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Getting Wiser, or Just More Crotchety?

JOSEPH H. FRIEDMAN, MD

A long-standing patient of mine with Parkinson’s disease (PD) showed up for a routine appointment, much worse than when I had seen him last, four months prior. He had undergone a detox program and, for reasons unclear to me, placed on an antipsychotic drug that had made his motor function much worse. The literature, which I am very familiar with, since drug-induced movement disorders and psychiatric problems in PD are two of my long-time research interests, is quite clear that this drug is contraindicated in patients with PD. I am fully aware that most doctors, including psychiatrists and others treating substance abuse disorders, may not be aware of this problem, and I was cognizant of my lack of information concerning why my patient was put on the drug at all. The patient had no follow-up visits scheduled with the doctor so my stopping the drug was not going to create any conflicts in management. But I decided that this doctor needed to be educated to avoid causing similar problems in the future. So, I wrote him a letter, with citations referencing the published papers, explaining why this drug should be avoided in treating PD patients.

I have done this sort of thing before, but only rarely. I’m writing this column because I’ve realized that I seem to be doing it more in my senescence. One might argue that I’m leveraging my experience and my possible status in this small medical community, and embracing and expanding my role as an “educator.” Alternatively, I’m becoming increasingly narrow-minded, opinionated and irascible. I once chanced on a line I’ve taken to heart, working, as I do, in what is sometimes considered “geriatric neurology”: “Old people don’t grow crotchety. Crotchety people grow old.”

A few months ago I met a woman who had been taking metoclopramide for indigestion. This drug is not supposed to be used for more than three months at a time, but this patient had responded so well, after having suffered for many years, that she and her gastroenterologist were very reluctant to stop it. She saw me because she had developed a well-known complication of long-term use of this drug, tardive dyskinesia. Unfortunately, this is usually a permanent problem that does not go away, even if the drug is stopped. When I discussed this problem with the patient, she reiterated multiple times that her gastroenterologist had told her that she’d need to take the drug the rest of her life, but was doing so well she needn’t see him again. Although I could not be certain that the doctor had, indeed, told her this, I, nevertheless, wrote him a letter, pointing out that the package insert for the drug specifically limited how long the drug may be used because of this possibly permanent side effect. I’ve been an expert witness for malpractice claims due to this problem for this and other related medications. My letter was written to be gently persuasive, as a useful piece of advice from a colleague. I did not expect a response, although as I write this, I realized that the offending doctor really should have thanked me. I was helping him by helping his future patients. My letter to him was not calling him out in any way, although I could see how he might have interpreted it that way.

Last year one of my PD patients had what I thought was an unusual spine problem. I referred her to a spine specialist with a particular interest in PD. After a several-month wait she saw a physician’s assistant, who rendered an opinion, basically, “nothing to worry about.” This was not reassuring to me, given my expertise with PD and its manifold complications. So I wrote the doctor a letter, and, to top it off, a column in this journal about the sometimes inappropriate use of physician extenders.

Back to my being old and crotchety. In writing a paper this past month, an uninvited opinion paper about a topic no one else seems to care about, venting my spleen about lung physiologists not evaluating a very uncommon but interesting breathing problem in my
PD patients and, instead, explaining their shortness of breath on an incorrect mechanism, I came upon a recent paper that quoted James Parkinson’s monograph of 1817. I was surprised. “He fetched his breath hard,” was the quote. I’ve read the monograph a few times. It’s a beautifully written rococo work, and I couldn’t recall any reference to breathing. Luckily the book is short and I found the quote without much trouble, but discovered that not only was the quote a phrase that Parkinson, himself, quoted from another doctor, but it was an example of patients who did not have “the Shaking Palsy” (Parkinson’s name for the disease later named after him) and was an example of why he wrote the monograph. I was surprised that none of the several co-authors of this recent publication responded to my email. Perhaps it was never received. Perhaps they were embarrassed. Should they care? Perhaps they thought I was an odd crank. I thought I’d save them the embarrassment of repeating this error.

Am I older and wiser, or older and more crotchety? ♦

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Losing Our Way: Caring for Patients Who May, Too Soon, Become Organ Donors

LYNN E. TAYLOR, MD, FACP, FAASLD

Iread with interest Leesley’s, “Transplantation of Hepatitis C-Infected Kidneys into Uninfected Recipients: A Review of the Literature.” I appreciate the work and expertise of Rhode Island’s (RI) kidney transplant specialists and the lives saved through transplantation. The authors mention that persons who die from overdose provide a source for hepatitis C virus (HCV)-infected donor kidneys, and underscore increasing overdose deaths during the COVID-19 pandemic. However, further discussion of public health priorities around overdose death organ donors is warranted.

In the United States (U.S.), the rising number and proportion of HCV-infected organs from young people who overdosed are being utilized for transplantation. Both overdose deaths and HCV incidence have skyrocketed with our opioid crisis, making HCV increasingly common among organ donors. With the advent of curative anti-HCV direct-acting antivirals (DAAs) coinciding with these public health tragedies, harvesting grafts from HCV-infected overdose victims has become a novel opportunity to expand the donor pool. The solid organ quality is ‘better’ because those dying en masse are young adults, with fewer years of wear on their organs.

U.S. overdose deaths tripled over the past 15 years, killing 70,237 people in 2017. From 2000 to 2016, the number of overdose-death donors (ODD, the new acronym) climbed by 17% annually, a 24-fold increase in transplants using organs from ODDS. RI is one of two states with the highest percentages of ODDS. In a registry study, ODDS were more likely to be HCV-infected (18.3%) versus medical- and trauma-death donors, consistent with other recent data demonstrating one-quarter of ODDS being HCV-seropositive, and increasing HCV RNA-positivity over time (8.6% to 15.7% from 2014 to 2017). From 2010 to 2017 the percentage of deceased donors with drug intoxication as cause of death mushroomed 200%, the proportion of these with reported injection drug use (IDU) surged 500%. People who inject drugs (PWID) are the fastest-growing donor category. National HCV incidence rose over 300% since 2010, mostly among adults under 40, predominantly among PWID.

What is becoming accepted is transplanting HCV-infected organs not only into HCV-infected recipients, but into HCV-uninfected recipients, then treating their newly acquired HCV infection with DAAs post-transplantation. This may be the first time in medical history that we are deliberately infecting our patients with a non-attenuated virus that can cause considerable morbidity and mortality. Studies to date in liver, kidney and thoracic organ transplant recipients demonstrate DAA safety and efficacy following transplantation (albeit with short-term follow-up).

I understand the gains. The growing pool of HCV-infected organs reduces waiting time, enhances survival and quality of life, and save lives of people who may otherwise die. Families can find comfort in donating their loved ones’ organs after overdose; something good comes from tragedy. But what about consideration from the standpoint of the opioid crisis – to some extent with iatrogenic origins? The technical marvel of transplanting HCV-infected kidneys exists in stark contrast to the failures of preventive medicine. We must prioritize upstream prevention strategies.

There is some acknowledgment of the young people at risk of acquiring HCV and becoming ODDS. For example, in the transplant literature, “…although transplant recipients benefit from the availability of HCV-positive organs, it is incumbent upon the public health and healthcare provider community to become more engaged in education and intervention through harm-reduction strategies to prevent HCV transmission and their consequences in young individuals.” Nonetheless, we are acquiescing too soon. “In areas where HCV-infected organs are plentiful, strong evidence now supports the strategy of accepting these organs to reduce waiting time.” We must also see that in areas where HCV-infected organs are plentiful, more is done to prevent and treat addiction, address contributory social and economic forces, reduce overdoses, stem HCV transmission and bolster HCV treatment. Further, “From a societal perspective, viable kidneys from HCV-infected donors must be treated as a valuable resource and not discarded…” From a societal perspective, people with opioid use disorder (OUD) must be treated as valuable human beings and not discarded. We need enhanced preventive care while accepting this new norm in a nation where most people in need cannot obtain methadone, people are incarcerated more than treated for OUD, and there is insufficient syringe access. There are roadmaps to follow.

In life, people becoming ODDS face barriers to care. For example, in the regional medical system providing kidney transplants, a major HCV program had a policy not to treat PWID for HCV, and to terminate DAAs should a
patient endorse substance use during therapy. Until July 2018 when RI Medicaid lifted “sobriety” restrictions limiting DAA access for its recipients under threat of lawsuit, drug-involved patients eligible to donate organs after overdose death, could not access DAs. Should a Medicaid recipient denied DAs due to a state’s Medicaid ‘sobriety’ or other restrictions, who overdoses, be used as a donor, with the recipient then getting DAs? DAA restrictions are being lifted albeit slowly, one state and sometimes one rationing category [fibrosis stage, substance use, clinician type] at a time, but myriad obstacles remain. This is despite the ever-growing body of evidence demonstrating the efficacy, safety and imperative of treating the transmitting population. A next step could be scrutinizing state Medicaid DAA restrictions and overlaying the map of HCV-infected ODDS and their Medicaid status. Hopefully Medicaid recipients do not disproportionately comprise this contemporary cache of donors, further widening the health disparities gap of the HCV epidemic.

We have entered a brave new world without sufficiently examining the ethics of capitalizing on the overdose crisis. Potentially, in the U.S., there are financial gains for some around exploiting these deaths, where medicine is a business and often for profit, money can drive healthcare priorities. Most of my patients are Medicaid recipients. Most can secure transplant evaluation. It can be harder to find an internist or psychiatrist accepting new RI Medicaid recipients. The staggering differences in reimbursement for primary versus tertiary, procedure-based and subspecialty care, and RI’s low Medicaid payments, contribute to the challenges well-meaning physicians face. Fixing this is an essential part of the solution. There are resources, where they are channeled requires modification. For example, it was stated for years that insufficient funds existed for RI Medicaid recipients’ DAs. Meanwhile RI Medicaid’s largest provider scored $1,366,000,000 revenue in 2017, 35.1% growth percentage, and $354,625,064 revenue growth, as RI’s second fastest growing private company.

Pre-COVID-19, U.S. life expectancy fell for three years in a row – a reversal not seen since 1918 or in any other wealthy nation in modern times. This is in large part due to the rise in “deaths of despair,” from causes including drug overdose and HCV. There is no rebellion by soon-to-be ODDS. My patients are too disenfranchised to speak up or organize. They contend with OUD, polysubstance addiction, infectious consequences of IDU, unstable housing, stigma, educational and economic disadvantage, and substance use-and poverty-related interaction with the criminal justice system which erects barriers to a better future. It is dizzying to ponder this while other nations (Iceland, Portugal, Switzerland, Australia, to name a few) stride towards meeting World Health Organization HCV elimination goals and medicalize and decriminalize addiction. But physicians are inquiring. At a recent American Association for the Study of Liver Diseases conference presentation on renal transplantation outcomes, a doctor asked the speaker if the donors received the equivalent optimal care that the recipients received. Few seemed to understand the question. It is time we all do.

References


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The SARS-CoV-2 (COVID-19) pandemic has all but brought the Global Polio Eradication Initiative to a halt. Nonetheless, the global quest to stamp out the polio scourge provides a uniquely salient point of comparison for the ongoing battle against SARS-CoV-2. At the time of this writing, two of the three wild poliovirus (WPV) serotypes (WPV2 and WPV3) have been eliminated, and WPV1 remains endemic in only Afghanistan and Pakistan.1 Though the near-elimination of endemic polio marks the successes of more than 85 years of eradication efforts, the race towards development, testing, and distribution of vaccines against poliovirus – most notably exemplified by the 1950s’ competition between American researchers Jonas Salk and Albert Sabin – stands in striking parallel to that ongoing in the United States’ fight against COVID-19. The lessons learned through this odyssey can and must inform the gargantuan task of vaccinating the American populace against SARS-CoV-2. Herein we lay out the successes and failures of the polio vaccination campaign with an eye toward informing policymakers entrusted with securing, distributing, and administering a safe and effective SARS-CoV-2 vaccine. Special emphasis will be placed on the principles of national unity, racial and ethnic equity, as well as vaccine safety and efficacy.

Research efforts aimed at elucidating the biology of the poliovirus family date back to the early 20th century. However, it took the 1932 election of President Franklin Delano Roosevelt (FDR), a polio survivor himself, to align the requisite political and scientific forces against the deadly disease. It was not until 1938, and the establishment of the National Foundation for Infantile Paralysis (NFIP), later renamed the March of Dimes Foundation, that the national quest for a polio vaccine was launched. What followed was a 17-year race for the development of a safe and effective polio vaccine. Jonas E. Salk, MD, of the University of Pittsburgh, sought to develop an inactivated poliovirus vaccine (IPV). Albert B. Sabin, MD, of the University of Cincinnati, in turn, pursued a live attenuated poliovirus vaccine (OPV) option.2 By 1952, preliminary trials of the Salk vaccine were deemed promising enough to warrant an unprecedented, nationwide, year-long field trial involving nearly 2 million children who were to be known as the “polio pioneers.”2 The success of this trial and the widespread dissemination of the Salk vaccine that followed – bringing American polio cases down by half each year from 1955 to 1959 – would serve as a foundation for future mass vaccination efforts of the modern era.3

In stark contrast to the political dynamics surrounding the SARS-CoV-2 pandemic, FDR and the NFIP were able to insulate the polio eradication efforts from the politics of the day by calling for individual participation in a national cause. Hollywood executives and A-list stars were recruited to churn out films and radio broadcasts emphasizing the dangers of polio.2 Simultaneously, grassroots fundraising programs, from the FDR Birthday Balls and March of Dimes fundraising drives (wherein millions of Americans sent dimes to the White House towards the eradication of polio), to the Mothers’ Marches of the 1950s, enabled millions of Americans to find a sense of personal affiliation with the cause of polio eradication.4 Slogans such as “Polio Wears No Party Label” stood as unity cries amidst the political strife engendered, for example, by the attack on Pearl Harbor, amongst many other points of stark political division.2 After years of personal involvement in the fight against polio, Americans saw the vaccination effort not only as a means to protect themselves but also as a means of fulfilling their national duty. Though such rally-round-the-flag dynamics may be difficult to muster in the current political climate, depoliticization of the fight against SARS-CoV-2 stands as a crucial step to counter the spread of vaccine hesitancy and related anti-vaccination sentiments. Ongoing vaccine distribution efforts can only be successful if local authorities, regardless of party affiliation, continue to promote the uptake of available vaccines.

The search for a polio vaccine is often portrayed as a fierce battle between the Salk and Sabin vaccines. The evident competition notwithstanding, the two vaccines played complementary roles in the long-term journey towards polio
eral on May 6, 1955. The culprit, improper inactivation of weeks only to be belatedly halted by the U.S. Surgeon General, even so, vaccination efforts continued for three additional reports of post-vaccine paralysis followed within days. The variety of vaccines being developed against SARS-CoV-2 should be seen as a boon for a fight that will inevitably outlive the current pandemic. It is beyond cavil that the U.S. must continue to invest in vaccine research and development while searching for therapeutics that can eliminate SARS-CoV-2 safely, efficiently, and reliably.

Though the Salk and Sabin vaccines often dominate discussions of polio vaccine development, earlier efforts trace back to the 1930s. In 1935, John A. Kolmer, MD, of Temple University pushed for large-scale trials of his attenuated poliovirus vaccine. Nine deaths and at least twelve cases of paralysis followed. A similar fate befell trials of the inactivated poliovirus option developed by Maurice Brodie, MD, of New York University Medical College. Not unexpectedly, any and all efforts to develop a polio vaccine came to a temporary, but costly halt. Nearly 13,000 children would become permanently paralyzed each year vaccines remained unavailable and thousands more would vow to avoid potentially dangerous vaccines to come. Similar failures plagued the Salk vaccine which was declared “safe and effective” on April 12, 1955. Mass inoculation followed a day later. Reports of post-vaccine paralysis followed within days. Even so, vaccination efforts continued for three additional weeks only to be belatedly halted by the U.S. Surgeon General on May 6, 1955. The culprit, improper inactivation of the poliovirus by the Cutter Laboratories, resulted in over 40,000 cases of vaccine-induced polio, 200 cases of paralysis, and 10 deaths nationwide. Avoiding more of the same with the COVID-19 vaccines will require that the FDA thoroughly oversee the manufacturing processes. Equally important will be the monitoring and reporting of any and all adverse effects by the National Vaccine Program Office. The latter, dismantled under the Trump administration by the Department of Health and Human Services, should, if possible, be prioritized for reinstatement. Putting speed ahead of safety should not be tolerated. In an era of heightened vaccine hesitancy, avoiding rollout errors – most notably, infection-via-vaccination – likely stands out as the single most crucial step in the successful dissemination of a SARS-CoV-2 vaccine.

Though many regard SARS-CoV-2 as a great equalizer, infecting any and all who come in its path, the disproportionate burden the pandemic has placed on the Black and Latinx communities recapitulates lamentable disparities not unlike those noted during the polio era. Although the Salk vaccine was made available to all, deference to local authorities in the process of vaccine distribution rendered racial equity a focus which would only be realized in certain parts of the country. In many Southern states, the requisite presence of parents during the vaccination of their children posed a greater challenge to communities of color wherein the attendant financial strain often required both parents to work. Additionally, mandates of some state and city health departments relegated much of the vaccinations effort to then-segregated white public school districts. Though Rhode Island’s current efforts to prioritize vaccine access in Central Falls highlights a local understanding of the degree to which communities of color have been disproportionately burdened by the ongoing pandemic, such local attempts to counter the stark racial discrepancies in pandemic burden fail to protect those whose own local authorities have failed to make racial justice a priority in their vaccine distribution plans. Racial inequities in pandemic burden reflect national disparities in health outcomes and therefore require national responses to cement the prioritization of racial justice in vaccine distribution.

The import of the aforementioned lessons of the polio epidemic to its SARS-CoV-2 counterpart notwithstanding, success of the national vaccination effort may well flounder on the rocks of reality. National unity may well prove untenable in the current political climate. However, vaccine safety and efficacy can and must be assured during the development, production, and distribution of SARS-CoV-2 vaccines. Ensuring that all Americans, regardless of race, color, or creed, are afforded equal access to the vaccine must be a top priority. Vaccines serve their purpose only when and if welcomed by the public and guided by intentional and swift plans for distribution. Further erosion of the public trust must be guarded against at all costs. As we look, yet again, at vaccinating a nation, we must take stock of the lessons of the past. The polio epidemic is one notably informative place to look.

The import of the aforementioned lessons of the polio epidemic to its SARS-CoV-2 counterpart notwithstanding, success of the national vaccination effort may well flounder on the rocks of reality. National unity may well prove untenable in the current political climate. However, vaccine safety and efficacy can and must be assured during the development, production, and distribution of SARS-CoV-2 vaccines. Ensuring that all Americans, regardless of race, color, or creed, are afforded equal access to the vaccine must be a top priority. Vaccines serve their purpose only when and if welcomed by the public and guided by intentional and swift plans for distribution. Further erosion of the public trust must be guarded against at all costs. As we look, yet again, at vaccinating a nation, we must take stock of the lessons of the past. The polio epidemic is one notably informative place to look.
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Tales of Two Vaccinations: From Polio to COVID

MARY KORR
RIMJ MANAGING EDITOR

We walked in pairs down the long school hallway and descended to the gymnasium – a parade of first- and second-graders on a polio vaccination march. The field trials of the Salk vaccine in 1954 had proven effective against poliomyelitis, and in 1955 the Salk vaccine was deemed safe and effective, and mass vaccination programs followed in public, private and parochial elementary schools nationwide over the next few years, including mine in Queens, NY.

Inside the gym, sleeves rolled up, we inched past long cafeteria tables filled with boxes of vials, syringes, bottles of alcohol and cotton swabs. The school nurse and volunteer local doctors were armed and ready. One by one, we advanced to the ‘sticking’ station and surrendered to the inevitable. It stung! I think the needles were thicker back then. A “Stars ‘n Strips” Band-Aid was taped to the injection site (mine was red with white stars). We were told there would be a booster shot in two months.

By the exit door, there were bowls of Tootsie Rolls, Chuckles, and silver-wrapped Hershey’s Kisses; the monitor watched to make sure we only picked one. And then we lined up and walked up the stairwell and down the long hallway and back to our classroom, passing the next group of little marchers on their way down.

No one, to my recollection, contracted polio in my school or neighborhood, which teemed with kids. But 16 years later, on my first day of graduate school, as I began to unpack in the women’s journalism housing co-op, Mary, vaccinated for COVID-19 in 2021, and at right, for polio in 1957.

Early Polio Pioneers, 1954
In 1954, The March of Dimes organized testing of the Salk polio vaccine with 1.8 million schoolchildren who became known as “Polio Pioneers” and were part of the largest peacetime mobilization of volunteers in our history. In all, 1.3 million children took part as vaccine recipients, placebo recipients, or observed controls. The vaccine was declared “safe, effective, and potent” against paralytic polio on April 12, 1955. [MARCH OF DIMES, MARCHOFDIMES.ORG]

(COURTESY OF JOHNSON & JOHNSON ARCHIVES)
I saw a new arrival struggling in the hallway with her suitcase. She had canes attached to metal rings around her wrists. Polio, I immediately thought. Eventually, she shared what it was like to have polio as a child, and said she was one of the lucky ones. She never experienced an iron lung and was not wheelchair-bound. And she had reconciled herself to becoming an editor rather than a reporter on the beat.

And now, decades later, the COVID-19 vaccines, another vaccination development milestone, has recently become available for the Baby Boomer cohort in many locations. The scramble to get appointments and not have them canceled is unnerving, but I did secure one after multiple attempts. Upon arrival at the dispensing facility we filed in, six feet apart, and went through a series of checkpoints and showed IDs. There were 500 slots filled for that day.

When it was my turn to be vaccinated, I walked up a stairwell to the second floor, checked in at the desk, and then down a long hallway following the blue arrows taped on the floor, and entered an exam room. I rolled up my sleeve and the provider checked my medical record on the computer and asked the required questions. After receiving the Moderna vaccination, she put a plain Band-Aid on my arm and gave me a paper sticker: “I Got My COVID-19 Vaccination” and the appointment card for dose 2. No red, starry Band-Aid, no candy, but nevertheless I felt relieved to have the insignia.

During the obligatory 15-minute observation period, there was a man in a wheelchair nearby, and I thought of my J-school roommate and hoped she had received the vaccine. I noted the cadre of masked Baby Boomers coming and going, and my thoughts drifted back to that day so long ago when we kids walked down the long school hallway and descended to the gymnasium, extended our small arms and became participants in and eyewitnesses to vaccination history – as well as the recipients of free candy!
Escalating Overdose Deaths Necessitate an Overdose Prevention Center in Rhode Island

SETH CLARK, MD, MPH; ANNAJANE YOLKEN, MPH; STEVE DETOY

The United States (US) documented its deadliest year of overdoses (ODs) in May 2020 with 81,230 lives lost to drug overdoses in the preceding 12 months. Rhode Island (RI) remains one of the most severely impacted states, with annual OD deaths expected to exceed 400 for the first time in 2020. In October 2020, the Rhode Island Department of Health (RIDOH) released fatal overdose data for the first 6 months of 2020, demonstrating an increase in all-drug fatal overdoses by 24% and opioid-involved overdose deaths by 33% compared to the first 6 months of 2019. While 2020 RI ODs primarily occurred in adults 25–65 years old [93%] and non-Hispanic whites [78.5%], East Coast trends show increasing mortality rates among younger people of color living in urban areas.

Over the past decade, community-based organizations, the healthcare system, and the Governor’s office have provided increased time and resources to address this issue. OD deaths were beginning to plateau in RI after a peak in 2016 (n=336). However, due to several factors, including COVID-19, OD deaths have seen a dramatic escalation, despite an increasing number of Rhode Islanders on medications for opioid use disorder (MOUD) and augmented naloxone prescribing.

Increasing OD numbers in RI and nationwide continue to be driven by illicitly manufactured, high potency fentanyl contaminating the drug supply. More potent fentanyl analogs are continually being developed, resulting in an even more unpredictable and dangerous supply. Fentanyl is also being detected in the non-opioid drug supply (pressed pills, powder cocaine), which poses an even greater risk for ODs in people without opioid tolerance.

Given current unparalleled OD numbers despite augmented treatment efforts, additional timely evidence-based approaches are critically needed. One such intervention is to establish an overdose prevention center (OPC). OPCs [aka safer consumption sites, supervised injections facilities, harm reduction centers] serve as a location where people can use pre-obtained substances in a hygienic, well-lit environment with new equipment, trained medical supervision, drug checking, social service support, and facilitated entry to treatment if requested.

OPCs were first established in Switzerland in the mid-1980s and have since spread worldwide, with approximately 120 OPCs currently in operation across 11 countries. These centers exist primarily in Europe, but also include 39 sites operating in Canada. There are currently no sanctioned OPCs in the US. These sites have been extensively studied and repeatedly demonstrate decreased overdose mortality, decreased spread of infectious diseases, decreased injection-related complications, increased entry into treatment, improved public order metrics (injecting in public, injection-related litter), and increased medical and social services utilization, with no increase in substance use or drug-related crime. Zero fatal overdoses have occurred at any of these sites worldwide, despite the millions of doses of substances used in these facilities. Additionally, these sites allow for drug checking, not currently provided in RI and recently recommended by the CDC. Evaluation of existing unsanctioned OPCs in the US demonstrate similar population benefits, including decreased criminal activity. While utilization rates of OPCs vary greatly among published reports, a recent analysis of people who use drugs in Providence found that a majority expressed a willingness to use an OPC if established.

This approach is not only medically and morally imperative, but also cost effective. Models extrapolating data from Vancouver’s Onsite OPC to Baltimore projected a cost savings of $5.98M annually and $4.35 for every $1 spent. Another recent review determined that an OPC in Boston would save over $4M annually, primarily via decreased 911 calls, ED visits, hospital admissions, and ambulance rides.

Resistance to implementation of OPCs in the US stems largely from a perceived violation of the federal “crack house” statute that makes it illegal to “knowingly open, lease, rent, use, or maintain any place for the purpose of manufacturing, distributing, or using any controlled substance.” RI law has a similar provision that also prohibits this on a state level. In February 2020, a US District Court Judge in Pennsylvania ruled that operating an OPC would not violate this statute, stating a “focus on factual nuances overlooks the complexity of determining the proper application of the law.” A civil lawsuit was subsequently filed by the US Attorney for the Eastern District of Pennsylvania challenging this ruling and
delayed the opening of a facility in Philadelphia. In January 2021, a Philadelphia federal appellate court ruled 2–1 that an OPC would violate the federal statute, reversing the 2020 decision.21 Despite the anticipated pushback, the initial groundbreaking federal ruling has cities across the country poised to push forward plans for opening OPCs.

Advocates have been working on efforts to open an OPC for several years in RI. In 2019 the RI Senate unanimously approved legislation sponsored by Senate Health and Human Services Committee Chairman Joshua Miller “to explore the creation of a pilot program to create ‘harm reduction centers’ to help prevent drug overdose deaths.”22 Unfortunately, this bill has yet to pass the RI House.

Given the efficacy of OPCs and the recent affirmative ruling by a US federal judge, establishing an OPC in RI is the logical next step to address this escalating crisis. Seeing the need for urgent action, a group of community advocates recently circulated a call to the Governor’s office to issue an executive order to authorize an OPC. Noting that they have been working without much reception from the Governor’s office, they wrote:

“Three years ago the Rhode Island Medical Society, the Rhode Island Health Center Association, the American Nurses Association Rhode Island chapter, and Preventing Overdose with Narcan Intervention wrote to the Governor and co-chairs asking for the Governor’s Overdose Task Force to appoint a Harm Reduction Committee, stating: ‘Specifically, we would ask that this working group study the feasibility and advisability of Rhode Island establishing a pilot medically supervised consumption center, aka Safe Injection Facility [SIF]. In particular, we would ask that results of that study be reported back to the Task Force within 3 months for potential action.’ Three years later, we still do not have a plan.”

Governor Raimondo’s office responded, stating that while she understood the scope of the overdose crisis and supported the Governor’s Overdose Task Force’s commitment to reviewing the feasibility of a pilot overdose prevention site, she could not do anything else due to federal law.

The medical community can support state legislation that would codify these practices into state law while awaiting change at the federal level. While the bills from 2020 were not heard due to the shutdown of the legislature, we anticipate they will be heard again this session. Ultimately, we will need state law to implement such facilities in RI and provide medical professionals with liability protection to work at such a site.

Overdose deaths continue to rise across RI and the US despite increasing interventions and resources. OPCs have repeatedly demonstrated efficacy and safety. A report in January 2021 from the Institute for Clinical and Economic Review [ICER] supports implementation of OPCs in the US, stating, “The evidence is adequate to demonstrate that [OPCs] save lives and save money. Community, state, and federal policy leaders should move forward to take the steps needed to launch pilot [OPC] programs in areas of established need and with strong local involvement of many sectors of the community, including, most importantly, people who use drugs themselves.”20 It is time for Rhode Island to take bold action and utilize this evidence-based approach to establish an OPC to stem the tide of escalating loss of life where other interventions have failed.

References
AMA supports pilot Overdose Prevention Site (OPS) in RI

On behalf of the American Medical Association (AMA) and our physician and medical student members, the AMA is writing in support of Rhode Island developing and implementing a pilot Overdose Prevention Site (OPS). Specifically, we support this effort as the OPS would be designed, monitored, and evaluated to generate data to inform policymakers on the feasibility, effectiveness, and legal aspects of an OPS in reducing harms and health care costs related to, among other things, injection drug use.

Notably, the AMA has supported a similar effort in Pennsylvania.1 We were supportive of the Pennsylvania effort due to the need, in that state, for prioritizing individual and community health and well-being through evidence-based solutions to address the harms of drug-related overdose, including the implementation of pilot supervised consumption sites.

