."

The Lifespan Board of Directors instituted the Excellence in Research award in 1999 to honor Judge Bruce M. Selya, chairman of the Lifespan Board from the creation of Lifespan in 1994 until 1999. Lifespan recognizes Judge Selya's "steadfast commitment to academic medicine and his keen insight concerning the importance of academic programs to quality health care at Lifespan." The award is intended to recognize a rising star in research, an independent investigator who has demonstrated excellence through a record of high-quality peer-reviewed publication and ability to attract research funding. ❖

Ortho Rhode Island celebrates opening of flagship campus in Warwick

At the ribbon-cutting ceremony were, from left, **Steve Federico**, Calspan Development & Construction; **John Yurtchuck**, Calspan Development & Construction; **Mary Ellen Ashe**, Executive Director of Ortho Rhode Island; Congressman **Jim Langevin**; **Frank Picozzi**, Mayor of Warwick; and **Michael Bradley, MD**, President, and CEO of Ortho Rhode Island [JORDAN INKLEY]

Ortho Rhode Island hosted a ribbon-cutting ceremony on March 25th to celebrate the opening of their new flagship campus at 300 Crossings Blvd. in Warwick. The new facility officially began patient care March 29th.

The 66,000 square-foot facility has been designed around a patient-centered workflow to reduce wait times. The first floor features Ortho RI Express injury care, physical and occupational therapy, Ortho RI Biologics, and MRI services, allowing patients with brief appointments to come and go without the elevator or stairs. The second floor contains orthopedic and podiatric office space and exam rooms, divided into four pod areas, each with its own digital x-ray equipment. The third floor houses the Ortho RI Surgery Center, with eight operating rooms and two procedure rooms.

"This is an exciting advancement for Rhode Island in terms of musculoskeletal care – through patient-focused care, innovation, and technology this campus will provide a one-of a-kind patient experience, with easy access to the full spectrum of orthopedic care in one location," said **MICHAEL P. BRADLEY, MD**, President and CEO of Ortho Rhode Island.

The building design also offers an abundance of natural light, outdoor walking space, terraces, and ample free parking. It will be the new home of Ortho Rhode Island's Warwick and East Greenwich offices, and is an addition to their current facilities in Providence, Wakefield, and Westerly, as well as their satellite locations. ❖

Roger Williams Medical Center opens Behavioral Health and Substance Use Emergency Treatment Unit

From left, **Dr. Daren Girard**, Chair of Emergency Medicine, **Candy Wray, RN**, ED Clinical Nurse Manager, **Dr. Greg Allen**, Medical Staff President, and **Jeffrey Liebman**, CharterCARE CEO. [CHARTERCARE]

Roger Williams Medical Center has opened Rhode Island's first completely dedicated emergency treatment unit to treat mental health, drug and alcohol medical emergencies that features private rooms for comfort, safety and privacy. The new 9-bed unit is the second and final phase of the hospital's $18 million expansion and renovation of its Emergency Department, which treats approximately 25,000 patients each year.

The newly opened behavioral health and substance use emergency treatment unit will operate in the space formerly occupied by the hospital's old emergency department, which was replaced by a new 12,000 square-foot addition in 2018. The specially designed locked unit includes 9 private treatment rooms and is staffed by personnel who are trained and experienced in treatment of mental health and substance use emergencies. Direct care will be provided by emergency nurses and physicians in collaboration with mental health clinicians. The Detoxification service will continue to be available and will be overseen by a board-certified emergency medicine physician.

JEFFREY LIEBMAN, CharterCARE CEO, stated, "Our new behavioral health emergency treatment unit will be a vital resource in our state's continuing challenge from mental health and substance use. We have long specialized in addiction medicine and mental health, but too many patients die before they can access that level of care. It is our hope that this new unit will save hundreds of lives each year and become a gateway to specialized addiction and mental health care."

"The new unit at Roger Williams Medical Center will help to fill a tremendous need, providing treatment and hope for Rhode Islanders with mental health and substance use conditions," said **KATHRYN POWER**, Director of the Rhode Island Department of Behavioral Healthcare, Developmental Disabilities and Hospitals. "It is gratifying to see this investment in behavioral health services, because we know it will result in greater access to care for individuals who need help and are seeking recovery."

