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SPECIAL SECTION

UPDATES *in* CANCER GENETIC TESTING, MANAGING, *and* COUNSELING

GUEST EDITORS: JENNIFER SCALIA, MS; ASHLEY STUCKEY, MD

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Jennifer Scalia, MS

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SPECIAL SECTION

Updates in Cancer Genetic Testing, Managing, and Counseling

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On the cover

Scientist holding futuristic smart tablet analysis of DNA structure molecule chain in laboratory of biochemistry.
[CREDIT: PHUTTAPHAT TIPSANA, ISTOCK]

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Cancer Genetics: From Then to Now

JENNIFER SCALIA, MS
ASHLEY STUCKEY, MD
GUEST EDITORS

The impact of cancer genetics on the field of oncology has dramatically altered the care we provide our patients. In the early 1990s the discovery of BRCA1 and BRCA2 variants laid the framework for cancer genetic counseling and testing as we know it today. Over the last 25 years, the cancer genetics field has grown exponentially from single syndrome testing to the standard of care demanding the simultaneous analysis of over 50 cancer susceptibility genes by routine next-generation sequencing.

The field of cancer genetics has also expanded its purpose, from the simple process of determining individual cancer risks, to assisting patients and their healthcare providers with critical decisions related to surgical choice and treatment. Excitingly, this has led to advances in clinical care, evident through the earlier detection of cancer, decreased mortality due to personalized treatment, and the prevention of cancers that otherwise would have developed. However, due to the high number of individuals now eligible for genetic testing, greater demands are placed on exploring novel methods for the delivery of cancer genetic counseling, especially considering the limited number of trained professionals available. These new applications of genetic testing and the exploration of novel strategies related to cancer counseling are focal points in this everchanging era in oncology genomics. As a result, there are dedicated research efforts examining this constant fluctuation in cancer care, resulting in guidelines to assist practitioners in the translation and application of these complex genetic outcomes.

This issue of the *Rhode Island Medical Journal* (RIMJ) presents a variety of articles devoted to the past, present, and future of cancer genetics, advances in the field, and a glimpse of what to expect next. The manuscript by **JASMINE EBOTT** et al provides a historical background of cancer genetic testing, discusses the criteria necessary for testing referral, describes service delivery models, and provides insight regarding the challenges of insurance coverage.

SANDRA TOMLINSON-HANSEN et al begin with a review of well-established genetic cancer syndromes, including Lynch and Hereditary Breast and Ovarian Cancer Syndrome. This manuscript also describes novel hereditary oncology genes such as PALB2, BRIP1, RAD51C/D, and BARD1, as well as their everchanging, and often uncertain, associated cancer risks.

KATHERINE CRAWFORD et al begin with the intricacies of genetic counseling and testing interpretation and review national guidelines for identifying and screening patients who are at increased risk to develop breast cancer. Finally, they provide informative case studies to illustrate the genetic testing and counseling processes.

The current landscape of gynecologic cancer care is dependent on both somatic and germline genetic testing. **JESSICA DISILVESTRO** et al explain the difference between somatic and germline testing and the implications on current treatment algorithms with respect to FDA-approved or experimental targeted treatments and immunotherapies.

We hope readers enjoy this issue of RIMJ and that it provides cancer genetic updates that will be relevant for clinicians practicing in a wide variety of fields.

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A Genetic Revolution: Cancer Genetic Testing and Counseling

JASMINE A. EBOTT, MD; JENNIFER SCALIA, MS

ABSTRACT

Genetic counseling is a relatively young profession that has advanced rapidly over the last 50 years. The term "genetic counseling" was first coined by Sheldon Reed in 1947 to describe the advice he would give to physicians regarding their patient's genetic conditions. Today, more than 5,000 genetic counselors are licensed through the American Board of Genetic Counselors. Clinically, genetic counselors practice in a variety of specialties, including pediatrics, prenatal, neurology and psychiatry; however, oncology remains the most common.[1] This article is centered on the most common areas of genetic counseling and addresses the topics of cancer genetic testing, genetic counseling, and explores past and current practices.

KEYWORDS: genetic counseling, genetic testing, service delivery

BRIEF HISTORICAL REVIEW

In the 1970s genetic counseling consisted mostly of reviewing family history and the patient's personal medical history. From this discussion, patients were given the option of karyotyping and/or cytogenetics pending an institution's testing capability. In the 1980s fluorescence in situ hybridization (FISH) was developed, allowing for chromosome rearrangements to be detected more easily. These techniques identified large genomic changes such as deletions, duplications, and translocations; however, smaller genetic variants were being missed. It was not until the 1990s when Mullis and Smith won the Nobel Prize in Chemistry for their discovery of PCR technique that launched genetics into a new higher level of clinical diagnostics.[2]

Directly following the implementation of PCR, Mary-Claire King discovered the Breast Cancer Susceptibility Gene1 (BRCA1) located on chromosome 17q21, which in its altered form, is primarily responsible for 57–66% of early-onset breast cancers and 39–59% of ovarian cancers.[3-5] In 1994, Michael Stratton and Richard Wooster mapped the BRCA2 gene by linkage analysis on chromosome 13.[6] The BRCA2 gene, like BRCA1, in its altered form, is responsible for 45–61% of breast and 11–20% of ovarian cancers; however, typically with onset at later ages.

The discovery of the BRCA1 and BRCA2 genes launched the field to start routine genetic testing for cancer susceptibility and gave way to current-day, multi-gene cancer panel testing over the last 26 years.[7] Multi-gene panel testing allows a patient to have multiple genes analyzed from one blood or saliva sample. This type of panel testing is the direct result of the major advancements in genetic testing technology, primarily next-generation sequencing (NGS). NGS is high throughput technology that reads massive parallel sequencing and can generate whole exome or genome results at a much lower cost than prior testing. Most recently, in the early 2000s, RNA analysis was added to multi-gene panel analysis proving an increase in the detection of pathogenic variants in a variety of genes that were not previously detectable with DNA testing alone.[8,9] In some cases, RNA analysis has been helpful to reclassify variants of uncertain significance (VUS), which are genetic variants undetermined to be benign or pathogenic. Although the addition of RNA testing is thought to detect only a small percentage of missed variants, these novel findings have had a significant impact on patient care.[10]

TESTING CRITERIA

The National Comprehensive Cancer Network (NCCN) guidelines are a comprehensive set of guidelines and management strategies created from an alliance of 32 cancer centers in the United States. These guidelines are updated yearly according to the current literature and are most referenced to assist with cancer genetic testing and management for hereditary breast, ovarian, colon, pancreatic, prostate, and kidney cancers. Individuals can meet the outlined criteria for cancer genetic testing in several ways, including: enough of the same or related cancers in the family, rare cancers related to genetic causes, cancers diagnosed at a young age, or a known pathogenic or likely pathogenic variant in the family. As the field of cancer genetics expands due to scientific advancement and better testing technology so does the criteria for being considered for cancer genetic testing.

These NCCN testing guidelines continue to routinely lengthen and have resulted in an elaborate list for healthcare practitioners to reference to understand if their patients may benefit from cancer genetic testing. Although most insurance companies use these guidelines to determine genetic

testing coverage, this is not the case for all policies.[11] Some companies have their own guidelines while others place a testing limit on the number of hereditary cancer genes they will cover.[12.] On the laboratory side, the restrictions are currently far fewer, with many allowing the inclusion of additional genes without an increase in cost. Because testing and insurance requirements are transient, patients should be counseled to update their practitioner as to any changes to their personal and/or cancer family history since they may qualify for testing or have access to test coverage that they may not have had previously. Additionally, aside from genetic testing, for the unaffected patient national guidelines also recommend risk calculations to determine breast and other cancer susceptibility percentages, which is often based on cancer family history. These cancer-risk estimates help guide providers in counseling their patients regarding appropriate screenings (i.e., younger and/or more frequent colonoscopy) and risk-reducing measures such as the use of aromatase inhibitors for breast-cancer risk reduction.

It is important to note that for patients who meet NCCN's hereditary breast and ovarian cancer testing guidelines, it is no longer standard of care to only analyze the BRCA1 and BRCA2 genes alone. National guidelines now recommend routine clinical testing that includes the analysis of multiple high penetrant genes such as, BRCA1, BRCA2, CDH1, PALB2, PTEN, and TP53, as well as moderate-risk genes related to an increased risk of breast and other cancers. At this time, due to the rapid growth of this field with the desire for testing laboratories to gain knowledge, the number of genes analyzed on panel testing typically does not impact the test cost. However, it remains unclear if or how this may change in the future.

GENETIC CONSULTATION–SERVICE DELIVERY MODELS

The typical cancer genetic counseling model involves pre-test counseling, results disclosure, and post-test counseling. Pre-test counseling occurs before a test is ordered. During this meeting, genetic counselors develop rapport and trust with patients. They may discuss many topics, including but not limited to, how the patient does or does not meet testing criteria, the possible cost of appropriate testing, the benefits and limitations of testing, how the test results could impact the patient as well as their family members, and the applicable testing options. Cancer genetic specialists will answer patient questions and review how test results may affect their current medical management regimen as related to cancer risk. A detailed personal and family history will occur, which is critical to ensure that the most appropriate testing is ordered.[12] Discussion about the different types of test result outcomes and, if applicable, the possibility of genetic discrimination will also take place during the pre-test counseling session. Testing options are finalized and through shared decision-making the best testing modality is facilitated.

Results and post-test counseling vary significantly depending on the outcome of the test. A positive result will lead to a discussion regarding cancer risks, screening implications, inheritance patterns, testing recommendations for family members, and referrals to subspecialists if applicable. Positive results often breed empowerment; however, at times can have psychosocial effects that warrant management through appropriate supportive care resources.[12] Genetic counselors often provide patients with a family letter detailing the results as well as addressing testing and clinical implications for family members. Coordinating cascade testing for at-risk relatives is an additional and important role that genetic counselors take on for their patients.[12] Understanding if relatives carry the family mutation can aid in early cancer detection and prevention, as well as provide relief for those identified not to have inherited the family pathogenetic variant. In the event of a negative result, the patient and genetic counselor review the limitations of the test, the clinical and testing implications for the patient and their family members, as well as the patient's feelings about the outcome. Instructed by medical guidelines, genetic counselors also may provide cancer-risk assessments, even in the setting of a negative genetic test, that can result in additional cancer screenings (i.e., breast MRI, colonoscopy) that may detect cancers earlier or prevent them altogether. The last possible result type is a variant of uncertain significance (VUS), which triggers a discussion between the patient and their practitioners about the uncertainty as it relates to a possible increased risk of cancer and the possibility of reclassification. Fortunately, because these uncertain results are commonly reclassified as harmless, changes to medical management are generally not recommended.

The time necessary for traditional face-to-face genetic counseling in oncology has been challenged by the persistent rise in the demand for these services while having a limited number of trained genetic professionals.[13] These challenges preceded major genetic advancement in diagnostic testing and treatment, further broadening the need for counseling and increasing the difficulty of accommodating all of those who now qualify for testing. As a result, different methods of service delivery have been adopted in efforts to expand genetic counseling services in oncology which include telehealth, educational videos, counseling using artificial intelligence (AI) technology, as well as the expansion of genetic provider type.[14] One silver lining of the recent COVID-19 pandemic is that it has accelerated the application of telemedicine in the field of genetic counseling. This built upon previous limited examinations of cancer genetic telemedicine services which had already proven to be a viable and non-inferior strategy as compared to traditional counseling methods.[15] AI genetic counseling and the training of non-genetic professionals (i.e., navigators, nurse practitioners)

have also generated positive responses regarding their integration into the education of high-risk cancer patients; however, this continues to be closely studied.[16] With the implementation of novel genetic counseling service delivery methods obstacles also naturally developed that include changes in clinical workflow, insurance reimbursement, and language translation, which are calling for attention.[14] These barriers are being examined in efforts to increase the effectiveness of these new patient education strategies and have exposed the growing need for a transdisciplinary approach to cancer counseling during this era of precision oncology.

Finally, we would be remiss not to mention the direct-to-consumer (DTC) marketing of DNA sequence-based cancer testing, given its popularity in the mainstream population. Importantly, DTC testing is not a replacement for comprehensive, clinically approved, germline genetic testing. These tests do not fully sequence the genes being tested, have a false positive rate of approximately 40%, and vary widely in the information provided and in the accuracy of their interpretations.[17]

INSURANCE

The genetic testing cost for individuals meeting the established national testing criteria is commonly fully covered by commercial insurance carriers if the required procedures are followed. Even without insurance coverage, testing companies have made great strides in making testing more affordable with most laboratories offering an out-of-pocket cost of approximately $250 for large, multi-gene cancer panel testing that includes both DNA and RNA analysis.

During pre-test counseling, before the patient's test is ordered, there is often a discussion about the Genetic Information Non-discrimination Act (GINA). This is a federal law that became active in 2008 and protects individuals from being discriminated against based on their genetic test results by their health insurance carrier and employer. However, this law does not address protection as it relates to other forms of insurance, such as life, long-term care, and disability, as well as for those who are in the military. It is possible that for individuals who receive a positive genetic test result, adjusting or adding one of these policies could be more expensive or they may be denied coverage. For this reason, it is discussed during the pre-test genetic counseling process when patients can choose to delay testing until they are able to update or obtain the desired life or long-term care policy. This is especially relevant for young patients who have never had a cancer diagnosis since they often have not yet considered life insurance enrollment and are commonly without a serious existing or preexisting medical condition.

Lastly, the military are not protected under GINA. The intent was to prevent susceptible individuals from injury or disease exacerbation in the line of duty. Patients' sensitive genetic information can also be accessed when determining military promotion. Although these practices were put in place to develop a strong military force, the downstream consequences can be psychologically and emotionally catastrophic.

DIVERSITY/EQUITY/INCLUSION

The NSGC Professional status survey (PSS) has sought to understand the demographic composition of the field of genetic counseling throughout the years. Their survey over the last 40 years demonstrated the static landscape of the profession, which mainly consists of Caucasian women under the age of 40.[18] Recognizing this lack of diversity in race, gender, and age is the first step toward changing the discourse and understanding the biases within the field of genetic counseling. There is a substantial amount of scientific evidence that supports diversifying the healthcare field, including the field of genetic counseling, as this will lead to increased access to care, improved patient-provider relationships, greater patient choice, and satisfaction, and ultimately improve the educational experience of the healthcare workforce.

Genetic counseling and the services provided are significantly intertwined with extremely sensitive issues surrounding social and ethical implications as they relate to advances in these fields. Many population groups are skeptical of genetic services due to past harm from the medical community. The community of genetic counselors recognizes the importance of diversity, equity, and inclusion and has taken an active role in confronting the lack of diversity. Specifically, many institutions have sought out community organizers and experts to help provide education and guidance to understand the cultures of the communities they serve.[18]

LOOKING TO THE FUTURE

Genetic testing today is commonly performed using germline DNA testing and, due to the rapid expansion of novel genes included in routine testing, the identification of VUS is high (2–44%).[19] Although not routinely performed by all cancer genetic testing laboratories, the addition of RNA analysis is providing the ability to identify intronic variants and classify putative splicing variants not possible with DNA testing alone.

Karam et al demonstrated that RNA genetic testing has great promise in decreasing the number of VUS classifications. Their study showed that RNA testing as an adjunct to DNA analysis clarified 88% of inconclusive results. Although there is promise that RNA testing may be added to routine cancer panel testing in the future, this is currently not the case due to technical limitations within testing laboratories as well as other logistical challenges such as sample collection.[19]

CONCLUSION

Genetic counseling is a relatively young field that has had significant implications on understanding cancer genomics, screening, and familial inheritance patterns. The technological advances have allowed us to identify more high and moderately penetrant cancer susceptibility genes, which have translated to the earlier detection and prevention of cancer, testing strategies, guidelines, and recommendations are changing rapidly to align with this quickly advancing field and present new challenges for the healthcare community. The next 40–50 years will likely prove to have many more advances and developments that will allow us to better care for individuals despite their race, ethnicity, age, gender, or creed.[20]

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Conflicts of Interest

The authors report no conflicts of interest.

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Hereditary Cancer Genes and Related Risks

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KEYWORDS: hereditary cancer, cancer syndromes, Lynch syndrome, clinical features

INTRODUCTION

The recent explosion of knowledge in the field of cancer genetics dates to 1961 when Henry Lynch described an autosomal dominant pattern of gastrointestinal and gynecological cancers in two large families, coining the condition as "Lynch syndrome" as we know it today. Lynch syndrome affects 1 in 279 individuals, representing the most common cause of hereditary colorectal cancer.[1] It then took another 30 years for the discovery of the two, now well-known genes responsible for the majority of inherited breast and ovarian cancers named BRCA1 and BRCA2. Hundreds of ancient pathogenic variants have been discovered to alter BRCA1/2, which have been established to grossly increase cancer risks and cause the familiar condition known as Hereditary Breast and Ovarian Cancer Syndrome (HBOC). Over the last three decades, there has been an exponential growth of knowledge in how genetics can lead to cancer development, and more recently how genetics can help inform specific treatment for a cancer patient. It began with common cancers striking younger patients with strong cancer family histories, which allowed genetic mapping to identify candidate genes and the establishment of what are now well-known cancer syndromes (i.e., Lynch syndrome, HBOC, Li-Fraumeni). Early genetics work led to the identification of genes associated with hereditary cancer conditions such as Cowden Syndrome, Peutz-Jeghers syndrome, and Hereditary Diffuse Gastric Cancer, among others. Over the past 15 years, we have continued to discover more about cancer genetics and have identified other high and moderate risk genes, such as PALB2, ATM, CHEK2, BRIP1, RAD51C, RAD51D, and BARD1. Our understanding of the early discovered tumor suppressor genes such as BRCA1 and BRCA2 has evolved over time, with risk predictions and disease management being constantly refined as our understanding deepens. The National Comprehensive Cancer Network (NCCN) guidelines have come to reflect this changing landscape of cancer care with recent editions more closely tailoring management based on genetic profile.[2]

The rapidly evolving nature of cancer genetics makes writing a comprehensive review elusive because as data is reported, new research is constantly refining what is known. Therefore, the purpose of this article is to highlight well-established genetic cancer syndromes as well as novel hereditary oncology genes, to review the associated cancer risks, and to emphasize the field's rapid evolution. It should be noted that because the terms "pathogenic" and "likely pathogenic" are clinically interchangeable, for brevity, only the term pathogenic is used throughout this overview.

LYNCH SYNDROME

Some of the most well-established tumor suppressor genes result in a condition called Lynch syndrome when pathogenic variants are present. Also known as hereditary nonpolyposis colorectal cancer (HNPCC), Lynch syndrome is inherited in an autosomal dominant fashion, and therefore commonly evident in each family generation. This hereditary condition is caused by the inheritance of a germline pathogenic variant in one of five mismatch repair genes, MLH1, MSH2, MSH6, PMS2, or less commonly an EPCAM variant which silences MSH2.[1] These pathogenic variants result in increased cancer risks of various types.[3,4] Initially, our understanding of this condition was limited such that medical management recommendations were identical regardless of the altered mismatch repair gene. Continual research over the past decades, with an even greater focus over the past 10 years, helped clarify the unique cancer risks associated with each Lynch syndrome gene. Depending on the gene, the cancer risks can include colorectal (10% to 61%), endometrial (13% to 57%), ovarian (general population to 38%), gastric (general population to 9%), small bowel (general population to 11%), hepatobiliary (general population to 4%), renal pelvis and/or ureter (general population to 28%), pancreatic (general population to 6%), and central nervous system (general population to possibly as high as 7.7%).[5–9] These wide risk ranges are reflective of the varying levels of cancer risk among the five mismatch repair genes. Following the discovery of MSH2 in 1993, cancer risks were initially reported to be the same among Lynch syndrome genes. However, over time it was discovered that each mismatch repair gene results in unique cancer risks or degree of risk. For example, MLH1 carries a colon cancer risk that is

three times that of PMS2[10,11] and as a result of the increased risk of ovarian cancer in MLH1 carriers there are clinical recommendations for prophylactic ovary removal while the evidence remains insufficient in those who carry variants within MSH6 and PMS2.[2,5–9] Fortunately, due to the specific genotype-phenotype relationship among Lynch syndrome genes, medical management recommendations are tailored to each Lynch gene, preventing unnecessary medications, screenings, and surgeries.[2]

Although rare, these genes are also associated with an autosomal recessive conditional known as constitutional mismatch repair deficiency (CMMRD). Biallelic pathogenic variants in MLH1, MSH2, MSH6, or PMS2 cause this childhood cancer predisposition syndrome. Colorectal cancer and cancer of the small intestine have been seen in individuals with this condition prior to age 20 and cutaneous findings are like that seen in individuals with neurofibromatosis type I (café au lait macules). Counseling regarding CMMRD is part of the informed consent process, especially for those who are of reproductive age having a partner with a cancer history suspicious for HNPCC.

HEREDITARY BREAST AND OVARIAN CANCER SYNDROME (HBOCS)

HBOCS is also relatively common and caused by well-established tumor suppressor genes, BRCA1 and BRCA2, which were discovered in 1994 and 1995, respectively. Although reported rates vary, breast cancer risk by age 80 for BRCA1 carriers is estimated to be 72% and 69% for BRCA2 carriers in a 2017 cohort study.[12] Additionally, the same study found the risk of contralateral breast cancer to be approximately 40% for BRCA1 carriers and 26% for BRCA2 carriers.[12] Interestingly, the probability of developing cancer varies within each individual BRCA1/BRCA2 carrier (even within the same family) which is likely attributable to other yet to be identified factors including epigenetic modification or environmental factors that are influencing cancer penetrance. Breast cancer risk has also been discovered to be influenced by polygenic risk scores (PRS), which are a collection of single nucleotide polymorphisms (relatively common genetic variants) that together serve to either increase or decrease risk. Individually, these genetic variants have little impact. However, collectively, the impact may someday be determined large enough to alter medical management recommendations. Current research is also investigating how PRS may modify cancer risks, even within those already found to carry an altered cancer predisposition gene such as BRCA1, BRCA2 or CHEK2.[13] Although identified as the BReast CAncer (BRCA) gene by name, pathogenic BRCA1 and BRCA2 variants are known to increase the risk of additional cancers including ovarian (also fallopian tube and peritoneal cancers) prostate, pancreatic, and cutaneous melanoma. Approximately 48% of BRCA1 and 20% of BRCA2 female carriers will develop ovarian cancer by age 70.[14] BRCA1 and BRCA2 male carriers have an estimated 29% and 60% lifetime risk of prostate cancer, respectively.[15] Patients diagnosed with pancreatic cancer are more likely than the general population(1.6%) to have a pathogenic variant in BRCA1 (11%) and BRCA2 (17%).[16,17] BRCA2 may have a link in patients with cutaneous melanoma although studies have produced conflicting results.[18]

Pathogenic variants in BRCA2 gene in their recessive form have important reproductive implications as well. In addition to the gene's association with autosomal dominant HBOCS, this gene is also linked to autosomal recessive Fanconi anemia.[19] Far less common, but still reported, Fanconi anemia is also connected to pathogenic variants in the BRCA1 gene.[20]

Different types of autosomal recessive Fanconi anemia are linked to other hereditary cancer genes; however, the type associated with biallelic pathogenic BRCA2 variants, Fanconi anemia type D (FANCD1), is particularly severe in comparison. Characteristics include bone marrow failure, short stature, abnormal skin pigmentation, developmental abnormalities in multiple organ systems, and early-onset cancers (acute leukemia and solid tumors). The cumulative probability for malignancy is estimated to be up to 97% by age 6.[19,21-24] Therefore, discussions with a mutation carrier of reproductive age include the option of testing his/her partner to clarify their future children's risk of Fanconi anemia.

COWDEN SYNDROME

This is a rare autosomal dominant disorder with an incidence of approximately 1 in 200,000 resulting from germline variants in the PTEN gene.[25] It is notably associated with hamartomas,[26] along with a higher incidence of breast cancer (60%),[27] thyroid disease (30–68%),[28,29] thyroid cancer (3–10%),[26] and other malignant and nonmalignant features. One study found the cumulative lifetime risk of any type of cancer in patients diagnosed with Cowden syndrome was 85% overall, with females found to have an increased cancer risk compared with males.[30]

LI-FRAUMENI SYNDROME (LFS)

LFS is another well studied but rare genetic cancer syndrome and is caused with a germline pathogenic variant in the TP53 gene.[31] This cancer syndrome is generally associated with a devastating lifetime cancer risk of essentially 100% and often strikes at a young age.[32] The breadth of associated cancer risk spans from soft tissue sarcomas, breast cancer, colon cancer, adrenocortical carcinoma, brain tumors,[33] gastric cancer,[34] acute lymphoblastic leukemia,[35] and possibly melanoma.[36] Red flags for this condition include breast cancer diagnosed prior to the age of 31, a diagnosis or family history of LF associated tumors before age 45, or pediatric

acute lymphoblastic leukemia.[37] Interestingly, large panel testing is uncovering families who do not fit this expected phenotype, highlighting the value in multi-gene panel testing as well as ongoing research of what are thought to be rare cancer syndromes.