The implementation of the OPS in Rhode Island may be particularly timely and essential due to the fact that drug overdose rates in Rhode Island – as in nearly every other state in the nation – have increased in 2020.2 The AMA is deeply concerned by increasing death involving illicit fentanyl, methamphetamine, and cocaine. We further acknowledge that while overdose involving prescription opioids and heroin may have “stabilized,” it remains far too high.

For these reasons, the AMA supports the development and implementation of the pilot OPS under consideration in Rhode Island.

Sincerely,

James L. Madara, MD

References
2. Data from the Rhode Island Department of Health (DOH) indicates a 26 percent increase in drug overdose deaths in the six-month period from January 1, 2020–July 31, 2020 compared to January 1, 2019–July 31, 2019. Preliminary data from the RI DOH also indicates drug-related deaths are at an all-time high. See https://health.ri.gov/data/drugoverdoses/
Aetna® is proud to support the members of the Rhode Island Medical Society.
Impact of NIH’s Institutional Development Award (IDEA) Programs in Rhode Island

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

The National Institute of General Medical Sciences (NIGMS) is one of the 27 Institutes and Centers that the National Institutes of Health (NIH) maintains. The NIGMS’ Institutional Development Award (IDEA) program, which was formerly located in the National Center of Research Resources (NCRR) in the NIH, supports biomedical research, enhances investigators’ competitiveness in securing research funding, student training, and enables clinical and translational research in states where NIH research funding levels have historically been low.1

The IDEA program has three primary mechanisms: [1] Centers of Biomedical Research Excellence (COBRE) that supports thematic, multidisciplinary research centers; [2] IDEA Networks of Biomedical Research Excellence (INBRE), a statewide biomedical research development network that partners research-intensive institutions with primarily undergraduate institutions [PUI]; [3] Infrastructure for Clinical and Translational Research (IDEA-CTR) that supports clinical and translational research capacity. There is also an IDEA co-funding mechanism that provides a funding boost, and an STTR Regional Technology Transfer Accelerator Hub that supports infrastructure and builds an entrepreneurial network at IDEA institutions, one each in the four IDEA regions (Central, Northeastern, Southwestern, Western).

Rhode Island funding
Rhode Island [RI] has been very active in securing IDEA awards early on, receiving its first 5-year COBRE funding in 2000 for Brown University’s COBRE Center for Genetics and Genomics. This was followed by a series of COBRE successes in RI’s vibrant hospital research community: Rhode Island Hospital (COBRE Center for Cancer Research Development), Woman & Infants Hospital (COBRE for Perinatal Biology), and Roger Williams Hospital (COBRE Center for Stem Cell Biology). The trend has continued in recent years with a dozen newer COBRES focused on other innovative biomedical and translational themes (Table 1).

In 2001, the State was awarded its first exploratory Biomedical Research Infrastructure Network (BRIN) grant. It successfully transitioned to RI-INBRE in 2004 and has been renewed for four continuous 5-year grant cycles. The RI-INBRE award has enhanced and improved students’ and faculty’s ability to gain biomedical research opportunities in all eight network institutions [University of Rhode Island, Brown University, Bryant University, Providence College, Rhode Island College, Salve Regina University, Roger Williams University, the Community College of Rhode Island].2 The latest in the IDEA category is Advance-CTR, which was awarded in 2016 to focus on the clinical and translational research program in collaboration with Brown University, the University of Rhode Island, and the area’s healthcare systems. The translational mission of Advance-CTR complements RI-INBRE’s biomedical focus, and together these comprehensive capacity-building programs have made outstanding contributions. Through funding, research resources trigger discoveries, improve health in the State and provides networking opportunities among researchers. For example, RI-INBRE’s annual Summer Undergraduate Research Fellowship (SURF) conference is the largest of its kind in the State, featuring next-generation biomedical scientists. The Advance-CTR organizes the annual RI-IDEA Symposium that brings together investigators in the State to collaborate on IDEA-funded projects. Recently, RI-INBRE hosted a virtual seminar series, which highlighted RI-IDEA programs and recognized their impact in improving RI’s biomedical research capacity. These IDEA programs have been truly transformative in building a vibrant community of biomedical and translational researchers. Faculty, students, and support staff at the various universities are now routinely networking and collaborating on their research projects. This is a seismic culture change in the academic research community, especially at the primarily undergraduate institutions.

Economic impact in RI
The economic impact of the IDEA support for the State is enormous. In 2020, RI received a total of 16 IDEA awards comprising RI-INBRE, IDEA-CTR, 12 COBRE, 2 IDEA Co-funding and INBRE-COBRE Collaborative Supplement, amounting to $32M (7.4% of the total IDEA funding) Additionally, RI is a leading site in the ECHO3 [Environmental Influences on Child Health Outcomes] and ISPCTN4 [IDEA State Pediatric Trials Network], a major NIH initiative to investigate the impact of environmental exposures on children’s health and development, and to provide underserved and rural populations the opportunity to participate in high quality clinical trials.

In 2020, RI held the most COBRE grants among the IDEA states. It is worth noting that a significant portion of the
Idea funding is used to support research and related capacities, demonstrating its real impact, fueling discoveries, networking, and collaborations among institutions. For example, RI-INBRE (2001–2020) and Advance-CTR (2016–2020) have spent approximately 80% of their total funding directly on investigator-initiated research projects, student training, and associated core facilities. A similar impact is seen in COBRE grants. An additional example – during its entire grant period (2013–2020) the CardioPulmonary Vasculat Physiology center of Biomedical Research excellence (CPVB CoBRE) spent approximately 85% of its funding on research pilot projects, junior investigator projects and core facilities. In addition, the Idea programs over the years have supported research and administrative staff and undergraduate and graduate student training, directly contributing to the State’s workforce and economy.

Biomedical Idea programs

We requested each of the Idea directors to provide a program description. In this Journal issue, we present contributions from ‘basic science’ biomedical research-oriented Idea programs in RI. Christopher Hemme, PhD, et al., describe the impact of RI-INBRE’s capacity-building efforts in RI. Benjamin D. Greenberg, MD, PhD, et al., discuss their new COBRE Center for Neuromodulation. Alan L. Rothman, MD, et al., highlight the significant impact of their Phase I COBRE in translational infectious diseases immunology. Neill Y. Li, MD, and coworkers review the current understanding of how aging affects peripheral nerve regeneration following injury. Surendra Sharma, MD, PhD, explains the arduous research journey from preeclampsia to Alzheimer’s disease. Sharon Rounds, MD, et al., describe the capacity-building efforts in vascular biology in RI. David M. Rand, PhD, and Ashok Ravendran, PhD, provide a program update on the COBRE Center for the Computational Biology of Human Disease at Brown University and affiliated hospitals.

In the subsequent April issue of the Journal, we will include the contributions from ‘clinical’ and ‘translational’ programs. Our goals are to make the clinical, biomedical, and scientific research community aware of the extraordinary resources that have been made available through these programs. We are blessed with this endowment of resources that have significantly enhanced biomedical enterprise in Rhode Island.

Table 1. Recent Idea (Institutional Development Awards) Programs in Rhode Island

<table>
<thead>
<tr>
<th>Name</th>
<th>Principal Investigator</th>
<th>Organization</th>
<th>Topic</th>
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<tr>
<td>COBRE Center for Addiction and Disease Risk Exacerbation (CADRE)</td>
<td>Peter M. Monti, PhD</td>
<td>Brown University</td>
<td>Addiction</td>
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<tr>
<td>COBRE Center for Central Nervous System Function (CCNSF)</td>
<td>Jerome N. Sanes, PhD</td>
<td>Brown University</td>
<td>Neuroscience</td>
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<td>COBRE Center for Computational Biology of Human Disease (CCBHD)</td>
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<td>Brown University</td>
<td>Computational Biology</td>
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<tr>
<td>COBRE Center for Neuromodulation (CCN)</td>
<td>Benjamin D. Greenberg, MD, PhD</td>
<td>Butler Hospital</td>
<td>Neuroscience</td>
</tr>
<tr>
<td>COBRE Center for Antimicrobial Resistance and Therapeutic Discovery (CARTD)</td>
<td>Eleftherios Mylonakis, MD</td>
<td>Miriam Hospital</td>
<td>Infectious Disease</td>
</tr>
<tr>
<td>CardioPulmonary Vascular Biology COBRE (CPVB)</td>
<td>Sharon Irene Rounds, MD; Elizabeth Harrington, PhD</td>
<td>Ocean State Research Institute, Inc.</td>
<td>Pulmonary Cardiovascular</td>
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<tr>
<td>COBRE Stem Cells and Aging</td>
<td>Peter J. Quesenberry, MD</td>
<td>Rhode Island Hospital</td>
<td>Stem Cells and Aging</td>
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<td>COBRE Center on Opioids and Overdose</td>
<td>Josiah D. Rich, MD, MPH</td>
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<td>Opioids, Overdose</td>
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<td>Surendra Sharma, MD, PhD</td>
<td>Women and Infants Hospital</td>
<td>Reproductive Health</td>
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<td>Rhode Island Idea Network of Biomedical Research Excellence (RI-INBRE)</td>
<td>Bongsup P. Cho, PhD</td>
<td>University of Rhode Island</td>
<td>Cancer, Environmental Health Sciences, and Neuroscience</td>
</tr>
<tr>
<td>Center for Clinical and Translational Science (Advance-CTR)</td>
<td>James F. Padbury, MD</td>
<td>Brown University</td>
<td>Clinical Translational</td>
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<td>COBRE Center for Cancer Research Development (CCRD)</td>
<td>Bharat Ramratnam, MD</td>
<td>Rhode Island Hospital</td>
<td>Cancer</td>
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<td>COBRE for Perinatal Biology</td>
<td>Sunil K. Shaw, PhD</td>
<td>Women and Infants Hospital</td>
<td>Perinatal Biology</td>
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<tr>
<td>COBRE Center for Immune-based Interventions Against Infectious Diseases</td>
<td>Alan L. Rothman, MD</td>
<td>University of Rhode Island</td>
<td>Infectious Disease</td>
</tr>
<tr>
<td>IdeaA States Pediatric Clinical Trials Network (ISPCTN)</td>
<td>Phyllis Dennery, MD; Abbot Laptook, MD; Thomas Chun, MD, MPH</td>
<td>Rhode Island Hospital</td>
<td>Pediatric</td>
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<tr>
<td>COBRE for Skeletal Health and Repair</td>
<td>Qian Chen, PhD</td>
<td>Rhode Island Hospital</td>
<td>Musculoskeletal</td>
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   pediatric-clinical-trials-network

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RI-INBRE: A Statewide NIH Program Grant to Improve Institutional Biomedical Research Capacity in Rhode Island

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ABSTRACT
The overarching goal of the Rhode Island IDEA Network of Biomedical Research Excellence (RI-INBRE) is to improve institutional capacity for biomedical research excellence and expand student experiential training opportunities in the State of Rhode Island. RI-INBRE comprises five major core components: The Administrative Core, the Bioinformatics Core, the Centralized Research Core Facility, the Training Core, and the Developmental Research Project Program Core. Since its inception in 2001, RI-INBRE has made significant investments and marked advancements in the biomedical research infrastructure of Rhode Island. RI-INBRE funding has increased the scale and quality of faculty research and engaged undergraduate students, graduate students, and postdoctoral fellows in structured and mentored research training experiences. Over the last 19 years, RI-INBRE has supported 212 faculty researchers and over 533 projects and has provided research-training opportunities for nearly 2,000 students, resulting in 757 publications. Through its student-training program, RI-INBRE has contributed to regional workforce development by engaging students and encouraging them to pursue careers in biomedical fields. Many of these students have been admitted to graduate or medical schools and obtained biomedical industry jobs following graduation. RI-INBRE has been particularly influential in building the research infrastructure at primarily undergraduate institutions, which have seen significant improvements in research quality and output, student training, and research infrastructure.

KEYWORDS: biomedical research capacity, cancer, neuroscience, environmental health sciences

INTRODUCTION
The Institutional Development Award (IDEA) is a congressionally-mandated program administered by the National Institute of General Medical Sciences (NIGMS) of the National Institutes of Health (NIH). The IDEA Network of Biomedical Research Excellence (INBRE) program is designed to foster the development, coordination, and sharing of research resources and expertise, and to increase the number of competitive investigators in states where NIH research funding levels have historically been low. While most institutions are eligible to participate in INBRE, an additional emphasis is on institutions such as primarily undergraduate institutions (PUs) that typically lack the resources and research infrastructure of larger public and private institutions. The goals of RI-INBRE include 1) financial support of early career scientists to help them achieve sustainable research programs, 2) provide resources to network institutions to increase research infrastructure through facilities upgrades and the hiring of research support staff, 3) to train undergraduate and graduate students and postdoctoral researchers with the goal of encouraging them to apply to graduate or medical school and/or find jobs in the biomedical sector, and 4) to enhance the local state and regional economies by providing a trained workforce in biomedical sciences.

The RI Biomedical Research Infrastructure Network (RI-BRIN) program began in 2001 and was replaced by RI-INBRE in 2004. The network includes the University of Rhode Island (URI), Brown University, associated local hospitals, and the Rhode Island (RI) PUs: Bryant University, Providence College, Rhode Island College (RIC), Roger Williams University, Salve Regina University, and most recently the Community College of Rhode Island (CCRI). The funds allocated to these institutions support hiring of new biomedical faculty who can devote time to research, which has led to an increase in undergraduate student researchers and research productivity. In 2008 RI-INBRE began the Summer Undergraduate Research Fellowship (SURF) program to fund summer undergraduate research opportunities at the network institutions and local hospitals. This program has grown significantly in the years since and now constitutes an important training component of the RI-INBRE program.

STRUCTURE
RI-INBRE is organized around several cores. The Administrative Core manages the administrative and financial aspects of the grant and is led by Program Director Bongsup Cho and Program Coordinator Niall G. Howlett and supported by Program Assistant Laura Arrighi and Program Business Manager Laura Bellavia. The major goals are to manage the functions of the External Advisory Committee
biOMEdiCAL/TRANSLATiONAL RESEARCh iN Ri – PART 1

The Developmental Research Project Program (DRPP or Research core) led by Program Coordinator Niall G. Howlett develops, solicits, and awards developmental research project funding to investigators at RI-INBRE network institutions (Figure 1A). The current scientific focus areas of RI-INBRE are cancer, neuroscience, and environmental health sciences. Research areas funded under these focus areas are broad and inclusive and include biochemistry and molecular biology, biomedical engineering, toxicology and natural products, psychology, neurodegenerative diseases, and environmental health sciences. A variety of support mechanisms are available to researchers depending on their career stage and specific needs. The primary funding mechanism of the Research Core is the Early Career Development (ECD) award. This is a 2–3-year award designed to support research program development of early career investigators at URI, Brown University, and the RI PUIs. ECD-supported investigators choose an experienced senior investigator to guide them in all aspects of research and professional career development over the course of the funding period. RI-INBRE also promotes innovative collaboration between well-established senior faculty at URI and Brown University and junior faculty at PUIs through the Collaborative Research (CR) award. This is a 2-year award that provides funding to both the junior and senior investigators. By partnering established investigators with junior PUI investigators, we aim to enhance the level of mentorship, thereby facilitating and accelerating research productivity and increasing the level of preparedness of the PUI investigators for submitting competitive independent or collaborative research proposals, e.g. NIH R15 or NSF RUI/ROA applications. The Research Core also supports pilot awards and summer undergraduate research fellowship (SURF) awards to faculty at the PUIs. Recent additions to the Research Core portfolio of funding opportunities include the Enhanced Virtual Education, RESearch, and Training (EVEREST) award to promote novel virtual/remote tools for education, research, and training, and Bioinformatics Pilot Project (BPP) vouchers to fund small-scale next-generation sequencing projects. Together, these mechanisms have supported over 500 faculty projects and led to a significant increase in research productivity as measured by scientific talks, poster presentations and publications (Figure 1B).

The goal of the Training Core, led by Dr. Samantha Meenach, is to establish a robust biomedical workforce pipeline in RI by providing research training opportunities for students, postdoctoral researchers, and occasionally faculty (Figure 2). The SURF program is the major component of this core and involves pairing undergraduate researchers with faculty mentors at URI, Brown University, and the PUIs to conduct research projects during the summer months. Students undergo training in research standards, lab safety, data handling, and other professional development topics. The program ends with a SURF conference where the students are given the opportunity to present their research to the community in a public poster session. The annual SURF conference is the largest of its kind in the state and draws approximately 400 attendees. Additional programs administered by the Training Core include the Bridges to Graduate School Program, which encourages RI-INBRE undergraduates to attend graduate school in RI, CCR Summer Research Sabbatical Program, which places CCR faculty in established labs at URI or Brown, giving them the opportunity to learn new skills to take back to their campus, and Teaching Postdoctoral Fellowships (TPF) Program. The latter is a partnership between RI-INBRE and the PUIs designed to advance the teaching and research mission of the PUIs, and to help train the next generation of teacher-scholars. Nearly 2000 students have been trained in the 19 years of the RI-INBRE program and student research productivity has increased in kind as measured by the growth in the number of student coauthors on manuscripts (Figure 2B).
RI-INBRE also funds two core facilities to provide research services and support to the RI-INBRE and the state’s biomedical community. The **Centralized Research Core Facility (CRCF)** based at the URI College of Pharmacy provides a central location for over $4 million of instrumentation, including microscopes, centrifuges, cell culturing, chromatography, and mass spectrometry. The CRCF is managed by Dr. Al Bach and Kim Andrews and provides training services free to RI-INBRE investigators and at subsidized rates to all other investigators. This facility is the only one of its kind in RI and is often cited by junior faculty as a significant resource in helping them establish and develop their laboratories. The **Bioinformatics Core** led by Dr. Christopher Hemme provides services and training in 1) bioinformatics and data science, 2) molecular modeling and other 3D science visualization tools such as 3D animation and projection, and 3) virtual and augmented reality applications.

**DATA AND IMPACTS**

From 2001 to 2024, RI-INBRE will have distributed $81 million dollars in research and training funding. As of 2020, this has supported 212 faculty researchers over 533 projects and the training of 1975 students. The research funded by the program has resulted in 757 publications with 176 undergraduate co-authors. RI-INBRE funding has been quite impactful in facilitating faculty research. For example, from 2001–2021, RI-INBRE spent 76% of its annual budget to support investigator-initiated research projects ($54M) [Figure 3]. Through 2024, this number is expected to rise to $63M. RI-INBRE’s impact is most dramatic at PUIs in terms of resources and research culture change. For example, RI-INBRE has provided Rhode Island College with over $10.0M in grants and equipment support since 2001. In 2001, faculty research and student training were not recognized as a requirement for achieving tenure and promotion at RIC and federal research funding, especially that provided by NIH, was rare. RIC faculty are currently securing ~$10M per year in external funding. In addition, hundreds of students are now participating in experiential research training during the academic year and summers. RI-INBRE funding has also contributed to facilities and infrastructure upgrades at PUI network institutions. Many of the faculty funded by RI-INBRE have graduated from the program by achieving research independence, often by being awarded NIH R01 and R15 and NSF RUI awards. Given the length of the RI-INBRE program, some former student researchers who are now independent scientists in RI have returned to the program as grant reviewers and research mentors for the next generation of student researchers.

Workforce development is a key goal of the RI-INBRE program. To assess the impact on the state and regional workforce, RI-INBRE staff have attempted to track students for at least five years to assess their career paths, whether they attended graduate or medical school, and whether they remained in the Northeast. Given the length of time the program has run and the large number of students, collecting and processing accurate data is a significant challenge. However, the data collected suggests a strong positive impact of the program on student career developments. Based on the sample of students we were able to track, >70% of

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**Figure 2. A)** Number and type of students supported by RI-INBRE per grant period. **B)** Number of students co-authors listed on RI-INBRE publications per grant period.

**Figure 3.** Monetary support of RI-INBRE network institutions by grant period.
undergraduate students who participated in the program are currently employed in the broader biomedical sector in the greater New England area (Figure 3). These jobs tend towards the pharmaceutical industry, but include biomedical engineering, chemistry, academic positions, entrepreneurs, and medical jobs (clinicians, nursing, pharmacy, etc.). Upon graduation, most students remained in Massachusetts, Rhode Island, and Connecticut. While most students ended their education with undergraduate (bachelor’s or associate) degrees, data suggests ~25% of former RI-INBRE undergraduates went on to earn at least one graduate (masters or PhD) or medical degree. One indication of the improvement of research infrastructure at the PUIs is that many of these students were admitted to prestigious research programs around the country. All indications are that the program has been enormously successful at stimulating student interest in careers in the biomedical sciences and the retention of those students in Rhode Island and the Northeast.

PARTNERSHIPS
Collaboration between IDEA programs and networks is strongly encouraged by the NIH. Five states make up the Northeast IDEA region: Rhode Island, Maine, Vermont, New Hampshire, and Delaware. The Northeast INBRE programs frequently communicate to exchange ideas and determine best practices. Part of this effort includes the Northeast Bioinformatics Collaborative (NEBC), a collaboration between the five Northeast INBRE bioinformatics cores. This collaboration has included such efforts as the Northeast Cyberinfrastructure Consortium to enhance cyberinfrastructure for researchers in the Northeast and coordinated efforts at training through the Maine-New Hampshire Train-the-Trainer workshop, to train students and researchers in bioinformatics and data analysis skills. The NH-INBRE and DE-INBRE programs have been cooperating with RI-INBRE to provide sequencing services for the Bioinformatics Pilot Projects. To complement the mass spectrometry resources provided by RI-INBRE, the CRCF cooperates with the Oklahoma and Arkansas INBRE programs, both of which manage strong proteomics programs. In August 2021, RI-INBRE will host the biennial NorthEast Regional IDEA Conference (NERIC), bringing together all IDEA programs in the Northeast region to present research results, network, and build collaborations. Finally, many of the existing INBRE programs regularly cooperate on this issue of administrative data gathering and management for reporting and metrics tracking. Many of these programs utilize the PieStar software to manage reporting and eventually analysis of legacy data used to judge the effectiveness of the programs.

In addition to RI-INBRE, Rhode Island currently has 12 COBRE programs and an Advance-CTR program. Regular communication is maintained to identify synergistic activities between programs. The multiple core facilities periodically gather to discuss cooperative opportunities and needs of the RI IDEA programs. The Bioinformatics Core has individually cooperated with the Advance-CTR Brown Center for Biomedical Informatics (BCBI) and the COBRE Brown Center for Computational Biology of Human Disease (CBHD) on a variety of efforts. These efforts have included inviting speakers to URI from the BCBI, a metagenomics workshop with the CBHD, and the Rhode Island Microbiome Symposium 2020 with CBHD. The symposium was an effort to bring together both environmental and clinical microbiome researchers from around RI and New England to discuss microbiome-related research. Over 100 researchers attended the conference and a follow-up conference will be organized once the COVID-19 pandemic has passed. This past summer, RI-INBRE organized a weekly virtual seminar series that involved the 12 IDEA program directors in RI. The series highlighted the state’s capacity building and training programs and recognized the directors’ valuable contributions in improving RI’s biomedical research capacity. This virtual event was the first of its kind in RI and provided the state’s biomedical community with great networking opportunities.

RI-INBRE has also established cooperative efforts with non-IDEA programs. Traditionally, the RI-INBRE SURF program collaborates with the NSF EPSCoR C-AIM to hold a single SURF conference at the end of each summer where all SURF participants are given the opportunity to present their research to the community. This year the RI-INBRE SURF program welcomed Maximizing Access to Research Careers (MARC) Undergraduate Student Training in Academic Research (U-STAR) program trainees to participate in professional development and research training activities and to present their data at the annual SURF symposium. The MARC U-STAR program is a research and professional development program supported by NIGMS for undergraduate students from underrepresented backgrounds. To promote entrepreneurship and intellectual property development by RI-INBRE researchers, RI-INBRE collaborates with the NIH-funded Northeast DRIVEN Acceleration Hub and RI Bio life sciences industry group to share best practices and provide workshops, webinars, forums, and resources to the RI’s innovative and entrepreneurial community.

FUTURE EFFORTS
The RI-INBRE program has undergone significant changes since its inception 20 years ago and has had a truly transformative effect on RI’s biomedical research community. The program has inspired a culture change among researchers, especially at the PUIs, launching and supporting the independent careers of multiple faculty and promoting new collaborations across all the RI colleges and universities. The two goals of student training and junior scientist support will
remain priorities in the future. We will continue to adapt and innovate moving forward. The RI-INBRE program is also committed to promoting a diverse, equitable, and inclusive biomedical research culture across the state of Rhode Island. The program actively supports and promotes the hiring of both faculty and postdoctoral research fellows from diverse/unrepresented backgrounds at the RI PUIs and will continue to support and lead statewide efforts to diversify the biomedical and scientific workforce. A centralized data reporting and tracking system will simplify annual reporting and metrics tracking and will provide an accurate assessment of trends within the RI-INBRE program and between INBRE and other IDeA programs. New initiatives such as the EVEREST and BPP funding mechanisms will expand the scope of existing research funding mechanisms allowing the maximum number of faculty to participate and stimulating new ways to train the next generation of biomedical researchers. The program will continue to recruit quality students and engage them in research activities while encouraging them to pursue biomedical careers following graduation. Ultimately, these activities will continue to greatly enhance the biomedical infrastructure of Rhode Island, meeting the primary goal of the IDeA INBRE mechanism.

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The COBRE Center for Neuromodulation (CCN) at Butler Hospital: Clinical-Translational Research in Human Brain Stimulation

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ABSTRACT
The COBRE Center for Neuromodulation (CCN) at Butler Hospital supports clinical research in neuromodulation and investigators’ career development in this field. The work couples brain stimulation methods with readouts of brain activity (e.g., using various neuroimaging, behavioral, and physiological assessment methods) in clinical or clinically relevant populations. Its guiding principle is that for noninvasive brain stimulation to gain efficacy and implementation, it is essential to better characterize clinically relevant target circuits and mechanisms of action. The CCN includes a Design and Analysis Core (DAC) to support rigorous and innovative experimental design and data analytic strategies and a Neuromodulation and Neuroimaging Core (NNC) to facilitate the acquisition and processing of high-quality data using noninvasive neurostimulation and neuroimaging methods. This article will describe the CCN’s research focus and how it enhances research capacity in neuromodulation in our state. It will introduce our current investigator Project leaders, their projects, and our pilot project program. It will also detail the CCN’s links to Centers and research cores in Rhode Island researching allied areas of clinical neuroscience, neurology, psychiatry, and psychology, current collaborative efforts across those centers, and opportunities to collaborate in research and training.

KEYWORDS: neuromodulation, TMS, tTDS, neuroimaging, neuronavigation

INTRODUCTION
To quote this issue’s Introduction, “the impact of behavioral and mental health problems on the overall health of individuals and populations has become increasingly recognized” (Padbury and Cho). Neuromodulation is typically used in combination with pharmacotherapies and psychotherapies to address the burdens mental illness [and other brain disorders] impose on individuals, families, and population health. Here, we use CCN members’ work to illustrate important aspects of the therapeutic and research contexts of neuromodulation. And we highlight the new infrastructure and resources that the CCN has made available to enhance work in this promising area, and to help train and support the new generation of neuromodulation researchers in Rhode Island.

“Neuromodulation” might be any method modifying the nervous system. So, medications, devices, psychotherapies, mind-body approaches, and more might qualify. The term, however, has a narrower definition: device-based methods affecting the CNS. Typically, devices emit energy (e.g. electrical, magnetic, ultrasonic) to modify brain activity directly or via peripheral nervous system components. This definition of neuromodulation dovetails with the use of brain networks as a fundamental unit of analysis in understanding brain-behavior relationships in health and disease. A network can be thought of as a collection of nodes that are structurally and functionally related. This, in turn, lends itself to translational research involving an exchange between cognitive and affective neuroscience and clinical disciplines. Models of illness pathophysiology envision dysfunction at multiple levels: within regions, within networks, and in the smooth flow of information across networks. For an example of how brain functional architecture might relate to illness symptoms [in this case of post-traumatic stress disorder, PTSD], see Barredo et al.1 Regarding how neuromodulation might be understood to act at the level of brain networks in PTSD and major depression, see Philip et al.2

Another translational aspect of neuromodulation is using clinically relevant affective or cognitive processes as the basis for research [complementing the focus on anatomical networks]. Examples include studies by CCN Project Leaders, e.g., by Nicole McLaughlin on response inhibition in obsessive-compulsive disorder3, or Mascha van’t Wout-Frank and colleagues on affective elements in decision-making.4 The abilities to flexibly inhibit responses, or to incorporate the experience into decision-making, are essential to adaptive behavior in health or illness. Another example is using brain stimulation to augment extinction of conditioned fear, thought to underlie therapeutic change in PTSD.5 These studies represent essential steps guiding development of brain stimulation methods for eventual clinical use, and will generate results that advance fundamental knowledge in cognitive and affective neuroscience.

Neuromodulation is seeing the application of increasingly powerful tools, both in the array of devices used and their combination with neuroimaging, electrophysiology, and computational modeling to understand impacts of
stimulation on brain and behavior. Mechanistic insights, in turn, guide research refinement, with each next step addressing goals and hypotheses relevant to health and therapeutics. These include identifying specific brain regions, circuits, or oscillatory signals to be engaged and modulated; establishing efficacy and safety of a neuromodulatory treatment at a group level; selecting specific stimulation methods for individuals most likely to benefit; tailoring neuromodulation to optimize effects in each participant or patient; and developing technologies and implementation steps required for widespread dissemination of a new treatment to meet the large and manifest clinical need. This research can exemplify multiple stages along the translational research continuum, and its success requires an ongoing interplay between clinicians, clinical researchers, basic and cognitive neuroscientists, and biomedical engineers.

