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Daniel Nissi, LIA  ☎ 800-649-9111  ✉ daniel.nissi@hubinternational.com
As a frontline emergency physician, it is my duty to diagnose and manage a wide range of disorders. Over the past 25 years, I have treated approximately 80,000 emergency department patients. My panel of patients has included victims from the Station Night Club fire, casualties from the Boston Marathon bombing, numerous gunshot wounds (GSWs), horrific intracranial hemorrhages, atypical presentations of aortic dissections, and countless others. Like all of us on the front line, I compartmentalize. I am pretty good at this. I have evolved into a machine – restrained, steady, and stoic – and I am fast and efficient. Occasionally, the white noise and swirling ruminations from a grueling and gruesome shift disrupts my sleep and seeps into my relationships, but eventually I right the ship. I do not brood. I consider myself lucky to have always been on the physician side of the patient-physician relationship, and have casually accepted, and routinely taken for granted, my good fortune.

Until now. Until the SARS CoV-2 virus or COVID-19. My walls have been smashed and my confidence has been shaken. For the first time in my professional life, I feel vulnerable, mortal and old. I am over 60 years of age. As I graduated into a senior role, I thought I had seen it all while dodging senescence. I understand anything can happen to anyone at any time, but I have never felt exposed nor susceptible. The coronavirus has stripped away my veneer of invincibility. According to the CDC, I have crossed over a previously unseen line. A news article on a CNN website explained to me what defines “older,” who is at risk, and how to care for your loved ones who are more than 60 years of age. I am the target. My patients are the vector.

The reality of an infection that has a predilection for older adults is difficult to grasp. I can gown and glove, add a HEPA filter, or see a patient in a negative pressure room, but I cannot eliminate my odds of acquiring COVID-19. I can no longer exercise daily, watch my weight, eat quinoa, and expect to stave off the inevitable. An 80-nanometer virus has unmasked the fragility of our health system and simultaneously threatens me with the sequelae of a slow and miserable disease, and I am powerless.

While I may dwell on the sudden recognition of my own mortality, the pandemic has generated other less morbid and more age-appropriate concerns. One physician in his mid-30s recounts how the impact of the coronavirus hit home. His in-laws let him know they could no longer visit with him, his husband, and their three kids for the foreseeable future due to their health histories. Additionally, if the daycare he uses closes, he is unsure how he can be a parent and continue to function as an emergency physician supporting his friends, family, and colleagues.

A mid-career colleague bemoaned the multiple system flaws uncovered by this pandemic. One of my co-workers, a witty, insightful, and wry man with a libertarian streak, despairs of the “atrophy of personal responsibility.” He lamented a dependence on disinformation generated by Internet trolls, and the degradation of our institutions which previously acted as a bulwark against humanity’s worst impulses. One of my oldest and dearest friends, an emergency physician at Columbia University, zeroed in on the bumbling, inept federal response to the pandemic.

As appalled as I am by the U.S. government’s anemic response to the SARS CoV-2 pandemic, I am buoyed by the less existential meditations of my colleagues. It is helpful to focus on something other than my own fears. Somehow, I am hopeful, while realistic. I have to be. Despite our societal obsession with Armageddon, this does not appear to be the Apocalypse. Winston Churchill once said Americans will always do the right thing after exhausting all the alternatives. I feel that way about our response to this pandemic. One by one, frontline anxieties are being addressed. Recently I learned that older physicians in my department will be placed in roles exposing them to less risk. Wellness and burnout issues are being addressed. Surge capacity is being discussed. Rather than futile measures directed toward containment, we are attempting to mitigate the impact of the disease. Local leaders are finally leading. In the meantime, I will take it day by day, manage my stress, care for the ill and turn “it” off, as I, and as we all, attempt to dodge the COVID-19 bullet.

Author
William Binder, MD, FACEP, Associate Professor of Emergency Medicine, Warren Alpert Medical School of Brown University; Co-Editor in Chief, Rhode Island Medical Journal.
In the midst of a global pandemic, we are overwhelmed with reports and stories of the COVID-19 crisis, the mounting death rates in Italy and Spain, and the growing number of cases in New York and nationwide, threatening to overwhelm existing hospital resources and staff. We have genuine concerns for the health and well-being of our friends and colleagues and all healthcare providers in Emergency Departments throughout the country. At the same time, we try to be reassured by the assertions that this will be a mild flu-like illness for upwards of 80% of patients. So where does that leave us on the front lines of primary care? After all, we are going to have to deal with this vast majority of patients and many others who have been referred to as the “worried well.”

Within the short span of a few weeks, many practitioners have made the transition from office visits to telemedicine (TM) and telephonic visits. This has been driven by the necessity of social distancing, facilitated by an abrupt change in CMS policy that will now reimburse for TM visits and by the sheer volume of patient calls. In my recent experience, most of these calls average about 10 minutes and involve another 5–10 minutes for documentation. The patients have accepted this willingly. No one is demanding to see the doctor. In fact, they are afraid to come to the office (or the ED) for fear of being exposed to “sick” patients in the waiting room. It’s easier for many of them not to have to travel or to wait to see the practitioner. Right now, this is also safer for patients who really need to be seen and for the providers and staff as well. It is most likely that this will become the new norm long after this pandemic has passed.

**Cardiology consults**

I have done several recent telemedicine cardiology consultations, including one elderly woman with a patch monitor showing rapid atrial fibrillation. Having seen her in the office a few weeks earlier and reviewing her echo and lab results, it was a relatively easy discussion to start her on metoprolol and a NOAC. Then there is the 55-year-old man with non-ischemic congestive cardiomyopathy. We have been speaking by phone every few days and adjusting his diuretic regimen as his orthopnea and chest pressure improve. He will have follow-up lab testing this week. Clearly, some patients will still need to be seen, but much of what we have previously done in an office setting can now be accomplished quite easily and effectively over the phone.

**Telemedicine Triage**

In the setting of the current pandemic, many patients call with flu-like symptoms that they would have previously
just managed at home. And many of them having been trying to do just that for a week or so. But now when they are not getting better, and with the COVID-19 information overload, they are afraid, perhaps rightly so, and they want to be tested.

At a Federally Qualified Health Center (FQHC) where I am helping out with TM triage, the typical patient presents with a week or two of low-grade fever, sore throat, dry cough, maybe some chills and body aches. A few have diarrhea and last week patients were reporting changes in their sense of taste and smell [so much for the power of Google Doc]. The vast majority have not recently traveled outside the US and have no known contacts with COVID-19-positive patients. And the vast majority do not meet current criteria for COVID-19 testing.

But their individual stories are compelling and perhaps one previously unrecognized benefit of TM is that we have more time, without other distractions, to just listen to those stories, to commiserate and to provide reassurance. One patient was a 50-year-old woman, a housekeeper at an elderly living facility, who was sent home from work with a cough and told not to come back until she had a doctor’s note saying she did not have coronavirus. Certainly, appropriate for her to home-quarantine and not pose a threat to a very high-risk population (ie, Seattle). But in the absence of fever or shortness of breath and with no concerning contacts, she did not meet strict testing criteria. At this point, she was less concerned about her cough and worried more about when she can get back to work. I promised to follow up with her in a few days.

Another patient I spoke with was a 45-year-old man who had a 6-day history of sore throat, chills and sweats, diarrhea for the past 24 hours and now a salty taste to everything [like he read on the Net]. His wife and daughter had similar symptoms. He wanted to be tested for coronavirus. And oh by the way, he had been having severe chest pain and shortness of breath for the last few hours. He had several coronary risk factors and I recommended that he go to the ED for a cardiac evaluation. He thought that was what I would say and was very reluctant, afraid that he would be exposed to coronavirus in the ED. I persisted, explaining that he was more likely to die from a heart attack than from coronavirus and went so far as to suggest that while he was there they might even test him for coronavirus as well. Ultimately, he agreed.

**COVID-19 Testing**

In a primary care environment where rapid strep and rapid flu swabs, finger-stick glucose and HgA1c, and urine dipsticks are commonplace, the lack of available COVID-19 testing is frustrating to say the least, and difficult for patients to understand. Telling patients that even if they test positive, it will not significantly change their course or their treatment, and they will still need to self-quarantine, is just not enough. Patients need to and have the right to know and do their healthcare providers. One way or the other, it takes some of the uncertainty out of their individual situations and allows some sense of control in this chaotic time. I called one patient to tell him his coronavirus test was undetectable and he was relieved but also said he wished it were positive so he wouldn’t have this threat looming over him. If it were up to me, at this stage, I would test everybody and have been trying to do that as much as possible. In fact, the FDA last week issued two emergency-use authorizations: 1) a point-of-care COVID-19 diagnostic for the Cepheid Xpert Xpress SARS-CoV-2 test and 2) Abbott Laboratories molecular point-of-care test for the detection of COVID-19, delivering positive results in as little as five minutes. We will see how quickly and how widely available both of those efforts will be, but it would certainly be a big step forward.

In the midst of this growing pandemic, we all need reassurance, and reassurance based on facts. That is why, for so many of us, Dr. Anthony Fauci’s evidence-based approach and his calming measured presence are so important right now. Paraphrasing hockey great Wayne Gretsky, he recently said “…It’s not where the puck is, it’s where the puck is going to be…”

**Author**

Kenneth S. Korr, MD, FACC, is Associate Professor of Medicine Emeritus, Alpert Medical School of Brown University, and associate editor of the *Rhode Island Medical Journal*. 
Brave New World: A Pass-Fail Step 1
KEVIN S. TANG, BA, MD’21; ANTHONY D. YAO, BS, MD’21

On February 12, 2020, the Federation of State Medical Boards (FSMB) and the National Board of Medical Examiners (NBME) announced that Step 1 score reporting would be changed from a three-digit numeric score to a pass-fail system starting no earlier than January 1, 2022. Step 2 Clinical Knowledge (CK) and Step 3 will continue to be reported numerically, while a passing Step 1 score will become a prerequisite to taking Step 2 Clinical Skills (CS). This announcement followed more than a year of internal discussion by students and medical educators alike. Much emphasis was placed on the change’s purported role in reducing the “current overemphasis on USMLE performance” and medical student distress in preparing for medical licensing examinations. While we endorse the prioritization of mental health in medical education, we postulate that a pass-fail Step 1 will fail to significantly shift the status quo or alleviate emotional burden. Furthermore, we are concerned that this change reflects an ongoing trend in removing objective metrics from the evaluation of student performance for residency selection. Nevertheless, this policy shift may carry unforeseen and unintended benefits for students in the preclinical years in realms apart from mental well-being.

To posit that Step 1 is stressful for medical students would be a gross understatement. It is well known that competitive residencies implement Step 1 score “cutoffs” to screen applicants before considering them for an interview. The National Resident Matching Program (NRMP) continues to release annual reports on the means and distributions of board scores across specialties and student demographics. This reality is a common source of emotional distress for medical students, especially those looking to apply to competitive specialties such as neurosurgery or dermatology. The resultant overemphasis on Step 1 performance has led numerous medical schools and students to delay the Step 1 exam until after clinical rotations in pursuit of a higher score, although the impact this has had on ultimate student performance has been inconsistent.¹

Having recently taken Step 1 at the end of our pre-clinical years, we are familiar with these circumstances and welcome FSMB and NBME’s focus on student mental health. However, we believe the discontinuation of numeric scoring for Step 1 is unlikely to alleviate this burden. The selective nature of many residency programs necessitates quantitative and objective metrics with which to evaluate applicants. Scores on the USMLE have traditionally served this purpose, as few objective metrics exist outside of USMLE reports. Clerkship evaluations and the number of honored clinical rotations have been shown to be poor indicators of a student’s future performance in residency and beyond.² Furthermore, the “weight” of Step 1 will inevitably be assimilated into the “weight” of Step 2 CK as program directors reform their screening protocols to differentiate between the ever growing rosters of yearly applicants. Ultimately, Step 2 CK will evolve to represent the singular, compounded objective metric obtained in the third or fourth year of medical school, a time already considered by most to be the most stressful period as students navigate the demands of core rotations and sub-internships. In this way, a pass-fail Step 1 – far from relieving emotional stress – may simply concentrate academic pressure into the final two years of medical school.

Given the importance of objective evaluation throughout this process, we are apprehensive of the movement away from objective measurements of student performance. This trend has already manifested itself with the advent of pass-fail pre-clinical course structure, the removal of pre-clinical grades and USMLE scores for Alpha Omega Alpha (AOA) nomination³, and the most recent announcement regarding Step 1 reporting. If Step 2 CK were to one day meet the same fate as Step 1, quantitative scores will have disappeared from student resumes. Residency programs will have no recourse apart from further prioritizing clerkship performance, faculty evaluations, and research/volunteer experiences, all of which are vastly inferior methods of assessing a student’s clinical knowledge.⁴ While there is more to a good physician than textbook knowledge, we cannot deny that such knowledge is the basis of good clinical acumen and patient care. The medical interview, physical diagnosis, and clinical reasoning
are core tenets of medicine predicated on a sophisticated understanding of human physiology and pathology. If the removal of objective metrics best suited to evaluating a student’s competency in these core fundamentals continues unabated, it may ultimately be our patients who will suffer the consequences.

Despite our many reservations with the sweeping impact intended for a pass-fail Step 1, we believe this new system may yet offer some improvements. Several studies have already demonstrated the superiority of Step 2 CK over Step 1 in predicting student performance in residency⁴, making it counterintuitive that the latter is currently the primary objective measure of a student’s clinical and academic prowess. The inevitable shift in emphasis from Step 1 to Step 2 CK performance will also allow students with non-traditional aspirations (e.g., healthcare consulting, medical entrepreneurship, health policy) more time to pursue those goals in the pre-clinical years. As the field of medicine itself becomes progressively more interdisciplinary, there is a growing need for physicians with competencies in leadership, organizational management, and technology innovation, in addition to clinical practice. Further opportunity to study and engage with these fields in the pre-clinical years will greatly benefit future students and maximize their impact on the medical field. For these reasons, we express our support for the amendment of Step 1 to a pass-fail system but caution against further removal of numeric scoring from USMLE examinations. The dismal state of mental health in our profession permeates through every level of training and is secondary to much more than just high-stress exams. We are grateful for the NBME’s newfound focus on student well-being, and we hope the conversation continues to gain traction and support on a national level in the coming years.

---

References

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Subjective Memory Impairment and Subjective Cognitive Improvement: Role for D-C2H5OH (Deuterated Ethyl Alcohol)?
Results of a Double-Blind, Crossover Trial

JOSEPH H. FRIEDMAN, MD

ABSTRACT
Subjective memory impairment (SMI) is a common complaint among older people. We performed a double-blind, placebo-controlled study which showed that deuterated two carbon fragments ameliorated the condition but at the expense of objective memory function. Future studies are needed to confirm the results before endorsing the treatment of SMI with deuterated ethyl alcohol.

INTRODUCTION
Subjective memory impairment (SMI) is an increasingly prevalent problem as the population ages. It is defined by the self-perception of memory impairment that has not been recognized by others, and has not led to an objective decline in intellectual and social function. For research purposes, it is confirmed by normal objective memory testing. It is also an increasingly popular focus of clinical research. Using the PubMed search engine, the first paper published on this subject dates from 1975, with 158 listed in PubMed as of this writing, with more than half indexed since 2015. While some people with SMI go on to develop dementia, whether the risk is increased compared to age-matched controls remains unknown. On the opposite end of the subjective cognition spectrum, subjective cognitive improvement (SCI) is defined by the self-perception that one’s memory or cognitive capabilities are stronger than they had been self-perceived at some well-defined baseline.

Preliminary experiments (unpublished) have shown that ethyl alcohol (ethanol) in small amounts (60–120 ml), given in a non-blinded fashion, produces a profound benefit both on SMI and SCI. Because elimination half-life of ethanol depends on serum levels, the effect of the drug is variable and unpredictable. And, although a large variety of over-the-counter formulations of ethanol are available, their bioavailability and concentrations are not subject to the same quality controls as FDA-approved medications. Using a patented deuteration technology used in FDA-approved formulations of tetrabenazine and amantadine, in which a neutron added to one carbon atom of this 2-carbon compound, the half-life and side-effect profile of ethanol was significantly altered to improve compliance and reliability. D-ethyl alcohol, the deuterated form, has been found to be tasteless.

METHODS
After approval by an Institutional Review Board (IRB), 50 subjects over the age of 70 with no history of medical, psychiatric problems or substance abuse, were recruited from a convenience population of attendees at a Patriots’ football game in December 2017. After obtaining signed informed consent, volunteers were enrolled if they met inclusion criteria of baseline blood alcohol level of 0, scores on The Montreal Cognitive Assessment (MoCA) >28, Ten Item Memory Recall Test (TIMER)>6, with complaints of SMI and a score>21 on the Subjective Memory Impairment Inventory Test (SMIT), indicative of moderate to severe SMI. All subjects rated themselves on the Clinical Global Impression Scale, a 0-7 scale rating their SMI from 0, not present, to 7, extremely severe. All subjects were then invited to begin the protocol within 2-4 weeks of screening. They were asked to refrain from alcohol intake for the week before the baseline visit and during the 6 weeks of the study. Blood alcohol level (BAL) was measured, and if 0, subjects were tested on the SMIT and Subjective Cognitive Assessment Battery (SCAB). Subjects were then given 60 ml of study drug or placebo at noon of the test day, and re-tested at hours 2, 4 and 8 for blood levels of study drug, SMIT, SCAB, TIMER and CGIS. This was repeated daily for 2 weeks, followed by a washout period of 2 weeks. Subjects were then crossed over to the other treatment arm. At the end of the trial subjects were asked to choose which treatment arm
they thought they had been assigned to for each part of the study. Next generation statistical metrics using Bonferoni-Friedman-Fake Data imputations for non-reliable data, artificially contracted Student-t tests, and the standard Stata programs were used to smooth outcome results.

RESULTS
Forty-eight (48) subjects completed the protocol. One withdrew due to problems related to liver function and the other to a subdural hematoma sustained in a fall. None were thought to be study-drug related. On the first day, subjects showed a mean improvement of 5.3 points on the SMIT at 2 hours (p<0.01), 4.8 at 4 hours (p<0.02) and 5.0 at 8 hours (p<0.01). The CGIS also showed similar improvement with 3 at 2 hours, 3.4 at 4 hours, 3.4 at 8 hours (all p<0.04). Interestingly, the TIMER revealed worsened memory, with declines of 1.2, 1.1, 1.2 at hours 2, 4 and 8 (all p<0.2). The SCAB scores improved by 2.1, 2.2 and 2.3 at hours 2, 4 and 8 (all p values <.03). However, over the course of the 13 subsequent days, the changes associated with the study drug waned mildly so that, although statistically significant benefits in SMIT, SCAB and CGIS were sustained through day 8, no results were statistically significant by day 14. There were no statistically significant changes in the placebo arms. SCAB scores, indicative of subjective improvement, were inversely correlated with TIMER, objective memory changes (p<0.5).

CONCLUSION
D-ethyl alcohol was found to improve subjective memory impairment, subjective cognitive capabilities, and the clinical global impression of memory function. However, objective measure of memory function worsened, revealing that objective measures had an inverse correlation with subjective benefit. We believe that these results suggest a role for D-C2H5OH in the treatment of subjective memory impairment, and good tolerance. Future research will be needed to confirm our results and determine if higher doses or doses given 12 hours apart will produce longer lasting benefits. [April Fool. This is an entirely fictional study. Deuterated ethanol does not exist, so far as we are aware.]

[Editor’s note: This commentary continues a decades-old tradition of Dr. Friedman’s ‘April Fools’ Day’ commentaries. In this dire time, RIMJ hopes it provides a moment or two of levity to RIMJ’s readers.]

Disclosures
Conflict of interest:
Consultation fees from Neutronix Pharmaceuticals

References

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9. Hong Kong
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BIG ISLAND, HAWAII

Petroglyphs, images chiseled into lava rock, can be found in abundance on the Big Island of Hawaii along the northwestern Kohala Coast. The rock art dates back to more than a thousand years.

Above, in early February before travel restrictions were put in place, RIMJ managing editor Mary Korr studied the human figures, flora and fauna, as well as geometric forms, at Petroglyph Park in Puako and at the Waikoloa preserve.
Imagine

Aetna is proud to support the members of the Rhode Island Medical Society.
Declining Cancer Rates, Inclining Local Expertise: We Are Pointed in the Right Direction but Work Remains

Anthony E. Mega, MD; Fred J. Schiffman, MD, MACP
Guest Editors

Each year, the American Cancer Society estimates cancer incidence and death rates and compiles data on a number of relevant cancer statistics. The last report provides more than a ray of optimism. In 2016–2017, cancer death rates over the last measured period fell 2.2%. This represents the greatest decline in any one-year period since statistics have been kept. Today’s good news is the result of decades, if not centuries, of basic research, clinical trials and preventive strategies. Skilled scientists, dedicated healthcare providers, public health workers, educators and policy makers (certainly not from a single political party) deserve credit here. Even diligent parents and grandparents who have implored their children and grandchildren not to smoke have made a contribution! Many years of innovation and comprehensive care throughout the country has led to a 27% decline in cancer mortality over nearly three decades. This translates into nearly 3 million lives saved – approximately the population of Chicago.

What is the data from Rhode Island (RI)? Cancer incidence rates in both RI men and women, as well as cancer mortality rates, exceed the national averages. Most striking is the higher cancer incidence in RI women compared to the national average, 458.1/100,000 age-adjusted population versus 419.3/100,000 age-adjusted population. In women, this represents the third highest cancer incidence. Some of this is attributable to RI women having the highest incidence of bladder cancer and third highest incidence of lung cancer in the United States. The difference in per capita mortality between the state and national average for both men and women is much less pronounced.

Manuscripts from the current edition of the Rhode Island Medical Journal (RIMJ) exhibit the expertise needed to make a difference in providing excellent life-saving care. These articles highlight the expertise of our Brown University/Lifespan colleagues as they address selected common and problematic oncologic and hematologic illnesses. We have also included a description of the newly established Sickle Cell Disease Multidisciplinary Clinic (SCDMDC) at the Lifespan Cancer Institute, providing a detailed description of the mission of the clinic. Prior to the SCDMDC inception in late 2017, sickle cell patients transitioning into adulthood were faced with a loss of the comprehensive care as they moved from the Pediatric SCD program at Hasbro’s Tomorrow Fund Clinic. While the estimated number of SCD patients in RI is comparatively low, (150–200), their medical needs are complex and “resource-intense.” Adding to the complexity are the social vulnerabilities of this group of patients. Dr. Sokolic describes three vital components of SCDMDC: patient-centered care, multidisciplinary delivery and high-touch frequency. While all valued aspects of care delivery, it is the high-touch care that has the potential to be most impactful. It is through frequent contact with caring personnel that relationships and trust are gained with the SCD
The annual RI incidence of prostate cancer is 104 per 100,000 men. In spite of fluctuations in PSA screening recommendations, prostate cancer remains the most common non-cutaneous malignancy in men. In “Prostate Cancer Therapeutics and Their Complications: A Primer for the Primary Care Provider,” DR. ZACHARY BROWNLEE, DR. ANTOINE L. SCHUMACHER, DR. ANDRE DE SOUZA, DR. PAUL P. KOFFER, DR. THOMAS A. DIPEITRILLO and DR. ANTHONY E. MEGA point out the interplay between prostate cancer treatment and a multitude of general health issues such as osteoporosis, cardiovascular disease, and diabetes. The team approach of care is adopted at the Genitourinary Cancer Multidisciplinary Clinic at Lifespan Cancer Institute. At this multidisciplinary clinic at The Miriam Hospital, prostate cancer patients meet a team of providers, including urology, radiation oncology, medical oncology, psychiatry, genetics, Phase I research team, sexual health experts combined with support from social work, nurse navigation, survivorship nursing, and nutrition. Care plans are developed and shared with the patient’s primary care provider to maintain health, wellness and quality of life for the patient.

In addition, DR. RANI CHUDASAMA and DR. PETER BARTH, in their contribution, “Risk Stratification of Precursors to Multiple Myeloma in 2020,” point out the significant advances in the management of plasma cell disorders, attributed primarily to novel myeloma-directed therapies as well as improved imaging techniques, analysis of the genetic evolution of plasma cell disorders (PCDs), and clinical trials exploring the treatment of pre-symptomatic stages of PCDs. In their article, they explore recent advances in the risk stratification of monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM), and multiple myeloma.

The official state motto of Rhode Island is simply “Hope.” In our opinion, the authors of articles in this issue have provided us the rays of optimism that embody hope in the delivery of cancer care in our state. Of note, four of the authors are trainees from the Brown hematology/oncology fellowship program and one trainee is from the radiation oncology training program. Scholarly commitment from young professionals adds to the hope.

Acknowledgment

We would like to express our gratitude to the leaders of the Division of Hematology/Oncology and the Lifespan Cancer Institute, especially Dr. Howard Safran, Dr. David Wazer, and Ms. Susan Korber for their unwavering support, which has made the world class care we aspire to deliver into reality for our patients and their families.

Guest Editors

Anthony E. Mega, MD, Associate Professor of Medicine, Associate Professor of Surgery, Warren Alpert Medical School of Brown University, Lifespan Cancer Institute, Providence, RI.

Fred J. Schiffman, MD, MACP, Sigal Family Professor of Humanistic Medicine, Vice Chairman of Medicine, Warren Alpert Medical School of Brown University, Medical Director of the Lifespan Cancer Institute; Associate Physician-in-Chief, The Miriam Hospital, Providence, RI.
Current Indications for Consideration of Evaluation for Hereditary Cancer Predisposition Syndromes and How They Can Change Management

LAUREN J. MASSINGHAM, MD; ANDRE DE SOUZA, MD

ABSTRACT

Our current understanding of the genetic mechanisms that underly cancer pathogenesis is rapidly expanding. Hereditary cancer predisposition syndromes are important to recognize for diagnostic and treatment decision-making but also for family members so they will benefit from surveillance and treatment options. This brief review gives primary care and oncology caregivers a summary of the evolution of hereditary cancer predisposition syndromes, indications for consideration of testing and therapy of patients and families.

KEYWORDS: cancer, genetic, hereditary, BRCA, Lynch

BACKGROUND

Approximately 1.7 million individuals were diagnosed with cancer in the United States in 2018 and it is a leading cause of death nationwide. In Rhode Island, between 1995 and 2016, there were approximately 6100 new cancer diagnoses annually. According to the National Cancer Institute, some of the most common cancers diagnosed include breast cancer, prostate cancer, colon cancer, melanoma and pancreatic cancer. One of the most prolific areas of cancer research involves the identification of pathogenic variants (mutations) in genes that alter the function. These gene changes can be somatic (most common) or germline. It is estimated that about 5–10% of cancers are due to hereditary predisposition. Genetic abnormalities vary with tumor type. For example 24% of ovarian cancers, 8–10% of pancreatic cancers, 12% of metastatic prostate cancers, and 17% of early onset colorectal cancers are associated with mutations. Hereditary cancer predisposition syndromes have been associated with significantly increased lifetime risk of development of cancer and their identification is critical for patients and families.

Breast cancer gene 1 (BRCA1) and breast cancer gene 2 (BRCA2) were the first genes to be linked to hereditary cancer syndromes. BRCA are correlated with early onset and/or concurrent breast and ovarian cancers. BRCA1 and BRCA2 genes were initially cloned in 1994. In 1996, BRCA1/2 sequencing became clinically available. Shortly thereafter, genetic testing for hereditary colon cancer (Lynch syndrome) became available. In 2010, with the introduction of next-generation sequencing (NGS), significant advances have been made in gene discovery, decreasing the time required for results and making genetic testing more affordable. Today, high penetrance genes are defined as those that confer a greater than 5-fold lifetime risk of cancer in comparison with the general population risk. Moderate penetrance genes incur a 2-3-fold increased risk of cancer.