CharterCARE through its two hospitals, Roger Williams and Our Lady of Fatima Hospital, is one of the state's leading providers of behavioral health and addiction treatment services, including the state's only Level I designated inpatient unit for substance use care, adult and geriatric psychiatry units, specialty programs such as partial hospitalization and intensive outpatient. ❖

Obituaries

WILLIAM D. GRAHAM, MD, 85, died peacefully at home on March 14th. He was the beloved husband of the late Nancy (Miller) Graham for 45 years. Upon graduation from Dartmouth College, he joined the Navy and served as a pilot and later taught formation flying in Pensacola, FL. Upon discharge, he attended Rochester Medical School and rejoined the Navy, and served as flight surgeon on the Quonset-based carrier Essex.

Dr. Graham worked in the Kent Hospital emergency room for 30 years and served his Jamestown community as a family doctor. He retired to Jupiter, Florida in 1996. He was an enthusiastic golfer and sailor.

He leaves three children from his first marriage to Susan Van Ness; Julia Taylor, John Graham and Nancy Graham all of South County, RI; two stepchildren, Steve Rogers and Linda Rogers of Florida and also seven grandchildren.

A celebration of life is planned for April. ❖

HOWARD STURIM, MD, died peacefully in his home the evening of March 12th, surrounded by his three sons. He was married to Jeanne Sturim for 56 years and together they raised their sons in Barrington, RI. He was a loving husband and father, and friend to many. The family enjoyed summers on their sailboat and sailed extensively throughout the Northeast. After he retired in 1998, they moved to Providence and after Jeanne's death in 2018, he moved to Kettle Point in East Providence. For 21 years they spent half of the year in Sundance, Utah. There they skied in the winter, hiked in the summer, and enjoyed the beautiful mountains and local adventures and friends.

He attended Syracuse University and graduated at age 19. He then entered University of Rochester School of Medicine, graduating in 1957 at age 23. He trained in General Surgery at Barnes Hospital in Saint Louis, Missouri and served as Chief Resident in 1965. His training was interrupted by serving 2 years of active duty with the US Navy, as a surgeon on Air Craft Carriers. He was the surgeon on the Super Carrier flagship "Independence" at the Bay of Pigs invasion. Following his active duty experience, he trained at the University of Pittsburgh in Plastic Surgery, completing his training in 1967.

He received his boards in both Surgery, and Plastic Surgery and was Chief of Plastic Surgery at Roger Williams Hospital, the Miriam Hospital, and for a time the VA Hospital. He was also on the staff of Rhode Island Hospital. He was a member of most of the prestigious Plastic Surgery and Hand Surgery Associations, and served on the board of many of them.

When he came to Rhode Island, the Brown Medical School was starting, and the training program in Plastic surgery was entering its second year. This was the only Plastic Surgery Program in New England at that time. He loved teaching and was a Clinical Associate Professor of Surgery at Brown University and Boston University.

He leaves three sons and their families, Douglas and Kris of Framingham, MA; Robert and Judy of Wenham, MA; Richard and Polly of Charlotte, VT; and his grandchildren, Nicholas Jennifer, Lilly, Abby and Jake, and Elias and Sam.

Contributions in his memory can be made to the Rhode Island Philharmonic. ❖

LEONARD JASON TRIEDMAN, MD, died surrounded by his family on the afternoon of March 19. A loving husband to Cynthia Knapp Triedman for 63 years, he was a devoted father, grandfather and friend to many.

He graduated from Moses Brown School in 1946, and from Brown University in 1949 at age 19, where he was elected to Phi Beta Kappa. He earned his medical degree from Harvard Medical School at age 23. Upon graduation, he joined the United States Air Force during the Korean War, during which he was stationed at Otis Air Force Base in Hyannis delivering babies to the wives of enlisted men – earning him the affectionate nickname "The Flying Obstetrician." After his service, he moved to Boston and married Cynthia, the love of his life. He did his residency in surgery at the Peter Bent Brigham Hospital in Boston and did a fellowship in head and neck surgery at Memorial Sloan Kettering Cancer Center in New York.

He then returned back home to establish his surgical practice in Providence. Over four decades, he cared for generations of Rhode Islanders, serving on the surgical staff of many Rhode Island hospitals, including the Miriam and Women & Infants hospitals, and was a clinical associate professor of surgery at Brown University Medical School. He and Cynthia raised their children on Providence's East Side and spent the last 33 years in Narragansett, where the extended family gathered frequently over the years for holidays, summer weekends, and just quiet dinners overlooking Narragansett Bay.

Lenny was a driven athlete with a passion for all sports. As a fan, he adored his New England Patriots and Boston Red Sox, and in the '60s and '70s, he was the team physician for both the Rhode Island Reds and the Pawtucket Red Sox. At various times, he was a ski patrolman; the R.I. men's tennis state champion;

and an avid runner who finished the Boston Marathon numerous times. Among his favorite past-times, especially in his later years, was the game of golf; Lenny was a proud member of the Point Judith Country Club and he traveled to the British Isles, Ireland and the Caribbean to play with family and friends.