Devices used can be invasive (implanted) or noninvasive. An example of the former is deep brain stimulation, currently used clinically in Parkinson’s disease, essential tremor, dystonia, and obsessive-compulsive disorder (OCD; see Greenberg, et al. for the latter). The CCN’s focus, in contrast, is noninvasive methods. The best-known noninvasive therapy is transcranial magnetic stimulation (TMS, also ‘repetitive TMS’), a standard-of-care treatment for severe major depressive disorder (MDD). The other non-invasive method we will describe here, which thus far has not gained regulatory approval for clinical treatment, is transcranial direct current stimulation (tDCS).

**TRANSCRANIAL MAGNETIC STIMULATION**

Here, a pulsed magnetic field delivered through the scalp and skull stimulates relatively superficial brain. The magnetic flux generates electrical activity in the cerebral cortex, producing both local and, via networks, distant effects. TMS is “supra-threshold,” meaning that enough energy is delivered to induce action potentials in target neurons. TMS research in MDD began in the early 1990s, with subsequent development through extensive clinical trials. Results converged on the effectiveness of TMS. In practice, patients come to the clinic for repeated TMS therapy sessions, delivered in each session as brief “trains” of pulses with rest between trains. Typically these are once per weekday for up to six weeks, often followed by several weeks during which TMS is tapered. See Carpenter et al. for an example of research on clinical effectiveness and also a recent update on TMS in depression.

During each session, a patient receives many TMS pulses over a defined region, usually left or right dorsolateral prefrontal cortex. Researchers continue to develop new devices, one of many examples being a device using a multiple electromagnetic coil array instead of the single-coil design of all currently approved devices. Novel approaches for selecting stimulation parameters and new methods for identifying the best brain targets are under investigation, many informed by electroencephalography and neuroimaging findings generated by senior CCN researchers. TMS treatment protocols have shown preliminary clinical efficacy for numerous neuropsychiatric and behavioral disorders; randomized clinical trials recently led to the US FDA approvals for TMS to treat OCD and for smoking cessation. TMS is increasingly available across healthcare systems in the United States and elsewhere.

In Rhode Island, there are active neuromodulation clinical programs (or TMS clinics) at Butler Hospital, the Providence VA Medical Center, and Rhode Island Hospital, with several others in private-practice settings. Despite increasing public awareness that TMS therapy is an option for patients who do not achieve adequate benefit with more traditional depression treatments, it has remained underutilized since its 2008 FDA approval. The substantial time commitment required may be one reason for slow uptake. Recent research has led to the approval of a novel stimulation pattern, intermittent “theta-burst” TMS, which can be delivered in the clinic much more rapidly than “traditional” TMS (2-3 minutes rather than 20-30 minutes per session). Research applying the theta burst TMS method to other conditions, like PTSD, has generated substantial interest.

**TRANSCRANIAL DIRECT CURRENT STIMULATION (tDCS)**

tDCS involves low-energy electrical current, following the principle that applying current to the skin generates an electrical field. Although there are commercially available devices for transcranial electrical stimulation (largely marketed directly to consumers), here, we restrict ourselves to tDCS, which delivers a constant (“direct”) current waveform. See Philip et al. for a comprehensive review of tDCS and related methods. Devices deliver a predefined intensity of electric current of several milliamperes, using a variety of electrode arrays for current “focusing.” For example, a single anode typically using multiple smaller cathodes around a single anode [or vice versa], for more focal tDCS. While the skin and skull are transparent to the magnetic pulses delivered by TMS, there is resistance to energy flow between electrodes during tDCS. The electrical fields used in tDCS are considered subthreshold, i.e., stimulation at the intensities used does not independently cause neuronal depolarization. Rather, it is thought to bias neurons’ activity to influence the ongoing flow of information in a pathway. The factors involved are complex, but the basic point is that even a small tDCS-induced change in membrane voltage may impact activity. An example is a pilot study by CCN investigators who evaluated tDCS concurrently with psychotherapy in depression. Most tDCS devices are relatively inexpensive, have a good safety profile, and can be deployed either in a clinical research laboratory or in a nonresearch
environment; recently tDCS devices have been designed for self-administration at home, with remote "supervision" functions to support investigation of their effects in randomized controlled trials comparing active or sham stimulation.

THE COBRE CENTER FOR NEUROMODULATION (CCN) AT BUTLER HOSPITAL

The CCN [https://www.butler.org/services/cobre/] was established in 2019 as part of the NIH-NIGMS-funded IDEa [Institutional Development Award] program. CCN has a primary focus on device-based neuromodulation, and particularly that using noninvasive methods. A guiding principle of our Center is that for neuromodulation methods to gain acceptance and implementation by the clinical community, it is necessary to understand their mechanisms of action (requiring clinical-translational research) and their therapeutic efficacy (the domain of clinical trials). That, in turn, opens an interplay between our understanding of mechanisms underlying impairments in mental health or neuropsychiatric conditions more broadly. These can either be understood as traditional diagnostic categories (a categorical diagnosis requires that an individual “meets criteria” for an illness; the person either has it or not) or be based on a dimensional view of maladaptive behavior. In the latter view, clinically significant problems emerge when actions that occur along a continuum in the general population are expressed with problematic severity or frequency.

Our Center’s components is overseen by the CCN Administrative Core, aided by three advisory committees. One of these committees’ overall work is based at the home institution, Butler Hospital. Its members are leaders in various hospital departments required to facilitate and support core operations of the CCN; the second committee also includes representatives of local research institutions, and finally, an External Advisory Committee composed of leading national experts in neuromodulation research. The CCN Administrative Core works closely with our program partners in the state.

CCN is a “Phase 1” COBRE, built around multiyear projects in human neuromodulation, each led by a Project Leader developing a research career. Currently, there are four Project Leaders, each advised by mentors providing scientific, technical, and career guidance. The projects and leaders are: 1) Brain Circuitry of inhibitory control in young adults: Modulation with tDCS, Nicole C. McLaughlin, PhD; 2) Effects of tDCS timing on safety memory in PTSD, Mascha van’t Wout-Frank, PhD; 3) Modulating prefrontal circuits underlying behavioral flexibility in OCD: a TMS study, Sarah Garnaat, PhD; and 4) Determining whether TMS changes the brain through brain synaptic plasticity, Joshua Brown, MD, PhD.

The projects are supported and facilitated by two CCN research cores. The cores are also designed to serve a separate Pilot Project Program, which allows faculty researchers at Rhode Island institutions to collect preliminary data in clinically relevant neuromodulation studies to support external grant proposals. The Design and Analysis Core (DAC; Director Richard Jones, PhD; Co-Director Jennifer Barredo, PhD), as its name implies, supports the experimental design, data processing methods, and general statistical aspects appropriate to human subject’s research. Given that understanding possible mechanisms underlying effects of neurostimulation on the brain and behavior is central to the mission of CCN, this core also specifically addresses needs particular to neuroimaging and neurophysiology research (e.g., fMRI, brain connectivity or evoked responses measured with EEG or electromyography). A new high-capacity CCN computing center at Butler Hospital houses dedicated workstations for MRI and for EEG analyses with internet access, software, external storage devices, and direct connection to a dedicated data storage server.

The aspects of “hands-on” brain stimulation training and data acquisition are the Neuromodulation and Neuroimaging Core [NNC, Director, Linda Carpenter, MD, Co-Director, Noah Philip, MD]. The NNC hosts an array of TMS equipment, including several different devices and “neuro-navigation” platforms that permit stimulation to particular brain regions with an individual’s MRI. There are TMS coils for both active and sham stimulation to permit controlled studies. The TMS coils themselves have different designs producing different magnetic field shapes for stimulating brain regions that differ in location and extent, and the TMS stimulators have various features as needed for the application of theta-burst stimulation or electrophysiological studies of cortical excitability; the latter is used in combination with pharmacological probes to investigate plasticity mechanisms of TMS action [see Brown et al.12,13] Similarly, there are multiple tDCS devices available in the core, allowing investigators to select different electric field geometries as needed for their research purposes. There are also computational modeling platforms available via the NNC, which use neuroimaging and/or brain models to design the optimal montage for the desired stimulation effect with either TMS or tDCS; such models ensure the resulting electrical current will engage particular brain targets with a degree of selectivity. The NNC also supports EEG recording with several research-grade electrophysiology platforms, with additional modules and accessories to permit collection of other psychophysiological data (e.g., cardiac data, galvanic skin response, and other physiological responses). Both the NNC and DAC work closely with the Brown MRI Research Facility to support the collection of high-quality neuroimaging data in concert with neuromodulation procedures.

It is to our great advantage that senior researchers at CCN also lead active neuromodulation clinical programs in Rhode Island, the TMS Clinic at Butler Hospital, directed by one of the authors [Carpenter], and the Neuromodulation Clinic at the Providence VA Medical Center, led by another
The NNC is, in fact, adjacent to the space used by the Butler TMS Clinic. This has allowed it to draw upon and utilize additional clinically trained staff support and other resources from Butler’s TMS clinical service. Researchers in the core facility at Butler thereby have immediate access to the infrastructure of the TMS Clinic and other clinical service resources including a pool of physicians, technicians, and a nurse trained in TMS and other neuromodulation techniques, access to medical equipment, emergency response teams, and physician supervision for management of potential adverse events as well to address any clinical issues that may arise in the patient populations under study. This arrangement allows our Center and the NNC specifically to be an essential resource for the safety and success of projects involving clinical samples, particularly in cases where the principal investigator is not medically trained and/or does not have access to neurostimulation-trained physicians on his or her research team. The two research cores collectively host training in brain stimulation and neuroimaging methods, including the safe and experimentally rigorous use of brain stimulation devices, MRI, EEG, data acquisition, data management, quality control and analytic methods. CCN’s cores have worked hard during the COVID-19 pandemic to implement procedures ensuring safe research in this evolving environment, a complex and ongoing task involving multiple institutions and facilities, and IRBs. Our personnel’s dedication has enabled research protocols to be adapted flexibly as needed, and to be restarted as soon as possible after a pandemic-imposed pause. We share tremendous optimism regarding our Center’s capacity to enhance research in this exciting and rapidly developing field, and welcome interest and engagement by the research community.

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Immune-Based Interventions Against Infectious Disease – Impact of a Phase I Center for Biomedical Research Excellence in Translational Infectious Diseases Immunology

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ABSTRACT
In 2011, faculty from the University of Rhode Island [URI]’s Institute for Immunology and Informatics and Lifespan’s Center for International Health Research collaborated to develop a successful application for a Phase I Center of Biomedical Research Excellence around the scientific theme of translational infectious diseases immunology. From 2013 to 2020, this COBRE supported significant discoveries in research on dengue, HIV, and malaria, among other diseases, and facilitated the career development of several independent Rhode Island [RI]-based early-stage investigators. Our experience illustrates both the potential and challenges for investigators with shared scientific interests to leverage the NIH COBRE program to enhance cross-institutional interactions.

KEYWORDS: immunology, infectious diseases, global health, translational research, host-pathogen interactions

INTRODUCTION
Research on infectious diseases is essential both in the U.S. and globally. Well-known infectious diseases continue to cause significant morbidity and mortality, and new and re-emerging infectious disease threats are being increasingly recognized, most recently exemplified by the COVID-19 pandemic.1,2 The diversity of human pathogens requires a broad research strategy, including efforts to utilize or enhance innate and adaptive immune mechanisms for preventive strategies and as broad-spectrum therapeutics. There is also increasing attention to the need to modernize the structure and organization of scientific investigation.

The University of Rhode Island [URI], the state’s primary public research university, lacks a medical school, and its infectious diseases research is divided among several colleges. In 2009, URI founded the Institute for Immunology and Informatics (iCubed) in the Biotechnology Center on the Providence campus, with a research mission in the immunology of human infectious diseases. Brown University has the state’s only medical school. Its infectious disease and immunology research is spread across multiple departments and programs within the medical school and its affiliated teaching hospitals. In 2005, Rhode Island Hospital founded the Center for International Health Research [CIHR], an interdepartmental center with a research mission on immunity to malaria and schistosomiasis. These two centers were thus both actively conducting NIH-funded translational infectious diseases immunology research in downtown Providence. At the same time, both groups faced challenges associated with a small size and distinct mission, particularly limited resources to expand strategically into new research opportunities, provide career advancement for young scientists, and fund the purchase of advanced equipment.

The common scientific interests and philosophy and the proximity of iCubed and CIHR led us to institute a combined Journal Club/research-in-progress meeting and initiate discussions in 2011 regarding potential collaborative opportunities. The NIH Centers for Biomedical Research Excellence [COBRE] program provided an attractive solution. In contemplating a collaborative COBRE proposal, we defined two key priorities and objectives: a) achieving a “critical mass” of at least 8–10 full-time funded investigators with related scientific interests to make the groups competitive for institutional training grants and shared instrumentation grants; and b) creating a sustainable mechanism to promote career advancement of junior investigators and launch new research initiatives.

CONCEPT FOR THE PHASE I COBRE
In our COBRE Phase I application, “Immune-Based Interventions Against Infectious Diseases,” we outlined a vision to build an entrepreneurial, multidisciplinary, and trans-institutional research team to address infectious diseases of global importance. The COBRE proposed to catalyze the
partnership between the vital independent research programs in iCubed and CIHR around the unifying scientific theme of translational research in pathogen-host interactions (Figure 1).

This proposed COBRE’s significance and innovation lay in its intent to pursue transformational advances in infectious disease immunology research, bypassing traditional paradigms of departmental growth to address high-priority research objectives. Distinctions from existing research programs in RI included: 1) applied research, 2) a global health focus, 3) interdisciplinary research including both MDs and PhDs, and 4) an emphasis on collaboration, shared governance of common resources, and recognition of faculty teamwork.

URI/iCubed served as the primary grantee for the COBRE, with a substantial component at RI Hospital/CIHR (Figure 2). Leadership was provided by a senior Program Director, a Steering Committee of established URI and Lifespan faculty, and an External Advisory Committee of 5 senior NIH-funded MD and PhD investigators. Support was solicited from the broader RI community of infectious disease and immunology researchers; affiliated faculty members were asked to participate in conferences and seminars, and in turn, would have priority access to COBRE core facilities.

**Our Phase I COBRE proposed four Specific Aims:**

Aim 1 was to provide leadership to the RI research community in translational infectious diseases immunology. Visibility and identity for the COBRE would be established through support for conferences and pilot projects. These had already been accomplished on a smaller scale at iCubed, including through R13 and U19 grants. Support for conferences would include the established Vaccine Renaissance Conference, Journal Club, seminars, and an annual Research Retreat. The Pilot Projects program would support promising early-stage investigators and new interdisciplinary collaborations.

Aim 2 was to build infrastructure for immunology research. COBRE-supported scientific cores (Figure 2) were designed to provide COBRE investigators with the tools to generate and manage complex immunologic datasets. Our efforts focused on platforms with high-throughput capacity and multiparameter read-outs. The Cell Analysis and Sorting Core would provide immunoassay, flow cytometry, and cell sorting services focused on automation, throughput, and biosafety. The Core would leverage existing equipment (e.g., LSR II analyzer and AutoMACS) and would fund the purchase of a new Miltenyi MACSQuant Analyzer. The Core would focus on training and advising research staff and facilitating their use of the equipment. The Luminex High-Throughput Analysis Core would provide assays on an existing Luminex platform in a high-throughput mode. Under COBRE support, this equipment would be available for use by a more extensive cadre of researchers. Additional sample handling equipment would be acquired to increase assay capability. The Statistics and Data Management Core would support COBRE investigators in managing and analyzing these and other research data. The Core would assist COBRE investigators with managing complex datasets and performing sophisticated data analyses incorporating clinical predictors and outcomes collected in the field. The Core would also serve an educational role by providing both project-specific, tailored advice and broader education in epidemiology, data management, and biostatistics to facilitate communicating with collaborators, analyzing complex data, and writing grants.

Aim 3 was to recruit and mentor promising junior investigators. The strategic plan for the growth of the COBRE involved the direct investment in three junior investigators and new investigators’ recruitment. Mentoring of these individuals was critical to this plan. We proposed a detailed mentoring plan, including the designation of a primary mentor and co-mentor for each of the junior investigators. Milestones and timelines were defined, with plans for regular meetings and evaluations, to be reviewed by the Steering Committee and External Advisory Committee.

Aim 4 was to support translational infectious diseases immunology research by junior investigators. Our COBRE proposal identified three junior investigator-led projects that would build on established iCubed and CIHR research...
programs but introduce novel study populations or models and new research techniques [Figure 2]. “Autophagy Regulation of Innate and Adaptive Immunity in Dengue,” led by Dr. Carey Medin, focused on host cell responses to dengue virus [DENV]. This project proposed to analyze the induction of autophagy by DENV and its effects on innate immune signaling and activation of T lymphocytes by DENV-infected antigen-presenting cells. The significance of the project lay in the expanding global impact of dengue and the potential relevance of autophagy to dengue disease pathogenesis. Translational aspects of this project included the analysis of primary human cells and clinical isolates of DENV. “HIV Exposed-Uninfected Infant Immunity,” led by Dr. Barbara Payne, focused on the impact of in utero exposure to HIV on development of the immune system. This project proposed to compare the repertoire of T lymphocytes in HIV-uninfected infants born to HIV-infected or uninfected mothers and define the maternal characteristics that affect the development of the infant immune system and the effects of a narrowed T cell repertoire on subsequent immune responses to infant vaccinations. The significance of the project lay in the increased risk for morbidity and mortality in infants of HIV-infected mothers despite preventing maternal-fetal transmission of HIV. Translational aspects of this project included the analysis of clinical specimens and clinically relevant outcomes. “Novel Vaccine Candidate for Pediatric Falciparum Malaria,” led by Dr. Ian Michelow, focused on defining the mechanisms of protection by antibodies to a novel malaria antigen. This project proposed to analyze the expression of this antigen and its association with protection. The significance of the project lay in the need to identify protective malaria antigens for vaccine development. Translational aspects of this project included the focus on vaccine development and the use of clinical specimens.

**EXECUTION AND OUTCOMES OF PHASE I COBRE ACTIVITIES**

Through Phase I COBRE funding, iCubed and CIHR generated new and productive research collaborations, recruited additional investigators, and expanded the reach of these collaborations within RI.

Under Aim #1, iCubed and CIHR solidified the weekly joint research-in-progress/journal club meeting, which expanded to include several Pilot Project investigators and new hires. We also organized three local retreats/workshops bringing together RI-based academic and industry investigators in immunology, infectious diseases, and bioinformatics/big data, which served to catalyze several collaborative research and teaching initiatives. With an institutional contribution to the program from Lifespan, the COBRE Pilot Projects program supported a total of 14 projects over the phase I period [Figure 3]. In addition to supporting junior investigators within iCubed and CIHR, pilot project funding supported investigators in other units within URI (Pharmacy, Cell and Molecular Biology), Lifespan (Gastroenterology, Pediatrics, Oncology, Infectious Diseases), and Brown University (Molecular Microbiology and Immunology). Overall, these activities succeeded in raising the profile of infectious diseases immunology research within RI and encouraged new and interdisciplinary research collaborations. The COBRE triggered stronger interactions between URI and Brown University and its affiliated hospital systems that are an ongoing positive outcome of the COBRE.

Under Aim #2, COBRE funding expanded the laboratory infrastructure and made these resources available to the local scientific community through CoresRi.org and shared scheduling calendars. The Data Management and Statistics Core served as a model for other programs. Its personnel were recruited to participate in several other RI COBREs, and the Brown University Environmental Influences on Child Health Outcomes (ECO) program. Equipment added to the Cell Analysis and Sorting Core and the High-Throughput Luminex Immunoassay Core continues to support research at URI, Lifespan, and Brown University.

Under Aim #3, we recruited additional faculty members to iCubed and CIHR and paired younger investigators with senior mentors. During the Phase I period, we recruited five new faculty investigators, two at iCubed and three at CIHR. One of these investigators was recruited using COBRE Research Project support, and three of the other investigators received COBRE pilot project funding. All of the Research Project Leaders and nearly all Pilot Project Investigators submitted applications for external grant funding. Several Pilot Project investigators successfully transitioned to independent status, and others received smaller NIH or foundation grants as PI. Two Research Project leaders were promoted within their respective institutions.

Under Aim #4, we supported a total of four full Research Projects and 14 Pilot Projects during the Phase I period. All of the Research Project leaders had success at obtaining some external funding for their research; two achieved “independent” status as overall or local PI on an NIH R01 grant. Overall, 13 published manuscripts from Research Project leaders cited COBRE support. The Pilot Projects program...
contributed to 4 R01s, 5 R21s, at least 15 smaller (e.g., foundation) grants, and 17 additional published manuscripts.

Major scientific outcomes from COBRE Research Projects included the following:

- COBRE research described a novel system for live-cell imaging of DENV-infected cells and demonstrated that DENV infection resulted in the suppression of mitochondrial fission through a reduction in intracellular levels of dynamin-related protein 1. These findings identified a novel effect of DENV on cell function and provided insights into dengue pathogenesis.

- COBRE research demonstrated that maternal HIV infection was associated with elevated serum cytokine levels, elevated levels of cytokines in the cord blood of their HIV-exposed, uninfected (HEU) infants, and reduced T cell receptor beta chain gene diversity in a subset of these infants. These findings demonstrated that maternal HIV infection affected in utero development of the immune system in HEU infants, potentially contributing to the higher risk of illness in these infants.

- COBRE research characterized a novel malaria parasite antigen expressed both on the parasite surface and on the surface of infected RBCs selectively recognized by cohort subjects at lower risk of illness. These findings identified a novel candidate for vaccines to prevent malarial disease.

- COBRE research identified malaria parasite antigens selectively recognized by individuals with low/undetectable gametocytaemia. These findings point to a vaccination strategy to block parasite transmission.

**CHALLENGES**

Characteristics that made our Phase I COBRE unusual unfortunately also created challenges. Our COBRE aimed to catalyze a collaborative effort between groups at two different institutions that was at a very early stage. None of the senior or junior COBRE investigators held tenure-track faculty positions. The research projects targeted for support were at a very early phase, as COBRE support provided the resources to launch these independent research projects. While we envisioned the COBRE program as an excellent fit for our objectives, our model did not include more established (yet still early-stage) investigators and projects who could provide the “quick success” that some COBRES rely on and NIH study sections expect. The increasing time needed for the senior or junior COBRE investigators held tenure-track faculty positions. The research projects targeted for support at institutions like URI and others, which will further constrain the opportunities for such investigators. The period of COBRE support for individual Research Projects has been tightened, which further incentivizes “padding” of COBRE productivity by short-term appointments of investigators already poised to obtain R01 funding. Finally, current FOA requirements require that the lead institution keep most Research Projects and Scientific Cores in a COBRE and limit the total number of Projects and Cores an institution can hold as a subawardee. These changes make a truly balanced collaboration between institutions, such as in our COBRE, extremely difficult. Although these changes have rationale and seek to enhance the productivity and sustainability of COBRES, they may constrain the COBRE mechanism’s ability to transform the research landscape.

**CONCLUSION**

In perhaps a stroke of irony, our Phase I COBRE focused on translational research in infectious diseases immunology closed in early 2020, just as the first wave of the COVID-19 pandemic was cresting in RI. Although we did not succeed in navigating the transition to Phase II, participation in the NIH COBRE program provided a significant direct and indirect financial impact to RI, a valuable learning and growth experience for the senior investigators involved, and incalculable career benefit to several of the young investigators supported.

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ABSTRACT
Peripheral nerves are crucial to the motor and sensory function provided by our upper and lower extremities to our brain and spinal cord. Following trauma or illness, these nerves may be injured, leading to a loss of function that can be significantly debilitating. Fortunately, given the type of injury and under the right conditions, peripheral nerves can regenerate through well-coordinated biochemical processes. However, as individuals age, the ability for nerves to regenerate becomes less efficient, reducing nerve’s potential for the nerve to return to its prior level of function. In this article, we review the research that has been conducted to illustrate the reasons for such a decline in regenerative capacity. In doing so, we explore the concept of inflammaging alongside aging-related impairments of the macrophage and Schwann cell during nerve regeneration.

KEYWORDS: COBRE, bone and joint, aging, nerve regeneration

HISTORY OF THE COBRE FOR SKELETAL HEALTH AND REPAIR
The Center of Biomedical Research Excellence (COBRE) for Skeletal Health and Repair was established in 2007 by National Institutes of Health in Rhode Island Hospital, which is affiliated with the Alpert Medical School of Brown University. It consists of three five-year phases (Phase I: 2007–2012, Phase II: 2012–2017, and Phase III: 2017–2022), which is in its 14th year currently. The COBRE goal is to develop a multi-disciplinary translational research center focusing on discovering mechanisms of cartilage joint diseases and developing prevention and treatment strategies. In the first two phases, seven full project junior investigators received R01 or R01-equivalent federal grants, “graduated” from the COBRE training program, and become leaders in their research fields. They published more than 240 peer-reviewed articles, including landmark discoveries in Nature, Molecular Cell, and PNAS. All 20 pilot-project junior investigators received extramural funding as Principal Investigators. New state-of-the-art laboratories and core facilities have been built in bioengineering, imaging, molecular biology and nanomedicine.

The current Phase III COBRE’s main objective is to strengthen and transition the COBRE research infrastructure into a competitive, independent, and self-sustaining academic center of excellence. It consists of an Administrative Core, which provides strong leadership in translational research, evaluates the performance of technical Core Resources and Facilities, guides mentoring efforts in the Pilot Projects Program, and implements the COBRE transitioning plan; the Bioengineering Core, which enhances an interactive research environment and provides the unique resources of biomechanical testing at the cell, tissue, and organ levels; the Imaging, Molecular Biology, and Nanomedicine Core, which enhances translational research from bench to bedside, provides critical expertise and equipment in small animal live imaging analysis, and facilitates development of novel nanomaterial delivery vehicles for diagnostics and therapeutics; and the Pilot Projects Program, which mentors a new generation of researchers in multiple disciplines of musculoskeletal research including clinicians, biologists, and engineers, facilitates research collaborations, and sustains the strong research environment.

The COBRE vision that by sustaining and transitioning the established high-caliber research infrastructure will enable clinicians to work side-by-side with basic research scientists, junior investigators with senior investigators, and biologists with bioengineers for the long term into the future. The COBRE for Skeletal Health and Repair has been recognized as one of the country’s premier skeletal research centers by the NIH review panels. It carries out cutting-edge research in injury- and aging-associated degenerative bone and joint diseases and develops tissue repair and regeneration strategies. Peripheral nerve injury and regeneration in the extremities is one of the research areas of the COBRE and the review’s focus.

INTRODUCTION TO PERIPHERAL NERVE INJURY AND REGENERATION
Peripheral nerve injuries (PNI) may occur following traumatic mechanisms such as laceration, crush, or stretch injuries resulting from medical conditions such as diabetes, medications, or cancer. In America, over 20 million people suffer from peripheral nerve injuries as a result of trauma and illness. Treatment of these injuries has cost upwards of...
1.5 billion dollars, and even after treatment, PNIs may still severely affect patients’ quality of life.

Studies have shown that, in general, nerve regeneration occurs about 1 mm per day or an inch a month. The process for regeneration stems from Wallerian degeneration, involving the removal and recycling of axonal and myelin debris distal to the injury site to begin creating an environment favorable for regeneration. This process serves as the innate immune response to nerve damage, and in the peripheral nerve system, primarily involves Schwann cells and macrophages as opposed to oligodendrocytes and microglia in the central nervous system. Wallerian degeneration begins with the death of the damaged nerve to the nearest node of Ranvier via a process called chromatolysis followed by clearing the area of regeneration of axonal and myelin debris. The removal of myelin is a crucial step, as myelin debris contain molecules, such as myelin-associated glycoproteins, that can severely affect Schwann cell migration and regeneration of axons. Both macrophages and Schwann cells have been shown to remove myelin from the environment independently.

Soon after a nerve injury, Schwann cells begin to dedifferentiate and proliferate to aid in clearance and longitudinally realign themselves to form bands of Büngner. The bands of Büngner create a direction and environment that promotes axonal regeneration and remyelination. Axonal regeneration starts with forming growth cone at the intact nerve from which axonal sprouting occurs. Through contact guiding and neurotrophic factors, the axons extend until reaching the formed bands of Büngner, where the axons and fascicles are then covered by Schwann cells for myelination.

In evaluating this regenerative process’s efficiency and effectiveness, studies have found regeneration speeds of peripheral nerves slow with age. With age, cells and systemic function become less efficient compared to younger individuals. In addition, with age comes the propensity to develop comorbidities that may affect the health of peripheral nerves due to such conditions as rheumatoid arthritis, Parkinson’s diseases, lupus, and Sjögren’s syndrome. Peripheral neuropathy may become a symptom of such systemic diseases that may be exacerbated by the decline in the efficiency of nerve regeneration in an aging population.

The purpose of this review is to evaluate the current understanding of how aging affects peripheral nerve regeneration following injury. In doing so, we explore differences in the microenvironment of nerve regeneration between the young and old by evaluating the inflammatory response to nerve injury alongside the decline macrophages and Schwann cells’ function with age.

**INFILTRATING**

As individuals age, their biology becomes less conducive towards nerve regeneration than those who are younger.

One reason this may occur is through inflammaging. Inflammaging is characterized by chronic, low-grade inflammation in the human body that carries risks for poor inflammatory responses when faced with injury or illness. In older individuals, the overall environment is found to be pervasively inflammatory due to an increase in the variety of stressors on the immune system leading to an imbalance between pro- and anti-inflammatory responses.