PALB2

Similar to BRCA1/2 genes, PALB2 is considered a high-risk gene in its association with hereditary breast cancer. It was originally identified as a BRCA2-interacting protein critical for BRCA2 function and subsequently discovered to encode proteins involved in BRCA1 and RAD51 pathways. It is a partner and localizer of BRCA2, and deleterious PALB2 variants increase similar cancer risks.[38] Inherited in an autosomal dominant fashion, loss of function variants are associated with an approximate 35% increased risk of breast cancer by the age of 70 compared to women without a pathogenic variant in this gene.[38] There is strong evidence that pathogenic PALB2 variants are also associated with a small increased lifetime risk of ovarian cancer (up to 5%) as well as pancreatic cancer (5–10%).[39] There is also emerging evidence for the increased risk of male breast, prostate, and possibly colorectal cancer.[40] However, more research is needed. Pathogenic variants in the PALB2 gene are also associated with autosomal recessive Fanconi anemia type N (FANCN), giving it the same reproductive considerations as BRCA1 and BRCA2 carriers.[38]

ATM

Research shows pathogenic ATM variants are associated with moderately increased risk for the development of breast cancer in women. A meta-analysis suggests the lifetime risk for breast cancer by age 80 in those with pathogenic ATM variants is 33%.[41] Pancreatic cancer risk is also increased in ATM carrier to a lifetime risk of approximately 5% to 10% compared to the 1.6% general population risk.[42] Lastly, studies connect this gene with an elevated risk of ovarian cancer (2–3%); however, in comparison, this is much lower than the 20–48% risk associated with pathogenic variants found in BRCA1 and BRCA2.[43]

ATM variants can result in the development of autosomal recessive ataxia telangiectasia, which is typically identified in early childhood with the development of progressive cerebellar ataxia. Ataxia telangiectasia is also associated with oculomotor apraxia, telangiectasias of the conjunctiva, and frequent illness due to immunodeficiency. Childhood leukemia and lymphoma are the most common malignancies.[44]

CHEK2

Inherited in an autosomal dominant fashion, pathogenic variants in the cell cycle checkpoint kinase 2 (CHEK2) gene have a cumulative lifetime risk for breast cancer estimated to range from 28% to 37%, categorizing it as another moderate risk gene.[43,45] Although the risks remain unclear, studies have shown CHEK2's possible connection with colon, thyroid, and prostate cancers, among others.[46,47]

BRIP1

Pathogenic variants in this gene have a clear association with autosomal dominant risk for ovarian cancer and type J autosomal recessive Fanconi anemia (FANCJ).[48] Breast cancer risk has been suggested, but not supported by subsequent research. The lifetime risk for developing ovarian cancer by age 80 is estimated to be 5% to 10%.[49]

RAD51C/RAD51D

These genes are involved in homologous recombination and DNA repair. Pathogenic variants in RAD51C and RAD51D were initially identified as causing an increased risk for ovarian cancer, which is estimated to be 10–15% and 10–20% respectively. More recent studies have shown a strong association with an increased lifetime risk of female breast cancer (20–40%) changing breast screening recommendations.[50] RAD51C also has reproductive implications given its association with type O autosomal recessive Fanconi anemia (FANCO).[51]

BARD1

Pathogenic variants in the BRCA1-associated RING domain 1 (BARD1) gene are known to be associated with an increased risk of breast cancer. The risks were recently refined to 20–40%.[52]

CONCLUSION

We acknowledge this review does not include descriptions of all hereditary cancer syndromes and genes. Therefore, a more exhaustive list is summarized in **Table 1,** which includes inherited cancer genes associated with hereditary colorectal polyposis (APC, MUTYH, and others) as well as genes related to rare inherited cancer syndromes such as Hereditary Diffuse Gastric Cancer Syndrome (CDH1), Birt-Hogg-Dube Syndrome (FLCN), and Von Hippel-Lindau Syndrome (VHL).

The progression of knowledge surrounding hereditary cancer syndromes continues to change our understanding of cancer risk for all those affected. As a result, there are positive influences on clinical management. Through genetic awareness and targeted screening cancers can be diagnosed earlier, intervened on, and even prevented.[53] As cancer genetic testing becomes more common due to increased media and medical attention, as well as from the rapid

Table 1. Hereditary Cancer Syndromes

Gene	Disorder	MOI	Associated Cancers/Clinical Features
MLH1, MSH2, MSH6, PMS2, EPCAM	Lynch syndrome	AD	**Cancers:** CRC, endometrial, ovarian, gastric, renal pelvis and/or ureter, bladder, small bowel, pancreas, biliary tract, CNS, skin
APC	Familial adenomatous polyposis (FAP) Attenuated-FAP (AFAP)	AD	**Clinical Features:** Polyposis **Cancers:** CRC, small intestine, stomach, hepatoblastoma, pancreatic, thyroid, brain Other manifestations (FAP only): desmoid tumors, osteomas, CHRPE
MUTYH	Polyposis syndrome	AR	**Clinical Features:** Colorectal and extracolonic polyps **Cancers:** CRC, duodenal
AXIN2, BMPR1A, GREM1, POLE, POLD1	Polyposis syndromes	AD	**Clinical Features:** polyposis **Cancers:** CRC
NTHL1	Polyposis syndrome	AR	**Clinical Features:** polyposis **Cancers:** CRC
BRCA1, BRCA2	HBOC	AD	**Cancers:** Breast, ovarian, pancreatic, prostate, melanoma
TP53	Li Fraumeni syndrome	AD	**Cancers:** premenopausal breast, soft-tissue sarcoma, osteosarcoma, CNS tumor, adrenocortical carcinoma
PTEN	Cowden syndrome		**Clinical features:** macrocephaly, thyroid lesions, hamartomatous polyps, lipomas, cutaneous lesions **Cancers:** breast, endometrial, thyroid, renal
CDH1	HDGC	AD	**Cancers**: diffuse gastric, lobular breast
PALB2	HBOC	AD	**Cancers**: breast, ovarian, pancreatic
ATM	HBOC	AD	**Cancers**: breast, ovarian, pancreatic
CHEK2	Hereditary breast	AD	**Cancers:** breast, colon
BRIP1	Hereditary ovarian	AD	**Cancers:** ovarian
RAD51C	HBOC	AD	**Cancers**: breast, ovarian
RAD51D	HBOC	AD	**Cancers**: breast, ovarian
BARD1	Hereditary breast	AD	**Cancers:** breast
FLCN	Birt-Hogg-Dube	AD	**Clinical features:** lung cysts, pneumothorax, renal tumors, skin lesions (fibrofolliculomas/trichodiscomas) **Cancers**: renal
MEN1	MEN1	AD	**Clinical features:** endocrine tumors
RET	MEN2	AD	**Cancers:** medullary thyroid
SDHx	PGL/PCC	AD	**Clinical features:** paraganglioma, pheochromocytoma
VHL	von Hippel-Lindau syndrome		**Clinical features:** hemangioblastoma, pheochromocytoma, renal cysts, pancreatic cysts, endolymphatic sac tumors. **Cancers**: renal

MOI: Mode of Inheritance; AD: autosomal dominant; AR: autosomal recessive; CRC:colorectal cancer; CNC:central nervous system; GI: gastrointestinal; HBOC: Hereditary breast and ovarian cancer syndrome; HDGC: Hereditary Diffuse Gastric Cancer; MEN1; Multiple Endocrine Neoplasia type 1; MEN2: Multiple Endocrine Neoplasia type 2; PGL/PCC: Hereditary paraganglioma-pheochromocytoma syndrome

influx of direct-to-consumer genetic testing, the greater the demand on healthcare practitioners to increase their knowledge and resources to access genetic services. Although access to updated national guidelines greatly assist practitioners in understanding who is at risk for an inherited cancer syndrome and how to manage those testing positive, the interpretation and management are nuanced and complex. Therefore, additional methods of service delivery for pre-test education continue to be investigated to accommodate the increasing number of individuals qualifying for genetic testing with the small number of trained professionals available. As this gap widens it becomes more important to stay current in this rapidly advancing field to fulfill the duty of best clinical care and to address practice limitations with education, available resources, and patient referral if deemed necessary.

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Management of Cancer Genetic Testing: A Brief Overview

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KEYWORDS: cancer genetic testing, variant of uncertain significance, familial risk, preliminary risk gene

GENETIC TESTING

Genetic testing has taken a prominent role in the workup of new cancer diagnoses as well as the management of individuals unaffected by cancer with and without cancer family history. Hereditary genetic testing in oncology is equally applicable to both males and females and is a catalyst for the development of many cancer types including, breast, ovarian, endometrial, colon, pancreatic and prostate cancers. As female breast cancer represents the most common cancer subtype in the US, representing 15% of all new cancer diagnoses, and has one of the largest bodies of genetic research to date, beginning with the discovery of BRCA1 and BRCA2 in 1994, this cancer will be the primary focus of this review.[1,2] Studies have estimated that as many as 1 in 4 women with breast cancer undergo genetic testing.[3] Additionally, genetic testing panels have expanded dramatically in recent years to include as many as 100 genes that predispose patients to breast, ovarian, colon, gastric, pancreatic, skin, and other cancers. Patients can now undergo genetic testing simply by mailing salivary samples from the comfort of their home and be provided with a wide array of information about their genomic risk profile. With the increased utilization of genetic testing as well as the increased knowledge our patients have about the role of genetic testing, providers must familiarize themselves with genetic testing as well as the potential results to determine the best methods of monitoring and screening patients in the future. Genetic counselors play a vital role defining the appropriateness as well as the potential risks and benefits of genetic testing.

Several guidelines have been constructed by various nationally accredited organizations to assist providers in identifying patients for whom genetic testing is appropriate based on identified patient-specific breast cancer risk factors (i.e., the National Comprehensive Cancer Network (NCCN), the American College of Medical Genetics and Genomics, the National Society of Genetic Counselors, the American Society of Clinical Oncology, the American Society of Breast Surgeons). Broadly speaking, the goal of genetic testing is to determine whether an individual harbors a pathogenic variant (mutation) that might predispose him/her/them to an increased risk of a future malignancy. For example, in patients with breast cancer undergoing genetic testing, a pathogenic variant ("positive" result) is identified in approximately 3–10% of patients.[3-5] If a pathogenic variant is not present and the results indicate only benign findings this is defined as a negative result. While the rate of overall pathogenic variants does not differ between individuals of different races, racial/ethnic differences do exist between specific pathogenic variants.[6,7] There also exists a third category of genetic testing results called a variant of unknown significance (VUS). These represent variations in genetic sequencing for which the association with disease risk is not yet well characterized, and, at this time, the vast majority of VUS do not change management for a patient with respect to high-risk screening or preventative surgeries.[8]

GENETIC TESTING IN HIGH-RISK INDIVIDUALS

In accordance with national guidelines, many individuals without a breast cancer diagnosis also meet the criteria for genetic testing which is based on family history and/or other patient risk factors. For example, in patients with a significant family history of breast, ovarian, pancreatic, or colon cancer, it may not always be possible to test affected relatives. For these individuals, genetic testing may still be warranted, and a referral to a genetic professional can be helpful in achieving informed consent. Importantly, a patient may still be deemed at increased breast cancer risk, even in the setting of negative cancer genetic testing. As guided by national recommendation, this lifetime risk can be calculated by incorporating cancer family history, negative genetic test results and other personal risk factors using risk assessment tools such as the Tyrer-Cuzick Risk Calculator and the Gail Model.[9-12] These lifetime breast cancer risk estimates are then used to guide increased surveillance and risk-reducing strategies for breast cancer risk reduction and prevention.[1] The Tyrer-Cuzick risk calculator utilizes various personal, reproductive, and family history characteristics, as well as the patient's probability to harbor a genetic predisposition (if not yet tested) to calculate lifetime breast cancer risk.[9,10] Patients with a lifetime risk >20% qualify for high-risk breast imaging consisting of 6-month staggered mammograms with MRI of the breast.[13] The Gail Model

utilizes similar patient characteristics to calculate both an overall relative risk and a 5-year risk of developing breast cancer to determine the possible use of medication for breast cancer risk reduction.[12] Per NCCN guidelines, patients with a 5-year Gail Model risk >1.7% qualify for consideration of chemoprevention (such as Tamoxifen or Raloxifene), while the American Society of Clinical Oncology (ASCO) recommends consideration of chemoprevention for patients having a 5-year risk of >3%.[14,15] Both models calculate a patient's risk and compares this to the risk of a patient of similar age within the general population. Based on these results patients can be further stratified for increased screening, additional testing, and/or other prophylactic interventions. Additionally, these risk models are often used by insurance companies to determine coverage for these screenings and additional interventions.

NEGATIVE GENETIC TESTING RESULTS

Patients with prior negative genetic testing results may still require further evaluation as ongoing genetic research has identified several novel malignancy-associated genes. It is recommended that all providers consider the role of genetic testing in patients with any newly diagnosed malignancy. For example, patients and families with individuals who were diagnosed with breast cancer prior to 2014 and previously underwent genetic testing with no pathogenic variant identified should consider further evaluation since prior to 2014, high risk genes such as PALB2 and other high and moderate cancer genes were not yet discovered. Additionally, testing also applies to patients with prior negative BRCA1/2 only germline testing, or gene-limited testing. Today there are approximately 23 genes that are associated with an increased breast and ovary risk that are routinely tested and may help to explain a patient's personal or family history that were not available to test in the past.[16,17] Additionally, newer gene-testing techniques such as BRCAnalysis Rearrangement Testing (BART) and RNA analysis also may not have been available at the time a patient previously completed testing, and these advances in technology have been demonstrated to identify other clinically relevant genomic variants that previously could not have been identified.

Additionally, in individuals with current or previous negative genetic testing, it may still be beneficial to test other family members in addition to the patient as negative genetic testing in one individual does not preclude other family members from having genetic mutations as some mutations are *de novo* or may run in the family without having been passed to the patient undergoing testing. It is important that both providers and patients recognize that negative genetic testing results do not mean that an individual will never develop cancer; they simply mean that the patient does not carry the genetic variants tested and, to the best of our knowledge, they are not predisposing them to an increased risk of cancer. However, patients may still have an elevated cancer risk based on personal and/or family history which can be further elucidated through discussions with genetics professionals as well as through risk models.

VARIANTS OF UNKNOWN SIGNIFICANCE

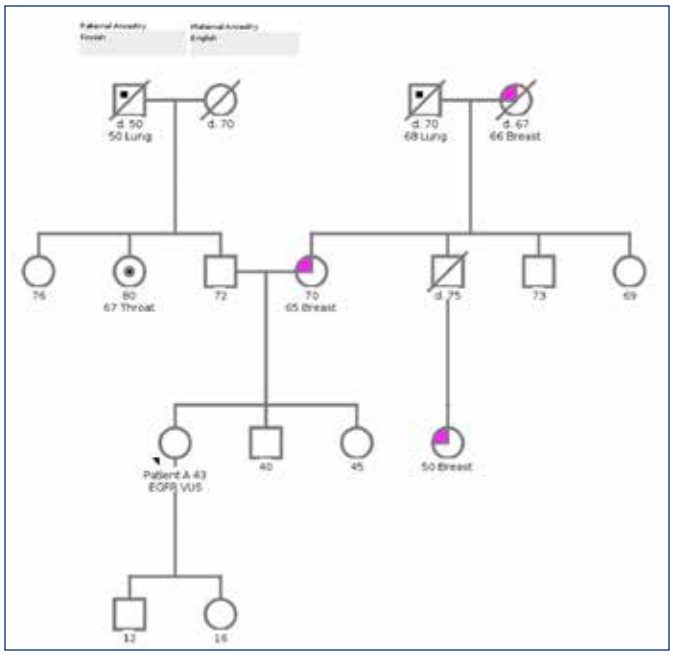
VUS results can be a source of anxiety for patients and present clinical challenges for treating providers. For patients, the knowledge that they harbor a genetic variant, for which the risk of associated malignancy has not yet been defined, can make it difficult to provide reassurance or provide confidence that the patient will not need cancer screenings beyond that of the general population. However, even in the presence of a VUS, it remains important to consider a patient's personal risk factors as well as his/her/their family history when estimating lifetime breast cancer risk. For example, individuals found to carry a VUS having an elevated lifetime or 5-year breast cancer risk as calculated by a recommended risk assessment model (i.e., Tyrer-Cuzick or the Gail Model), management should be based only on this familial risk without influence from their VUS result.[17]

CASE EXAMPLES

Case 1

A 43-year-old patient (Patient A) presents to a genetic counselor referred by her OB/GYN because of a family history of breast cancer and dense breast tissue. She is of Northern European descent. Her family history is collected and presented in **Figure 1.**

Figure 1. Patient A's cancer family history and multi-gene panel genetic testing results.



She undergoes a large panel test and is found to be negative for pathogenic mutations but has a variant of unknown significance in the gene EGFR known as c.797C>A. EGFR is a preliminary evidence cancer gene, meaning there is limited or conflicting evidence about the risks associated with the gene at this point. Preliminary evidence genes do not yet have standardized guidelines and may not be included in all panel tests. The genetic counselor reviews that this VUS has not been well characterized; however, it is reported in the publicly available National Center for Biotechnology Information (NCBI) database by other laboratories, which also classify the finding as uncertain. They review that over 90% of variants are reclassified as benign and, as a result, national guidelines instruct that uncertain variants should not be considered clinically actionable.[24] However, as EGFR is preliminary evidence gene for non-small cell lung cancer, the counselor and patient reviewed the family history of lung cancer, which the patient clarified was related to smoking exposure.[25]

The patient and counselor review the family and medical history to assess if a familial risk score needs to be calculated for appropriate follow-up screening recommendations. Based on the patient's breast cancer history, her medical history is collected for the purposes of accurately estimating her familial risk of breast cancer. Information such as age at cancer diagnoses, her negative BRCA carrier status, age of menarche and menopause, breast density, and parity are collected to calculate breast risk using the Tyrer-Cuzick and Gail models.[9-12] Patient A's Tyrer-Cuzick risk was estimated to be 26.37%, which supports increased breast surveillance defined as yearly breast MRI screening in addition to her annual mammogram. The patient's Gail Model risk was estimated to be 1.28% which falls under the recommended threshold for the consideration of chemoprevention medications for breast cancer risk reduction. Further, the genetic counselor discussed the importance of multi-gene cancer panel testing for other maternal family members as well as her siblings because they could harbor a family mutation that she did not inherit, which would impact the cancer risks of these relatives, close family members as well as her own.

Studies have demonstrated that the rate of variants of unknown significance appears to be higher in Non-White individuals, and the probability of finding a variant of unknown significance increases with the number of genes tested in a multi-gene sequencing panel.[7] Within the state of Rhode Island, the 2020 Census estimates 61.6% of the population to be of Caucasian descent, 18.7% of Hispanic descent, and 12.4% of Black ancestry.[18] Historical records also indicate Rhode Island contains a unique admixture of individuals with unique heritages such as Cape Verde and the Azores.[19,20]

With continued genomic sequencing research, genomic VUS are routinely reclassified. A study conducted between 2006–2018 demonstrated that approximately 6.4% of variants holding various classifications including pathogenic, unknown significance, or benign, were reclassified. In this same study, of those variants that were reclassified, only 0.7% were variants initially classified as pathogenic or likely-pathogenic, and only 0.2% were variants initially classified as benign or likely-benign. However, as many as 7.7% of VUS were reclassified, with 80–90% being downgraded to benign or likely-benign and 10–20% being upgraded to pathogenic or likely-pathogenic which seriously impacted patient medical management.[21,22] This further emphasizes the importance of involving genetic professionals in the management of both established and novel genes identified through multi-gene cancer testing. Genetic testing laboratories will typically contact the ordering physician with details of reclassification leaving the burden to patient contact and updated discussion on the provider who originally ordered testing. It is important for practices to have a plan in place for how to go about recontacting patients to discuss reclassifications as they become available before ordering genetic testing. Legally laboratories do not have an obligation to recontact patients with genetic reclassifications, though some may argue ethically they should; however, ethical and legal perspectives agree ordering physicians must play a role in the notification of their patients in this regard.[23]

POSITIVE GENETIC TESTING RESULTS

When a pathogenic genetic variant has been identified demonstrating increased risks of cancer, patients should be managed appropriately, whether this involves prophylactic intervention, medication for risk reduction, or increased screening. It is important that providers familiarize themselves with hereditary cancer genes that are routinely identified on panel analysis as well as the related recommended medical interventions prescribed when a pathogenic or likely- pathogenic (LP) variant is discovered. Likely-pathogenic variants should be treated as pathogenic; they are defined as being variants that the laboratory has over 90% certainty of being pathogenic.[26] According to the 2023 NCCN guideline, **Table 1** provides a broad description of increased screening and surgical options as related to specific cancer genes. These are the most commonly referenced management guidelines for patients carrying a pathogenic or LP variant and, although these guidelines are elaborate, there are areas that require interpretation from a genetic professional for accurate clinical implementation.[27,28] The NCCN's detection, prevention, and risk-reduction guidelines provide comprehensive medical recommendations that are updated yearly based on currently published literature as well as expert opinion and are accessible online without cost (https://www.nccn.org/guidelines/category).

NCCN guidelines are regularly updated with recommendations for specific genes and should be referenced for up

Table 1. Medical Management for Commonly Inherited Cancer Genes

	Mammogram <40	Breast MRI	BSO***	Increased Frequency of Colonoscopy	Pancreatic Screening
ATM			Consider*		Consider*
BARD1					
BRCA1					Consider*
BRCA2					Consider*
BRIP1	Consider*	Consider*			
CDH1					
CDKN2A					
CHEK2					
Lynch Syndrome**			Consider*		Consider*
NF1					
PALB2			Consider*		Consider*
PTEN			Consider*		
RAD51C					
RAD51D					
STK11					
TP53					

Based on the NCCN Version 1.2023: Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines (https://www.nccn.org/guidelines/category_2), this is an abbreviated summary of management recommendations for the most common genes associated with inherited cancer risk.

*Recommendations requiring cancer family history review and genetic professional interpretation

** MSH2, MLH1, MSH6, PMS2, and EPCAM mismatch repair genes

*** Bilateral salpingo-oophorectomy

to date recommendations and risks.[28,29] These guidelines recommend ages at which to begin screening and surgical interventions; however, the starting age is sometimes lowered if younger cancers are present in the family that are thought to be related to the identified family variant.

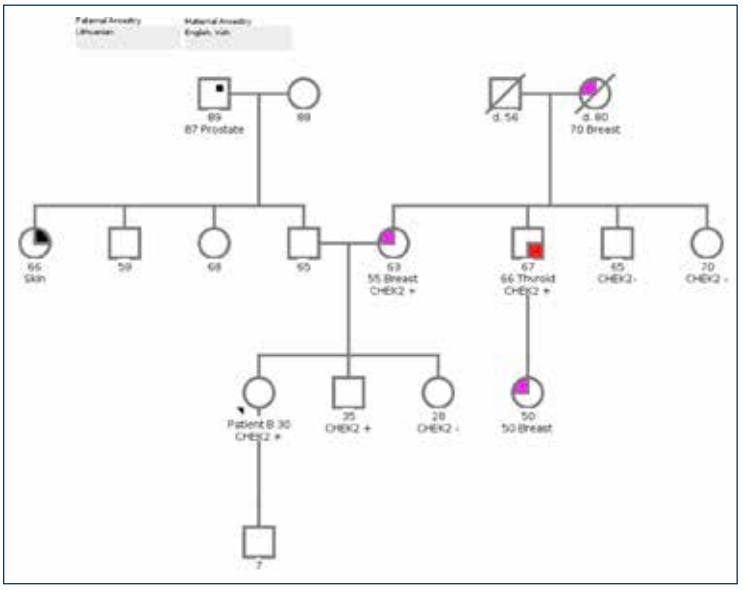
It is important to involve genetics professionals in both the management of established genes and preliminary evidence genes as evidenced by the following case examples.

CASE 2

A 30-year-old patient (Patient B) presents to a genetic counselor referred by her primary care physician because of a family history of breast cancer. She is of Northern and Eastern European descent. Her cancer family history is collected and presented in **Figure 2.**

Patient B underwent cancer genetic counseling and testing and was found to have inherited the pathogenic CHEK2 variant called c.1100delC. This is a well-characterized genetic variant that carries an approximate 40% lifetime risk for the development of female breast and a risk for colon cancer up to 10%.[30-34] As a result, the NCCN Guidelines recommends

Figure 2. Patient B carries a pathogenic CHEK2 variant. The patient's unaffected brother has also inherited the CHEK2 variant however her sister is negative. The patient's mother, diagnosed with breast cancer at age 55, and maternal uncle who was diagnosed with thyroid cancer at age 66, also carry the same CHEK2 variant. This family variant was not passed to the patient's unaffected maternal uncle and aunt.