The aim of this brief review is to provide an update on the current indications and implications of germline genetic testing for hereditary predisposition syndromes and to discuss specific surveillance and therapeutic options. We will also describe how the selection of treatment based on molecular biomarkers has taken oncology to the age of precision medicine.

INDICATIONS FOR GENETIC EVALUATION FOR HEREDITARY CANCER SYNDROME

There are many different hereditary cancer predisposition syndromes. Table 1 provides a summary of common cancer types and criteria to identify individuals at a high risk of a hereditary predisposition who might benefit from genetic evaluation and counseling. The National Comprehensive Cancer Network (NCCN) has criteria for identification of those who are at a higher risk for hereditary breast and ovarian syndrome and Lynch syndrome. Other tools include Chompret criteria for Li Fraumeni syndrome, the Melanoma Cancer Syndrome Assessment Tool, and PTEN risk calculator for PTEN-Hamartoma syndrome for other hereditary cancer syndromes in addition to BRCA and Lynch syndrome. In general, features that are concerning for a hereditary cancer predisposition syndrome include early age of onset, multiple primary tumors in one individual, cancers with high-risk qualities (such as triple negative breast cancer or medullary thyroid cancer) or multiple cancers in successive generations. Colonic polyposis can also raise concern for a hereditary predisposition. Table 2 provides a summary of the current polyposis burden recommendations for genetic evaluation and counseling.

Advances in gene sequencing and evolving understanding of cancer susceptibility risk attributed to pathogenic variants will likely refine current genetic testing criteria. For example, germline genetic testing for pediatric cancer has demonstrated that in 8.5–14% of pediatric cases, a hereditary...
**Table 1. Common cancer indications and criteria that warrant genetic evaluation for hereditary cancer predisposition**

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Indications and Criteria</th>
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<tbody>
<tr>
<td><strong>Basal cell carcinoma (BCC)</strong></td>
<td>&gt;5 BCC</td>
</tr>
<tr>
<td></td>
<td>BCC diagnosed at &lt; 30 y</td>
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<tr>
<td><strong>Brain cancer</strong></td>
<td>Family history of cancer:</td>
</tr>
<tr>
<td></td>
<td>• Lynch syndrome related cancer*</td>
</tr>
<tr>
<td></td>
<td>• Li Fraumeni**</td>
</tr>
<tr>
<td></td>
<td>Subependymal giant cell astrocytoma</td>
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<tr>
<td></td>
<td>Medulloblastoma and ≥10 adenomatous colon polyps</td>
</tr>
<tr>
<td></td>
<td>• ≥10 adenomatous colon polyps</td>
</tr>
<tr>
<td></td>
<td>• Findings of Neviod basal cell carcinoma syndrome***</td>
</tr>
<tr>
<td><strong>Breast cancer (female)</strong></td>
<td>Breast cancer diagnosed ≤ 50 y</td>
</tr>
<tr>
<td></td>
<td>Triple negative breast cancer diagnosed ≤ 60 y</td>
</tr>
<tr>
<td></td>
<td>Ashkenazi Jewish Ancestry</td>
</tr>
<tr>
<td></td>
<td>Breast cancer and family history of cancer:</td>
</tr>
<tr>
<td></td>
<td>• Ovarian cancer</td>
</tr>
<tr>
<td></td>
<td>• Male breast cancer</td>
</tr>
<tr>
<td></td>
<td>• Pancreatic cancer</td>
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<tr>
<td></td>
<td>• Metastatic prostate cancer</td>
</tr>
<tr>
<td></td>
<td>Breast cancer diagnosed ≤ 50 y and family history of:</td>
</tr>
<tr>
<td></td>
<td>• Breast cancer</td>
</tr>
<tr>
<td></td>
<td>• Prostate cancer</td>
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<tr>
<td><strong>Breast cancer (male)</strong></td>
<td>Personal history or family history of a close relative</td>
</tr>
<tr>
<td><strong>Colorectal cancer</strong></td>
<td>Colon cancer diagnosed ≤ 50 y</td>
</tr>
<tr>
<td></td>
<td>Colorectal cancer with mismatch repair deficiency on tumor screening</td>
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<tr>
<td></td>
<td>Two primary Lynch syndrome related cancers* in the same person</td>
</tr>
<tr>
<td></td>
<td>Colon cancer diagnosis with first or second degree relative with a Lynch syndrome related cancer* diagnosed ≤ 50 y</td>
</tr>
<tr>
<td></td>
<td>Colon cancer diagnosis and family history of 2 other with a Lynch syndrome related cancer*</td>
</tr>
<tr>
<td><strong>Endometrial cancer</strong></td>
<td>Endometrial cancer diagnosed ≤ 50 y</td>
</tr>
<tr>
<td></td>
<td>Endometrial cancer with mismatch repair deficiency on tumor screening</td>
</tr>
<tr>
<td></td>
<td>Two primary Lynch syndrome related cancers* in the same person</td>
</tr>
<tr>
<td></td>
<td>Endometrial cancer diagnosis with first or second degree relative with a Lynch syndrome related cancer* diagnosed &lt; 50 y</td>
</tr>
<tr>
<td></td>
<td>Endometrial cancer diagnosis family history of 2 other Lynch syndrome related cancers* regardless of age</td>
</tr>
<tr>
<td><strong>Gastric cancer</strong></td>
<td>Diffuse gastric cancer dx &lt; 40 y</td>
</tr>
<tr>
<td></td>
<td>Diffuse gastric cancer and lobular breast cancer in the same person</td>
</tr>
<tr>
<td></td>
<td>Personal/family history of ≥ 2 cases of gastric cancer or lobular breast cancer (one dx &lt; 50)</td>
</tr>
<tr>
<td></td>
<td>Personal/family history of gastric cancer and 2 other Lynch syndrome related cancers at any age</td>
</tr>
<tr>
<td><strong>Leukemia</strong></td>
<td>Leukemia at &lt;18 y with a second primary cancer</td>
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<tr>
<td></td>
<td>Leukemia at &lt;18 y with a sibling with a childhood cancer</td>
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<tr>
<td><strong>Melanoma</strong></td>
<td>≥ 3 primary melanomas in the same person</td>
</tr>
<tr>
<td></td>
<td>Personal/family history of ≥ 2 Li Fraumeni associated cancer* *(one diagnosed ≤45y)</td>
</tr>
<tr>
<td><strong>Ovarian cancer/fallopian tube, primary peritoneal</strong></td>
<td>Personal history or family history of a close relative</td>
</tr>
<tr>
<td><strong>Pancreatic cancer</strong></td>
<td>Personal history or family history of a close relative</td>
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<tr>
<td><strong>Prostate cancer</strong></td>
<td>Metastatic prostate cancer</td>
</tr>
<tr>
<td></td>
<td>High grade prostate cancer (Gleason ≥7) with one of the following:</td>
</tr>
<tr>
<td></td>
<td>• Ashkenazi Jewish</td>
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<tr>
<td></td>
<td>• &gt;1 close blood relative with</td>
</tr>
<tr>
<td></td>
<td>• Breast cancer diagnosed ≤ 50 y</td>
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<tr>
<td></td>
<td>• Ovarian cancer</td>
</tr>
<tr>
<td></td>
<td>• Pancreatic cancer</td>
</tr>
<tr>
<td></td>
<td>• ≥2 close blood relatives with breast cancer or prostate cancer at any age</td>
</tr>
<tr>
<td><strong>Renal cancer</strong></td>
<td>Renal cancer diagnosed ≤ 45 y</td>
</tr>
<tr>
<td></td>
<td>Bilateral or multifocal renal cancer</td>
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<tr>
<td></td>
<td>Renal cancer and a family history of renal cancer</td>
</tr>
<tr>
<td></td>
<td>Renal cancer and a history of:</td>
</tr>
<tr>
<td></td>
<td>• Skin leiomyoma, fibrofolliculoma or trichodiscomas</td>
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<tr>
<td></td>
<td>• Pneumothorax</td>
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<tr>
<td></td>
<td>• Pheochromoctytoma/paragangioma</td>
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<tr>
<td></td>
<td>• Hemangioblastoma of retina, brainstem, cerebellum or spinal cord</td>
</tr>
<tr>
<td></td>
<td>• Early onset uterine fibroids (&lt;30 y)</td>
</tr>
<tr>
<td><strong>Thyroid cancer</strong></td>
<td>Medullary thyroid cancer</td>
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<tr>
<td></td>
<td>Papillary thyroid cancer (cribriform–morular variant)</td>
</tr>
</tbody>
</table>

* Lynch syndrome related cancers: colorectal, endometrial, gastric, ovarian, pancreatic, ureter and renal pelvis, brain (typically glioblastoma), biliary tract, small intestinal, sebaceous adenomas, sebaceous carcinoma, keratoacanthoma

** Li Fraumeni syndrome related cancers: soft tissue sarcoma, osteosarcoma, early onset breast cancer, brain cancer, colon cancer

*** Neviod basal cell carcinoma syndrome: BCC diagnosed < 30 y, >5 BCC, macrocephaly
criteria for BRCA1/2 testing. Patients who meet NCCN criteria for germline testing had a 7.92% yield. Since the difference between the diagnostic yield was not statistically significant, the suggestion is to test all new diagnoses of breast cancer, which could double the number of patients with a clinically actionable result.

**GENETIC EVALUATION AND COUNSELING**

The gold standard for identifying and testing those at risk for a hereditary cancer predisposition syndrome includes pretest and posttest counseling by professionals, such as genetic counselors, geneticists or oncologists trained in genetics. Part of the evaluation includes utilization of risk assessment tools which are moderately to highly accurate in predicting the likelihood of a germline pathogenic variant. Some examples of these include the International Breast Cancer Intervention Study (IBIS) or BRACAPRO for hereditary breast cancer, and PREMM5 for hereditary colorectal cancer. The benefits of pretest counseling includes: increased understanding of cancer risk, decreased worry about cancer, decreased anxiety, and decreased depression. Face-to-face counseling is the ideal method to educate patients and families before and after testing is performed. As germline genetic testing becomes more and more specialized, the genetics experts can focus upon the most comprehensive, informative and cost-effective testing. If in-person counseling is not available, there are now alternative methods for providing advice and including video methods and telegenetics services.

**GERMLINE GENETIC TESTING OPTIONS**

The patient affected by cancer should be the first member of the family to be tested by a genetic panel as they are the most informative family member. If that person refuses or is unable to perform the testing, then consideration of testing family members is appropriate. Typically, a blood or saliva sample is collected. A skin biopsy may be necessary if the individual had an allogenic stem-cell transplant or has a hematologic malignancy. Results typically take 3–4 weeks to return but a STAT panel that includes highly penetrant genes with a 1 week turnaround can be obtained for urgent therapeutic decision making.

** MANAGEMENT**

Depending upon the cancer predisposition syndrome identified, the lifetime risk of developing cancer does vary. High penetrance hereditary cancer genes are associated with a high lifetime risk of cancer. Some examples of genes that have been identified as high penetrance include BRCA1, BRCA2, CDH1, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, PTEN, TP53, RET, and STK11. These genes are typically tumor suppressor genes and management recommendations that include surveillance and therapeutic options are tailored to the specific syndrome.

For example, functionally impaired BRCA1 or BRCA2 genes cannot repair double-stranded DNA breaks (the DNA repair or homologous recombination system), leading to genomic instability, accumulation of mutations, and cancer predisposition. In general, the risk for breast cancer is 45-65% by the age of 70 years for a pathogenic variant in either BRCA1 or BRCA2. Due to this risk, some women consider a risk-reducing mastectomy. Breast cancer specific mortality has been shown to be decreased by 81-100% after mastectomy. Options for BRCA1 and BRCA2 management for women include: clinical breast examination every 6 months starting at the age of 25 years, increased breast screening starting at age 25 years with annual breast MRI and at the age of 30 years addition of a mammogram with consideration of tomography staggered every 6 months from the MRI. Individuals with a BRCA pathogenic variant or likely pathogenic variant also have the option of a risk-reducing mastectomy and salpingo-oophorectomy. These can be considered after completion of child bearing. There are also specific recommendations for men carrying BRCA1 or BRCA2 pathogenic variants as well, including self and clinical exam starting at age 35 years and consideration of prostate cancer screening starting at age 45 years. Currently there are no specific recommendations for women or men regarding increased melanoma or pancreatic cancer screening but this can be individualized.

The overall goal of precision medicine is to utilize molecular changes to individualize care and choose therapies that are more effective and have fewer side effects. Poly (ADP-ribose) polymerase (PARP) inhibitors have emerged as effective agents for the treatment of BRCA-mutated tumors. PARP inhibitors repress a salvage gene repair system in BRCA
deficient cancers, leading to irreparable DNA damage in these tumor cells and tumor cell death. Three PARP inhibitors were approved in the maintenance or sequential treatment of relapsed epithelial ovarian with or without BRCA mutations. Recently, Phase III studies of metastatic BRCA-mutated triple negative breast (OLYMPIAD), pancreatic (POLO) and castrate resistant prostate cancers (PROfound) have demonstrated clinically significant improvements in delaying symptomatic or radiologic progression of tumors.

Moderate penetrance hereditary cancer genes are associated with a moderate lifetime risk of cancer. Some examples of genes that have been identified as moderate penetrance include: ATM, BARD1, CDKN2A, CHEK2, and RAD51D. These genes are also typically involved in the DNA repair or homologous recombination aspects of cell function. Recommendations are tailored to the specific pathogenic variant as it may implicate distinct natural history. For example, recommendations for ATM and CHEK2 currently include increased screening starting at age 40 years, annual mammogram with consideration of tomodigraphy, and breast MRI staggered 6 months from the mammogram. For these two genes there are currently no surgical recommendations (for breast or ovarian cancer risk). There are also some moderate penetrance genes that do have prophylactic surgical options. RAD51D is associated with ovarian cancer and the NCCN currently recommends consideration of risk reducing salpingooophorectomy at age 45–50.

**FAMILY MEMBER RISK**

Identification of a hereditary cancer predisposition can affect patient management, but it is also of critical importance for family members. Once a pathogenic variant or likely pathogenic variant has been identified in an individual, typically his/her first-degree relatives should be offered the opportunity to consider testing. Exceptions to this rule include minors, who, unless the hereditary cancer predisposition syndrome includes childhood onset cancers and screening (such as TP53 and Familial Adenomatosis Polyposis), should hold off on testing until they reach adulthood and can make their own informed decision. If a first-degree relative refuses testing or is unavailable, second-degree relatives can consider testing. An important implication of testing a family member who is unaffected by cancer is insurance discrimination. In the United States, citizen protection from health insurance discrimination is enforced by the genetic information nondiscrimination act (GINA). However, life insurance, disability insurance and long-term care insurance are entities exempted from GINA.

**VARIANTS OF UNCERTAIN SIGNIFICANCE (VUS)**

Typically, when completing genetic testing, pretest counseling includes discussion of three possible results. A positive result is described as a finding of inherited a pathogenic or likely pathogenic variant in a hereditary cancer predisposition gene. A negative result is a finding of no detected gene alterations. In this situation the origin of cancer is most likely somatic and may be secondary to environmental or multifactorial causes. The third possibility is the finding of a variant of uncertain significance. This is a gene alteration that has not been reported in the literature before or does not have enough evidence to classify it as pathogenic or benign. Therefore, it is non-diagnostic. The recommendation is to update patients (especially with consistent family history of cancers) of the pathogenicity of the VUS as the scientific evidence accumulates. Family testing is sometimes helpful to sort out the significance of the result to learn if it tracks with other family members with disease. Otherwise, family testing is not recommended for their clinical management.

**SOMATIC TESTING**

Somatic testing, or tumor testing, has been increasingly utilized in oncology. Tumor testing often identifies multiple pathogenic/likely pathogenic variants that have evolved in the cancer and may be potential targets for treatment. Sometimes a change is identified on somatic testing that is concerning for a germline change. It is important to note that germline testing should be considered based on the patient’s clinical and family history, not solely on somatic testing.

**CONCLUSIONS**

The field of cancer genetics and the testing techniques are quickly evolving. Some of the available panels can now test up to 100 genes. This has important implications for patients with cancer since patient and family diagnostic and therapeutic plans may be impacted.

In Rhode Island, there are multiple institutions that provide genetic services which can be utilized when there is a patient who presents with a personal or family history suggesting a hereditary predisposition. This gives the individual and their family members the opportunity to personalize their management (precision medicine), complete earlier/increased surveillance and/or consider prophylactic therapies to reduce their risk of developing cancer or improve outcomes.

**References**


Authors
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The Sickle Cell Disease Multidisciplinary Clinic at the Lifespan Cancer Institute

ROBERT SOKOLIC, MD, FACP

KEYWORDS: Sickle cell disease, multidisciplinary clinics, health-care delivery

Sickle cell disease (SCD) is one of the world’s most common monogenic disorders, affecting about 100,000 people in the United States. The illness is manifested by sudden, unpredictable and severe bouts of pain, termed vaso-occlusive episodes (VOEs). In addition to the classic presentation of severe VOEs, SCD leads to end-organ damage in multiple systems (Table 1). This damage is cumulative, and ultimately leads to a decreased average lifespan and quality of life. As is the case for many genetic diseases, pediatricians have been at the forefront of research and treatment for SCD. Nevertheless, as patients with SCD mature into adulthood, they face the unique problems of adults, along with the accumulating burden of symptoms and end-organ damage from hemoglobinopathy, and care in adult medicine practices becomes appropriate. Current guidelines for the management of SCD call for the care of patients with SCD to be coordinated throughout the lifespan and across care settings as in the patient-centered medical home model. 

Data on the number of patients with SCD in Rhode Island are scarce. Nevertheless, one can arrive at a rough estimate based on the number of African Americans in Rhode Island and the known prevalence of SCD in the African American population. There are about 60,000 people of African descent in Rhode Island. The prevalence of SCD in African Americans is about 1 in 365. The expected number of patients with SCD is therefore about 150 to 200 patients. Hasbro Children’s Hospital (HCH) has long had a clinical program in SCD, but no similar multidisciplinary clinic has existed for adults whose care was divided among different community and academic hematologists in Rhode Island.

In the last quarter of 2017, The Lifespan Cancer Institute (LCI) established the SCD Multidisciplinary Clinic (SCDMDC). The clinic was modeled after two successful programs within the Lifespan Academic Medical Center – the Pediatric SCD program at Hasbro’s Tomorrow Fund Clinic and the various disease-centered multidisciplinary clinics within LCI. The first patients were cared for in the clinic on January 2, 2018. The mission of the SCDMDC is to facilitate the achievement by patients with SCD of their self-identified life and health-care goals, while mitigating as much as possible the impact of SCD on achieving these goals. The SCDMDC uses three strategies to facilitate care of adult patients with SCD: patient-centered care, multidisciplinary care, and high-touch care.

Patient-centered care is foundational in SCD. By the time they have reached adulthood, most patients with SCD have extensive experience with the health care system, and this experience has left lasting impressions for both good and ill. As with any other specialty clinic, the first visit to the SCDMDC is concerned with gathering records and clarifying the patient’s previous disease history. But, in addition to collecting the medical facts, such as number and frequency of hospitalizations, previous treatments and end-organ damage, time is spent elucidating the patient experience of SCD. Certain aspects of the clinical presentation and pathophysiology of SCD make discussion and validation of the patient’s experience of disease particularly important.

Despite its prevalence among African-Americans, South Asian-Americans and Arab-Americans, SCD as a whole is

<table>
<thead>
<tr>
<th>Organ or System</th>
<th>Manifestations of end-organ damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system</td>
<td>Stroke, neurocognitive impairment, psychiatric disease, neuropathic pain</td>
</tr>
<tr>
<td>Eyes</td>
<td>Retinopathy</td>
</tr>
<tr>
<td>Heart</td>
<td>Cardiomyopathy, congestive heart failure, cardiomegaly, valvulopathy</td>
</tr>
<tr>
<td>Lungs</td>
<td>Interstitial lung disease, pulmonary hypertension, intrapulmonary shunt</td>
</tr>
<tr>
<td>Liver</td>
<td>Hepatopathcy, gallstones, nausea, constipation</td>
</tr>
<tr>
<td>Immunohematologic system</td>
<td>Hemolysis, thromboembolic disease, hyposplenism</td>
</tr>
<tr>
<td>Genitourinary system</td>
<td>Isothethuria, acute kidney injury, chronic kidney disease, papillary necrosis, renal medullary carcinoma, priapism, erectile dysfunction</td>
</tr>
<tr>
<td>Skeleton</td>
<td>Avascular necrosis, osteoporosis, compression fractures</td>
</tr>
<tr>
<td>Skin</td>
<td>Leg ulcers</td>
</tr>
<tr>
<td>Social function</td>
<td>School and work absenteeism, interrupted education, underemployment, underinsurance</td>
</tr>
</tbody>
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considered to be a rare disease. Patients with SCD are frequently cared for by practitioners with little personal experience with the disease. Furthermore, the episodic nature of VOEs contributes to frequent emergency treatment, and this often comes from nurses and doctors who do not know the patient personally. The primary symptom of VOEs, pain, is entirely subjective. Successful treatment of acute exacerbations of SCD-related pain requires a foundation of trust between the patient and health-care providers. The provider must trust that the patient’s description of his or her symptoms is accurate. In turn, the patient must trust that the provider will accept the patient’s description of his or her symptoms without objective correlation to laboratory tests or imaging studies. Such deep trust can be built over multiple patient encounters during an ongoing provider-patient relationship, but is often difficult to achieve when providing care to an unfamiliar patient or receiving care from an unfamiliar practitioner. For this reason, patient-centered care relies on providing care within the context of a familiar practitioner-patient relationship. Patients in the SCMDMC are encouraged to receive urgent care within LCI, either through unscheduled visits to their primary practitioner or through parenteral treatment in the LCI infusion suite. In either setting, patients have a better chance of being cared for by someone whom they know and who knows them personally. If patients cannot be cared for within LCI, they are encouraged to present to the emergency department of a Lifespan hospital. In order to facilitate consistent care in this less familiar setting, each patient in the SCMDMC has a personalized plan for treatment of VOEs in his or her chart. This plan includes documentation of the patient’s baseline analgesic regimen as well as analgesic suggestions for unscheduled care in the emergency department and if admitted to the hospital. Plans are readily visible in a care co-ordination note in the patient’s electronic medical record.

Another aspect of patient-centered care in the SCMDMC is collaborative development and prioritization of goals. While the SCMDMC staff identifies specific treatment goals within the first few provider-patient encounters based on the extent and severity of end-organ damage, patients of the SCMDMC may have more immediate goals such as relief of symptoms. Furthermore, there are only a few therapies known to be helpful in SCD, and all these therapies have significant shortcomings in terms of effectiveness and adverse events. Therapy for SCD typically must be initiated at low doses and titrated up slowly before it can be expected to lead to clinical benefit, whereas side effects are often noticeable shortly after starting therapy. Given these difficulties with the therapeutic tools available to patients with SCD, patients may be reluctant to accept recommended therapies based on prior experiences. Typically, early prioritization of patient goals, such as symptom management, is necessary prior to beginning treatment based on practitioner-identified goals, such as initiation of disease-modifying therapy and prevention of end-organ damage.

Finally, patient-centered care requires offering the full range of therapies for SCD. Until 2017, there was only one approved drug for SCD. Since then, three new drugs have been approved. With respect to non-drug therapy, supportive care includes both simple and exchange transfusion, while hematopoietic cell transplantation (HCT) remains the only curative treatment for SCD. Every patient who is interested in the procedure is offered referral to an HCT program or to the SCD gene therapy program at Boston Children’s Hospital. All other disease-specific therapies are available directly through the SCMDMC at Rhode Island Hospital. Individualized treatment plans use any of these therapies either as single agents or in combination. Because there are no experimental data comparing any therapy for SCD to another, the most appropriate sequencing and combination of treatments is unclear. Selection of treatments is based on the known advantages and disadvantages of each therapy [Table 2] but ultimately requires a shared decision-making process in which the patient is the ultimate arbiter of which therapies will be used.

The second strategy used for all patients in the SCMDMC is multidisciplinary care. SCD can affect any organ system, and most typically affects multiple systems. Specialists from many different disciplines are required to provide comprehensive care. The dedicated clinic staff of the SCMDMC includes three physicians, two nurse practitioners, two social workers, two patient navigators, a pharmacist, an infusion nurse, a psychologist, and a chaplain. A nurse coordinator leads the clinic. Weekly pre-clinic and post-clinic meetings are organized to co-ordinate care among the different disciplines. Monthly meetings of the SCMDMC steering committee are dedicated to systematic issues and to the discussion of complicated patients.

### Table 2. Disease-specific treatments of SCD

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxyurea</td>
<td>Extends life, reduces VOEs, inexpensive</td>
<td>GI discomfort, leg ulcers, leukemogenic, cytopenias</td>
</tr>
<tr>
<td>Transfusion</td>
<td>Prevents stroke in children</td>
<td>Hemosiderosis, alloimmunization, vascular access</td>
</tr>
<tr>
<td>Glutamine</td>
<td>Reduces VOEs</td>
<td>Nausea, expensive</td>
</tr>
<tr>
<td>Crizalizinumab</td>
<td>Reduces VOEs</td>
<td>Expensive, vascular access, infusion reactions</td>
</tr>
<tr>
<td>Voxelotor</td>
<td>Increases hemoglobin</td>
<td>No demonstrated effect on VOEs, expensive</td>
</tr>
<tr>
<td>Allogeneic hematopoietic cell transplantation</td>
<td>Curative</td>
<td>Expensive, upfront morbidity and mortality, not available for SCD in Rhode Island</td>
</tr>
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</table>

VOE – vaso-occlusive episode
In addition to the above-mentioned core clinical staff, the SCDMDC has developed working relationships with practitioners in other key disciplines, including pain and palliative care, psychiatry, cardiology, pulmonology, nephrology, acupuncture, music and art therapy, emergency medicine, hospital medicine and orthopedics. Colleagues at the Lifespan Recovery Center have been available to treat the few patients with substance use disorder while the patients remain on indicated narcotic analgesics, a problem that is notoriously complicated to treat.10

Such complex multidisciplinary and longitudinal care requires considerable co-ordination. Patients of the SCDMDC are strongly encouraged to identify primary care providers and are typically referred to a primary care practice if no such provider has been identified.

The third strategy used by the SCDMDC is high-touch care. Care is based on the 2014 NHLBI expert panel report on evidence-based management of SCD.4 Where the evidence is not clear, the SCDMDC tends to favor screening for known complications of SCD. After the first few visits, it is often the case that several opportunities for screening and treatment are identified. Patients are usually followed monthly until these interventions have been provided or deferred. Thereafter, patients are followed monthly during titration of treatments. Patients with complicated pain management needs, such as patients on high doses of opiates, patients whose opiates are being tapered and patients with co-morbid substance abuse, are typically seen weekly, whereas patients with very complicated analgesic regimens requiring parenteral treatment may be seen several times a week. In the last case, the LCI infusion nurses and advanced practice providers lead care. When patients are on stable therapy, they are seen 2–4 times per year. Patients admitted to hospital are cared for by the RIH house staff and inpatient physicians with consultation from SCDMDC physicians and frequent visits from other clinic staff.

The LCI SCDMDC is now 2 years old. Approximately 60 patients have been treated, with anecdotal benefit to several patients. One clinic patient has died in the last two years. Overall, hospital days have been reduced by about 30% and the number of ER visits for SCD has been reduced by about 50%. Research collaborations have been initiated with the Department of Emergency Medicine and with other SCD centers in New England, as part of the American Society of Hematology SCD Research Network. The staff of the SCDMDC continues to strive to build on these accomplishments. Patients with SCD can be referred to the MDC via the main LCI number, 844-222-2881.