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**Figure 1A.** The injury and regenerative process of a nerve in a mature individual. Factors such as MCP1 and CCL11 are upregulated in response to injury. Macrophages are recruited as Schwann cells dedifferentiate to mediate healing. Bands of Büngner formed by Schwann cells then serve to guide regeneration as the distal aspect of the nerve degenerates. Once regeneration is complete, the Schwann cells differentiate to further establish a healthy environment.
Inflammatory stimuli that arise from dead cells or debris combined with the declining capacity of the body to clear these materials leads to an autoimmune or autoreactive response that can speed up the aging process in such areas, making them less suitable for regeneration. In such inflammatory environments, PNi in aged rats have demonstrated delayed recruitment in macrophages, which subsequently linger at the site of injury longer, producing additional pro-inflammatory cytokines compared to younger rats. While macrophages are typically important for clearing debris, such pro-inflammatory macrophages subsequently suppress Schwann cell function and ultimately axonal regeneration. Rats with crush injuries treated with acetylsalicylic acid (ASA), used as an anti-inflammatory treatment, were found to have accelerated functional recovery, decreased macrophage count, and more advanced remyelination. As a result, the authors suggested that anti-inflammatory treatments may help the progression of nerve regeneration.

**MACROPHAGE IMPAIRMENT**

Delayed macrophage recruitment and impairment is a key component behind the slowing of nerve regeneration in aged animals. Following peripheral nerve injury, macrophages help in the clearance of myelin and axonal debris and facilitate angiogenesis and Schwann cell migration to create an environment conducive to regeneration. Given their crucial role, the decline in the recruitment and function of these cells with age has a dire consequence for regenerative ability.

Response to nerve injury is found to be delayed in aged animals due to an accumulation of macrophages later than in young or adult rat models. After about eight days, macrophage count was found to be at comparable levels to younger rats, indicating the magnitude of recruitment may be consistent between ages. Thus, impaired regeneration in aged models could partially be caused by the delay in the recruitment process during the critical early stages of recovery. In addition, studies on age conditioned media (CM) have shown that monocyte migration is significantly less in aged CM than young CM and point towards cytokine signaling of the microenvironment responsible for the delayed recruitment of immune cells. When bone marrow transplants were performed across old and young rats, there was no difference in macrophage counts found across the transplant recipients, indicating that the presence of a young environment or young bone marrow was enough to create a more responsive regenerative environment.

Studie...
expressed increase with age. These proteins’ continued production ultimately leads to macrophage and Schwann cell-related impairment during the nerve regeneration process. Having specifically pinpointed these cytokines, the connection between inflammaging and macrophage impairment in nerve regeneration has become apparent with the potential to act as therapeutic targets.

SCHWANN CELL IMPAIRMENT

Schwann cells (SCs) support peripheral nerves by playing a key role in myelination and axons’ remyelination. Upon injury, SCs dedifferentiate into repair cells to secrete regenerative factors, clear debris, recruit macrophages, and lay a path for axonal growth (Figure 1A).8 Like macrophages, SCs also experience negative effects in response to an aging environment. They are not as efficient as in younger animals.8,14,18 As for the cause of a decrease in SC responses, some studies have investigated varying secretion of regenerative factors, genetic changes, and increased damage and fragmentation in the area.

In a study on SCs by Koniyama and Suzuki, the proliferation of SCs throughout Wallerian degeneration in rats of various ages was analyzed.22 Using thymidine incorporation, the authors were able to measure the proliferation of SCs and fibroblasts. Previous studies have shown that myelin processed by macrophages contribute to SC proliferation during Wallerian degeneration. Koniyama and Suzuki also revealed that axonal components’ loss had an inhibitory effect on SCs in actively myelinating nerves.22 From this data, they were able to determine that the proliferative capacity declined because of both age-related loss of axonal mitogens and a reduction of mitogens from myelin components.

Genetic changes in SCs themselves occur as individuals age, and their functionality also decreases as a result. One example of this is the c-Jun gene (Table 1). c-Jun is a critical transcription factor for the presence and proliferation of SCs at injury, and it has been found to vary in levels depending on age.23 c-Jun is a master regulator in Wallerian degeneration. It controls expression of trophic factors, adhesion molecules, regeneration tracks, and myelin clearance.24 c-Jun is responsible for the activation of repair mechanisms within SCs by specifying the phenotype of denervated SCs and control over the interactions between axons and SCs.24 c-Jun presence is induced by injury, as demonstrated by transection of a facial nerve that led to an upregulation of c-Jun during the immune response a few days after injury.25 In animals without c-Jun, studies discovered the failure of functional recovery, insufficient myelin clearance, failure of axon growth and reinnervation, and death of injured sensory neurons.25 In a study on aged mice, it was found that aged mice had impaired axonal regeneration while also having a defective cell body response, which lacked both c-Jun expression and phosphorylation.23 Previous studies have
shown that deletion of the c-Jun gene would cause a delay in recovery and a reduction in innervation, revealing that the regeneration process isn’t entirely dependent on the presence of c-Jun. C-Jun has also been known to initiate expression of other regeneration-associated molecules such as CD44, galanin, and α7β1 integrin.

As SCs age, there is also the danger of an impairment in the dedifferentiation mechanisms, causing the SCs to remain in a differentiated state. In injury responses, SCs undergo a process of change that alters their structure, molecular profile, and function, creating two distinct differentiation states. p75 is a marker for the repair cell phenotype and has been compared to young animals in aged animals, SCs also marked early delay in SCs in injuries in aged animals when compared to young animals. In aged animals, SCs also exhibit deficiency in myelin clearing ability along with the delayed p75 expression. Inefficient SC differentiation shows a decrease in SC plasticity and SC senescence, which may contribute to the delay in regeneration in the critical stages of injury. Macrophage recruitment is dependent on factors secreted by dedifferentiated SCs, thus delayed recruitment is one of the downstream effects of inefficient dedifferentiation.

As mentioned previously, macrophage impairment leads to myelin clearance inefficiency. When combined with SCs’ impaired ability to clear myelin, the repair response becomes even more inefficient due to age-related changes. It reveals even more downstream effects of the loss of plasticity. Furthermore, because of the plethora of changes SCs undergo with injury responses, they could be especially vulnerable to age-acquired errors in transcription or expression. Studies have shown that older SCs undergo significant karyotype changes when bred in vitro with no anchorage dependency and no increase in telomerase activity: cellular characteristics resembling tumor cells. Overall, genetic instability and genetic changes of aged SCs contributes to the decline of SC function and dedifferentiation capabilities in aged individuals.

**DISCUSSION**

Nerve regeneration is a coordinated process of cellular dedifferentiation and cellular chemotaxis to generate a microenvironment conducive to healing. In the study of aging as it relates to this regenerative process, a chronic inflammatory state, age-related alterations to the microenvironment, and genetic changes of Schwann cells and macrophages lead to an age-related decline in response to injury and regeneration. We have reviewed that an aging immune system induces an inflammatory environment called inflammaging, delaying Wallerian degeneration. This inflammatory process also contributes to additional complications associated with delayed macrophage recruitment and impaired macrophage function. Combined with age-related genetic changes leading to poor SC dedifferentiation and SC senescence, nerve injury’s response becomes further compromised, negatively affecting the regenerative process.

Potential treatment modalities to improve regeneration in an aged environment involve targeting key cytokines and improving upon cellular function. Chronic elevation of CCL11 with age and its additional expression by macrophages following injury have shown to impair Schwann cell repair activity. Inhibition of this pro-inflammatory target may improve nerve maintenance and repair in the elderly population. In a similar fashion, delayed and subsequent chronic elevation of MCP-1 has been shown to reduce the regenerative support of Schwann cells. Through a timely and controlled application of MCP-1 following injury, axonal regeneration may be improved and better supported.

Genetic impairments of SCs leading to decreased ability of dedifferentiation and increased SC senescence has been demonstrated to be detrimental to nerve regeneration. Potential treatment modalities may involve genetic alterations of aged SCs to increase the expression of c-Jun and the underlying molecular mechanisms for p75 expression to improve the reparative ability of SCs. In addition, to combat against the development of an increasing senescent cell population and its accumulation, senolytics are a potential option. Senolytics are drugs that target and kill senescent cell populations, which present a promising solution to clear senescent cell populations and help restore SC activity and nerve regeneration in aged individuals.

Through a continued understanding of the fundamental aspects of how aging affects regenerative nerve processes, we may be better able to develop therapies to improve upon the response following injury. Suitable interventions will require continued mechanistic studies to improve the localization and targeting of such treatments and further ensure their safety and effectiveness in a vulnerable patient population.

**Acknowledgment**

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Our Arduous Research Journey from Preeclampsia to Alzheimer’s Disease – Report from the Center of Biomedical Research Excellence (COBRE) for Reproductive Health

SURENDRA SHARMA, MD, PhD

ABSTRACT
This article is contributed by the COBRE for Reproductive Health. The programmatic and scientific goals of this COBRE support a multidisciplinary, translational, and innovative program in women’s reproductive health. The research projects focus on using pre-clinical and human models to understand mechanisms of preeclampsia, gestational diabetes, preterm birth, IVF pregnancies, and the application of contemporary computational approaches to identify the networks and pathways underlying these devastating pregnancy complications. We discuss how novel observations emanating from the preeclampsia project can be leveraged to understand chronic diseases such as Alzheimer’s disease (AD). Proteinopathy is a hallmark feature of neurodegenerative disorders such as AD. We recently reported that preeclampsia (PE), a severe pregnancy complication, is another prevalent proteinopathy disorder in a younger population. This review provides a comprehensive discussion on shared etiology between PE and AD, establishing a novel blood test for their prediction and diagnosis, and a novel therapeutic option for these disorders.

KEYWORDS: preeclampsia, Alzheimer’s disease, proteinopathy, autophagy, blood test

INTRODUCTION
Diseases rarely manifest in isolation. Instead, most are part of a more complex pathway or “pattern” of connected conditions via underlying biological mechanisms. One common denominator in chronic and complex diseases is the role of inflammation and protein mimicry (misfolding and aggregation), which have gained recognition in several human diseases, including Alzheimer’s disease (AD)1-3. Symptoms may emerge across the life course, and large longitudinal databases may help recognize such patterns. Although pregnancy represents a modest portion of the life course, it is now recognized as a window into a woman’s future health. It often unmasks predispositions to conditions that only become symptomatic decades later. Preeclampsia (PE) is a pregnancy complication that entails both maternal and offspring health consequences.4 Recent observations suggest that there is an epidemiological connection between PE and AD.1,2,5-7 Below, we will discuss the biological and clinical aspects of these devastating disorders and provide details that may lead to their early detection and treatment.

PREECLAMPRIA
Preeclampsia (PE) is a severe pregnancy complication with many manifestations for both mother and offspring. It is a multi-factorial and multi-organ pregnancy complication that affects 3–8% of all pregnant women. It is diagnosed by de novo onset of hypertension and proteinuria at or after 20 weeks of gestation.1-3,8-10 PE can be diagnosed as an early (<34 weeks gestation) or late (>34 weeks gestation) onset severe complication as well as post-partum.11-13 This devastating pregnancy complication is a placenta-specific disease. In normal pregnancy, the placenta develops in a highly choreographed biological environment programmed by post-implantation cross-talk between the developing placenta and the maternal immune system in the decidua-ized endometrium. The placenta develops a trophoblast layer comprised of inner villous cytotrophoblasts and...
multi-nucleated syncytiotrophoblasts. A subpopulation of cytotrophoblasts further differentiate into invading trophoblasts while syncytiotrophoblasts remain in direct contact with maternal blood and act as a storage hub. A subgroup of invading trophoblasts acquires endovascular properties and migrates into constricted endometrial spiral arteries to remodel them into dilated, resistance-free vessels. These resistance-free arteries allow the free flow of nutrients and blood products from the mother into the intervillous space. After that, nutrients and oxygen can cross the syncytiotrophoblast layer into fetal capillaries inside each villous structure. It has been shown that PE is associated with defective spiral artery remodeling. This creates the onset of local ischemia/hypoxia, oxidative stress, and dysregulated immunity at the maternal-fetal interface. The result is a production of an inflammatory milieu and pathological placental nanoparticles (exosomes) containing misfolded proteins, which are released into the maternal circulation. Most importantly, we recently demonstrated that PE is a disease of proteinopathy (e.g., pathologic protein aggregation). We have reported that serum from PE patients can induce PE-like features in pregnant mice. In contrast, depletion of protein aggregates in serum blocks the onset of such features, including elevated blood pressure, proteinuria, glomerular endotheliosis, and fetal growth restriction. In this regard, the question arises on what precipitating events lead to the accumulation of protein aggregates in the placenta. We recently demonstrated that the PE placenta is associated with impaired autophagy. Autophagy is intricate cellular machinery to maintain homeostasis by its ability to clear cells of misfolded, aggregated protein structures and damaged organelles. We proposed that impaired autophagy allows the accumulation of misfolded, aggregated proteins in the PE placenta, causing trophoblast cell death, low differentiation into invading trophoblasts, and defective spiral artery remodeling. Moreover, we have shown that PE is associated with gasdermin D/caspase 3-mediated sterile inflammation in the placenta, a possible trigger for the onset of protein aggregation and trophoblast cell death. We anticipate that impaired autophagy and protein aggregation can be targeted for therapeutic intervention in PE.

ALZHEIMER’S AND RELATED NEURODEGENERATIVE DISEASES

The pathological hallmark of AD and its related neurodegenerative diseases is the accumulation of hyperphosphorylated tau as intracellular tangles and amyloid-β as extracellular plaques in AD and its prodromal condition, mild cognitive impairment (MCI). α-Synuclein accumulates as aggregated protein in Lewy bodies in AD and Parkinson’s disease, and other distinct proteins in other neurodegenerative diseases. Like PE, protein misfolding, aggregation, and impaired autophagy are also intertwined in AD. Tau can manifest in diverse isoforms stemming from distinct phosphorylation patterns and sites, imbalanced isomerization involving trans and cis configurations, and the preponderance of C-terminal microtubule-binding peptide region. Tau aggregates without amyloid-β involvement are also present in frontotemporal dementia and corticobasal degeneration. Although pathological protein misfolding and aggregation in neurodegenerative diseases have been accepted for a long time now, it has been difficult to leverage these findings for prediction or therapeutic intervention. To date, no well-defined, cost-effective, non-invasive blood test has been developed to diagnose AD. The widely used tests currently rely on cerebrospinal fluid protein analysis and positron emission tomography (PET) imaging, which are invasive and expensive. Recently, efforts have focused on blood tests for AD and MCI. However, they still depend on the identification of a single, non-aggregated protein with prescreening manipulation of plasma samples.

DO THE SAME PROTEINS UNDERGO AGGREGATION IN PE, AD, AND MCI?

An important question that is often asked is whether we have access to pathological markers or a blood test that can enable diagnosis in much larger populations at a pre-AD age. Similarly, this argument can also be made for PE. We took advantage of our observations of impaired autophagy and protein aggregation in PE. We hypothesized that autophagy-deficient trophoblasts would not clear protein aggregates, and the accumulated aggregated structures can then be identified by an immunofluorescence probe. We have established an autophagy deficient human extravillous trophoblast cell line by stably transfecting a mutant autophagy gene that blocks the assembly of autophagosomes and reduces lysosomal expression machinery proteins. Our novel blood test for detecting serum protein aggregates depends on the exposure of autophagy-deficient trophoblasts to serum for 12–24 hours, fixing the cells, and then staining with an immunofluorescence dye for estimation of total protein aggregates. With specific antibodies, we can co-localize and identify individual proteins. Our data suggest that transthyretin,

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Figure 2. Identification of protein components of serum aggregates from patients with preeclampsia, Alzheimer’s disease, and mild cognitive impairment.
amyloid-β, and hyperphosphorylated tau are common in the protein aggregates among PE, AD, and MCI. In contrast, the protein aggregates in AD, and MCI also contain α-synuclein. This suggests that PE and AD share etiological biomarkers, and these observations may suggest a common therapeutic option(s) for both disorders.

CAN IMPAIRED AUTOPHAGY AND PROTEIN AGGREGATION BE USED AS THERAPEUTIC TARGETS FOR PE AND AD?: COMMON THERAPEUTIC OPTIONS FOR PE AND AD

To date, no effective therapy is clinically available for PE. The most effective treatment is the delivery of the placenta and fetus. PE is accompanied by severe health consequences not only during pregnancy but also in later life. PE patients are at higher risk of developing cardiovascular disease, diabetes, and possibly AD as suggested by our lab and that of others.1,2,5,7,14,15 Our group’s preliminary data are innovative in their support of a predictive assay for PE and investigation of a small, non-mammalian disaccharide molecule targeting autophagy and proteinopathy. This molecule can reverse the cellular and pathological events associated with PE. Our preclinical model for screening possible therapeutic options is a novel approach that is likely to lead to novel therapeutic options for PE.

Since both PE and AD share impaired autophagy and protein aggregation as key pathological factors, it is fair to predict that a drug that targets these cellular pathways may have therapeutic potential to prevent and/or treat these devastating conditions. We plan a similar therapeutic approach to prevent or treat the onset of AD-like symptoms. The disaccharide drug blocks appearance of AD-like pathology in h-tau AD transgenic mice. In in vitro experiments, this drug is quite potent in restoring autophagy and blocking protein aggregation in response to endoplasmic stress inducers such as hypoxia. The drug entails no detrimental effects in non-pregnant, pregnant, or wild-type mice. Notably, the offspring born to disaccharide-treated mothers were of normal weight and showed no ill effects through a few months of their life. As described above, the novel blood test and the disaccharide drug have become the focus of our recent efforts for planning pilot prediction and clinical trials for PE and AD.

CONCLUSIONS

A syndrome of younger age can rarely provide mechanistic and therapeutic insights for devastating chronic diseases such as AD, which entail a huge socio-economic burden on the healthcare systems. Diagnosis and treatment of such conditions have suffered from a lack of appropriate animal models, non-invasive blood tests, and target-based therapies. Thus, it is clinically important that a well-defined treatment modality be pursued that may eventually lead to randomized clinical trials. We discuss here that a pregnancy complication, preeclampsia, share etiological and therapeutic insights with AD and its prodromal MCI condition.

Acknowledgments

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References


ABSTRACT
The CardioPulmonary Vascular Biology Center for Biomedical Research Excellence (CPVB COBRE) was funded in 2013 by the National Institute for General Medical Sciences to establish a collaborative center for research excellence in vascular biology in Rhode Island. The CPVB COBRE has funded successful junior faculty investigators and pilot projects spanning the research spectrum from basic vascular development mechanisms using zebrafish to clinical research on pulmonary hypertension to the effects of mindfulness on hypertension in pregnancy. The Administrative Core has united the group with an active seminar program with visiting experts, a focus on career development, and the use of evaluation to support continuous improvement. The Cell Isolation and Organ Function Core has provided high-quality research services and expertise. Most importantly, hard-working and creative physicians and basic scientist investigators and mentors have worked together to expand the spectrum of vascular biology research in Rhode Island.

KEYWORDS: vascular biology, pulmonary, cardiology, interdisciplinary

INTRODUCTION
Cardiovascular and pulmonary diseases are among the leading causes of morbidity and mortality in the US and the world. Coronary artery disease (CAD) is the leading cause of morbidity and mortality globally, with greater than 8 million deaths in 2019. Chronic obstructive pulmonary disease and lower respiratory diseases are the 3rd and 4th leading causes of death worldwide, respectively, with greater than 5 million deaths in 2019, and are frequently complicated by pulmonary vasculopathy and cardiovascular co-morbidities that markedly worsen prognosis. In 2020, COVID-19, caused by the SARS-CoV-2 virus, has become the 3rd leading cause of death for persons aged 45 through 84 years and the 2nd leading cause of death for those aged 85 years or older, as compared to other leading deaths in 2018. Most patients with COVID-19 die from respiratory failure or vascular complications, including stroke, myocardial infarction, or thromboembolism, and COVID-19 is recognized as a disease directly impacting the endothelium. In addition, deaths due to cardiopulmonary vascular diseases manifest health inequality and are increased in lower socio-economic populations and settings. Thus, cardiopulmonary vascular diseases are important causes of human suffering, for which more effective treatments and prevention are needed.

VISION AND PROGRAMS OF THE CPVB COBRE
In 2013, the CardioPulmonary Vascular Biology (CPVB) Center of Biomedical Research Excellence (COBRE) was established through funding from the National Institutes of Health, National Institute of General Medicine and Sciences (NIH, NIGMS) and is currently in Phase 2 of funding. This center’s visions are to unite clinical and basic scientific investigators from multiple disciplines and foster research career development of those who have not yet established an independent research program (Figure 1). The goals are to enhance understanding of vascular cell injury mechanisms and develop and strengthen an interdisciplinary collaborative research center with strong technical support and career development activities across Rhode Island institutions. The CPVB COBRE has brought together investigators from the Vascular Research Laboratory at Providence VA Medical Center (PVAMC), the Surgical Research Laboratory, Cardiovascular Research Center, Cardiothoracic Surgery Research Laboratory, and the Division of Pulmonary/Critical Care/Sleep Medicine at Rhode Island Hospital (RIH), as well as...
from Brown University departments within the Division of Biology & Medicine (Figure 2). Investigators are supported as either Project PIs for 2–5 years or as Pilot Project PIs for 1–2 years, with funding prioritized by scientific review in the manner of NIH study sections. A key feature of the CPVB COBRE program is fostering interactions among clinicians and biologists, in the strong belief that interdisciplinary research is most likely to successfully translate discoveries to patient care.

Each CPVB COBRE junior faculty investigator is supported by a mentoring team of experienced senior researchers who provide scientific expertise and guidance, career advice, leadership skills, professional development, organizational advancement, networking opportunities, and examples of work-life balance. In addition, institutional and administrative support from the PVAMC, Ocean State Research Institute (OSRI), RIH, and Brown University has provided an infrastructure for CPVB COBRE investigators, enabling them to focus their efforts on establishing a productive research program.

The CPVB COBRE has two core facilities that are available to all investigators and mentors. These include an Administrative Core and a Cell Isolation/ Organ Function (Cell/ Organ) Core (Table 1). The Administrative Core facilitates the research activities and career development of junior investigators by providing fiscal assistance, organizing career development opportunities, managing mentorship committee meetings, organizing meetings with our external and internal advisory committees and other activities, as described in Table 1. The Cell Isolation and Organ Function Core is a scientific core that focuses on cultured cells and whole organ structure and function to investigate vascular injury and repair. The Cell/Organ Core provides a unique skill set and expertise to Rhode Island vascular biologists by providing high-quality cell isolation, characterization, and propagation of vascular-derived cells, tissue morphometry and image analysis, and heart and lung function. The Cell/Organ Core services are described in Table 1. A new scientific core to assess Respiratory Function is in the planning stages.

A vigorous program of research seminars provided by visiting speakers and local experts is a critical aspect of the CPVB COBRE program. The CPVB COBRE sponsors twice-monthly seminars. Each project and pilot project investigator presents results of “work-in-progress” and research and professional achievements at least twice per year. In addition, the CPVB COBRE seminar series is complemented by the monthly Brown Investigators in Respiratory Diseases (BIRDS) lecture series and [in 2020] the “Decoding COVID” and “Decoding Disparities” seminar series, sponsored by the Division of Biology and Medicine. These seminars feature both local experts and visiting speakers. Junior faculty investigators serve as the primary host for guest lecturers, providing them with an opportunity to become acquainted with the distinguished visiting researcher, thereby increasing their professional network. Indeed, these visits have led to scientific collaborations for some junior investigators. To

Table 1. Services provided by CPVB COBRE Cores

<table>
<thead>
<tr>
<th>Core Service</th>
<th>Service</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administrative</td>
<td>Junior Investigator fiscal assistance</td>
</tr>
<tr>
<td></td>
<td>Organize and manage career development opportunities</td>
</tr>
<tr>
<td></td>
<td>Managing mentorship committee meetings</td>
</tr>
<tr>
<td></td>
<td>Manage meetings with our internal and external advisory and executive committees</td>
</tr>
<tr>
<td></td>
<td>Maintains the cpvb.org website</td>
</tr>
<tr>
<td></td>
<td>Provides financial management of entire program</td>
</tr>
<tr>
<td></td>
<td>Tracks investigator outcomes</td>
</tr>
<tr>
<td></td>
<td>Manages evaluations of the mentor-mentee teams</td>
</tr>
<tr>
<td></td>
<td>Assesses scientific core efficiency and program effectiveness</td>
</tr>
<tr>
<td></td>
<td>Manages seminar series and guest lecturers</td>
</tr>
<tr>
<td></td>
<td>Manages intramural and extramural progress reports</td>
</tr>
<tr>
<td>Cell Isolation &amp; Organ Function Core</td>
<td>Provides high quality cell isolation, characterization, propagation and functional assessment of vascular-derived cells; including endothelial cells from heart, lung, and other organs, cardiomyocytes, fibroblasts, and epithelial cells</td>
</tr>
<tr>
<td></td>
<td>Provides tissue morphometry and image analysis</td>
</tr>
<tr>
<td></td>
<td>Assessment of heart, lung, vessel structure and function and angiogenesis</td>
</tr>
<tr>
<td></td>
<td>Transient gene manipulation in vivo</td>
</tr>
<tr>
<td></td>
<td>Acquire, establish, and disseminate technologies and instrumentation to provide state of the art research tools for vascular biology research in Rhode Island</td>
</tr>
<tr>
<td></td>
<td>Establish processes and procedures that support the sustainability of the Cell/Organ Core</td>
</tr>
</tbody>
</table>
leverage resources, the CPVB COBRE has co-sponsored lectures with other research seminar series at Brown, including the Pathobiology, Molecular Pharmacology and Physiology; and Grand Rounds in Cardiology, Pulmonary, and Internal Medicine. With funding partners, the CPVB COBRE and BIRDS seminar series have sponsored 70 visiting speakers from 29 universities since 2013.

In 2020, the CPVB COBRE Principal Investigators [PIs] partnered with the University of Mississippi Medical Center Cardiorenal and Metabolic Disease Research Center COBRE and the University of Louisville COBRE in Diabetes and Obesity Research PIs to establish a monthly multi-COBRE seminar series. This seminar series features research talks by COBRE investigators and brings together investigators from related disciplines to build a network of collaborations among the COBRE programs.

Finally, the CPVB COBRE has contributed significantly, both administratively and financially, to the Rhode Island IDEa annual symposium since 2015. At these day-long symposia, the junior investigator from each of the Rhode Island INBRE or COBRE programs present their work in short talk or poster format. Thus, the CPVB COBRE has regularly scheduled opportunities to highlight the junior investigator’s work both within and outside of Rhode Island, fostering professional growth and career development.

A key element to the CPVB COBRE program and junior investigator successes has been the engagement of the advisory committees, including the executive committee (EC), an internal advisory committee (IAC), and an external advisory committee (EAC). Both the IAC and EAC meet twice annually, while the EC meets every other month. For each meeting, the PIs provide updates, including successes and challenges to the program. While the EC meetings discuss financial expenditures, junior investigator issues, and current and immediate future goals, the IAC and EAC meetings discuss the program’s overarching vision. In addition to meeting with the CPVB COBRE PIs, the EAC meets with each junior investigator and mentoring team to discuss achievements, hurdles, and next steps. In these private meetings, the EAC members provide frank feedback to the junior investigators, to help them achieve research independence. The dedication, consistent participation, and wise advice provided by each of the committees have been crucial in the program’s ongoing success and junior investigators.

**OUTCOMES OF CPVB COBRE**

Since 2013 the CPVB COBRE has supported 10 junior faculty investigators from 5 academic departments and 18 pilot project investigators with 24 distinct pilot projects. In addition, the COBRE has supported two administrative personnel and 65 research assistants. Thus, the COBRE has substantially impacted vascular biology research in Rhode Island.

The Administrative Core of the CPVB COBRE supports on-going quantitative and qualitative program evaluation. More than half (6/10) junior faculty project investigators have achieved RO1 funding, and 5/18 pilot project Investigators have achieved RO1 funding since 2014. CPVB COBRE Junior faculty investigators have also been awarded substantial research support from foundations, such as the Falk Foundation and the Harold S. Geneen Foundation, and other federal sources, such as the Departments of Defense and Veterans Affairs CPVB COBRE investigators have contributed to the knowledge of vascular biology by publishing 83 publications with CPVB COBRE support. In keeping with our goal of enhancing scientific collaboration, 12 investigators supported by the CPVB COBRE have published manuscripts documenting collaborations with other CPVB investigators and/or mentors.

The CPVB COBRE strongly espouses continuing quality improvement and has therefore used survey methodology to assess program effectiveness. In collaboration with Judy Kimberly, Evaluation Director of the Brown University Division of Biology and Medicine, survey instruments were developed for junior faculty investigators and mentors. The semi-annual surveys address investigator self-efficacy, research mentor interactions, and effectiveness of core support activities. Although generally the program has been considered effective, there continue to be areas for improvement. The content and results of these surveys have been published in the Journal of Clinical and Translational Science.

**CONCLUSIONS**

The CardioPulmonary Vascular Biology COBRE was established in 2013 to develop interdisciplinary research in lung, heart, and vascular diseases in Rhode Island. Critical elements of success include institutional support, interdisciplinary collaborations, a focus on career development and networking, a vigorous program of visiting researchers, and ongoing program evaluation. The most important element of success has been the expertise of outstanding, hard-working, and collaborative junior faculty researchers and mentors with whom the CPVB COBRE has been privileged to work.

After 7.5 years of funding, there has been substantial progress toward the ultimate goal of improving outcomes of vascular diseases in Rhode Island. Continued challenges include maintaining a “pipeline” of junior faculty engaged in vascular biology research, sustaining research in difficult pandemic times, and growing sustainability of scientific cores.

