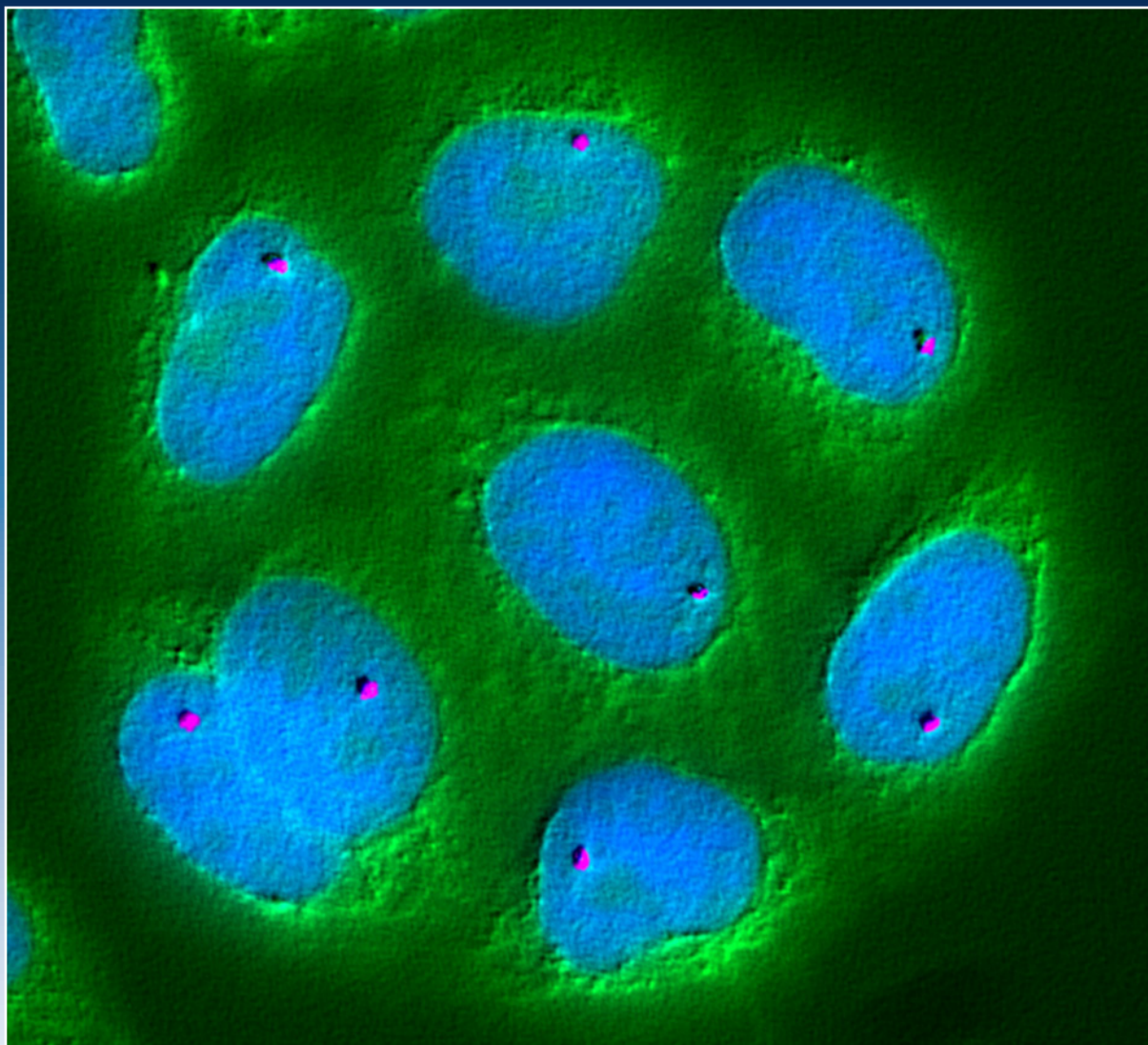

RHODE ISLAND
MEDICAL JOURNAL



SPECIAL SECTION
UPDATES *in* ONCOLOGY: PART I

GUEST EDITORS KIMBERLY PEREZ, MD; MURRAY B. RESNICK, MD, PhD

OCTOBER 2015

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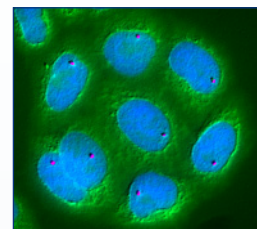
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On the cover: Mapping the position of genes in the cell nucleus sheds light on basic principles governing the genome. Here, a single gene called Pem (purple) has been localized using fluorescence in situ hybridization. DNA is stained blue; the cell cytoplasm is stained green. This image was originally submitted as part of the 2015 NCI Cancer Close Up project and selected for exhibit. See also <https://visualsonline.cancer.gov/closeup>.

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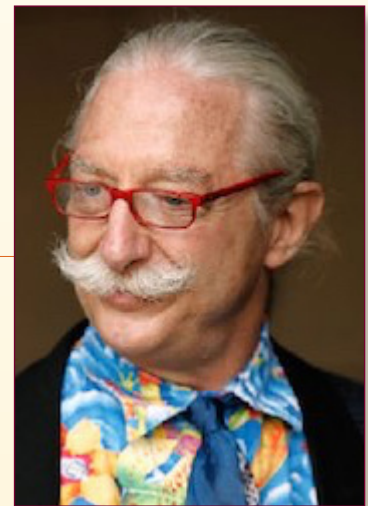
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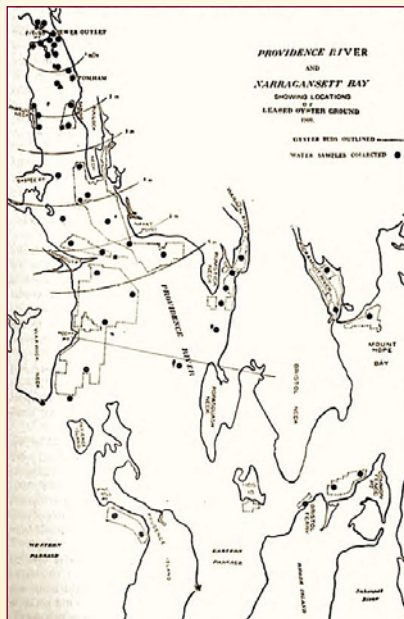
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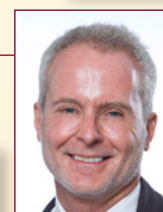
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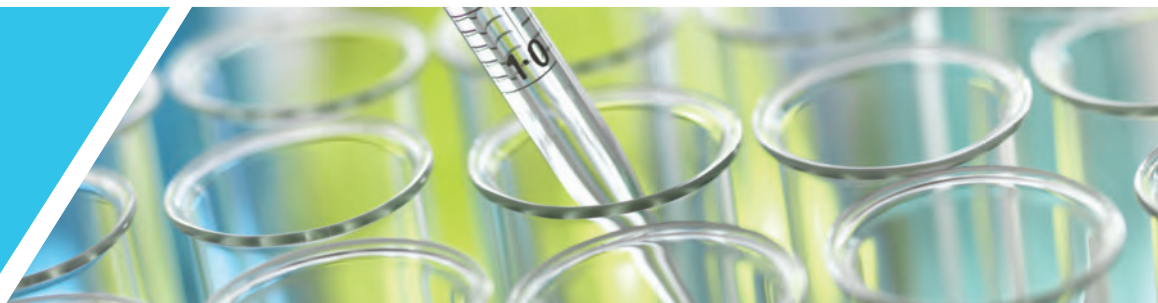
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Ageism in Health Care?