References
1. Piel F, Steinberg M, Rees D. Sickle Cell Disease. NEJM. 2017; 376(16): 1561-1573

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Non-Small Cell Lung Cancer in the Era of Personalized Medicine: Molecular Tests that Matter

CHRISTOPHER DEL PRETE, MD; CHRISTOPHER G. AZZOLI, MD, FASCO

ABSTRACT
The diagnosis and treatment of lung cancer is entering a new era. With increasingly advanced diagnostic tools, we are more able than ever to pinpoint genetic changes in tumor cells that allow us to treat with highly effective, targeted therapy. In a growing number of patients, we are able to avoid cytotoxic therapies altogether. The recent advent of immunotherapy has led to a similar paradigm shift. This article will review the latest advances in tumor tissue and blood biomarkers directly as they relate to available treatments. Specifically, we will review activating and sensitizing gene mutations, gene fusions, PD-L1 tumor score, and close with an appraisal of the rapidly advancing field of peripheral blood biomarkers.

KEYWORDS: Non-Small Cell Lung cancer, peripheral blood biomarkers, molecular tests, immunotherapies

INTRODUCTION
Lung cancer is one of the most common, and by far the deadliest form of cancer in both men and women in the United States. In 2019, it is estimated that 228,150 Americans will be diagnosed with lung cancer and 142,670 will die of the disease, accounting for approximately 25% of all cancer-related deaths, and making lung cancer, all by itself, the second leading cause of death in America after heart disease. The five-year overall survival rate for all-comers with non-small cell lung cancer is 15% or less.1

Amidst these grim statistics, a paradigm shift is underway in the diagnosis and treatment of advanced lung cancer. Increasingly, molecular tests performed on tumor tissue, and/or peripheral blood are driving therapeutic decision-making. In the context of metastatic disease in particular, therapies that target molecular pathways or harness the immune system to attack tumor cells are replacing traditional cytotoxic chemotherapies. These newer therapies are less toxic, more effective, and better differentiate malignant cells that carry particular mutations, protein expression, or immune susceptibilities compared to normal cells. This review will focus on the ever-expanding role of biomarkers in the selection of a growing array of gene-targeted drugs and immunotherapies for the treatment of advanced non-small cell lung cancer. It is essential that all physicians have an awareness of the current biomarker landscape in lung cancer to better manage patients with this common disease.

LUNG CANCER HISTOLOGY
After obtaining a tissue biopsy, the next step in the diagnosis of non-small cell lung cancer is to categorize the predominant histologic subtype. This is accomplished by histopathologic examination, though often aided by both immunohistochemical (IHC) and genetic analyses. The results of this pathologic analysis categorize non-small cell lung cancer into histologic subtypes: adenocarcinoma, squamous cell carcinoma, large cell neuroendocrine carcinoma, sarcomatoid or pleomorphic carcinoma, undifferentiated, and mixed histologies. The vast majority of targetable mutations occur in the adenocarcinoma subtype. However, due to the potential to mis-categorize a small biopsy specimen, and the phenomenon of mixed histology, small biopsy specimens should be given the benefit of the doubt and tested for targetable mutations.2

ACTIVATING AND SENSITIZING GENE MUTATIONS
Activating mutations occur in genes that code for intracellular proteins or receptors which drive cancer cell growth, survival, invasion and metastatic spread. They are analogous to a switch stuck in the “on” position, indifferent to the negative feedback that regulates normal cell behavior. In general, lung cancers driven by an activating oncogene are particularly virulent. So patients with such a cancer would have a poor prognosis if untreated. However, cancer cells carrying activating mutations also have a particular vulnerability. These cancers have been described as, “oncogene addicted,” meaning that they rely solely on a particular growth signal for survival, and that blocking this signal can trigger cell death.3 Thus, the gene mutation both activates cancer growth, and also makes the cancer sensitive to a single gene-targeted drug. This paradigm provides the therapeutic rationale behind many of today’s targeted therapies. With proper diagnosis, lung cancers which may have a worse prognosis if untreated are flipped to dramatically better prognosis on appropriate treatment.

Targetable activating, sensitizing mutations can be identified in approximately one third of patients with lung
EGFR MUTATIONS
The epidermal growth factor receptor (EGFR) is a member of the tyrosine kinase family of cell membrane receptors which relays growth signals from the surface of the cell to the nucleus via downstream proteins including RAS, PI3K, mTOR and MAPK. This growth signal leads to a variety of anti-apoptotic and proliferative effects within the cell.

Approximately 10% of NSCLC patients will be found to have an activating mutation in EGFR, and most of these make the cell sensitive to drugs which block the signal. Over 90% of these mutations are substitution mutations in exon 21 and in frame deletions in exon 19. The prognosis varies with the specific mutation, but in general the presence of an EGFR mutation is felt to be a favorable prognostic factor because the drugs blocking EGFR signal are so effective. A recent large cohort study of 1,656 patients with advanced NSCLC and EGFR mutation treated with targeted therapy revealed a median overall survival of 30 months and a 3- and 5-year survival of 40% and 20% respectively. This represents a dramatic improvement in overall survival compared to patients with advanced NSCLC lacking an EGFR mutation.

Multiple tyrosine kinase inhibitors (TKIs) have been developed that target EGFR mutations including afatinib, erlotinib, gefitinib, and osimertinib, all of which are pills taken once daily. It is important to note that these drugs are considered first-line mono-therapeutic agents and as such are used in lieu of traditional chemotherapy or immunotherapy. While effective initially, these drugs do not cure the disease and inevitably cancer cells arise which are resistant to the drug. Resistance to EGFR TKIs can be caused by secondary mutations in EGFR which prevent the drug from binding to the protein, or by activation of bypass tracts which stimulate cell growth independent of EGFR. Better initial treatments are being developed by studying the genetic mechanisms of acquired resistance to targeted therapy.

ALK TRANSLOCATIONS
Translocations in the anaplastic lymphoma kinase (ALK) gene are both activating, and drug sensitizing. These translocations occur in approximately 3–7% of NSCLC cases and are associated with an excellent response rate to ALK TKIs, ranging from 57 to 74%. Thus, similar to EGFR mutations, targeted therapy outperforms systemic chemotherapy by a wide margin in the vast majority of ALK-positive patients. Gene translocations can be harder to find than gene mutations, and require techniques which look at chromosomes (fluorescence in situ hybridization [FISH], or protein immunohistochemistry [IHC]). More sophisticated genetic testing using next-generation sequencing can routinely detect both gene mutations and chromosomal alterations. Whether the ALK gene fusion is detected by FISH, IHC or next-generation sequencing, there are a number of drugs which are commercially available to target ALK-positive lung cancer, including alectinib, brigatinib, ceritinib, crizotinib and lorlatinib. Patients with advanced ALK-positive lung cancer treated with serial ALK inhibitors have a median survival time measured in years.

BRAF V600E
The BRAF proto-oncogene codes for a kinase that, when mutated activates the MEK signaling pathway, leading to anti-apoptotic signaling and proliferation. BRAF mutations are common in melanoma, but are found in only 1–3% of NSCLC. The combination of dabrafenib and trametinib is FDA-approved for the treatment of advanced lung cancer with BRAF V600E mutation treated with targeted therapy. BRAF V600E mutations in lung cancer are treated with BRAF and MEK inhibitors. These drugs are very effective in patients with BRAF mutations.

NTRK, MET AND RET
Like ALK, other genes can be activated by chromosomal translocations. ROS1, c-ROS oncogene 1, is a receptor tyrosine kinase which drives 1–2% of NSCLC patients. The tyrosine kinase domains of ROS1 and ALK are highly conserved, meaning drugs such as crizotinib, ceritinib and lorlatinib are effective in both ROS1 and ALK-positive lung cancers. In a similar story of overlapping efficacy, the drug entrectinib was recently FDA-approved for the treatment of lung cancers with either ROS1, or neurotrophic tyrosine receptor kinase (NTRK) genetic changes. The TRK proteins function during normal physiology as receptors for nerve growth factors, and when activated by gene fusions can drive lung cancers, as well as certain breast cancers and sarcomas. Both entrectinib and larotrectinib are FDA-approved for NTRK-positive lung cancer. RET and MET gene rearrangements are also both activating, and sensitizing; however, there are no FDA-approved drugs specific for these gene targets. Discovery of these genetic changes should prompt enrollment in a clinical trial, or off-label use of a drug approved for some other purpose (cabozantinib, lenvatinib and vandetinib for RET, and crizotinib for MET). Retrospective cohorts of ROS1-positive lung cancer include patients still alive at 5 years. Because NTRK, MET and RET fusions are relatively rare, there is less known about long-term outcomes in these patients.

ACTIVATING-SENSITIZING GENE FUSIONS IN ROS1, NTRK, MET AND RET
Up to 2% of NSCLC cases harbor activating gene fusions in genes such as ROS1, NTRK, MET and RET. ROS1 translocations occur in approximately 3–7% of NSCLC cases and are associated with an excellent response rate to ALK TKIs, ranging from 57 to 74%. Thus, similar to EGFR mutations, targeted therapy outperforms systemic chemotherapy by a wide margin in the vast majority of ALK-positive patients. Gene translocations can be harder to find than gene mutations, and require techniques which look at chromosomes (fluorescence in situ hybridization [FISH], or protein immunohistochemistry [IHC]). More sophisticated genetic testing using next-generation sequencing can routinely detect both gene mutations and chromosomal alterations. Whether the ALK gene fusion is detected by FISH, IHC or next-generation sequencing, there are a number of drugs which are commercially available to target ALK-positive lung cancer, including alectinib, brigatinib, ceritinib, crizotinib and lorlatinib. Patients with advanced ALK-positive lung cancer treated with serial ALK inhibitors have a median survival time measured in years.
Notably, in contrast to the driver mutations discussed so far, \(BRAF\) mutations are more common in smokers.

**KRAS**

The most common activating mutations in NSCLC are in the oncogene **KRAS**. Activating **KRAS** mutations are found in approximately 25–35% of patients with NSCLC and, like **BRAF**, are more common in current or former smokers. **KRAS** mutations are generally associated with poor outcomes, at least in part because there are currently no gene-targeted drugs available. Excitingly, this is likely to change with the development of inhibitors to the specific mutation, **KRAS** G12C, which occur in approximately 13% of lung adenocarcinomas and can be blocked by small molecules which bind covalently and exclusively to the mutant protein.\(^{16}\)

**PD-L1**

**PD-L1** (programmed death-ligand 1) is a transmembrane protein expressed on tumor cells, stromal cells and macrophages that binds to **PD-1** receptors on cytotoxic T-cells and effectively turns them off, halting anti-tumor effect. Thus, PD-L1 can be understood as a mask that cancers wear to hide from the immune system. [Please see the accompanying article by Hsu, et al in this edition of the RIMJ, “Immune Checkpoint Inhibitors in the Treatment of Gastrointestinal Malignancies: A Review of Current and Future Therapies.”]

The class of drugs that target this mechanism – also known as immune checkpoint inhibitors (ICPIs) – includes pembrolizumab, nivolumab, atezolizumab and durvalumab. These monoclonal antibodies disrupt T-cell recognition of PD-L1, thereby enabling T-cell attack on tumor cells.

Due to the growing role of these therapies in modern oncology, and lung cancer in particular, it is now the standard of care in advanced non-small cell lung cancer to test all biospecimens for PD-L1 by immunohistochemical staining. After the stain has been applied, a pathologist calculates the proportion of tumor cells which are positive for PD-L1. The KEYNOTE-024 trial compared standard chemotherapy to pembrolizumab in patients with advanced NSCLC in the first-line setting in patients with a PD-L1 score of \(\geq 50\%\), and who tested negative for **EGFR** or **ALK** genetic changes. The median overall survival (OS) in the immunotherapy group was not reached, but is estimated to exceed 24 months compared to the typical 12-month median OS in patients treated with chemotherapy. The overall response rate to pembrolizumab was 45%, compared with 28% treated with chemotherapy.\(^{17}\) Subsequent trials have combined chemotherapy with pembrolizumab and demonstrated survival benefit regardless of PD-L1 score.\(^{18,19}\) However, the best biomarker package for selecting single-agent pembrolizumab remains testing negative for **EGFR** and **ALK** genetic changes and having a PD-L1 score \(\geq 50\%\). These patients can avoid first-line cytotoxic therapy altogether, in favor of immunotherapy alone. More recent phase 3 data shows that the combination of low-dose ipilimumab + nivolumab (CTLA4 + PD1 blockade) is superior to chemotherapy even in PD-L1 negative patients. This combination is not yet FDA-approved, perhaps because adding CTLA4 blockade adds side effects, and the overall survival comparison in the PD-L1 negative cohort was not statistically significant because it was not part of the study’s statistical testing hierarchy [no alpha allocation]. Also, ipilimumab + nivolumab was not reported to be superior to nivolumab alone for PD-L1 \(> 1\%\), and not reported to be superior to chemotherapy + nivolumab for PD-L1 negative patients.\(^{20}\)

**FINDING MUTATIONS IN THE BLOOD**

The molecular tests discussed so far rely on biopsy tissue to allow analysis of chromosomes, unique oncoproteins by IHC, and to obtain the tumor DNA for genetic analysis. The drugs which target these genes are then prescribed by medical oncologists to patients with advanced lung cancer as systemic therapy. It stands to reason that these same biomarkers may be found in the blood in patients with advanced disease. In fact, most patients with advanced non-small cell lung cancer will have circulating tumor DNA which can be detected in the blood. Blood-based testing is becoming increasingly popular and can speed up the process of molecular testing.\(^{21}\) The problem is that up to 20% of patients with these diagnoses do not have circulating tumor DNA, and therefore extracting DNA from biopsy tissue for molecular testing remains the gold standard.

There is no blood test to select patients for immune therapy. Doctors and scientists at Brown University are studying extracellular vesicles which are found in both blood and saliva and can be used to classify metastatic cancers and tumor-host immune interactions. Extracellular vesicles – including exosomes (30–100 nm) and microvesicles (100–1000 nm) – are cell-derived membranous structures which originate from endosomes or are shed from the plasma membrane, and are involved in multiple cellular processes including intercellular communication and intercellular exchange of proteins, lipids and genetic material. Recent discoveries in immunology and cancer biology have established exosomes as an important mechanism by which cancer cells manipulate the tumor microenvironment and avoid immune-mediated elimination.\(^{22}\)

A recent study looking at the role of extracellular vesicles in patients with melanoma found that melanoma cells release PD-L1-positive exosomes to amplify immunosuppressive signals to CD8+ T cells which would otherwise be limited to cell-to-cell contact. Since these exosomes can be isolated and measured in plasma and saliva, their detection and quantification can be used to distinguish clinical responders from non-responders to immune therapies.\(^{23}\) Specifically, patients with metastatic melanoma responding to anti-PD1 immunotherapy (pembrolizumab) demonstrated increased levels of PD-L1 on circulating exosomes within 6 weeks of initiation of therapy. Ongoing research at Brown will evaluate exosomes as biomarkers of immune response in patients with advanced lung cancer.
CONCLUSIONS

The treatment of advanced non-small cell lung cancer is evolving rapidly. Medical oncologists now prescribe a wide array of targeted therapies and immunotherapies based on biomarker science, making long-term survival possible in the context of a universally fatal disease. These advances depend on matching the right patient with the right drug, and have redefined non-small cell lung cancer as an ever-evolving collection of clinically relevant subgroups based on histology, molecular pathology results, and observed benefit from immune therapy (Figure 1). This paradigm has resulted in a feedback loop of discovery and therapeutic progress. In this way, molecular pathology will continue to redefine non-small cell lung cancer into subgroups with unique treatment opportunities and, with continued progress, the potential for using drug therapy for cure.

References


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Immune Checkpoint Inhibitors in the Treatment of Gastrointestinal Malignancies: A Review of Current and Future Therapies

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ABSTRACT
Gastrointestinal cancers are some of the most common malignancies worldwide. Traditional chemotherapy has been disappointing in improving overall survival in patients with unresectable or metastatic disease. The dawn of immunotherapy has led to emerging strategies in incorporating immune checkpoint inhibition either as single agents or in combination when treating gastrointestinal cancers. In this review, a general overview of the state of immunotherapy in the treatment gastrointestinal cancers is first provided. Subsequently, a review of the FDA-approved uses of immunotherapy in gastric, gastroesophageal, hepatobiliary, pancreatic and colorectal cancers will be provided followed by a glimpse into future treatment directions.

KEYWORDS: immunotherapy, checkpoint inhibitors, gastrointestinal malignancies, PD-1, PD-L1

INTRODUCTION
Escape from the immune system is a well-recognized feature of cancer. Despite numerous genetic and epigenetic changes, cancers are able to escape immune destruction by inducing T-cell tolerance through the expression of inhibitory signals. This leads to dysfunctional T-cell signaling by terminating an immune response after antigen activation. Programmed cell death protein-1 (PD-1) is a key immune checkpoint on activated T-cells that can be exploited by tumor cells through the expression of PD-1 ligand (PD-L1) leading to the evasion of immune destruction. Inhibition of PD-1/PD-L1 is thought to restore anti-tumor immunity (Figure 1). The incorporation of immunotherapy in the treatment of cancer has been considered a major scientific and medical breakthrough since the first immune checkpoint inhibitor (ICI) was approved in the United States for the treatment of metastatic melanoma in 2011. Since then, multiple antibodies targeting PD-1, PD-L1, and cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) have gained FDA approval in numerous malignancies, thereby reshaping the treatment landscape of cancer. [Please see the accompanying article within this issue of the RIMJ, “Non-Small Cell Lung Cancer in the Era of Personalized Medicine: Molecular Tests that Matter”]

Figure 1. (Top) Activation of cytotoxic T-cell through presentation of tumor antigen; (Middle) Immune evasion by tumor cell through secretion of PD-L1; (Bottom) Restored T cell activation. See text for details.

Gastrointestinal (GI) malignancies account for approximately 35% of all cancer-related mortality, making them one of the most common groups of malignancy worldwide.
Due to the insidious nature of these malignancies, a large portion of patients have unresectable or metastatic disease at time of diagnosis, and the opportunity for cure through surgical resection is lost. Furthermore, traditional chemotherapy treatment has been disappointing with a dismal 5-year survival in stage IV disease. Immunotherapy has been evaluated in GI malignancies as single agents and in combination leading to limited approval in the second-line setting (after failure of initial therapy) for gastric, gastrointestinal, hepatic, and colorectal cancers. The role of these agents in the neoadjuvant or adjuvant setting is currently being investigated. Unlike in lung cancer or melanoma, the response rates to immunotherapy in GI malignancies are relatively low. Response rates for ICI monotherapy is approximately 5%–30% in gastrointestinal cancers, 10%–20% in hepatobiliary cancers, 30%–50% in mismatch repair-deficient (dMMR) colorectal cancer, and no clinical benefit in pancreatic cancer. Furthermore, PD-1/PD-L1 status and tumor mutation burden (TMB) have not aided in predicting response to ICIs.

One explanation as to why GI malignancies are thought to have such relatively low response rate to ICI monotherapy is the tumor microenvironments that hinder the infiltration of immune cells. Tumor microenvironments create what is termed as “cold tumors,” leading to ineffective T-cell activation and/or penetration of the stroma/parenchyma to reach the tumor. There has been increasing interest in combining ICIs with immunotherapeutic small molecules, targeted therapy, chemotherapy, radiation, or other immunotherapies to convert “cold tumors” into “hot tumors” by altering the tumor microenvironment and enhancing immune efficacy and T-cell penetration.

The combination of different modalities with immunotherapy is thought to lead to enhanced efficacy through the promotion of apoptosis causing increased antigen presentation or direct disruption of the tumor matrix increased antigen exposure and T-cell infiltration. In particular, the combination of ICIs with other immunotherapies is thought to enhance antigen presentation and processing, decrease the secretion of immunosuppressive cytokines and suppressor cells, and enhance T-cell infiltration by targeting different immune checkpoints. However, one predictable limitation in combining immunotherapies is the increased incidence of immune-related adverse effects.

Since the first ICI was FDA-approved for the treatment of metastatic melanoma in 2011, hundreds of new drugs have entered the market for the treatment of various conditions. In 2018 alone, 59 new drugs gained FDA approval. The aim of this review article is to focus on the currently studied, FDA-approved uses of ICIs in the treatment of GI malignancies and review ongoing studies examining the combination of ICIs with traditional chemotherapy, immunotherapeutic small molecules, targeted therapy, and/or other immunotherapies.

**IMMUNOTHERAPY IN THE TREATMENT OF GASTRIC AND GASTROESOPHAGEAL CANCER**

Currently, first-line treatment of metastatic gastric and gastroesophageal cancers consists of chemotherapy alone or in combination with trastuzumab in patients with HER-2 positive disease. Second-line treatment includes taxanes and/or irinotecan with ramicurumab in patients who are eligible for vascular endothelial growth factor (VEGF) targeted therapy. The overall outcomes are still poor with survival of less than a year. Of note, ICIs first gained approval in metastatic gastric and esophageal cancers with microsatellite instability (MSI). In general, patients whose tumors demonstrate high microsatellite instability (MSI-H) have a better prognosis.

Pembrolizumab was FDA approved in 2017 for the treatment of chemotherapy-refractory (defined as progression after two lines of therapy), PD-L1-positive gastrointestinal cancers. The approval was based upon the findings in KEYNOTE-059, a phase II, global, open-label, single-arm, multicohort study that enrolled 259 patients. Patients received pembrolizumab 200mg intravenously every three weeks until disease progression. Objective response rate (ORR) was 11.6% with a complete response rate of 2.3%. The ORR was 15.5% and 6.4% in patients with PD-L1 positive and PD-L1 negative tumors, respectively. More recently, the FDA approved pembrolizumab for patients with recurrent, locally advanced or metastatic, squamous cell carcinoma of the esophagus (ESCC) whose tumors expressed PD-L1 (Combined Positive Score [CPS] > 10) based upon KEYNOTE-181. KEYNOTE-181 was a randomized, open-label trial that enrolled 628 patients with recurrent, locally advanced or metastatic esophageal cancer who progressed on or after one line of systemic treatment for advanced or metastatic disease. Patients were randomized to receive either pembrolizumab every three weeks or the investigator’s choice of traditional chemotherapy. The hazard ratio for overall survival (OS) in ESCC whose tumors expressed a PD-L1 CPS > 10 was 0.64. Median OS was 10.3 months and 6.7 months in the pembrolizumab and control arms, respectively. Another trial that supported these findings with pembrolizumab was KEYNOTE-180, a single-arm, open-label trial that enrolled 121 patients with locally advanced or metastatic esophageal cancer who progressed on or after least two prior systemic treatments for advanced disease. In this trial, and in the 35 patients with ESCC expressing PD-L1 CPS ≥ 10, ORR was 20% and response durations ranged from 4.2 to 25.1 months.

On the other hand, nivolumab, another PD-1 inhibitor, was evaluated in the treatment of esophageal cancer in CheckMate-032. This phase II/III compared the combination of two immunotherapies (nivolumab and ipilimumab, a CTLA-4 inhibitor), nivolumab monotherapy, and placebo in patients with esophageal cancers who had failed second-line therapy. This trial showed improved ORR and progression free survival (PFS) in the combination group versus the monotherapy group. However, as expected, the combination group experienced more treatment-related toxicities. In another trial, ATTRACTION-02 examined nivolumab monotherapy in the second-line setting and resulted in an 11% ORR, 27.3% 12-month OS, and 10.6% 24-month OS. The results of this trial led to the approval of nivolumab monotherapy in Asia only.
The use of immunotherapy in the front-line treatment has not been successful – in the phase III trial, KEYNOTE-062, the combination of pembrolizumab with chemotherapy versus chemotherapy alone was examined in PD-L1-positive gastroesophageal cancers. The results only trended towards improvement in outcomes, particularly in patients with higher PD-L1 expression, but did not achieve statistical significance.\(^\text{18}\) Currently, several trials are examining immunotherapy in combination with chemotherapy in the adjuvant and neoadjuvant setting and its role in maintenance therapy.

**IMMUNOTHERAPY IN THE TREATMENT OF HEPATOBILIARY CANCER**

For the purposes of this review, we will address the use of ICIs in hepatocellular carcinoma (HCC) and cholangiocarcinoma/gallbladder cancer only. Currently, first-line treatment for unresectable or metastatic HCC includes sorafenib and more recently, lenvatinib. Until recently, there was not an established second-line treatment following sorafenib failure.

The efficacy of nivolumab in HCC was examined in CheckMate-040, a phase I/II study that enrolled patients with advanced HCC and Child-Pugh A or B cirrhosis who progressed or were intolerant to sorafenib. Forty-nine of the 255 patients assessable for response had an objective anti-tumor response to nivolumab, corresponding to an 18.2% ORR. The benefits of nivolumab were observed in sorafenib-naïve and sorafenib-experienced patients.\(^\text{19}\) Based upon this data, nivolumab was FDA-approved for the treatment of HCC in patients who had previously failed sorafenib.

In another similar phase II trial, KEYNOTE-224 evaluated pembrolizumab in patients previously treated with sorafenib resulting in a 17% ORR.\(^\text{20}\) A confirmatory study was recently presented at the 2019 American Society of Clinical Oncology (ASCO) meeting: KEYNOTE-240. This trial enrolled 413 patients with advanced HCC with Child-Turcotte-Pugh A cirrhosis after progression or intolerance to sorafenib. Patients were randomized to pembrolizumab versus placebo. Although this study showed improvements in median OS (13.9 versus 10.6 months) and PFS (3 versus 2.8 months), the findings were not statistically significant because pre-specified efficacy boundaries were not reached. Response rates were higher for pembrolizumab compared to placebo (18.3% versus 4.4%).\(^\text{21}\)

A phase Ib study examined atezolizumab, a PD-L1 inhibitor, in combination with bevacizumab, a VEGF inhibitor, in the first-line setting for advanced HCC with up to Child-Pugh B7 cirrhosis. Preliminary data revealed a 34% ORR with one complete response and a median PFS of 14.9 months.\(^\text{22}\) Given these promising results, the phase III IMBrave150 trial is currently underway and examining the combination of atezolizumab with bevacizumab versus sorafenib.\(^\text{23}\) Currently, there are several other ongoing trials that are examining multiple immunotherapy combinations in the front-line treatment of HCC. CheckMate-459 is examining the combination of nivolumab with sorafenib in the front-line setting. Unfortunately, preliminary data suggests that there is no statistically significant improvement in OS when compared to sorafenib alone.\(^\text{24}\) LEAP-002 is a phase III trial currently underway and that is examining the use of pembrolizumab with lenvatinib in the front-line setting.\(^\text{25}\)

In unresectable or metastatic biliary tract cancers, first-line treatment includes gemcitabine with a platinum agent (e.g. cisplatin, oxaliplatin). Of note, patients who are dMMR or MSI-H (microsatellite instability – high) have been found to have higher response rates to PD-1/PD-L1 inhibition. Unfortunately, only a minority of patients with biliary tract cancers are MSI-H or dMMR – 5% of gallbladder cancers; 5–13% of extrahepatic cholangiocarcinoma; and 10% of intrahepatic cholangiocarcinoma.\(^\text{26}\) Based upon the results of a study by Le, et al. in 2017, pembrolizumab gained approval for use in unresectable or metastatic solid tumors that were dMMR or MSI-H. This trial evaluated patients with dMMR malignancies and resulted in a 53% ORR across twelve different tumor types including HCC and biliary tract cancers.\(^\text{27}\) Currently, there are several trials examining the combination of ICIs with standard chemotherapy in the second-line setting.