**Acknowledgments**

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References

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COBRE for Computational Biology of Human Disease at Brown University: Progress and Prospects

DAVID M. RAND, PhD; ASHOK RAGAVENDRAN, PhD

ABSTRACT
We provide a program update on the COBRE Center for the Computational Biology of Human Disease (CBHD) at Brown University and affiliated hospitals. High-throughput data from multiple ‘omics-level’ technologies are fundamental factors in identifying and treating human disease. The acquisition of these data is now straightforward, but the efficient and creative interpretation of these data remains a serious impediment to progress for faculty at all levels in both the basic and translational aspects of biomedical science. The CBHD COBRE seeks to build close collaboration between laboratory scientists working with model systems and data scientists working with computational and bioinformatics tools that can accelerate human disease research implementation. We describe the accomplishments of junior faculty Project Leaders [9] and Pilots Project leaders [8] and the objectives of the CBHD COBRE’s core facility: The Computational Biology core (CBC). To extend the CBHD COBRE’s reach in the future, we encourage one and all to visit the CBHD COBRE and bring your data sets and questions. Only by engaging with new people and challenges can the program grow to serve the broader biomedical research community in the State of Rhode Island.

KEYWORDS: bioinformatics, data science, genomics, reproducibility

INTRODUCTION
Discovery in the biomedical sciences today requires expertise in computational biology and bioinformatics. The diversification of genome-enabled technologies has created a data deluge that can only be rendered useful by accelerating computational and bioinformatic innovation. Notable examples are the discoveries emerging from the Pan Cancer Analysis of Whole Genomes1, the Genome Aggregation Database (gnomAD)2 and the ENCODE3 release. These massive efforts by teams of computational, laboratory, and clinical scientists are defining the molecular and bioinformatic landscapes for new research in the biomedical sciences. All researchers will benefit from accessing, engaging, and contributing to these resources through their research programs. For junior faculty in early stages of their independent careers, or more senior researchers employing wet-lab or clinical approaches, realizing the full benefits of these computational resources can be a significant challenge.

This reciprocal relationship between biomedical advances and computational sophistication demands that scientists pursuing the basic biology of human disease must have a working knowledge of the effective application of computational and bioinformatic resources. When the revolution in molecular biology began in the 1980s, disparate biology fields were unified by a common language of DNA cloning, hybridization, expression, and creative manipulation. The boundaries between biochemistry, cell biology, evolution, and genetics were rendered permeable by methods that allowed researchers to ask common questions. The computational revolution has the same effect today but on a broader scale. Researchers across all the STEM fields are making significant contributions to computational biology with relevance to human disease’s basic biology. The engineering advances allowing long-read sequencing, or single-cell transcriptomics have the needs for data structures enabling efficient processing of massive sequence files, which has spurred statistical geneticists to develop novel analysis tools. These, in turn, allow clinicians and wet-bench molecular biologists to pursue entirely new questions about human disease.

This context is the motivation for the COBRE for the Computational Biology of Human Disease (CBHD). To keep pace with biomedical progress, all researchers need to build ‘omics-enabled’ computational approaches into the ecosystem of their research program, and to be successful, most people will need support for the development of these skills. In many institutions, bioinformatic analyses are commonly provided in a core facility that performs analyses for biomedical researchers. In this kind of service role, the science behind the computational and algorithmic analyses may be ‘outsourced’ by the biomedical researcher, reducing the need for those individuals to develop skills in these areas. The CBHD COBRE seeks to extend this service model by building a community where the biomedical researcher and the computational biologist are part of the same team and work together to design, execute, analyze, and interpret genome-enabled inquiry as a unified workflow. The CBHD COBRE aims to help researchers from complementary disciplines build advanced computational and bioinformatics approaches into collaborative research programs. To
make this effort thrive, the COBRE seeks to assemble a diverse community of biomedical researchers whose individual questions may differ widely, but whose underlying analytical questions share lots of common ground. By building a community where these approaches and ideas can cross-fertilize, junior faculty will not only reach independence more rapidly, but faculty at all levels will be better equipped to advance the later stages of their careers by managing the data deluges that will undoubtedly emerge in the future.

Most COBRE programs invest in a Core Facility that provides critical equipment that individual researchers cannot acquire independently. The CBHD COBRE has devoted all its core facility resources to hiring data scientists and building a Computational Biology core (cBc) facility. The four cBc staff members have the necessary computational or bioinformatic expertise to support junior faculty Project leaders (Pls). Through collaboration with Brown University’s Advance Research Computing group, they eventually provide this service to the broader biomedical community in Rhode Island. This approach has filled a much-needed gap in the research environment at Brown leading to multiple successful NIH and NSF awards to the junior faculty Project leaders. In the first five years of the CBHD COBRE program, we have learned how to support for a wide range of researchers from molecular biologists with no computational skills to statistical geneticists seeking help with software engineering. Based on these learned experiences, in the next phase of the CBHD COBRE we seek to extend and strengthen the Center with support for a new cohort of Project Leaders and increased support for the CBC staffing that will broaden the reach of the CBHD COBRE beyond COBRE investigators. The COBRE

### Table 1. Grant support to junior faculty members who have been supported by the CBHD COBRE. The top half of the table lists the initial Project Leaders, the bottom half lists Pilot awardees, four of whom have transitioned to Project Leader status (Belenky, Crawford, Ené, Wood), and one who is a Project Leader in this Phase 2 proposal (Beura). Names in red are Project Leaders awarded R01/R35 support and have or will graduate. The total costs listed are for the duration of the grants awarded.

<table>
<thead>
<tr>
<th>Project Leader</th>
<th>Grant</th>
<th>Institute</th>
<th>Project Title</th>
<th>Dates</th>
<th>Total Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jamieson</td>
<td>R01</td>
<td>NIHLB</td>
<td>Influence Of The Lung Microbiome On Macrophage Responses To Lung Damage</td>
<td>4/18–3/23</td>
<td>$2,437,369</td>
</tr>
<tr>
<td>Neretti</td>
<td>R01</td>
<td>NIA</td>
<td>The Role Of Somatic Transposition In Age-Associated Genomic Instability</td>
<td>9/17–8/22</td>
<td>$2,176,898</td>
</tr>
<tr>
<td>Ramachandran</td>
<td>R01</td>
<td>NIGMS</td>
<td>Novel Statistical Methods To Localize Genomic Elements Underlying Adaptive Evolution</td>
<td>2/17–1/21</td>
<td>$1,607,269</td>
</tr>
<tr>
<td>Vaishnava</td>
<td>R01</td>
<td>NIDDK</td>
<td>Role Of Epithelial Cell Intrinsic Vitamin A Metabolism In Regulating Immune Function In The Gut</td>
<td>7/18–6/23</td>
<td>$2,256,411</td>
</tr>
</tbody>
</table>

**Phase 1 Pilot Awardees**

<table>
<thead>
<tr>
<th>Project Leader</th>
<th>Grant</th>
<th>Institute</th>
<th>Project Title</th>
<th>Dates</th>
<th>Total Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belenky</td>
<td>R21</td>
<td>NCCHI</td>
<td>Dietary Fiber To Mitigate Antibiotic-Induced Microbiome Dysbiosis: A Multi-Omics Approach</td>
<td>7/18–6/20</td>
<td>$487,500</td>
</tr>
<tr>
<td>Beura</td>
<td>R01</td>
<td>NIDDK</td>
<td>Relating Impacts of Antibiotics on the Gut Metabolome and Microbiome to Host Physiology and Weight</td>
<td>9/20–8/25</td>
<td>$2,536,655</td>
</tr>
<tr>
<td>Crawford</td>
<td>R35 MIRA</td>
<td>NIGMS</td>
<td>Interpretable Machine Learning for Characterizing Broad-sense Heritability in Complex Traits and Rare Diseases</td>
<td>9/20–8/25</td>
<td>$1,869,560</td>
</tr>
<tr>
<td>Ené</td>
<td>R21</td>
<td>NIAID</td>
<td>Defining The Roles Of Perseverance And Hetero-resistance In Persistent Human Fungal Infections</td>
<td>6/18–5/20</td>
<td>$446,875</td>
</tr>
<tr>
<td>Webb</td>
<td>R01</td>
<td>NIA</td>
<td>Molecular Mechanisms Underlying The Preservation Of Neural Stem Cell Quiescence During Aging</td>
<td>7/17–6/22</td>
<td>$2,269,826</td>
</tr>
<tr>
<td>Wood</td>
<td>R03</td>
<td>NIA</td>
<td>Transcriptomic and epigenomic landscape of neurodegenerative disease models</td>
<td>1/21–12/22</td>
<td>$318,000</td>
</tr>
</tbody>
</table>

**Total**

$18,223,963

**Total: R01s and R35 only**

$15,153,988

**Initial COBRE Grant**

$11,500,000
welcomes new requests for analyses of ‘omics scale data sets, experimental designs, and software engineering to be successful. Only though the increased engagement with the larger community can we hope to reach the goal of sustainable computational biology support for the broader biomedical community at Brown University, its affiliated hospital research centers, and all researchers in Rhode Island.

PROGRESS
Research grants from junior faculty Project Leaders (PLs)
The CBHD COBRE has provided support for five initial PLs, six replacement PLs and eight Pilot Awardees in Phase 1. The PLs and Pilot awardees have successfully obtained external funding, with six R01s and an R35 MIRA awarded to date. Four of these awards were to the initial PLs and the remaining three were to Pilot awardees, two of whom transitioned to PLs after initial PLs graduated with R01 funding. Other notable grant successes are a T32, a USDA grant, two R21s, an R03, Searle Scholar Award and a Sloan Research Fellowship (see Table 1).

Publications and Presentations
The Project Leaders and Pilot awardees have been productive in publishing during Phase 1 of this COBRE. Table 2 lists the number of peer-reviewed publications by each COBRE investigator, whether a Project Leader or Pilot awardee. A similar activity is apparent in the number of conference presentations by these Project Leaders, or students in their laboratories.

Table 2. Peer-reviewed publications and conference presentations by CBHD PLs and Pilot Awardees.

<table>
<thead>
<tr>
<th>Project Leader</th>
<th>Year started</th>
<th>Peer-reviewed Publications</th>
<th>Conference Presentations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belenky</td>
<td>2017</td>
<td>17</td>
<td>10</td>
</tr>
<tr>
<td>Beura</td>
<td>2020</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Crawford</td>
<td>2018</td>
<td>8</td>
<td>26</td>
</tr>
<tr>
<td>DeCecco</td>
<td>2019</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Ene</td>
<td>2018</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Huang</td>
<td>2019</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Jamieson</td>
<td>2016</td>
<td>12</td>
<td>29</td>
</tr>
<tr>
<td>Lisi</td>
<td>2019</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Neretti</td>
<td>2016</td>
<td>16</td>
<td>22</td>
</tr>
<tr>
<td>Ramachandran</td>
<td>2016</td>
<td>15</td>
<td>36</td>
</tr>
<tr>
<td>Singh</td>
<td>2020</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Uzun</td>
<td>2016</td>
<td>12</td>
<td>21</td>
</tr>
<tr>
<td>Vaishnava</td>
<td>2016</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Webb</td>
<td>2017</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Wood</td>
<td>2019</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>115</td>
<td>178</td>
</tr>
</tbody>
</table>

Transitions of junior investigators
The Phase 1 project included five initial junior faculty PLs. Four of these PLs have received independent R01-level funding and graduated from COBRE support. The CBHD Pilot Program funded two one-year awards each year for four of the five years, supporting eight Pilot Awardees. As the initial PLs graduated, Pilot awardees applied to fill these positions, ultimately supporting 11 PLs. Seven PLs have graduated from the CBHD COBRE program during Phase 1. Of the eight Pilot awardees, five have been recruited to full Project Leader status with a sixth Pilot awardee being recruited as a PL in Phase 2.

Build the Computational Biology Core (CBC)
An important accomplishment of the Phase 1 project, and an ongoing goal of the CBHD COBRE, is to build and maintain the CBC. Based on surveys of analysis needs across the Brown biomedical community, three requests emerged: 1) to provide analysis and computing support for large-scale biomedical datasets for COBRE PLs, 2) to create and maintain a shared data repository and interfaces for projects within the COBRE and for additional projects in the local research community; and 3) to serve as a locus of formal and informal training, discussion and exchange of ideas on computational and statistical issues related to human disease (See Figure 1A). Hiring staff in this area is challenging given the competitive market for computational skills in the biotechnology industry. Four PhD-level data scientists staff the Computational Biology Core, and efforts are in place to continue the COBRE support to ensure this level of expertise can be maintained. The primary responsibility of the CBC staff is to support the COBRE PLs and Pilot Project awardees. To date this has included a wide range of activities from data analysis (RNA-seq, microbial 16S analysis as metagenomics, variant calling, CutandRun analyses for mapping DNA binding, and single-cell RNAseq) to software engineering (new software tool or expanding the application of a PL's in-house development). This work with COBRE PLs has led to joint publications in both biomedical discoveries and software development.1,5

To expand CBC’s reach to the broader Rhode Island biomedical community outside the COBRE PLs, the CBC staff have been developing reproducible bioinformatic workflows that are freely available and built-in Docker or Conda environments that increase portability to different operating systems ranging from personal laptops to Linux clusters. The focus has been on developing an infrastructure for long-term sustainability following best practices for: a) reproducibility in analysis, b) software engineering processes and procedures for building tools, and c) documentation (See Figure 1B). The tools for running standard bioinformatics workflows and streamlined storage of reference data are available at the CBC website (cbc.brown.edu). In addition, the CBC has partnered with other research centers at Brown, such as the
Brown Center for Biomedical Informatics (BCBI), the Center for Computational Molecular Biology (CCMB), and Brown’s central computing operation the Center for Computation and Visualization (CCV), to develop standardized procedures for the transfer and storage of large and restricted data sets (e.g., Globus, dbGaP). An advantage of devoting a COBRE Core facility to human resources (four data scientists) rather than specific pieces of equipment, is that equipment can become obsolete, but engaged data scientists can continue to learn. Clearly, both kinds of resources require continued support to remain a cutting-edge service facility. The main approach the CBHD COBRE is taking in pursuit of this goal is by learning from the broader community and integrating with other centers and RI IDEa programs.

Outreach, training and workshops for the broader community

The CBHD COBRE and CBC’s long-term goal is to serve as a hub for training by offering workshops and other forms of outreach to the broader Brown biomedical community. This has been realized through workshops on several bioinformatics workflows, such as RNAseq, microbiome analyses, and Ingenuity Pathway Analysis (IPA), among others. An important component of this outreach is the Open Office Hours program. Any user from the Rhode Island biomedical community can receive guidance on computational or bioinformatics analyses (the schedule for making an appointment is on the CBC website: cbc.brown.edu/services/#consulting). The CBC has had more than 228 participants in workshops from 59 departments (including 8 clinical), 41 participants in Office Hours from 17 departments, 86 participants in the IPA sessions, and 49 general consulting sessions (see Table 3 and Figure 2). These outreach activities provide service.
to the broader community and provide a picture of future needs for sustainability. The diversity of departments that have participated indicates there is a broad user base for future analyses. It has led to plans for collaborative efforts to seek external funding to support additional CBC staff in the future.

Accommodating this growing base of researchers has been greatly facilitated by the collaborative relationship between the CBHD COBRE and the Advanced Research Computing (ARC) group that resides within Brown’s Center for Computation and Visualization (CCV). The ARC group provides computing services for other units at Brown outside the biomedical sciences, offering depth in computational, statistical and informatics expertise that can strengthen the domain-specific skill sets behind computational biology sensu stricto. This affiliation creates an integrative working environment where new approaches are freely shared enabling creative solutions to researchers’ needs (see Figure 3). Extracting useful information from high-throughput technologies has blurred the boundaries between traditional topics in biostatistics (e.g., experimental design, multi-hypothesis testing), applied mathematics (e.g., graph and network theory, diffusion processes), and computer science (efficient algorithms, software engineering, database management, machine learning, etc.). This affiliation between the four CBC data scientists and 15 ARC staff creates an integrative working environment where new approaches are freely shared. By working in a diverse, supportive ecosystem, the team will learn more and stay current with best practices.

**PROSPECTS**

**Lessons learned**

The first five years of the CBHD COBRE have provided lessons in how to achieve sustainability into the future. A key factor is to adapt to changing service needs as the COBRE investigators graduate and are replaced, and as other members of the RI biomedical community seek assistance with their research. The pace of change in genomic and computational technologies has only accelerated in recent years, as has the breadth of researchers needing access to these technologies in the Rhode Island biomedical community. Microbiome analyses were in high demand among our initial cohort of PLs, and this has been replaced with single-cell RNAseq and various methods for quantifying chromatin accessibility. Single cell transcriptomics was an emerging technology a few years ago but has become a routine application. Notably, there are at least 15 different computational analysis pipelines for interpreting these data. Moreover, machine learning has exploded across all of data science with deep and wide applications in biology and medicine.

Thus, the ‘computational biology of human disease’ covers a wide range of topics from wet-bench molecular biology to ‘omics’-scale data sets, to software engineering. Sustaining excellence in this area for the State of Rhode Island can only be achieved by integrating with the other Centers, Institutes and IDEA programs across the State.

**Integration with Centers, Institutes, and IDEA Programs**

All of the IDEA programs in Rhode Island, by definition, strive to enhance biomedical research excellence in the State. The focus on medical and translational concerns is explicit in some programs [e.g., Advance-CTR], but research on non-human model organisms can take center stage in other programs. An important goal for the breadth of IDEA programs in RI is to maintain this support by coordinating resources across programs to avoid redundancies and enhance collaboration. The CBHD COBRE initiated a coordinating meeting with of Core Facilities Managers for all IDEA program in December 2019 to share goals, identify possible overlaps and collaborations, and ensure that resources are complementary. While all IDEA program had Design and Analysis Cores to meet each program’s specific needs, there was little overlap among the various Core facilities in immediate goals or expertise. From the perspective of computational and bioinformatic analyses of omics-scale biomedical data, the CBHD COBRE’s Core (CBC) remains highly complementary to other IDEA Program Core facilities, as well as other research entities at Brown, the affiliated hospitals and URI. The RI-INBRE supports several Core facilities including a dedicated PhD staff person in Bioinformatics [Dr. Chris Hemme]. The relationship between the RI-INBRE Bioinformatics Core and the CBHD COBRE is highly collaborative and complementary, especially in microbiome research. Dr. Hemme has worked with COBRE PL graduate Dr. Peter Belenky at Brown to initiate the Rhode Island Microbiome Consortium, hosting a Symposium in late 2019. In addition to being at different institutions, the demand for bioinformatics work through the RI-INBRE network is such that there is no overlap in our COBRE CBC services and the RI-INBRE bioinformatics services. This kind of collaboration is what will increase capacity and sustainability in the future.

In seeking to build the strength of biomedical research excellence in RI, we will continue to maintain
communications among these programs and ensure that the resources developed by each program can build the network of excellence that the IDEa program intends. The relationships among these entities is illustrated in Figure 4. In conclusion, and looking to the future, the simplest thing a researcher in Rhode Island can do is to come visit the CBHD COBRE and bring your data sets and questions. Only by engaging with new people and challenges can the program grow to serve the broader biomedical research community in Rhode Island.

Figure 4. Relationships between the COBRE Computational Biology Core (CBC) and other academic and service units at Brown, its affiliated hospitals and other IDEa programs in Rhode Island. The CBC is the only entity offering genome-enabled computational services to the Brown biomedical community. CCV is the Center for Computation and Visualization.

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CASE REPORT

Splenomegaly, Non-Traumatic Splenic Rupture, and Pancytopenia in Patient with Human Granulocytic Anaplasmosis

KATIE HSIA, MD’21; JENNIE JOHNSON, MD; DONALD RICE, MD

ABSTRACT

BACKGROUND: Splenic rupture is a well-described complication of babesiosis but is rarely associated with anaplasmosis.

CASE PRESENTATION: We report a case of a 37-year-old man with no significant past medical history who presented with malaise, myalgias, arthralgias and severe left upper quadrant pain. He was found to have splenic rupture secondary to infection by *Anaplasma phagocytophilum*. He reported a single tick bite the week prior to onset of his symptoms. On presentation, he was found to have left upper quadrant abdominal tenderness, pancytopenia, and splenomegaly with evidence of splenic rupture and hemoperitoneum on contrasted computed tomography. Blood smear did not demonstrate intraerythrocytic parasites or morulae. His hemoperitoneum was treated conservatively and he was empirically treated for babesiosis. Diagnosis was confirmed by a positive serum PCR for *Anaplasma phagocytophilum*.

CONCLUSIONS: This case study adds to the small number of prior case reports and provides evidence for anaplasmosis-associated splenic rupture.

KEYWORDS: splenic rupture, splenomegaly, anaplasmosis

BACKGROUND

Anaplasmosis is a tick-borne disease caused by *Anaplasma phagocytophilum* and was first identified in 1994. It typically occurring in summer months, anaplasmosis has an incidence of 6.3 cases per million, and is predominately reported in New England and the upper Midwest. Vermont, Maine, Rhode Island, Minnesota, Massachusetts, Wisconsin, New Hampshire, and New York report 90% of all cases, with incidence ranging from 6.5 per million to 32.1 per million in Rhode Island from 2000 to 2007. *Anaplasma* is primarily transmitted by the *Ixodes scapularis* tick, which is also competent vector for *Borrelia burgdorferi sensu lato* [infectious agent of Lyme disease], *Babesia microti*, *Borrelia miyamotoi*, and *Ehrlichia chaffeensis*. Coinfection with *Babesia* and *Anaplasma* have been reported at a rate of 7% in New York and 5.3% in the Wisconsin and Minnesota. In the literature, splenic rupture is a well-known complication of babesiosis. However, to date there has been only two case reports of non-traumatic splenic rupture in the setting of anaplasmosis. Those cases ultimately resulted in splenectomy and death. This case study adds to the limited body of literature of non-traumatic splenic rupture in anaplasmosis, unique in a relatively mild hospital course and absence of long-term sequelae of splenic rupture.

CASE PRESENTATION

A 37-year-old man with no significant past medical history presented with severe left upper quadrant pain. He worked outdoors as a stonemason’s aide and reported a single tick bite one week prior to presentation. About five days after the tick bite, he developed fatigue, myalgias, arthralgias, and malaise. Two days later, he developed acute onset of left upper quadrant abdominal pain radiating to the ipsilateral shoulder. The pain increased over the following 12 hours until he could not find a position of comfort, prompting him to seek medical care. He also reported a new retroorbital headache, but denied fever, rash, or neurologic changes.

He initially presented to the emergency department with a heart rate of 101, blood pressure of 107/79, respiratory rate of 16, and temperature of 97.9°F. On admission, his laboratory studies were notable for aspartate transferase of 24 iu/l, alanine transferase of 13 iu/l, white blood cell count of 1.5 x 10⁹/l (87% neutrophils and 7% lymphocytes), hemoglobin of 10.3 g/dl (baseline 15.4 g/dl), and platelet count of 56 x 10⁹/L. Blood smear did not demonstrate intraerythrocytic parasites or morulae. On contrasted CT, he was found to have moderate hemoperitoneum, splenomegaly to 15.4 cm, and hypodense focus in the periphery of the posterior spleen, which could represent a site of splenic rupture. He remained hemodynamically stable and his hemoperitoneum was treated conservatively.

Based on findings of anemia, leukopenia, thrombocytopenia, and splenic rupture with recent tick exposure in a highly endemic area, he was started on empiric treatment with azithromycin and atovaquone for concern of babesiosis. Additional workup included negative Lyme serology, Rickettsial serology including Rocky Mountain Spotted Fever and *Rickettsia typhi*, Epstein - Barr virus serology, Cytomegalovirus serology and PCR, Parvovirus serology, Hepatitis B serology,
and Hepatitis C serology. His white cell count and platelet count improved over the next two days, with resolution of lymphopenia, and his hemoglobin remained stable. His abdominal pain and malaise improved rapidly.

Prior to discharge, serum PCR testing was positive for *Anaplasma phagocytophilum* and had not yet resulted for *Babesia microti*. He was discharged on doxycycline for treatment of anaplasmosis and empiric azithromycin and atovaquone for presumed babesiosis coinfection. His serum PCR later resulted as negative for *Babesia microti*. He was evaluated in the outpatient infectious disease clinic a week after discharge and reported complete resolution of his symptoms. He completed a ten-day course of doxycycline as well as azithromycin and atovaquone.

**DISCUSSION AND CONCLUSION**

The initial presentation of anaplasmosis is often non-specific and overlaps with other tick-borne diseases, with symptoms including fever, chills, malaise, nausea, vomiting, arthralgias, headache. Symptoms usually develop five to fourteen days after tick bite. To date, the only two case reports of non-traumatic splenic rupture in the setting of anaplasmosis had positive PCR at a rate of 75.9% and microscopic detection at a rate of 60.7%. In babesiosis, the *Babesia* parasites can be identified on Giemsa- or Wright-stained thin or thick blood smears, where thin smear analysis adds information about degree of parasitemia. DNA PCR is more sensitive than blood smears, with a high sensitivity and specificity with little cross-reactivity with similar pathogens. However, it can remain positive weeks to months after parasitemia is no longer found on blood smear. IgM/IgG antibody serologic testing by indirect immunofluorescent assay can be performed, however seropositivity does not necessarily indicate active infection and may not immediately become positive in an active infection. Blood smear and PCR are the primary modes of confirming the diagnosis for both anaplasmosis and babesiosis.

This case study presents the diagnostic challenge of non-traumatic splenic rupture with normal LFTs, leukopenia, and mild anemia. A previous study found low platelets or low WBC in 81.3% of patients with anaplasmosis, with 49.3% with both low platelets and low WBC. Decreased hemoglobin was found to be statistically significant only in women, not men. The majority of patients initially present with lymphopenia and a minority of patients initially present with neutropenia. Neutropenia is more common in patients that had a longer duration of symptoms, typically greater than 4 days. This patient presented with neutropenia, thrombocytopenia, and normal LFTs. The significant drop in hemoglobin could be explained by the hemoperitoneum more so than anaplasmosis.

Diagnosis of anaplasmosis and babesiosis are primarily determined by clinical presentation in compatible season and geography, peripheral blood smear, and/or serum PCR. For *Anaplasma*, morulae in granulocytes can be seen on blood smear or buffy coat. Buffy coat and DNA PCR have a sensitivity of 77–80%. Serologic testing requires both acute and convalescent titers, as acute titers are not sufficiently sensitive. Microscopic detection of *Anaplasma* lacks sensitivity compared to PCR. In New York, patients with known anaplasmosis had positive PCR at a rate of 75.9% and microscopic detection at a rate of 60.7%. In babesiosis, the *Babesia* parasites can be identified on Giemsa- or Wright-stained thin or thick blood smears, where thin smear analysis adds information about degree of parasitemia. DNA PCR is more sensitive than blood smears, with a high sensitivity and specificity with little cross-reactivity with similar pathogens. However, it can remain positive weeks to months after parasitemia is no longer found on blood smear. IgM/IgG antibody serologic testing by indirect immunofluorescent assay can be performed, however seropositivity does not necessarily indicate active infection and may not immediately become positive in an active infection. Blood smear and PCR are the primary modes of confirming the diagnosis for both anaplasmosis and babesiosis.

This case study presents the diagnostic challenge of non-traumatic splenic rupture with normal LFTs, leukopenia, and thrombocytopenia. Splenic rupture is a known complication of babesiosis particularly in patients that present like this one. A case series from the same endemic area found splenic rupture in babesiosis at a rate of 1%, and was notable for being found in younger, healthier males with lower degrees of parasitemia. Anaplasmosis has been shown to be responsible for non-traumatic splenic rupture in only two reported cases of sicker patients. In this case, splenic rupture

![Figure 1. CT Abdomen Pelvis with contrast of the patient on admission demonstrating splenic rupture (arrow) and hematoperitoneum (H).](image-url)
and hemoperitoneum were the presenting symptoms of anaplasmosis, however the normal LFTs and low hemoglobin raise the question of an occult co-infection with Babesia microti. Serum PCR testing confirmed the presence of Anaplasma and absence of Babesia. Direct testing for potential coinfections is warranted in endemic areas for Babesia and Anaplasma in atypical presentations such as non-traumatic splenic rupture.

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Non-bacterial thrombotic endocarditis (NBTE) is characterized by the deposition of fibrin and platelet thrombi on previously undamaged heart valves in the absence of bloodstream infection. It is associated with chronic disease states and can present with systemic embolic disease. Here we report a case of NBTE presenting as recurrent strokes in a patient with bladder cancer. Importantly, transthoracic echocardiography has limitations to detecting valvular lesions in NBTE, and providers should consider obtaining transesophageal echocardiography in the setting of high clinical suspicion.

**KEYWORDS:** endocarditis, cryptogenic stroke, transthoracic echocardiography, transesophageal echocardiography, non-bacterial thrombotic endocarditis

**ABBREVIATIONS:** NBTE, TTE, TEE, LMWH, LSE

**INTRODUCTION**

Non-bacterial thrombotic endocarditis (NBTE) is characterized by the deposition of fibrin and platelet thrombi on previously undamaged heart valves in the absence of a bloodstream infection. NBTE is associated with both underlying malignancy as well as severe autoimmune disease. True prevalence may be underappreciated, as NBTE usually reaches clinical detection in the setting of cryptogenic stroke. Here, we report a case of NBTE presenting as a stroke in a patient with a known malignant disease.