JOSEPH H. FRIEDMAN, MD
joseph_friedman@brown.edu

I RECENTLY RECEIVED, OUT of the blue, an email notifying me of what was deemed a particularly important letter to the editor of *Lancet* that I had to read (Lloyd-Sherlock et al). It accused the UN Sustainable Development Goals for Health of ageism. I was even given a link to allow me to set up



a teleconference with the lead author of the letter, co-authored by several other British geriatricians. I've never gotten an email blast like that, and wondered why a letter about a UN recommendation would generate such heat. I noticed that the email blast emanated from the public relations department at the author's university, East Anglia University, and wondered if this was simply a way of advertising the university. Luckily the letter was available via a link, without having to decline an interview with the author.

Why did I become interested? Being a senior myself and having spent a small amount of time teaching neurology and practicing medicine in some very poor countries in Africa, and, at home, in a subset of what is sometimes considered "geriatric neurology," I thought that I might have some opinions that were at least partly informed by personal experience.

One percent of the American population takes 30% of the health care

budget for their last year of life. Half of these are elderly. This is one starting point. Comparing the U.S. and the third world (aka "resource poor countries" in the current vernacular) is somewhat like comparing apples and oranges but the basic commodity is resources and the targets are people.

In some ways, poor countries aim at emulating the wealthy, but not the American health care system.

For a variety of reasons, primarily that health care costs are rationed, poor countries have made choices that lead to multi-tiered health care on a routine basis. Since there is so little to go around, planning is more important than in the west. Government-sponsored care provides the bedrock for most people, supplemented in many ways by private funds. For example, in Rwanda, for \$5/year, a citizen gets unlimited hospital level of care, including plain x-rays and medications that happen to be in the hospital pharmacy. Computed tomography, magnetic resonance imaging, medications not in the pharmacy, are paid for by the patient in advance, including transportation to the radiology site. The patient's family brings medications to the hospital. Private doctors and private clinics are used for most services by those who can afford them.

The letter opines that it is discrimina-

tory for the UN millennial development goals to be "focused on maternal and child health and HIV, thereby reducing the available resources for other interventions. As such, it is expected... to drain resources from services of relevance to older people; services which in many countries are already woefully inadequate. Older people suffer higher rates of common conditions that are amenable to prevention and management and will contribute more to achieving targets for reduction in mortality and morbidity than focusing only on younger people."

As a "senior citizen," I am so stunned by this statement that I'm writing this column. We live in a world of limited resources, and, when not restrained, we suffer problems created by dying old people taking up precious resources that lead to denial of services to others. The United States is a good example of this. Poor people in parts of our country have health care problems that equal that of poor countries yet we drain even our own limited resources to pour them down a black hole. We are not all equals in the eyes of our communities and to think we are, in order to maintain a political consistency, reflects an old truism that "consistency is the hobgoblin of small minds."

What does it mean for old people to get the same resources as children, mothers and HIV patients? This is unclear. Poor countries with health care plans always invest in the public

health measures that produce the best return on the investment. These have traditionally been in sanitation, maternal and child nutrition, vaccinations, health screenings and high-yield disease prevention interventions such as DDT-treated mosquito nets. When affordable, preventive measures like blood pressure, cholesterol and diabetes control are included. In Rwanda the health minister pointed out that a patient pays less for HIV treatment than for diabetes. The problem with treating the elderly is that they require a great deal of investment and are not worth as much, in general, to their country. The notion of person-value is embedded in the American and other western legal systems used to determine compensation for injuries or illnesses. The amount of money given to an injured person or deceased person's family is partly determined by age. A younger person, with a greater earning capacity, is reimbursed more than an older person, closer to retirement. In addition, the older person, as noted

above, will have much greater and more expensive health needs. And there are other reduced yields for the investment. Older people get sick again more quickly than the young. The investment in HIV has an even more compelling rationale. Aside from these patients getting sick in their most economically productive years, also putting their families at risk for financial catastrophe, they are public health hazards. Sick old people certainly jeopardize their family's financial security, but this is an expectation that societies have lived with forever. Old people get sick and die. This is in our genes.

The UN resolution does not call for not funding health care for the elderly, it simply de-emphasizes it. Perhaps they are trying to avoid the slippery slope of a health care system like our own, a model to be avoided?

We are not all equal. The responsibility of poor countries is to invest in public health, not necessarily to be age-fair. ❖

Author

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

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IN MEMORIAM

The Rhode Island Medical Society notes the passing of **DR. JOSEPH E. CARUOLO**, 94, former president of the Rhode Island Medical Society (1978–1979), and active on many RIMS committees during his professional career, who died on July 16, 2015. He

was also a past president of the Providence Medical Association.

Dr. Caruolo was a graduate of Classical High School, the University of Rhode Island, and Tufts University Medical School. A general surgeon, he did a Fellowship at the Mayo Clinic after completing his internship at the Beth Israel Hospital in Boston.



Video on pulsatile proptosis

Dear Dr. Friedman:

I noted with interest the video of the patient with pulsatile proptosis published in the September issue of RIMJ. It may be of value for readers to know that this memorable finding was associated with important ophthalmic complications affecting the patient's vision, including:

- Diplopia from a combined vertical and horizontal deviation of the patient's left eye which was treated with eye muscle surgery with marked improvement in the diplopia and recovery of some stereopsis.
- Mild optic atrophy from a low-grade glioma of the optic nerve and/or a retro orbital cyst.
- Elongation of the left eye with unilateral myopia.
- Ptosis, surgically corrected by Dr. Michael Migliori.
- Nasolacrimal duct stenosis alleviated by a balloon ductoplasty and intubation of the nasolacrimal duct.