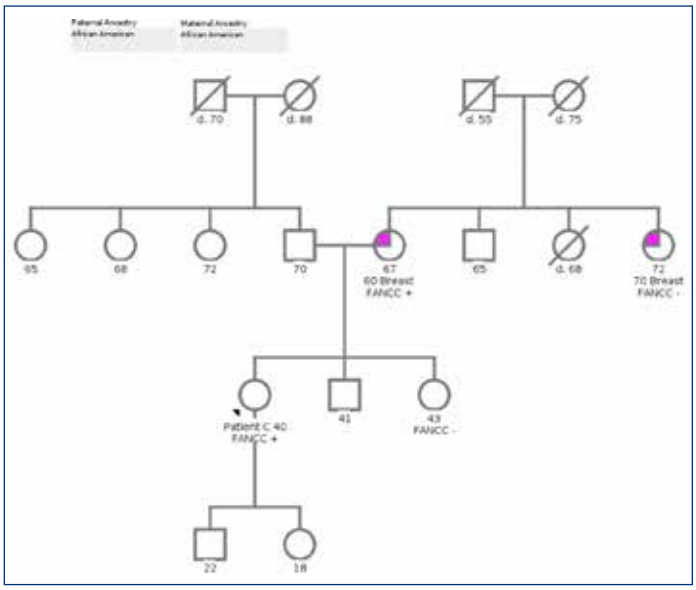
that Patient B consider beginning breast MRI screening, at the age of 30, integrating yearly mammogram at age 40. Additionally, the patient should begin colonoscopy at 40 repeating every 5 years.

The genetic counselor emphasized the importance of family testing due to the autosomal dominant nature of this condition. Therefore, testing a parent was recommended to define from which lineage this variant is traveling. Following her mother's genetic counseling and large panel testing it was discovered that her mother also harbors the family CHEK2 1100delC variant. The patient's uncle who was diagnosed with thyroid cancer was also found CHEK2 positive, and as a result, the counselor discussed with the patient that there is evidence suggesting a change in medical management due to a possible increased risk of papillary thyroid cancer associated with CHEK2 pathogenic variants.[35,36] Therefore, the counselor counseled the patient that evidence and field experts deem it reasonable to her to consider enhanced thyroid screening even in the absence of established guidelines.

CASE 3

A 40-year-old patient (Patient C) presents to a genetic counselor referred by her OB/GYN because of a family history of breast cancer and dense breast tissue discovered on mammography screening. She is of African American descent. Her family history is collected and presented in **Figure 3.**

Figure 3. Patient C's cancer family history and multi-gene cancer test results.



Following cancer genetic counseling and large panel testing, Patient C was found to be positive for the pathogenic variant in the FANCC gene known as c.355_360delTCTCATinsA. This is a protein-truncating variant in a preliminary gene having only early evidence for an increased risk of breast cancer.[37] Although, this variant has been linked to a possible increase in female breast cancer risk,[38] this has not been well documented, and therefore guidelines for increased breast cancer screening have not been established based on a FANCC pathogenic variant alone. The genetic counselor explains the current research and emphasizes the limited evidence. However, as instructed by national guidelines, the genetic counselor proceeds to estimate the patient's lifetime breast cancer risk using the Tyrer-Cuzick model which is high enough to support the addition of yearly breast MRI screening. The implementation of this enhanced breast imaging could potentially diagnose an earlier stage breast cancer ultimately impacting the patient's future health and possibly mortality. The patient was compliant with breast screening recommendations and established a one-year visit in the genetics clinic to discuss updates related to FANCC gene cancer risks and possible medical management changes based on newly acquired evidence.

Take-Away Points
National consensus guidelines (NCCN, ACMGG, NSGC, ASCO, ASBrS) should be utilized by healthcare providers to identify patients qualifying for genetic testing.
Genetic testing results can be positive for a pathogenic variant, negative, or identify a variant of unknown significance.
Patients with prior or current negative genetic test results may benefit from a consultation with a genetic professional to discuss expanded multi-gene panel testing.
Family members may benefit from genetic testing regardless of a relative's negative result since genetic variants are NOT inherited by every family member.
Variants of unknown significance (VUS) are common, (generally) not associated with increased cancer risk and should not change medical management.
Establish a process to recontact patients carrying VUS because important medical management changes may need to be recommended when reclassifications are received by ordering practitioners, at times, years later.
The Tyrer-Cuzick and Gail Models are recommended breast cancer risk assessment tools utilized to determine screenings and/or risk reducing strategies for cancer early detection and prevention.
Genetics professionals play an important role interpreting positive, negative, and uncertain results and patients can be referred at any point during the testing process.

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Conflicts of Interest

The authors report no conflicts of interest.

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Germline vs. Somatic Genetic Testing: Their Increasing Use and Application

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KEYWORDS: genetic testing, germline, somatic, genomic, targeted therapeutics

INTRODUCTION

With the rise of personalized medicine within oncology, genetic testing has become increasingly important. At the time of initial diagnosis, many patients are candidates for upfront evaluation of their germline (inherited) DNA and/or their somatic (tumor) DNA, depending on their cancer type. These results can determine therapy in the adjuvant, maintenance, and recurrent setting. Germline and somatic variants also can have a significant impact on a cancer prognosis, determining additional cancer risks and recommended screening. In addition, this information can help to determine if family members have an elevated risk to develop cancer and if so, management options for early detection or risk reduction.

Prior to the implementation of wide-panel genomic sequencing of tumors, multiple techniques were used to identify oncogenic markers such as immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) which are still commonly used today. In 2013, Foundation Medicine first published validation of their somatic next-generation sequencing assays which demonstrated a high sensitivity of 95-99% as well as a three times higher identification rate of actionable mutations compared to diagnostic tests.[1] The most common tumor specimens analyzed in this study were lung (18%), breast (14%), and cancers of unknown primary (9%). With the introduction of this technology, there has been a rapid increase in the use of somatic genomic sequencing over the past decade.

This article is dedicated to describing the differences between germline and somatic testing and reviewing their applications. Although both testing methods are used within a variety of cancer types, for the purposes of this article, we will focus primarily on their application within gynecologic oncology.

GERMLINE TESTING

An individual's germline DNA is formed by combining half of the mother's DNA from the egg and half of the father's DNA from the sperm. Pathogenic variants (PVs) are passed from parent to offspring and since that variant is present at the time of fertilization, it gets copied into every cell of the body. Many hereditary cancer syndromes follow autosomal dominant inheritance patterns, which translates to a 50% chance for a parent to pass the PV to their offspring.

Germline genetic testing is typically performed on lymphocyte DNA from blood or a combination of lymphocyte and buccal cells from saliva. There are some cases where blood and saliva cannot be used to perform germline testing. For example, DNA extracted from blood or saliva of a patient that has been diagnosed with a hematological cancer may be tumor DNA and therefore not indicative of a germline variant. A blood or saliva sample from patients who have undergone an allogeneic bone marrow transplant would analyze the DNA of the donor rather than the patient. In these cases, a skin punch biopsy with fibroblast culturing is recommended to obtain DNA.[2]

Germline testing is the standard test offered to patients with a personal and/or family history of cancer suggestive of a hereditary cancer predisposition syndrome. Germline PVs account for approximately 5–10% of all cancers. When an inherited PV is identified, it predicts what types of cancers a patient is at risk to develop. The type of cancer risk changes depending on the affected gene because genes are assigned different functions depending on the body part.

In gynecologic oncology, the National Comprehensive Cancer Network's (NCCN) criteria for germline testing for ovarian cancer are less stringent as compared to endometrial cancer. All patients with epithelial ovarian cancers, regardless of age at diagnosis, are recommended to pursue germline testing, whereas patients with endometrial cancers must be diagnosed under age 50, have a synchronous or metachronous Lynch syndrome-related cancer (colorectal, endometrial, gastric, ovarian, pancreatic, urothelial, brain, biliary duct, and small intestine) or have a family history of endometrial cancer.[2,3] Although every year the NCCN's genetic testing criteria broadens to encompass more patients with endometrial cancer, studies such as Levine et al involve an even wider population recommending germline testing for all endometrial cancers regardless of age at diagnosis and family history.[4]

SOMATIC TESTING

Somatic testing is performed on surgical pathology or a cancer tissue biopsy to elucidate the genomic profile of cancer cells (sequencing hundreds of genes) and assess for PVs that can be targeted for treatment. While germline genetic testing identifies PVs that exist within every cell in the body, somatic testing identifies PVs that exist within cancer cells only. The cancer cells may have distinct genetic mutations, new and different from the patient's germline cells, that are responsible for malignant proliferation. The potential for the discovery of additional genetic mutations within the cancer cells beyond which exists in the patient's germline is why this separate testing is recommended. The main questions being asked are: What is the genetic profile of the tumor and how is it different from the genetic profile of the patient's germline or normal tissue? Does one, or both, have a genetic variant that led to the patient's cancer diagnosis and do we have treatments to target it?

The commencement of The Cancer Genome Atlas (TCGA) project in 2006 by the National Cancer Institute and National Human Genome Research Institute deepened our understanding of the molecular characteristics of cancer.[5,6] They developed a genomic database of over 20,000 primary tumors spanning 33 cancer types. Analysis of this data introduced us to new subclassifications within cancer types, as well as revealed important genomic similarities between cancers of different primary organ types. The TCGA project, in addition to the International Cancer Genome Consortium, laid the foundation for subsequent research on the clinical implications of these genomic alterations and their use as targets for novel therapeutics.[7] For an assortment of cancer types, there are a wide array of targeted treatments and immunotherapy, in addition to numerous genomic-based clinical trials that are available to patients depending on their individual tumor genomic profile.

GENETIC TESTING AND TREATMENT

Precision medicine is a growing field utilizing genomic sequencing to therapeutically target patient-specific genomic alterations. Within gynecologic oncology, there is a growing need for targeted therapy and immunotherapy for both initial cancer treatment as well as maintenance therapy. Given these impactful clinical applications, healthcare providers should be aware of when germline and somatic genomic testing is appropriate for their patients.

In February 2022, the American Society of Clinical Oncology (ASCO) published a clinical opinion statement on the indications for somatic genomic testing in patients with metastatic or advanced solid tumor cancer types.[8] This statement supports performing somatic multigene panel genomic sequencing in patients if there is a known biomarker-linked approved therapy for that cancer. For example, the FDA-approved PARP inhibitor, olaparib, is used within germline or somatic BRCA1/2 mutated patients with ovarian, pancreatic, prostate, or HER2-negative breast cancer. The guidelines also recommend multigene panel genomic sequencing in solid tumors to assess microsatellite instability status and tumor mutational burden for the application of the FDA-approved immunotherapy, pembrolizumab. Somatic genomic sequencing for these purposes should be performed at appropriately certified laboratories.[8]

In the setting of recurrent disease, somatic testing is increasingly important with the expanding targeted therapy and immunotherapy applications. Particularly with the introduction of tissue and tumor site-agnostic treatments, such as pembrolizumab, which was the first FDA-approved tumor-agnostic treatment in 2017, multigene panel genomic sequencing can provide options for alternative therapies, especially in successive lines of treatments.[8] Evaluation of a multigene panel genomic sequencing not only evaluates the application of treatments already FDA-approved but also allows for assessment of eligibility for biomarker-selective clinical trials. Utilizing the National Institutes of Health's clinical trial database (http://clinicaltrials.gov) can potentially offer patients a wider scope of treatment options, if not restricted by location, and should be considered in the clinical decision-making process.

GENETIC TESTING AND HEREDITARY CANCER SURVEILLANCE

Somatic testing alone can reveal genetic variants that are suggestive of a germline PV. This should then prompt the need for subsequent germline testing due to its association with additional cancer risks for the patient and their family members.[2,3] A 2019 study of 2,308 patients diagnosed with a variety of tumor types found that 5% of patients had PVs on somatic testing that triggered referral for germline testing.[9] Of the 41% who completed germline testing, 74% had a germline PV identified.[9] The somatic genes found to harbor a PV prompting follow-up germline testing included, but are not limited to, BRCA1/2, PALB2, BRIP1, MSH2/6, and RAD51C/D. When this occurs, the patient should be referred to a genetic counselor/professional for follow-up counseling and germline testing. For example, a physician may order somatic genomic testing for a patient with recurrent metastatic endometrial cancer (not meeting guidelines for somatic testing in the upfront setting) that identifies a PALB2 pathogenic variant. Assuming she did not previously qualify for germline testing based on age or family history, she is now a candidate for blood or saliva testing to assess for the presence or absence of this somatic PALB2 variant. If the PALB2 variant is also identified within her germline this would increase cancer risks for both the patient and her family members who would benefit from additional medical care that could detect cancers earlier or reduce the risk of developing cancer.

Knowing that a patient has a germline PV provides additional treatment options, but it can also identify when high-risk cancer surveillance is necessary. The NCCN provides recommended medical management guidelines for the majority of established hereditary cancer genes/syndromes.[2,3] These guidelines allow providers to offer patients more intense screening such as breast imaging every 6 months (BRCA1/2) or colonoscopy screening every 1–3 years (Lynch syndrome).[2,3] The guidelines also provide the option of risk-reducing surgeries such as removal of the ovaries (i.e. BRCA1/2, BRIP1, RAD51C/D)[2] which has demonstrated a decrease in morbidity and mortality.[10]

Genetic testing not only benefits the patient but also has a meaningful impact on the family. Discovering that a germline PV exists allows for cascade testing to identify relatives who also carry the family PV and, therefore, have an increased risk of cancer. The majority of known hereditary cancer genes travel in an autosomal dominant inheritance pattern. This means that the patient's first-degree blood relatives have a 50% chance of also inheriting the same PV. Once a relative undergoes counseling and testing and is found to carry the known family PV, the respective recommendations for increased screening, and medical or surgical management can be made. Additionally, in most cases, relatives who test negative for an established family PV (true negatives) do not need risk reducing surgeries or high-risk surveillance which can be a relief to that individual.

Cancers arise when two events cause genetic damage which stops the gene from functioning, known as the Two-Hit hypothesis. The two genetic events could be a combination of two random events (sporadic cancers) or one inherited germline PV and one random event (germline cancers). Paired somatic and germline testing can help to clarify what cancers were caused sporadically. Two PVs identified in tumor tissue (double somatic PVs) with negative germline testing have been shown to cause sporadic cancers.[11] Similar to true negative testing, relatives of patients with sporadic cancers would not have to pursue high-risk screening but may tailor screening based on the family history. For example, individuals with no known hereditary cancer syndrome, but whose first-degree relative was diagnosed with colon cancer, should pursue colonoscopies at age 40 (or 10 years prior to the relative's age of diagnosis) and repeat this exam every 5 years compared to the general population screening recommendation that starts at age 45 and repeats every 10 years.[12]

INFORMED CONSENT

Multiple organizations have written position statements regarding informed consent for genetic testing, which include discussing incidental or secondary findings as well as the accuracy and limitations of genetic testing.[13-15] With both somatic and germline genetic testing, it is common to identify incidental PVs that have no association with the primary reason for testing. For example, informed consent should include making patients aware that the identification of a germline PV, and thus germline validation testing, may be recommended based on their therapeutic somatic test result.

Accuracy and testing limitations are important components that need explanation before patients make a decision about genetic testing. Not all labs offering somatic testing have the option of including germline validation testing. Laboratories having only the capability to perform somatic testing can inform the ordering provider that a PV may be germline; however, additional samples will need to be collected and sent to a secondary laboratory for confirmatory germline analysis.

Both germline and somatic testing can miss identifying PVs. In 2022, Terraf et al found that somatic testing alone failed to detect 10.5% of clinically actionable germline PVs.[16] On the other hand, Hampel et al (2021) identified that 3.5% of germline negative endometrial cancers had double somatic PVs in the mismatch repair genes.[17] For this reason, providers should consider the combination of upfront somatic and germline genetic testing in order to provide accurate and effective patient care.

TREATMENT IMPLICATIONS AND GYNECOLOGIC ONCOLOGY

Ovarian cancer is an example within gynecologic oncology in which both germline and somatic testing are recommended at the time of initial diagnosis. Per the NCCN guidelines, all patients with a personal history of epithelial ovarian cancer should undergo germline genetic testing.[2] Additionally, multigene somatic sequencing is increasingly important for prognosis and treatment of ovarian cancer and should be performed upfront at the time of diagnosis. There is growing evidence of favorable outcomes with targeted therapy in both BRCA1/2 and homologous recombination deficient tumors. For patients diagnosed with ovarian cancer having the inability to repair double-strand DNA breaks, 13–21% harbored a germline BRCA1/2 mutation, and an additional 6–7% had somatic BRCA1/2 variants.[8,18-21] Furthermore, approximately 50% of high-grade serous ovarian carcinomas are homologous recombination deficient.[22-24]

Poly-ADP ribose polymerase (PARP) is an important protein involved in DNA repair pathways, particularly in base excision repair of single strand breaks.[25] PARP inhibitors block these repair pathways, ultimately leading to double strand breaks and targeted cell death of tumors with homologous recombination repair deficiencies, such as BRCA1/2 mutations.[26] This mechanism has been the focus of numerous studies on the various PARP inhibitors within several tumor types.

The PARP inhibitor olaparib is FDA-approved for use as upfront maintenance therapy in patients with advanced

high-grade serous or endometrioid ovarian, fallopian tube or peritoneal cancer and either a germline or somatic BRCA1/2 variant. This approval was based on the 2018 data reporting an incredibly promising progression free survival advantage with a 70% lower risk of disease progression or death.[27] The SOLO1 randomized, double-blind, placebo-controlled, international phase III trial recently published powerful overall survival data on olaparib as upfront maintenance therapy.[28] Patients were randomly assigned olaparib 300 mg BID or placebo for up to 2 years after demonstrating a complete or partial response after platinum-based chemotherapy. At 7 years, 67% of patients receiving olaparib were alive, compared to 46.5% of patients receiving placebo (HR 0.55, 95% CI, 0.40 to 0.76; P<0.0004). Patients receiving olaparib had a median time to first subsequent treatment of 64 months, compared to only 15 months for patients receiving placebo (HR 0.37, 95% CI, 0.28–0.48).[28] The potential to achieve long-term remission is an exciting breakthrough and further highlights the importance of identifying those harboring BRCA1/2 germline and somatic variants early in their treatment course to provide all eligible patients the opportunity towards a cure.

TAKE HOME POINTS

- Germline genetic testing evaluates a patient's inherited DNA while somatic genetic testing evaluates tumor DNA. A patient may qualify for germline and/or somatic genetic testing based on family history or a specific cancer diagnosis.
- Somatic genomic sequencing has increasing clinical applications for cancer prognosis and treatment. Based on results, patients may be candidates for either FDA-approved or experimental targeted treatments and immunotherapies.
- Somatic test results may prompt germline testing. These incidental findings must be included in the informed consent process.
- Genetic counselors/professionals are valuable resources to help determine and facilitate the necessary genetic testing, interpret test results, and work closely with the patient's healthcare team to implement the most effective cancer risk-reducing and preventive plan.

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Conflicts of Interest

The authors report no conflicts of interest.

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Inflammatory Arthritis in a 19-month-old with Von Hippel-Lindau Disease

MARIA C. BRYANT, MD; LAUREN J. MASSINGHAM, MD; ALI YALCINDAG, MD

ABSTRACT

Von Hippel-Lindau disease (VHL) is a rare autosomal dominant disease characterized by progressive development of cysts and tumors. Juvenile idiopathic arthritis (JIA) is a chronic inflammatory disorder and the most common arthritis in children. Although the mechanism of pathogenesis is not fully understood, JIA is thought to be a polygenic, autoimmune-mediated disease. Inherited or acquired disorders resulting in immune dysregulation can lead to neoplastic and autoimmune disease, but very few cases of patients with VHL and concomitant autoimmune disease are reported in the literature. Herein, we describe, to the best of our knowledge, the first reported case of a child with VHL and inflammatory arthritis, and we discuss three possible pathophysiologic mechanisms that could link VHL and JIA. Understanding the shared pathophysiology and genetics of both diseases may help guide future direction of targeted therapies and lead to improved clinical outcomes.

KEYWORDS: Von Hippel-Lindau disease; inflammatory arthritis; autoimmune disease; immune dysregulation; neoplastic disease; pediatrics

BACKGROUND

Juvenile idiopathic arthritis (JIA) is the most common type of arthritis in children. Oligoarticular JIA is the most prevalent subgroup of JIA,[1] and involves <5 joints.[2] It has an estimated annual incidence of 5-20 cases per 100,000 children.[1,3] The peak age of onset is 1 to 3 years and females are affected twice as frequently as males.[4] Treatment involves intraarticular glucocorticoids, nonsteroidal anti-inflammatory drugs and disease-modifying antirheumatic drugs (e.g., methotrexate).[5–9] Biologic agents (e.g., infliximab) are usually reserved for children with uveitis or extensive joint involvement.[6,10,11]

Von Hippel-Lindau disease (VHL) is a rare autosomal dominant disease characterized by progressive development of cysts and tumors including hemangioblastomas, renal cell carcinoma, pheochromocytoma, pancreatic neuroendocrine tumors, and cysts of the genitourinary tract. It results from a germline pathogenic variant (sequencing change or deletion) in the VHL gene. VHL is a tumor suppressor gene on the short arm of chromosome 3.[12,13] The incidence of VHL is 1 in 36,000 live births with the mean age of symptom onset at 26 years.[14]

There are very few reports of patients with VHL and concomitant autoimmune disease.[15,16] In this report, we present the first reported case of inflammatory arthritis in a 19-month-old female with VHL to highlight possible shared pathophysiologic mechanisms as an exciting area for further study and potential therapeutic development for both diseases.

CASE REPORT

A previously healthy 19-month-old female with no significant past medical history presented to the emergency department for left elbow pain and swelling after falling from a chair. Radiographic imaging showed a non-displaced type 1 supracondylar fracture. After a one-month immobilization period, her course was complicated by an elbow contracture and limited range of motion (ROM) for which she underwent arthrogram and manipulation under anesthesia. The arthrogram revealed no fractures, loose bodies, or elbow instability. Her elbow was immobilized at full extension for one month. Three months later, her ROM decreased again, prompting an MRI that demonstrated a joint effusion with synovial proliferation suggestive of inflammatory arthritis. She was referred to pediatric rheumatology for further evaluation.

Labs were notable for an ANA titer of 1:640 in a homogeneous pattern. C-reactive protein and erythrocyte sediment rate were elevated at 58 mg/L and 35 mm/h respectively. ANA titer 2 was 1:640 in a speckled pattern. Her rheumatoid factor was negative. CBC was unremarkable aside from an elevated platelet count of 475 x10^9/L.

One week after her initial evaluation by pediatric rheumatology, she developed non-traumatic swelling of her right knee and a prominent limp. Radiographic imaging revealed a joint effusion. Joint aspiration showed inflammatory synovial fluid with a white blood cell count of 6,960 cells/uL and no crystals. Lyme serology was negative. She was diagnosed with JIA and started on naproxen and weekly methotrexate (5 mg) with significant improvement in her symptoms. After 20 months of methotrexate treatment, she completed a methotrexate wean due to tolerability issues and stable

disease without active inflammation, synovitis, or uveitis. She did well off methotrexate for 15 months before she presented with active arthritis in her right knee. She had an intraarticular steroid injection in her knee with improvement in her swelling and pain. She restarted methotrexate (7.5 mg weekly) and has not had recurrence of her arthritis.