**CASE REPORT**

A 60-year-old male with a history of muscle invasive bladder urothelial cancer presented to the emergency department with acute onset of confusion and aphasia. Per the patient’s family he had been in his usual state of health in the days prior to presentation. A code stroke was called on arrival in the emergency department. On exam the patient demonstrated expressive aphasia, right-sided neglect, and right upper extremity hypertonia. His initial NIHSS score was 12. No cardiac murmur was noted and there was no evidence of embolic phenomena on exam. The patient was not on cancer-directed therapy at the time of presentation; his oncologic treatment history to that time consisted of six cycles of cisplatin and gemcitabine completed two years prior, transurethral resection of the bladder, consolidative radiation therapy and four cycles of immunotherapy. His last treatment was a course of pembrolizumab, one year prior to presentation.

Notably, the patient had been recently admitted to the hospital three weeks prior for chest pain and was found to have bilateral subsegmental pulmonary emboli. His hospital course at the time was complicated by recurrent headaches which prompted brain magnetic resonance imaging (MRI) that revealed multiple punctate areas of diffusion restriction, believed to represent embolic infarcts. A transthoracic echocardiogram (TTE) was obtained to evaluate for valvular vegetations; however, no pathology was demonstrated (Figure 1). The patient received anticoagulation with therapeutic dose low molecular weight heparin (LMWH) to treat the pulmonary emboli, and was discharged home on enoxaparin 80 mg subcutaneously twice daily.

On this admission, after stabilization in the emergency department, the patient was admitted to the neurology service and continued on therapeutic LMWH. Computed tomography (CT) angiography of the brain and neck was negative for hemorrhagic stroke or occlusion of a major cerebral vessel. Brain MRI showed multiple new bilateral supra- and infratentorial acute non-hemorrhagic infarcts, worsened since his prior study, and most consistent with...
thromboembolic disease [Figure 2A, 2B]. With the interval worsening of apparent embolic disease, a repeat TTE was obtained. Echocardiography now showed thickened mitral leaflets with new moderate mitral regurgitation (Figure 3). There was no evidence of a right to left shunt following injection of agitated saline contrast, nor signs of a cardioembolic source of emboli, and no apparent tricuspid or pulmonic valve pathology. Transesophageal echocardiography (TEE) revealed a homogenous irregular fixed thickening of the anterior and posterior mitral valve leaflets suspicious

Figure 2A. Brain Magnetic Resonance imaging (MRI) on prior hospitalization showing patchy multifocal cerebral foci of diffusion restriction suggestive of multiple small acute and subacute cardioembolic ischemic infarcts.

Figure 2B. Brain MRI on index hospitalization showing multiple new bilateral supra- and infratentorial acute non-hemorrhagic infarcts, consistent with progression of embolic disease.

Figure 3. TTE image on index hospitalization displaying thickened mitral valve leaflets, with a restricted posterior leaflet and color doppler evidence of new mitral regurgitation when compared to prior.

Figure 4. Transesophageal Echocardiography (TEE) image on index hospitalization showing a homogenous irregular fixed thickening of the anterior and posterior mitral valve leaflet tips concerning for a thrombus or vegetation, with evidence of moderate mitral regurgitation.
for a thrombus versus vegetation and highly concerning for NBTE (Figure 4). Peripheral blood cultures, which had been obtained on admission, remained negative and the patient remained afebrile without a leukocytosis. In addition, the patient received abdominal CT imaging which demonstrated splenic infarcts, renal infarcts, and diffuse peritoneal thickening and omental nodularity, all concerning for progression of malignancy and systemic emboli. Anticoagulation was transitioned briefly to warfarin; however, the patient was ultimately treated with an increased LMWH dosage titrated to elevated anti-Factor Xa levels. A baseline anti-Factor Xa level was obtained at 4 hours after the prior dose, and LMWH dosage was increased to achieve a 25% greater peak anti-Factor Xa level.

Unfortunately, given his functional limitations, the patient was not a candidate for further cancer-directed therapy. Palliative care services were enlisted, and hospice services were offered but ultimately declined. The patient was discharged from the hospital to a rehab facility. He passed away two weeks after the admission.

**DISCUSSION**

In 1924 Dr. Eugene Libman categorized endocarditis into four major classes: rheumatic, syphilitic, bacterial and indeterminate. This indeterminate class was further characterized in a case series completed with Dr. Benjamin Sacks. Within this indeterminate category the authors included ‘terminal or cachectic endocarditis’ and noted the association between this entity and advanced chronic diseases such as malignancy, tuberculosis and chronic nephritis. Today we classify this indeterminate group as NBTE, also referred to as marantic endocarditis or verrucous endocarditis, and within it include the classic Libman-Sacks endocarditis (LSE) associated with systemic lupus erythematosus. The pathogenesis is thought to be related to a complex interplay between immune complexes, hypoxia, increased tissue factor (TF) and the hypercoagulable state of malignancy or other inflammatory conditions. Malignancy and rheumatological disorders lead to increased levels of circulating proinflammatory cytokines such as interleukin-1, interleukin-6 and tumor necrosis factor alpha. The effects of these cytokines can lead to endothelial injury, one of the three hallmarks of Virchow’s Triad contributing to thrombosis. Endothelial damage leads to exposure of subendothelial connective tissue to platelets, promoting aggregation and propagating thrombus formation. The host’s inflammatory response also plays a role, with increased leukocyte TF expression, and increased levels of factor VIII, fibrinogen and von Willebrand factor.

Prevalence data regarding NBTE and NBTE related to malignancy remains sparse. An autopsy series from the 1990s found 10 cases of NBTE among 1640 adult patients, 8 of which were associated with malignancy. An earlier autopsy series from the 1970s performed in patients with known malignant disease noted 75 cases of NBTE in 7,840 patients. The most comprehensive epidemiological review of NBTE to date comes from Lopez et al who examined 82,676 patients across fourteen autopsy studies and found prevalence rates of NBTE ranging from 0.4–9.3 %, with a combined total prevalence of 1.3%.

Echocardiography is critical to diagnosing NBTE. Lack of sensitivity in detecting valvular vegetations with TTE may necessitate the need for TEE in cases where high clinical suspicion exists, as was evident in this case. A randomized controlled trial compared the diagnostic accuracy of TTE compared to TEE in detecting LSE. TEE was significantly more likely to detect LSE than TTE, and TTE demonstrated a subpar sensitivity [63% overall, 11% for valve vegetations] and low negative predictive value (40%). The authors concluded that TEE should be considered as the initial test, or complement to a negative TTE, in cases of suspected cardiac embolism in patients with LSE. Additionally, a prospective study evaluated patients with acute embolic stroke of undetermined source (ESUS) and the effects of TEE findings on therapeutic management for secondary stroke prevention. These patients had received TTE prior to TEE as part of the diagnosis of ESUS. Of sixty-one patients who underwent TEE, abnormal findings were discovered in 52% of patients and these findings affected therapeutic management in ten (16%) of the cases.

Patients with NBTE are managed with anticoagulation, in contrast to patients with infective endocarditis and acute ischemic stroke. Vegetations in NBTE are easily dislodged, owing to the scant inflammatory reaction at the attachment site. As evidenced in this case, recurrent thromboembolism can occur despite treatment with subcutaneous LMWH. In instances of treatment failure, an increase in the dose of LMWH or a transition to direct oral anticoagulants are reasonable alternatives.

In conclusion, we report a case of recurrent stroke due to NBTE in a patient with a known malignant disease. A high clinical suspicion is paramount for diagnosis in these cases, and in patients with recurrent stroke and malignancy, TEE should be pursued to rule out valvular vegetations given the lack of sensitivity with TTE. Anticoagulation remains the cornerstone of management, as well as treatment of the underlying disease. Unfortunately our patient continued to have embolic disease despite anticoagulation. Further research is needed to clarify disease prevalence and to compare anticoagulation strategies.

**References**


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A Young Man with Herpes Zoster Meningitis

THOMAS M. GOMES, MD; NICHOLAS J. MUSISCA, MD, FACEP

From the Case Records of the Alpert Medical School of Brown University Residency in Emergency Medicine

DR. THOMAS M. GOMES: A 22-year-old man presented to the emergency department with a chief complaint of a rash, headache, neck stiffness and chills. The patient first noticed a cluster of red vesicles appear over his left elbow five days prior to arrival. The rash spread proximally and distally along the posterior aspect of his arm over the next few days, and he began to experience “electric” pains along the affected arm. The rash was never pruritic. He was seen by his primary care physician via a telehealth appointment on day 3 of his symptoms and was prescribed oral steroids due to concern for an allergic rash, but his symptoms did not improve. On the night prior to presentation, the patient developed gradual onset of a new occipital headache, neck stiffness and chills. He was referred to the emergency department the following day.

The patient denied any past medical, surgical or allergic history and was not taking any medications aside from the recent steroids. He denied tobacco use, but endorsed occasional alcohol and marijuana. Family history was significant for his mother in 2016, but he denied any close contact with her at that time.

DR. JONATHAN VALENTE: This patient had a localized rash, as well as a headache, neck stiffness and chills. Do you have any information regarding his immune status? Did he have any HIV risk factors? Was he up to date with vaccinations, and in particular, did he receive meningococcal vaccination?

DR. GOMES: Whereas a complete vaccination history was not available to us initially, he was reported to have received the VZV vaccine at age one and thirteen. He did attend college and was required to receive meningococcal vaccination. In order to attend public high school in RI the following vaccinations are necessary: DTaP (diphtheria, tetanus, pertussis), MMR, polio, varicella, HPV (human papillomavirus vaccine) and meningococcal conjugate vaccine (MCV4), as well as Hepatitis A, B, and Haemophilus influenzae. Of note, religious and medical exemptions are allowed. The patient had no HIV risk factors.

Figures 1a, 1b, 1c. A vesicular rash was present over the posterior aspect of his left upper extremity in the C8 dermatome, extending from the mid-triceps down to the ulnar aspect of his 5th finger.
**DR. JARED ANDERSON:** What was the patient’s physical exam?

**DR. GOMES:** The patient’s physical exam revealed a temperature of 36.4°C, HR 93, BP 119/60 mmHg, and oxygen saturation 99% on room air. He was fully alert and oriented and was otherwise well appearing. He had mild bilateral conjunctival injection, a clear oropharynx and normal auditory canals and tympanic membranes. A vesicular rash was present over the posterior aspect of his left upper extremity in the C8 dermatome, extending from the mid-triceps down to the ulnar aspect of his 5th finger. It was painful to touch and blanched with pressure (Figures 1a, 1b, 1c). A full skin exam was otherwise normal. The patient had slightly reduced range of motion in his neck with negative Kernig and Brudzinski signs and no midline tenderness. His cardiac, lung, and abdominal exam were normal and a full neurological exam was nonfocal.

Initial labs revealed a WBC count of 13.4 x 10^9/L with 78% segmented neutrophils and 12.3% lymphocytes. There were no bands reported. His hemoglobin was 14.6 g/dl, hematocrit 44.7%, and platelets 217,000. The BMP and liver enzymes were unremarkable.

**DR. THOMAS GERMANO:** What were your main considerations for this patient and what did you do?

**DR. GOMES:** The painful vesicular rash was most consistent with herpes zoster (i.e. shingles) given the gross C8 dermatomal distribution, the shooting electric quality of pain and the lack of improvement with steroids. Other diagnoses considered were contact dermatitis, dermatitis herpetiformis, a vasculitis or herpes simplex virus (HSV). Reports of SARS-CoV-2 infections producing vesicular lesions have also been reported in some individuals.1

The patient’s headache, neck stiffness and chills raised concern for meningitis. Examination maneuvers assessing for Kernig and Brudzinski signs, which were absent in this patient, have reported specificities of 95% and sensitivities of 5%, and therefore cannot be used to reliably exclude meningitis.2 Subarachnoid hemorrhage, encephalitis and migraine were also considered but thought to be less likely given the gradual onset of symptoms, absence of trauma, clear mental status and no migraine history. A varicella zoster virus (VZV) infection resulting in both herpes zoster and meningitis was a probable unifying diagnosis for his symptoms. Given these concerns, we performed a lumbar puncture (LP) in the emergency department.

**DR. SHIDEH SHAHIE:** Was there an indication for CT imaging prior to lumbar puncture?

**DR. NICHOLAS J. MUSISCA:** Lumbar puncture is a well-tolerated procedure with a low overall complication rate.3 However, there is a risk of potentially devastating cerebral herniation if performed on patients with elevated intracranial pressure (ICP). CT scans are often used to evaluate ICP status and mitigate this risk. Guidelines published by the Infectious Diseases Society of America (IDSA) recommend CT imaging prior to LP in patients who have any of the following: immunocompromised status, history of CNS disease, new-onset seizures within 1 week of presentation, papilledema, altered level of consciousness or focal neurological deficits.4 Adherence to these guidelines among American physicians is suboptimal, as evidence suggests that CT scans are obtained in greater than 60% of patients who do not meet these IDSA criteria.5 This liberal use of imaging is well-intentioned, but providers must also consider the cost, radiation and potential delays to treatment incurred by CT scans, especially since evidence suggests earlier antibiotic administration leads to better patient outcomes.6 Furthermore, inter-rater reliability among radiologists for identifying elevated ICP in patients with suspected meningitis may only be moderate at best.7

We did not think a CT scan before LP was necessary in our patient, because he did not meet any of the IDSA criteria and had no signs or symptoms suggestive of elevated ICP. The procedure was completed without complications.

**DR. SHAFIE:** Were antibiotics initiated before or after the lumbar puncture?

**DR. GOMES:** There is ample evidence demonstrating that delayed initiation of antibiotics leads to worse patient outcomes and increases the risk of both residual neurological deficits and mortality among patients with meningitis.5,8 Alternatively, there is concern that starting antibiotics prior to an LP may confound interpretation of CSF results and decrease the likelihood of growth in CSF cultures. Isolating the culprit pathogen is crucial, as it allows for antibiotic susceptibility testing to guide selection of an effective, narrow treatment regimen. These considerations are both reflected in the current IDSA practice guidelines, which suggest initiating antibiotics immediately after the LP, except for in cases where LP is likely to be delayed.4

All patients with suspected meningitis should be started on empiric treatment. Even if CSF cultures are able to be collected before the start of antibiotics, results will not be immediately available. The most frequently used regimen includes vancomycin and a third-generation cephalosporin. Evidence suggests that dexamethasone can improve outcomes and reduce mortality, but this benefit has only been observed in S. pneumoniae meningitis.9 Additional antibiotics and antiviral medications are added to this regimen based on patient risk factors, age, exposures, immune status and allergies. Patients above the age of 50 or under 1 month should receive ampicillin to cover for *L. monocytogenes*, and patients with symptoms suggestive of HSV or VZV should receive acyclovir.
Our patient was provided supportive treatment and started on intravenous vancomycin, ceftriaxone, dexamethasone and acyclovir immediately following LP.

DR. WILLIAM BINDER: What were the CSF results? Were there any other significant lab results?

DR. GOMES: The CSF appeared clear and colorless. Polymyxin was present with nucleated cell counts in the first and last tubes measuring 28 and 45 per mm³, respectively. The differential was significant for high PMNs (31%) and low lymphocytes (42%). No organisms were seen on Gram stain. Protein was slightly elevated at 85mg/dL and glucose was normal at 61mg/dL. RBC count in tube one was 218 per mm³ and decreased in tube four to 1 per mm³, which corresponds with a traumatic tap. An opening pressure was not obtained. The overall results suggested viral meningitis. Note that a predominance of PMNs, as seen in this patient, is often described early in viral meningitis that precedes the later lymphocyte predominance.¹⁰

PCR testing of the CSF was positive for VZV. Serum screening for VZV antibodies was positive for IgG and equivocal for IgM.

CSF testing for HSV and enterovirus were negative. A respiratory pathogen panel including SARS-CoV-2 was also negative. The CSF culture showed no growth after 48 hours.

Our patient was immunocompetent and had a negative HIV test in the emergency department, he was prescribed oral steroids two days prior to the development of meningitis symptoms. The overall results suggested viral meningitis.

DR. GOMES: Is this an unusual course of disease for this infection? Is it unusual for a young, healthy individual to have herpes zoster? Did he have risk factors?

Varicella zoster is a neurotropic double-stranded DNA virus and member of the Herpesviridae family. It infects nearly all humans.¹¹ An initial infection with VZV most often manifests with systemic symptoms and a diffuse vesicular rash termed Varicella zoster (i.e. chickenpox). After the clinical manifestations resolve, the virus persists in the dorsal root ganglia (DRG) indefinitely, and is kept latent by the immune system. Reactivation of the virus is common among older adults due to immune senescence and frequently results in the herpes zoster rash (i.e. shingles). Reactivation along branches of the trigeminal or facial nerves – referred to as herpes zoster ophthalmicus and herpes zoster oticus (i.e. Ramsay-Hunt Syndrome), respectively – can threaten vision or hearing. VZV reactivation can lead to necrotic destruction of ganglia and migration of the virus out of nerves and into the blood or CSF, which puts patients at risk for a number of complications like vasculitis and meningitis.¹² This destruction of nerves is also responsible for the lingering pain of post-herpetic neuralgia that may follow shingles.¹²

DSR. MUSISCA: An estimated one million cases of herpes zoster are diagnosed annually in the United States.¹³,¹⁴ Major risk factors for herpes zoster include history of VZV exposure, advanced age and immunocompromised status.¹³ The vast majority of cases occur in adults >55 years of age, although the incidence of HZ among those aged 18 to 54 has been steadily climbing since 1993.¹⁴ Proposed explanations for this trend include heightened provider awareness and more frequent use of immunosuppressive medications, but no definitive answer has been discerned. Therefore, the occurrence of HZ and VZV meningitis in our patient – a previously immunized 22-year-old with no history of chickenpox – was unusual.

Although the VZV vaccine series is nearly 90% effective,¹⁵ recipients may still become infected if exposed to VZV – termed “breakthrough varicella.”¹⁶ Breakthrough infections most often result in mild or even asymptomatic disease, but reports of serious complications including pneumonia, transverse myelitis, pancytopenia, hepatitis, myocarditis, and even death have been noted.¹⁷ Even in the absence of community exposure to VZV, the strain delivered in the live-attenuated vaccine may itself re-activate. A study of immunized patients with active HZ lesions found that both the wild-type and vaccine-type VZV strains were present in almost equal frequency.¹⁸ Therefore, our patient’s symptoms were likely due to either re-activation of wild-type VZV from a past subclinical exposure, or re-activation of the vaccine-type VZV strain.

Varicella zoster virus accounts for an estimated 7% of viral meningitis cases¹⁹ and may be more prevalent among those <50 years of age.²⁰ More commonly, viral meningitis is due to infection with enteroviruses or HSV.¹⁹ Notably, there was a sharp decline in the incidence of bacterial meningitis following the introduction of vaccines against H. influenza, S. pneumoniae and N. meningitidis.²¹ Although our patient was immunocompetent and had a negative HIV test in the emergency department, he was prescribed oral steroids two days prior to the development of meningitis symptoms. The immunosuppressive effects of steroids have been implicated in a case report of HZ and VZV encephalitis seen in a 19-year-old female who, like our patient, had been vaccinated, was otherwise healthy and had no history of chickenpox.²²

DR. ELIZABETH SUTTON: What was the outcome for this patient?

DR. GOMES: We are happy to report a good outcome for this patient. He received supportive care and was continued on IV acyclovir throughout the 4 days of his hospitalization. His symptoms gradually improved and he was asked to complete a 10-day course of oral valacyclovir at the time of discharge. His overall hospital course and recovery were uncomplicated.
References


A Cross-sectional Survey on the Use of Tranexamic Acid in the Pre-hospital Setting

MEAGAN KOZHIMALA, MD-ScM’21; NICHOLAS ASSELIN, DO, MS; MARK R. ZONFRILLO, MD, MSCE

ABSTRACT

STUDY OBJECTIVE: Tranexamic Acid (TXA), an anti-fibrinolytic, has been used in military trauma cases and civilian Emergency Departments for several years. This study aimed to evaluate protocols for the administration of TXA across Emergency Medical Services (EMS) regions in the United States.

METHODS: An anonymous survey was distributed by the National Association of Emergency Medical Technicians (NAEMT) to its members.

RESULTS: A total of 264 eligible responses were received. Respondents included paramedics (62.5%), emergency medical technicians (EMTs) (9%), critical care paramedics (11%), and other healthcare professionals (19%). The majority of protocols included criteria for blood pressure (67%), heart rate (53%), and age (66%). Notable variations included TXA dilution and indications for traumatic brain injury.

CONCLUSION: TXA has been widely implemented in EMS protocols since the CRASH (Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage) trials. However, there remains significant variations in indications and dose concentrations.

KEYWORDS: TXA, Tranexamic Acid, Pre-hospital, EMS protocol

INTRODUCTION

Tranexamic Acid (TXA), an anti-fibrinolytic, was originally used in the military to control hemorrhage in trauma victims.1 The Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage (CRASH) trials indicated that early use of TXA for trauma patients with or at risk of hemorrhage was correlated with a significant reduction in mortality.2 Since the 1960s, TXA has been part of civilian care in obstetrics and gynecology,3 otolaryngology,4 and emergency medicine. More recently, it has been used by Emergency Medical Services (EMS) prior to the patient’s hospital arrival.5 Several published research studies over the years show benefits and complications of TXA. The use of TXA was shown to decrease mortality in uterine hemorrhage.6 One randomized controlled study showed that topical use of TXA significantly decreased bleeding time and recurrence rates of epistaxis compared to acute packing.7 There have been several published studies and case reports regarding the use of TXA in emergency medicine for various indications, including gastrointestinal hemorrhage,8 traumatic hemorrhage,9 and hemoptysis.10 However, its use in EMS is more recent and there is limited knowledge on the use of protocols for pre-hospital administration of TXA and how they might differ across the United States (US). This study aimed to evaluate the prevalence of specific protocols in the EMS setting across US regions and identify the inclusion/exclusion criteria utilized.

METHODS

This cross-sectional survey study was determined to be exempt from review by our institutional review board. Participation was voluntary and anonymous. Consent was implied by clicking on a link. The survey targeted paramedics and emergency medical technicians (EMTs). Participants also included nurses, physicians, and other healthcare professionals involved in transport of patients to a hospital. Participants were excluded if they did not provide civilian care in the pre-hospital setting in the US. The 23-item survey was designed with Qualtrics (Qualtrics, LLC; Provo, Utah). It included multiple choice and free text questions and incorporated skip logic. The survey was reviewed by content and methods experts, as well as by the National Association of Emergency Medical Technicians (NAEMT) technical board. To ensure clarity of survey items, the questionnaire was piloted with survey design experts and paramedics prior to wider distribution to the NAEMT website. The complete survey instrument is available upon request.

Questions focused on the presence of prehospital TXA protocols and the inclusion/exclusion criteria utilized. Specific survey items were based upon the published literature from the CRASH-2 trials2 as well as the protocol by Strosberg and colleagues.11 Participants were also asked to indicate in which region of the US they practice. The five NAEMT regions consist of the following states:

- East region: CT, DE, ME, MD, MA, NH, NJ, NY, PA, RI, VT, VA, DC, WV
- South region: AL, AR, FL, GA, KY, LA, MS, NM, NC, OK, SC, TN, TX
- Great Lakes region: IL, IN, MI, MN, OH, WI
- Western Plains region: CO, IA, KS, MO, MT, NE, ND, SD, UT, WY
- West region: AK, AZ, CA, HI, ID, NV, OR, WA

Responses were collected in December 2019.
RESULTS

Demographics and Existence of Protocols

Of the 268 responses received, 264 were included for this study. Four were excluded for the following reasons: did not provide care in a pre-hospital setting (n=2), part of military care (n=1), and located outside of the U.S. (n=1). Of the 264 responses, 62.5% [n=180] of respondents were paramedics, 8.7% [n=25] were EMTs, 10% [n=29] were critical care paramedics, and 19% [n=54] identified as another health care professional, including flight nurses, transport physicians, EMS physicians, and respiratory therapists. The respondents’ demographics are shown in Table 1.

Table 1. Demographics of survey participants

<table>
<thead>
<tr>
<th>Role</th>
<th>#</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paramedic</td>
<td>180</td>
<td>62.5</td>
</tr>
<tr>
<td>Critical care paramedic</td>
<td>29</td>
<td>10.1</td>
</tr>
<tr>
<td>Emergency medical technician (EMT)</td>
<td>25</td>
<td>8.7</td>
</tr>
<tr>
<td>Flight paramedic</td>
<td>12</td>
<td>4.2</td>
</tr>
<tr>
<td>Advanced EMT (or other intermediate)</td>
<td>7</td>
<td>2.4</td>
</tr>
<tr>
<td>Flight nurse</td>
<td>6</td>
<td>2.0</td>
</tr>
<tr>
<td>Critical care transport nurse</td>
<td>4</td>
<td>1.4</td>
</tr>
<tr>
<td>Emergency medical services physician</td>
<td>5</td>
<td>1.7</td>
</tr>
<tr>
<td>Other physician</td>
<td>3</td>
<td>1.0</td>
</tr>
<tr>
<td>Respiratory therapist</td>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td>Emergency medical responder</td>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td>“Other”</td>
<td>15</td>
<td>5.2</td>
</tr>
</tbody>
</table>

* There were 288 roles selected by 264 respondents

Three-quarters [n=198] of survey participants stated that TXA administration was within the scope of practice for EMS and used at their institution. Of survey participants who use TXA in their setting, a majority (62%), stated its use is controlled by a protocol or standing order, followed by provider judgement (20%), and medical director (13%). Few participants (5%) selected “Other,” which included the use of an online medical control system or physician authorization. Of the 198 respondents who stated that TXA administration was within the scope of practice for EMS, not all completed the subsequent questions which is reflected in the following analyses.

Development of Institutional Protocols

Participants shared how their existing protocol for TXA was developed and 37% [n=72] indicated development by a medical director. Several (31%, n=50) indicated a multi-disciplinary approach to development, involving medical directors, EMS services, trauma committee, and State Departments of Health. An individual breakdown of the various means of creating a protocol were reported as follows: State Departments of Health or other state agency (14%, n=28), EMS services (13%, n=26), adopting an existing protocol from another system or source (8%, n=15), regional EMS Agency (10%, n=17), internal committee (9%, n=18), and an external committee (4%, n=7).

Comparison of Existing Protocols

Inclusion Criteria: In all 5 regions, the majority of responses indicated their institutions’ protocols had requirements for evidence of age-appropriate shock determined by vital signs. A majority (54%, n=61) of participants indicated a minimum age criterion for administering TXA. Minimum age criteria ranged from 2-18 years old with a mode of 16 years old. Minimum heart rate criteria were included in 53% (n=60) of the respondents’ institutions’ protocols, most commonly >110 bpm (55%, n=33) and >120 bpm (23%, n=14). Other minimum heart rates included 115 bpm (n=3), 100 bpm (n=4), and 130 bpm (n=2). A systolic blood pressure (SBP) requirement was indicated in 60% (n=70) of participants’ protocols, nearly all with the threshold of SBP<90 mmHg (94%, n=66). Time criteria was indicated by 74% (n=85) and a requirement of injury or bleeding occurrence within 3 hours of TXA administration was selected by 93% (n=79). Other responses had the following time windows: 1 hour (n=2), 2 hours (n=2), and 8 hours (n=1).

Exclusion Criteria: An allergy or hypersensitivity to TXA was indicated by 45% (n=77) as an exclusion criterion and disseminated intravascular coagulation was part of the exclusion criteria for 20% (n=34). In addition, 23% (n=39) of participants stated their protocol had exclusion criteria that were not included as survey options which included: traumatic brain injury (TBI), drowning, prior thromboembolic disease, dialysis, renal failure, cardiac arrest, and pregnancy (specifically > 24 weeks gestation). Approximately 11% (n=18) of participants stated their protocols had no exclusion criteria.

Medication Administration

Intravenous [IV] delivery of TXA was indicated in 56% (n=109) of responses, with 41% (n=79) also allowing intranasal [IO] delivery. Alternative delivery such as transdermal, topical, and intranasal was reported by 3% (n=6).

All participants who indicated their institution had a TXA protocol (100%, n=165) stated that their protocol had dose requirements, with 16% (n=18) of participants stating, “1000 mg in 250 cc NS” and 29% (n=32) had “1 g mixed in 50 cc”. However, the majority of the respondents, (46%, n=51), stated a different concentration from the options offered. Of those 51 respondents, 90% (n=46) stated their protocol had a concentration of 1 gm in 100 cc of NS. One participant had “Trauma arrest 1 gm IVF” and one indicated weight-based dosing.

A majority (83%, n=137) of participants with TXA protocols at their institutions stated that their system did not have other options for treating acute blood loss, such as administration of blood products. And 17% (n=28) stated they did have other options, including packed red blood cells, plasma, fresh frozen plasma, and QuickClot® (kaolin impregnated gauze).
Actual Use of Protocol in Possible Administration of TXA
The survey also assessed how many times participants assessed a patient for use of TXA over the past year, most commonly more than 4 times within the year (31%, n=34) and zero instances in the past year (28%, n=36). The remaining frequencies for TXA assessment were as follows: 1 time (14%, n=15), 2 times (15%, n=16), 3 times (5%, n=5), and 4 times (4%, n=4). The regional distribution of frequencies for TXA administration across regions is shown in Table 2.

For those situations where patients were assessed regarding the administration of TXA, a majority (42%, n=86) were related to trauma. Other instances comprised of the following: gastrointestinal hemorrhage (10%, n=21), signs of shock (9%, n=18), obstetrics/gynecological hemorrhage (7%, n=15), epistaxis (5%, n=11), wounds (5%, n=11), TBI (4%, n=9). TBI was indicated as a reason for assessment for TXA administration in all regions, except the East region.