Sincerely,

David Robbins Tien, MD

Clinical Associate Professor of Surgery (Ophthalmology)
Warren Alpert Medical School of Brown University



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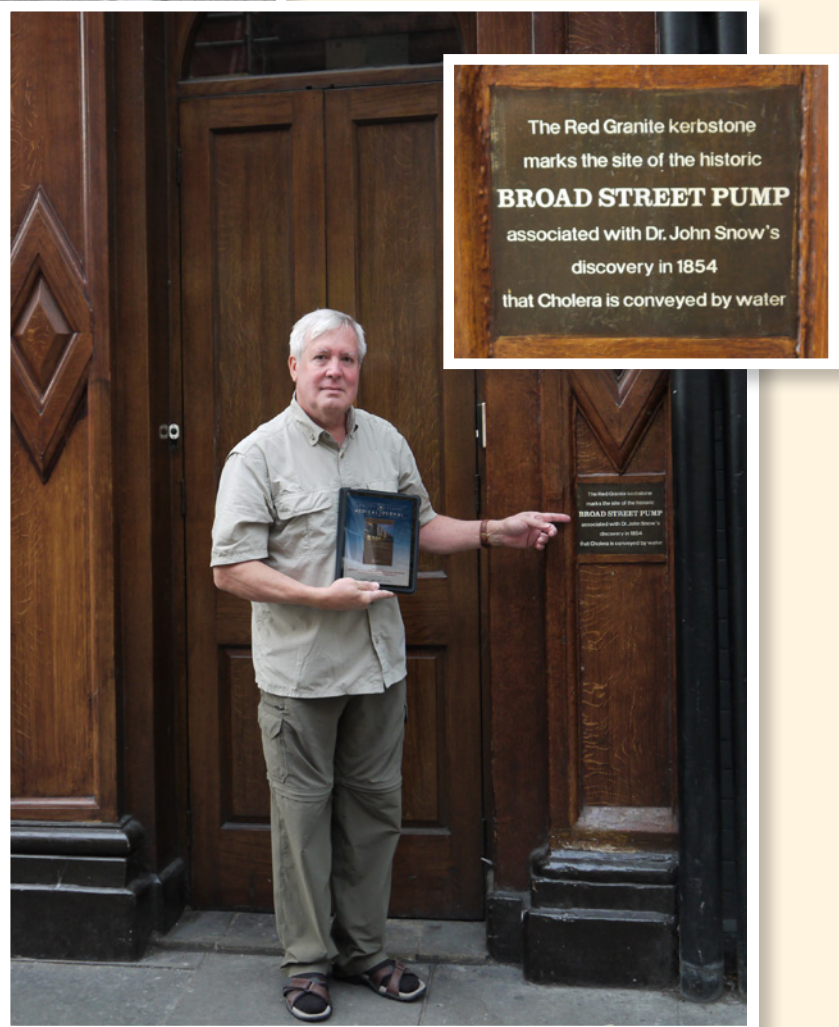
BERGEN, NORWAY

The husband-and-wife team of **Knut B. Kvist, MD**, and **Berit Kvist** accessed the September edition of the *RI Medical Journal* from the top of Fløyen, one of the seven mountains above their home town of Bergen, Norway.



LONDON, ENGLAND

RIMS executive director **Newell Warde, PhD**, opened the September edition of the RIMJ at the site of John Snow's famous water pump near the corner of Broadwick and Cambridge Streets in the Soho section of Westminster, London.



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MARIN HEADLANDS, CALIFORNIA

Attorney **Josh Korr**, a former volunteer at Miriam Cardiology, and now a judicial clerk on the Ninth Circuit Court of Appeals, glances at the Sept. issue of RIMJ on the Marin headlands overlooking the Golden Gate Bridge.

GUERNEVILLE, CALIFORNIA

Dr. Kenneth S. Korr and **Mary Korr**, managing editor of RIMJ, check out the Sept. issue of the Journal on a recent visit to Armstrong Redwoods State Natural Reserve, a temperate rain forest, in Sonoma County, California. They are standing in front of the 1,300 year-old Parson Jones Tree, the tallest Sequoia in the coastal redwood grove, measuring more than 310 feet in height.



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Advances in the Molecular Profiling of Tumor Tissue

KIMBERLY PEREZ, MD; MURRAY B. RESNICK, MD, PhD

In the realm of cancer care, complete sequencing of the human genome has supported a move away from the traditional paradigm in which histopathologically defined disease is treated primarily with cytotoxic chemotherapy, toward the use of molecularly targeted drugs. The cancer genome typically contains numerous mutations; however, a select number are considered “driver” mutations. When specific drugs are developed either targeting these driver mutations, or pathways associated with these mutations, they are also termed “actionable” mutations. Early success stories demonstrated in breast cancer with trastuzumab in ERBB2 amplified cancer, imatinib in Philadelphia chromosome positive chronic myelogenous leukemia, erlotinib in EGFR mutated non-small cell lung cancer, cetuximab in KRAS wild-type colorectal cancer and vemurafenib in BRAF-mutant melanoma. The Cancer Genome Atlas is a comprehensive program in cancer genomics that began in 2006 and has been the foundation of the molecular profiling movement. As a result of the associated and consequential genomic discoveries, there are now hundreds of compounds in clinical development targeting more than 100 actionable mutations in cancer-related genes representing multiple cellular pathways.

Cancer treatment has entered a new frontier. The advent of new sequencing technologies such as next generation sequencing (NGS) allows for rapid, relatively inexpensive profiling of individual cancer genomes. This technologic advancement offers the opportunity to “individualize” cancer care.

Despite all of the hype regarding molecular profiling of individual tumors certain caveats need to be considered: 1: The fact that a given mutation is actionable in a tumor

from one organ does not necessarily mean it is actionable in another. For example, encouraging results have been obtained targeting the BRAF mutation in melanoma; however, these same compounds are not active against BRAF mutated colonic cancer. 2: It appears that many tumors are able to develop resistance towards drugs targeting single mutations and in all likelihood combination therapy targeting several mutations or multiple steps along a single pathway will be necessary to combat resistance. 3: Several other cancer-associated pathways other than actionable mutations are being successfully targeted. Angiogenesis, the immune microenvironment, tumor sensitization, induction of cell death, tumor vaccines and monoclonal antibody delivery of toxic molecules are but a few of these novel therapeutic pathways.

The success of molecular profiling will require continued collaboration between oncologists, biostatisticians, pathologists, geneticists, policy-makers and members of the biopharmaceutical industry in order to develop new clinical models that enable rapid translation of many new biomarkers and cancer targets into new clinical tests and therapeutic interventions to benefit cancer patients.

Guest Editors

Murray B. Resnick, MD, PhD, is Professor of Pathology at the Alpert Medical School of Brown University and Vice Chair of Pathology and Director of Gastrointestinal Pathology at Lifespan/Rhode Island Hospital. He is also director of the molecular pathology core facility of the COBRE Center for Cancer Research Development.

Kimberly Perez, MD, is an Assistant Professor of Medicine, Division of Hematology/ Oncology, at The Warren Alpert Medical School of Brown University.