He leaves his wife, Cynthia Knapp Triedman; five children – Nancy Shalek (James Shalek) of Weston, MA; John Triedman (Susan Hellerstein) of Brookline, MA; Kim Triedman (Eric Oldsman) of Arlington, MA; Scott Triedman (Mary Jo Kaplan) of Providence, RI; and Julie Triedman (Anthony Mace) of Brooklyn, NY; and 15 grandchildren – Alex, Nick, Peter, Hanna, Charlotte, Natalie, Nellie, Sophie, Lucy, Andy, Jamie, Liv, Hal, Cole and Bea, all of whom he absolutely adored. He also had six great-grandchildren.

In his memory, donations can be made to the Decoff Cancer Institute at the Miriam Hospital Foundation, P.O. Box H, Providence, RI 02901. https://giving.lifespan.org/LCI ❖

ROBIN WALLACE, MD, of Middletown, crossed the bar at home on March 20, 2021, after a long struggle, without complaint, with prostate cancer. Born Alan Robin Gordon Wallace on November 20,1936, in Weymouth, England, he was the only child of Dr. Gordon and Muriel Wallace.

He graduated with a Degree in Medicine from Exeter College in Oxford University. He first visited Newport in 1964, when his father was Commodore of the Royal Dorset Yacht Club, the Challenger of Record, for the British America's Cup Challenge, as well as Fleet Surgeon; the same position his son would hold years later for the New York Yacht Club.

He desired to do his residency in the United States, and did so at the Children's Hospital in Boston. After completing his residency in the United States, he moved to Newport, and established his practice in association with Dr. Fred Pearce at the Aquidneck Medical Associates. Soon after he commenced his practice, although a British Citizen, he was drafted into the U.S. Army where he served in Vietnam as a Major in the Medical Corps. After his service, he returned to his practice on Memorial Boulevard until retirement in 2003. He remained however the 'school doctor' for St. George's School until 2017.

To describe him as an icon in Newport is an understatement. Robin quickly established himself, not only as a sought after pediatrician but also as an avid promoter of sailing. As a member of the Ida Lewis Yacht Club he and his predecessor, Race Committee Chairman Robert Conner, were determined to establish new standards of excellence in race management. They trained the members of the Club and at the same time introduced to America a European type of level ocean racing called "ton" racing. The race series for the Sail Cup was an instant success and showcased the race management competence of the Ida Lewis Yacht Club, for which it is nationally recognized today.

He not only worked on the water, he promoted sailing events for Newport. As the Chairman of the State Yachting Committee, for over seventeen years, he educated the state legislators of the tremendous economic impact that sailing produced for the state. Probably the most successful events for Newport and the State of Rhode Island were the Volvo Races in 2015 and 2018 which, it is fair to say, would not have stopped in Newport without the efforts of the State Yachting committee advocating for the release of state funding required to support the event.

He was devoted to St. George's School. He conducted morning "sick call" at the school for over thirty-five years and was instrumental in upgrading the health center and the general wellness of the St. George's community. His gentle and respectful manner gained the confidence of many teenagers and they often sought his counsel and advice. He attended football and hockey games, home and away, to provide immediate medical attention to players on both teams in the event of injury. His devotion to the student athletes was recognized by the school when he was inducted into its Athletic Hall of Fame several years ago.

After the loss of the America's Cup in 1983, he was one of the founding members of Sail Newport, a public sailing organization that provides sailing instruction and boating facilities to the public. Currently all 4th graders in the Newport school system are introduced to sailing at Sail Newport. The organization also runs regattas and hosts many different sailing events and activities that contribute to the betterment of the entire community.

He was a Commodore of Ida Lewis Yacht Club and also a long time member of the New York Yacht Club. He was active in race management at both clubs this past season as sailing was one of the sports that one was able to participate in during the pandemic. He was also a long time active member of the Newport Reading Room.

He has been long loved by several generations of his pediatric patients and their parents and will be greatly missed by them and a wide spectrum of friends.

He leaves two cousins in England, his St. George's family, his Sail Newport family, his Ida Lewis family, the Murphy family, his loyal friends Bill and Pat Steel, and a host of friends in Newport and beyond.

Those wishing to commemorate him may do so by donating to Sail Newport, 72 Fort Adams Drive, Newport RI 02840. Additional information at www.memorialfuneralhome.com. ❖