When she was 4 years old, our patient was referred to genetics for concern of VHL. Her family history was significant as her 30-year-old biological father, paternal grandmother, and 12-year-old paternal half-brother have VHL. No family member with VHL had a known history of inflammatory arthritis or autoimmune soft tissue disease. She completed single site testing for VHL and was found to harbor the pathogenic variant in VHL, c.448_449del (p.Asn150Tyrfs*23), confirming her diagnosis of VHL. There are specific childhood surveillance recommendations for VHL, and these were initiated in our patient. Plasma metanephrine (0.27 nmol/L) and normetanephrine (0.65 nmol/L) levels were within normal limits. She currently has no physical manifestations of VHL and continues to be followed per VHL Alliance Surveillance Guidelines and National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology.[17,18]

DISCUSSION

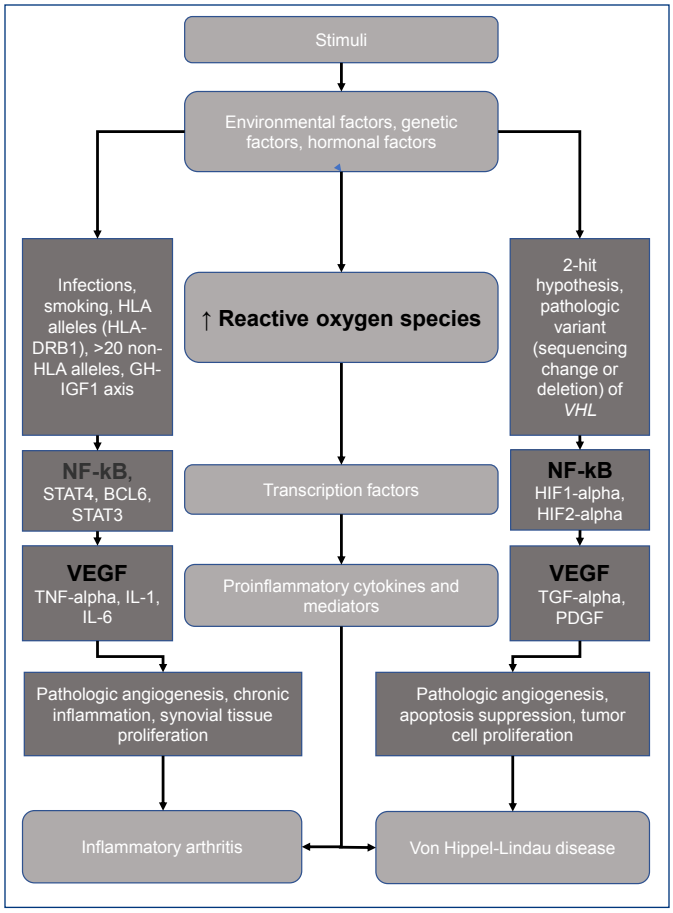
The case presented in this study is the first to show an unusual and previously unreported association between two very different disease processes: inflammatory arthritis and VHL in a young child. Although pure coincidence is possible, it is also possible that a pathologic variant of VHL contributed to the development of inflammatory arthritis in our patient. Based on the incidence of JIA in females under 5 years old (12.2 per 100,000)[3] and the incidence of VHL (1 per 36,000),[14] the likelihood of pure coincidence explaining our patient's co-occurring diseases would be approximately one in 300 million. Thus, the probability of chance alone explaining our patient's presentation is extremely low, but it is not zero.

A review of the literature found several possible pathophysiologic mechanisms including overproduction of reactive oxygen species, dysregulation of the NF-kB signaling pathway, and pathogenic angiogenesis that could link VHL and inflammatory arthritis in children (**Figure 1**). The causal link between VHL and inflammatory arthritis has not been established but may be due to changes in the cytokine milieu with dysfunction of NF-kB, overproduction of reactive oxygen species and pathologic angiogenesis leading to worsening inflammatory arthritis.

Reactive Oxygen Species

Reactive oxygen species (ROS) are oxygen-derived free radicals that are endogenously produced in the mitochondria and play an essential role in oxidative stress. ROS are a natural byproduct of energy metabolism, and their accumulation

Figure 1. Overproduction of reactive oxygen species, dysregulation of the NF-kB signaling pathway, and pathogenic angiogenesis play important roles in the pathophysiology of VHL and inflammatory arthritis. Examples of environmental, genetic, and hormonal factors, transcription factors, proinflammatory cytokines and mediators in both diseases are included.



can lead to cellular damage. They also induce tumorigenic functions such as proliferation and metastasis.[19] ROS play an important role in the pathogenesis of VHL. In cells that lack VHL, hypoxia-inducible transcription factor alpha (HIF1-alpha) is relatively stable irrespective of changes in oxygen, leading to constitutive activation of hypoxia-inducible genes despite normal oxygen levels. This causes ROS accumulation.[20] Additionally, patients with VHL show downregulation of key antioxidant enzymes in charge of ROS homeostasis.[21] The role of ROS in inflammatory arthritis has also been studied with Lipinska et al, showing that the imbalance between the production of ROS and their neutralization leads to oxidative stress. Children with JIA have higher serum concentrations of nitric oxide (NO) end products (a measure of oxidative stress), suggesting that overproduction of NO is involved in the pathogenesis of inflammatory arthritis in children.[22] HIF-alpha is a transcription factor that has been the target of therapies to treat renal cell carcinoma in VHL[23] and many studies show

that HIF-alpha also plays an important role in the pathogenesis of inflammatory arthritis by inducing the production of inflammatory cytokines and autoantibodies.[24,25]

Nuclear Factor Kappa B (NF-kB) Signaling Pathway

NF-kB is a family of transcription factors that play essential roles in apoptosis and inflammation. In normal cells, NF-kB activation is a highly regulated process that controls DNA transcription, cytokine production and cell survival. Disruption of the NF-kB [24,25] absence of functional VHL, expression of NF-kB is enhanced which leads to impaired apoptosis and tumor progression.[26,27] Approximately 70% of patients with VHL develop renal cell carcinoma (RCC) by the age of 60, and the NF-kB signaling pathway has become an exciting target for treatment of RCC in these patients.[28-30] Studies have shown that RCC cells that lack functional VHL have significantly higher expression and activity of NF-kB than RCC cells with functional VHL.[31] NF-kB has also been identified as a pivotal regulator of inflammation in RA.[32] There is increasing evidence that NF-kB activation plays an integral role in the initiation and perpetuation of chronic inflammation in inflammatory arthritis.[33,34] In fact, activated NF-kB has been found in the synovial tissue of patients in early stages of joint inflammation and in those with late-stage disease.[35]

Angiogenesis and Vascular Endothelial Growth Factor

Angiogenesis is the process of new blood vessel development, which is essential for normal physiological functioning as well as pathological processes such as synovial inflammation in inflammatory arthritis and tumor progression in VHL.[36,37] The vascular endothelial growth factor (VEGF) signaling pathway plays pivotal roles in regulating angiogenesis.[36–38] In JIA, there is strong correlation between the expression of VEGF and the inflammatory activity of affected joints.[39] Additionally, increased serum levels of VEGF in children with inflammatory arthritis strongly correlate with disease activity.[40] In VHL, inactivation of the VHL gene leads to pathologic and dysregulated angiogenesis by causing constitutive activation of HIF1-alpha which in turn, upregulates VEGF. VEGF is highly expressed in many of the tumors seen in VHL and targeted therapies with anti-VEGF antibodies (i.e., bevacizumab) are currently in clinical trials. Belzutifan, a HIF2-alpha inhibitor, was recently approved by the FDA for patients with RCC associated with VHL.[41] Belzutifan interrupts pathologic angiogenesis by inhibiting HIF2-alpha and downregulating angiogenesis. Anti-angiogenic therapies are also increasingly recognized as important targets for the treatment of adults and children with inflammatory arthritis, and clinical trials are ongoing.[42]

Overproduction of ROS, impaired NF-kB signaling, and pathogenic angiogenesis play important roles in the pathophysiology of VHL and inflammatory arthritis. Genetic susceptibility may also contribute to the pathogenesis of both diseases. The genetics of VHL is well established; in contrast, JIA is polygenic with multiple HLA alleles and >25 non-HLA susceptibility loci associated with the disease.[43–45] Genome-wide association studies have led to a better understanding of the genomic architecture influencing the risk of JIA and have identified numerous susceptibility loci. Our report highlights three possible associations between the pathogenesis of inflammatory arthritis and VHL. Understanding the shared pathophysiology and genetics of both diseases may help guide future direction of targeted therapies and lead to improved clinical outcomes.

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Bowel Obstruction from an Incidentally Ingested Foreign Body

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ABSTRACT

Small bowel obstructions are common surgical presentations that are most often caused by adhesions following abdominopelvic surgeries. However, in patients with no history of abdominal surgical interventions, assessment of the cause of a small bowel obstruction is more complex, and such patients frequently require operative intervention. We present a case of a 65-year-old man who presented with a small bowel obstruction caused by an inadvertent ingestion of a bread tag that was not identified on preoperative imaging. The sharp end of the bread tag had eroded through the small bowel leading to a walled-off perforation of the small bowel. Surgical resection was required.

KEYWORDS: small bowel obstruction; perforation; ingested foreign body

INTRODUCTION

Small bowel obstructions (SBOs) are a common surgical presentation, the majority of which are caused by adhesions from prior abdominal operations. SBOs usually present with intermittent, colicky abdominal pain, with a combination of nausea or vomiting, abdominal distention and potentially constipation.[1] SBO patients without a history of abdominal or pelvic operations very often have surgical causes to the bowel obstruction that require operative intervention to resolve. The predominant causes of non-adhesive SBOs are either due to hernia or malignancy. On rare occasions, an obstructing foreign object may be the cause of the bowel obstruction. We present a case of a 65-year-old man with a long-standing small bowel obstruction caused by an unlikely etiology. This case highlights the importance for the primary care provider and surgeon to consider atypical causes of SBO presentation, particularly in patients without a history of abdominopelvic surgeries.

CASE REPORT

A 65-year-old man had a 3-month history of intermittent crampy abdominal pain associated with mild bloating. He also noted that his bowel movements had become increasingly watery and loose. His only medical history was gastro-esophageal reflux disease and he had no history of any abdominopelvic operation. The patient had previously presented twice to the emergency department. During the first presentation, both physical examination and radiographic studies, including CT scan imaging, were unrevealing and the patient was not admitted. At the second presentation, one month prior to this presentation, the patient again reported ongoing abdominal pain, but this time it was associated with nausea and worsening abdominal distention. Physical examination noted a moderately distended but non-tender abdomen and no evidence of hernia. Imaging revealed a possible small bowel obstruction. Repeat CT scan did not demonstrate a transition point. He was admitted to the surgical service and a small bowel follow- through study was undertaken which was reported as normal and demonstrated passage of contrast into the colon. The patient's symptoms resolved and he was able to tolerate a diet. Upon return of bowel function, he was discharged home with close follow-up.

One month later, the patient again presented to the emergency department with a third episode of exacerbation of his abdominal pain. On this occasion, the patient had associated nausea, one episode of vomiting, significantly increased abdominal distention, and noted no flatus or bowel movements for the 2 days prior to presentation. Physical examination demonstrated localized tenderness. There was no guarding, rebound or rigidity, and again no appreciable hernias. Laboratory investigations noted no leukocytosis and a normal lactic acid level. This time, a CT scan of the abdomen and pelvis noted distended small bowel with a transition point located within the mid-pelvic region, but no obvious obstruction source. There was a small amount of free fluid in the pelvis. He was admitted and serial abdominal exams over the next 12 hours noted progressive tenderness.

At this point, the patient was counselled regarding the potential etiologies, including the possibility of a small bowel malignancy. The patient was taken to the operating room and underwent an initial diagnostic laparoscopy. Intraoperatively, an inflamed mass was encountered in the mid-jejunum, with a sharp foreign body protruding from the bowel with associated surrounding inflammation (**Figure 1A**). The bowel proximal to this was noted to be distended

Figure 1A. Sharp edge protruding through the bowel wall.

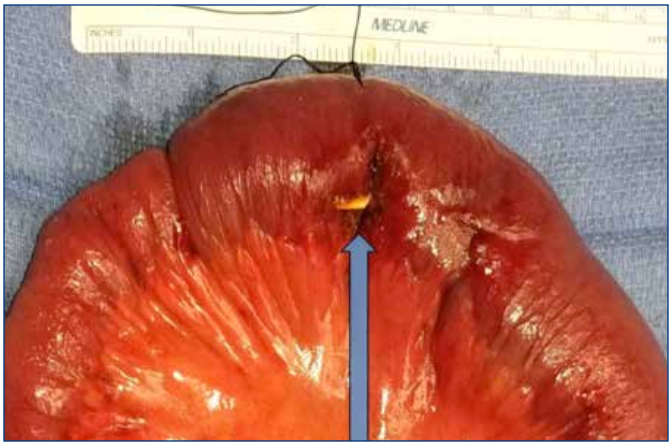


Figure 1B. The sharp "bread tag" rotated out of the perforated bowel wall.

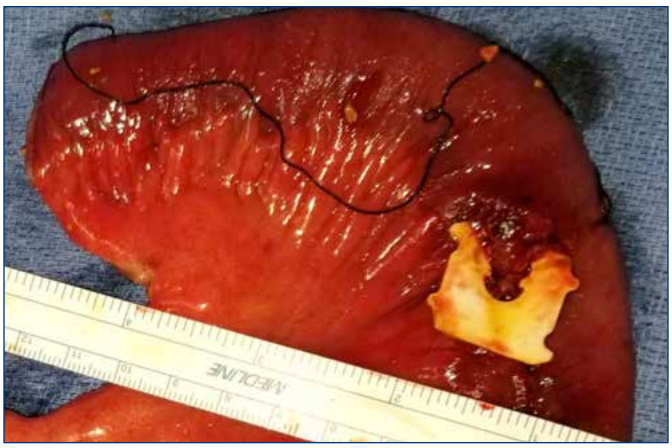


Figure 2A. Piece of undigested food proximal to the obstructing foreign object

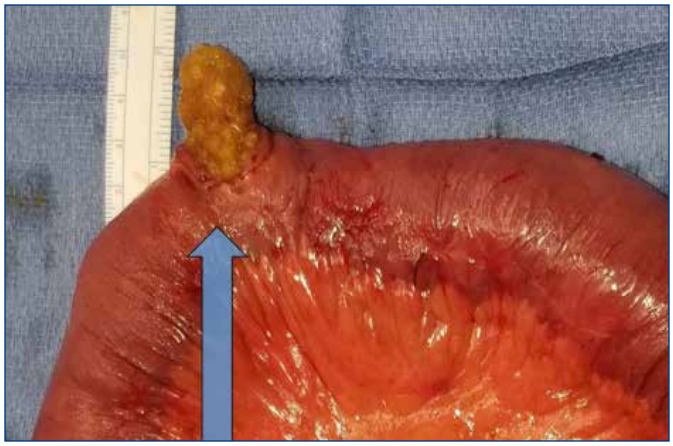
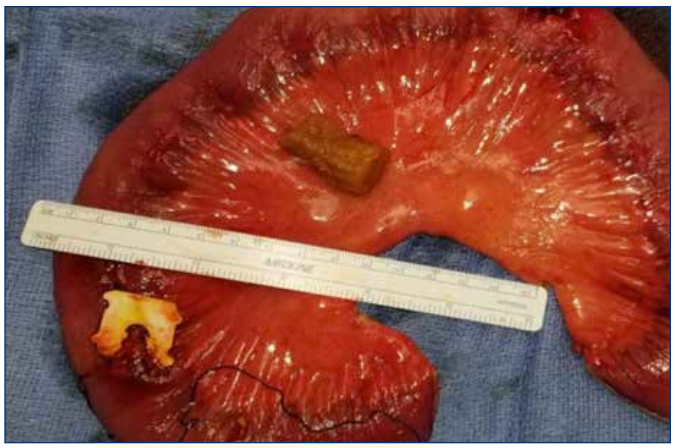


Figure 2B. Bread tag and piece of baby corn leading to SBO and perforation.



and the bowel distal to this area was noted to be decompressed. The case was converted to an open laparotomy. During exploration, a second intraluminal foreign body with an associated perforation was noted just proximal to the first perforation (**Figure 2A**). There was no obvious abscess, and no other masses or lymphadenopathy. The rest of the exploration was unremarkable. Two small bowel resections with primary anastomosis were performed to include each of the areas of perforation. The specimens were opened on the back table. The first perforation involving the sharp foreign object was noted to be a plastic bread tag wherein the sharp edge had perforated the small bowel (**Figure 1B**). The more proximal foreign body was noted to be an undigested piece of baby corn which had perforated through the distended bowel (**Figure 2B**). The patient tolerated the procedure well. The remainder of his hospital course was uneventful; the patient recovered well and was discharged on post-operative day 5. The patient had no recall of swallowing the bread tag. However, when the findings were related to the patient, he did report that due to poor dentition, he often was unable to chew and would merely swallow his food, which may explain why he did not sense the bread tag within his food. The patient has been seen twice in follow-up in the general surgery clinic and has reported complete resolution of his symptoms.

DISCUSSION

Small bowel obstructions (SBOs) are a common surgical presentation leading to more than 300,000 inpatient admissions per year in the United States. Postsurgical adhesions account for approximately 85% of cases of SBO and the significant majority are successfully managed with nonsurgical management.[2] Unusual and atypical causes must always be considered in a patient presenting with a clinical SBO who has neither a history of intra-abdominal or pelvic operations nor an obvious abdominal wall hernia. Worldwide, infectious disorders including parasites or tuberculosis constitute leading causes of both small and large bowel obstruction.[1,3] More uncommon causes include strictures, neoplasms,

perforations, or inflammatory diseases. Other more rare etiologies that often require emergent operative intervention include small bowel obstruction due to volvulus or malrotation, gallstones, or bezoars and foreign bodies.[1] In children, ingested foreign bodies tend to be blunt or round such as a button or small battery, whereas in adults, there is a higher incidence of sharp foreign bodies such as toothpicks, bristles from wire brushes or, as in our case, ingestion of plastic bread tags.

Plastic bread tags were first introduced in the US in 1952. Sealing a bag of bread with the plastic tag is believed to preserve the bag's content keeping it fresh for longer. Intestinal complications due to plastic bag clips were first reported in 1975.[4] Interestingly, the original case presentation was very similar to our current patient wherein the patient presented several times over many months with crampy abdominal pain, finally presenting with nausea and abdominal distention consistent with small bowel obstruction without any history of abdominal or pelvic operation. Further, at exploration the surgical team identified a partial perforation of the sharp edge with obstruction from undigested vegetable matter proximal and surrounding the bread tag. The next report of plastic bread tags within the intestine involved 3 incidentally identified tags within bowel resected for other reasons.[5] Ingestion of plastic bread tags remains a relatively rare event, but often with severe surgical consequences.[6] Anderson et al have reported that the acute presentation is usually for erosion or perforation with most requiring operative intervention and several deaths have been reported.[7]

Among patients who did ingest a plastic bread tag, individuals reported consuming their food too quickly. The vast majority of patients were noted to be elderly, intoxicated, and visually or cognitively impaired. It has been postulated that the history of either cognitive impairment or substance use disorder may contribute to the prolonged nature of the symptoms of a patient with small bowel obstruction in the absence of abdominal surgical interventions.

Since clinical symptoms may not sufficiently be reliable alone to either fully rule out a cause of the possible SBO or assess the need for operative intervention, radiographic imaging plays an important role. CT scan of the abdomen with IV contrast is recommended for potential cases to better elucidate severity, location, grade, and etiology.[8,9] However, imaging has limited efficacy, with a reported 50–75% accuracy in identifying a cause for the SBO in patients without prior abdominopelvic operation.[1,10] To identify whether plastic bread tags were radiopaque, and thereby potentially detectable with imaging, Newall et al undertook CT scans of isolated plastic bread tags placed directly onto CT scan gantry.[11] Importantly none of the tags was identifiable by imaging. Laboratory studies play a very limited role in either diagnosing an etiology or directing management. Although patients with a perforated bowel may present with a leukocytosis, it is critical to understand that, as was noted in our patient, a normal white cell count does not rule out a bowel perforation or an intra-abdominal infection. Further, although a lactic acidosis may be concerning for ischemic bowel, it is very important to remember that a normal lactic acid level does not rule out ischemic bowel. This is particularly true in patients with closed loop obstructions or with enteric venous outflow obstruction.

It has been postulated that the high perforation rate from plastic bread tags is due to the uniquely shaped sharp claws of the tag. Bowel mucosa becomes entrapped within the plastic tag leading to mucosal ischemia and necrosis. The free solid edge of the tag is sharp and can penetrate the opposing wall of the bowel with peristalsis.

Management of patients with SBO without a history of abdominopelvic surgeries is challenging given the lack of a widely accepted algorithm for these patients.[9,10] Indications for surgery depend on the duration and severity of symptoms, including nausea, abdominal pain, and obstipation, as well as physical examination findings of peritonitis, including rebound, guarding or rigidity. Radiographically, free air is a clear sign of perforation of a hollow viscus, and free fluid is highly suggestive of an etiology requiring operative intervention. Signs of perforation and ischemia are clear indications for urgent surgical management. If the ingestion is rapidly identified, then there is a potential for endoscopic retrieval; however, to date, the overwhelming predominance of retrievals have been undertaken surgically. Determining the need for surgery and appropriate timing is also critical. SBO-related morbidity and mortality increase with delays in surgical management, particularly beyond 24 hours in patients with symptoms of complete obstruction without response to nonsurgical treatment.[12]

Both surgical abdominal emergencies as well as airway obstructions have resulted from ingested bread tags and have been noted to occur worldwide. In response to a child choking from a plastic bread tag, distributors in the UK in the 1990s discarded their plastic bread clips in favor of resealable twist ties.[13] In Australia in a response to eliminating single use plastic, Australian bread makers removed plastic bread tags in favor of cardboard or paper-based bread tags.[14] Recently, Canada followed in similar fashion with several large breadmaking companies using cardboard-based compostable bread clips. Efforts to transition to more environmentally friendly non-plastic material retain some of the problems of the nature of a bread tag should it be ingested. Degradable materials including wood, cotton, or potato starch still retain the physical properties of sharp edges and toothed jaws or clamps necessary to hold the bread bag in place, and thus retain the potential to 'grasp' the folds in the small bowel mucosa and cause bowel perforation. However, ongoing efforts are underway to replace the plastic tags with rapidly biodegradable materials such as paper-based materials that would rapidly soften with intestinal secretions.

CONCLUSION

This case highlights the complexity of managing SBO in the absence of diagnostic radiologic findings. In patients with atypical presentations, an increased awareness for a surgical cause to the SBO is important. Our patient presented with an atypical cause of SBO that was not identified on CT scan. A careful consideration of an etiology that would require operative intervention is critical in a patient without prior abdominopelvic operation who presents with recurrent SBO symptoms.

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Cranial Polyneuropathy from Multiple Myeloma with CNS Involvement

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KEYWORDS: multiple myeloma, neurooncology, nervous system neoplasms, chemotherapy, radiation therapy

A 77-year-old woman was diagnosed with non-secretory multiple myeloma (MM) of IgA kappa subtype, with 17p (*TP53*) deletion. There was an initial response to radiation and chemotherapy, but she eventually developed extramedullary involvement and multifocal plasmacytomas.

Inpatient neurology consultation was requested for evaluation of 2 months of severe right hemifacial pain, profound right-sided hearing loss, prominent right peripheral-type facial palsy, and blurry vision affecting the right eye (**Image 1**). Brain MRI showed enhancing lesions involving the right internal auditory canal, cerebellopontine angle, anterior clinoid process, optic canal, right middle cranial fossa floor, and tentorial margin (**Image 2).** These lesions were not present on a pre- and post-gadolinium MRI performed for disease staging approximately a week before the onset of the patient's symptoms. The patient received cranial radiotherapy (20 gray over 5 fractions) and salvage chemotherapy (daratumumab, pomalidomide, and dexamethasone), with no substantial improvement. She transitioned to hospice and died 7 months after the onset of cranial neuropathies.

Image 1. Multiple cranial neuropathies due to central nervous system involvement by multiple myeloma

In these images, the patient was asked to smile (**A**) and frown (**B**). She had severe right peripheral-type facial palsy. In addition, she reported severe, stabbing, near-constant right-sided facial pain that could affect the V1, V2, or V3 divisions of the trigeminal nerve, marked right-sided hearing loss, and blurry vision affecting the right eye.

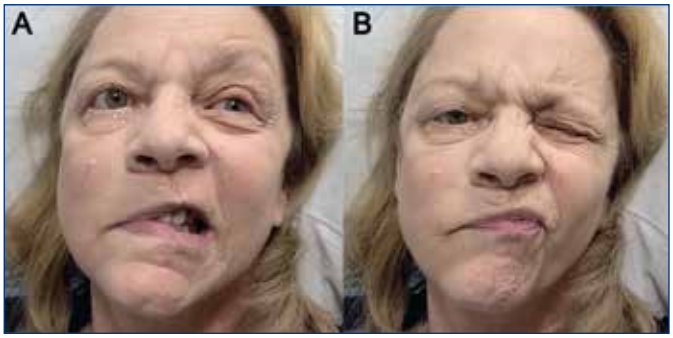
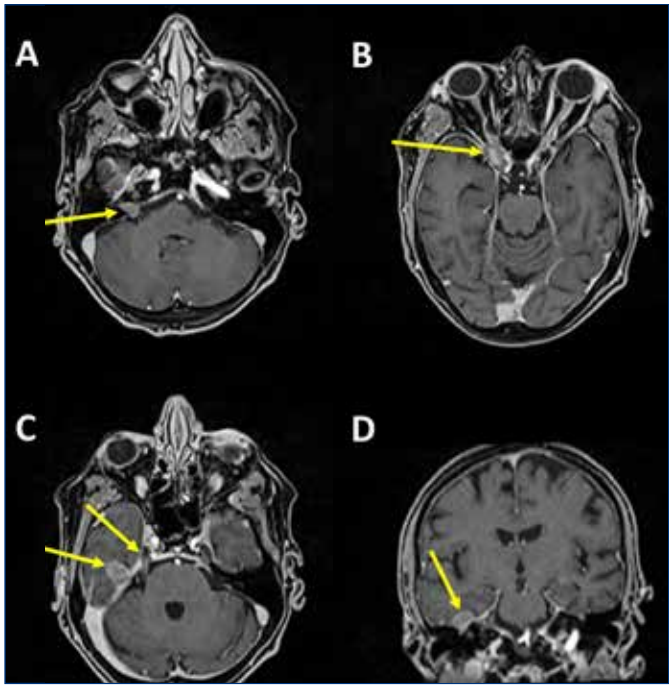


Image 2. T-1 weighted post-contrast brain MRI showing central nervous system involvement from multiple myeloma

(**A**) Contrast-enhancing soft tissue tumor involving the right internal auditory canal and extending into the cerebellopontine angle (arrow), encasing cranial nerves VII and VIII. (**B**) Contrast-enhancing soft tissue tumor infiltrating and expanding the right anterior clinoid process with extension into the right optic canal (arrow). (**C**) and (**D**) Dural-based contrast-enhancing soft tissue tumor at the floor of the right middle cranial fossa (arrows), extending laterally and anteriorly to involve the tentorial margin with encroachment on the adjacent cranial nerve V.