Mutation Profiling of Clinically Advanced Cancers Using Next-Generation Sequencing for Targeted Therapy: A Lifespan Experience

KENNETH FRIEDMAN, MD; HOWARD SAFRAN, MD; MURRAY B. RESNICK, MD, PhD

ABSTRACT

The application of modern molecular tests such as next-generation sequencing (NGS) to human malignancies has led to better understanding of tumor biology and the design of targeted molecular therapies. In the research setting, important genomic alterations in tumors have been discovered with potential therapeutic implications but data regarding the impact of this technology in a real world oncology practice is limited. As a result, we decided to review the results of NGS in 144 advanced-stage cancer patients referred to the oncology practices of Lifespan-affiliated centers in Rhode Island. Most cancers revealed genomic alterations in genes commonly mutated in cancer. However, several unexpected genomic alterations were discovered in certain cancers with potential therapeutic intervention. Most cancers contained "actionable" genomic alterations despite being of advanced stage. Our experience demonstrates that application of NGS in the clinical setting contributes both to increasing the therapeutic armamentarium as well as our understanding of tumor biology.

KEYWORDS: Next generation sequencing, genomic alterations, targeted therapy, actionable

INTRODUCTION

The biology of cancer is incredibly complex. An important concept in carcinogenesis is the presence of alterations in the tumor genome, which lead to various degrees of prolonged cell survival, decreased cell death, and changes to the tissue microenvironment. Cancer genomes are often riddled with a myriad of mutations, but only a few mutations are believed to drive a cell toward uncontrolled clonal expansion; the so-called "driver" mutations. Mutations in "driver" genes confer a growth advantage to the cell, are causally implicated in cancer development and have thus been positively selected for.^[1] Other "passenger" mutations may develop along the way, but these are generally not thought to confer a biologic advantage to the cancer cell.

Understanding the importance of driver mutations paves the road for targeted molecular therapy. Successful examples already abound in the field of oncology and include *BRAF* mutations in melanoma, *ERBB2*/HER2-Neu amplification

in breast and gastroesophageal cancer, and *ALK* fusions in lung cancer among many others. Recently, with the advent of newer technologies such as Next Generation Sequencing (NGS) and the cooperation of large international consortia such as The Cancer Genome Atlas (TCGA), genomic alterations and therapeutic targets are increasingly being identified.

What separates NGS from prior technologies is the ability to sequence up to millions of fragments of DNA simultaneously, referred to as "massively parallel" sequencing. The technology begins by fragmenting tumor DNA into small single-stranded fragments. The DNA fragments are modified by attaching "adapters," or short DNA segments of a known sequence, which are then bound to a surface, usually a glass slide or a well depending on the platform. The DNA strands are then amplified and ready to be sequenced. As nucleotides are added and incorporated into the DNA strands, a signal is released and recorded by the instrument. Each commercial platform has a proprietary approach to the chemistry used and method of detection. The final result is a set of sequencing data that requires tremendous bioinformatics support and interpretation. For utilization in clinical oncologic practice, only genes implicated in the carcinogenesis of solid tumors require sequencing and so most commercial NGS platforms use a targeted gene panel.^[2]

Comprehensive evidence on improved treatment outcomes using NGS technology to detect genomic alterations in solid tumors is still lacking. However, oncologists, insurers and medical organizations generally agree that NGS plays a valuable role in detecting possible actionable genomic alterations in patients with advanced cancer as well as contributing to our understanding of cancer biology. To that end, we decided to assess our institutional experience with a targeted NGS gene panel in 144 patients with advanced solid tumors.

MATERIALS AND METHODS

A total of 144 patients with metastatic or treatment refractory tumors treated at Lifespan partner hospitals (Rhode Island Hospital, The Miriam Hospital, and Newport Hospital) between 2012 and 2015 were included. Consent was obtained at the time of visit with the oncologist responsible for their care. Tumor type was confirmed by routine histology, immunohistochemistry and clinical/radiologic correlation. Tissue samples included primary resections, biopsies,

and cytology specimens. Formalin-fixed paraffin embedded (FFPE) tissue sections of tumor were sent to Foundation One (Cambridge, MA) and analyzed using a customized next-generation sequencing assay.^[3] The current assay interrogates at least 315 genes (more than 4,500 exons) as well as introns of 28 genes known to be somatically mutated in human cancers. All of the genes included are either unambiguous drivers of carcinogenesis based on current knowledge and/or validated targets for therapy (FDA-approved and/or in clinical trials). The types of alterations include base substitutions, insertions/deletions, copy number alterations, and rearrangements. *Actionable* genomic alterations (or mutations) are defined as either linked to: (I) an FDA approved therapy in the patient's tumor type; (II) an FDA-approved therapy outside the patient's tumor type, or; (III) non-FDA approved therapies in clinical trials or preclinical testing.^[4]

RESULTS

A total of 144 tumors were submitted for analysis, including tumors from 80 males (56%) and 64 females (44%) with a mean age of 62.9 years. There were a total of 4 (2.8%) sample failures due to inadequate tissue volume or failure during the analytic phase. Therefore, data was available for 140 tumors. A summary distribution of tumor types submitted for NGS is represented in **Figure 1**.

A total of 620 genomic alterations were detected in 171 genes. The most common genomic alterations were in *TP53* (13.5%), *APC* (7.9%), *KRAS* (7.3%), *CDKN2A* (4.7%), and *ARID1A* (2.1%) (**Figure 2**). An average of 4.5 genomic alterations were detected per tumor (range 0–24). No reportable genomic alterations were detected in 2 tumors (1 ovarian serous carcinoma, 1 colon cancer) and these were not included in the subsequent analysis.

Colorectal carcinoma

A total of 203 genomic alterations were identified in 83 genes in 41 colorectal adenocarcinomas with an average number of 5.0 alterations per tumor. The most common genomic alterations included *TP53* (85%), *APC* (75%), *KRAS* (48%), *PTEN* (15%), *SMAD4* (13%), *FBXW7* (13%), *ARID1A* (13%), *PIK3CA* (10%), and *BRAF* (8%). Our cohort had higher rates of *TP53*, *APC*, and *KRAS* mutations compared to the Catalogue of Somatic Mutations in Cancer (COSMIC) database of all colorectal adenocarcinomas (**Table 1**).

Pancreatic ductal adenocarcinoma

A total of 68 genomic alterations were identified within 21 genes in 18 pancreatic ductal adenocarcinomas with an average number of 3.8 alterations per tumor. The most common genetic alterations included *KRAS* (100%), *TP53* (76%), *CDKN2A* (29%), *SMAD4* (18%) and *ATM* (12%). Concurrent loss of *CDKN2A* and *CDKN2B* occurred in 3 tumors (18%). Our cohort had higher rates of *KRAS*, *TP53*, *ATM* and *CDKN2A* alterations compared to the COSMIC database