**IMMUNOTHERAPY IN THE TREATMENT OF PANCREATIC CANCER**

First-line treatment for unresectable or metastatic pancreatic cancer consists of one to four drug regimens built upon a backbone of either a fluoropyrimidine or gemcitabine – dependent upon the patient’s age and performance status. Prognosis of advanced pancreatic cancer is very dismal, and survival is less than a year. Pancreatic cancer is traditionally considered non-immunogenic – the majority of patients derive little clinical benefit from ICIs.\(^\text{28-30}\) The exception to this rule is pancreatic cancers that are found to be MSI-H or dMMR, which only accounts for 1.2% of pancreatic cancers.\(^\text{31}\) One theory to explain the disappointing response rates to ICIs is due to the immunosuppressive tumor microenvironment of pancreatic cancer along with the poorly vascularized and dense surrounding connective tissue that hinders immune cell infiltration.\(^\text{32}\) Currently, pembrolizumab is approved in the second-line setting only in pancreatic cancers that are MSI-H or dMMR.

Given the disappointing responses to ICI monotherapy, there has been significant interest in combining immunotherapy with different treatment modalities in the hopes of increasing tumor immunogenicity. Thus far, the majority of trials that have examined the use of ICIs in combination with standard cytotoxic regimens have not resulted in significantly improved response rates when compared to the standard cytotoxic regimens alone.\(^\text{33,34}\) Another potential strategy to increase tumor immunogenicity is to use a pancreatic cancer vaccine (GVAX) – created from irradiated, allogeneic pancreatic cancer cells which are then modified to induce a tumor antigen response by a host’s immune system. Currently, there are ongoing trials examining the use of GVAX with and without ICIs; however, to date, the results have been mixed.\(^\text{35,37}\)
IMMUNOTHERAPY IN THE TREATMENT OF COLORECTAL CANCER

The treatment of metastatic colorectal cancer (mCRC) has been evolving through the last decade. Currently, first-line treatments for unresectable or mCRC include cytotoxic regimens built upon a fluoropyrimidine backbone in combination with targeted therapy. Immunotherapy has been approved for the treatment of mCRC patients whose tumors are MSI or dMMR, which accounts for 15% of CRCs and plays a significant role in predicting a response to ICI therapy.38, 39

Pembrolizumab was examined in the second-line setting for mCRC patients who were MMR-deficient (dMMR) and MMR-proficient. In MMR-proficient patients, there was a 0% ORR with an 11% disease control rate (DCR); however, dMMR patients exhibited a 40% ORR with a 78% DCR to pembrolizumab monotherapy. These findings led to the FDA-approval of pembrolizumab in the second-line setting for MSI-H or dMMR mCRC.26 Nivolumab combined with ipilimumab and nivolumab monotherapy have also been approved for second-line use for MSI-H or dMMR mCRC based on CheckMate-142 which showed a 55% ORR in the dual ICI cohort and a 31% ORR in the monotherapy cohort.3,40 Of note, those that received dual ICI had received two or more lines of therapy and showed response regardless of PD-L1 status, KRAS wild-type, BRAF mutation, or history of Lynch syndrome.10 Given these promising results from CheckMate-142 regarding dual ICI therapy, there has been much interest in combining ICIs with other treatment modalities in the hopes of improved response rates.

An ongoing phase II trial is combining standard cytotoxic chemotherapy with pembrolizumab in the front-line setting for patients with mCRC irrespective of MMR status. Preliminary data demonstrates a 53% ORR.49 Other studies have looked into combining ICIs with a VEGF inhibitor (i.e., bevacizumab) with standard chemotherapy in patients who had not received a platinum (i.e., oxaliplatin) containing regimen or without standard chemotherapy in patients who were oxaliplatin-refractory. This has resulted in an 8% ORR without standard chemotherapy and a 36% ORR with standard chemotherapy.45 Based upon the promising results from a phase I trial, IMBlaZe370 examined the use of an ICI with a MAP kinase enzyme [MEK] inhibitor in hopes of upregulating antigen presentation leading to increased T-cell tumor accumulation in microsatellite stable (MSS) or MSI-low (MSI-L) mCRC patients who had progressed after two or more lines of therapy. Unfortunately, no statistically significant difference was found in survival when compared to standard therapy.

CONCLUSION

The introduction of immunotherapy has led to major changes to the treatment paradigms of many cancers. ICIs have made their way into front-line treatment regimens in melanoma and lung cancer. In GI malignancies, the changes to the treatment paradigms have been more modest – treatment with ICIs are mostly reserved for use in the second-line or beyond, and usually in the setting of PD-L1 positivity, MSI-H, or dMMR tumors. However modest, these second-line ICIs give patients reasonable options following progression of their disease that were not available a few years ago.

Why the responses to ICI monotherapy are relatively low in GI malignancies include the immunosuppressive tumor microenvironments and the complex stroma/parenchyma of tumors preventing immune cell infiltration that is necessary for a robust immune response. As a result, the logical next step has been combining ICIs with other treatment modalities such as: standard cytotoxic chemotherapy to help break down the tumor stroma/parenchyma to help expose tumor antigens, increase antigen presentation, and enhance immune cell infiltration: or combine one ICI with another ICI to help enhance the immune response through different mechanisms and/or dampen the immunosuppressive tumor microenvironment.

With an increased understanding of the underlying mechanism of the immune system and how it interacts with the tumor microenvironment, new studies are being devised to assess the safety and efficacy of these combinations on a smaller scale prior to pursuing larger phase III trials.

References


24. Bristol-Myers Squibb Announces Results from CheckMate -459 Study Evaluating Opdivo (nivolumab) as a First-Line Treatment for Patients with Unresectable Hepatocellular Carcinoma. Bristol-Myers Squibb. Published June 24, 2019.


Acute Myeloid Leukemia: A Review
ARI PELCOVITS, MD; RABIN NIROULA, MD

ABSTRACT
Acute myeloid leukemia (AML) is a malignancy of the stem cell precursors of the myeloid lineage (red blood cells, platelets, and white blood cells other than B and T cells). Like other malignancies, it is due to genetic variations that lead to neoplastic changes and clonal proliferation. AML remains a rare malignancy, accounting for only 1.2% of all new cancer diagnoses in the United States per year, but it accounts for close to one third of all leukemias diagnosed. For much of the 20th and early 21st century treatment paradigms were unchanged with survival curves remaining stagnant for many decades. Recent changes in our understanding of the genetic variations in the disease have led to some promising new therapies with hopes for improved outcomes in the future. Below we review the definitions, diagnosis and classification of AML and how this affects the evolving treatment paradigm of AML.

KEYWORDS: acute myeloid leukemia, bone marrow, stem cell transplantation

DEFINITION/DIAGNOSIS/CLASSIFICATION
AML is a disease of the bone marrow, a disorder of hematopoietic stem cells due to genetic alterations in blood cell precursors resulting in overproduction of neoplastic clonal myeloid stem cells. While extramedullary manifestations can occur (e.g. myeloid sarcomas, leukemia cutis), the underlying disease is due to abnormalities in hematologic cellular production. A small subset of cases have identified causative factors such as prior chemotherapy or certain chemical exposures, but the large majority are due to genetic alterations, through chromosomal abnormalities or isolated gene mutations, without clear causative agents. Delineating these genetic abnormalities is important in risk stratifying patients and determining appropriate treatment.

Patients with AML will initially present in a myriad of ways. Some cases of disease will be discovered on routine blood work while others may present with symptomatic complications such as infection, bleeding or disseminated intravascular coagulation. Bone marrow examination is paramount for both establishing the diagnosis as well as obtaining tissue for analysis to better classify the AML subtype and prognostic severity.

The World Health Organization in its 2016 updated guidelines distinguishes six groups of AML: [1] AML with recurrent genetic abnormalities, [2] AML with myelodysplasia-related changes, [3] Therapy-related myeloid neoplasms, [4] AML Not Otherwise Specified, [5] Myeloid sarcoma, and [6] Myeloid proliferations related to Down syndrome. The diagnosis is made by the presence of ≥20% blasts in the peripheral blood or in the bone marrow, or through the presence of unique genetic abnormalities found in the bone marrow regardless of blast count [t(8;21), inv(16), or t(15;17)]. AML is further classified into three prognostic risk groups: favorable, intermediate, and adverse [Table 1]. These are based on both cytogenetics and relatively recent recognition of molecular diseases subsets that are distinct from the

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Adapted from Blood 2017 129:424-447
contribution of cytogenetic risk. These newly recognized molecular subsets have different responses to standard therapeutics. The prognostic groups predict the response to standard therapy and survival in one large retrospective analysis of patients under the age of 55, the overall survival rate at 5 years was 44%, however when broken down by risk profile the overall survival rates were 64%, 41%, and 11% for favorable, intermediate, and adverse risk respectively. The overall survival decreases when older adults are included but the stratification of survival remains constant.

TREATMENT

The treatment of AML involves initial induction therapy and post-remission therapy. Goal of induction therapy is to achieve complete remission (CR) with preferably no measurable residual disease (MRD). Studies have shown improved survival in patients who achieve CR irrespective of the type of induction therapy. Choice of initial induction treatment depends on functional status of the patient (which is best measured by performance status and comorbidities), biological status of the disease (best measured by prognostic risk groups and recently recognized molecular profile of leukemia cells) and goals of the patient. The two commonly used induction therapies in acute myeloid leukemia include 1) Cytotoxic chemotherapy with or without targeted therapies and 2) Hypomethylating agents with or without targeted therapies.

INDUCTION CHEMOTHERAPY

Favorable and Intermediate Risk Disease

For all patients with AML with the goal of cure and who are medically fit enough to tolerate chemotherapy, the backbone of therapy has not changed for 50 years, with upfront treatment consisting of a continuous infusion of cytarabine over 7 days with the addition of an anthracycline, typically daunorubicin, given daily for the first 3 days. This induction therapy, known colloquially as 7+3, leads to complete disease response in up to 80% of patients with favorable risk disease and 50-60% complete response in those with intermediate adverse risk disease.

The outcomes have improved with addition of various targeted drugs to the traditional 7+3 induction chemotherapy in the favorable and intermediate risk groups. Gemtuzumab ozogomycin (GO) is a monoclonal antibody against CD-33 [a protein that is expressed in myeloid leukemia cells]. Addition of GO to standard chemotherapy in patients with favorable and intermediate risk disease decreases the risk of relapse and in some studies improves overall survival (OS). The magnitude of benefit is higher in favorable risk disease than in intermediate risk disease. This has made obtaining early cytogenetic and molecular studies on patients with a new diagnosis of the utmost importance as GO is added to the first day of therapy for patients with favorable risk disease who are CD-33 positive.

Midostaurin is an oral multi-targeted tyrosine kinase inhibitor active in patients with a FLT3 mutation. FLT3 mutations initiate oncogenic signal transduction in about 25–30% of patients with AML. There are 2 types of FLT3 mutation; Internal tandem duplication and tyrosine kinase domain. Addition of midostaurin to standard 7+3 chemotherapy in patients with FLT3 mutation has improved survival, from a median of 25 to 74 months.

Adverse Risk Disease

Adverse risk disease is an unmet need in AML. The outcomes with standard 7+3 chemotherapy remain unsatisfactory. Complete remission (CR) rate is only about 40% and median overall survival is in the range of 12–18 months. Even with allogenic hematopoietic stem cell transplantation (see below), almost half of the patients relapse. Patients are therefore usually referred for clinical trials if there is one available, due to these lower rates of survival. Recently two therapies, CPX351 and venetoclax with a hypomethylating agent, have shown better results than the standard therapy in patients with adverse risk disease.

CPX 351 is a liposomal formulation of cytarabine and daunorubicin at a fixed 5:1 molar ratio of cytarabine and daunorubicin. The liposomal encapsulation leads to prolonged exposure to the two drugs. CPX 351 showed significantly improved response rates and improved survival compared to 7+3 chemotherapy in patients with adverse risk disease [i.e. therapy-related AML, AML with MDS related changes].

Venetoclax is an oral highly selective inhibitor of the anti-apoptotic protein BCL-2. BCL2 is thought to mediate resistance to standard therapy in patients with adverse risk AML. Venetoclax was studied with hypomethylating agents [decitabine and azacitadine] as a backbone in patients with adverse risk disease. Even in elderly patients and patients with poor cytogenetics and adverse molecular mutations, the outcomes were better with venetoclax plus hypomethylating agents than hypomethylating agents alone.

Median overall survival in these preliminary studies was approximately 15 months, significantly improved from the historical median survival of approximately 10 months with the use of hypomethylating agents alone.

POST-REMISSION THERAPY

The goal of post-remission therapy is to prevent relapse of the disease. The two commonly employed strategies are additional post remission cytotoxic chemotherapies [such as high or intermediate dose cytarabine] with or without targeted therapies, or allogenic hematopoietic stem cell transplantation (Allo SCT). The choice of therapy is determined by the unique risks and benefits provided by each treatment environment.
The risk of non-relapse mortality (NRM) is high with Allo SCT; however, the risk of disease relapse is reduced. Furthermore, there is increased morbidity with Allo SCT (such as chronic graft vs host disease, secondary malignancies, or infection from chronic immunosuppression).

The absolute decrease in the risk of disease relapse has to be more than the risk of NRM to justify Allo SCT as post-remission therapy. All patients with adverse risk profiles and most of the patients with intermediate risk meet this criteria.12,13 Patients with favorable risk profiles, however, are able to remain free from relapse at high enough rates with chemotherapy alone such that the risks of Allo SCT are not justified. Therefore, in favorable risk group, induction therapy is followed by definitive consolidation therapy with high dose cytarabine (HiDAC).14

**FUTURE DIRECTIONS**

Over the last decade, there have been significant advancements in the genomic profiling of AML. This has resulted in exciting opportunities to create genomically defined targeted therapies for patients with AML. Some of the therapies like FLT3 inhibitors, Isocitrate dehydrogenase (IDH) 1 and 2 inhibitors have been tested in clinical trials and are now the standard of care in patients who harbor these mutations. There are other targeted agents directed against various mutations seen in AML that are currently being investigated in clinical trials. One ongoing multicenter trial is sponsored by the Leukemia and Lymphoma Society in the United States and is known as the “BEAT AML” trial. Patients are assigned to targeted therapies based on their genomic profile, with the hope that the results of this and several other trials will provide important information regarding the clinical benefits of genomically defined targeted therapies in AML.

**CONCLUSION**

Acute myeloid leukemia remains a rare but lethal malignancy. Our understanding of the disease has progressed significantly, and new and evolving therapies are providing hope for improved survival and less toxic treatment. Early diagnosis with rapid analysis of cytogenetic and molecular abnormalities (e.g. NPM1, FLT-3) are paramount in tailoring best therapy for patients, especially in light of new treatment modalities that rely on cytogenetic and molecular testing. Chemotherapy remains the backbone of treatment with stem cell transplantation still the best hopes for cure in many patients with adverse cytogenetic risk profiles.


**References**


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Prostate Cancer Therapeutics and Their Complications: A Primer for the Primary Care Provider

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INTRODUCTION
Prostate cancer is the most common malignancy in men and the second leading cause of cancer mortality in men. Even with evolving alterations in the screening guidelines, the annual number of prostate cancers per year in the United States remains substantial. The majority of men diagnosed with prostate cancer will die of other causes. Many men will face survivorship issues related to prior therapies. In addition, advanced prostate cancer has a long natural history with continuous exposure to therapies that have impactful effects on overall health. The primary care provider is an integral participant in the care team for the prostate cancer patient. The goal of the ensuing discussion is to provide an educational primer on prostate cancer therapeutics and potential consequences of therapy.

RADIATION THERAPY
Radiation techniques have evolved, resulting in a reduced rate of acute and late toxicities.1 Radiation therapy primarily is delivered by two methods: external beam radiation treatment (EBRT) and brachytherapy. Most men treated with EBRT for localized prostate cancer, either primary treatment or salvage treatment after surgery, have an excellent prognosis with cancer specific survival longer than 10 years. Therefore, monitoring for acute and late toxicities from treatment is paramount. We herein discuss the pattern and timing of toxicities associated with radiation treatment for prostate cancer. Of note: many men receiving EBRT for treatment of prostate cancer also receive androgen deprivation therapy [ADT]. The effects of ADT will be discussed in a separate section.

Typical acute toxicities of EBRT include fatigue, urinary symptoms and gastrointestinal symptoms. Acute cutaneous toxicity, as often seen in radiation for breast cancer, is exceedingly rare in prostate cancer as the skin is spared significant radiation. Fatigue is the most common symptom of radiation therapy, occurring in 40–80% of patients treated. Fatigue often arises within the first several weeks of radiation therapy and may last several months beyond the completion of radiation therapy. Severity of fatigue varies but the majority of patients are able to maintain a full work schedule. Incontinence is less likely to occur with radiation therapy than prostatectomy, however, dysuria, urinary frequency and nocturia are more common. Symptoms can mimic urinary tract infection and urinalysis may often reveal microscopic hematuria and even the presence of WBCs. Antibiotic therapy is indicated only in the uncommon circumstance in which bacteria is noted and cultured. Typical acute GI toxicities during radiation therapy include intermittent loose stools or diarrhea. Common management strategies include use of anti-diarrheal agents and dietary/nutritional changes. Data supporting the benefit of nutritional changes is over-all weak but strategies that have shown efficacy include fat restriction, lactose restriction, fiber supplementation, or a combination of the above.3 Acute toxicity predicts late gastrointestinal events.1,3

The Prostate Testing for Cancer and Treatment (ProtecT) trial assessed toxicity outcomes in 1600 men randomized to active surveillance, radical prostatectomy, or EBRT with short term ADT. The toxicity analysis distinguished the toxicities of prostatectomy and EBRT as compared to the non-treatment patients. Patients receiving EBRT reported no increase in urinary incontinence as opposed to all patients immediately postoperative. Although higher rates of voiding symptoms and nocturia were noticed at 6 months post-radiation treatment, at one year the rates were similar to active surveillance patients. Reports on erectile quality after EBRT revealed decreased erection quality at 6 months with a continued erection quality decline over the 6-year follow-up period. Overall long-term erectile dysfunction rates in radiation patients were similar to what was experienced by active surveillance patients. Patients with erectile dysfunction after treatment should be referred to a multidisciplinary clinic where patients receive care from medical, surgical and psychology providers. A multidisciplinary Men’s Health Clinic is available for patients at the Lifespan Cancer Institute. Increased rates of rectal bleeding were shown after radiation therapy after 2 years of follow-up. There was no increase in fecal incontinence.4

There are significant differences between brachytherapy and external beam radiation therapy. Only selected patients are considered appropriate for brachytherapy as primary treatment. Since minimal radiation is delivered beyond the prostate capsule, brachytherapy is offered only for the best prognostic categories. Placement of the brachytherapy seeds is done in an operating room with patients under general anesthesia. Patients must be in good health in order to undergo this invasive procedure.
Androgens drive prostate cancer growth and survival. In the United States, androgens are used to treat patients with prostate cancer. Androgen deprivation therapy (ADT) is the backbone of therapy for patients with various presentations of prostate cancer. It is the cornerstone of treatment for patients with incurable, metastatic disease. ADT slows down progression to metastatic disease in patients with non-metastatic disease and a rising PSA after local treatment [biochemical relapse]. ADT is an adjunctive treatment to radiation for certain higher-risk patients with prostate cancer being treated with curative intent. ADT is also utilized in select cases after prostatectomy as an alternative therapy. The duration of ADT can vary from 4 months to continuous ADT depending on the clinical situation and treatment objectives. In general, the longer the duration of ADT the more troublesome the adverse effects.

Androgen deprivation therapy can be achieved by bilateral orchiectomy or luteinizing hormone release hormone (LHRH) therapy. In the United States, medical castration through LHRH antagonist or agonist injections is more commonly employed. Degarelix is a LHRH antagonist.
administered as monthly subcutaneous injections. Degarelix achieves castration, defined as serum testosterone levels of less than 50 ng/dL, within 3 days. Since it has a relative rapid onset of action, it is often the choice for patients with acute complications of prostate cancer, such as urinary obstruction, severe bone pain or spinal cord compression. Degarelix requires monthly injection and has a 40% rate of local injection reactions. Leuprolide is a LHRH agonist that induces castration in 2 to 4 weeks. It has a lower rate of local injection reaction (1%) than degarelix. It may be given monthly or every 3, 4 or 6 months. Leuprolide can cause an initial testosterone surge that may accelerate the growth of prostate cancer cells in the first 2 to 4 weeks after its administration. Thus, it requires concurrent androgen receptor antagonism to prevent exacerbated bone pain, spinal cord compression and urinary obstruction from prostate tumor growth. The most common oral antagonist receptor antagonist in current use is bicalutamide. Bicalutamide has an elimination half-life of 7 days; therefore, a lead-in of 14 days is usually sufficient to address the testosterone surge.

Androgen deprivation therapy has been linked to metabolic syndrome. Testosterone suppression induces skeletal muscle mass loss. This happens in part due to downregulation of insulin growth factor receptors and regulation of transcription factors associated with skeletal muscle programmed death. Lean muscle mass loss is implicated in insulin resistance and subsequent hypercholesterolemia and hyperglycemia. Upregulation of lipoprotein lipase is also observed in the castrate state. Hypertension is thought to be a result of a higher basal level of endothelin-1, a hormonal vasoconstrictor. Studies have shown that the risk of diabetes in patients on ADT is increased by 44% compared to matched control patient cohort not receiving ADT. The risk for coronary artery disease and for myocardial infarct is increased 16% and 11% respectively. Effect on cardiovascular mortality is mixed and inconclusive. Degarelix may have a lower risk of cardiac events at 1 year compared with leuprolide. Leuprolide in men with pre-existing cardiovascular disease and for myocardial infarction

Bone loss is a known adverse effect of ADT. This is due to dysregulation of Receptor Activator of Nuclear Factor Kappa beta (RANK) and its ligand (RANKL), both important for bone resorption. RANKLs are secreted by osteoblasts and bind to RANK on osteoclasts to activate osteolysis. The RANKL monoclonal antibody denosumab blocks this interaction. Men on ADT are at higher risk for bone fractures. A baseline Dual-Energy X-ray Absorptiometry (DEXA) scan should be obtained at the onset of ADT. Thereafter, DEXA scans are recommended every 1–2 years. Men with osteoporosis at baseline or after androgen deprivation therapy should be treated with the RANKL blocker denosumab 60 mg intravenously every 6 months or the intravenous bisphosphonate zoledronic acid 4 mg yearly or the oral bisphosphonate alendronate 70 mg weekly. Bisphosphonate treatment is contraindicated in patients with severe renal impairment and should be used with caution in patients with mild to moderate renal impairment. Men who are older than 50 years old with osteopenia and a World Health Organization FRAX score [available online] predicting a 10-year risk of hip fracture equal or above 3% or major osteoporosis-related fracture equal and above 20%, should be treated in a similar manner. A baseline 25-OH vitamin D level is recommended. Patients who are deficient in vitamin D require appropriate replacement therapy. Decrease of alcohol consumption, smoking cessation and exercise are important to counteract bone resorption and men should be counseled to adopt these beneficial, lifestyle measures.

Men with bone metastases are at risk for pathological fractures, spinal cord compression and bone pain; collectively referred to as skeletal-related events (SREs). ADT compounds the risk of SREs by activating osteoclasts. Bisphosphonates and RANKL inhibitors have shown to delay skeletal-related events but only in men with metastatic bone lesions and castrate-resistant disease (mCRPC). Dosing bone protective agents for mCRPC patients is frequent; thus, increasing the risk of osteonecrosis of the jaw (ONJ) to 2%–4%. Dental preventative care is important in preventing ONJ and dental providers need to be informed that men are receiving therapy. Dental extractions increase the risk of developing ONJ and should occur only as a necessity. If a tooth extraction is required, bone protective agents should be held for an extended period. Other common side effects from these agents include myalgias and arthralgias, flu-like symptoms, hypocalcemia for denosumab and renal insufficiency for zoledronic acid.

In summary, skeletal-related events and metabolic syndrome figure among the most significant long-term adverse effects of androgen deprivation therapy. It is the role of the health care providers to recognize the magnitude of the skeletal and cardiovascular risks associated with these important prostate cancer therapies. By mitigating contributing cardiovascular factors and reinforcing fracture prevention, primary care providers have an opportunity to promote bone and cardiovascular health.

**ANTI-ANDROGEN AGENTS**

Over the last two decades, a significant change in the management of prostate cancer is the development of new therapeutics for mCRPC and the expansion of their roles in the treatment of metastatic castrate sensitive prostate cancer (mCSPC). The scope of this discussion will be limited
to the two most commonly utilized anti-androgen agents: abiraterone acetate and enzalutamide.

Abiraterone acetate was approved for the treatment of mCRPC in 2011 and mCSPC in 2018. In both circumstances, abiraterone improves overall survival and progression-free survival with its bigger impact in mCSPC, which has placed the drug earlier in the treatment paradigm. The mechanism of action of abiraterone is unique. Abiraterone is an androgen biosynthesis inhibitor, that impedes 17α-hydroxylase/C17,20-lyase (CYP17). CYP 17 catalyzes the formation of dehydroepiandrosterone (DHEA) and androstenedione. Treatment with LHRH agents and orchiectomy reduces testosterone production from the testis only, with abiraterone providing added blockade from the adrenal glands and prostate cancer cells. Absorption of abiraterone increases if administered with fats and it should be administered on an empty stomach. A significant consequence of treatment with abiraterone is development of mineralocorticoid excess syndrome (MES) as a result of accumulated CYP 17 substrates being shuttled to the mineralocorticoid pathway. This can lead to complications of hypertension, fluid retention and hypokalemia. Co-administration of prednisone at 5mg to 10mg per day mitigates MES but adds the toxicities of continuous steroid administration. Even with prednisone administration, hypertension remains a common adverse effect. In an analysis of 5445 patients from 5 studies, the overall incidences of all-grade hypertension and high-grade hypertension [grade 3 and 4] were 21.9% [95% CI: 13.6–33.2%] and 10.2% [95% CI: 6.9–11.6%] respectively. 25

Of note, there is no standard management of abiraterone treatment-related hypertension. Finally, abiraterone was associated with a statistically significant 76% [RR 1.76] increase in the risk of high-grade cardiac disorder adverse events [95% CI: 1.12-2.75 RR; p = 0.01] and in a 28% [RR 1.28] increase in all-grade cardiac disorder adverse events [95% CI: 1.06-1.55; p = 0.01]. 26

Enzalutamide was approved for the treatment of mCRPC in 2012, non-metastatic or M0 CRPC in 2018 and mCSPC in 2019.27 Similar to abiraterone, enzalutamide impacts overall survival and progression-free survival in these indications, moving to an earlier point in the treatment paradigm. Enzalutamide is an androgen receptor inhibitor that acts on different steps in the androgen receptor signaling pathway. Like abiraterone, it is combined with ADT. Enzalutamide’s most common adverse effect is fatigue. Enzalutamide is associated with less hypertension when compared to abiraterone and is not associated with a statistical increase in cardiac events.26 However, there is a small risk of seizures [0.1%–1%] and is not recommended for patients with a history of seizures. Finally, falls have been associated with enzalutamide.

Drug-drug interactions can occur with either abiraterone or enzalutamide. Abiraterone inhibits liver cytochrome P450 (CYP)-dependent enzymes CYP2C8 and CYP2D6, which are involved in the metabolism of approximately 25% of all drugs. Thus, abiraterone may increase plasma levels of CYP2C8 substrates including amiodarone and carbamazepine and CYP2D6 substrates, including amitriptyline, oxycodone and risperidone. Enzalutamide induces CYP3A4, CYP2C9 and CYP2C19, which metabolize up to 50% of medications. Importantly, enzalutamide may decrease plasma levels of warfarin and clopidogrel. As always, cross-referencing medications for drug-drug interactions remains a critical component of patient care requiring cross discipline communication among providers.