Central nervous system (CNS) involvement occurs in <1% of MM patients.[1] Patients can develop leptomeningeal myelomatosis (70%), direct extension of MM with dural involvement (35%), intraparenchymal metastases (26%), or combinations of these findings.[2] Both hematogenous and contiguous spread may contribute to CNS involvement.[3,4] CNS involvement is associated with poor prognosis, with median overall survival <6 months.[2,3] Negative prognostic factors include multiple lines of chemotherapy and an unfavorable cytogenetic profile.[5] Radiation therapy and CNS-penetrating immunomodulatory imide drugs (IMiDs)

are frequently used for symptom palliation.[2,3] Despite the outcome of this case, earlier recognition of CNS MM could potentially be associated with more favorable outcomes.[2]

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Dermal Toxicity from a Paraquat-Poisoned Patient's Urine

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CASE PRESENTATION

A nurse placed a Foley catheter in an intubated patient who had accidentally ingested approximately 50 mls of paraquat, a corrosive, restricted use herbicide. Despite using standard personal protective equipment for Foley catheter placement, including sterile latex gloves, some of the patient's urine got onto the nurse's right forearm.

Figure 1. Right forearm 30 minutes after contact with urine from a patient who had ingested paraquat.

Figure 2. Right forearm 24 hours after contact with urine from a patient who had ingested paraquat.

DISCUSSION

Paraquat dichloride, formally N,N′-dimeth yl-4,4′-bipyridinium dichloride, is one of the most widely used herbicides in the world. Access to paraquat is limited in the United States and therefore, it is not a frequent cause of poisoning in the U.S. It is widely available on an unrestricted basis in Asia. Its main mechanism of toxicity is through creating reactive oxygen and nitrite species.[1] Paraquat is known to be fatal at very small doses (30 ml), leading to its unfortunate use in low- and middle-income countries as a means of self-poisoning. Paraquat is eliminated primarily through the kidneys and has particular toxicity for the lungs, kidneys, and liver. Clinically, it can lead to nausea, vomiting, and abdominal pain on one end of the spectrum, while in more severe cases it can cause seizures, heart failure, and death.[1] There is no antidote available for paraquat toxicity, although immunosuppressive medications may have a slight mortality benefit.[2] While paraquat is known to cause mucosal and skin toxicity, and it can be absorbed through the skin, the effect of urine from someone who ingested paraquat on the skin is not well described.[3,4]

In the case discussed, the nurse immediately rinsed her forearm with water and washed it with soap and water. Despite this, the nurse developed a 1% body surface area partial thickness chemical burn progressing to blistering within 30 minutes of contact (**Figure 1**). The nurse was evaluated by the burn surgery service and discharged after observation in the burn center. Besides pain, the nurse had some nausea which resolved after one dose of ondansetron in the burn center. She had no other systemic symptoms. The blistered skin painfully sloughed off within 24 hrs. (**Figure 2**).

Despite using standard precautions and protective personal equipment (PPE) while inserting the Foley catheter, the nurse sustained a chemical burn due to paraquat in the patient's urine.[5] Based on EPA references and also what is available in an Emergency Department, we suggest extended PPE recommendations for staff caring for patients who have ingested paraquat.[6] Particular attention should be paid to any staff potentially coming into contact with the patient's urine. PPE should include long sleeves, chemical resistant gloves (i.e. nitrile rubber ≥ 14 mils), plastic gown, and face shield/eye protection. This recommendation should apply even after external decontamination since the urine itself can be a significant dermal toxin.

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Effectiveness of Monoclonal Antibody Therapy for Preventing COVID-19 Hospitalization and Mortality in a Statewide Population

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ABSTRACT

BACKGROUND: Monoclonal antibody (MAB) treatments for COVID-19 received Emergency Use Authorization in the United States.

METHODS: We used surveillance data from Rhode Island to conduct a retrospective, statewide cohort study to estimate the effectiveness of MABs for preventing hospitalization and death during periods when Alpha and Delta variants were predominant.

RESULTS: From 1/17/2021–10/26/2021, 285 long-term congregate care (LTCC) residents and 3,113 non-congregate patients met our eligibility criteria and received MAB; they were matched to 285 and 6,226 controls, respectively. Among LTCC residents, 8.8% (25/285) of patients who received MAB were hospitalized or died compared to 25.3% (72/285) of those who did not receive MAB (adjusted difference=16.7%, 95% confidence interval CI=11.0-22.3%). Among non-congregate patients, 4.5% (140/3,113) of patients who received MAB were hospitalized or died compared to 11.8% (737/6,226) of those who did not receive MAB (adjusted difference=7.2%, 95% CI=6.0-8.4%).

CONCLUSIONS: Administration of MABs led to an absolute reduction in hospitalization or death during periods when Alpha and Delta variants were predominant.

KEYWORDS: COVID-19; SARS-CoV-2; monoclonal antibody therapy; treatment effectiveness

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes Coronavirus Disease 2019 (COVID-19), is responsible for substantial morbidity and mortality across the United States (US).[1] Multiple monoclonal antibody (MAB) regimens have been granted Emergency Use Authorization (EUA) by the US Food and Drug Administration (FDA) for treatment of COVID-19[2-6] based on evidence from clinical trials suggesting a reduction in SARS-CoV-2 viral load[7-10] and hospitalization for any cause[11] after treatment. MABs are single treatments given early in the course of disease and have generally been approved for use among patients with mild to moderate symptomatic COVID-19 who were aged 12 years and older with eligible underlying conditions and/or aged 65 years and older.[2-6]

Despite evidence from the clinical trials that these MABs may help prevent medical visits, emergency department visits, and/or hospitalization for COVID-19,[7-11] evidence of their real-world effectiveness for preventing severe illness remains relatively limited, particularly for larger, population-based samples. Studies of the real-world effectiveness of MABs have similarly suggested benefits for preventing ED visits, hospitalization, intensive care unit admission, and/or death; however, all of these studies have been limited to specific integrated healthcare systems or medical centers, and most included a relatively small number of people receiving MABs.[12-17] We sought to estimate the real-world effectiveness of MAB treatment for preventing hospitalization and death among a large, statewide cohort of patients diagnosed with SARS-CoV-2 infection during periods when the Alpha (B.1.1.7 and Q lineages) and Delta (B.1.617.2 and AY lineages) SARS-CoV-2 variants were predominant.

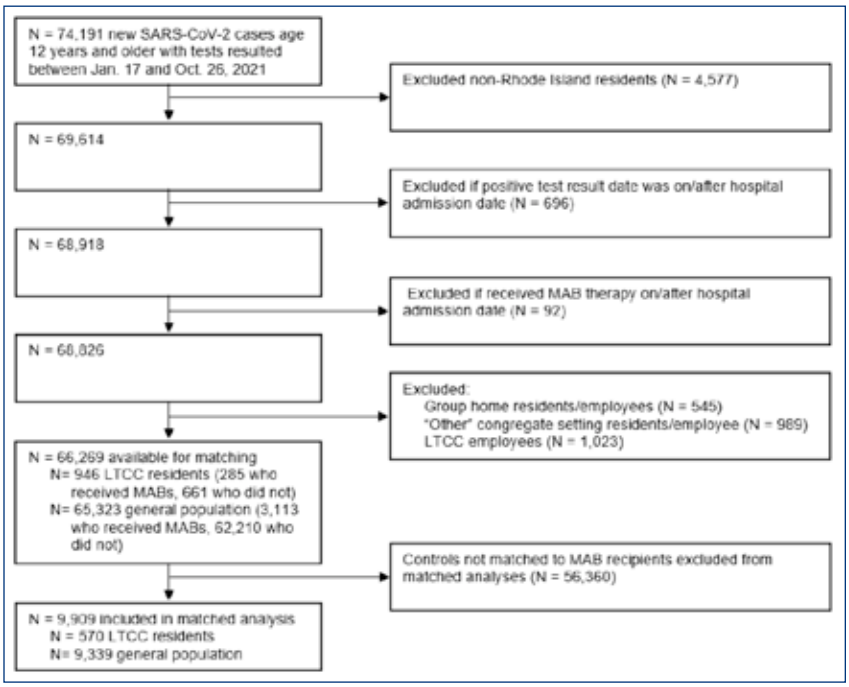
METHODS

Study design and population

We conducted a retrospective population-based cohort study using statewide surveillance data from the Rhode Island Department of Health (RIDOH) on lab-confirmed cases of SARS-CoV-2 infection among people aged 12 years and older between January 17 and October 26, 2021. Individual cases were linked to longitudinal follow-up data on MAB treatments provided for COVID-19, COVID-19 hospitalizations, and COVID-19-associated fatalities through November 11, 2021. We excluded 4,577 non-Rhode Island residents, 696 people whose first hospital admission date preceded the positive test result date, and 92 whose MAB administration came after hospitalization (**Figure 1**).

We divided our sample into two separate populations: (1) residents of long-term congregate care (LTCC) settings, which included nursing homes and assisted living facilities, and (2) patients not associated with congregate settings. LTCC residents were analyzed separately due to the high risk of morbidity and mortality in this population. We did not include group home residents or employees (n=545), "other" congregate setting residents or employees (n=989), or LTCC employees (n=1,023) in our analyses. Following

Figure 1. Application of inclusion and exclusion criteria to arrive at the final analytic sample



Abbreviations: COVID-19, Coronavirus Disease 2019; LTCC, long-term congregate care; MAB, monoclonal antibody; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

exclusions, our database included 946 LTCC residents and 65,323 residents from the general population not associated with congregate settings.

Data management and statistical methods

The study database was assembled by linking data from five surveillance systems maintained by RIDOH: SARS-CoV-2 vaccinations, cases, MAB treatments, hospitalizations, and fatalities. Linkage was done using name, date of birth, and address. In Rhode Island, vaccination data are reported to RIDOH through the Rhode Island Child and Adult Immunization Registry. Additionally, positive PCR or antigen tests are reported to RIDOH, and new cases are investigated to collect health and demographic information. Using RIDOH's statewide Hospital Incident Reporting System, hospitals report to RIDOH patients who are admitted to an inpatient bed, have recently tested (or been clinically diagnosed) positive for SARS-CoV-2 infection, and are being placed on SARS-CoV-2 precautions. RIDOH derives data for lab-confirmed COVID-19-associated fatalities from three sources: the Office of the State Medical Examiner, Vital Records death certificate data, and the Hospital Incident Reporting System. During the study period, all MAB providers in Rhode Island reported data to RIDOH on patients who were provided MAB treatments.

Our analysis was designed to estimate the average treatment effect among those treated with MAB therapy.[18] Within each stratum, we used nearest-neighbor matching based on propensity scores to match those receiving MABs to suitable controls, using a 2:1 ratio for non-congregate residents and 1:1 for LTCC residents. The propensity score model included age (years), sex assigned at birth (female, male, unknown), race/ethnicity (Hispanic or Latino, Black or African American, White, other race, unknown), symptom status (asymptomatic, symptomatic, not interviewed, unknown), timing of positive test result (number of days since January 17, 2021), and vaccination status at time of the positive test result (completed primary vaccination series, partially completed primary vaccination series, unvaccinated). For the non-congregate sample, we also included a ZIP-code-based 3-tier community risk classification created by RIDOH to help guide COVID-19 surveillance and response efforts (low-, moderate-, and high-risk tiers). The tier classification was based on community characteristics such as population density, sociodemographics, and COVID-19 burden.

For each matched sample, we estimated the difference in the percentage who were hospitalized or died (i.e., a combined outcome) between those receiving and not receiving MAB therapy. We also fit a regression model adjusted for the covariates used in matching to correct for potential post-matching imbalances. The estimated difference from these models corresponds to the average increase in hospitalization or death, among those who received MABs, that would have been realized had they not received MAB treatment. In other words, the effect estimates apply to the subset of the population who actually received MABs.

Although we used a combined outcome to improve efficiency for our primary analysis, we also fit a multinomial logistic regression model with the two outcomes modeled separately (hospitalization only, death) to determine whether the results were driven by one outcome. Finally, to understand the potential influence of cases who received MABs later in the course of their COVID-19 infection, we conducted a sensitivity analysis restricted to people who received MABs within five days of their positive test result date and their matched controls.

This study was classified as exempt by the RIDOH Institutional Review Board. We utilized SAS 9.4 (Cary, North Carolina) and Python 3.8.5 (Wilmington, Delaware) for data management and Stata 17 (College Station, Texas) for statistical analyses. Counts of less than five are suppressed in accordance with RIDOH's Small Numbers Policy. (Additional detail on the data systems, definitions, data sources, and linkage methods is available in a supplementary appendix by emailing corresponding author.)

RESULTS

A total of 3,398 patients received MABs and were included in our analyses. This included 285 of 946 LTCC residents and 3,113 of 65,323 non-congregate setting patients who received MABs (1,234 bamlanivimab monotherapy, 639 bamlanivimab and etesevimab, and 1,514 casirivimab and imdevimab, 9 sotrovimab, and <5 unknown). Within each subsample, we used propensity scores to match MAB recipients to controls (1:1 for LTCC and 1:2 for general population). Our analysis datasets were based on 570 LTCC residents (285 MAB recipients and 285 matched controls) and 9,339 individuals not in a congregate setting (3,113 MAB recipients and 6,226 matched controls).

Sociodemographic and health characteristics of the matched samples are shown in Tables 1 and 2 and indicate that the samples are well balanced on these covariates. The sample of MAB recipients among LTCC residents had average age 80.4 years (standard deviation SD 12.2), was 57.2% female, with 26.7% confirmed symptomatic (42.1% had unknown symptom status) and 41.0% unvaccinated; race/ethnicity was unknown for 80.3%. In this sample of LTCC residents who received MABs, mean number of days from January 17, 2021, to positive SARS-CoV-2 test was 105.1 days (SD 105.7) (**Table 1**). For MAB recipients not in congregate settings, mean age was 58.7 years (SD 15.5); 53.6% were female, 77.9% were white, 86.3% were confirmed symptomatic, and 67.5% were unvaccinated. In this sample of MAB recipients not associated with congregate settings, timing of positive test relative to January 17, 2021, was 148.0 days (SD 103.0). Residents of moderate- or high-risk communities, per RIDOH's ZIP-code-based community COVID-19 risk classification, comprised 42.8% of the non-congregate sample (**Table 2**).

In the matched sample, 25 of 285 (8.8%) LTCC resident patients who received MABs were hospitalized only (n=9) or died (n=16) with COVID-19 compared to 72 of the 285 (25.3%) who did not receive MABs (n=42 hospitalized only, n=30 died); the adjusted risk difference for the combined outcome of hospitalization or death was 16.7% (95% CI 11.0 to 22.3%) (**Table 3**). Among non-congregate setting residents, hospitalization or death occurred for 140 of 3,113 MAB recipients (4.5%; n=131 hospitalized only, n=9 died) and 737 of 6,226 who did not receive MABs (11.8%; n=599 hospitalized only, n=138 died), with adjusted risk difference 7.2% (95% CI 6.0 to 8.4%).

When modeling hospitalization only and death separately to determine whether the results were driven by one outcome, MABs were protective against both hospitalization only and death for LTCC residents and the general population (**Table 4**). Importantly, death was a more frequent outcome for LTCC residents than non-congregate patients. Among LTCC residents, there was some evidence that the relative impact of MABs was greater for preventing hospitalization only than death. Conversely, among non-congregate patients, the relative impact of MABs was somewhat greater for preventing death than hospitalization only.

Finally, in our sensitivity analysis restricted to cases who received MABs within five days of their positive test result date and their matched controls, the results were similar (supplementary appendix Table S1 available by emailing corresponding author).

Table 1. Summary of matching covariates for the matched sample of LTCC resident patients

Characteristic	MAB N=285 n (%)	No MAB N=285 n (%)	Standardized difference
Age (years), mean (SD)	80.35 (12.2)	79.70 (12.1)	0.054
Days since 1/17/21, mean (SD)	105.1 (105.7)	113.3 (103.2)	-0.077
Sex			
Female	163 (57.2)	166 (58.3)	-0.021
Male	75 (26.3)	67 (23.5)	0.063
Unknown	47 (16.5)	52 (18.2)	-0.047
Race/ethnicity			
White*	49 (17.2)	49 (17.2)	0.000
Hispanic or Latino	<5†	<5†	†
Other race*	5 (1.8)	<5†	†
Unknown	229 (80.3)	228 (80.0)	0.009
Symptom status‡			
Asymptomatic	87 (30.5)	87 (30.5)	0.000
Symptomatic	76 (26.7)	77 (27.0)	-0.008
Not Interviewed	<5†	<5†	†
Unknown	120 (42.1)	119 (41.8)	0.007
Vaccination status			
Completed primary vaccination series	98 (34.4)	101 (35.4)	-0.022
Partially completed primary vaccination series	70 (24.6)	62 (21.8)	0.065
Unvaccinated	117 (41.0)	122 (42.8)	-0.036
Community COVID-19 risk§			
High	26 (9.1)	27 (9.5)	-0.012
Moderate	43 (15.1)	45 (15.8)	-0.020
Low	208 (73.0)	202 (70.9)	0.047
Unknown	8 (2.8)	11 (3.8)	-0.064

Abbreviations: COVID-19, Coronavirus Disease 2019; LTCC, long-term congregate care; MAB, monoclonal antibody; RIDOH, Rhode Island Department of Health; SD, standard deviation.

* Patient reported non-Hispanic or unknown ethnicity.

† Counts of 1-4 and calculations based on those counts are suppressed, in accordance with RIDOH's Small Numbers Policy.

‡ Summary of symptom information reported to RIDOH as the reason for testing, during case investigation, and/or through symptom self-monitoring. Congregate setting residents often are not interviewed for symptom information.

§ ZIP-code-based community risk classification created by RIDOH based on community characteristics such as population density, sociodemographics, and COVID-19 burden to help guide COVID-19 surveillance and response efforts.

Table 2. Summary of matching covariates for the matched sample of patients not associated with a congregate setting

Characteristic	MAB N=3,113 n (%)	No MAB N=6,226 n (%)	Standardized difference
Age (years), mean (SD)	58.7 (15.5)	58.8 (16.0)	-0.006
Days since 1/17/21, mean (SD)	148.0 (103.0)	145.0 (97.4)	0.028
Sex			
Female	1,667 (53.6)	3,250 (52.2)	0.027
Male	1,324 (42.5)	2,757 (44.3)	-0.035
Unknown	122 (3.9)	219 (3.5)	0.021
Race/ethnicity			
Hispanic or Latino (any race)	360 (11.6)	691 (11.1)	0.015
Black or African American*	105 (3.3)	216 (3.5)	-0.005
White*	2,425 (77.9)	4,914 (78.9)	-0.025
Other race*	103 (3.3)	170 (2.7)	0.032
Unknown	120 (3.9)	235 (3.8)	0.004
Symptom status‡			
Asymptomatic	119 (3.8)	222 (3.6)	0.013
Symptomatic	2,685 (86.3)	5,362 (86.1)	0.004
Not Interviewed	308 (9.9)	640 (10.3)	-0.013
Unknown	<5†	<5†	†
Vaccination status			
Completed primary vaccination series	879 (28.2)	1638 (26.3)	0.043
Partially completed primary vaccination series	134 (4.3)	254 (4.1)	0.011
Unvaccinated	2,100 (67.5)	4,334 (69.6)	-0.046
Community COVID-19 risk§			
High	471 (15.1)	916 (14.7)	0.012
Moderate	861 (27.7)	1654 (26.6)	0.024
Low	1,765 (56.7)	3,623 (58.2)	-0.030
Unknown	16 (0.51)	33 (0.53)	-0.002

Abbreviations: COVID-19, Coronavirus Disease 2019; MAB, monoclonal antibody; RIDOH, Rhode Island Department of Health; SD, standard deviation.

* Patient reported non-Hispanic or unknown ethnicity.

† Counts of 1-4 and calculations based on those counts are suppressed, in accordance with RIDOH's Small Numbers Policy.

‡ Summary of symptom information reported to RIDOH as the reason for testing, during case investigation, and/or through symptom self-monitoring.

§ ZIP-code-based community risk classification created by RIDOH based on community characteristics such as population density, sociodemographics, and COVID-19 burden to help guide COVID-19 surveillance and response efforts.

Table 3. Number and percentage who were hospitalized only or died with COVID-19 by MAB treatment status, among matched samples (combined outcome)

	MAB n (%)	No MAB n (%)	Unadjusted difference (95% CI)	Adjusted difference (95% CI)
LTCC residents	25/285 (8.8%)	72/285 (25.3%)	16.5% (10.4–22.5%)	16.7% (11.0–22.3%)
Hospitalized only	9	42		
Died	16	30		
Non-congregate setting patients	140/3,113 (4.5%)	737/6,226 (11.8%)	7.3% (6.1–8.6%)	7.2% (6.0–8.4%)
Hospitalized only	131	599		
Died	9	138		

Abbreviations: CI, confidence interval; COVID-19, Coronavirus Disease 2019; LTCC, long-term congregate care; MAB, monoclonal antibody.

Table 4. Number and percentage who were hospitalized only or died with COVID-19 by MAB treatment status, among matched samples (separate outcomes)

	MAB n (%)	No MAB n (%)	Unadjusted relative risk ratio (95% CI)*	Adjusted relative risk ratio (95% CI)*
LTCC residents				
Hospitalized only	9/285 (3.2%)	42/285 (14.7%)	0.18 (0.08–0.37)	0.17 (0.08–0.36)
Died	16/285 (5.6%)	30/285 (10.5%)	0.44 (0.23–0.82)	0.42 (0.22–0.80)
Non-congregate setting patients				
Hospitalized only	131/3,113 (4.2%)	599/6,226 (9.6%)	0.40 (0.33–0.49)	0.39 (0.32–0.48)
Died	9/3,113 (0.3%)	138/6,226 (2.2%)	0.12 (0.06–0.24)	0.12 (0.06–0.24)

Abbreviations: CI, confidence interval; COVID-19, Coronavirus Disease 2019; LTCC, long-term congregate care; MAB, monoclonal antibody.

* Relative risk ratio (RRR) for the effect of receiving MABs. For example, if Ω_H is the relative risk of hospitalization (risk among those receiving MABs divided by risk among those not) and Ω_N is the relative risk of no adverse outcome, then Ω_H = (RRR)* Ω_N. Hence, as RRR decreases, so does the risk of hospitalization for those who receive MAB. The same reasoning holds for the mortality endpoint.

DISCUSSION

This was among the first population-based studies to evaluate the real-world effectiveness of MAB treatment for mild-to-moderate COVID-19 for preventing severe illness. In statewide, population-based samples matched on age, sex, race/ethnicity, symptom status, vaccination status, community COVID-19 risk, and timing of positive SARS-CoV-2 test relative to January 17, 2021, we found that the effect of MABs among those who received it was to reduce probability of hospitalization or death from 25.3% to 8.8% for residents of LTCC residents and from 11.8% to 4.5% for non-congregate settings patients, during periods when the Alpha and Delta strains of SARS-CoV-2 were predominant. The overall rates of hospitalization and mortality were higher than for the general population because the subpopulation who receives MABs, which was the focus of this analysis, is at much higher risk for these outcomes.