Figure 1. Most common tumors submitted for analysis

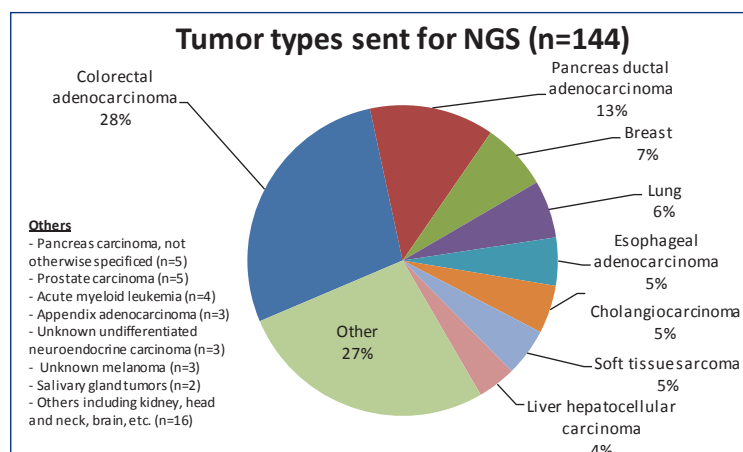


Figure 2. Most common genomic alterations in all cancers

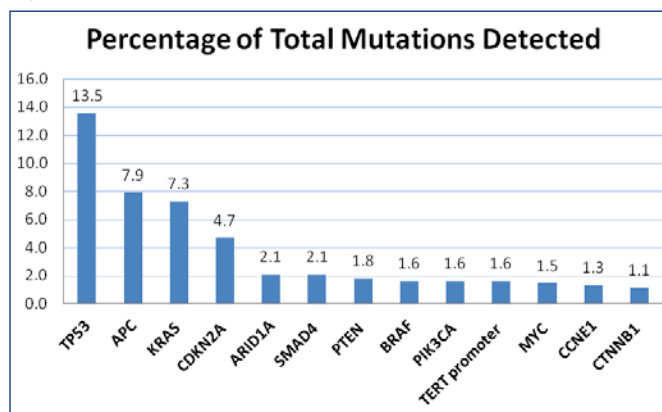


Table 1. Differences in colorectal adenocarcinoma genomic alterations between Lifespan and COSMIC cohorts

Genes altered in colorectal adenocarcinoma (n=41)	Lifespan (% cases with mutation)	COSMIC Database (% cases with mutation)
TP53	85	48
APC	75	42
KRAS	48	35
PTEN	15	25
SMAD4	13	23
FBXW7	13	20
ARID1A	13	17
PIK3CA	10	22
BRAF V600E	8	14

of all pancreatic adenocarcinomas (Table 2). Interestingly, *CDK6* and *MYST3* alterations were detected in 12% of tumors in our cohort and not found in any of the tumors included in COSMIC.

Other carcinomas

Many tumors had alterations in genes known to be recurrently mutated for that tumor type. Carcinomas of the breast frequently contained *PIK3CA*, *PTEN*, *TP53* and *GATA3* alterations. Esophageal adenocarcinomas contained *TP53*, *CDKN2A* (p16), *KRAS*, and *ERBB2/Her2-Neu* alterations. Cholangiocarcinomas contained *TP53*, *IDH1*, *MLL3*, and *ARID1A* alterations. Hepatocellular carcinomas contained frequent alterations in *TERT*, *CTNNB1* (β-catenin) and *CDKN2A* (p16). Prostate adenocarcinomas contained *TP53*, *PTEN*, and *TMPSST-ERG* fusion alterations. All unknown primary melanomas contained *BRAF* mutations.

Table 2. Differences in pancreatic adenocarcinoma genomic alterations between Lifespan and COSMIC cohorts

Genes altered in pancreatic ductal adenocarcinoma (n=18)	Lifespan (% cases with mutation)	COSMIC Database (% cases with mutation)
<i>KRAS</i>	100	71
<i>TP53</i>	76	49
<i>CDKN2A</i>	29	22
<i>SMAD4</i>	18	20
<i>ATM</i>	12	3
<i>CDK6</i>	12	0
<i>MYST3</i>	12	0

Table 3. Actionable mutations by tumor type

Cancer	FDA Tx ^a	FDA-GA ^b	NonFDA Tx ^c	NonFDA-GA ^d	Clinical trials ^e
Total (n=138)	19 (14%)		93 (67%)		129 (93%)
Appendix adenocarcinoma (n=3)	0	-	1	<i>KIT</i> , <i>KRAS</i>	2 (67%)
Colorectal adenocarcinoma (n=41)	3	<i>BRAF</i>	27	<i>KRAS</i> , <i>FLT3</i> , <i>NF1</i> , <i>ALK fusion</i> , <i>ERBB3</i> , <i>ERBB4</i> , <i>FGFR1</i> , <i>MAP2K1</i> , <i>BRCA1</i>	40 (98%)
Cholangiocarcinoma, intra- and extrahepatic (n=8)	0	-	6	<i>BRAF</i> , <i>DDR2</i> , <i>PTEN</i> , <i>IDH2</i>	8 (100%)
Acute myelogenous leukemia (n=4)	0	-	3	<i>DNMT3A</i> , <i>IDH2</i> , <i>PTPN11</i> , <i>NF1</i> , <i>NRAS</i> , <i>TET2</i>	3 (75%)
Brain; anaplastic astrocytoma (n=1)	0	-	0		1 (100%)
Breast carcinoma; ductal, lobular and NOS (n=9)	6	<i>PIK3CA</i> , <i>AKT1</i> , <i>NF1</i> , <i>PTEN</i>	7	<i>FGFR2</i> , <i>FGFR4</i> , <i>GNAS</i> , <i>MET</i> , <i>NF1</i>	9 (100%)
Esophagus and gastroesophageal junction adenocarcinoma (n=8)	2	<i>ERBB2/Her2-neu</i>	5	<i>EGFR</i> , <i>TOP2A</i> , <i>KRAS</i> , <i>CCND1</i> , <i>PIK3CA</i>	8 (100%)
Head and neck squamous cell carcinoma (n=1)	0	-	0	-	1 (100%)
Kidney carcinoma; clear cell and urothelial (n=4)	2	<i>VHL</i> , <i>STK11</i>	4	<i>DDR2</i> , <i>ERBB3</i>	4 (100%)
Hepatocellular carcinoma (n=6)	0	-	2	<i>TSC2</i> , <i>PTEN</i> , <i>STK11</i>	5 (83%)
Lung carcinoma; including adeno-, small cell and squamous (n=9)	2	<i>MET</i> , <i>ERBB2</i>	5	<i>PIK3CA</i> , <i>STK11</i> , <i>PTEN</i> , <i>FLT3</i> , <i>KRAS</i>	9 (100%)
Pancreas; including adenocarcinoma and NOS (n=23)	0	-	22	<i>KRAS</i> , <i>ERBB2</i> , <i>PIK3RA</i> , <i>STK11</i> , <i>FBXW7</i>	22 (100%)
Prostate carcinoma (n=3)	0	-	1	<i>PTEN</i>	3 (100%)
Salivary gland tumors (n=2)	0	-	1	<i>BRIP1</i>	2 (100%)
Soft tissue tumors (n=7)	0	-	2	<i>NF1</i> , <i>PTEN</i>	5 (70%)
Stomach adenocarcinoma (n=1)	0	-	1	<i>MET</i> , <i>BRAF</i>	1 (100%)
Thyroid medullary carcinoma (n=1)	1	<i>RET</i> , <i>VHL</i>	1	<i>RET</i> , <i>VHL</i>	1 (100%)
Unknown primary adenocarcinoma (n=2)	0	-	2	<i>BRAF</i> , <i>PIK3CA</i>	2 (100%)
Unknown primary melanoma (n=3)	3	<i>BRAF</i>	3	<i>BRAF</i>	3 (100%)
Unknown primary undifferentiated neuroendocrine carcinoma (n=3)	0	-	0	-	0 (0%)

a – FDA-Tx: Number of cases with FDA-approved therapies for genomic alterations in patient's tumor type

b – FDA-GA: Genomic alterations in patient's tumor with FDA-approved targeted therapies.