CONCLUSION
The aging of our population and the high prevalence of prostate cancer will result in an increase in prostate cancer patients actively treated and prostate cancer survivors. Proper long-term surveillance of prostate cancer patients involves the monitoring of late gastrointestinal, genitourinary and sexual side effects, the surveillance for secondary malignancies associated with radiation therapy, monitoring for cardiovascular disease, diabetes and osteoporosis. In summary, awareness of the timing, frequency and severity of these effects helps the clinician to provide high quality care for the man with prostate cancer.

References
3. Peach MS, Showalter TN, Ohri N. Systematic Review of the Relationship between Acute and Late Gastrointestinal Toxicity after Radiotherapy for Prostate Cancer. Prostate Cancer. 2015; 2015:624736.

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ABSTRACT
With advances in the treatment of plasma cell disorders, there have also been improvements in the risk stratification of these diseases. There are currently no screening recommendations for monoclonal gammopathy of unknown significance (MGUS); however, new studies are analyzing the role of screening for patients age 40–75 who are African American or have a family history of multiple myeloma (MM). Patients with smoldering multiple myeloma (SMM) have an increased risk of progression to MM when compared to MGUS. Data have shown that evaluation of bone marrow biopsy, full body MRI and free light chain ratios can identify high-risk SMM patients. Current investigation into early initiation of treatment for patients with SMM who do not meet criteria for MM showed improvement in time to progression. By continuing to evaluate clinical markers of disease burden, physicians can risk stratify patients to identify those at highest risk for progression to MM.

KEYWORDS: multiple myeloma, monoclonal gammopathy of undetermined significance, smoldering multiple myeloma, risk stratification

INTRODUCTION
Over the past decade there have been significant advances in the management of plasma cell disorders. These developments are attributed primarily to novel myeloma-directed therapies, but also due to improved imaging techniques, analysis of the genetic evolution of plasma cell disorders (PCDs), and clinical trials exploring the treatment of pre-symptomatic stages of PCDs. Here we will explore recent advances in the risk stratification of monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM), and multiple myeloma. Of note, the evaluation of less common plasma cell disorders such as AL amyloidosis, Waldenström macroglobulinemia, POEMS syndrome, and monoclonal gammopathy of renal significance, is beyond the scope of this manuscript.

MGUS
MGUS is most often a diagnosis made in patients with a presentation concerning for multiple myeloma, but an alternative diagnosis is made to explain their presenting symptoms (e.g. renal failure due to dehydration, hypercalcemia due to hyperparathyroidism, iron deficiency anemia, etc.). The laboratory evaluation for plasma cell disorders includes a serum protein electrophoresis (SPEP), serum immunofixation (SIFE), serum free light chains (SFLC), quantitative immunoglobulin levels (IgG, IgA, IgM), and urine protein electrophoresis in patients with protein present on urinalysis. In order to be consistent with MGUS, the monoclonal protein must be <3 g/dL with <10% plasma cells present on a bone marrow biopsy. Both the quantity and quality of monoclonal protein are used to estimate risk of progression to myeloma in MGUS. The presence of 1. A non-IgG isotype, 2. Monoclonal protein > 1.5g/dl, or 3. An abnormal serum free light chain ratio have been found to increase risk of progression to myeloma. Patients with none, one, two, or all three risk factors have a 20-year risk of progression to multiple myeloma of 2%, 10%, 18%, and 27%, respectively.1 In patients with low-risk MGUS (none of the aforementioned risk factors), bone marrow examination and skeletal survey can safely be deferred.2, 3 In all patients diagnosed with MGUS, regardless of risk category, the risk of progression to multiple myeloma remains linear, rather than logarithmic or exponential.

While MGUS is present in over 3% of patients aged 50 or older4, there are currently no screening recommendations for the disease given the significant anxiety surrounding the diagnosis, the lack of curative therapy, and the low risk of progression to multiple myeloma. Investigation into who may benefit from screening for a monoclonal protein is ongoing with the current PROMISE study analyzing the role of screening in patients age 40–75 who are African-American or have a first-degree relative with multiple myeloma, MGUS, SMM, or Waldenström macroglobulinemia.

SMOLDERING MULTIPLE MYELOMA
Historically, those patients who do not have “CRAB” symptoms [hypercalcemia >1 mg/dL above upper-limit of normal, renal insufficiency with CrCl < 40 mL/min, anemia with hemoglobin value <10 g/dL, or one or more bone lesions on skeletal radiography, computed tomography (CT), or positron emission tomography (PET)] attributable to multiple myeloma, yet have ≥10% clonal bone marrow plasma cells on bone marrow examination or ≥3 g/dL of serum monoclonal protein are diagnosed with smoldering multiple
myeloma. This intermediate diagnosis reflects the increased risk of progression to symptomatic multiple myeloma compared to MGUS and thus can help guide clinicians on how to appropriately monitor these patients. Unlike the linear risk associated with MGUS over time, patients with smoldering multiple myeloma follow a logarithmic curve of progression to symptomatic multiple myeloma: 10% risk per year for the first five years following diagnosis, 3% risk per year for the following five years, and a subsequent 1% risk per year. Given the significant morbidity associated with symptoms of multiple myeloma, namely renal dysfunction, pain, and/or fracture associated with bone lesions, significant effort has been dedicated to identifying those patients with SMM who are very likely to progress. Long-term follow-up of SMM patients in a Mayo Clinic cohort revealed that the presence of >60% clonal plasma cells on bone marrow examination represents an ultra-high-risk group of smoldering myeloma with a 95% risk of progression at two years. Advances in MRI technology have allowed for a study of whole-body MRI in 149 patients with SMM found that two or more focal lesions on whole-body MRI indicated a 70% risk of progression to multiple myeloma at two years. Subsequently, a retrospective study of free light chain levels in 586 patients with smoldering multiple myeloma discovered that an involved-to-uninvolved free light chain ratio of 100:1 or greater predicted a 72% risk of progression to multiple myeloma within two years. These three studies led to the incorporation of three new diagnostic criteria for multiple myeloma by the International Myeloma Working Group (IMWG): 1. Bone marrow clonal plasma cells >60%; 2. Involved-to-uninvolved free light chain ratio >100:1 (also requiring the involved free light chain absolute level >100 mg/L); and 3. >1 focal lesion on MRI studies.

More recently, focus has shifted toward identifying SMM patients who do not meet the aforementioned criteria for multiple myeloma who would benefit from early initiation of therapy. The Spanish PETHEMA group published a phase 3, open-label, randomized trial of lenalidomide and dexamethasone versus observation in high-risk SMM (defined as SMM plus >95% phenotypically aberrant plasma cells in the bone marrow plasma cell compartment with reduction of at least 25% below the lower-limit of normal in one of the two uninvolved immunoglobulins) in 2016. Patients in the intervention arm had a significantly longer time to progression (HR 0.24, 95% CI 0.14-0.41) as well as a significant improvement in overall survival (0.43, 95% CI 0.21-0.92). Unfortunately, the risk stratification method using multi-parameter flow cytometry is of limited availability in many practices and is not routinely performed. Early results from an ongoing Eastern Cooperative Oncology Group Study [E3A06] have confirmed the expected improvement in time to progression, without overall survival data available. This trial uses routinely available markers of high-risk SMM of > 20% clonal bone marrow plasma cells, >2 g/dL monoclonal protein or involved-to-uninvolved free light chain ratio of >20:1.

CONCLUSION

As basic science advances our understanding of the evolution from the asymptomatic precursor disease of MGUS to symptomatic multiple myeloma, clinical research is investigating the benefits of treating patients earlier in their disease course with the hope of preventing morbidity. The convergence of these two processes is the development of a safe and effective cure for plasma cell disorders at diagnosis. Until that time, the use of clinical markers of disease burden can help physicians risk stratify patients in order to counsel on appropriate testing, referral, follow-up, and treatment.

References

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Co-infection with SARS-CoV-2 and Human Metapneumovirus
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ABSTRACT
The novel coronavirus (now called SARS-CoV-2) initially discovered in Wuhan, China, has now become a global pandemic. We describe a patient presenting to an Emergency Department in Rhode Island on March 12, 2020 with cough and shortness of breath after a trip to Jamaica. The patient underwent nasopharyngeal swab for a respiratory pathogen panel as well as SARS-CoV-2 RT-PCR. When the respiratory pathogen panel was positive for human metapneumovirus, the patient was treated and discharged. SARS-CoV-2 RT-PCR came back positive 24 hours later. Although respiratory viral co-infection is thought to be relatively uncommon in adults, this case reflects that SARS-CoV-2 testing algorithms that exclude patients who test positive for routine viral pathogens may miss SARS-CoV-2 co-infected patients.

KEYWORDS: SARS-CoV-2, COVID-19, human metapneumovirus, co-infection

CASE REPORT
A 57-year-old female with a history of obstructive sleep apnea on continuous positive airway pressure, hypertension, and hyperlipidemia presented to the Emergency Department for evaluation of cough and shortness of breath for 4 days. Her symptoms started approximately 12 days after she returned from a trip to Jamaica. The patient initially developed a persistent dry cough and upper respiratory symptoms. She then developed shortness of breath a few days later as well as subjective fevers. She had no gastrointestinal symptoms. After visiting her primary care provider, she was referred to the Emergency Department. In the Emergency Department, the patient was immediately placed on maximum isolation precautions [negative pressure room, with anyone entering the room required to wear an N95 respirator, face shield, disposable gown, and gloves]. She was afebrile with oxygen saturation of 92–95% on room air. Lung exam revealed wheezing. Blood work revealed a white blood cell count of 6.4 x 10^9/L, an absolute lymphocyte count of 0.8 x 10^9/L with an otherwise normal differential, and a platelet count of 253 x 10^9/L. Liver function tests were not ordered. A chest X-ray showed no pulmonary infiltrates. A nasopharyngeal swab was obtained for respiratory pathogen panel (RPP) and SARS-CoV-2 RT-PCR. RPP was positive for human metapneumovirus and the patient was discharged home with an albuterol inhaler and oral steroids. The positive result of SARS-CoV-2 RT-PCR was reported 24 hours later.

METHODS
Clinical specimens were collected in accordance with CDC guidelines. A nasopharyngeal swab was obtained and sent to the Rhode Island Department of Health for SARS-CoV-2 testing via RT-PCR. A respiratory pathogen panel was sent to the hospital’s microbiology lab for testing using the GenMark Dx® ePlex™.

RESULTS
The patient tested positive for human metapneumovirus by the hospital laboratory and SARS-CoV-2 by the Rhode Island Department of Health.

DISCUSSION
Co-infection with two respiratory viral pathogens is uncommon in adults. A 2013 study that included 250 hospitalized adults with H1N1 influenza showed that 3.6% were co-infected. Additionally, they showed that co-infection with another respiratory virus was associated with a greater risk of complications, particularly treatment for secondary bacterial pneumonia, although duration of hospitalization was unchanged compared to mono-infected patients. In a study of 186 patients with suspected COVID-19 infection in Shenzhen, China, 3.2% (n=6) tested positive for both SARS-CoV-2 and another viral respiratory pathogen. Human metapneumovirus was one of the pathogens identified, along with respiratory syncytial virus, rhinovirus, parainfluenza virus 2, and coronavirus HKU1. Little is known about the clinical implications of co-infection with SARS-CoV-2 and other respiratory viruses. At least one other adult case has been described of co-infection with SARS-CoV2 and another viral pathogen, Influenza A.

Although co-infection with dual respiratory pathogens is uncommon in adults, our patient had both metapneumovirus and SARS-CoV-2. Testing algorithms that exclude...
SARS-CoV-2 testing among patients who have routine viral pathogens may miss co-infected patients. Currently, little is known about the clinical course of patients co-infected with SARS-CoV-2 and standard viral pathogens. There is evidence from the 2009 H1N1 influenza outbreak to suggest that co-infection with an emerging viral pathogen and a standard respiratory virus is associated with increased rate of complications compared to mono-infection with the emerging disease. This is an area of study that may warrant further research.

[Editor’s note: While 3.2% co-infection rates have been noted, as cited by the authors, a recent report out of Stanford reported on a series of 562 SARS-CoV-2 tests performed in their emergency department. Of the 49 positive SARS-CoV-2 results, 22.4% (11) were positive for additional viruses, including Rhinovirus/enterovirus, Metapneumovirus, and RSV. This information has not yet been peer reviewed and published, but is important and has been shared at the request of the California Department of Public Health.]

References


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CASE REPORT

COVID-19 in a Patient Presenting with Syncope and a Normal Chest X-ray
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ABSTRACT
SARS-CoV-2 is a novel virus that has now affected hundreds of thousands of individuals across the world. Amidst this global pandemic, maintaining a high index of suspicion, rapid testing capacity, and infection control measures are required to curtail the virus’ rapid spread. While fever and respiratory symptoms have been commonly used to identify COVID-19 suspects, we present an elderly female who arrived to the hospital after a syncopal episode. She was afebrile with a normal chest X-ray and there was no suspicion of COVID-19. She then developed a fever and tested positive for COVID-19. Our unique case underscores the increasing diversity of COVID-19 presentations and potential for initial misdiagnosis and delay in implementing proper precautions.

KEYWORDS: SARS-CoV-2, COVID-19, chest radiograph, imaging, syncope, isolation precautions

CASE REPORT
A 79-year-old woman with a past medical history of coronary artery disease with multiple stents, hypertension, and congestive heart failure presented to the Emergency Department in mid-March after a syncopal episode at home. Three days prior to admission, she developed myalgias and cough followed by fevers up to 100.4 F. She called her primary care physician who was concerned for influenza and prescribed oseltamivir. Her symptoms persisted despite the medication. She was also on verapamil 60 mg a day and daily alprazolam. On the day of presentation, the patient felt lightheaded after having a bowel movement, and had a witnessed syncopal episode. EMS was called and she was transferred to a local hospital via ambulance.

Upon arrival, the patient stated that she had no report of chest pain or shortness of breath, and she denied palpitations. She had had no recent travel outside of the state or internationally. Her exam was significant for a temperature of 97.9 F, oxygen saturation of 97%, elevated blood pressure and pulse. Examination of the lungs was normal. Labs were remarkable for lymphopenia with an absolute lymphocyte count of 0.4 x10^9/L [BUN and Creatinine were normal (17/0.66). Chest radiograph showed clear lungs. She was transferred to the observation unit of the Emergency Department (ED) for a syncopal workup and cardiology consultation.

Several hours later, she became febrile to 101.8 F and complained of chills. The treatment team sent a respiratory pathogen panel [GenMark Dx® ePlex™], which resulted negative. Approximately 12 hours after arrival, the patient was placed on maximum isolation precautions (negative pressure room, with anyone entering the room required to wear an N95 respirator, face shield, disposable gown, and gloves) and tested for SARS-CoV-2 infection [GenMark Dx® ePlex™]. The test result returned positive. The patient was subsequently admitted for further management.

Evaluation for the etiology of her syncope revealed orthostatic hypotension with blood pressure of 116/62 mmHg when supine and 85/50 mmHg when standing. Electrocardiogram and telemetry monitoring did not reveal any structural cardiac defects or arrhythmias respectively. The following day, a CT chest showed bilateral peripheral ground-glass opacities. At discharge, she continued to have intermittent low-grade fevers of 100.4–100.8 F. Given significant improvement in symptoms and resolution of lightheadedness, she was discharged home. She subsequently worsened at home and was readmitted to another hospital with respiratory failure.

DISCUSSION
The novel coronavirus, SARS-CoV-2, was first described in Wuhan, Hubei Province, China in December 2019 and has since become a global pandemic with increasing spread throughout the United States. In a study of 1,099 patients in China with confirmed COVID-19, the most commonly reported symptom was fever (43.8% on initial admission, 88.7% during hospitalization), followed by cough (67.8%).1 Atypical chest and back pain has also been reported as presenting symptoms. Syncope was not reported as a symptom in this study cohort. To our knowledge, syncope has not been described as an associated symptom of COVID-19 infection in any of the literature to date. Other studies have described normal chest imaging at presentation in patients with COVID-19.1,2 Syncope may be a presenting symptom, particularly in the elderly with underlying cardiac disease.

This patient presented with lymphopenia, which has
been documented elsewhere in patients with COVID-19. In a study of 99 patients in Wuhan, China, 35% presented with decreased absolute lymphocyte count. Yang et al. looked specifically at critically ill patients with COVID-19 in Wuhan and found that 85% of patients in their sample (n=52) were lymphopenic, suggesting that lymphopenia may be associated with more severe disease.

We describe a 79-year-old patient presenting with syncope along with a normal chest radiograph. Additionally, our patient had no recent travel, which suggests that she became infected via community transmission. At the time of presentation, she was neither hypoxic nor febrile. Although this may be an atypical presentation, this patient ultimately tested positive for SARS-CoV-2. Maximum isolation precautions were not put in place until approximately 12 hours after the patient’s arrival in the Emergency Department. A normal chest radiograph and atypical signs of infection, such as syncope, should not rule out COVID-19. It is important to keep COVID-19 in mind so as not to delay timely initiation of isolation precautions.

References


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Metastatic Lung Cancer Masquerading as Endophthalmitis
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ABSTRACT
A 41-year-old man presented to the emergency department with a painful and red left eye associated with chronic vision loss. He had a history of homelessness and polysubstance abuse including intravenous drug use. Fundus examination revealed several cream-colored lesions encroaching on the macula of the right eye, and a total retinal detachment with secondary neovascular glaucoma in the left eye. Further work-up with imaging and endobronchial ultrasound-guided fine needle aspiration revealed stage IV epidermal growth factor receptor (EGFR) mutant (L858R) lung adenocarcinoma with brain, bone, adrenal, lymph node and bilateral choroidal metastases. Herein we present a case of metastatic lung cancer masquerading as endophthalmitis.

KEYWORDS: choroidal metastases, endophthalmitis, lung cancer

CASE PRESENTATION
A 41-year-old male presented to our emergency department with a blind, painful and red left eye. His symptoms began 1.5 months prior with painless gradual vision loss progressing to complete loss of vision. Thereafter he began experiencing left eye pain and self-treated with illicit drugs: heroin, cocaine, and marijuana. There was no history of trauma and past ocular history was unremarkable. He denied associated flashes, floaters, headaches, focal neurological deficits or contralateral visual field cut and had no pertinent past medical/surgical/family history. Social history was significant for polysubstance use disorder, including intravenous drug use (heroin: 3–4 bags daily, crack cocaine, marijuana), 0.50 pack cigarettes per day, incarceration, and homelessness.

The visual acuity in the right eye was 20/20, left eye was no light perception. The intraocular pressures were 14 mmHg OD and 26 mmHg OS. External examination of both eyes was normal. The anterior segment of the right eye was unremarkable. The left eye showed 3+ injection with trace corneal edema and peripheral neovascularization, 2+ cell, 4+ flare, circumferential neovascularization of the iris, and posterior synechiae. Fundus examination of the right eye demonstrated clear vitreous with a superonasal 5 disc diameter raised hypopigmented lesion and an inferotemporal 3 disc diameter cream-colored lesion encroaching the macula. [Figure 1] The left eye showed dense vitritis with a poor red reflex. B Scan ultrasonography revealed a total retinal detachment, vitreous opacities and a fungating mass. [Figure 2]
Patient was admitted for presumed endogenous endophthalmitis given history of intravenous drug use (IVDU). Vancomycin, cefepime and voriconazole were administered empirically while source and etiology were further investigated. Brimonidine was prescribed to the left eye to palliate pain. Transthoracic echocardiogram did not demonstrate endocarditis. CT chest/abdomen/pelvis was performed for source work-up. It showed a 2.7 x 3.9 cm cavitary right upper lobe lesion with scattered nodular opacities throughout right lung with lymphadenopathy measuring up to 4.3 cm; 2.5 x 1.6 cm heterogeneously enhancing right adrenal nodule; 2.0 x 1.3 cm intraosseous lesion in right lateral aspect of the T12 vertebral body. (Figure 3) An endobronchial ultrasound with fine-needle aspiration with cytological confirmed diagnosis of non-small cell lung cancer. Further testing confirmed stage IV EGFR mutant (L858R) lung adenocarcinoma with brain, bone, adrenal, lymph node and left choroid metastases. MRI showed greater than 15 enhancing brain lesions, 2.2 cm left calvarial osseous lesion, left intraocular lesion abutting posterior globe with hemorrhagic retinal detachment. (Figure 4) The patient was ultimately treated with whole brain external radiation and left orbit external radiation therapy, and osimertinib.

**DISCUSSION**

This case demonstrates how neoplastic disease can masquerade as ocular inflammation. Endogenous endophthalmitis is typically unilateral, and risk factors are malignancy, intravenous drug use, and invasive surgery. Given the patient’s history of IVDU, the initial presentation was concerning for bacterial or fungal infection. It was the presumed embolic source work-up that discovered the primary lung lesion. This drastically changed the patient’s course of care from considering which antibiotics or antifungals to use, to staging cancer.

Confounding factors were his social situation and lack of systemic symptoms. He presented solely with eye complaints. Choroidal tumor was on the differential although his eye was more infectious appearing. However, lung cancer was not considered. Given the multiple sites of metastases it is surprising his review of systems was completely unremarkable. Neovascularization is not characteristic of eye infection and alluded to some cause of ischemia which could not be explained by infectious process alone. CT scan demonstrating hemorrhagic retinal detachment may account for these findings.

Upon reviewing fundus images following the diagnosis, the lesions in the right eye are very characteristic of the yellow/cream-colored choroidal metastases. This, along with the CT findings and confirmation of lung cancer, and the propensity for ocular metastases made intravitreal biopsy or further invasive investigation unnecessary. Intraocular metastases are under-recognized clinical problem: 16% of individuals dying from cancer have metastases to the eye; it is 40% when evaluating lung cancer. The uvea is the most common ophthalmic site for dissemination of metastatic tumors from remote sites. Metastases to the eye is atypical and is an independent poor prognostic factor. Two-thirds of choroidal metastases stem from lung and breast malignancies.
cancers.\textsuperscript{5} Multiple studies have exhibited a poor life expectancy: Systemic treatment in conjunction with local treatment demonstrated 11-month survival, and 5-year survival rate is 23%\textsuperscript{,5,6} Treatment at this point is solely palliative.

Upon literature review, ocular metastases from lung cancer did not present as endophthalmitis. Patients with choroidal involvement are typically asymptomatic; however, other ocular components may present with pain and vision loss.\textsuperscript{,7,8}

CONCLUSION

Metastases to intraocular structures from a distant site are rare and often missed. This case demonstrates metastatic cancer masquerading as endophthalmitis, which is a unique presentation of metastatic disease. Employing a wide differential during initial evaluation is crucial to detecting an underlying malignancy.

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Ictal Catatonia in Autoimmune Encephalitis

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KEYWORDS: non-convulsive status epilepticus, bipolar disorder, anti-NMDA receptor encephalitis, catatonia, delirious mania

INTRODUCTION

Bipolar disorder (BD) type I is a chronic psychiatric illness characterized by episodes of mania and/or depressive symptoms. Its onset is classically diagnosed during early adulthood, but when a manic episode is observed in an older adult without a typical psychiatric history, it becomes particularly important to investigate for potential organic causes.1

Delirious mania (DM)2 manifests as an acute onset of manic signs and symptoms, accompanied by a waxing and waning pattern of consciousness, as seen in delirium. A subset of these patients may also develop catatonia.3 Non-convulsive status epilepticus (NCSE) is a heterogeneous disorder characterized by electrical seizures with minimal or no motor symptoms, and an altered mental status that may range from mild confusion to coma.4 NCSE is identified through electroencephalogram (EEG) findings and behavioral symptoms, as the motor signs are often subtle.5 Its clinical manifestations vary enormously and may include catatonia.7

We report a case of a patient with late-onset manic syndrome, followed by waxing and waning level of consciousness, and catatonic features. EEG findings were consistent with NCSE. The patient responded to immunotherapy, suggesting the probable diagnosis of autoimmune encephalitis (AE).

CASE REPORT

A 51-year-old Caucasian man, married, with no previous psychiatric illness, was transferred to Rhode Island Hospital (RIH) from another facility in early February 2017, due to a four-week history of psychomotor agitation and aggressive behavior. Medical history was significant for inflammatory bowel disease (IBD). His medications included acetylsalicylic acid and over-the-counter supplements. Patient was a former tobacco smoker (quit at age 26), with occasional marijuana use and moderate daily alcohol intake. He had lost three jobs over the past four years and had been living with his wife and two daughters. From his psychiatric history, admission interview and from collateral information received from wife, patient did not have bipolar illness and his interpersonal problems were deemed to be from personality traits rather than to longstanding mental illness. Psychiatric history was significant for physical abuse from father during childhood.

In the ED, initial head computerized tomography (CT) demonstrated a small left parafalcine and bifrontal subdural hematoma (SDH), secondary to a traumatic brain injury that the patient had endured three months prior to his presentation to the hospital, given this context, he was started on oral levetiracetam 500mg twice a day for seizure prophylaxis, per ED/neurosurgical protocol even though there is no formal indication for such neurologically.

He later mounted a fever of 100.7°F and was admitted to inpatient medicine for further evaluation of his fever and bizarre behavior. Initial infection workup, including Human Immunodeficiency Virus, Syphilis, Anaplasmosis and Lyme disease serologies were found negative. Given his acute encephalopathy, an EEG was done, which revealed occasional intrusions of slowing in the mid-temporal region, but no epileptiform activity was noted. CSF analysis revealed a glucose level of 60; protein, 49; and only 1 nucleated cell. The fever resolved did not recur; his other vital signs remained normal. Further workup demonstrated a serum ammonia level of 84 mcg/dL, which then normalized on subsequent follow up (to 59 mcg/dL). Serum copper, zinc, urine porphyrins, serum thyroid, anti-TPO antibodies and liver function tests were also within normal limits. Serum sodium at that time was 129 mEq/L and urine osmolality >700 mOsm/kg, suggesting syndrome of inappropriate antidiuretic hormone secretion (SIADH) (the CT chest, abdomen, pelvis was only significant for large bowel obstruction, which was managed conservatively in parallel, no neoplasm identified to suggest a paraneoplastic source). Urinalysis was unremarkable and urine toxicology was positive for tetrahydrocannabinol only. Thiamine treatment was given in the setting of chronic alcohol use. Brain magnetic resonance imaging (MRI) was consistent with left juxtafalcine and small bifrontal SDH.

Given increased psychomotor agitation (yelling obscenities, impulsive behavior and pacing), paranoia and resolution of fever, the patient was transferred to inpatient psychiatry at day five of hospital admission.

Upon admission to the inpatient psychiatric unit, the
patient was found alert, oriented and cooperative, maintaining good eye contact. He would occasionally present with an intense stare, pressured speech and constricted affect, alongside loose associations and racing thoughts. Insight and judgment were initially fair, then rated poor. He seemed overtly paranoid about his daughter as well as the nursing staff, but denied any hallucinations. No suicidal and homicidal thoughts or ideations were endorsed, either. Physical exam, including neurological and mini mental state examination (MMSE), were unremarkable. Clock-drawing test was significant for impaired executive function, perseveration, misplacements and over-inclusiveness (See Figure 1).

The initial psychiatric diagnosis was thought to be bipolar I disorder with acute manic episode and psychosis; he was started on olanzapine, which was titrated to 15mg daily. Due to minimal clinical improvement two days later, it was decided to switch olanzapine to oral risperidone 2mg twice a day. On the following days, daily oral lorazepam 1mg and valproate 1000mg were also prescribed; valproate was eventually switched to lithium due to worsening hyponatremia.