When asked to describe the settings where they delivered care, most participants stated Urban [32.59%, n=132] or Rural [33.83%, n=137]; 26.17% [n=106] were suburban, and about 7% [n=28] were “Austere/Very Rural.” Of those participants, the distribution of those that indicated the existence of a protocol at their institution was as follows: 86% [n=24] for austere settings, 73% [n=101] for rural, 64% [n=68] for suburban, and 61% [n=81] for urban.

In all 5 regions, the majority of responses indicated that TXA administration was regulated by a protocol or standing order. The exact breakdown by region is seen in Figure 1.

Of participants that did administer TXA to patients in the pre-hospital setting, a majority (36%, n=44) indicated that they administered TXA within 16–30 minutes from onset of injury or bleed. The rest of the time frames from onset of injury or bleed are detailed in Table 4. The ascending order of regional distribution of overall survey participants did not exactly match that of NaemT members. However, the ascending order of survey participants who stated they had a TXA protocol did align with that of NaemT members’ regional distributions.

Table 3. Geographic distribution of survey participants and NAEMT members based on EMS regions

<table>
<thead>
<tr>
<th>Region</th>
<th>East</th>
<th>South</th>
<th>Great Lakes</th>
<th>Western Plains</th>
<th>West</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survey (n=164)</td>
<td>36%</td>
<td>31%</td>
<td>17%</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>NAEMT (n=101,805)</td>
<td>24%</td>
<td>38%</td>
<td>13%</td>
<td>10%</td>
<td>15%</td>
</tr>
</tbody>
</table>

Regional Distributions
The regional distribution of responses were: East [36%, n=62], South [31%, n=52], Great Lakes [17%, n=29], Western Plains [8%, n=14], and West [8%, n=13]. This distribution compared to the regional distribution of NAEMT members can be seen in Table 3. The region with the highest percentage of respondents who reported TXA administration protocols were from the South region [38%, n=37], followed by the East region [24.7%, n=24], Great Lakes [16.5%, n=16], Western Plains [9.3%, n=9], and West [11.3%, n=11]. The ascending order of regional distribution of overall survey participants did not exactly match that of NAEMT members. However, the ascending order of survey participants who stated they had a TXA protocol did align with that of NAEMT members’ regional distributions.
injury or bleed were as follows: 5–15 min (36%, n=44), 31–60 minutes (27%, n=33), >61 minutes (3%, n=4). Across all 5 regions, TXA administration was predominantly 16–30 minutes from onset of injury. Only the South and Great Lakes regions indicated TXA administration >1 hour from injury onset. The regional distribution for time of TXA administration from injury onset is presented in Table 4.

Average transport times varied across regions (Table 5). However, all 5 regions had a majority (49%, n=63) of its participants indicate an average transport time of 15–30 minutes. An average transport time of over an hour was only indicated by the South region. The West region did not have any average transport time greater than 45 minutes.

DISCUSSION
The results offer a novel, national perspective on EMS TXA protocols. The creation of protocols varied among participants and many indicated several means of development. A majority of responses indicated that protocols shared similarities for inclusion criteria for heart rate, age, and blood pressure. Additionally, these criteria values matched those that were introduced by Strosberg et al and aligned with the findings of the CRASH-2 trials. The CRASH-2 trial demonstrated that TXA administration after 3 hours of injury was correlated with increased mortality. The majority of protocols described in this survey study indicated an inclusion criteria of < 3 hours from onset of bleed for TXA to be administered, although there were outliers. Similarly, most participants who received TXA were administered a concentration of 1 gm/100cc over ten minutes. This concentration is different from the original protocol included in Strosberg et al, which recommended a 1g/50 cc dose. This could be explained by the known adverse effect of hypotension with rapid infusion of TXA at >100mg/min.

The survey responses identified variability in inclusion and exclusion criteria. Some institutions included TBI as an indication for TXA use while others stated it was a clear contraindication. The 2018 TICH-2 trial (tranexamic acid for hyperacute primary intracerebral hemorrhage) results showed no significant difference in functional status of patients receiving TXA vs placebo. However, the more recent CRASH-3 trial results showed that TXA administration within 3 hours for mild-moderate head injury resulted in significant mortality reduction and improved functional status without increased adverse effects. In contrast, there was no significant difference in mortality for severe head injuries. These respective findings may have influenced the variability in use of TXA for TBI at the institutions surveyed. Differing interpretations of the CRASH-3 trial findings may have contributed to the variability in TBI as an identified for TXA administration. Similarly, several protocols had cardiac arrest as an exclusion criterion while one stated it was an inclusion criterion. Although there were differences in administration times and average transport times, none of these times surpassed the recommended 3-hour window for administering TXA.

This study is limited by its small sample size and is subject to selection bias. The survey was directed towards members of a national EMS organization, limiting the generalizability of results. However, the representation of participants across regions offers a reasonable sample of the current state of protocols for TXA administration in EMS. Compared to the regional distribution of NAEMT members, where majority were from the South region, participants showed a majority of responses from the East region. One possibility is bias of recognition due to participants knowing our institution is located in the East region. However, the participants that had a TXA protocol at their institution did align with the regional distribution of NAEMT members, possibly showing a link to protocols and the influence of the organization. Additionally, information that was provided might not be accurate if participants answered questions based on memory of protocol criteria, subjecting this study to recall bias and subjective survey language could have been misinterpreted.

CONCLUSION
Protocols are an important part of TXA administration in the pre-hospital setting. In our survey, the majority of reported protocols had several similarities, including inclusion criteria for blood pressure, heart rate, and age. While many of these criteria aligned with original TXA protocols, there was variability in the relative inclusion of TBI and the admixture concentration for TXA. The persistence of these variations along with those in inclusion and exclusion criteria suggest a joint scientific statement from national organizations that oversee EMS care may be beneficial in encouraging evidence-based protocols. In 2019, the National Highway Traffic Safety Administration created broad guidelines for EMS care in the National EMS Scope of Practice model, however, this guidance does not include any medications. Based on the variation in protocols observed in our survey, it may be beneficial to consider the addition of specific medications to this model, including TXA, to optimize a standard of care for patients in the pre-hospital setting.

References


**Acknowledgments**

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**Disclaimer**

The views expressed herein are those of the authors and do not necessarily reflect the views of NAEMT or Brown University.

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Association Between Cancer Diagnosis and Mental Health Among RI Adults, 2018

EMILY GOODSPeed, BS; ANNIE GJELSVIK, PhD; C. KELLY SMITH, MSW

INTRODUCTION
Cancer is a pressing public health issue as it is the second leading cause of death in the United States today. The National Cancer Institute (NCI) estimates that 39.5% of all Americans will be diagnosed with cancer at some point in their lives. There were an estimated 16.9 million cancer survivors in the United States as of 2019, and this number continues to increase over time. The incidence of cancer in the United States is 442.4 cases per 100,000 people. In Rhode Island, cancer incidence is just as concerning, with 468.5 new cases per 100,000 people annually. Nationally, cancer has been shown to disproportionately affect different racial/ethnic and socioeconomic groups such as Black individuals and those with lower annual incomes and levels of education.

While an increasingly larger number of Americans are being diagnosed with cancer each year, overall cancer mortality is decreasing due to improved screening and early detection and advances in cancer treatment. This means that more and more Americans are considered cancer survivors and are living with this chronic condition. Cancer treatment has been shown to negatively impact aspects of a cancer survivor’s health related quality of life (HRQoL). Among these effects is mental health. Psychological well-being among cancer patients is an unmet need that needs to be addressed. Approximately 10% of cancer survivors need formal mental health support within one year of diagnosis. Additionally, 73% of cancer survivors with depression do not receive necessary mental health treatment. The relationship between cancer diagnosis and mental health in Rhode Island is not fully understood. This paper examines the relationship between a cancer diagnosis and self-reported days of poor mental health among Rhode Island adults. Based on the literature, we hypothesized that individuals with cancer will have significantly more reported days of poor mental health compared to those who have never been diagnosed with cancer.

METHODS
We analyzed data from the 2018 Rhode Island Behavioral Risk Factor Surveillance System (RI BRFSS). The RI BRFSS surveys non-institutionalized adults (18 years or older) who live in Rhode Island via telephone interviews. This survey, sponsored by the Centers for Disease Control and Prevention (CDC), collects self-reported data on preventive health behaviors, risk behaviors, and health status. The 2018 Rhode Island BRFSS contains a total of 5,607 observations. For the purposes of this study, we included only individuals who had valid data for responses to questions about cancer and mental health (Table 1). We therefore excluded 101 observations (1.8% of the eligible population) from our analytic sample. Our final analytic sample included 5,506 observations.

According to the American Cancer Society, “an individual is considered a cancer survivor from the time of diagnosis, through the balance of his or her life.” Therefore, we categorized individuals who answered “Yes” to the question: “Has a doctor, nurse, or other health professional ever told you that you had any other types of cancer [other than skin cancer]?” as cancer survivors. For those who responded “I don’t know” to this question, we categorized them as not having cancer. Additionally, we chose to exclude individuals with skin cancer in our analysis because 8 out of 10 cases of skin cancer are basal cell carcinomas. This type of skin cancer is slow-growing, rarely spreads to other parts of the body, and rarely requires lengthy treatment.

The outcome of interest in this study was mental health status. To operationalize this variable, we included participants who answered the question: “Now thinking about your mental health, which includes stress, depression, and problems with emotions, for how many days during the past 30 days was your mental health not good?” Based on their responses, we placed participants into either the 0–1 days or the 2+ days category. We selected sex, race/ethnicity, age, sexual orientation, education, and income as sociodemographic variables to describe the study sample. Because of small frequencies, we categorized sexual orientation as a binary variable. Respondents who indicated that they were “Straight, that is, not gay” were categorized as Heterosexual and respondents who indicated either “Gay or Lesbian”, “Bisexual”, or “Something else” were categorized as Sexual Minority. We analyzed weighted data using the statistical software STATA version 16.0 to obtain population-based estimates for Rhode Island adults. We conducted cross tabulations of our outcome variable (mental health), sociodemographic variables, and potential confounders with our exposure variable (cancer). By doing this, we were able...
to obtain frequencies and weighted percentages for each variable (Table 1). We also calculated unadjusted and adjusted odds ratio using logistic regression (Table 2).

**Table 1.** Characteristics of Rhode Island adults by cancer status: 2018 RI BRFSS.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Ever Diagnosed with Cancer (n=5,506)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n=4,895)</td>
<td>Yes (n=611)</td>
</tr>
<tr>
<td>Days of Poor Mental Health</td>
<td>Weighted %</td>
<td>Weighted %</td>
</tr>
<tr>
<td>0–1</td>
<td>66.4% (3413)</td>
<td>70.9% (440)</td>
</tr>
<tr>
<td>2+</td>
<td>33.6% (1482)</td>
<td>29.1% (171)</td>
</tr>
<tr>
<td>*Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>48.9% (2191)</td>
<td>38.6% (237)</td>
</tr>
<tr>
<td>Female</td>
<td>51.1% (2690)</td>
<td>61.4% (372)</td>
</tr>
<tr>
<td>*Race/Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td>74.3% (4018)</td>
<td>87.7% (558)</td>
</tr>
<tr>
<td>Black, non-Hispanic</td>
<td>5.3% (187)</td>
<td>16.1% (11)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>13.8% (408)</td>
<td>4.6% (15)</td>
</tr>
<tr>
<td>Other, non-Hispanic</td>
<td>6.7% (282)</td>
<td>6.1% (27)</td>
</tr>
<tr>
<td>*Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–44</td>
<td>47.4% (1319)</td>
<td>8.8% (27)</td>
</tr>
<tr>
<td>45–54</td>
<td>16.2% (843)</td>
<td>14.4% (53)</td>
</tr>
<tr>
<td>55–64</td>
<td>17.4% (1138)</td>
<td>19.6% (121)</td>
</tr>
<tr>
<td>65 or older</td>
<td>18.9% (1595)</td>
<td>57.2% (410)</td>
</tr>
<tr>
<td>Sexual Orientation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterosexual</td>
<td>92.9% (4342)</td>
<td>95.7% (558)</td>
</tr>
<tr>
<td>Sexual Minority</td>
<td>7.1% (266)</td>
<td>4.3% (30)</td>
</tr>
<tr>
<td>Education (highest level)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below high school graduate</td>
<td>12.5% (339)</td>
<td>11.0% (37)</td>
</tr>
<tr>
<td>High school graduate</td>
<td>27.9% (1189)</td>
<td>27.0% (129)</td>
</tr>
<tr>
<td>Some college or technical school</td>
<td>29.7% (1262)</td>
<td>27.9% (159)</td>
</tr>
<tr>
<td>College graduate +</td>
<td>29.9% (2079)</td>
<td>34.1% (286)</td>
</tr>
<tr>
<td>Income</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than $35,000</td>
<td>27.3% (1341)</td>
<td>28.4% (169)</td>
</tr>
<tr>
<td>Less than $50,000</td>
<td>9.3% (452)</td>
<td>9.5% (69)</td>
</tr>
<tr>
<td>Less than $75,000</td>
<td>11.5% (591)</td>
<td>14.3% (90)</td>
</tr>
<tr>
<td>$75,000 or more</td>
<td>33.0% (1608)</td>
<td>27.3% (159)</td>
</tr>
<tr>
<td>Missing</td>
<td>18.9% (903)</td>
<td>20.4% (124)</td>
</tr>
</tbody>
</table>

1 Weighted column percentages are reported.
*(p<0.01)

**Table 2.** Unadjusted and Adjusted Odds Ratios of Multiple Days of Poor Mental Health among Adult Cancer Survivors in Rhode Island. RI BRFSS 2018.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Unadjusted OR (95% CI)</th>
<th>*Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>Female</td>
<td>1.9 (1.1, 3.0)</td>
<td>1.3 (0.7, 2.4)</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>Black, non-Hispanic</td>
<td>3.5 (0.9, 13.7)</td>
<td>8.3 (1.3, 54.7)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.5 (0.1, 2.2)</td>
<td>0.3 (0.1, 1.9)</td>
</tr>
<tr>
<td>Other, non-Hispanic</td>
<td>1.9 (0.6, 5.6)</td>
<td>1.6 (0.5, 5.3)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65+</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>18–44</td>
<td>3.7 (1.5, 9.2)</td>
<td>3.5 (1.3, 9.9)</td>
</tr>
<tr>
<td>45–54</td>
<td>2.2 (1.0, 4.7)</td>
<td>2.4 (1.0, 5.6)</td>
</tr>
<tr>
<td>55–64</td>
<td>1.6 (0.9, 2.8)</td>
<td>1.5 (0.7, 3.0)</td>
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<tr>
<td>Sexual Orientation</td>
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<tr>
<td>Heterosexual</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>Sexual Minority</td>
<td>2.5 (1.7, 3.5)</td>
<td>2.0 (0.8, 4.8)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graduated from college/technical school</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>Did not graduate HS</td>
<td>1.7 (0.7, 4.2)</td>
<td>2.3 (0.7, 7.0)</td>
</tr>
<tr>
<td>Graduated HS</td>
<td>1.5 (0.8, 2.7)</td>
<td>1.5 (0.7, 3.2)</td>
</tr>
<tr>
<td>Attended college/technical school</td>
<td>1.0 (0.6, 1.8)</td>
<td>0.9 (0.4, 1.7)</td>
</tr>
<tr>
<td>Income</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$75,000 or more</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>Less than $35,000</td>
<td>1.9 (1.0, 3.9)</td>
<td>1.8 (0.8, 4.1)</td>
</tr>
<tr>
<td>Less than $50,000</td>
<td>1.6 (0.7, 3.5)</td>
<td>1.9 (0.8, 4.4)</td>
</tr>
<tr>
<td>Less than $75,000</td>
<td>1.1 (0.5, 2.5)</td>
<td>1.2 (0.5, 2.7)</td>
</tr>
</tbody>
</table>

*Controlled for all covariates shown in Table 2.

**RESULTS**

According to the 2018 RI BRFSS, 7.3% of Rhode Island adults have ever been diagnosed with any type of cancer other than skin cancer (are cancer survivors). Among Rhode Island adult cancer survivors, fewer (29.1%) reported multiple days of poor mental health in the past 30 days compared to 33.6% of those without a cancer diagnosis. Most adult cancer survivors in Rhode Island were female (61.4%) and White, non-Hispanic (87.7%). The prevalence of cancer diagnosis varied significantly among different age groups. Among those who have been diagnosed with cancer, 57.2% were 65 years or older and 19.6% were aged 55–64. Furthermore, the percentage of individuals in each income group with and without a cancer diagnosis was relatively similar. For example, 28.4% of cancer survivors have an income of
of reporting multiple days of poor mental health in the past 30 days than those who have never been diagnosed with cancer (OR=1.26, CI: 0.93, 1.70). Non-Hispanic Black adult cancer survivors were 8.3 (95% CI 1.3, 54.7) times more likely to report multiple days of poor mental health compared to non-Hispanic White adult cancer survivors in Rhode Island. Furthermore, cancer survivors ages 18-44 were 3.5 times (95% CI 1.3, 9.9) more likely to report multiple days of poor mental health in the past 30 days compared to cancer survivors ages 65 and older.

DISCUSSION

These findings have important public health implications. By identifying disparities in poor mental health among cancer survivors, medical and behavioral health professionals can target interventions to groups most at-risk for poor mental health in Rhode Island such as non-Hispanic Black cancer survivors. While this sample size is small and the confidence interval is large, this result is consistent with current literature, which has found that, when compared to White Americans, Black Americans have increased exposure to psychosocial stressors and are more likely to self-report psychological distress.16,17 This is due to discrimination and negative cultural stereotypes in the United States.18,19,20 While this can provide insight into mental health among Black adult cancer survivors in Rhode Island, these results are not generalizable to the Rhode Island adult population. This warrants further study in this area with a larger sample size. Furthermore, Rhode Island adults ages 18-44 are less likely to be diagnosed with cancer but are more likely to report multiple days of poor mental health compared to adults 65 and older. Research comparing mental health among young adult cancer survivors to that of older adult cancer survivors is scarce; however, a plausible explanation for this difference in mental health by age group is that younger adults experience a magnified impact of life disruptions related to cancer diagnosis compared to older adults. These life disruptions include ones related to body changes, changes in social relationships, sudden dependence on others, and facing one’s own mortality.21 Clearly, mental health support for younger adult cancer survivors in Rhode Island is an important area to improve upon. While overall prevalence of multiple days of poor mental health among Rhode Island adults is high at 33%, it is encouraging to find that cancer survivors in Rhode Island are no more likely to report multiple days of poor mental health compared with those who have never been diagnosed with cancer. Further study is needed to understand the impact of cancer diagnoses and treatment on HRQOL of Rhode Island adult cancer survivors.

LIMITATIONS

Small sample sizes are one limitation of the present study, particularly among non-Hispanic Black cancer survivors. Future research should include further study of HRQOL among larger samples of this population. This data relies on self-reported measures, which may lead to a variety of biases in participant responses. We chose to exclude individuals who indicated that they have only ever been diagnosed with skin cancer from our analyses because, as previously mentioned, a majority of skin cancer cases are benign. As a result of this exclusion, individuals with more severe types of skin cancer such as squamous cell carcinoma and melanoma were not considered to be cancer survivors unless they also had another type of cancer. Furthermore, because the RI BRFSS is a cross-sectional study, we are unable to determine time since cancer diagnosis or stage at diagnosis. Further research should focus on a deeper-dive analysis into whether self-reported mental health differs by cancer severity and/or prognosis.

References


Authors
Emily Goodspeed, BS, Master of Public Health Candidate (2021), Brown University School of Public Health.

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C. Kelly Smith, MSW, Comprehensive Cancer Control Program Manager, Rhode Island Department of Health, Adjunct Faculty at Providence College.

Correspondence
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EmilyGoodspeed@brown.edu
Rhode Island Monthly Vital Statistics Report
Provisional Occurrence Data from the Division of Vital Records

<table>
<thead>
<tr>
<th>VITAL EVENTS</th>
<th>REPORTING PERIOD</th>
<th>12 MONTHS ENDING WITH SEPTEMBER 2020</th>
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<tbody>
<tr>
<td></td>
<td>SEPTEMBER 2020</td>
<td>12 MONTHS ENDING WITH SEPTEMBER 2020</td>
</tr>
<tr>
<td></td>
<td>Number (a)</td>
<td>Number (a)</td>
</tr>
<tr>
<td>Live Births</td>
<td>895</td>
<td>11,160</td>
</tr>
<tr>
<td>Deaths</td>
<td>881</td>
<td>11,537</td>
</tr>
<tr>
<td>Infant Deaths</td>
<td>3</td>
<td>60</td>
</tr>
<tr>
<td>Neonatal Deaths</td>
<td>2</td>
<td>46</td>
</tr>
<tr>
<td>Marriages</td>
<td>776</td>
<td>4,869</td>
</tr>
<tr>
<td>Divorces</td>
<td>162</td>
<td>2,219</td>
</tr>
</tbody>
</table>

* Rates per 1,000 estimated population
# Rates per 1,000 live births

<table>
<thead>
<tr>
<th>Underlying Cause of Death Category</th>
<th>REPORTING PERIOD</th>
<th>12 MONTHS ENDING WITH MARCH 2020</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MARCH 2020</td>
<td>12 MONTHS ENDING WITH MARCH 2020</td>
</tr>
<tr>
<td></td>
<td>Number (a)</td>
<td>Number (a)</td>
</tr>
<tr>
<td>Diseases of the Heart</td>
<td>218</td>
<td>2,402</td>
</tr>
<tr>
<td>Malignant Neoplasms</td>
<td>196</td>
<td>2,261</td>
</tr>
<tr>
<td>Cerebrovascular Disease</td>
<td>34</td>
<td>457</td>
</tr>
<tr>
<td>Injuries (Accident/Suicide/Homicide)</td>
<td>75</td>
<td>894</td>
</tr>
<tr>
<td>COPD</td>
<td>65</td>
<td>521</td>
</tr>
</tbody>
</table>

(1) Cause of death statistics were derived from the underlying cause of death reported by physicians on death certificates.
(2) Rates per 100,000 estimated population of 1,059,361 for 2019 (www.census.gov)
(3) 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

February 1, Monday
Legislative hearing
RIMS Council meeting:
Catherine A. Cummings, MD, President

February 2, Tuesday
RIMS Physician Health Committee (PHC): Herbert Rakatansky, MD, Chair (via teleconference)
American Medical Association (AMA) webinar on the Future of Virtual Care
RI Health and Privacy Alliance virtual meeting
Legislative hearings

February 3, Wednesday
Legislative hearings
Vaccine planning discussion with Medicaid Managed Care Organizations (MCOs)
Workers’ Compensation Advisory Council

February 5, Friday
New England Medical society executives virtual meeting regarding regional telemedicine

February 8, Monday
Legislative hearing

February 9, Tuesday
National Roadmap on State-Level Efforts to End the Drug Overdose Epidemic by Manatt Inc./AMA
Legislative hearing

February 10, Wednesday
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

February 11, Thursday
Legislative hearing

February 12, Friday
Rhode Island Parity Coalition call
Womxn Project regarding legislation, virtual meeting
Meeting with RI Health Center Association (RIHCA), Providence Community Health Center (PCHC) and Neighborhood Health Plan of RI (NHPR) regarding COVID-19 vaccine hesitancy strategy

February 15, Monday
RIMS’ Member-only State House Update

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

February 17, Wednesday
RIDOH Primary Care Physician Advisory Committee (PCPAC):
Elizabeth Lange, MD, President-elect
Coalition to Save Lives follow-up to January 24 event

February 18, Thursday
RIMS’ Annual Health Care lobbyist meeting
Womxn Project regarding legislation, virtual meeting
American Board of Medical Specialties (ABMS) call regarding legislation
IQVIA Prescription Opioids Trends in the United States webinar

February 21, Monday
Legislative hearing

February 22, Tuesday
AMA National Advocacy Conference: Elizabeth Lange, MD, President-elect
Diabetes Prevention Programs (DPP) Stakeholder’s call
Legislative hearings

February 24, Wednesday
AMA National Advocacy Conference: Elizabeth Lange, MD, President-elect
Diabetes Prevention Programs (DPP) Stakeholder’s call
Legislative hearings

February 25, Thursday
Meeting with congressional staff by Zoom: Elizabeth Lange, MD, President-elect; Heather Smith, MD, incoming chair, AMA Council on Legislation, current chair AMA Foundation
Legislative hearings

February 26, Friday
Legislative hearing

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.
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 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.

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

Ob-Gyn Associates
A Lifespan Physician Group Practice

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

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Over the past 12 months, more than 39,000 unique viewers from 132 countries have read articles in the Rhode Island Medical Journal (RIMJ) or researched topics in its archives.

Top 10 countries in 2021:
1. US
2. Canada
3. Australia
4. UK
5. India
6. Germany
7. China
8. Brazil
9. Italy
10. Japan

WARREN AND NEWPORT, RHODE ISLAND

Natalie and Joseph Migneault, of Cranston, parents of RIMJ designer Marianne Migliori, received their first dose of the Moderna vaccine on February 14, and with relief, display their stickers and immunization cards. Both were eligible in early February in the age 75+ group, but due to limited availability statewide, spent their Valentine’s Day traveling to separate appointments at two CVS locations: 1:30pm in Warren and 3pm in Newport. At left, Natalie, with mask and face shield, viewed the journal on her phone before leaving. At both locations, they found excellent safety measures in place and reported it was well-organized, from initial check-in to inoculation, and through the 15-minute observation period that followed. The next day, other than minor tenderness at the injection site, they experienced no side-effects.

Wherever you happen to be quarantining or social distancing, visit the Journal on your mobile device, and send us a photo: mkorr@rimed.org.
National Press Foundation honors Dr. Sanjay Gupta for his coverage of COVID-19

Dr. Gupta shares his ‘lessons learned’ from the past year

MARY KORR
RIMJ MANAGING EDITOR

One year ago this month, on March 11, 2020, the World Health Organization used the word “pandemic” to describe the spread of COVID-19; two days later it was the term CNN chief medical correspondent Dr. SANJAY GUPTA used on the air.

At the National Press Foundation’s (NPF) Awards Celebration, held virtually on Feb. 18th, Dr. Gupta, a practicing neurosurgeon, was among the honorees, and received the Chairman’s Citation award for 2020. “Sanjay Gupta’s ability to translate the complexity, nuance and art of medicine to make it understandable for a broad audience has made him the nation’s doctor,” said NPF Chair Donna Leinwand Leger. He was recognized for his “tireless and distinguished coverage of COVID-19.”

In brief remarks following the presentation, Dr. Gupta, speaking from his home in Atlanta, described life during the pandemic. “We’re living in a bubble – all of us. When it’s data, facts and evidence, it’s easier to be sure what we are reporting, telling patients, or family, but it is challenging when we are dealing with uncertainty, and when demand for information is immediate. What do you do then?”

Lessons learned: Humility, honesty and hope
He cited his three “lessons learned” during the pandemic. “Humility is always important. Sometimes there’s a desire to think of science and expect certainty. It’s clearly harder to describe what you don’t know, but you have to be transparent. Remember, COVID is a novel virus – something new,” he said.

“All these firsts make me think about the significance of the word ‘novel,’” he continued. “When was the last time we, as adults and as a society, truly experienced anything for the first time, or have been in a situation for which we had no context?”

He said too often people try to understand a new entity by comparing it to what we already have experienced, looking for patterns. “We have a tendency to put things in a box, as something you know; but, as in this case, some things are new – and we are not always comfortable with that. We have to be transparent about that, honest. But being honest and direct, and telling people the truth is sometimes hard. I deal with this as a doctor all the time.”

He paraphrased poet, writer and Civil Rights activist, the late Maya Angelou, who, among others, said: “It’s not what you say that people remember, but how you made them feel – that’s what people remember.” He said as a communicator and physician, he tries to achieve a balance. “Transparency and honesty must lead the way. Whether you are talking to your patients, or family or a TV audience – find the humanity but be transparent.”

In addition to his work at CNN, Dr. Gupta is the author of “Keep Sharp, Build a Better Brain at Any Age,” a New York Times bestseller. His new book, “World War C: Lessons from the Pandemic and How to Prepare for the Next One,” will be published this fall. He also hosts a podcast: Coronavirus: Fact vs. Fiction.

Dr. Gupta is an associate professor of neurosurgery at Emory University Hospital and associate chief of neurosurgery at Grady Memorial Hospital in Atlanta. He serves as a diplomate of the American Board of Neurosurgery and, in 2019, was elected to the National Academy of Medicine.
PROVIDENCE – Lifespan, Care New England and Brown University signed a definitive agreement to create an integrated academic health system (AHS) on February 23. It would combine Lifespan’s Rhode Island, Miriam, Hasbro, Newport and Bradley Hospitals, and Care New England’s Women & Infants, Kent, and Butler Hospitals. Brown has committed to provide a minimum of $125 million over five years in support of the development of the integrated AHS. It will participate on the governing board and play a key role in integrating medical education and research with clinical practice across the combined system’s hospitals.

The merger requires state and federal approvals, from the Rhode Island Dept. of Health, the Office of RI Attorney General Peter F. Neronha, and the Federal Trade Commission, which are underway. Lifespan, Care New England and Brown anticipate the regulatory approval process will take several months.

The following remarks were released from the leadership of AHS in prepared statements on Feb. 23.

“What I am most excited about is the ability of our new, locally based, academic health system to compete at a national level, innovate, attract top talent, develop new scientific knowledge, improve the care we deliver and serve as an economic engine for Providence and the state,” said Lifespan President and CEO TIMOTHY J. BABINEAU, MD. “This is an exciting moment-in-time, we cannot let it slip through our grasp yet again.”

“The positive reaction that we’ve seen, really across the board, to the creation of this new system has been outstanding. Our partners across the region, especially our internal colleagues and physicians, really support this because it’s a very exciting proposition. Creating something new and visionary, but with concrete goals and true work plans, sets the integrated AHS up to achieve high quality care with local access for the people that we serve. It is something to be proud of,” said JAMES E. FANALE, MD, Care New England President and CEO.