c – NonFDA-Tx: Number of cases with FDA-approved therapies for a genomic alteration present in the patient's tumor but approved for a different tumor type

d – NonFDA-GA: Genomic alterations in patient's tumor with FDA-approved therapies for a different tumor type

e – Clinical trials – Number of cases containing a targetable genomic alteration being investigated in a clinical trial as of this writing

Actionable mutations

Of 138 tumors, 130 (94%) had actionable genomic alterations. These included 19 (14%) with an FDA-approved therapy for the specific tumor type, 93 (67%) with a mutation for which an FDA-approved therapy exists for a different tumor type, and 129 (93%) with mutations being studied in clinical trials. There were 8 patients (6%) that had no actionable genomic alterations. A summary of actionable mutations specific for tumor type is presented in **Table 3**.

DISCUSSION

This analysis provides a unique appraisal of a single health system's experience using NGS for identifying potential therapeutic genomic targets in patients with metastatic and treatment-resistant cancers. Out of 138 patients with advanced or metastatic cancer, 94% had potentially actionable genomic alterations in their tumors. Most of these included clinical trials studying a targeted therapy with regards to the tumor specific mutation and 67% of all cases had FDA-approved therapy for the patient's specific tumor mutation but in a different tumor. Nonetheless, NGS discovered that 14% of the patients in our cohort had genomic alterations with FDA-approved therapies their specific tumor type.

The tumors with FDA-approved therapies, and therefore, of most clinical interest included colon, breast, esophagus, kidney, lung, thyroid, and melanoma. Twenty (48%) patients with colonic adenocarcinomas had mutations in *KRAS* and therefore would not benefit from anti-EGFR therapy.^[5] Three colonic adenocarcinomas had activating mutations in *BRAF*, a gene which promotes cell proliferation via the MAPK signaling pathway. Present in about 8–15% of colon cancers, *BRAF* mutations in advanced stage colon cancer have been associated with decreased overall survival, lack of response to anti-EGFR therapy, and decreased sensitivity to vemurafenib.^[6–8] However, regorafenib has been FDA-approved for the treatment of metastatic colon cancer and has shown increased survival benefit in patients with metastatic, previously treated disease.^[9, 10] The lack of response to *BRAF* inhibition may be due, in part, to *EGFR* activation, and early evidence suggests that dual inhibition therapy may have clinical benefit.^[11] Other targeted FDA-approved therapies were discovered in 16 patients including 6 breast carcinomas (*PIK3CA*, *AKT1*, *NF1*, *PTEN* mutations), 2 gastroesophageal adenocarcinomas (*ERBB2*/Her2-neu mutations), 2 kidney carcinomas (*VHL*, *STK11*), 2 lung adenocarcinomas (*MET*, *ERBB2*/Her2-neu), 1 medullary carcinoma of the thyroid (*RET*, *VHL*) and 3 melanomas (*BRAF*). All of the therapies have been approved because they target the mutant protein (or more commonly the downstream effector protein) and have showed various degrees of success.

Two-thirds of patients had genomic alterations in their tumors with targetable FDA-approved therapies but for a

different histologic tumor type. Unexpected or uncommon mutations accounted for a subset of these patients. One patient had an *ALK* fusion positive colon cancer, which has rarely been described and has not undergone enough clinical testing to merit treatment as is in *ALK* mutated lung cancers.^[12] Two intrahepatic cholangiocarcinomas were positive for the *BRAF* V600E mutation and *ERBB2*/Her2-neu amplification. Bonilla and colleagues reported an excellent response to *BRAF* inhibitors in a patient with a *BRAF* V600E mutated poorly differentiated intrahepatic cholangiocarcinoma with multiple metastases.^[13] A similar dramatic response was seen in a patient with *ERBB2*/HER2-neu amplified metastatic cholangiocarcinoma treated with trastuzumab.^[14] Alterations in *ERBB2*/Her2-neu were discovered in 2/18 (11%) of pancreatic carcinomas. Although uncommon (<1% of all pancreatic carcinomas in COSMIC), there is some evidence that *ERBB2* alterations are associated with higher rates of brain and lung metastases.^[15] In the single patient with gastric adenocarcinoma in our cohort, a *BRAF* V600E mutation was detected, the significance of which is yet unclear.^[16] Interestingly, two patients with unknown primary adenocarcinoma had actionable genomic alterations (*BRAF*, *PIK3CA*). Traditionally thought of as having poor prognoses, patients with carcinomas of unknown primary may benefit from NGS targeted gene panels although systematic evidence is still in its infancy.^[17]

The applications of NGS are not just limited to targeted therapeutic information, but have far reaching implications with regards to cancer biology, genotype-phenotype correlations, and prognostics. Our colorectal carcinoma cohort had significantly more *TP53*, *APC* and *KRAS* mutations compared to the COSMIC database. In addition, 100% of our pancreatic adenocarcinoma cohort had *KRAS* mutations compared to 71% in the COSMIC cohort. While these data are not surprising given our cohort consisted entirely of advanced stage/treatment resistant cancers, it underscores the importance these driver mutations play in cancer progression, especially since they are present even in precancerous lesions.^[18, 19] Not all driver mutations, however, imply a biologic or therapeutic significance. In melanomas, for example, *BRAF* mutations are usually mutually exclusive of other mutations, which may explain the success of *BRAF* and downstream MEK inhibitors, either alone or in combination.^[20] However, in our small cohort of 3 *BRAF* mutated colon cancers, each case had anywhere from 3 to 23 additional mutations in several important cancer promoting genes such as *TP53*, *SMAD4* and *PTEN*. Thus while common driver mutations exist across many cancer types, one cannot assume that the same applies for therapeutic effect. Additional complications arise from molecular heterogeneity within the same tumor. Some studies have shown that mutations may vary by more than 50% depending on the region of tumor sampled as well as information regarding treatment options and prognosis.^[21, 22]

CONCLUSION

For the 144 patients in the Lifespan system with advanced cancers that have progressed on therapy, next generation sequencing using a targeted gene panel detected a clinically actionable genomic alteration in nearly all patients. Most of the opportunities consisted of clinical trials and off-label therapies, but at least 14% of patients had FDA-approved therapies for a mutation in their specific tumor. Next generation sequencing technology can profile a tumor's genomic landscape and generate important clinical and biological information but is not without limitations. The true clinical utility of NGS needs to be explored in rigorously designed clinical trials and with clinical outcomes in institutions implementing the technology, including the Lifespan system.