Our large, statewide study suggests that, prior to the emergence of the Omicron variant (B.1.1.529, BA.1, BA.1.1, BA.2, BA.3, BA.4, and BA.5 lineages), MABs were effective for preventing hospitalization and death in the context of real-word utilization. This finding is generally consistent with prior studies of real-world MAB use for preventing emergency department visits, hospitalization, intensive care unit admission, and/or mortality among patients of specific integrated health care systems or medical centers.[12-17] Although overall MAB utilization in our study was relatively low (30.1% among LTCC residents, 4.7% among non-congregate setting patients), this generally makes sense given the EUA criteria for MAB treatment, which generally required patients to be symptomatic (all ages) and have qualifying underlying conditions (ages 12–64 years).[2-5] We accounted for differences in underlying risk of hospitalization or death between patients who did and did not receive MABs by propensity score matching on available sociodemographic and clinical characteristics and time. We were not able to match on unmeasured factors that may have impacted likelihood of receiving MABs and risk of severe illness, such as key comorbidities that were required for younger people to receive MABs under the EUAs[2-5] and other social and structural factors that may influence access to MABs and health outcomes. Although the supply of MABs was limited during portions of the study period, we included the timing of patients' positive test results in our propensity score matching, which should help to account for temporal trends in MAB availability. Importantly, our results suggest that MABs were effective among both LTCC residents and non-congregate setting patients; however, the average age of non-congregate setting patients who received MABs in our study was about 60 years. Although we included younger patients who received MABs, additional research on the effectiveness of MABs specifically among eligible young patients would be useful.

Our study was conducted during a period where Rhode Island, like the rest of the United States, was experiencing the rapid emergence of multiple SARS-CoV-2 variants of concern or interest. For roughly the first half of the study period, the largest number of variants of concern detected in Rhode Island were Alpha 19, which has been found to be susceptible in-vitro to the four MAB regimens utilized during the study period.[2-5] The Delta variant emerged rapidly during the second half of our study period[19] and has reduced susceptibility to bamlanivimab monotherapy[20] (which was no longer in use in Rhode Island after April 2021)[21] and bamlanivimab/etesevimab[3], while susceptibility to casirivimab/imdevimab and sotrovimab were unchanged.[4, 5] Importantly, MAB effectiveness is expected to vary over time and by geography, depending on the SARS-CoV-2 strains in circulation and the MAB regimens utilized. In particular, although it was not in circulation during our analysis period, in-vitro studies suggest that the Omicron variant has reduced susceptibility to the MABs that were available during the study period,[3-5] and recently emerging Omicron sub-variants may have reduced susceptibility to a newer MAB that was granted EUA following the study period,[6] highlighting the need to reformulate, test, and manufacture MABs rapidly in response to circulating SARS-CoV-2 strains.

Our report has limitations. First, as mentioned above, we did not have full information on certain comorbidities required for MAB eligibility among young people under the EUAs [2-4] and associated with increased risk of hospitalization or death. Although we aimed to account for differences between patients who did and did not receive MABs using propensity score matching, our results may be subject to residual confounding by indication. Second, our MAB and hospitalization data systems only collected data from providers and hospitals in Rhode Island. Thus, we may be missing MAB treatment data and/or hospitalization data for Rhode Island residents treated or hospitalized out of state; however, this constraint is not likely to contribute systematically to bias in estimation of treatment effect. (In our manual review of notes from a subset of calls about MABs to patients who live in cities/towns bordering Massachusetts and Connecticut, we did not identify patients voicing their intention to receive MABs out of state. Additionally, of all deaths among Rhode Island residents, only 0.2% are known to have occurred out of state, which may suggest that a relatively small percentage of Rhode Islanders with severe illness were hospitalized out of state.) Third, the limited sample size of patients receiving MABs prevented us from stratifying our analysis by MAB drug type and time-period. As additional data are accrued, a follow-up stratified analysis would be useful. Fourth, data on symptom status are limited to the information reported to RIDOH as the reason for testing, during case investigation, and/or through symptom self-monitoring and may be incomplete. Finally, we required at least two weeks of follow-up time for assessment of hospitalization and fatality outcomes based on the usual time

between the positive SARS-CoV-2 test result date and hospital admission and death with COVID-19 in Rhode Island. Nonetheless, for patients diagnosed with SARS-CoV-2 at the end of our study period (e.g., late October 2021), we may be missing some delayed outcomes that occurred after November 11, 2021.

In conclusion, our analysis provides evidence that, prior to the emergence of the Omicron variant, MABs were an effective tool for preventing hospitalization and death among patients with mild to moderate COVID-19. Our analysis supports the idea that state and local health jurisdictions, health care systems, LTCC facilities, and individual health care providers strengthen efforts to make MABs with activity against currently circulating variants readily available and easy-to-access, even in the context of widespread SARS-CoV-2 vaccination, given challenges rapidly achieving herd immunity in all populations. Future research on real-world MAB effectiveness by drug type, time-period, and SARS-CoV-2 strain, as well as among young people with underlying conditions, would be useful to inform our understanding of which patients are most likely to benefit from MAB treatment over time.

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Disclosures

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Adoption of Complete Bilateral Salpingectomy for Permanent Contraception at Time of Cesarean Delivery in Rhode Island

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ABSTRACT

OBJECTIVE: Complete bilateral salpingectomy (CBS) can decrease the risk of developing ovarian cancer, although adoption of CBS at cesarean delivery (CD) for permanent contraception has been low. The primary objective was to measure the annual rates of CBS at CD before and after an educational initiative. The secondary objective was to assess rates of providers who offer CBS at CD and their comfort level with the procedure.

METHODS: We performed an observational study of OBGYN physicians who perform CD at a single institution. We compared the annual rates of CBS among CD with permanent contraception procedures from the year before and the year after an in-person OBGYN Grand Rounds presentation on December 5, 2019 reviewing the latest research on opportunistic CBS at the time of CD. To evaluate the secondary objectives, anonymous surveys were administered to physicians in-person the month before the presentation. The statistical analysis included chi-square, Fisher's exact test, T-test, ANOVA, and the Cochran-Armitage trend test.

RESULTS: After our educational intervention, annual rates of CBS at CD increased from 5.1% [12/05/2018–12/04/2019] to 31.8% [12/5/2019–12/4/2020] ($p<0.001$), and up to 52% in the last study quarter ($p<0.001$). Surgical outcomes were similar between tubal ligation and CBS, except for a 5-minute increased total operative time for CBS ($p=0.005$).

Fifty physicians completed the survey prior to the presentation (93% response rate). All physicians offered CBS at time of hysterectomy and interval sterilization, while only 36% offered CBS at time of CD. More physicians felt comfortable performing a CBS with bipolar electrocautery (90%) than suture ligation (56%).

CONCLUSION: Our presentation-based educational initiative was associated with a significant increase in performance of CBS at the time of CD.

KEYWORDS: complete bilateral salpingectomy, cesarean delivery, permanent contraception, risk reduction

INTRODUCTION

Permanent contraception procedures are commonly utilized postpartum and occur with 8–9% of all live births.[1] When performed at cesarean delivery, permanent contraception methods historically employed a tubal ligation approach which transects and removes a small mid-portion of the fallopian tube. Recent literature has found that up to 70% of serous ovarian cancer originates in the ends of the fallopian tube, which if removed, can theoretically decrease a woman's risk of ovarian cancer by 26–34% when compared to ligation alone.[2-4] Due to this potential risk reduction, ACOG recommended in 2015 that providers counsel women on the potential benefits of a complete bilateral salpingectomy (CBS) who are planning to undergo hysterectomy, routine pelvic surgery, or desire permanent contraception.[5] Since this publication, CBS has been rapidly adopted at time of hysterectomy, as well as interval sterilization; however, this trend has not yet been seen at time of cesarean delivery (CD) despite literature demonstrating its feasibility and safety.[6–8] Perceived barriers to implementation include higher rates of surgical complications due to increased vascularity of the gravid uterus and a lack of equipment.[9-11] There is a dearth of evidence about how to change providers' behavior to increase CBS at CD with only one prior study analyzing provider behaviors after an practice recommendation.[12] In this study, fewer than 10% of providers were performing CBS as the method of permanent contraception at time of CD, even after the practice recommendation.

The aim of this study was to assess physician practices in offering and performing CBS at CD before and after an educational initiative. The primary objective was to measure the annual rates of CBS at CD. The secondary objective was to assess rates of providers who offer CBS at CD and their comfort level with the procedure. Our hypothesis was that after an educational initiative, rates of CBS at CD would increase.

METHODS

We performed an observational study of obstetric and gynecologic (OBGYN) physicians who perform CD with the primary objective of assessing utilization of CBS at CD after an educational initiative. The study was performed at a high-volume hospital in Rhode Island that provides labor and delivery care to 80% of the pregnant patients in the state.

The educational initiative comprised of an OBGYN Department Grand Rounds presentation reviewing the latest research on opportunistic CBS at the time of cesarean delivery. The presentation highlighted current practices both nationally and at our home institution. The literature on feasibility, surgical outcomes, particularly on comparisons to tubal ligation, and cost effectiveness was reviewed. The different techniques to perform a CBS at CD and counseling discussion points for patients were outlined. The presentation comprised of a literature review and did not include a hospital-based position statement or policy. Handouts summarizing the presented material were made available in the physician lounge for independent review following the presentation. Otherwise, no further study-initiated interventions were performed.

Our primary objective was to compare the annual rates of CBS among CD procedures with permanent sterilization from the 12 months before and 12 months after the Grand Rounds presentation on December 5, 2019. All cases of cesarean deliveries with permanent contraception procedures, identified by procedure coding, were collected from the year before and after the presentation. The cases were reviewed and the type of permanent sterilization procedure was confirmed. Cases of cesarean hysterectomy were excluded from the analysis. Surgical techniques and operative details were abstracted from the charts. Intraoperative records were utilized to collect procedure techniques, total operative time (surgery start to end) and recorded estimated blood loss (based on discussion between surgical and anesthesia team). We described the types of sterilization methods applied during this time frame and also compared surgical outcomes between tubal ligation and CBS. Quarterly rates of CBS at CD were analyzed in the year following the intervention. Sub analysis was performed to determine annual rates of performing CBS at CD for sub-specialized maternal-fetal medicine physicians and generalist OBGYN physicians.

To examine our secondary objectives, anonymous surveys were administered to OBGYN attendings who perform CD. The paper survey was distributed in person to available physicians in the hospital one month before the educational intervention. Physicians were approached only once and no reminders were sent. The survey comprised of eight questions on patient counseling, surgical preferences, and perceived barriers.

The statistical analysis included chi-square and Fisher's exact test for categorical variables, T-test and ANOVA for continuous variables, and the Cochran-Armitage trend test. Based on our 2018 data of 388 CD with sterilization procedure (of which only 4.9% were CBS), we anticipated a sample size of at least 159 each year would allow us to detect a difference of 10% between rates of CBS at CD prior to and after the intervention with 80% power (alpha 0.05). The data was abstracted, coded and stored in REDCap and analyzed with SAS 9.4 (SAS Institute, Cary NC). STROBE guidelines for reporting observational studies were followed.[13] The study was approved by the Care New England Women & Infants Institutional Review Board (#1437846). Consent was obtained by the physician's willingness to complete the survey.

RESULTS

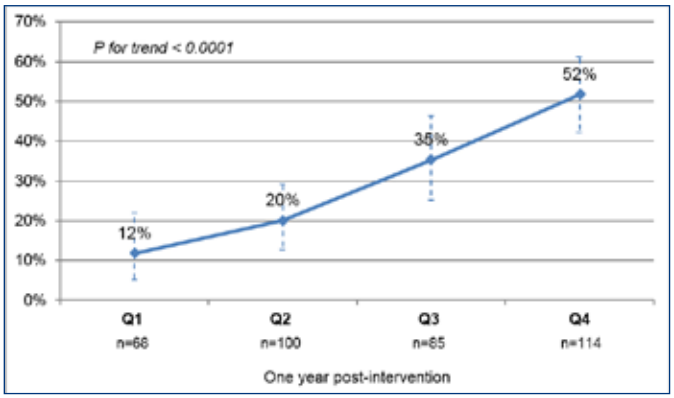
There were 370 CD with permanent contraception procedures (comprising 14% of all CD) during the year prior to our intervention, and 367 (13%) in the subsequent year (**Table 1**). Our primary objective analysis identified an increase in annual rates of CBS at CD from 5.1% [12/05/2018–12/04/2019] to 31.8% [12/5/2019–12/4/2020] (p<0.001). Moreover, rates of CBS increased with each quarter after the intervention (Q1: 12%, Q2: 20%, Q3: 35%, Q4: 52%; p<0.0001) (**Figure 1**). A rise in utilization was seen in both maternal-fetal medicine physicians (3% to 41%, p<0.0001) and generalist OBGYN physicians (5% to 30%, p<0.0001).

Data were aggregated over the two-year study period and comparisons in surgical outcomes were made between cases with tubal ligation (n=589) and CBS (n=136) (**Table 2**). There was no difference in estimated blood loss (p=0.48), although CD with CBS had a five minute longer total operative time (51 vs. 56min, p=0.005). When completing a CBS, suture ligation and bipolar electrocautery were utilized at similar rates

Table 1. Details of permanent contraception procedures performed at the time of cesarean delivery in the year prior to and following an intervention designed to increase the use of complete bilateral salpingectomy at the time of cesarean delivery

	One year pre-intervention n (%)	One year post-intervention n (%)	P-value
Cases			
Total number of cesarean deliveries	2706	2829	
Total number of cesarean deliveries with sterilization	370 (14)	367 (13)	
Complete bilateral salpingectomy	19 (5)	117 (32)	<0.0001
Tubal Ligation	351 (95)	238 (65)	
Mixed (unilateral salpingectomy)	0 (0)	12 (3)	
Type of Sterilization			
Tubal ligation method:			
Modified Pomeroy	263 (75)	198 (83)	0.05
Parkland	78 (22)	37 (16)	
Mixed	10 (3)	3 (1)	
Salpingectomy method:			
Suture ligation	8 (42)	53 (45)	0.18
Bipolar electrocautery	11 (58)	64 (55)	

Figure 1. The trend of quarterly rates of complete bilateral salpingectomy at cesarean delivery after the Grand Rounds educational presentation. Rates of complete bilateral salpingectomy at cesarean delivery increased with each quarter during the year after the educational intervention.



*quarterly rates with 95% CI error bars

Table 2. Comparison of delivery characteristics and surgical outcomes between tubal ligation and complete bilateral salpingectomy at cesarean delivery over a two-year period.

	Tubal Ligation (n=589)	Complete bilateral salpingectomy (n=136)	P-value
Delivery characteristics			
Repeat cesarean delivery, n (%)	490 (83)	105 (77)	0.11
Emergent cesarean delivery, n (%)	15 (3)	3 (2)	1.00
Total operative time (min) mean, [range]	51 [17, 140]	56 [24, 168]	0.005
Estimated blood loss (cc), mean, [range]	682 [200, 2500]	698 [300, 2400]	0.48

(45% and 55% in the year after the presentation, p=0.18). The two techniques had similar estimated blood loss (688 vs 710cc, p=0.59) and total operative time (55 vs 57min, p=0.55).

Survey data was analyzed to examine our secondary objectives. Of the 82 OBGYN physicians who performed CD at the time of survey data collection, 54 physicians were approached in person at faculty events during the month before the Grand Rounds presentation to complete the anonymous survey. Fifty physicians completed the survey prior to the presentation (93% response rate). All providers reported offering a CBS at the time of hysterectomy and interval sterilization, but only 36% providers reported offering CBS at CD (**Table 3**). The most common reasons providers listed for not offering a CBS at CD were increased bleeding, increased operative time, and inexperience. Seventy percent of survey respondents reported ever having completed a CBS. While

Table 3. Survey responses from OBGYN physicians regarding patient counseling, surgical preferences, and comfort level with performing opportunistic complete bilateral salpingectomy (n=50)

	Physician Responses n (%)
Patient counseling*	
Yes, I offer salpingectomy at time of hysterectomy	44 (100)
Yes, I offer salpingectomy at time of interval sterilization	43 (100)
Yes, I offer salpingectomy at time of cesarean delivery to patients who are considering permanent sterilization	18 (36)
Salpingectomy at Cesarean Delivery	
Has ever completed a salpingectomy at CD	35 (70)
Has completed a salpingectomy at CD using:	
Suture ligation	31 (89)
Bipolar electrocautery	16 (46)
Would feel comfortable completing a salpingectomy at CD using:	
Suture ligation	28 (56)
Bipolar electrocautery	45 (90)

*Percent refers to providers who perform the listed procedure and offer salpingectomy (excludes providers who do not perform the listed procedure).

90% of physicians reported that they would feel comfortable completing a CBS at CD with bipolar electrocautery, only 56% reported feeling comfortable using suture ligation.

DISCUSSION

After the educational intervention, there was a six-fold increase in rates of CBS at CD. By the last quarter of our one-year study period, over half of the sterilization procedures were CBS.

The literature on CBS at CD to date has largely revolved around feasibility, safety, technique, and only few have focused on practice changes. A 2017 study analyzed surgical patterns within a large integrated health care system after a system-wide practice recommendation was issued.[12] They found an increase in overall opportunistic CBS from 0.4% to 35%, and specifically for CBS at CD an increase from 0.1% to 9.2% over a five-year period. This study was performed shortly after the initial publication of the risk-reducing impact of CBS and explored its adoption within all sterilization procedures. Over recent years, opportunistic CBS has been implemented at varying rates, with one of the lowest seen at CD. Based on these inconsistent adoption practices, our study specifically focused on increasing opportunistic CBS at CD.

The limited published data comparing tubal ligation to CBS have found no difference in surgical outcomes including blood loss, wound infection, reoperation, or length of stay.[6,7,12,14] We similarly found no difference in estimated blood loss; however, we did note a slightly increased total

operative time (five minutes). Current literature has contradicting findings for increased operative time with CBS at CD when compared to ligation, with estimates ranging from 0–15 min, which is unlikely clinically significant. Similarly, we found no significant differences in surgical outcomes between the two methods to perform a CBS: suture ligation and bipolar electrocautery.

Multiple providers listed "inexperience" as a deterrent to offering CBS at CD which highlights the need for expanded educational efforts. Surgical simulation has previously been shown to be beneficial in development of technical skills and provider comfort with abdominal OBGYN surgery in low-fidelity models.[15,16] Application of simulation to CBS at CD may also improve physician comfort, continue to increase rates of CBS at CD, and possibly shorten operative time, although further research needs to be conducted.

This study illustrates the rising trend of CBS utilization at time of CD after an educational initiative and contributes to the limited data on physician performance of and patient counseling on opportunistic CBS. Although performed at a single institution, the physician survey sampled a large portion (61% [n=50/82]) of providers performing CD at a hospital that provides approximately 80% of deliveries within the state of Rhode Island.

Limitations of this study includes restricted external validity to institutions other than high-volume academic hospitals. Results were suspectable to the Hawthorne effect with physician completion of the survey thereby potentially further increasing rates of CBS at CD. The surveys were anonymous and their results cannot be cross referenced with the data abstracted from patient charts. External influences that cannot be accounted for include peer to peer discussions and journal publications that may have contributed to a larger culture shift within the hospital, as seen by the continued rise in CBS adoption throughout the year following the presentation. Data was not collected on providers motivation for behavior change which could further guide future targeted efforts.

Our observational study demonstrates the feasibility of increasing utilization of CBS at CD. Within a single year, we saw an increase in quarterly rates of CBS at CD from 5 to 52% in the first to final quarter. Targeted educational efforts can continue to increase knowledge and improve skills in performing a CBS at CD. Expansion of CBS at CD may potentially reduce future ovarian cancer diagnoses.

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Suicide-Related Mortality and Morbidity: Insights from Rhode Island's Violent Death Reporting and Syndromic Surveillance Systems

JONATHAN BARKLEY, MPH

INTRODUCTION

Suicide is a serious public health concern and leading cause of death among individuals 10–64 years old in the United States and Rhode Island.[1] Suicide deaths only reflect part of the problem as suicide-related morbidity also contributes to loss of productivity, healthcare costs, and long-term impacts within communities.[2] Through the Rhode Island Violent Death Reporting System (RIVDRS), the Rhode Island Department of Health (RIDOH) has collected data on suicides occurring in the state since 2004. Data are reported as part of the CDC's National Violent Death Reporting System and variables collected include demographics, toxicology, injury mechanism, and circumstances associated with the death. Complete mortality data in RIVDRS lag by approximately two years, thus timely data for suicide-related morbidity is helpful to inform prevention activities. Since June 2020, all 10 of Rhode Island's acute care hospitals have reported emergency department (ED) visit data into RIDOH's Electronic Surveillance System for the Early Notification of Community-Based Epidemics (ESSENCE) syndromic surveillance system. The suicide-related syndrome definition in ESSENCE aims to identify visits relating to suicide attempts and/or suicidal ideation based on chief complaint text and discharge diagnoses codes that are reported with the visit.[3] These data can estimate suicide-related morbidity and detect potential changes in a timely manner.

In this article, characteristics of suicide decedents are summarized and compared across the two most recent five-year time periods in RIVDRS. Characteristics of suicide-related ED visits during the two most recent completed years are also compared.

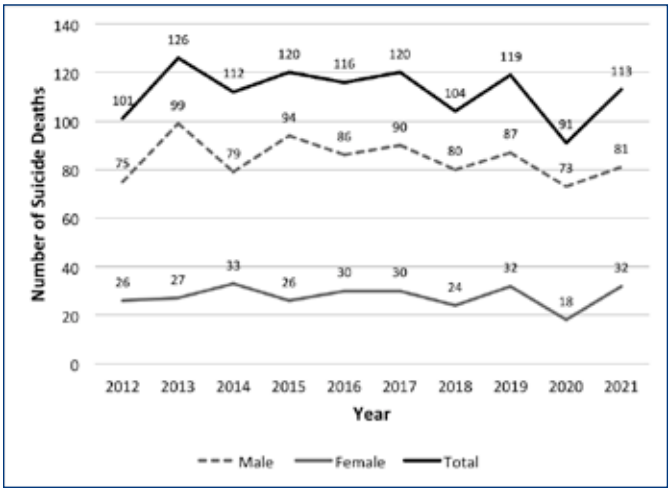
METHODS

Suicide deaths among Rhode Island residents during 2012–2021 were pulled from RIVDRS. Due to small numbers, deaths were combined into two five-year periods (2012–2016 and 2017–2021) and differences by sex, age group, race/ethnicity, residence county, and death mechanism were analyzed. Proportions were calculated based on the denominators for each characteristic and chi-square tests (α=0.05) were performed to determine whether proportions were significantly different over time. ED visits that met the suicide-related syndrome definition in ESSENCE[3] were pulled during 2021 and 2022. Visits among RI residents, ages 10 years and older, were included for this analysis. Similar methodology was used to calculate and compare proportions of suicide-related ED visits in ESSENCE by sex, age group, race/ethnicity, and residence county between 2021 and 2022. All analyses were performed using SAS (version 9.4).

RESULTS

A total of 1,122 suicide deaths among Rhode Island residents were reported in RIVDRS during the 10-year period of 2012–2021 (**Figure 1**). The number of deaths was observed to decrease in 2020; however, it has remained stable over time (annual average of ~112 suicide deaths).

Figure 1. Suicide deaths among Rhode Island residents that occurred in Rhode Island, total by year and sex, 2012–2021.
Data source: Rhode Island Violent Death Reporting System (RIVDRS).



No significant changes have been observed over time for several key characteristics, including sex, age group, mechanism of death, county, or race/ethnicity (**Table 1**, p>0.05). During both time periods, more than three-quarters of deaths occurred among males, and decedents were most likely to be White, Not Hispanic, between 45 and 64 years old, Providence County residents, and to die by means of strangulation/suffocation (**Table 1**).

More than half of the suicide-related ED visits were observed among females during both 2021 and 2022; no

significant differences by sex were observed over these years (**Table 2**, p>0.05). Significant changes over time were also not observed by race/ethnicity or residence county. Differences were observed by age group between 2021 and 2022 (data not shown); however, when stratified by sex, significant changes by age were only observed among females (p=0.0012). While the greatest proportion of suicide-related ED visits were observed among the 10–24 age group for both males and females, the proportion of visits observed among females in this age group was much higher. Notably during 2021, more than half of suicide-related ED visits detected among females were observed among those 10–24 years old, compared to approximately one quarter of the visits observed among males.

Table 1. Characteristics of Rhode Island suicide deaths reported in the Rhode Island Violent Death Reporting System (RIVDRS) during the five-year periods of 2012–2016 and 2017–2021.*

Decedent Characteristics	2012–2016 N=575 n (%)	2017–2021 N=547 n (%)	p–value†
Sex			
Male	433 (75.3)	411 (75.1)	0.9483
Female	142 (24.7)	136 (24.9)	
Age Group			
10–24	55 (9.6)	52 (9.5)	0.3884
25–34	81 (14.1)	87 (15.9)	
35–44	87 (15.1)	91 (16.6)	
45–54	148 (25.7)	112 (20.5)	
55–64	112 (19.5)	120 (21.9)	
65+	92 (16.0)	85 (15.5)	
Race/Ethnicity			
Hispanic	32 (5.6)	45 (8.2)	0.1281
White, Not Hispanic	515 (89.6)	471 (86.1)	
Black, Not Hispanic	22 (3.8)	19 (3.5)	
Other, Not Hispanic	6 (1.0)	12 (2.2)	
Residence County			
Bristol	33 (5.7)	28 (5.1)	0.8754
Kent	96 (16.7)	94 (17.2)	
Newport	48 (8.4)	46 (8.4)	
Providence	321 (55.9)	294 (53.9)	
Washington	76 (13.2)	83 (15.2)	
Mechanism of Death			
Strangulation, suffocation	236 (41.0)	223 (40.8)	0.8882
Firearm	148 (25.7)	148 (27.1)	
Poisoning	107 (18.6)	104 (19.0)	
Other	84 (14.6)	72 (13.2)	

*Percent calculations based on the characteristic totals with available data, thus some categories do not sum to the yearly totals. Percentages may not sum exactly to 100 due to rounding.
†Chi-square test; α=0.05.