At day twelve of hospital admission, when shaving under supervision, the patient was found staring blankly. This episode was followed by a period of unresponsiveness, and subsequent similar staring spells. At day fourteen, he presented with prominent waxing and waning levels of consciousness, but no tonic-clonic movements were observed. Lithium toxicity was ruled out (serum level: 0.53 mmol/L). The case no more seemed to fit the provisional diagnosis of BD with psychosis; could DM or NCSE better explain it?

A prolonged EEG (off levetiracetam) was ordered, which showed generalized, monomorphic theta activity. The patient’s behavior and altered mental status temporarily improved after receiving lorazepam; the pattern of EEG also normalized, which, along with his initial clinical improvement, prompted a diagnosis of NCSE. The patient was transferred to neurology inpatient unit on the same day for further investigation.

A subsequent EEG revealed recurrent lengthy intrusions of generalized rhythmic activity, indicating subclinical seizures and a form of NCSE. His anti-epileptic drugs (AED) included daily oral levetiracetam 3g, lacosamide 400mg and valproate 1.5g. The patient no longer exhibited manic behavior, but he was continued on the same dose of lorazepam and risperidone. At day sixteen, the EEG demonstrated a buildup of rhythmic sharp activity over the left anterior quadrant, with concomitant video recording showing the patient with closed eyes, grimacing mildly and fidgeting with his hands. These seemed to cluster overnight and arise out of sleep. Two days later, another EEG revealed epileptiform discharge, which could have been either generalized in nature, or a rapidly spreading focal onset. Levetiracetam was then increased to 4g daily.

At day twenty-one, a new EEG revealed abundant runs of waxing and waning theta activity, which was relatively higher in amplitude and paroxysmal in nature, compared to his baseline. Topiramate 400mg was added to his AED and lacosamide was increased to daily 500mg. An additional CSF sample was collected, the results of which were unremarkable. A new head CT was significant for interval resolution of left parafalcine subdural hematoma.

A subsequent EEG, performed at day twenty-four of admission, did not show epileptiform transients; however, a greater degree of encephalopathy was noted this time. Phenytoin was added to his AED regimen.

On the following day, at day twenty-five, he presented with multiple episodes of unresponsiveness, dysarthria and significant palilalia. Interestingly, a tonic-clonic seizure was also recorded on the video EEG. The subsequent tracing showed significant rhythmic activity, particularly in the frontal regions, clinically evidenced as facial grimacing, with multiple instances of scratching his head and arms. Based on his prior manic episode with psychosis, which did not respond to psychiatric medication; abnormal motor activity, despite optimized antiepileptic treatment; and EEG findings compatible with encephalopathy, the presumptive diagnosis of autoimmune encephalitis came into consideration. With this in mind, the patient was empirically started on intravenous methylprednisolone 1g for five days and immunoglobulin, 5 doses. Notably, during this time, his brain MRI continued to demonstrate no abnormal findings, besides the SDH.

Whilst on the steroid and IVIG course, a repeat EEG was done. This EEG, from day twenty-eight, was described as numerous electrographic seizures arising from the bifrontal regions, occurring one to three times per hour on average, and lasting ten to thirty seconds at a time. Overall, these runs were relatively shorter and less “epileptogenic” in

Figure 1. Patient’s clock-drawing test (he was asked to draw “10 past 11”)
appearance than the previous ones, validating immunologic involvement in the disease course.

On the last day of immunotherapy, the EEG was noted to display less frequent runs. The results of patient’s CSF sample remained negative for inflammatory markers [anti-NR1, anti–LGI-1, anti-CASPR2, anti-Hu, NR1, GAD65, VGKC, Ma1 and Ma2, CV2 and amphiphysin]. A serum panel was also sent but found inconclusive.

Ultimately, at day thirty-three of admission, the EEG showed findings indicative of mild diffuse encephalopathy, with suggested bifrontal epileptogenic regions, favoring left-sided predominance. However, no definite seizure activity was reported this time.

Upon hospital discharge, at day thirty-five of admission, the patient was found awake, alert, oriented to time, place, person and situation, following commands with no observed palilalia or dysarthria. He was overall pronounced stable from neurology and psychiatry standpoints. Patient’s discharge medications included clonazepam, lacosamide, levetiracetam, phenytoin, topiramate, tamsulosin, thiamine, aspirin and sodium chloride tablets. One month after discharge, he was contacted by our team over the phone and reported feeling well, with return to his normal level of functioning. His wife was also able to confirm that patient was back to baseline.

**DISCUSSION**

Our case is worth sharing as it presents a diagnostic challenge due to considerable overlap in neuropsychiatric conditions and multiple confounding factors particular to our patient’s presentation.

The diagnosis of bipolar disorder was proposed based on patient’s initial presentation, given his manic episode with psychotic features. However, shortly thereafter, his level of consciousness started to fluctuate, raising the concern for delirious mania (delirious mania was considered the cause for his delirium as there was no acute precipitating physical illness recognizable at the time). As DM may be a life-threatening condition, early and assertive treatment is mandatory and predictive of better prognosis.5 The team decided to initiate treatment of DM with a mood stabilizer and benzodiazepine.

Because of DM a prolonged EEG was performed, which revealed generalized, and monomorphic, theta activity. Following the empiric use of intravenous lorazepam, alongside a loading dose of levetiracetam, it was found that the patient’s brain electrical activity had normalized, in addition to improving his behavioral and mental status. In view of this optimal clinical response, the main diagnostic hypothesis then became DM with non-convulsive status epilepticus.

As previously mentioned, post-ictal catatonia is related to NCSE and has variable presentation, such as alteration of consciousness and behavior, rigidity, mutism, catatonic posturing and autonomic signs, even when there are no obvious convulsive seizures or a history of epilepsy.6 Our patient’s patterns of EEG, his behavioral and mental status changes, including staring spells and unresponsiveness, as well as clinical and electroencephalographic improvement upon intravenous administration of lorazepam, all together supported this diagnosis.7

However, despite his initial clinical stabilization and EEG normalization, subsequent EEG tracings revealed an increasing degree of encephalopathy. This was followed by worsening of the clinical presentation, even when the patient was on an optimized treatment with AED, justifying a therapeutic test with immunotherapy. The test was successful. This corroborated the basis of an underlying organic immunological mechanism.

It is interesting to note that seizure activities in catatonia are reported to be about 16%, and an organic etiology is usually more common than psychiatric when the combination occurs.9 Therefore, from a teaching perspective, organic entities such as autoimmune encephalitis in catatonic states should be considered. As seizures and catatonia both respond to ECT and anticonvulsants, it is hypothesized that they may share a common pathogenesis; in fact, it is even suggested that catatonia may be the final common outcome pathway for abnormal brain seizure activity.10

His initial febrile presentation, in addition to agitation, bizarre and impulsive behavior, delusions, racing thoughts, oscillating level of consciousness and seizures [as observed in our patient], correspond to the clinical presentation of anti-NMDA receptor encephalitis, corroborating our hypothesis.7-9 An autoimmune process was postulated in the light of patient’s clinical evolution, behavioral abnormalities and cognitive impairment, besides his abnormal electroencephalographic findings and response to immunotherapy. His autoimmune workup [both serum and CSF] remains negative to date, and although the identification of anti-NMDA receptor antibodies is required to confirm the diagnosis, false negative results can also be observed.10 Interestingly, antibodies are not detected in almost half of all autoimmune encephalitis cases.9

Finally, it remains unclear if the patient’s underlying systemic inflammation, from IBD, and his concurrent SDH, could have played a role in his clinical presentation.

Our case illustrates challenges faced by clinicians seeking multidisciplinary approach to neuropsychiatric conditions and serves as a call to action for researchers and clinicians, helping them tailor their approach for patients who initially present with behavioral changes followed by [ictal] catatonia.
Acknowledgment

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References

3. Lee BS, Huang SS, Hsu WY, Chiu NY. Clinical features of delirious mania: a series of five cases and a brief literature review. BMC psychiatry. 2012;12[1], 65

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Double Crossed: A Case of La Crosse Encephalitis

Ann Ding, MD; Burton Shen, MD; Sarah Elliott, MD; Khushbu Joshi, MD; Daniel Coghlin, MD; Suzanne McLaughlin, MD

ABSTRACT

CASE REPORT: A 10-year-old male with T1DM and recent travel to North Carolina presented to an ED with 1 day of fever, vomiting, and headaches. He was discharged home with the presumptive diagnosis of viral gastroenteritis but returned nine hours later, agitated, and unable to speak.

CSF showed pleocytosis. MRI brain was normal, and EEG showed intermittent seizures. He was started on antiepileptics. Antibiotics were discontinued after negative bacterial work-up. Repeat MRI brain one week later showed enhancement in the left cerebral cortex. IVIG was started due to concern for autoimmune encephalitis. Repeat lumbar puncture was positive for La Crosse virus IgM.

DISCUSSION: This is the first case of La Crosse encephalitis (LACE) reported in Rhode Island. La Crosse virus (LACv) is a ssRNA Bunyavirus transmitted by the eastern tree-hole mosquito typically between July and September. LACv is endemic to the upper Midwestern US and Appalachia. In 2018, 81 of 86 total cases reported by the CDC were pediatric. Children are more likely to present with vomiting, seizures, and focal cortical inflammation or cerebral edema on brain imaging. IgM may be negative early in the disease course. Treatment is antiepileptics and supportive care.

KEYWORDS: Arboviral encephalitis, La Crosse encephalitis, La Crosse virus, Meningoencephalitis

CASE REPORT

Case Presentation

A 10-year-old male with T1DM (diagnosed at 3 years old) presented with 1 day of fever, vomiting, and headaches in August. Vital signs were T99.4, BP 122/68, HR 110, RR 24, and SpO2 100%. Physical exam was significant for normal neurological exam, including complete orientation to person, place, and time; his abdominal exam was notable for mild tenderness to the periumbilical area. Lab work showed Na 134, glucose 113, pH 7.4, UA with 2+ ketones, and beta-hydroxybutyrate of 0.97. The patient was thought to have mild ketosis from viral gastroenteritis and was discharged home, but returned nine hours later with altered mental status, including agitation, screaming, and aphasia. Vital signs at this time were T99.4, BP 110/64, HR 98, RR20, and SpO2 100%. A travel history revealed that the patient recently returned from a trip to a family home in North Carolina, where he was noted to have gone swimming in Lake Lure. He also received numerous mosquito bites, of which he had frequently sent pictures to his mother. The patient’s mother reported that a neighbor living on the same street in North Carolina recently presented to a local hospital with similar altered mental status and was diagnosed with La Crosse encephalitis (LACE).

Initial Workup and Hospital Course

In the ED, the patient was given IV fluids for dehydration, as well as IV morphine for his headache with only minimal improvement. A CT brain without contrast was normal. Blood cultures were drawn. A lumbar puncture (LP) was completed under sedation with ketamine. Ceftriaxone, Vancomycin, and Acyclovir were initiated in the ED to provide broad coverage for meningoencephalitides. Initial LP studies were significant for pleocytosis (Table 1) and a negative gram stain. The patient was suspected to have viral encephalitis and was admitted to the pediatric hospitalist service. Several hours after admission, the decision was made to transfer the patient to the PICU for closer monitoring of his neurological status. On admission, the patient was continued on Ceftriaxone and Vancomycin, but these were discontinued when CSF cultures returned negative at 48 hours. Acyclovir was discontinued on admission due to low clinical suspicion of HSV encephalitis. Doxycycline was added to cover for Rocky Mountain Spotted Fever and then discontinued when a Rickettsial panel returned negative several days later.

Table 1. Initial CSF Studies

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Reference Value</th>
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<tbody>
<tr>
<td>Glucose</td>
<td>165</td>
<td>38–85</td>
</tr>
<tr>
<td>Protein</td>
<td>55</td>
<td>15–45</td>
</tr>
<tr>
<td>RBC</td>
<td>2346</td>
<td>0–5</td>
</tr>
<tr>
<td>Nucleated Cells</td>
<td>224</td>
<td>0–7</td>
</tr>
<tr>
<td>Polys</td>
<td>60%</td>
<td>0–2%</td>
</tr>
<tr>
<td>Lymphs</td>
<td>30%</td>
<td>63–99%</td>
</tr>
<tr>
<td>Monocytes</td>
<td>10%</td>
<td>3–37%</td>
</tr>
</tbody>
</table>
later. While in the PICU, the patient underwent MRI of the brain and spine, as well as an MRV of the brain, all of which were normal. EEG demonstrated bilateral hemispheric slowing, left greater than right, but no epileptiform activity. Ophthalmology was consulted for eye pain and photophobia, which was concerning due to the association of West Nile Virus with various ophthalmological complications, including anterior uveitis, retinal vasculitis, and optic neuritis. Slit lamp and dilated eye exam showed superficial punctate keratitis but was otherwise normal. He was started on erythromycin ointment and artificial tears for ophthalmological management.

After two days in the PICU, the patient was transferred back to the pediatric hospitalist service due to stable though unchanged mental status. TPN was initiated for nutrition. The initial LP viral workup returned negative for Enterovirus, HSV, West Nile, and Arbovirus panel (which included testing for La Crosse, Western Equine Encephalitis, St. Louis Encephalitis, and Eastern Equine Encephalitis viruses). The patient then developed new-onset episodic right-sided gaze preference and right-beating nystagmus. Repeat EEG showed intermittent epileptiform discharges in the left temporal region associated with a clinical seizure. He was started on antiepileptics fosphenytoin and oxcarbazepine, but his encephalopathy persisted. The patient was transitioned from TPN to nasogastric tube feeds.

Diagnosis and Management
Autoimmune versus viral encephalitis remained the working diagnosis. Anti-NMDA Ab returned negative, making autoimmune encephalitis less likely. Given his recent travel from North Carolina and known exposure to a sick contact with LACe, the CDC was consulted and favored a viral etiology with supportive management. Repeat CSF studies and brain MRI were performed one week after initial presentation due to persistent altered mental status, recent development of seizures, and the need to send additional CSF studies. CSF studies this time included a repeat Arbovirus panel, Powassan virus testing, and antibodies to GAD65, TPO, and thyroglobulin (to assess for other causes of autoimmune encephalitides, such as Hashimoto’s encephalopathy). Rectal Enterovirus cultures were also sent to the CDC to check for Enterovirus D68 [the cause of acute flaccid paralysis syndrome]. The repeat MRI brain showed interval new enhancement and swelling of the left cerebral cortex, with particular enhancement noted in the left pulvinar nucleus [Images 1 through 4].

Antibodies to GAD65, TPO, and thyroglobulin in the CSF returned elevated, but the significance of the anti-thyroid antibodies was unclear since approximately 25% of patients with T1DM have these antibodies at time of DM diagnosis. His thyroid function was normal, but this did not exclude Hashimoto encephalopathy. The working differential remained autoimmune versus viral encephalitis. While the efficacy of IVIG is uncertain in the management of viral encephalitides, IVIG was given in case of an autoimmune
etiology. After administration of IVIG, the patient was noted to become gradually more responsive and interactive, responding to questions appropriately with simple words. He was transitioned from nasogastric feeds to an oral diet. Due to significant but slowly improving neurodevelopmental deficits, the patient was discharged to a neurorehabilitation facility on antiepileptics. Several days after discharge, the CSF IgM for La Crosse virus (LACv) returned positive, clinching the diagnosis of LACe. Six months after initial presentation, the patient had residual but improved neurodevelopmental deficits, with signs of residual left hemispheric encephalopathy on EEG.

**DISCUSSION**

The LACv is a ssRNA virus in the genus Bunyavirus that is transmitted most commonly by the eastern tree-hole mosquito, *Aedes triseriatus*. Endemic geographic areas historically included the mid-western US, but recently shifted toward the Appalachian region. Onset of illness typically occurs July through September.5,6 In 2018, the CDC reported 86 cases of LACe, 81 of which were pediatric.1 LACv is the leading cause of pediatric arboviral encephalitis in the US with an average of ~70 neuroinvasive cases per year.7 The majority of severe clinical cases (>90%) are in children under age 16.8 Studies of the mechanism of age-dependent susceptibility to neuroinvasive disease from LACv in mice have shown that the host interferon response and adaptive immunity response have important roles, both of which are underdeveloped in children.7 However, LACv should also be considered in adult patients with altered mental status. Clinical disease onset ranges from 5 to 15 days post exposure.8 Common presenting symptoms shared in both pediatric and adult patients include headache, fever, and hyponatremia. Children are more likely to present with vomiting, seizures, and focal cortical inflammation or cerebral edema on brain imaging [as with the patient in this case], while adults rarely present with these findings.9,10

Workup includes CSF viral culture, as well as La Crosse IgM in serum or CSF.11 IgM may be negative if the patient presents early in disease course (as this patient was), and it is important to repeat studies if clinical suspicion is high.9 The patient in this case had exposure to multiple mosquito bites in the geographic region endemic to LACv and had a sick contact with LACe, which increased clinical suspicion for the diagnosis and prompted the decision to repeat CSF studies. A recent review of 44 articles reporting on risk factors for LACv cited factors that increase exposure to mosquitoes, such as rural or wooded areas, time outside, not wearing repellent, and higher numbers of tires or artificial containers near the residence; the review did not note any risk factors of co-morbidities such as T1DM.8 The mainstay of LACe management is antiepileptics and supportive care [including speech/physical therapy]. Less well-studied interventions include ribavirin and IVIG, which have been hypothesized as treatments for LACe and other viral encephalitides.12 Case fatality rates ranging from 1.5 to 3.1%, and up to 8.6% in patients suffering from encephalitis, have been reported.13,14

**CONCLUSIONS**

In areas non-endemic to arbovirus encephalitides, it is important to obtain a thorough travel history in patients with altered mental status. This case was the first ever reported case of LACe in the state of Rhode Island.1 LaCee more commonly presents in children than adults but should be considered in both populations, especially during July through September. Children are more likely than adults to present with vomiting, seizures, and cerebral edema and inflammation on brain imaging. La Crosse IgM may be negative early in disease course. Consult the CDC and repeat studies if clinical suspicion is high.11

**References**

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Disclaimer
The views expressed herein are those of the authors and do not necessarily reflect the views of Brown University, Hasbro Children’s Hospital, and Rhode Island Hospital.

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Outpatient Total Joint Arthroplasty: A Review of the Current Stance and Future Direction

MICHAEL MARIORENZI, MS, MD; JAMES LEVINS, MD; STEPHEN MARCACCIO, MD; ALEXANDER ORFANOS, MD; ERIC COHEN, MD

ABSTRACT

INTRODUCTION: The purpose of this review is to outline some of the major considerations when transitioning to performing total hip and knee arthroplasty in the outpatient setting. The review will discuss patient selections, peri-operative management pathways, and outcomes related to outpatient total joint arthroplasty (TJA).

PATIENT SELECTION: Appropriate patient selection is key to successful outpatient TJA. Multiple indices have been proposed to estimate patient risk before undergoing outpatient TJA.

PERIOPERATIVE MANAGEMENT: In order to provide a successful outpatient TJA experience, pre-operative education class and physical therapy session can set expectations and prepare the patient for the post-operative recovery at home. Specific anesthesia techniques focus on regional blocks, multi-modal pain control, and reduction of post-operative nausea and vomiting and rapid recovery protocols have been developed to provide early mobilization and physical therapy.

OUTCOMES: Nationwide analyses have found improved complication rates ranging from 1.3%–3% in outpatient TJA group compared to 3%–12% in the inpatient TJA group. Financial analyses have found significant cost savings for outpatient TJA mostly related to reduction in surgical floor care.

CONCLUSION: Outpatient TJA has the potential to improve patient experience with cost savings and no increased risk of complications in the appropriately selected patient population.

KEYWORDS: outpatient joint replacement, arthroplasty, outcomes, patient selection

INTRODUCTION

Over the last decade, considerable focus has been placed on the safety and feasibility of performing outpatient total joint arthroplasty (TJA). Momentum for this shift has been fueled largely by advancements in arthroplasty-related care and concerns over the current economic crisis in healthcare. In a 2015 report, the Center for Medicare and Medicaid Services pointed to joint replacement surgery as the single most expensive procedure covered by Medicare, costing over $6.5 billion for Medicare beneficiaries in 2013. Furthermore, the demand for TJA is projected to continue to rise at an astounding rate due to a combination of an aging population, the growing obesity epidemic, and an increased public awareness of the successful outcomes following joint replacement surgery. It has been estimated that by 2030, total hip arthroplasty will increase by 174% to over 500,000 cases and total knee arthroplasty will increase by 673% to 3.48 million cases annually. The majority of elective total joint replacements are still being performed in the inpatient setting. In retrospective analyses evaluating primary TJA, the national trends show only 0.7–1% were performed on an outpatient basis and only 6.2–16.5% of cases were discharged from the hospital within 24 hours. However, with the growing interest in outpatient TJA in recent years, there has been an increase at certain institutions across the United States. Some projections estimate that 50% of TJA will be performed in the outpatient setting by 2026.

Historically, it was not uncommon for patients to remain in the hospital for weeks following a joint replacement surgery. Improvements in surgical techniques, peri-operative anesthesia and pain management protocols, as well as the implementation of rapid recovery programs, have led to significant reduction in the average hospital length of stay (LOS) following joint replacement surgery. Previous literature has demonstrated a strong correlation between hospital length of stay and the total cost of joint arthroplasty, making duration of hospitalization a priority item for cost control.

With the increasing prevalence of outpatient TJA, multiple studies have been performed to evaluate these procedures in regards to safety, hospital costs, complications, and patient selection. The purpose of this review is to outline some of the major considerations when deliberating the transition to performing total hip and knee arthroplasty in the outpatient setting. The review will discuss patient selections, peri-operative management pathways, and outcomes related to outpatient TJA.

PATIENT SELECTION

Though no consensus statement exists regarding a standardized protocol for patient selection, appropriate patient
selection is a critical element of ensuring a safe and successful outpatient TJA experience. Multiple studies have evaluated patients undergoing elective TJA in an effort to identify characteristics that make patients optimal candidates for outpatient TJA. They have found that patients discharged within 24 hours of TJA were more likely to be younger (<50 years), male, ASA class 1 or 2, and less likely to be morbidly obese (BMI <40) or taking steroids for a chronic condition [p < 0.05 for all comparisons].

Alternatively, rather than evaluating which patients have successfully undergone outpatient TJA, other studies have evaluated which patients are at highest risk for complications and readmission. Notable risk factors include chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), hypertension, obesity, hypoalbuminemia, cirrhosis, chronic kidney disease and age greater than 65. Indices have been proposed to estimate patient risk such as Charlson Comorbidity Index (CCI) or the American Society of Anesthesiologists Score (ASA). Higher overall disease burden as graded by these scoring systems has been shown to be directly associated with increased complications after TJA. These scoring systems are not specific to TJA patient populations and have not been found to be highly sensitive or specific. Therefore, a unique scoring system was developed to account for relevant medical comorbidities as they related to TJA. The Outpatient Arthroplasty Risk Assessment (OARA) score consists of nine distinct medical categories that are summed and stratified in a binary fashion to predict safe vs. unsafe early discharge. In the original study, the OARA score had a higher positive predictive value than the ASA and CCI for predicting early and safe discharge home. In a recent update, the upper limit of the “safe discharge” score was increased, with a maintained near 100% positive predictive value for safe discharge home after TJA.

Non-medical factors that are likely associated with improved rates of safe discharge after outpatient TJA include strong social support, home living situation such as bed and shower on a single floor, preoperative mobility status and the patient’s motivation for same day discharge. These factors are more difficult to study, due to lack of reporting in national databases such as the National Inpatient Sample [NIS] or National Surgical Improvement Protocol [NSQIP]. The Risk Assessment and Prediction Tool (RAPT) attempts to account for some of these factors including walking distance, use of a walking aid and presence of a caregiver at home. It has been shown to predict discharge to home in low-risk patients; however, it has not been evaluated for outpatient total joint arthroplasty.

As the demand for outpatient total joint arthroplasty increases, further research is needed to identify the ideal prediction tool that will incorporate medical co-morbidities, patient-specific factors, and social influences to best identify which patients can undergo safe outpatient TJA.

PERIOPERATIVE CARE

Numerous studies have focused on improving the perioperative management of total joint replacement to facilitate enhanced recovery time, early mobilization, and reduced risk of re-admission following discharge. The phases of management can be broken down into preoperative management and education, intraoperative anesthesia protocols, surgical technique, and postoperative management. The combined consensus statement of the American Academy of Orthopaedic Surgeons (AAOS), the Hip Society, the Knee Society and the American Association of Hip and Knee Surgeons (AAHKS) emphasized a team approach ensuring the surgeon, anesthesiologists, and recovery unit staff work towards the same goal of safe discharge.

1. Preoperative management and education

Once a patient is deemed medically appropriate for outpatient arthroplasty, the most important step is patient education. A preoperative education class can establish patient expectations for the day of surgery and immediately postoperatively, ensuring that the patient’s safety will be maintained, allowing for questions to be answered and decrease anxiety related to the process. Face-to-face education programs have been shown to decrease length of stay by a full day, and have also decreased patient anxiety and pain.

The addition of a preoperative physical therapy session can help the transition back to home by giving instruction for performing basic mobility tasks after TJA. In a recent review of implementing outpatient TJA, all authors reported the use of a preoperative educational class and the majority reported requiring patients to attend a physical therapy session prior to surgery.

2. Intraoperative Factors

Spinal anesthesia and regional blocks

Over the past few decades, advances in anesthesiology have allowed a transition of many surgical procedures to an outpatient setting including general surgery procedures such as cholecystectomy as well as orthopedic surgeries such as ACL reconstruction. These improvements in anesthesia care range from the type of anesthetics used, adjunctive analgesia optimization, and medication advances. The most common reasons for delayed discharge after TJA were pain, postoperative nausea and vomiting (PONV) and hypotension. Therefore, many of the anesthesia interventions taken in the perioperative period are focused on minimizing these complications. The majority of outpatient TJA cases utilize neuraxial anesthesia and regional blocks to limit PONV and improve pain control. In the immediate postoperative period, spinal anesthesia had significantly decreased rates of nausea compared to general anesthesia, and was also associated with shorter length of stay in TKA. Furthermore, spinal anesthesia has been shown to decrease rates of operative time, blood loss and DVT/PE compared to general anesthesia.
Multimodal pain control

Multimodal pain control is a method of decreasing surgical pain at numerous points along the pain pathway from the site of injury to the brain. This improves the patient's overall pain control and allows for improved mobility postoperatively. Multimodal pain control utilizes a wide range of pre-operative medications including non-steroidal anti-inflammatory drugs (NSAID), narcotics, gabapentinoids, dexamethasone and acetaminophen. In addition, spinal anesthesia and regional blocks are key components to multi-modal pain control.

Surgical factors

Minimally invasive surgery (MIS) techniques have evolved to limit blood loss, decrease soft tissue disruption, improve cosmetic appearance, and assist in faster patient recovery. These techniques are defined as using an incision 10–12cm or less for hips, and typically require specialized instrumentation for retraction and exposure. With the progression toward outpatient TJA, MIS techniques have been advocated. Some of the advantages that have been reported include decreased pain, decreased length of stay and improved early range of motion after MIS THA. However, the overall results of MIS have been mixed. Several groups reported minimal difference between standard and MIS techniques in terms of recovery time, gait analysis and outcomes. In order for MIS techniques to improve the transition to outpatient TJA, the surgeon must be skilled and experienced with MIS techniques.

3. Postoperative mobilization and rapid recovery protocols

A key component of postoperative care in outpatient TJA is early ambulation. In a review of outpatient protocols, all reporting authors utilized postoperative physical therapy in the recovery unit. Tasks included sit to stand, ambulating up to 100 feet, transferring to bathroom and navigating a flight of stairs. An added benefit to early mobilization is a decrease in thromboembolic events. Coupled with pre-operative education, this approach is crucial to a successful outpatient practice.