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Updates in Tumor Profiling in Gastrointestinal Cancers

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ABSTRACT

In the last decade there has been a focus on biomarkers that play a critical role in understanding molecular and cellular mechanisms which drive tumor initiation, maintenance and progression of cancers. Characterization of genomes by next-generation sequencing (NGS) has permitted significant advances in gastrointestinal cancer care. These discoveries have fueled the development of novel therapeutics and have laid the groundwork for the development of new treatment strategies. Work in colorectal cancer (CRC) has been in the forefront of these advances. With the continued development of NGS technology and the positive clinical experience in CRC, genome work has begun in esophagogastric, pancreatic, and hepatocellular carcinomas as well.

KEYWORDS: Tumor profiling, colorectal carcinoma, esophagogastric carcinoma, pancreatic carcinoma, hepatocellular carcinoma

INTRODUCTION

The prognosis for patients with gastrointestinal cancers is currently based on tumor-node-metastasis (TNM) staging; however, outcomes for patients with the same histologic-clinical staging can be heterogeneous. As a result, research efforts have shifted from identification of mutations of individual genes to genome-wide identification of genetic abnormalities in cancer. Identification of these somatic mutations and evaluation of gene expression patterns is key to understanding the molecular mechanism of cancer and the development of novel therapeutics.

The application of next generation sequencing (NGS) technology – the rapid sequencing of large stretches of DNA – has been in development in gastrointestinal malignancies. In the forefront is colorectal cancer, where there has been an improvement in mortality rates because of improvements in treatment as a result of several predictive and prognostic biomarkers.¹ The experience in CRC, as well as lung cancer, breast cancer and melanoma, has fostered the pursuit of genome profiles in other cancers as well.

TUMOR TYPES AND MUTATIONS

Colorectal Cancer

Sjoberg and Wood and colleagues were the first to perform exome-wide mutation analysis by sanger-sequencing to demonstrate the genomic profile of CRC, which included high-frequency mutated genes such as APC, KRA, TP53.^{2,3} With the development of NGS, The Cancer Genome Atlas (TCGA) network further expanded the genome profile. They demonstrated 32 somatic recurrently mutated genes, among the somatic mutations identified in 24 genes. The most frequent mutated genes were APC, TP53, KRAS, PIK3CA, FBXW7, SMAD4, TCF/L2, NRAS, ACVR2A, APC, TGFBR2, MSH3, MSH6, SLC9A9, TCF7L2 and BRAFV600E were noted.⁴

At the current time, there are previously identified genes, which are directing clinical treatment options or are used as prognostic indicators (see **Table 1**):

Table 1. Colorectal Cancer Molecular Profile

Tumor Type	Gene	Incidence	Clinical Implications
Colorectal Cancer	EGFR	70%	Therapeutic – anti-EGFR monoclonal antibodies Prognostic – none
	K-ras exon 2 (codon 12,13,61)	40%	Therapeutic – If wild-type, increased susceptibility to anti-EGFR monoclonal antibodies Prognostic – If mutated, associated poorer prognosis
	B-raf V600E	5%	Therapeutic – If mutated, decrease response to EGFR monoclonal antibodies Prognostic – If mutated associated poorer prognosis
	Microsatellite Instability	15%	Therapeutic – If present insensitive to fluorouracil but sensitive to irinotecan Prognostic – If present, good prognosis
	Dihydro-pyrimidine dehydrogenase (DPD)	3–5%	Therapeutic – If present patient is unable to metabolize fluorouracil Prognostic – none
	Uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1)	3–5%	Therapeutic – If present patient is unable to metabolize irinotecan Prognostic – none

EGFR gene expression: The epidermal growth factor receptor is a transmembrane receptor which is expressed in 70% of CRCs. Anti-EGFR monoclonal antibodies such as cetuximab competitively inhibit EGFR by preventing its binding to endogenous ligands and prolong survival when given in combination with chemotherapy.⁵

K-ras (v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog): Ras is an oncogene. K-ras is found in adenocarcinomas that transduce extracellular signals from the EGFR to the nucleus. Forty percent (40%) of CRC are positive for mutation in K-ras exon 2, which includes codons 12,13,61. A mutation in any of these sites in K-ras are currently the only predictive biomarker, which denotes anti-EGFR monoclonal antibody efficacy in CRC.⁶ Recent retrospective analysis is suggesting an adverse prognostic impact.⁷

B-raf (v-raf murine sarcoma viral oncogene homolog B) V600E gene mutation: B-raf is an oncogene that encodes a protein which belongs to the raf/mil family of serine/threonine protein kinases. This protein plays a role in regulating the MAP kinase/ ERKs signaling pathway, which affects cell division, differentiation, and secretion. B-raf mutations are found in 5–95% of CRC. A B-raf mutation has been associated with a negative response to EGFR inhibitors. Also its presence has been associated with overall poor prognosis.⁸

Microsatellite Instability (MSI): MSI is caused by defects in DNA mismatch repair genes, which include MLH1, MSH2, MSH3, PMS1, PMS2, and MSH6. Loss of function or expression of these genes leads to a higher than normal frequency of frameshift mutations and base-pair substitutions in regions of short tandem repeated nucleotide sequences found throughout the genome, also known as microsatellites.⁹ Approximately 15% of CRC show MSI. The following phenotypic characteristics have been described: location in the proximal bowel, and characteristic histologic findings (poor differentiation, mucinous, and marked lymphocytic infiltration). MSI has also been described in Lynch syndrome (LS) – a hereditary syndrome which is associated with increased risk of colorectal cancer. BRAF mutations are found in up to 50-70% of MLH1 mutated tumors, while LS rarely has BRAF mutations. Therefore if a patient is found to have a MLH1 mutation, an associated mutation in BRAF(V600E) supports a sporadic etiology.¹⁰ There is also data, which supports a role in pharmacogenomics by MSI. Presence of MSI has been associated with better prognosis and chemo sensitivity to irinotecan but Ribic and colleagues demonstrated an associated poorer response to 5-fluorouracil, two chemotherapeutic drugs commonly used to treat colorectal cancer.¹¹

Pharmacogenomic data: Two genes have been identified that impact metabolism of fluorouracil and irinotecan. A mutation in Dihydropyrimidine dehydrogenase (DPD) results in deficiency of the DPD enzyme, which is a major catabolizing enzyme of fluorouracil. It has been detected in 3-5% of the general population.¹ However, the presence of the mutation or deficiency of the enzyme does not always dictate clinical outcome.¹²

Uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1) is an enzyme that mediates glucuronidation. This enzyme enables conjugation of glucuronic acid to the active form of irinotecan, SN-38. Therefore if UGT1A1 is mutated resulting in a quantitative deficiency of the UGT1A1 enzyme, there will be a decreased rate of irinotecan metabolism resulting in clinically significant neutropenia and diarrhea.¹³

Gene Expression Assays: Oncotype Dx Colon, ColoPrint, ColdX are clinically available examples.¹⁴ The aforementioned assays assess 18 genes or more, the data is then used to predict an individual tumor's risk of recurrence.¹⁵ At this time trials have demonstrated the role of these assays in predicting recurrence risk for stage I-III CRC but none have proven to be reliable indicators of response to adjuvant therapy.