“It is gratifying to finally realize the vision of an integrated academic health system with Lifespan, Care New England and Brown University. Together, we are better able to serve as an economic engine for the state. The health sector in any region is a source of good paying jobs, not only within the hospital systems, but the businesses created and driven by goods and services that hospitals purchase. We want to be sure that these remain strong for many decades to come,” said LAWRENCE A. AUBIN, SR., Lifespan Board of Directors Chairman.

“Combining health system operations with leading-edge research and renowned medical expertise will improve the quality of medical care for patients across Rhode Island and surrounding regions. The uniting of health care with medical education and research serves to advance biomedical discovery, educate future physicians, nurses and health practitioners in medicine and health care, and create a vibrant economic nexus in the region based on the health care industry,” said CHARLES REPPUCCI, Care New England Board of Directors Chairman.

“If you learned from your doctor the devastating news that you had cancer, you want to go to a place that maximizes your chances of a having a great outcome,” said JACK A. ELIAS, MD, Dean of The Warren Alpert Medical School. “You want to go to a place where you have the best care you can get from a diagnostic and therapeutic perspective – a place that does cancer research, but that also has the latest in protocol-driven therapies so you can be with your family for many years to come. And, this is the difference that an integrated academic health system can make in patient lives. This is real.”

“We’re committed to creating an integrated health system that increases access to excellent health care and by doing so, reduces health disparities,” said CHRISTINA H. PAXSON, President of Brown University. “Great health care should be accessible to everyone, including people from communities that historically have experienced obstacles to accessing health care. The seamless integration of research and clinical care drives improvements in the health of patients by offering all Rhode Islanders access to state-of-the-art medicine.”
State-run vaccination sites open in Providence and Cranston; two more expected to open

Field hospitals shutting down as hospitalizations decrease

COVID-19 vaccination efforts in Rhode Island continue to accelerate with eligibility now open to all Rhode Islanders 65 years of age and older, who can now register to be vaccinated at one of two State-run vaccination sites, located in Providence at the Dunkin' Donuts Center and in Cranston at Sockanosset Cross Road. In addition, two new state-run vaccination sites will open in the coming weeks, one at the former Sears in Woonsocket and the other at the former Benny's in Middletown.

According to RIDOH last week, the state is now administering approximately 6,000 doses per day. The cumulative number of state residents vaccinated as of February 24th was 217,708.

Rhode Island residents can register at www.VaccinateRI.org or by calling the automated line at 844-930-1779, and also register to be vaccinated at select CVS or Walgreens retail pharmacies, or through their city and town, although many cities and towns are continuing to vaccinate their oldest residents first, and supply of vaccines remains limited at all sites. Instructions on how to register at all three types of locations are available online.

RIDOH plans to post available clinic appointments on Tuesdays at 9 a.m. and Fridays at 5 p.m. More than 30,000 appointments have been made for the two sites since Rhode Island moved to age-based vaccinating last week. This is in addition to the vaccinating being done by pharmacies and by cities and towns.

Vehicles stop at the National Guard check-point at 100 Sockanosset Cross Road for verification before gaining entrance to the vaccination site.

Field hospitals to close

As the state’s vaccine administration rate continues to increase, Rhode Island has seen significant declines in cases and hospitalizations. Overall, Rhode Island’s daily hospital admissions are down 47% since January. This improvement allows Rhode Island to suspend patient care at its two alternate hospital sites at the Rhode Island Convention Center and at Sockanosset Cross Road (near the current State-run vaccine site). The last day for patient care at the Rhode Island Convention Center hospital was February 26; Sockanosset is expected to close within two weeks.

After all patients are discharged, each facility will be cleaned and sanitized. The equipment and supplies will remain at the two alternate hospital sites, should a surge in hospitalizations require them to be reactivated.

Since the alternate hospital sites opened for patient care, they have treated 633 patients: 444 patients at the Convention Center and 208 at Sockanosset.
Brown-based IMPACT Collaboratory teams with CVS to monitor COVID-19 vaccine effects

$4.2M grant to track vaccine rates and safety for Medicare recipients

PROVIDENCE (BROWN UNIVERSITY) – The National Institute on Aging has awarded a $4.2 million grant to a research team based at Brown University and Hebrew SeniorLife to partner with CVS Health to develop a massive, data-driven monitoring system that tracks the long-term safety and efficacy of COVID-19 vaccination for Medicare beneficiaries.

“The goal is to leverage ‘big data’ to save lives,” said project leader VINCENT MOR, PhD, Professor of Health Services, Policy and Practice at Brown’s School of Public Health. “With this project, we’re uniquely positioned to securely monitor more than 13 million CVS customers who are Medicare beneficiaries. We’ll be able to determine the prevalence of known adverse reactions to the vaccine and whether the vaccine protects them from coming down with COVID in the future.”

The new two-year project is a supplement to a $53.4 million IMPACT Collaboratory grant awarded to Brown and Hebrew SeniorLife in 2019 – a nationwide effort to improve health care and quality of life for people living with Alzheimer’s disease and related dementias, as well as their caregivers.

Mor said that despite the disproportionate impact of COVID-19 on elderly adults, the population was largely underrepresented in clinical trials for the vaccine, given its quick development and authorization for emergency use. In addition, Mor said that adults of advanced age, especially those with Alzheimer’s and dementia, may face barriers to vaccination such as dependence on a caregiver for transportation. In order to ensure safe, effective, widespread immunization programs for communities around the country, there is a significant need for information about the effects of the vaccine on this vulnerable population.

“This system will help us understand who gets vaccinated and who doesn’t,” Mor said. “It will also help us to determine the prevalence of known adverse reactions to the vaccine and learn how long and how well it protects the immunized against getting sick with COVID in the future.”

Mor said the project marks the first big data effort to combine vaccination and pharmacy records with Medicare claims. Merging the data will enable researchers to explore associations between vaccination rates and factors like race and ethnicity, the presence of diagnoses of Alzheimer’s disease, and health care system variables.

The project builds on the mission of the Center for Long-Term Care Quality and Innovation, which will lead administration of the grant and is based at Brown’s School of Public Health.

ASHISH JHA, MD, Dean of the School of Public Health, said it’s an example of the center’s focus on partnering with innovators, including health care providers, to evaluate new practices and strengthen quality of patient care.

“As a result of this partnership with CVS, we will be able to develop a better understanding of how the pandemic and vaccinations are affecting older Americans. We’ll be able to estimate the rate of adverse events attributable to the vaccine and estimate breakthrough COVID-19 illness,” he said. “The potential to use these kinds of data to improve public health outcomes for older adults is so very important.”

The work is supported by the National Institute on Aging of the National Institutes of Health under Award No. 3U54AG063546-02S6.
Moderna announces it has shipped variant-specific vaccine candidate, mRNA-1273.351, to NIH for clinical study

Company also provides update on strategy for addressing SARS-CoV-2 variants of concern

CAMBRIDGE, MASS. – FEB. 24, 2021 – Moderna, Inc. announced that it has completed manufacturing of clinical trial material for its variant-specific vaccine candidate, mRNA-1273.351, against the SARS-CoV-2 variant known as B.1.351 first identified in the Republic of South Africa, and has shipped doses to the National Institutes of Health (NIH) for a Phase 1 clinical trial that will be led and funded by the NIH’s National Institute of Allergy and Infectious Diseases (NIAID). The Company also is providing an update on its strategy for addressing SARS-CoV-2 variants of concern.

While initial data confirms that the Moderna COVID-19 Vaccine (mRNA-1273) provides neutralizing activity against variants of concern, out of an abundance of caution, Moderna is pursuing two strategies against these variants, subject to U.S. Food and Drug Administration (FDA) review. First, the Company is evaluating booster doses of vaccine to increase neutralizing immunity against the variants of concern. Moderna plans to evaluate three approaches to boosting, including:

• A variant-specific booster candidate, mRNA-1273.351, based on the B.1.351 variant first identified in the Republic of South Africa, at the 50 µg dose level and lower.
• A multivalent booster candidate, mRNA-1273.211, which combines mRNA-1273, Moderna’s authorized vaccine against ancestral strains, and mRNA-1273.351 in a single vaccine at the 50 µg dose level and lower.
• A third dose of mRNA-1273, the Moderna COVID-19 Vaccine, as a booster at the 50 µg dose level. The Company has already begun dosing this cohort with the booster.

Second, the Company plans to evaluate mRNA-1273.351 and mRNA-1273.211 as a primary vaccination series for those who are seronegative. These candidates will be evaluated in a two-dose series at the 100 µg dose level and lower.

Consistent with the recently updated FDA Guidance for Industry, the Company plans to evaluate immunogenicity and safety in participants who have not received a COVID-19 vaccine as well as participants in clinical studies who previously received the mRNA-1273 vaccine.

NIAID, part of the National Institutes of Health (NIH), will conduct a Phase 1 clinical trial to determine if mRNA-1273.351 can boost immunity against the variants of concern. Moderna will provide doses of mRNA-1273.351 to the NIH. NIAID will initiate this study after receiving safe-to-proceed authorization from the FDA. NIAID will provide additional information when the trial begins, and details will also be available on clinicaltrials.gov. In parallel, the Company will be conducting its own clinical studies to support regulatory filings for any booster vaccine or updated primary vaccine.

“We look forward to beginning the clinical study of our variant booster and are grateful for the NIH’s continued collaboration to combat this pandemic,” said Stéphane Bancel, Chief Executive Officer of Moderna. “As we seek to defeat COVID-19, we must be vigilant and proactive as new variants of SARS-CoV-2 emerge. Leveraging the flexibility of our mRNA platform, we are moving quickly to test updates to the vaccines that address emerging variants of the virus in the clinic. Moderna is committed to making as many updates to our vaccine as necessary until the pandemic is under control. We hope to demonstrate that booster doses, if necessary, can be done at lower dose levels, which will allow us to provide many more doses to the global community in late 2021 and 2022 if necessary.”

These studies will inform the Company’s regulatory strategy with the U.S. FDA and regulatory agencies outside of the U.S. The current Moderna COVID-19 Vaccine protocol calls for two 100 µg doses.

A letter to the editor in the New England Journal of Medicine published February 17, 2021, showed vaccination with the Moderna COVID-19 Vaccine produced neutralizing titers against all key emerging variants tested, including B.1.1.7 and B.1.351, first identified in the UK and Republic of South Africa, respectively. The study showed no significant impact on neutralizing titers against the B.1.1.7 variant relative to prior variants. A six-fold reduction in neutralizing titers was observed with the B.1.351 variant relative to prior variants. ♦
Minimally Invasive Urology Institute at Miriam receives grant to establish a statewide Urologic Cancer Registry

Registry, funded with a grant from the Rhode Island Foundation, will help address why Rhode Islanders have disproportionately higher rates of bladder cancer

PROVIDENCE—The Miriam Hospital’s Minimally Invasive Urology Institute has established a Registry of Genitourinary Malignancy in Rhode Island, thanks to a grant from the Rhode Island Foundation. This project will lay the groundwork for a statewide, multi-institutional registry of urologic cancers to advance research, promote prevention, address treatment disparities and to improve health outcomes.

The proposed registry will facilitate comprehensive population-based research that will achieve the following objectives:

• Increase knowledge of the environmental, social, occupational and economic risk factors contributing to the high incidence of urological cancers in Rhode Island.

• Increase knowledge of ways to reduce treatment disparities and ways to improve prevention, screening, diagnoses and care delivery for individuals at risk for, or living with, urologic cancer in Rhode Island.

• Promote change in clinical practice by developing new guidelines for the medical community.

• Promote healthy behaviors and improve health literacy by developing inclusive educational materials and resources for the public that raise awareness of new or underappreciated risk factors and emphasize the importance of urologic health for disease prevention and healthy aging.

“We are grateful to our partners at the Rhode Island Foundation for their commitment in advancing urologic cancer patient care and research. By better understanding risk factors of bladder, prostate and kidney cancers, we will be able to promote healthy behaviors and lifestyles, improve screening and prevention to Rhode Islanders while reducing the burden of disease,” said DRAGAN GOLIJANIN, MD, Co-Director of the Minimally Invasive Urology Institute, Director of Genitourinary Oncology at The Miriam Hospital and Associate Professor of Surgery (Urology) at the Alpert Medical School.

“Establishment of a statewide registry and studying hundreds of characteristics and data elements per patient will enable us to take the next steps toward achieving our goal of ultimately improving health outcomes for the people of Rhode Island by reducing the morbidity and mortality resulting from the high incidence of urologic cancers,” said GYAN PAREEK, MD, Co-Director of the Minimally Invasive Urology Institute, Director of Kidney Stone Center at The Miriam Hospital and Professor of Surgery (Urology) and Medicine at the Alpert Medical School.

For more information about the Registry of Genitourinary Malignancy, contact CHRISTOPHER TUCCI MS, RN-BC, CURN, NE-BC, Program Manager of the Minimally Invasive Urology Institute at The Miriam Hospital: ctucci@lifespan.org

Senate OKs Miller bill to explore ‘harm reduction center’ pilot

STATE HOUSE—The Senate last week approved legislation sponsored by Senate Health and Human Services Committee Chairman JOSHUA MILLER to explore the creation of a pilot program to create “harm reduction centers” to help prevent drug overdose deaths.

The centers would be supervised facilities for drug users, staffed by health care professionals who could help in cases of overdose and make treatment referrals. Often referred to as “safe injection facilities” or “supervised consumption sites,” there are about 120 such facilities operating in 10 countries worldwide.

The legislation (2021-S 0016A) would authorize the Department of Health to establish regulations and explore the creation of a harm reduction pilot program for people to safely consume controlled substances they have obtained on their own. The centers must be staffed with health care professionals to prevent overdoses and make treatment referrals.

The bill also establishes a nine-member advisory committee made up of various stakeholders from the realms of health care, law enforcement and addiction to help the Department of Health maximize the effectiveness of the program and operate the centers in the safest possible way.

Under the bill, centers would be allowed only with the approval of the municipality in which they are located. In testimony on the bill, Providence Mayor JORGE ELORZA indicated willingness on behalf of Providence to be a host city, and two health care facilities indicated they would be willing to expand to incorporate the model. The bill also stipulates that the programs should be designed to provide liability protection to the centers’ property owners and to staff at the centers.

While there are currently no such officially sanctioned sites in the United States, several other states and municipalities are considering similar harm reduction measures, including Massachusetts, New York, New Jersey, California and Philadelphia. Somerville, Massachusetts, is working to formalize an existing effort.

It now goes to the House, where Rep. John G. Edwards (D-Dist. 70, Tiverton, Portsmouth) is sponsoring companion legislation (2021-H 5245).
Fatima Hospital introduces advanced visualization technology for minimally invasive surgery

NORTH PROVIDENCE – Surgeons at Our Lady of Fatima Hospital recently became the first in Rhode Island to perform surgeries using advanced visualization technology for laparoscopic procedures. In January, ABDUL SAIED CALVINO, MD, MPH, FACS, a surgical oncologist, and MICHAEL LIN, MD, a general surgeon with minimally invasive training, operated on the first two patients using this new technology which allows surgeons to make better clinical decisions during colon and gallbladder surgeries, and other minimally invasive surgical procedures.

Last year Fatima purchased the latest Stryker 1688 AIM 4K platform and SPY Elite Fluorescence imaging. Used together, this technology provides the surgeon with real-time images of important anatomy and blood vessels. For the imaging to work, a dye is given through the IV about 30 minutes before the procedure.

Dr. Calvino said, “This technology provides a roadmap to surgeons, allowing them to see more and do more during surgery. It is a clear indication that Fatima Hospital and CharterCARE are willing and able to invest in advanced technologies to enable the surgeon to reduce surgical complications, avoid bile duct injuries and achieve better clinical outcomes.”

“There is the risk of the dye injection is minimal while the benefit of the images during surgery is great,” said Dr. Lin, adding, “The hope is to use that additional information to reduce complications or more procedures for our patients.”

Dr. Calvino is also Program Director of the CGSO fellowship at Roger Williams Medical center and an Assistant Professor of Surgery at Boston University School of Medicine.

Stryker’s new platforms are less than a year old. Fatima is the first hospital in Rhode Island, and one of very few in New England, to have acquired this technology.

Fatima Hospital in North Providence is affiliated with Roger Williams Medical Center, part of CharterCARE Health Partners, a member of Prospect Medical Holdings.
Appointments

Saul N. Weingart, MD, PhD, named president of RIH, Hasbro

Saul N. Weingart, MD, PhD, has been named as the new president of Rhode Island Hospital and Hasbro Children’s Hospital, which became effective February 1.

Dr. Weingart most recently served as chief medical officer and senior vice president of medical affairs for Tufts Medical Center and Tufts Children’s Hospital in Boston, as well as Professor of Medicine, Public Health and Community Medicine at Tufts University School of Medicine.

At Tufts, Dr. Weingart led the physician response to COVID-19, managed the hospital board of trustees’ quality committee and annual goal-setting process, and oversaw the expansion of specialty pharmacy, palliative care, and addiction psychiatry programs. He also continued his clinical practice and mentored students, residents, fellows and faculty at the hospital.

Prior to Tufts, Dr. Weingart spent nine years at Dana-Farber Cancer Institute as the vice president for Quality and Patient Safety, gaining experience as a patient safety executive and quality expert. He established himself as a national leader in patient safety, with his team winning millions of dollars in grant funding to support initiatives including novel quality metrics and research focused on medication safety.

Dr. Weingart has held many leadership roles, including as a board member at MIT Medical, and several board positions of the National Patient Safety Foundation. His honors include international lectureships, academic appointments, and the John M. Eisenberg Patient Safety and Quality Award. A general internist and former primary care physician, Dr. Weingart earned his MD from the University of Rochester and his and his PhD from Harvard University.

“We are very fortunate to have someone with this wealth of experience and expertise joining the team,” said Lifespan Executive Vice President and Chief Operating Officer Todd Conklin. “There are still multiple challenges posed by the ongoing pandemic, but the rollout of the COVID-19 vaccine is offering a ray of hope, and I welcome Dr. Weingart’s leadership as Lifespan focuses on delivering health with care in the post-COVID years to come.”

Subhashini Ayloo, MD, to lead Brown Surgical Associates Hepatobiliary & Pancreatic Surgery Division

Brown Surgical Associates recently announced Subhashini Ayloo, MD, MPH, FACS, has joined the practice and will serve as the section chief for the Hepatobiliary and Pancreatic Surgery Division.

Dr. Ayloo, who also has a master's degree in Public Health from the University of Illinois at Chicago, focuses on transplantation, and complex HPB cancers in morbidly obese patients with minimally invasive techniques. She earned her medical degree and completed surgical residency from the Chicago Medical School/Rosalind Franklin University of Medicine and Science. She completed her first fellowship in minimally invasive surgery at SUNY/Upstate Medical University and a second fellowship in liver transplantation and hepatopancreatobiliary surgery at Dalhousie University.

Dr. Ayloo has also held numerous academic, administrative, and clinical appointments before joining BSA. She is an active member of several surgical committees on national and international societies, including the American College of Surgeons and the Society of American Gastrointestinal and Endoscopic Surgeons.

Elias Hyams, MD, joins Brown Urology

Dr. Elias Hyams has joined Brown Urology; previously he was at Columbia University-Irving Medical Center where he was Associate Professor of Urology. While in New York, he was also the chief of urology at New York Presbyterian-Lawrence Hospital.

Dr. Hyams is a graduate of Yale University and earned his MD from the University of Pennsylvania School of Medicine in Philadelphia. He completed his urology residency at New York University - Langone Medical Center and subspecialty training in Endourology at The James Buchanan Brady Urological Institute at Johns Hopkins in Baltimore.

“I joined Brown Urology to bring cutting edge and compassionate care to men with increased risk of prostate cancer, to use novel tools and shared decision-making to help identify dangerous prostate cancer early and intervene effectively while avoiding over-testing and over-treating those with lower risk,” Dr. Hyams said. “I look forward to working with the multi-disciplinary team at the Cancer Center and within the Urology Department to keep men living longer and better.”
Appointments

Diana Franchitto, HopeHealth President & CEO, named vice chair of National Partnership for Healthcare and Hospice Innovation Board

HopeHealth President and CEO DIANA FRANCHITTO has been named vice chair of the Board of Directors of the National Partnership for Healthcare and Hospice Innovation (NPHI).

Franchitto was elected to a two-year term effective January 1, 2021. She had previously served as treasurer of the national not-for-profit dedicated to innovation and advancing best practices in improving the delivery of end-of-life care.

“I am honored to serve on the board in this new role,” Franchitto said. “I look forward to continued collaboration with other mission-driven hospice leaders from across the country to provide the best care possible for people with serious illness and their families.”

Franchitto has been a strong, leading voice in hospice, palliative and home care for over a decade. Franchitto became President & CEO of HopeHealth in 2008 and has overseen the organization’s growth, partnership with many healthcare providers and academic institutions, and its expansion of services throughout Rhode Island and Massachusetts. HopeHealth is now one of New England’s largest not-for-profit home care, hospice and palliative care organizations.

Megan Ranney, MD, named Associate Dean for Strategy and Innovation

Dr. Ashish Jha, Dean of the Brown University School of Public Health, has announced that MEGAN RANNEY, MD, has agreed to serve as the School’s Associate Dean for Strategy and Innovation. Dr. Ranney has served in an informal advising role to the Dean for several months on many key initiatives critical to the School.

In her new role, Dr. Ranney’s guidance and expertise will be formalized as they relate to the School’s strategic governance and growth. Her initial focus will be on the School’s strategy for portfolio expansion – Pandemic Preparedness and Response, Climate Change and Health, and AI and Digital Health – as well as on building strategic bridges and further connecting the School within the University.

A graduate of Harvard University, Dr. Ranney served as a Peace Corps Volunteer prior to attending medical school at Columbia University. She completed internship, residency, and chief residency in Emergency Medicine, as well as a fellowship in Injury Prevention Research and a Master of Public Health, at Brown University.

Dr. Ranney has held a secondary appointment in the Department of Health Services, Policy and Practice since 2013 and has been involved with the School as an educator, researcher, and mentor for the last decade. She will now formally join the Dean’s leadership team, complementing her existing work in the Department of Emergency Medicine and as Director of the Brown-Lifespan Center for Digital Health.
Obituaries

DR. JENNIFER ZANNINI-CIPRIANI, 47, of East Greenwich passed away on February 3, 2021. Jennifer fought for three years with extreme courage and conviction against metastatic lung cancer that ultimately proved too elusive to contain. She will be missed by many in her beloved home state of Rhode Island where she was raised and where she returned in 2018 to focus on her fight for life. In between she lived in Massachusetts for over 20 years. She located to MA for her residency training program, met a husband, grew a family, and thrived in a career until her diagnosis and early retirement from Winchester Anesthesia Associates at Winchester Hospital.

Jen loved her parents, siblings, husband, children, and friends with joy and intensity, creating experiences and making memories to last a lifetime. From the little things: nightly songs of “You Are My Sunshine” to her children, and birthday parties with pony rides in the backyard; to world-class travel to Iceland, France, Ireland, Italian and California vineyards, and the slopes and spas of Stowe, Vermont, and Mont Tremblant. Jen’s zest for life and desire to share the world with her family and friends, to squeeze the richness out of every single day, was evident throughout her entire life. She never allowed day-to-day challenges to eclipse all the world had to offer, long before she knew that would be necessary. Jen will be remembered as a cherished friend to so many who despite her busy life consistently maintained meaningful friendships from childhood, college, medical school, residency, her career at Winchester Hospital, and her life as a mother.

Jen was raised in Barrington by her mother Rita [White] Zannini and her father Gaetano Zannini. Upon graduating Barrington High School in 1991, Jen went on to attend and graduate from Syracuse University, The Philadelphia College of Osteopathic Medicine, and a residency program at Boston University Medical Center. She met her husband Matt in Boston in 2003 and the two were married in 2006. They welcomed their first child, Charlotte Bari, in 2010 and their son, Jackson Quinn, in 2012. Her family lived and thrived in Lexington, MA, until Jen’s diagnosis in February of 2018. The family relocated back to Rhode Island that summer to be closer to both Jen and Matthew’s families to help support her fight against cancer. When not busily researching cancer treatments, Jen was always volunteering to help at the children’s schools or focusing on maximizing her time with her family and friends. Their family found many new and lasting friendships in East Greenwich. Matt, Charlotte, and Jackson will continue to live within this great community. In addition to her parents and children, Jen leaves behind a brother, Michael Zannini of Johnston, and a sister, Julie [Zannini] Bianco of Barrington.

Jen’s final wishes were to keep her memory alive for her 10-year-old daughter, Charlotte and her 8-year-old son, Jack, and to fight to rewrite the future of lung cancer treatment through funding medical research. To this end, donations can be made to Jen’s foundation Project Breathing Hope https://breathinghope.org/.

At the request of Jennifer, all services will be private.

HENRY GEWIRTZ, MD, of Cambridge, MA, formerly of Providence, passed away on February 17, 2021. He was the beloved husband of the late Nancy H. Gewirtz, and devoted and beloved father of Rebekah Gewirtz of Newton, MA, and Aaron Gewirtz of Wakefield, RI. He was the loving grandfather of Nina and Jacob Kuller and Gabriel and Julian Gewirtz, and dear brother of Eliot Gewirtz of New York City. Services will be private; donations in his memory can be made to the American Cancer Society for prostate cancer research.

Dr. Gewirtz was kind and compassionate and deeply interested in the world. He was a thinker. Dependable and honest, Dr. Gewirtz worked for most of his career as director of nuclear cardiology at the Massachusetts General Hospital. He cherished being outdoors and challenging himself to new adventures. He was an avid skier, sailboat racer and bicycle rider. He loved sailing his Etchells 22 and his Beetlecat, Huckleberry, with his late wife Nancy. First mates, together they won many races in Nantucket Sound. Later in his life, Henry hiked in the mountains of Nepal and always wished to return. On several of his treks he used his incredible eye for photography to capture beautiful images, which he has left for us to enjoy. Henry’s dream was to climb to the top of Mount Kilimanjaro in Tanzania.

Henry’s friend Renee Rulin of Providence, RI, has been his companion over the past 6 years and the source of much support, happiness and love. Henry will be sorely missed by his children and their spouses, his beloved grandchildren and all those whose lives he touched. May his cherished memory be a blessing.

BERNARD LOWN, MD, 99, of Newton, MA, a pioneering cardiologist and co-recipient of the Nobel Peace Prize, passed away on February 16, 2021.

For 73 years, he was the beloved husband of the late Louise Lown and the loving father of Fred and Barbara Lown, Anne Lown and Warren Green and Naomi Lown and Marvin Lewiton. He was the cherished grandfather of Melanie Lown, Zachary Lown, Emma Lown, Ariel Lewiton and Rachael Lewiton, and great-grandfather of Ezra
Moore. He was the fond brother of the late Harold Lown, Lillian Meyers, and Milton Lown.

Due to the current health crisis, a memorial service will be planned for a later date.

Dr. Lown was the author of “The Lost Art of Healing” and “Prescription for Survival: A Doctor’s Journey to End Nuclear Madness.” In 1960, during the tensions of the Cold War, he was one of the founders of Physicians for Social Responsibility. In 1980, he and Dr. Evgeny Chazov co-founded International Physicians for the Prevention of Nuclear War. They accepted the Nobel Peace Prize on behalf of the organization in 1985.

For four decades, Dr. Lown invited young physicians and scholars from low- and middle-income countries to Harvard and trained them in cardiovascular disease prevention and treatment. The Lown Scholars Program is a continuation of that vision. In his memory, donations may be sent to the Lown Scholars and Lown Community Health Centers programs. If you are interested in making a donation, please contact Michele Hudak at townscholars@hsph.harvard.edu.

The following is a statement on his passing from the Lown Institute, a think tank, in Brookline, MA, from Dr. Vikas Saini, president of the Institute.

“Dr. Bernard Lown, pioneering cardiologist, humanitarian, and founder of the Lown Institute, was a remarkable clinician, scientist, and visionary who will be remembered long into the future.

“As a scientist, Dr. Lown did seminal work on sudden cardiac death. He was co-inventor of the modern direct current defibrillator, a device that revolutionized the practice of cardiology and saved countless lives. He created one of the first cardiac intensive care units and transformed the treatment of heart attack patients. He was one of the first physicians to recognize the importance of overtreatment and the power of money to corrupt his beloved profession.

“Above all, he advocated for social justice and peace, and worked tirelessly to create the health system we all want and need. At the Lown Institute, we continue to be inspired by Dr. Lown’s bravery, heart, and vision, and we are proud to carry on his legacy in our work.”

Francis L. McNelis, MD, of Providence, passed away February 8, 2021 at the age of 100.

Dr. McNelis was the Chief of Staff for Otolaryngology at the Rhode Island Hospital in Providence and also treated patients at Miriam, Our Lady of Fatima, Pawtucket Memorial and St. Joseph’s Hospitals. He became a Clinical Professor of Surgery/Otolaryngology at the Brown University medical school.

He was a United States Navy Veteran of WWII, serving as a medical doctor.

Dr. McNelis was the husband of the late Shirley (Grube) McNelis and the late June (Stewart Bubier) McNelis. He is survived by his children: Frances Houser and her husband Lance of California, J. Kevin McNelis and his wife Karen of Rhode Island, Joanne K. Sheehan of Arizona, Stephen F. McNelis of Massachusetts, Brian F. McNelis (deceased) and Marian E. McNelis and her husband Tom Arnold of Arizona, and David Bubier and his wife Linda of Massachusetts, and 11 grandchildren and 11 great-grandchildren.