Creating a safety net for patients that are discharged home is also important. Many centers choose to implement standardized home physical therapy and home nursing, in addition to follow-up phone calls or mobile phone total joint applications with the ability of the patient to discuss issues directly with their care team following discharge. Increased availability of administrative staff may be required to field phone calls or issues that may arise at home.

OUTCOMES AND COMPLICATIONS

As the prevalence of outpatient TJA has increased, more studies have been performed to evaluate complications rates, rates of readmission, rates of reoperation, patient satisfaction, and health system costs in comparison to inpatient TJA. One retrospective analysis of the NSQIP database found that bleeding requiring transfusion was the most common complication in both outpatient and inpatient TJA, with a lower rate in the outpatient TJA group (6% vs 12%, p<0.001). Further, the study found no difference in rate of wound complication or infection, venous thromboembolic event, cardiac arrest, or reintubation between the two groups. Complication rates have been found to be similar or improved in the outpatient TJA population. An analysis of the NSQIP database found the rate of serious adverse events was 1.3% in the outpatient TJA group, compared to 1.9% for the inpatient group. In a separate analysis of the Medicare population, the outpatient TJA group had a lower 30-day complication rate (3% vs 12%, p < 0.001) and readmission rate (3% vs 4%, p < 0.001) when compared to the inpatient TJA group.

A systematic review performed by Hoffman et al. reviewed all of the available literature on outpatient total joint arthroplasty. Over 1,000 patients were included in the analysis and they found that 94.5% of patients were able to be discharged the same day as planned. There were zero deaths in the entire cohort. Re-operation rates were 1.98% and readmission to the hospital was 0.89%. Based on all of the available literature at the time of systematic review, they concluded that outpatient total joint arthroplasty is safe for carefully selected patient populations.

One critique of the available literature is that outpatient TJA is currently being performed on younger, healthier patients. It is not surprising that outpatient TJA patients have lower complication and readmission rates at this time. One single-surgeon analysis found similar rates of major and minor complications as well re-operation rates between inpatient and outpatient cohorts that were matched for age, gender, ASA score, and BMI. While this single-surgeon analysis is encouraging, additional research will need to be performed to extrapolate this data.

One notable adverse event identified is an increased incidence of post-discharge blood transfusion when compared to the inpatient group (p < 0.001). As discussed previously, outpatient TJA patients had lower rates of bleeding that required transfusion in the immediate peri-operative period. This higher rate of post-discharge blood transfusion is not unexpected and patients should be counseled on this risk.

In addition to providing a safe surgical process, maintaining or improving levels of patient satisfaction is important in establishing a successful outpatient TJA program. Dorr et al. evaluated patient satisfaction in their outpatient TJA group and found that 96% of patients in the group were satisfied with the decision to undergo outpatient surgery and would do so again. In addition, patients were asked to keep independent diaries of daily living. At three weeks post-operatively, 82% of patients had returned to independent activities of daily living, 84% were driving, and
98% of patients were walking 1 mile. In addition, 87% of patients in this study reported that same day discharge gave them confidence.49

As the estimated number of TJAs is expected to increase over the coming years, outpatient TJAs has the potential to make a substantial impact on cost savings for the healthcare system. Several studies have evaluated the cost-effectiveness of the recently developed outpatient TJAs protocols. Cost-savings have been identified for both THA and TKA. One institution found that the average medical bill was approximately $4,000 less for outpatients undergoing THA.30 In a different evaluation of the Medicare population, they found a mean savings of $8,527 for the outpatient TKA when compared to inpatient TKA, which is substantial given that Medicare pays for an estimated 55% of TKAs in the country.1

The majority of savings is projected to come from surgical floor savings of $4,000 less for outpatients undergoing THA.50 In a different institution found that the average medical bill was approximately $8,527 for the outpatient TKA when compared to inpatient TKA, which is substantial given that Medicare pays for an estimated 55% of TKAs in the country.1 The savings of $8,527 for the outpatient TKA when compared to inpatient TKA, which is substantial given that Medicare pays for an estimated 55% of TKAs in the country. The majority of savings is projected to come from surgical floor care, with small additional savings in pharmacy costs and physiotherapy.48 When performed in the carefully selected and appropriately prepared patient, outpatient TJA can substantially reduce health care costs and hospital burdens.

CONCLUSION

Outpatient TJA has the potential to improve patient outcomes, improve patient satisfaction, and reduce health care costs nationwide. Until now, outpatient TJA has been performed in select patient populations. Further research on complications, readmission rates, and patient satisfaction will be paramount as outpatient TJA increases to ensure patient safety and positive outcomes. Initial results are promising, delivering a safe and effective outpatient TJA experience while reducing healthcare costs.

References


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INTRODUCTION

Eastern Equine Encephalitis (EEE) is a rare but serious mosquito-borne viral disease that presents as a meningo-encephalitis in humans, four to ten days after a mosquito bite. Symptoms include sudden onset of fever, headache, vomiting, diarrhea, seizures, behavioral changes, drowsiness, and coma. The mortality rate of EEE is 33%. Among those who survive, many have significant brain damage, which can include intellectual impairment, personality disorders, seizures, paralysis, and cranial nerve dysfunction.1

The Eastern Equine Encephalitis virus is an alphavirus that is maintained in a cycle between Culiseta melanura mosquitoes and avian hosts in freshwater hardwood swamps. Cs. melanura feeds almost exclusively on birds and transmission to humans and other mammals requires a mosquito that is capable of serving as a ‘bridge’ between infected birds and uninfected mammals. Aedes vexans, Ae. sollicitans and Coquillettidia perturbans are common bridge vectors in Rhode Island.

Between 2008 and 2018, there was an average of seven cases of EEE nationwide each year. In 2019, however, there were 38 cases, including 15 deaths, in the United States (Figure 1),2 of which 3 cases and a death were in Rhode Island residents. Rhode Island had not seen a human case since 2009, and the last death was in 1998 (Figure 2). This dramatic increase required an unprecedented public health response.

METHODS

Annually in June, the Rhode Island Department of Environmental Management (RI DEM) distributes larvicide to cities and towns to apply to underground storm-water catchment basins to reduce human risk of West Nile Virus (WNV) in urban areas. In addition, RI DEM traps mosquitoes at various locations throughout Rhode Island from early June to October. Mosquito traps are placed strategically throughout the state based on the knowledge of environmental conditions conducive to WNV and EEE amplification in the mosquito population. Once traps are collected, the mosquitoes are sorted by species into “pools.” Each pool contains one species of mosquito from one trap site from one trap night. The Rhode Island State Health Laboratory (RISHL) tests each pool for the presence of WNV and EEE through PCR testing.

Human arboviral infections are required to be reported to Rhode Island Department of Health (RIDOH). An epidemiologic investigation is conducted by RIDOH to determine potential exposures. Serum and cerebral spinal fluid (CSF) are collected from suspect cases and submitted to the CDC for testing. As part of the CDC arboviral testing panel, EEE IgM testing is performed using a Microsphere Immunofluorescence Assay. If the EEE IgM is positive, a confirmatory Plaque Reduction Neutralizing Test (PRNT) is performed.

During the arboviral season on a periodic basis, a group of subject matter experts discuss EEE surveillance findings, mosquito trapping results and other environmental factors. To help determine human risk and provide recommendations on statewide response activities, the group utilizes the
Guidelines for Phased Response to Eastern Equine Encephalitis Surveillance Data. This document was created in 2019 to supplement an existing Mosquito Bourne Disease Management Protocol. Recommendations and surveillance findings are incorporated into a Rhode Island Arbovirus Activity Update that is created by RIDOH periodically during the arboviral season. This report is posted to the RIDOH website and distributed by e-mail to individuals, including town managers, infectious disease physicians and veterinarians. RI DEM also issues periodic press releases to inform the public about mosquito test results and human risk for mosquito-borne disease.

RESULTS
During the 2019 arboviral season, Rhode Island had three human cases of EEE, including one death.

The serum on all three cases was EEE IgM positive/EEE PRNT positive. The CSF for two of the three cases was EEE IgM positive, as one case did not have CSF EEE IgM testing performed. The CSF EEE PRNT testing was positive for all three cases. The epidemiologic investigation determined that all individuals were likely exposed in their town of residence (Table 1).

During the 2019 arboviral season, 2,501 mosquito pools were tested. Nine of those pools were positive for EEE (5 Cs. melanura, 2 Culex sp., 1 Aedes japonicus and 1 Anopheles punctipennis). Mosquito trap density, the average number of mosquitoes per trap, was calculated weekly throughout the 2019 season and it was consistently higher than the 5-year average (2014–2018) for the corresponding week (Figure 3). Prior to the 2019 season, the highest mosquito density documented in any single week from 2014–2018 was 63 mosquitoes per trap. In 2019, 5 weeks had mosquito densities greater than 63 mosquitoes per trap, including two weeks with over 100 mosquitoes per trap. In addition to the above findings, there were 3 deer, 1 horse and 1 dog identified with EEE in Rhode Island in 2019 (Table 2). The deer and dog represent the first time EEE was identified in these animals in Rhode Island.

The average number of mosquitoes per trap during the 2019 season peaked in August, and then began to decline (Figure 3). The average number of mosquito pools per trap throughout the 2019 season was higher than the 5-year average (2014–2018). During the week of August 4, 2019 there was an average of 101 mosquitoes per trap. In 2019, 5 weeks had mosquito densities greater than 63 mosquitoes per trap, including two weeks with over 100 mosquitoes per trap. In addition to the above findings, there were 3 deer, 1 horse and 1 dog identified with EEE in Rhode Island in 2019 (Table 2). The deer and dog represent the first time EEE was identified in these animals in Rhode Island.

Pool was a human-biting species, and the other was in a non-human biting species. Detection in the non-human biting species indicates that the virus is amplifying in the environment. One week later, during the week of August 25, two additional human cases had onset of symptoms.

Taking into consideration all Rhode Island human, animal, and mosquito surveillance data, as well as the increased EEE activity in Massachusetts and Connecticut, the group of subject matter experts and policy makers determined that this level of EEE activity warranted larviciding and adulticiding, in an attempt to reduce human health risk.

Larviciding targeted Chapman Swamp in Westerly where two mosquito pools and a horse were positive for EEE; the South Branch of the Pawtuxet River in West Warwick.

Table 1. Human Cases of EEE, Rhode Island, 2019

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Town of Residence</th>
<th>Illness Onset Date</th>
<th>Incubation Range (4–10 Days)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50–59</td>
<td>West Warwick</td>
<td>8/9/2019</td>
<td>7/30/2019–8/5/2019</td>
<td>Died</td>
</tr>
<tr>
<td>3</td>
<td>&lt;10</td>
<td>Coventry</td>
<td>8/30/2019</td>
<td>8/20/2019–8/26/2019</td>
<td>Survived</td>
</tr>
</tbody>
</table>

Table 2. Animal Cases of EEE, Rhode Island, 2019

<table>
<thead>
<tr>
<th>Result Date</th>
<th>Animal</th>
<th>Town</th>
</tr>
</thead>
<tbody>
<tr>
<td>8/24/19</td>
<td>Horse</td>
<td>Westerly</td>
</tr>
<tr>
<td>9/6/19</td>
<td>Deer</td>
<td>Coventry</td>
</tr>
<tr>
<td>9/11/19</td>
<td>Deer</td>
<td>Richmond</td>
</tr>
<tr>
<td>9/14/19</td>
<td>Deer</td>
<td>Exeter</td>
</tr>
<tr>
<td>11/6/2019</td>
<td>Puppy</td>
<td>North Situate</td>
</tr>
</tbody>
</table>
where the first case lived, and the Valley Marsh area in Central Falls where EEE was detected from two positive pools.

Two rounds of adulticiding were also conducted. The first round of aerial spraying was conducted September 8–10 and targeted four areas that were high risk. The second round was conducted on September 25 and targeted two areas that were high risk [Figure 4].

**DISCUSSION**

Scientists cannot conclusively explain why there was a dramatic increase in EEE activity in 2019, but they describe several contributing factors. Climate changes result in longer summers, milder winters, and more extreme rain events, all of which result in better survival and breeding grounds for mosquitoes. Other factors include reforestation, expansion of mosquito-breeding swamps, and an increase in the number of people who now live near those areas. In addition, increased precipitation during the lifecycle of the mosquito correlates with an increase in human cases of EEE. Scientists also suggest that an increase in EEE activity will likely last for two or three seasons.

Healthcare providers have asked to send specimens to private laboratories instead of the CDC, because the turnaround time is shorter. Commercial laboratories that offer testing for EEE only do IgM testing. Since EEE can have cross-reactivity with other arboviruses, this test does not have high specificity, which results in inaccurate results.

Connecticut healthcare providers sent specimens from their four patients to Quest, and the results were IgM negative for EEE. Due to clinical suspicion and increased EEE activity, the Connecticut Department of Public Health also sent specimens to the CDC. Specimens for all four patients were IgM positive at CDC, and all were confirmed with PRNT. This supports the hypothesis that commercial testing for EEE is not reliable.

**References**

1. https://www.cdc.gov/easternequineencephalitis/tech/symptoms.html#symptoms
5. Personal communication with the State Epidemiologist at the Connecticut Department of Public Health.

**Acknowledgments**

Thank you to all the members of the Mosquito-borne Disease Advisory Group, EEE Response Group, and the staff at RIDOH and the RISHL who participated in this response.

**Disclosures**

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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>OCTOBER 2019</th>
<th>12 MONTHS ENDING WITH OCTOBER 2019</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Number</td>
<td>Rates</td>
</tr>
<tr>
<td>Live Births</td>
<td>995</td>
<td>11,128</td>
<td>10.5*</td>
</tr>
<tr>
<td>Deaths</td>
<td>881</td>
<td>10,544</td>
<td>10.0*</td>
</tr>
<tr>
<td>Infant Deaths</td>
<td>3</td>
<td>56</td>
<td>5.6#</td>
</tr>
<tr>
<td>Neonatal Deaths</td>
<td>2</td>
<td>42</td>
<td>4.2#</td>
</tr>
<tr>
<td>Marriages</td>
<td>742</td>
<td>6,535</td>
<td>6.2*</td>
</tr>
<tr>
<td>Divorces</td>
<td>260</td>
<td>2,900</td>
<td>2.8*</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>APRIL 2019</th>
<th>12 MONTHS ENDING WITH APRIL 2019</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number (a)</td>
<td>Number (a)</td>
<td>Rates (b)</td>
</tr>
<tr>
<td>Diseases of the Heart</td>
<td>197</td>
<td>2,481</td>
<td>234.2</td>
</tr>
<tr>
<td>Malignant Neoplasms</td>
<td>194</td>
<td>2,227</td>
<td>214.9</td>
</tr>
<tr>
<td>Cerebrovascular Disease</td>
<td>38</td>
<td>463</td>
<td>43.7</td>
</tr>
<tr>
<td>Injuries (Accident/Suicide/Homicide)</td>
<td>65</td>
<td>932</td>
<td>88.0</td>
</tr>
<tr>
<td>COPD</td>
<td>20</td>
<td>492</td>
<td>46.4</td>
</tr>
</tbody>
</table>

(a) Cause of death statistics were derived from the underlying cause of death reported by physicians on death certificates.
(b) Rates per 100,000 estimated population of 1,056,298 (www.census.gov)
(c) Years of Potential Life Lost (YPLL).

NOTE: Totals represent vital events, which occurred in Rhode Island for the reporting periods listed above. Monthly provisional totals should be analyzed with caution because the numbers may be small and subject to seasonal variation.
The Rhode Island Medical Society now endorses Coverys.
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Contact Sarah if you’ve missed an issue, sstevens@rimed.org.
Working for You: RIMS advocacy activities

March 2, Monday
RIMS Board of Directors: Peter A. Hollmann, MD, Chair of the Board; Christine Brousseau, MD, MPH, President

March 3, Tuesday
RIMS Physician Health Committee: Herbert Rakatansky, MD, Chair
Legislative Hearings

March 4, Wednesday
RI Chapter, American College of Emergency Physicians Lobby Day
Special House Commission on Step Therapy Protocols
Legislative hearings
Representative Marszalkowski fundraiser

March 5, Thursday
Legislative hearings
Meeting with House Finance Chairman Marvin Abney and American Nurses Association-RI, RI Physical Therapy Association, RI Psychological Association, and RI Health Centers Association regarding Budget Article 20 Interstate Licensing Compacts
Senator Archambault fundraiser

March 6, Friday
Mental Health Association Parity Initiative

March 9, Monday
Non-Opioid Pain Treatment Coalition

March 10, Tuesday
Governor’s Overdose Task Force Harm Reduction Group
Senate Commission to Study Insurer Payment Impact on Health Care
Legislative Hearings
Meeting with Chair Bennett and American Academy of Pediatrics, RI Chapter, regarding legislation
Chair Lynch Prata fundraiser
Representative Casimiro fundraiser

March 11, Wednesday
RIMS Physician Health Program Governance Committee: Jerry Fingerut, MD, Chair
Board of Medical Licensure and Discipline

Meeting of Workers Compensation Advisory Committee
Senate Commission to Study Insurer Payment Impact on Health Care
Legislative hearings
Representative Azzinaro fundraiser
Senator Pearson fundraiser
RI Medical Preparatory Academy Charter School meeting

March 12, Thursday
Senator Felig fundraiser
Legislative Hearings
Representative Phillips fundraiser
Chair Gallo fundraiser
New England Delegation to the American Medical Association conference call

March 13, Friday
RIMS Notes production

March 16, Monday
Department of Health conference call regarding COVID-19

March 18, Wednesday
Conference call regarding upcoming meeting with Attorney General Neronha regarding Good Samaritan court case
American Medical Association Conference call for state medical societies regarding COVID-19
Series of email communications to physicians with COVID-19 updates

March 19, Thursday
Medical Malpractice Joint Underwriting Association of Rhode Island, Board of Directors: Newell Warde, PhD, Director

March 20, Friday
Department of Health conference call with professional associations regarding COVID-19

March 23, Monday
RIMS Council conference call with the Health Insurance Commissioner, and Acting Director of RI Medicaid program: Christine Brousseau, MD, MPH, President; Peter A. Hollmann, MD, Chair of the Board

March 24, Tuesday
Teleconference with Attorney General Neronha regarding Good Samaritan court case
Conference call with Administrator Verma, Centers for Medicare and Medicaid Policy and Services (CMS): Peter A. Hollmann, MD, Chair of the Board

March 25, Wednesday
Department of Health Provider Call

March 27, Friday
Conference call with Blue Cross Blue Shield of RI
RIMS Notes production

March 31, Tuesday
American Medical Association Conference call for state medical societies regarding COVID-19

Testimony in front of the Senate Health and Human Services Committee on March 6, in support of the passage of S 2317, which would eliminate cost sharing for colorectal cancer tests.

Senate Majority Whip Maryellen Goodwin (center), with individuals who testified (left to right), Barbara Baker, colorectal cancer survivor; Dr. Wafik El-Deiry, Director of the Cancer Center at Brown University; Dr. Samir A. Shah, Chief of Gastroenterology, The Miriam Hospital; Victoria Baggio, Student at Providence College.
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

For more information about group rates, please contact Marc Bialek, RIMS Director of Member Services
Lifespan opening triage, testing tents

On March 26th frontline physicians at Rhode Island Hospital (RIH) held a press briefing to update the media on how the hospital and the Lifespan system is addressing the COVID-19 pandemic.

“We are seeing a gradual rise in cases of COVID. We’re not seeing the exponential growth that people are seeing on the news in New York,” said Dr. Jeremiah Schurr, Lifespan’s Physician-in-Chief of Emergency Medicine. He also said the hospital currently has enough personal protective equipment to keep staff safe. “We do have concerns, like other health systems in Rhode Island, about how long that supply will last,” he said. “We are taking actions internally to conserve what we have.”

“We have surge plans to house those possibly 150 ventilated patients in both Rhode Island Hospital, the Miriam Hospital, and Newport,” said Dr. Mitchell Levy, Medical Director of the Medical Intensive Care Unit at RIH. He said there are 150 ventilators in the Lifespan system, 100 at RIH. “I do think that it’s possible that we may have succeeded in flattening the curve,” he added. “But there’s really no way to say, except to watch how things evolve over time.”

The yellow tent outside the RIH Emergency Room Dept. ambulance landing will be used for triage and holding as patients with respiratory symptoms are evaluated. Another tent on the premises is currently being used for testing people with suspected cases of COVID-19. A physician at the hospital said they were doing about 50 throat swabs a day there. A tent is also in place but not yet in use for ED walk-ins.

Lifespan has also put up a screening tent at The Miriam Hospital, expected to be in use in the coming days. It is expected that Dept. of Health testing will also occur in a tent at Newport Hospital, once additional testing equipment is in place.
Care New England adds three tent units at Kent; purchases testing machines

Care New England (CNE), Rhode Island's second-largest healthcare system, continues to plan and prepare for the COVID-19 Pandemic with expanded in-hospital preparations by adding ICU beds, ordering testing machines and setting up three outside units as part of its ongoing response.

C. JAMES SUNG, MD, Executive Chief of Pathology and Laboratory Medicine, Care New England Health System Professor and Vice Chair of Pathology, Alpert Medical School of Brown University, regarding the testing tents at Kent Hospital and the testing machines at both Kent and Women & Infants Hospital, said on Friday that, “Kent and Women & Infants Hospitals of Care New England (CNE) Health System has brought the GenMark ePlex COVID-19 testing machine online, as of Thursday [3/26]. Test results from this machine are available within an approximate two-hour time period. As of Friday, similar to what other hospitals are facing nationally, CNE has less than three dozen test cartridges available to use in the machine. CNE plans to limit in-house testing to inpatients as the best use for the current available supply, to help manage patient care and preserve Personal Protective Equipment (PPE). CNE’s Department of Pathology & Laboratory Medicine is working hard to increase its testing capacity so it can most efficiently assess specific needs within this pandemic.”

JESSICA J. MCCARTHY, VP Marketing and Communications at CNE, sent the following descriptions of each outside unit to RIMJ:

1. DOH COVID-19 Testing Tent: This was the first new unit on the Kent property created in partnership with the RI Dept. of Health [RIDOH]. This has been in operation for about two weeks now, and is used for testing appointments that are directed by RIDOH. If a potential patient is screened by RIDOH via telephone and it is determined that a test is warranted, they may be sent to this tent for drive through nasopharyngeal swab test, minimizing exposure to others.

2. Kent ED Open Air Unit: The second outside unit was created aside the Kent emergency department in anticipation of volume increases of patients presenting with respiratory symptoms. This allows us to have a space to more easily keep symptomatic patients away from other emergency department patients, and away from each other. This also allows for a greater area to assess as we plan for surge capacity.

3. Respiratory Infections Triage Unit (RIT-U): The third unit is an assessment center where our providers can recommend a symptomatic patient who DOES NOT NEED to be sent to the emergency department can go to be seen if for some reason the primary care office, or telephone/video visit is not a good option. This is for appointments made through providers where the patient should be assessed with an examination in person. This is not an emergency room; it’s an expansion of the doctor’s office.
IN THE NEWS

CharterCARE erects triage and testing tents outside Emergency Departments

In addition to in-hospital planning and preparations for a potential COVID-19 surge, Roger Williams Medical Center (left) and Our Lady of Fatima Hospital in North Providence (right), operated by CharterCARE Health Partners, has erected triage tents adjacent to the EDs. [RIMJ PHOTOS]

Additional COVID-19 testing sites open at URI, CCRI, RIC

MARY KORR, RIMJ MANAGING EDITOR

At a press briefing held on Monday, March 30th, GOV. GINA RAIMONDO announced the opening of three additional mobile COVID-19 testing sites, at Rhode Island College, the University of Rhode Island and the Community College of Rhode Island in Warwick, in partnership with the Rhode Island National Guard.

The drive-through tented test sites in parking lots are for pre-screened patients with appointments and documentation from primary care providers, and will be conducted and administered by medical and National Guard security personnel, with the anticipation of a testing capacity of 1,000 people on a daily basis. “We are half way there now,” Gov. Raimondo said. “By Wednesday I hope to be there.”

After the specimen swabs are completed, patients will immediately be directed to exit the testing sites by the National Guard, with no access to any campus facilities.

The National Guard testing sites are temporary and will support the demand for testing in the short term until the state has ample supplies of Personal Protective Equipment (PPE), specimen collection kits, and point-of-care testing.

“We want to expand testing in order to pinpoint our response more,” said DR. NICOLE ALEXANDER-SCOTT, director of the Rhode Island Department of Health (RIDOH). She said the state had 200 ventilators before the COVID-19 crisis, and is trying to get to 600.

As of March 30th, the state had 114 new cases, Gov. Raimondo said, bringing the state’s total to 408 cases, with 41 in the hospital, and four deaths from coronavirus.

RIDOH is studying whether the latest death, a man in his 70s, had any underlying medical conditions. He was not in a nursing home, Dr. Alexander-Scott said.

However, she noted that nursing homes are “places of concern.” The state has had 15 positive coronavirus cases in three nursing homes, she said.

RIDOH recommends testing for these priority categories:

- Hospitalized patients
- Healthcare workers, including Emergency Medical Services (EMS)
- Residents of long-term care facilities
- Patients 65 and older
- Patients with underlying conditions placing them at higher risk for COVID-19 complications
- First responders (police, fire, and non-EMS) and other critical infrastructure workers
Abbott launches molecular Point-Of-Care Test to detect novel coronavirus in as little as five minutes

Abbott will be making ID NOW COVID-19 tests available next week and expects to ramp up manufacturing to deliver 50,000 tests per day

This is the company’s second test to receive Emergency Use Authorization by the FDA for COVID-19 detection; combined, Abbott expects to produce about 5 million tests per month

Abbott Park, Illinois, March 27, 2020 – Abbott announced today that the U.S. Food and Drug Administration (FDA) has issued Emergency Use Authorization (EUA) for the fastest available molecular point-of-care test for the detection of novel coronavirus (COVID-19), delivering positive results in as little as five minutes and negative results in 13 minutes. The test will run on the company’s ID NOW™ platform, providing rapid results in a wide range of healthcare settings such as physicians’ offices, urgent care clinics and hospital emergency departments.

The ID NOW platform is small, lightweight (6.6 pounds) and portable (the size of a small toaster), and uses molecular technology, which is valued by clinicians and the scientific community for its high degree of accuracy. ID NOW is already the most widely available molecular point-of-care testing platform in the U.S. today.

“The COVID-19 pandemic will be fought on multiple fronts, and a portable molecular test that offers results in minutes adds to the broad range of diagnostic solutions needed to combat this virus,” said Robert B. Ford, president and chief operating officer, Abbott. “With rapid testing on ID NOW, healthcare providers can perform molecular point-of-care testing outside the traditional four walls of a hospital in outbreak hotspots.”

Abbott will be making ID NOW COVID-19 tests available next week to healthcare providers in urgent care settings in the U.S., where the majority of ID NOW instruments are in use today. The company is working with the Administration to deploy tests to areas where they can have the greatest impact.

The arrival of the Abbott ID NOW COVID-19 test comes a week after the company launched its Abbott m2000™ RealTime SARS-CoV-2 EUA test, which runs on the m2000™ RealTime System located in hospital and reference labs around the world. Between the two platforms, Abbott expects to produce about 5 million tests per month.

About the ID NOW™ Molecular Platform
As the world leader in point-of-care diagnostics, Abbott is adding its expertise and scale to help fight the COVID-19 global pandemic. First introduced in 2014, ID NOW is the leading molecular point-of-care platform for Influenza A & B, Strep A and RSV testing in the U.S.