Table 2. Characteristics of Rhode Island emergency department patients, ages 10 years and older, who were reported in RIDOH's syndromic surveillance system (ESSENCE) and found to meet the suicide-related syndrome definition during 2021 and 2022.*

Patient Characteristics	2021 N=6,004 n (%)	2022 N=5,935 n (%)	p–value†
Sex			
Male	2,872 (47.9)	2,900 (48.9)	0.2457
Female	3,126 (52.1)	3,025 (51.1)	
Age Group (Males)			
10–24	731 (25.5)	719 (24.8)	0.4584
25–34	626 (21.8)	581 (20.0)	
35–44	485 (16.9)	513 (17.7)	
45–54	459 (16.0)	485 (16.7)	
55–64	369 (12.8)	403 (13.9)	
65+	202 (7.0)	199 (6.9)	
Age Group (Females)			
10–24	1,568 (50.2)	1,363 (45.1)	**0.0012**
25–34	477 (15.3)	473 (15.6)	
35–44	319 (10.2)	348 (11.5)	
45–54	264 (8.4)	322 (10.6)	
55–64	251 (8.0)	263 (8.7)	
65+	247 (7.9)	256 (8.5)	
Race/Ethnicity			
Hispanic	840 (14.0)	786 (13.3)	0.5704
White, Not Hispanic	4,351 (72.6)	4,329 (73.2)	
Black, Not Hispanic	448 (7.5)	432 (7.3)	
Other, Not Hispanic	353 (5.9)	369 (6.2)	
Residence County			
Bristol	155 (2.6)	163 (2.7)	0.8779
Kent	1,319 (22.0)	1,340 (22.6)	
Newport	292 (4.9)	284 (4.8)	
Providence	3,471 (57.8)	3,411 (57.5)	
Washington	767 (12.8)	737 (12.4)	

*Percent calculations based on the characteristic totals with available data, thus some categories do not sum to the yearly totals. Percentages may not sum exactly to 100 due to rounding.
†Chi-square test; α=0.05.

DISCUSSION

Using the most recent 10 years of suicide death data from RIVDRS and two years of suicide-related ED visit data from ESSENCE, this article summarizes general characteristics of suicide mortality and morbidity in Rhode Island and changes over time. RIVDRS data show the burden of suicide deaths has remained relatively stable over time, without significant changes in the proportion of deaths by sex, age, race/ethnicity, county, or injury means. Decreasing suicide deaths during 2020 and increasing deaths during 2021 were observed in Rhode Island and nationally.[4] As characterized nationally, the risk for suicide death was consistently observed to be about three times higher among Rhode Island males compared to females.[5] White, Not Hispanic individuals represent the largest proportion of suicide deaths; however, these proportions have been observed to decrease relative to other racial and ethnic groups in Rhode Island and the United States.[6]

RIVDRS data are subject to some limitations of note. RIVDRS doesn't include Rhode Island residents who die in other states and several years of data often need to be aggregated to have sufficient sample size for analyses. Thus, year-to-year changes, if present, are difficult to identify due to limited sample power. Despite these limitations, RIVDRS data are critical to describe the burdens and trends in suicide deaths over time. RIVDRS data also include known circumstances associated with deaths, which help identify risk factors and inform prevention activities. These variables were not summarized in this analysis; however, should be considered in future publications.

ESSENCE syndromic surveillance data detected changes in suicide-related ED visits over time by age groups among females. This finding was likely driven by the increased proportion of suicide-related ED visits among females 10–24 during 2021. Increases in suicide-related morbidity among young females were also observed nationally during 2021. An analysis found ED visits relating to suicide attempts were higher during 2021 compared to 2019 and the largest relative increase was observed during March 2021.[7] These findings suggest young females may have suffered more distress due to impacts from the COVID-19 pandemic and should be targeted for prevention. Timely suicide-related morbidity data should continue to be analyzed among this group nationally and in Rhode Island.

Syndromic surveillance data are also subject to several limitations. Chief complaint and discharge diagnosis data are used to identify visits meeting the syndrome definition. Thus, visits may be misclassified as suicide-related visits based on word terms present in the chief complaint and coding errors for discharge diagnosis codes. Similarly, visits may be related to suicide attempts or suicidal ideation, but missing data in the chief complaint of diagnosis fields would prohibit the visit from being detected. Thus, syndromic data should be considered preliminary and may not represent the true burden of suicide-related visits. Despite these limitations, syndromic data are helpful to detect potential changes in real time and provide context to complementary data sources. While this analysis did not separate ED visits relating to suicide attempts from suicidal ideation, syndrome definitions exist for these conditions in ESSENCE. Suicide attempt-related visits represented approximately 15% of the suicide-related visits included in this analysis and further disparities among females were observed. In comparison to suicide-related visits shown in **Table 2**, approximately 63% of attempt-related visits were observed among females and more than 52% of these visits were observed among females in the 10-24 age group during 2021 and 2022.

This analysis was limited to patients 10 years old and older as suicide risk is difficult to ascertain among individuals less than 10 years old and no suicide deaths were observed in Rhode Island among individuals in this age group. Significant increases in suicide deaths among younger females was not observed in our analysis and has not been observed nationally; however, national data has shown rates of suicide deaths among females have generally decreased for age groups 25 years and older, while increasing for younger age groups.[5] Suicide death rates among females ages 10–15 were observed to increase by approximately 15% in 2021 compared to 2020; however, this increase was not statistically significant.[4]

Several factors likely contribute to the observed contrasts in suicide-related mortality and morbidity by sex and age. Attempt methods among males tend to be more violent, increasing the risk for suicide death. For example, 31.5% of suicide deaths among Rhode Island males involved firearms, compared to 9.7% among females. Younger individuals may be more likely to be seen at the ED for depression or other mental health concerns, which are linked with suicidal ideation. More frequent depression diagnoses among females have been observed and would contribute to the observed disparities. Younger females may also disproportionally experience feelings of isolation and other negative impacts from social media, which should be investigated further.

Despite significant changes in suicide mortality not being observed by the characteristics included in this analysis, findings from morbidity data suggest that it's important to continue to monitor data to identify and support people at greatest risk for suicide in Rhode Island. Strategies that promote healthy connections, improve access to care, and create protective environments are part of the comprehensive framework needed to reduce suicide-related mortality and morbidity.[2]

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COMPILED BY ROSEANN GIORGIANNI, DEPUTY STATE REGISTRAR

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

VITAL EVENTS	REPORTING PERIOD		
	OCTOBER 2022	12 MONTHS ENDING WITH OCTOBER 2022	
	Number	Number	Rates
Live Births	980	11,193	10.6*
Deaths	959	11,255	10.6*
Infant Deaths	3	43	3.8#
Neonatal Deaths	2	32	2.9#
Marriages	968	6,915	6.5*
Divorces	257	2,653	2.5*

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

Underlying Cause of Death Category	REPORTING PERIOD			
	APRIL 2022	12 MONTHS ENDING WITH APRIL 2022		
	Number (a)	Number (a)	Rates (b)	YPLL (c)
Diseases of the Heart	187	2,403	219.0	3,484.5
Malignant Neoplasms	174	2,197	200.2	4,034.5
Cerebrovascular Disease	36	503	45.8	537.5
Injuries (Accident/Suicide/Homicide)	82	1,101	100.3	15,803.0
COPD	26	447	40.7	395.0

(a) Cause of death statistics were derived from the underlying cause of death reported by physicians on death certificates.
(b) Rates per 100,000 estimated population of 1,097,379 for 2020 (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.

Embracing Change to Keep Finding Joy in Medicine

KEITH L. CALLAHAN, MD, MBA

The last few years living with the COVID-19 pandemic has given me a chance to think about my life choices. Being told to stay home gave me a chance to reassess what was important, the second time that this has happened to me. More about that later. What helped me to find the joy in medicine again and again was adapting to new circumstances. I may not want to continuously adapt, but I have found that this is the only path to reset my compass toward joy in life.

I have always wanted to be a physician. I can't explain it. I can remember as far back as second grade having the distinct feeling that I wanted to help others. My sixth-grade graduation yearbook has a caption under my picture where I said that I wanted to be a pediatrician so that I could help children. I knew that becoming a physician would be a very difficult road.

I went to medical school in Chicago. I was introduced to working long hours in the hospital during my third and fourth years. I rotated with cardiovascular surgeons during my first rotation. I was in awe of the power they had to save lives. Since I had very little experience in medicine, I felt that what I was witnessing was how medicine would always be. I remember a specific teaching point that the chief cardiovascular surgeon told me. The surgeon opened a clogged artery to show me how much plaque was in it. I was amazed that any blood could get through it at all. As he prepared the vein to bypass that artery, he said these words to me: "These cardiologists, they think they can get a balloon in this…it will never work." Of course, I took his words to be the final pronouncement on this topic as he was the experienced surgeon and I was the medical student. This was 1993 and our institution had a balloon angioplasty 6-month re-occlusion rate of about 50%. We did not have stents at my institution yet, so he can be forgiven for holding on to the present and fighting against the future. I am sure that over time, he had to adapt to the new circumstances as technology changed. I realized later that this was my first example of how medicine is constantly changing.

Changing pathways

I chose to go into an Ob/Gyn residency after medical school. I matched in Chicago at a program across the street from my medical school. So, I was able to stay in the same apartment complex. I thought, "this is great." I will be doing what I really enjoy and will not have to change a thing. There was one variable that I did not fully anticipate. This will sound unbelievable, but it turns out I like to sleep regular hours. I thought I would adapt to the new schedule but I just never did. I chose to switch career tracks and went through the match again and entered family medicine. It was the best move I could have made. But, it required me to change how I viewed my life trajectory and what I would be doing to help others. After I made that change, I found joy again.

Very early on as an attending physician, I was working for a hospital affiliated with my medical school in Chicago. This is where, for the first time, I had the real sense that the whole world could change permanently in an instant. I was working in the hospital seeing patients and there were television sets in every room. I had heard that morning before work that a terrible accident had happened in New York City. A plane had hit one of the towers of the World Trade Center. I went to the hospital and started seeing patients. While I was talking to a patient, I looked up and saw an airplane strike the other tower of the World Trade Center. I knew immediately that my whole life and the whole world had changed. Airplanes around the world were grounded. Very few people traveled. I had a year to think about what was important to me. I decided family and friends were most important and made a point of reaching out and reconnecting. I had been feeling so overworked and I did not have the perspective that I had a very fortunate life. I changed my view on many things and found joy in medicine again.

Health care shifts

In 2010, the Affordable Care Act (ACA) caused the whole health care system to move in a new direction. Health care would no longer be a cottage industry. It would become more like a series of integrated health systems. I had trained under the old set of rules and had the image of a solo office and going in to do the best job I could for the individual in front of me. I had to confront the new reality. I have joined a large group of other physicians and have adapted. Once I changed how I viewed how my future looked, I found the joy in medicine again.

I had always expected to see patients in the inpatient and outpatient setting. During training, I had heard that there were hospitals experimenting with a new concept called hospitalist medicine. I remember going to lectures 25 years ago where I was told that someday the United States would

have a system where physicians were either working in the hospital or in the outpatient setting, just like the system in the United Kingdom. I remember thinking to myself, "There is no way that doctors will only work in the clinic or the hospital…it will never happen." As the hospitalist movement dramatically accelerated after the 2010 ACA, I was forced to confront a new reality. I would have to give something up. I fought this change as long as I could and was miserable trying to hold on to the past. In the end I chose to be an outpatient only physician. Once I made the change, I again found the joy in medicine.

Hospitalist vs. outpatient medicine

Making the change to only outpatient medicine has allowed me to pursue a completely new way of thinking and become involved in another aspect of helping patients, my community, and my profession. I became involved in advocacy. I have more regular hours and I am now involved in organized medicine at the state and national level in a variety of ways. I sit on interesting Boards and have the opportunity to go to Washington D.C. and meet with Senators and Congressmen to discuss issues. None of this would have happened for me if I was not forced to change course yet again. I was unhappy with how my career was going. But, after making the change, I found the joy in medicine again.

Now I have lived through the COVID-19 pandemic. This surprisingly reminds me of the national response to the tragedy of 9/11 early in my career. We were told not to fly. This time, we were also told not to leave the house. I have had time to think about the nature of the work I am being asked to do. I have had the time to reflect on how much personal sacrifice I have made and what kind of work load is sustainable over the long-term. Many clinicians have decided to exit medicine all together. They cannot see a world where they will be happy working in this environment. I have decided that I will adapt again. I did not chose this new situation. But, just as I have made the change so many times before, I will adapt. I know that there will be new and interesting things that will make me happy to be working in the best profession I could imagine.

I have learned that the secret to finding the joy in medicine is to recognize that change is happening whether I like it or not. Nothing that I see in front of me is permanent. Everything is changing slowly, and then very fast. I have continuously changed course when new situations arise. Each time I was apprehensive about letting go of the past, but in the end, each time I changed, I found the joy in medicine again. ❖

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Cat N. Burkat, MD, FACS, (*left*) views the RIMJ archives during a break at the World Society of Ophthalmic Plastic Reconstructive & Aesthetic Conference 2023 which was held in Dubai, UAE. Dr. Burkat is a Professor in the Department of Ophthalmology and Visual Sciences, University of Wisconsin School of Medicine and Public Health. She was a member of the scientific program committee for WSOPRAS 2023.

Michael E. Migliori, MD, FACS, (*top*) in Dubai as a presenter at WSOPRS 2023, stands at Observation Level 154 in the Burj Khalifa, the world's tallest building since it opened in 2009. Towering over Dubai's skyline, the skyscraper has a height of 2,722 feet, or more than half a mile.

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W&I holds groundbreaking ceremony for Brown University Labor and Delivery Center

PROVIDENCE – Women & Infants Hospital broke ground on the Brown University Labor and Delivery Center at Women & Infants Hospital on May 10th. The event marked the first phase in the construction project to build the region's preeminent labor & delivery center, along with the Women's Health Research Institute.

Dimeo Construction Company has been selected to create the space, with an expected completion date of December 2024. The new unit will enhance birthing options, enlarge delivery rooms, and provide an equitable, state-of-the-art environment in which families can deliver their babies.

"I am so proud of our generous community whose continued philanthropic gifts have made this project a reality for local families. But we still need help. For decades, patients have turned to Women & Infants Hospital for high-quality care, especially in delivering their children safely into the world. But to care for future generations, it is imperative that we upgrade our facilities, so those who trust us to provide them with expert care receive the medically advanced environment they've come to expect and deserve from Women & Infants Hospital," said **SHANNON SULLIVAN**, W&I president and COO.

Women & Infants Hospital broke ground on the Brown University Labor and Delivery Center at Women & Infants Hospital on May 10th.

Plans for the new Brown University Labor & Delivery Center include larger rooms to accommodate a greater variety of birthing practices. And, the Women's Health Research Institute will tackle important projects including much-needed health equity research. Ultimately, the new unit will help meet Women & Infants Hospital's goal of eliminating disparities of care, as well as elevate every mother's birthing experience.

Outside rendering of the new center. The project will be comprised of a three-story addition including 20 labor and delivery rooms, as well as nurses' stations, a staff lounge, a locker room, and management offices.

A model of the new labor and delivery rooms.
[PHOTOS COURTESY OF WOMEN & INFANTS HOSPITAL]

During the event, Brown University President **CHRISTINA H. PAXSON** said, "What we're doing here matters for Rhode Island families. It matters because improved resources for clinicians and care providers translates into excellent patient and medical outcomes. And it means a more personalized birth experience for the families who come here, which is really important."

Gov. **DANIEL McKEE** called it a key step toward creating 21st century health care and investing in the future of Rhode Island. "This state-of-the-art facility will provide many new, good-paying job opportunities right here in our state, while contributing to a healthier Rhode Island." ❖

Researchers at Brown, NYU Langone, will measure impact of overdose prevention centers

NEW YORK CITY & PROVIDENCE – NYU Langone Health and Brown University's School of Public Health today announced a grant award from the National Institute on Drug Abuse (NIDA), part of the National Institutes of Health (NIH), to conduct research to measure the impact of some of the first publicly recognized overdose prevention centers (OPCs) in the United States, located in New York City and Providence, Rhode Island.

As part of this first-of-its kind research project, the interdisciplinary team of researchers will conduct a rigorous and comprehensive evaluation of the first publicly recognized OPCs in the country: two sites in New York City and one site that will open in Providence in 2024. The study seeks to enroll 1,000 participants in both New York and Providence over the age of 18 who already use drugs and have visited an OPC or other site providing harm reduction services.

According to the Centers for Disease Control and Prevention, more than 106,000 Americans died from drug overdoses in 2021 – the highest number in recorded history, reflecting a rate that has doubled since 2015. There are more than 200 overdose prevention centers in 14 countries globally, and international research shows they are associated with fewer overdoses, reductions in emergency department visits, increased access to addiction treatment, and improved public order.

There is an urgent need for data to determine the impact of overdose prevention centers in the United States, which has distinct healthcare delivery systems, social policies, and policing practices. The current U.S. overdose crisis is driven largely by fentanyl, a synthetic opioid up to 50 times more potent than heroin. Fentanyl is involved in about two-thirds of all U.S. overdoses.

"We have an unprecedented opportunity to study the first publicly recognized overdose prevention centers in the country across two different states, as well as the impact on the communities in which they operate," said **MAGDALENA CERDÁ, DrPH**, professor in the Department of Population Health at NYU Langone, director of its Center for Opioid Epidemiology and Policy, and one of the study's two lead investigators. "This research is urgently needed to inform policies that can best support public health, as more jurisdictions across the country consider implementing OPCs."

"The overdose crisis has touched every community across America. From coast to coast and across age, gender, and race/ethnicity – people are dying," said **BRANDON D.L. MARSHALL, PhD**, professor of epidemiology at the Brown University School of Public Health and the founding director of the People, Place & Health Collective at Brown University. "This groundbreaking study will help us determine whether and how OPCs are an effective public health tool as part of a more compassionate, evidence-based response to this crisis in the U.S."

From 2023 to 2027, a multidisciplinary team of researchers will conduct a multi-method, individual- and community-level evaluation of OPCs in New York City and Rhode Island. They will do the following:

- investigate whether enrolled participants who visit OPCs experience lower rates of fatal or nonfatal overdoses, drug-related health problems, and emergency department visits, and whether they are more likely to enter treatment for substance use disorders compared to people who use drugs but do not visit OPCs
- examine the community impact of OPCs by assessing whether neighborhoods surrounding OPCs experience a greater change in overdoses, public disorder such as drug-related litter, arrests and noise complaints, and economic activity compared to similar neighborhood blocks that do not have an OPC
- estimate the operational costs of OPCs and the potential cost savings to the healthcare and criminal justice systems associated with OPC use

No funds from the National Institutes of Health will be used to support the operation of overdose prevention centers. Grantees at NYU Langone and Brown will study the impact of sites already in operation to elucidate the study aims.

The study will involve repeated assessments over 4 years of the 1,000 study participants, with half from New York City sites and half from Providence, as well as qualitative and ethnographic methods and cost-effectiveness analysis.

"Overdose prevention centers have saved lives over the past year," said **ASHWIN VASAN, MD, PhD**, commissioner of the New York City Department of Health and Mental Hygiene. "Their operation in New York City also offers a unique opportunity in the years ahead to learn about their clients, the services offered, and their wider impact on the communities served. We look forward to partnering with NYU Langone, OnPoint, and the State of Rhode Island on a robust, long-term study. The findings, when they're ready, could have national implications as we all fight the rising tide of overdose deaths in the U.S. In the meantime, we will proudly continue to work with our partners at OnPoint, as they bring lifesaving resources to New Yorkers."

"We are so proud of the work we are doing in the first two overdose prevention centers in the U.S., and we look forward to providing access to the teams at NYU Langone and Brown to rigorously evaluate our services and related outcomes," said **SAM RIVERA**, executive director of OnPoint. OnPoint and Project Weber/RENEW are operating the OPCs in each jurisdiction but will not receive NIH funding as part of this study.

This study will be a part of the NIH Harm Reduction Research Network, which was established in 2022 to test harm reduction strategies in different community settings to inform efforts to help save lives.

Funding for the study was provided by the National Institute on Drug Abuse, part of the National Institutes of Health, under grant number R01DA058277. ❖

New data show health care spending in Rhode Island rebounded in 2021 after pandemic-driven declines

Office of the Health Insurance Commissioner's findings underscore need to remain vigilant about state health spending

CRANSTON – Overall health care spending in Rhode Island rebounded in 2021 following an increase in utilization of health care services that were delayed or canceled in 2020 at the height of the COVID-19 pandemic, according to new data from the Office of the Health Insurance Commissioner (OHIC). The data show that health care spending increased most significantly in the commercial market (9.7%) followed by Medicare (8.0%) during 2021 after a 2.9% decline in overall spending per person the year prior. On average, health care spending increased from $7,887 to $8,262 per person in the state.

Spending growth was driven by increased spending on hospital outpatient services (10.2%), professional physician services (7.9%), and other professional services (13.1%).

These findings come on the heels of research from the Health Care Cost Institute showing a 15% increase in health care spending nationwide for people with commercial health insurance in 2021. In addition to falling below the national average for spending growth, Rhode Island had lower commercial health care spending growth than other states with publicly available cost growth data, including Connecticut, Delaware, and Massachusetts.

"Rising health care spending in the commercial market erodes wage growth and places significant financial burdens on working Rhode Islanders," said Acting Health Insurance Commissioner **CORY KING**. "With the costs of housing, utilities, and other necessities rising, it is imperative that we attain insight into the drivers of health care spending growth," he continued. "This insight will guide policy to allocate our health care dollars more wisely so that we are able to make strategic investments in the health care workforce that are necessary to support the health and wellbeing of Rhode Islanders, while promoting affordability."

The new health care spending data are collected through OHIC's Health Spending Accountability and Transparency Program. OHIC will use the data to monitor the performance of the health care system and shape solutions to contain rising health care costs to promote more affordable, high-quality care for Rhode Islanders. In addition to the Health Spending Accountability and Transparency Program, OHIC convenes the Cost Trends Steering Committee, which is comprised of leaders from health care provider organizations, employers, academia, consumer advocates, and payers who are committed to producing more sustainable health care costs and improving the health care system more broadly.

The new OHIC analysis compares health care spending growth in 2021 to a "benchmark" that was determined in collaboration with health care leaders to keep increasing costs in check. The benchmark for health care spending growth in 2021 was 3.2 – equivalent to the long-term forecasted growth of Rhode Island's economy. In 2021, commercial spending grew three times faster than the benchmark at a rate of 9.7%. ❖

AMA applauds FDA committee on recommending over-the-counter birth control

JACK RESNECK JR., MD
PRESIDENT, AMERICAN MEDICAL ASSOCIATION

"The AMA strongly supports removing the prescription-access barrier to contraception by making oral contraceptives available over-the-counter. Given that access is one of the most cited reasons why patients do not use oral contraceptives, use them inconsistently, or discontinue use altogether, we are pleased that the Nonprescription Drugs Advisory Committee and the Obstetrics, Reproductive, and Urologic Drugs Advisory Committee voted unanimously today in support of allowing a progestin-only birth control pill to be available without a prescription.

"More than 60 years of safe and effective use of oral contraceptives have shown that the benefits of widespread, nonprescription availability far outweigh the limited risk associated with their use – with evidence showing that pregnancy poses much greater health risks. The data not only highlights the safety and efficacy of oral contraceptives, but also demonstrates that women are able to successfully use checklists to self-identify contraindications and determine whether they're eligible and safe to use. While it is important for patients to have ongoing relationships with their physician and stay up-to-date on appropriate screenings and treatments, those are not necessary before starting contraception.

"At this tumultuous time for reproductive health in the United States, allowing access to OTC oral contraceptives is a safe and necessary step that must be taken to ensure that all individuals are able to effectively limit unintended pregnancies, particularly those with limited access to health care options. We urge the FDA to act swiftly to approve over-the-counter access to oral contraceptives without an age restriction." ❖

APA panel issues recommendations for adolescent social media use

Calls for social media literacy training, screening for 'problematic' online behaviors

WASHINGTON – A presidential panel of the American Psychological Association (APA) has issued recommendations for the use of social media by adolescents, noting that while these platforms can promote healthy socialization, their use should be preceded by training in social media literacy to ensure that youth have skills that will maximize the chances for balanced, safe and meaningful experiences.