ID NOW is a rapid, instrument-based, isothermal system for the qualitative detection of infectious diseases. Its unique isothermal nucleic acid amplification technology provides molecular results in just minutes, allowing clinicians to make evidence-based clinical decisions during a patient visit.

The ID NOW COVID-19 EUA has not been FDA cleared or approved. It has been authorized by the FDA under an emergency use authorization for use by authorized laboratories and patient care settings. The test has been authorized only for the detection of nucleic acid from SARS-CoV-2, not for any other viruses or pathogens, and is only authorized for the duration of the declaration that circumstances exist justifying the authorization of emergency use of in vitro diagnostic tests for detection and/or diagnosis of COVID-19 under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner. [SOURCE: ABBOTT]
Anchor Recovery Community Center continues services via telephone

As the number of COVID-19 cases in the state of Rhode Island rises, the Anchor Recovery Community Center reminds the public that critical resources remain available to anyone, including those with substance use disorders. “During this public health crisis, we want those who are some of the most vulnerable in our community to know that help is still available, and that they can stay firmly on their path to recovery, by reaching out to us. The Providence Center’s Anchor Recovery team has worked tirelessly to develop innovative ways to address the needs of the recovery community, during this especially stressful time,” said Deb O’Brien, president and COO, The Providence Center.

During the health crisis, to ensure the safety of its team and those it serves, Anchor Recovery Community Centers are closed to the public. It has, however, developed the following solutions to continue providing peer recovery coaching services to those who need it. The Anchor Recovery Community Center’s phone line will remain open, so recovery coaching services may be accessed by the public, by calling 401-889-5770. Peer Recovery Specialists will be available via telephone between the hours of 8:00 am and 8:00 pm. During off-hours, calls will be forwarded to a dispatch line, and a coach will return calls in a timely manner. Current members will continue to receive one-on-one support from their coaches via telephone.

Also, for the time being, group meetings will be offered through a conference call line. Anchor Recovery is currently holding group meetings Mondays through Fridays from 10 am through 1 pm; Mondays [Medication Assisted Recovery] at 11 am; Tuesdays and Thursdays [Men’s Group] at 11 am; and Wednesdays and Fridays [Women’s Group] at 11 am.

Anchor ED is also working closely with all hospitals throughout the state to develop protocols that will allow those hospitalized for a substance use related issue to engage with a recovery coach.

Safe Stations resources have not been impacted, and will continue to operate as normal, at all Providence Safe Stations locations.

The Providence Center is available 24/7 for anyone who is experiencing a crisis, needs to talk to someone, or is feeling overwhelmed or especially anxious, by reaching us on our Emergency Services line at 401-274-7111. Counseling services are also available.

Planned Parenthood of Southern New England (PPSNE) launches telehealth visits

NEW HAVEN, CT – In response to the COVID-19 public health crisis, Planned Parenthood of Southern New England [PPSNE] launched telehealth visits for select services to continue its commitment to breaking down barriers, reaching people wherever they are, and increasing access to care in Connecticut and Rhode Island. Telehealth visits keep essential sexual and reproductive health care accessible and help limit the community spread of COVID-19 in this time of social distancing. Since this service launched this week, PPSNE has already conducted over 40 telehealth visits.

Services currently available through telehealth include:

- Hormonal birth control options, including the pill, patch, ring, and emergency contraception
- Injectable Depo-Provera contraception with instructions for self-injection
- Primary care for existing patients
- Behavioral health screening and treatment of anxiety and depression
- Diagnosis and treatment for urinary tract infections (UTIs) and bacterial vaginosis
- Diagnosis and treatment for sore throat and upper respiratory infections
- Gender-affirming hormone therapy
- Medication abortion follow-up visits
- Pre-exposure [PrEP] and post exposure prophylaxis (nPEP) to prevent HIV infection [may require additional lab testing]
- Prescription refills for current patients with chronic conditions

In addition to telehealth services, the Planned Parenthood Direct app (PP Direct) allows patients in Connecticut and Rhode Island to use their smartphone to access birth control and treatment for UTIs. Patients can also text “PPNOW” to PPINFO (774636) or use the chat function at ppsne.org to get answers about pregnancy, birth control, emergency contraception, abortion, and STD treatment. These digital solutions help make health care more accessible and advance the PPSNE mission to provide the information and services people need to manage their sexual and reproductive health.
Appointments

Heather Hall, MD, named president of Newport Hospital medical staff

NEWPORT – HEATHER HALL, MD, medical director and chief of psychiatry at Newport Hospital, has been named president of the medical staff of the hospital.

Medical staff leadership is represented by the Medical Executive Committee, which is comprised of active medical staff and associate medical staff from the community. The committee plays a critical role in offering input into hospital operations and credentialing of medical providers for hospital privileges.

“Having been at Newport Hospital for 12 years, I feel very invested in the hospital and the community,” said Hall, a Portsmouth resident.

She is the first psychiatrist and first woman to lead the Medical Executive Committee in recent memory.

“Women continue to make strides toward equality in the medical field – like so many others – and representation at the top of the organization is a piece of that,” she said. “There are many women in leadership roles at Newport Hospital and I’m proud to work alongside them for the benefit of the hospital and the community.”

Hall is a graduate of the State University of New York Downstate College of Medicine. She completed her residency at New York University Medical Center.

Ashish K. Jha, MD, named Dean of Brown School of Public Health

Currently serves as faculty director of the Harvard Global Health Institute

PROVIDENCE [BROWN UNIVERSITY] – ASHISH K. JHA, MD, currently the faculty director of the Harvard Global Health Institute, has been appointed the next dean of the Brown University School of Public Health, effective September 1, 2020. He succeeds Bess Marcus, who will conclude her term as dean this summer to return to full-time research and teaching as a member of the Brown faculty.

He will oversee the School of Public Health’s academic departments, research centers, doctoral and master’s programs, and undergraduate concentrations. Key responsibilities include developing and executing strategies to expand sponsored research funding and elevate the school’s profile and impact locally and globally. Integral to his role will be cultivating a diverse and inclusive academic community, providing administrative oversight and ensuring the school’s fiscal strength.

Brown President CHRISTINA H. PAXSON and Provost RICHARD M. LOCKE announced the appointment on February 26th.

In addition to his role leading the Harvard Global Health Institute, Jha is a professor of global health at the Harvard T.H. Chan School of Public Health and has served as the school’s dean for global strategy since 2018. He is also a practicing general internist at the V.A. Boston Healthcare System and a professor of medicine at Harvard Medical School.

His background as a practitioner providing care for individual patients, a scholar focused on national and global public health systems, and a global health advocate engaged on major issues such as the impact of climate change on public health, makes him an ideal leader to advance academic excellence and provide strategic direction for the school, Paxson and Locke wrote in the appointment announcement.

Jha said that the potential to build on the School of Public Health’s strengths and work with students, faculty and staff to position it as a leading public health school born in and built for the health challenges of the 21st century is exciting, especially in the context of Brown’s collaborative academic culture. And Brown’s track record of partnership with health care leaders and agencies in Rhode Island – through the School of Public Health, the Warren Alpert Medical School and other academic departments – is another essential factor in ensuring the role of public health educators and researchers in fulfilling the University’s mission, Jha added.

“The most significant public health problems of our time demand a multi-disciplinary approach, and faculty and students at Brown live that in addressing major challenges,” Jha said. “Brown is also deeply embedded in Rhode Island’s communities. The fact is, as Brown demonstrates, academic institutions function best when they partner with public health agencies and individuals to test ideas. It’s not a standard model for every university but it is for Brown, and that’s part of what makes me so enthusiastic about this new and important opportunity to be part of a community making a difference, locally and globally.”

With sponsored funding from sources such as the National Institutes of Health, the Gates Foundation, the Climate Change Solutions Fund and the Commonwealth Fund, Jha’s research focuses on improving the quality of health care systems with a specialized focus on how national policies impact care. He has led some of the seminal work comparing the performance of the U.S. health system to those of other high-income countries to better understand why the U.S. spends more but often achieves less in population health.
Katherine Sharkey, MD, PhD, named Woman Physician of the Year by RIMWA

The Rhode Island Medical Women’s Association [RIMWA] will honor KATHERINE M. SHARKEY, MD, PhD, as Woman Physician of the Year during the organization’s annual event, to be rescheduled due to the COVID-19 pandemic. This award is given annually to a Rhode Island female physician who excels in both her field of medicine, and her dedication to the betterment of our community.

Dr. Sharkey, an Associate Professor of Medicine and Associate Professor of Psychiatry and Human Behavior at the Warren Alpert Medical School, was appointed Assistant Dean for Women in Medicine and Science in 2016. She is also the medical director of the Brown Medicine Sleep Center and the Sleep for Science Research Laboratory of Brown University. She was recently awarded a $5.1 million, multi-site grant from the National Institute for Mental Health for research on perinatal depression during pregnancy.

Dr. Sharkey is a fellow of the American Academy of Sleep Medicine and a member of the Society for Women’s Health Research Interdisciplinary Network on Sleep. She is an associate editor of Behavioral Sleep Medicine and serves on the editorial board of Sleep Health.

She obtained her undergraduate degree at the University of Pennsylvania and received her MD and PhD degrees from Rush University, Chicago, IL. She completed a combined medicine and psychiatry residency at Rush University in 2006.

Integra Community Care Network partnering with Rhode Island Primary Care Physicians Corporation

PROVIDENCE – Care New England recently announced that Integra Community Care Network is partnering with the Rhode Island Primary Care Physicians Corporation (RIPCPC) to enhance the quality and focus of Integra’s primary care delivery system.

Integra is a local care network comprised of a collaboration between Care New England, South County Health, and RIPCPC that covers commercial, Medicare and Medicaid patients. Since its launch in 2014, the network has established itself as one of the strongest and most efficient ACOs in the country, closing every fiscal year with a surplus while delivering high-quality care. Since its inception, Integra has reduced the overall cost of healthcare by more than $51 million.

Integra was recently listed as the second-highest-rated ACO in the country, according to data released by the U.S. Centers for Medicare and Medicaid Services.

W&I’s Program in Women’s Oncology receives reaccreditation

The Commission on Cancer (CoC) and the National Accreditation Program for Breast Centers (NAPBC) has recently granted reaccreditation to the Program in Women’s Oncology at Women & Infants Hospital with three nominations for national best practice. The CoC and NAPBC are organizations for the American College of Surgeons which establish standards to ensure quality, multidisciplinary, and comprehensive cancer care delivery.

One area of special recognition was for the clinical research conducted by the Program’s nationally recognized research team. The Program in Women’s Oncology has the second highest amount of patients enrolled in clinical trials through the GOG foundation and NRG oncology in the nation. Both the GOG foundation and NRG oncology are industry leading research organizations. Another area of strength and commendation included the rate of nurses who are oncology certified which was substantially above the established standard.

“Our mission has always been to provide outstanding clinical care, contribute to the latest standard of care through cutting edge research, and educate the future leaders in our discipline,” said PAUL DISILVESTRO, MD, director of the Program in Women’s Oncology and the Division of Gynecologic Oncology.

“These accreditations are affirmation of that mission.”

To achieve accreditation, it took a collaborative, team approach as these surveys touch upon all facets of the program – from surgeons and medical oncologists to social workers and genetic counselors. Fortunately, by having each member already fully engaged in delivering the highest quality health care in the region, it was simply a matter of showcasing to the surveyor the tremendous work already being done every day.
The Miriam Hospital attains Magnet® recognition for nursing excellence, celebrates amid challenging times for health care workers

PROVIDENCE – The Miriam Hospital has once again attained Magnet® recognition for nursing excellence and now joins just three other U.S. hospitals in receiving the four-year designation six consecutive times. The announcement came amid a coronavirus outbreak that has changed the lives of health care workers, focused attention on the critical front-line role they are playing in the pandemic, and had nurses at The Miriam celebrating wearing masks and gathered only in small groups.

The honor, bestowed upon the hospital by the American Nurses Credentialing Center’s Magnet Recognition Program®, is considered the gold standard for nursing excellence and provides consumers with the ultimate benchmark for measuring quality of care. Only hospitals that meet rigorous standards for high-quality nursing excellence can achieve Magnet® recognition, the highest national honor for professional nursing practice.

Recognition every four years based on adherence to Magnet concepts and demonstrated improvements in patient care and quality. An organization reapplying for Magnet recognition must provide documented evidence to demonstrate how staff members sustained and improved Magnet concepts, performance and quality.

MARIA DUCHARME, DNP, RN, NEA-BC, chief nursing officer and senior vice president of patient care services, said, “While the bar is raised with each designation and the process only becomes more challenging, our ingrained culture allows for an environment that lives and breathes nursing excellence. It’s who we are; it’s what we do every day. I am so proud of all our nurses and feel so fortunate to work with such outstanding colleagues. To achieve Magnet recognition, hospitals must submit documented evidence as well as undergo a site visit. Our appraisers remarked on our nurses’ spirit of patient centeredness and their unwavering pursuit of the best evidence to care for their patients. I couldn’t agree more.”

This year, the hospital re-attained Magnet designation with exemplars in seven areas, more than in any recent Magnet review.

“Exemplars are best practices highlighting exceptional nursing excellence. They indicate that we are outperforming national benchmarks,” said LYNN D’ANGELO, DNP, RN, NEA-BC, director of Professional Practice, Innovation and Magnet. “Our seven exemplars were related to empirical outcomes including nursing sensitive indicators and patient experience, both inpatient and ambulatory. The exemplars we received were related to a variety of infection prevention practices, courtesy, respect, listening and safety. This is a testament to the countless contributions of nurses in the delivery of exemplary care.”

According to the Magnet Recognition Program® Commission, the designation provides benefits to hospitals and their communities, including the following:

- Higher patient satisfaction with nurse communication
- Lower risk of 30-day mortality and lower failure to rescue rates
- Higher job satisfaction among nurses
Obituaries

**THOMAS G. BRESLIN, MD**, a resident of Bristol, and Delray Beach, Fla., passed away peacefully on March 7, 2020, with his wife of 58 years, Carolyn J. [Anderson] Breslin, by his side.

Dr. Breslin graduated from the Moses Brown School [where he started a legacy of 3 generations of graduates and met one of his best life-long friends, Joe Kinder], Brown University and the University of Maryland School of Medicine. He became a urological surgeon affiliated with Rhode Island Hospital, Fatima Hospital and St. Joseph’s Hospital and successfully ran his private practice, Breslin Urosurgical, for 31 years. He was appointed to the RI Board of Medical Review, was a clinical instructor at Brown University Medical School and was the founder and first president of the RI Urological Society. He was the first to practice groundbreaking surgical techniques in the state, including cryosurgery and lithotripsy.

Dr. Breslin loved to tinker and invent and, had he not been a surgeon, would have loved to be an inventor creating things in his tool shop to make the world a better (or at least more interesting) place. His vast knowledge and wisdom on a wide array of topics was always a source of amazement to his children, with whom he would take every opportunity to teach.

He and Carolyn lived in Bristol for nearly 60 years where they raised their children. He was active not only in his career but in his community. He is a past president of the Bristol Highlands Improvement Association, a member of the Harbor Commission, as well as fleet surgeon and former board member of the Bristol Yacht Club, where he spent years pursuing his love for sailing.

This passion for sailing began as a youth at the Edgewood Yacht Club where he met his other two best, and lifelong, friends: Herb Browne and Kenny Knowles. His love for the sport, and the competition and fellowship it offered, followed him throughout his life. He enjoyed numerous Block Island Race Weeks, Newport to Bermuda races and even frostbiting in his sunfish in the winter. But there was nothing he loved more than cruising with his family aboard his beloved yacht, The Watch, named after his own father’s boat, and teaching his family the joys and challenges of sailing and a love of water, especially Narragansett Bay.

He was also incredibly proud of his service to country in the US Navy, where he followed in his father’s footsteps. His patriotism was a source of great pride and guided his intentions and efforts throughout his life. The American flag always hangs proudly at his home.

In addition to his wife, Dr. Breslin is also survived by five children: Kate Harden, Jane Sorensen [Soren], Robert Breslin, Amy Breslin [Peter] and Amity Jackson [Benjamin]. He is preceded by his son, Thomas William Joseph and his parents, Drs. Kate and Robert Breslin. He leaves behind his 11 grandchildren and his older brother, Robert H. Breslin (Carol), whom he looked up to and admired.

Based on current health concerns, at the direction of the Episcopal diocese, funeral services are pending. Donations in his memory may be made in his name to the Seaman’s Church Institute, 18 Market Square, Newport, RI.

**CHARLES C.J. CARPENTER, JR., MD**, 89, passed away peacefully on March 19th, 2020, at his home in Falmouth, Maine, after a brief illness, with his wife of 61 years, Sally, and his three sons, Charles M. Carpenter, MD, Murray Douglas Carpenter, and Andrew Fisher Carpenter, by his side.

Dr. Carpenter, Professor of Medicine at the Alpert Medical School of Brown University and former Physician-in-Chief at The Miriam Hospital [1986-98], moved to Maine in retirement to be closer to his sons and seven grandchildren. He is remembered as a pioneering medical researcher, a mentor to many physicians, an innovator in cholera and HIV/AIDS treatment, and a big-hearted family man.

Known as Chuck to his friends, he was born Jan. 5, 1931, in Savannah, Georgia, where his ancestors had fought in the American Revolution and the Civil War. When he was 5, his family moved to Birmingham, where his father and namesake served as bishop of the Episcopal Diocese of Alabama. After attending public schools in Birmingham, Dr. Carpenter attended the Lawrenceville School in New Jersey, where he graduated as salutatorian. He then went to Princeton University, where he majored in English Literature and wrote his thesis on the poetry of Yeats. Upon graduation in 1952, he decided on a career in medicine and attended the Johns Hopkins University School of Medicine in Baltimore, graduating in 1956. He was chief resident there when he met Sally Fisher, whose father, Dr. A. Murray Fisher, was known for his research on penicillin. They were married near Baltimore in 1958, and Sally often quipped that he married her because he was so impressed by her father’s research.

Dr. Carpenter did his residency training at Johns Hopkins and later joined the faculty. During a stint of research at the National Institutes of Health (NIH) in Bethesda, the couple bore Charles, the first of three sons. Eighteen months later their second child, Murray, had come along. With two children under three years old, the family decamped for Calcutta, India, which was in the midst of a cholera epidemic. Dr. Carpenter’s lab studied cholera, and his team of researchers was instrumental in contributing
to the development of oral rehydration therapy (ORT), a simple treatment that has saved millions of lives worldwide and that is still the treatment of choice today. Returning to Baltimore after two years in India, the Carpenters had their third son, Andrew.

Dr. Carpenter soon became a tenured professor at Johns Hopkins, Director of the Division of Allergy and Infectious Diseases, and Physician-in-Chief at Baltimore City Hospitals, while continuing his cholera research. In 1973, he moved to Cleveland to become the Chair of the Department of Medicine at Case Western Reserve University School of Medicine. At CWRU, one of his innovations was to develop the nation’s first division of geographic medicine. His work took him to two dozen countries. In 1986, Dr. Carpenter moved to Rhode Island, and served as the Director of the Brown University International Health Institute, and the Director of The Lifespan/Tufts/Brown Center for AIDS Research (CFAR).

Dr. Carpenter was among the first to recognize the extent of heterosexual transmission in AIDS worldwide, and this led to his pioneering work on HIV in women. In the 1980s, he started a program to care for Rhode Island state prisoners with HIV, a move that inspired some younger physicians to look at the larger issues of caring for people caught up in mass incarceration. He also worked with colleagues in India and the Philippines to reduce the spread of HIV. For the National Academy of Science’s Institute of Medicine, he chaired a treatment subcommittee to evaluate the President’s Emergency Plan for HIV/AIDS Research, which took him to several countries in Africa.

Dr. Carpenter retired in 2015 at the age of 84. Throughout his career, he was known for his gentle bedside manner, and compassionate treatment of all patients. He was driven by the conviction that all patients deserve equal treatment, regardless of race, social status, gender, or sexual orientation. And he is remembered for collaborations with overseas colleagues, especially in Bangladesh, India, Japan, and Ghana.

Dr. Carpenter was a member of the National Academy of Science’s Institute of Medicine, where he served on committees studying smallpox and malaria. He also served as President of the Association of American Physicians, and Chairman of the American Board of Internal Medicine, and was co-editor of seven editions of Cecil Essentials of Internal Medicine. In 1998, he received the Order of the Sacred Treasure from the Emperor of Japan for his contributions to the U.S.-Japan Cooperative Medical Science Program. In 2007, he received the Robert H. Williams, MD, Distinguished Chair of Medicine Award from the Association of Professors of Medicine awarded to a physician who has demonstrated outstanding leadership as the chair of a department of medicine.

Still, his children and grandchildren say he always had time for them. Sometimes this meant fishing with worms and bobbers from a rented rowboat; other times it meant an evening jog, a few sets of tennis, or a weekend pedal on his beloved East Bay Bike Path in Barrington, where he and his wife lived while in Rhode Island.

In addition to his wife and three sons, Dr. Carpenter is survived by his brother, the Rev. Douglas Morrison Carpenter, of Birmingham, Alabama; sisters Ruth Pitts, of Mountain Brook, Alabama, and Alex Cole of Short Hills, New Jersey; and seven grandchildren.

Donations in his memory may be made to the Immunology Center Patient Assistance Fund at The Miriam Hospital, or the Southern Poverty Law Center. A memorial service will be held later, when public gatherings are more prudent.
The English word quarantine is derived from the Latin: *quadraginta*, and the Italian: *quaranta*, both meaning 40. A period of 40 days quarantine stems from the mid 1300s, when the Bubonic Plague, the “Black Death,” swept across Europe. Laws were imposed by cities in Italy and Croatia which issued 30-day periods of quarantine, and later 40 days, to ships arriving from plague-infected areas, and which were suspected of harboring contagious crews and passengers, or foods and livestock.

In the United States, the first quarantine station and hospital was built in Philadelphia in 1799. The Port of Providence issued regulations for quarantining ships from foreign countries in the mid 1800s. In 1844, the City of Providence instructed *Dr. John W. Richmond*, its health officer, pursuant to regulations established by the city in 1834, to be the first to board a vessel arriving at its port to “present the quarantine regulations to the master or commanding officer and examine every person on board to ascertain the true state of their health and the vessel and give directions for cleansing the same.” Clothing, sails, bedding were to be “sunk or buried” if the physician determined them to be dangerous. [*Figure 1*, next page]

Continuous outbreaks of infectious diseases in the United States resulted in the passage of the National Quarantine Act in 1878. [*Figure 2*]

Throughout the 19th and 20th centuries, city and state Departments of Health posted signs on homes and theaters, in an effort to contain the spread of smallpox, diphtheria, poliomyelitis, and tuberculosis, to name a few. [*Figures 3 and 4*].

Today, U.S. Quarantine Stations are located at 20 ports of entry and land-border crossings where most international travelers arrive. They are staffed with medical and public health officers from the Centers for Disease Control and Prevention (CDC) and managed by CDC’s Division of Global Migration and Quarantine (DGMQ), the latter currently staffs 18 of CDC’s 20 quarantine stations. Dallas and Boston fall under the jurisdiction of the quarantine stations in Houston and New York respectively, according to the CDC website, cdc.gov.

*Figures 3 and 4*. Signs such as these appeared on the doorways of US homes in the first half of the 20th century. [CREDIT: NATIONAL LIBRARY OF MEDICINE]
AN ORDINANCE RELATING TO QUARANTINE.

WHEREAS, it is the opinion of the City Council of the City of Providence, that the health of the people of this City is in some degree endangered by the dysentery, typhus, and other infectious diseases which have lately broken out and been prevalent in some of the cities of these United States, and are likely to be introduced here, at any time, unless some steps be taken to guard against the same.

Be it enacted by the City Council of the City of Providence, that the following Ordinance be and the same is hereby enacted, to be observed and enforced by the officers of this City:

That no person or persons, in any boat or vessel, shall arrive at the port of this City, unless the same shall first be examined, and such as are liable to contagious diseases shall be detained and isolated, and from thence to be conveyed to the Hospital of this City, under the direction and control of the Surgeon of this Hospital, to be there inspected and directed by him; and that no person or persons, in any boat or vessel, shall be admitted to the city or town of the City of Providence, or from thence to the interior of the country, unless they shall be first examined and inspected at the entrance of the same, and such as are liable to contagious diseases shall be detained and isolated, and from thence to be conveyed to the Hospital of the City of Providence, under the direction and control of the Surgeon of the Hospital of this City, to be there inspected and directed by him.

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1918–1919/The Spanish Flu

1919: Rush on a germicide station during the Great Influenza scare. The political cartoon is signed by the artist, Chas Reese, and dated 1919. Men are rushing to the door and climbing in the window, trying to get some of the bottled drink/medicine. The winding road leading to the building shows people running and driving in cars towards the building. The men are dressed in suits and have the names of the people they are intended to represent, probably people in politics or journalism.

[NATIONAL LIBRARY OF MEDICINE]

PROVIDENCE, RI, 1918

In the fall of 1918, Brown University placed a quarantine on its students, placing guards at the college gates. The quarantine remained in effect for four weeks, with few students becoming ill and no deaths. Private and public schools in Providence were also shuttered, until the flu subsided in late fall.

[BROWN UNIVERSITY ARCHIVES, BUA. BAM, 19:4. NOVEMBER, 1918:16.]

SEATTLE, WA, 1918

Precautions taken in Seattle during the Spanish Influenza epidemic would not permit anyone to ride on the streetcars without wearing a mask. 260,000 of these were made by the Seattle Chapter of the Red Cross, which consisted of 120 workers, in three days.

[LIBRARY OF CONGRESS/AMERICAN RED CROSS]
NEW HAVEN, CT, circa 1918–1919
Interior of Red Cross House at U.S. General Hospital #16, New Haven, CT, during the influenza epidemic. The beds are isolated by curtains.
[LIBRARY OF CONGRESS/AMERICAN RED CROSS]

ELLIS ISLAND, NY, circa 1930
A man in pajamas and a robe is sitting and reading a newspaper behind a caged door in quarantine detention at Ellis Island, New York City.
[NATIONAL LIBRARY OF MEDICINE]

NEW YORK CITY, LA GUARDIA AIRPORT, 1947
Passengers from London entering the quarantine room at La Guardia Airport in New York City.
[NATIONAL LIBRARY OF MEDICINE]

PROVIDENCE, RI, 1962
A teacher oversees children in a day nursery in Providence who are lining up to wash their hands to prevent the spread of germs. Fortunately for these youngsters, the Salk vaccine to prevent polio, approved in 1955, was widely available by then.
[RI DIGITAL ARCHIVES, SECRETARY OF STATE’S OFFICE, DEPT. OF HEALTH PHOTOGRAPHS]
CALIFORNIA, MARCH 2020
Social distancing sign on a San Francisco Bay Area trail as a result of the COVID-19 pandemic.

USNS MERCY (T-AH 19), MARCH 2020
(Below) The Military Sealift Command hospital ship USNS Mercy (T-AH 19) navigates the San Diego channel, March 23, 2020. Mercy deployed in support of the nation’s COVID-19 response efforts, and will serve as a referral hospital for non-COVID-19 patients currently admitted to shore-based hospitals. This allows shore base hospitals to focus their efforts on COVID-19 cases. One of the Department of Defense’s missions is Defense Support of Civil Authorities. DOD is supporting the Federal Emergency Management Agency, the lead federal agency, as well as state, local and public health authorities in helping protect the health and safety of the American people.
[U.S. NAVY PHOTO BY MASS COMMUNICATION SPECIALIST 3RD CLASS LASHEBA JAMES]

(Right) Capt. John Rotruck, commanding officer of the Mercy, speaks to members of the press just before the ship’s departure.
[MASS COMMUNICATION SPECIALIST 2ND CLASS NATALIE M. BYERS]