"Social media is neither inherently harmful nor beneficial to our youth," said APA President **THEMA BRYANT, PhD**. "But because young people mature at different rates, some are more vulnerable than others to the content and features on many social media platforms that science has demonstrated can influence healthy development.

"Just as we require young people to be trained in order to get a driver's license, our youth need instruction in the safe and healthy use of social media."

In an effort to provide guidance to educators, parents, policymakers, mental health and health practitioners, technology companies and youths themselves, Bryant formed an advisory panel to examine relevant scientific literature to formulate recommendations to ensure that adolescents develop healthy social media practices. The result is the American Psychological Association Health Advisory on Social Media Use in Adolescence, which contains 10 recommendations.

The report also recommends psychological competencies that youth should possess before using social media, plus periodic booster training to minimize the chances for harm and maximize the benefits that social media can provide.

The health advisory notes that not all findings apply equally to all youth. "Scientific findings offer one piece of information that can be used along with knowledge of specific youths' strengths, weaknesses and context to make decisions that are tailored for each teen, family and community," it says. "Age-appropriate use of social media should be based on each adolescent's level of maturity (e.g., self-regulation skills, intellectual development, comprehension of risks, and home environment)."

Among the report's other recommendations:

- Tailor social media use, functionality and permissions to youths' developmental capabilities; designs created for adults may not be appropriate for children.
- For younger kids, adults should monitor social media use, including discussing and coaching around social media content. This should be balanced with youths' appropriate needs for privacy. Autonomy may increase gradually as kids age and gain more digital literacy skills.
- Minimize adolescents' exposure to social media content that depicts illegal or psychologically maladaptive behavior, including content that instructs or encourages youth to engage in self-harm or high-risk behaviors or those that encourage eating-disordered behavior (such as restrictive eating, purging or excessive exercise).
- Minimize adolescents' exposure to online content that promotes discrimination, prejudice, hate or cyberbullying, especially directed toward groups targeted because of race, ethnicity, gender, sexual orientation, religion or disability status.
- Monitor adolescents for signs of problematic social media use that can impair their ability to engage in daily roles and routines and may present risk for more serious psychological harms over time.
- Limit social media use so as not to interfere with adolescents' sleep or physical activity, as each is required for healthy brain and psychological development.
- Limit adolescents' use of social media for primarily beauty- or appearance-related content.

The report is careful to note that, given the publicly available research, it is not possible to determine if social media is the cause of harmful impacts on youth. In addition, there have been relatively few studies conducted with youth from racial, ethnic, sexual, gender, socioeconomic or differently abled populations, and/or youth with chronic developmental or health conditions.

The report calls for "a substantial investment in research funding" and access to more data, including data from tech companies.

"We hope these recommendations will be helpful as we all try to keep pace with the rapidly shifting social media ecosystem," said APA CEO **ARTHUR C. EVANS Jr, PhD**. "APA will continue to keep tabs on developments within the current and future platforms, with an eye toward safeguarding our youth and enabling them to benefit from the positive aspects of social media."

These recommendations are based on psychological science and research from related disciplines at the time of the report's writing (April 2023). Collectively, these studies were conducted with thousands of adolescents who completed standardized assessments of social, behavioral, psychological and/or neurological functioning, and reported (or were observed) engaging with specific social media functions or content.

The advisory panel was co-chaired by **MARY ANN McCABE, PhD**, associate clinical professor of pediatrics at George Washington University School of Medicine and an APA Board member, and **MITCH PRINSTEIN, PhD**, APA's chief science officer and the John Van Seters distinguished professor of psychology and neuroscience at the University of North Carolina at Chapel Hill. ❖

Alzheimer's drug studied at Butler Hospital's Memory and Aging Program shown to significantly slow cognitive and functional decline

Donanemab expected to be submitted soon for FDA approval

PROVIDENCE – Eli Lilly and Company announced on May 3 positive results of the TRAILBLAZER-ALZ 2 Phase 3 study showing that the investigational drug donanemab significantly slowed cognitive and functional decline in people with early symptomatic Alzheimer's disease (AD).

In a press release announcing the study findings, Eli Lilly reported that the study showed a 35% slowing of clinical and functional decline, and that 47% of participants on donanemab showed no decline on CDR-SB (a key measure of disease severity at one year), compared to 29% of participants on placebo. Participants also had a 40% less decline in the ability to perform activities of daily living at 18 months and a 39% lower risk of progressing to the next stage of disease compared to placebo.

"The TRAILBLAZER Phase 3 results represent a major advance in the treatment of AD," said **STEPHEN SALLOWAY, MD, MS**, founding director of the Memory and Aging Program and of Neurology at Butler Hospital and the Martin M. Zucker professor of Psychiatry and Human Behavior and professor of Neurology at the Warren Alpert Medical School of Brown University. Dr. Salloway was the principal investigator for the Phase 2 study of donanemab at Butler Hospital and was a co-author of the publication of that study in the *New England Journal of Medicine*.

Donanemab works by targeting the amyloid plaque build-up in the brain that is associated with the development of AD. The TRAILBLAZER Phase 3 study showed that, in addition to slowing cognitive and functional decline, donanemab produced significant reductions in brain amyloid plaque levels as early as 6 months after initiating treatment, with many patients reaching amyloid levels considered negative for pathology, as observed using amyloid positron emission tomography (PET) brain scans.

"The results of this study build on the positive results from previous studies, including the study of lecanemab which is currently under review for full approval from the FDA," Dr. Salloway said. "The TRAILBLAZER Phase 3 study also included important new innovations, such as using amyloid and tau PET scans to accurately identify individuals with early stages of the disease. It also implemented rules for stopping the medication once amyloid levels were considered negative for Alzheimer's based on PET findings."

Dr. Salloway says that taken together, these studies show that lowering amyloid plaque can improve quality of life for patients with early Alzheimer's disease. However, he notes that lowering amyloid plaque can also come with side effects, most notably temporary fluid shifts and swelling in the brain, called amyloid-related imaging abnormalities, or ARIA. ARIA is usually transient and without symptoms, but can be more serious or rarely, fatal.

Patients and families need to weigh the potential benefits of donanemab against the risks, and providers need to carefully monitor patients to safely manage this potential side effect. The Butler Memory and Aging Program is participating in ALZ-NET, a new network developed by the Alzheimer's Association and the American College of Radiology to help clinicians monitor the safety and efficacy of new disease-modifying medications for Alzheimer's such as donanemab. ❖

FDA approves first drug to treat agitation symptoms associated with Alzheimer's

WASHINGTON, DC – On May 11th, the U.S. Food and Drug Administration announced the supplemental approval of Rexulti (brexpiprazole) oral tablets for the treatment of agitation associated with dementia due to Alzheimer's disease. This is the first FDA-approved treatment option for this indication.

The effectiveness of Rexulti for the treatment of agitation associated with dementia due to Alzheimer's disease was determined through two 12-week, randomized, double-blind, placebo-controlled, fixed-dose studies. In these studies, patients were required to have a probable diagnosis of Alzheimer's dementia; have a score between 5 to 22 on the Mini-Mental State Examination, a test that detects whether a person is experiencing cognitive impairment; and exhibit the type, frequency, and severity of agitation behaviors that require medication. Trial participants ranged between 51 to 90 years of age.

In the first study patients received 1 or 2 milligrams (mg) of Rexulti; in the second study patients received 2 or 3 mg of Rexulti. The primary efficacy endpoint in these two studies was the change from baseline in the Cohen-Mansfield Agitation Inventory total (CMAI) score at week 12. CMAI is a survey tool that uses input from caregivers to rate the frequency of certain agitative behaviors in dementia patients on a scale from 1 to 7. In both studies, patients who received 2 mg or 3 mg of Rexulti showed statistically significant and clinically meaningful improvements in total CMAI scores compared to patients in the placebo group at week 12.

The recommended starting dosage for the treatment of agitation associated with dementia due to Alzheimer's disease is 0.5 mg taken once daily on days 1 to 7.

Patients should increase the dosage on days 8 through 14 to 1 mg once daily, and on day 15 to 2 mg once daily. The recommended target dose is 2 mg once daily. The dosage can be increased to the maximum recommended daily dosage of 3 mg once daily after at least 14 days, based on clinical response and tolerability.

The most common side effects among patients with agitation associated with dementia due to Alzheimer's disease include headache, dizziness, urinary tract infection, nasopharyngitis, and sleep disturbances (both somnolence and insomnia). Rexulti will retain the Boxed Warning for medications in this class that elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.

The FDA granted this application Fast Track designation. The supplemental approval of Rexulti was granted to Otsuka Pharmaceutical Company Ltd., and Lundbeck Inc. ❖

Reed & Whitehouse secure grants for Newport Mental Health Center

NEWPORT – U.S. Senators **JACK REED** and **SHELDON WHITEHOUSE** recently joined officials at the Newport Mental Health Center (NMH) to commemorate Mental Health Awareness Month in May and deliver $201,000 in federal funding to assist both youth and older adult residents with mental health needs and improve health outcomes.

According to the National Alliance on Mental Illness (NAMI), one in six American youth experience a mental health condition annually; with only half of them receiving treatment. And, according to data from the Centers for Disease Control and Prevention (CDC), suicide rates are highest among men 65 and older, a clear indication of unmet mental health needs in the older adult community.

Further, the COVID-19 pandemic exacerbated mental health challenges across age groups.

To help NMH address these challenges, Reed and Whitehouse secured a pair of federal earmarks to expand access to mental health services for younger and older residents:

- Senator Reed secured a $100,000 earmark for the expansion of free mental health services delivered to youth and young adults in Newport County. Under the project, NMH will expand its services to at-risk youth by enhancing its school and office-based treatment services and behavioral health interventions. NMH is adding specialized comprehensive mobile crisis services for 150 high-need students per year in four local school districts. The project will also expand emergency crisis services to children at risk of serious emotional disturbance.
- Senator Whitehouse secured a $101,000 earmark for a project called Mental Health Care for Older Adults to Meet Growing Demand. NMH will use the federal funds to increase outreach activities to better identify and engage older adults with substance use and mental health issues, and to provide evidence-based, age-appropriate treatment to at-risk seniors at their home or in their community.

Senator Reed noted that the most recent data from the CDC Youth Risk Behavior report shows teens – especially girls – are experiencing shockingly high levels of depressive symptoms, suicidal thoughts, and mental health challenges. Nearly 1 in 3 high school girls reported in 2021 that they seriously considered suicide and nearly 60 percent of teenage girls reported feeling so persistently sad or hopeless almost every day for at least two weeks in a row during the previous year that they stopped regular activities.

In 2022, Reed and Whitehouse helped include $3 billion for school and community-based mental health and trauma-informed care in the Bipartisan Safer Communities Act (P.L. 117-159), which President Biden signed into law. They also provided $280 million in FY23 to help meet students' mental health needs, including federal grants allowing school districts across the country to hire approximately 5,400 mental health professionals and train approximately 5,500 more to build a diverse force of mental health care providers in schools.

"I want to thank Senators Reed and Whitehouse for championing the needs of people with mental health and substance use disorders. These funds provided to Newport Mental Health address two of the largest unmet needs for mental health services in Newport County, those of children and our older adults. These age groups are experiencing the fastest growing demand for our services," said NMH President & CEO **JAMIE LEHANE**.

In addition to the federal funding announced, Rhode Island is one of 15 states that was recently awarded a $1 million, one-year planning grant to be considered among the final ten states that will be chosen in 2024 to participate in the Certified Community Behavioral Health Clinic (CCBHC) Medicaid demonstration program. ❖

Lifespan receives state licensure as approved nursing assistant training program

PROVIDENCE – Lifespan recently announced its nursing assistant school has been licensed by the Rhode Island Department of Health as an approved training program for nursing assistants. As a state-licensed school, Lifespan will provide both classroom and clinical instruction to nursing assistant students in a program that meets the Rhode Island Department of Health's training requirement for the nursing assistant license. The license significantly increases Lifespan's ability to prepare more individuals to serve in this critical health care role.

Through this program, Lifespan registered nurse educators will provide classroom instruction to nursing assistant students in addition to hospital-based clinical training on the practical application of nursing assistant duties, and lab instruction in the Lifespan Medical Simulation Center.

Unemployed and underemployed Rhode Islanders can apply to Lifespan's nursing assistant training program for free, through funding from the Papitto Opportunity Connection. This support provides a mutual benefit of no-cost career pathways for underserved individuals and a diverse pipeline of talent for hard-to-fill roles at Lifespan.

Additional unique advantages of the Lifespan nursing assistant training program include:

- Free tuition, classroom supplies, and wrap around support (i.e., books, childcare, transportation)
- Convenient virtual classroom instruction
- Employment transition coordinator services to bridge internships to future employment
- Opportunity for employment at Lifespan hospitals for qualified graduates

Students will be trained in Lifespan values, processes and systems from the start, so eventual hires can hit the ground running and will be well prepared for success.

Lifespan is currently recruiting for the first class in July. Class sessions will be held four times per year. ❖

Westerly Hospital reaps benefits of solar system

WESTERLY – Westerly Hospital is tapping into electricity from a solar farm in Smithfield.

Located an hour north of the hospital, a 28,000 ground-mounted solar panel farm is generating power for the hospital, resulting in annual savings of more than $400,000 through virtual net metering. The solar farm, operated by Kearsarge Energy, generates bill credits for every kilowatt-hour of energy produced. These credits are applied to Westerly Hospital's electricity accounts with Rhode Island Energy.

[PHOTO COURTESY OF YALE NEW HAVEN HEALTH]

"Participating in a community solar program enables us to be good stewards of our financial resources while also contributing to the growth of clean energy in Rhode Island," said **PATRICK GREEN**, president and CEO of Westerly Hospital, part of the Yale New Haven Health System.

Westerly Hospital is the first hospital to subscribe to Kearsarge Energy's newest solar farm project which will generate more than 14 million KWH annually. The hospital is also the first Yale New Haven Health facility to benefit from solar energy. The commitment to renewable energy sources at Westerly hospital follows on the heels of Lawrence + Memorial Hospital's installation of fuel cells on the hospital property last year.

According to the Rhode Island Office of Energy Resources, Virtual Net Metering allows eligible customers to connect their electric load regardless of whether the renewable system is located on the customers properties. Eligible Virtual Net Metering customers include state agencies, quasi-state agencies, municipalities, public housing authorities, public schools, private schools, non-profits, federal government and hospitals.

The emissions, air pollutants and water reductions are equivalent to greenhouse gas emissions from 2,264 passenger cars driven for one year, CO_2 emissions from 1,182,320 gallons of gasoline consumed and carbon sequestered by 12,435 acres of forest in one year. ❖

Appointments

Francesca Beaudoin, MD, PhD, appointed chair of the Department of Epidemiology at Brown School of Public Health

PROVIDENCE – After leading the Department of Epidemiology in an interim capacity for over a year **DR. FRANCESCA BEAUDOIN**, associate professor of epidemiology and of emergency medicine, has been appointed chair of the Department of Epidemiology effective July 1, 2023. A clinical epidemiologist and practicing physician, Dr. Beaudoin began her academic career as assistant professor in the Department of Emergency Medicine at the Warren Alpert Medical School in 2010. Conducting research at the intersection of pain, opioid use, and opioid use disorders, her work is widely recognized as impacting the landscape of pain management and improving post-overdose care in acute care settings. A frequent collaborator with state stakeholders, she also leads an initiative at Brown focused on the health effects of Long COVID and serves the community providing clinical care at the nation's first mobile methadone clinic. ❖

Sherri L. Sprague named Kent's Senior VP for Patient Care Services & Chief Nursing Officer

WARWICK – **SHERRI L. SPRAGUE, MHA, BSN, RN, CENP**, has been named as Kent Hospital's new Senior Vice President for Patient Care Services & Chief Nursing Officer.

Sprague has been part of the Care New England/Kent Hospital family since 2005 and has repeatedly proven herself to be a valuable leader in the healthcare system. She has held numerous leadership roles including interim CNO, Associate Chief Nursing Officer (ACNO) of ED and Ambulatory Services for Kent Hospital, ED Nurse Director at Kent, and ED Nurse Manager at Memorial Hospital.

Her leadership skills have also been recognized outside of the organization as she was awarded the 2022 Providence Business News–40 Under Forty Award and was appointed as a member of the special legislative commission at the RI State House to study and provide recommendations to RI political leaders.

Sprague is a graduate of Salve Regina University where she earned her Bachelor of Science in Nursing and Master of Science in Health Care Administration. ❖

Appointments

Gov. McKee nominates Richard Charest to serve as Executive Office of Health and Human Services Secretary

PROVIDENCE – Governor Dan McKee recently announced his appointment of current Department of Behavioral Healthcare, Developmental Disabilities & Hospitals (BHDDH) Director **RICHARD CHAREST** to serve as the next Secretary of the Executive Office of Health and Human Services (EOHHS). The Governor has sent Charest's name to the Rhode Island Senate for advice and consent.

Charest has more than 30 years of experience in the health care sector, leading not-for-profit and for-profit community hospitals with specialty programs and a for-profit specialty hospital. Previously serving as President and CEO of Landmark Medical Center, Charest successfully led hospital operations and finances through receivership, reassured the community and engaged employees and medical staff to ensure uninterrupted high-quality care. He also served as President and CEO of the Rehabilitation Hospital of Rhode Island and held several executive leadership positions with Landmark Medical Center. Charest has served as BHDDH Director since 2021.

ANA NOVAIS, who has been serving as Interim OHHS Secretary since the departure of Womazetta Jones, will return to her role as Assistant EOHHS Secretary.

DR. LOUIS CERBO, Deputy BHDDH Director, will serve as Interim BHDDH Director until a permanent selection is made. ❖

Recognition

HopeHealth gala supports exceptional care for hospice and palliative patients

PROVIDENCE – HopeHealth, the leading non-profit provider of hospice, palliative and home health care in the region, will host its annual gala, "An Evening of Hope & Gratitude," on June 8, 2023, 5:30pm, at WaterFire Arts Center in Providence. The event will raise funds to support HopeHealth's mission of providing compassionate care, support, and education to hospice and palliative care patients and their families.

During the gala, HopeHealth will honor outstanding individuals with three unique awards:

The Human Dignity Award will be presented to **RICHARD W. BESDINE, MD**, and **TERRIE FOX WETLE, PHD**, who have dedicated their careers to research, education and policy to improve the care of people at end of life. Dr. Besdine, until his stepping down from leadership in 2020, was inaugural Greer Professor of Geriatric Medicine at Alpert Medical School of Brown University and Interim Dean of Medicine from 2002 to 2005. Dr. Wetle, a gerontologist, was founding dean of Brown University's School of Public Health.

The Distinguished Advocate Award will be presented to U.S. Senator **SHELDON WHITEHOUSE**, a champion for end-of-life care in the U.S. Senate, emphasizing Rhode Island as a leader in patient-centered care. He is known on Capitol Hill for his passion about care at the end of life and his work to make healthcare better for all Rhode Islanders and Americans.

The Spirit of Hope Award will recognize the extraordinary expertise and compassion of HopeHealth hospice aide, **PATRICK WALLACE, CHPNA**, whose commitment to patients and families embodies hospice and palliative care at its best. Employed at HopeHealth since 2007, Wallace was nominated by his peers who praised his expertise and leadership. One nominator commented that he is "a shining example of the HopeHealth spirit."

The fundraiser is hosted by The Public's Radio morning host **LUIS HERNANDEZ**. Guests will enjoy cocktails, a three-course dinner, live music and a "Mystery Box" drawing for a getaway at Newport's Wellington Resort.

Sponsorship opportunities are still available for companies and individuals who wish to support HopeHealth's mission. "The support of our community makes it possible for HopeHealth to provide important services, such as grief support, veterans' programs, Alzheimer's and dementia services and free care for the uninsured," says **SUZANNE FORTIER**, chief philanthropy officer at HopeHealth. "And 100% of the proceeds from this event support patients and families in need of compassionate care."

For more information about "An Evening of Hope & Gratitude," please visit HopeHealthCo.org/2023Gala. ❖

Obituaries

JOHN B. CHRISTY, IV, MD, 29, of Cranston and Warwick, passed away unexpectedly on April 24, 2023. Born July 18, 1993, in Providence, he was the beloved son of John B. Christy III and Joan J. M. (Mancini) Christy, and the twin brother of Mary-Evelyn V. Christy. In addition to his parents and sister, John is survived by his loving fiancée Grace Chen and her adoring family of North Attleboro, MA.

John graduated high school from La Salle Academy in 2011 in Providence. He went on to graduate with a bachelor of science degree summa cum laude from the University of Rhode Island in 2016, where he was a founding member of the Sigma Chi Fraternity, an experience he always thought back on with much fondness. He went on to be accepted into the medical program at New York Medical College in 2017 and graduated in 2021, a feat he, his family, and his fiancé were so incredibly proud of. John went on to be accepted into the residency program at Kent Hospital, where he was able to care for patients alongside his incredible team.

John was a true Rhode Islander, he loved Narragansett Bay and a cold Narragansett beer, and never wanted to leave the state for long periods of time. He loved nothing more than a day out on the water. In 2021, his best friend Brock Thompson introduced John to fishing, which instantly became his beloved pastime, spending many hours at his favorite fishing spots around the State. On warmer days, you could find him racing around on his boat, The Blacktip, out on the waterways of Rhode Island. When he wasn't out chasing his next greatest catch, John was in the kitchen cooking up his latest gourmet recipe.

John's beloved dog Winston took up much of his time as well, with daily wrestling matches taking place on the kitchen floor, to the amusement of the whole family. John also had an affinity for music and would rock out on his drum set either solo, or in years past, with his band.

He tried to live his life to the fullest, a lesson his family and loved ones will carry on through their lives. John was an avid proponent of organ donation, and we ask if you ever find yourself in the position, please consider donating and saving a life. We are very proud to say that that was John's last act of selflessness on this earth. In lieu of flowers, memorial donations to the ASPCA or any animal shelter are greatly appreciated to honor John's memory and love for animals.

Please share memories and condolences at www.Woodlawn-RI.com ❖

MARCIA KATZ, MD, 65, died on March 26th after a three-year relentless battle against pancreatic cancer. Although she entered the world just five minutes behind her identical twin Debbie, Marcia forged her own path. Born to Trudy and the late Jerome Katz of Cranston, Marcia spent her early years exploring the flora and fauna of Roger Williams Park, which sparked her love for all things plant and animal.

After graduating at the top of her class at Cranston West, Marcia matriculated at Brown University, and graduated with a bachelor's degree in biology. She began her medical education at Boston University School of Medicine and then completed Internal Medicine Residency at Boston City Hospital, followed by a Pulmonary and Critical Care Fellowship at BU's Pulmonary Center.

She served as Baylor College of Medicine's Associate Chair of Medicine for Clinical Affairs and Medical Director of the Department of Medicine. In addition, she was the Chief of Adult Medicine at Texas Children's Pavilion for Women and spearheaded the development of Baylor's Lung Institute.

Her impact on the Cystic Fibrosis community is unsurpassed. She was the Medical Director of the Baylor Maconda Brown O'Connor Adult CF Center and sat on the Center Committee of the CF Foundation, the governing body of CF center accreditation. She also served as the Co-Principal Investigator of the CF Therapeutic Development Center.

In 2012, she was awarded the Ben and Margaret Love Foundation Bobby R. Alford Award for Academic Clinical Professionalism, Baylor's highest award given to a medical school faculty member, recognizing her outstanding humanism.

In 2016, she moved to Florida and was named Associate Dean of Clinical Affairs at University of Central Florida College of Medicine. During her time at UCF, she worked closely with UCF hospitals and the community to build an academic clinical service system that will benefit patients and students for years to come. When she retired in 2020 to spend time with her family and travel the world, she earned the title of UCF Professor Emerita.

While working as a full-time physician, Marcia was also a full-time mom to her two daughters, Becca and Jess. As Marcia faced cancer, Becca and Jess were by her side, laughing at her dark humor, hugging her tightly, and exploring the flora and fauna of the world.

Marcia faced cancer without missing a beat. She continued to travel the world with her husband Asher, visiting Rwanda,

Botswana, and Namibia, to name a few. She took a bike and river cruise on the Rhine with her twin sister Debbie and some of her best friends. On that trip she biked over 100 miles and made it look easy.

Before she passed, while wearing her red shirt that says "Optimist," Marcia instructed her family to reserve energy only for love and positivity. She is survived by her daughters Becca and Jess Wolinsky, mother Trudy Katz, twin Debra Katz, sisters Elyse and Michelle Katz, and husband Asher Aremband.

Contributions in Marcia's honor may be made to the Pancreatic Cancer Action Network, 1500 Rosecrans Ave., Suite 200, Manhattan Beach, CA 90266 (www.pancan.org) or to the Cystic Fibrosis Foundation, 4550 Montgomery Ave., Suite 1100 N, Bethesda, MD 20814 (www.cff.org). ❖