Associated genes of unclear clinical relevance:

In recent studies analyzing the correlation of treatment response and molecular profile, the data demonstrated mutational frequencies of: KRAS (45%), NRAS (5%), BRAF(7%), PIK3CA (9%), PTEN (6%), TP53(60%), EGFR (1%), AKT1(<1%) and CTNNB1 (2%).¹⁶ The role of these mutations individually is unclear but gene signatures have demonstrated some prognostic and therapeutic relevance. For example, Yu and colleagues characterized CRC genomes by NGS. A five-gene-signature (CDH10, COL6A3, SMAD4, TMEM132D, VCAN) was devised. In an analysis of 22 patients with CRC, a mutation in one or more of these genes was associated with a significant improvement in overall survival independent of tumor-node-metastasis (TNM) staging. The data demonstrate a median survival time of 80.4months in the mutant group versus 42.4 months in the wild type group (p=0.0051).¹⁷

Pancreatic and Biliary Cancers

To date, few DNA sequencing-based studies have been carried out to define the predominant mutations in pancreatic cancer. Due to the low survival rates and high proportion of late-stage and metastatic diagnoses associated with pancreatic cancer, it has proven difficult to assess prognostic and therapeutic markers. Therefore, currently there are no Food and Drug Administration (FDA) drug options that exploit known genomic alterations. Current implicated genes include KRAS, TP53, SMAD/DPC4 (SMAD family member 4/ deletion target in pancreatic carcinoma 4 homolog), and CDKN2A (cyclin-dependent kinase inhibitor 2A, p16).

Jones and colleagues were the first to characterize the tumor profile of pancreatic adenocarcinoma. The data demonstrated an average of 63 genetic alterations, resulting in dysregulation of 12 cellular signaling pathways in most tumors. Although this analysis identified frequently mutated genes, ie KRAS, there was no common mutation profile limiting our ability to further decipher the molecular carcinogenesis of pancreatic cancer.¹⁸

As with pancreatic cancer comprehensive genomic profiling is underway to further characterize intrahepatic

cholangiocarcinoma (IHCCA), extrahepatic cholangiocarcinoma (EHCCA) and gallbladder carcinomas (GBCA). Ross and colleagues performed comprehensive genomic profiling of the above tumors, which included 182 cancer-related genes. The most common genes identified included CDKN2B and ARID1A. Unique to IHCCA were FGFR, IDH1/2, BRAF and MET. EHCCA and GBCA shared common mutations in ERBB2, but differed in the frequency of KRAS mutations.¹⁹

Hepatocellular Carcinoma

As with the biliary cancers, initial analysis of the genetic landscape of hepatocellular carcinoma (HCC), as well as the related signaling pathways, is underway. Four pathways have been linked to HCC pathogenesis. The first is the Wnt/B-catenin pathway, which is now considered the main oncogenic pathway in HCC. The genes most commonly associated with pathway activation include CTNNB1 and AXIN1. The second is interruption of cellular regulatory mechanisms, which has been linked to recurrent mutations in ARID1A and ARID2 (AT-rich interactive domain 1A and 2). The third is NRF2/KEAP1 pathway, if activated, results in transcription of antioxidant genes, thereby giving proliferative and survival advantages to tumor cells. The fourth is the PI3K/Akt/mTOR and Ras/Raf/MAP kinase pathways, which are activated by mutation in PIK3CA, FGF19 and RPS6KA3.²⁰ Work is in progress to target these four pathways but none of the targeted therapy options have been approved yet.

EsophagoGastric Cancers

Esophagogastric carcinomas are heterogeneous, with multiple environmental etiologies and alternative pathways of carcinogenesis. With NGS the genes implicated in dysfunction of this pathway in gastric cancer include: ARID1A, MLL3, MLL, PIK3CA, FAT4 and MSI. As with CRC, microsatellite instability (MSI) has been identified as underlying a distinctive carcinogenic pathway in 15% of all gastric cancers.²¹

One of the most recent breakthroughs in targeted therapy is the use of HER2 antibody, Trastuzumab, in gastric cancer. HER2 overexpression is observed in 7–34% of gastric cancers; however, resistance within this cohort to targeted therapy is present. The culprits of resistance include alterations in HER2 structure and surroundings, dysregulation of HER2 downstream signal effectors and interaction of HER2 with other membrane receptors. Mutations in PIK3CA and PTEN can impact the PI3K-Akt pathway, which is a downstream signaling pathway of HER2. However at this time little is known about the association between HER2 expression and PI3K-Akt pathway alterations.²²

CONCLUSION

At this time large cancer sequencing initiatives, International Cancer Genome Consortium (ICGC) and The Cancer Genome Atlas (TCGA), have demonstrated heterogeneity in gastrointestinal malignancies. However, unlike CRC, the technology

has not yet elucidated the significant genetic downstream effectors in the other gastrointestinal malignancies. At this time CRC remains an example of where this technology can take disease prognostication and therapeutic medicine.

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NSCLC: An Update of Driver Mutations, Their Role in Pathogenesis and Clinical Significance

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ABSTRACT

Lung cancer is the most common malignancy in the US and causes the most cancer-related deaths. Non-small-cell lung carcinoma (NSCLC) accounts for the majority of cases. NSCLC historically was considered one entity, reflected by platinum-based therapy as the standard of care; however, with the discovery of EGFR mutations and ALK rearrangements, the landscape of treatment has become more personalized reflecting genomic heterogeneity. The molecular basis for tumor genesis was recognized and became a new method of classification. The availability of tumor sequencing and testing for these mutations is also becoming more accessible outside of major academic institutions. Targeted therapies offer alternatives to dangerous cytotoxic chemotherapy with equal or better efficacy. With these changes, driver mutations will play an increasing role in the diagnosis and treatment of NSCLC. In this review we will examine the characteristics of several NSCLC driver mutations and gene rearrangements and emerging data on therapies directed against them.

KEYWORDS: NSCLC, Driver Mutation, EGFR, ALK, ROS1, RET, BRAF, FGFR, MET, Targeted therapy

BACKGROUND

Lung cancer is the most common malignancy in the US and is also responsible for the most cancer related deaths. The American Cancer Society estimates there will be 221,200 new cases and 158,000 deaths from of lung cancer in 2015. Approximately 85% of all lung cancer is NSCLC and the median age of diagnosis for NSCLC is approximately 70 years. Worse yet, more than half (approximately 57%) of all lung cancers are at an advanced stage at diagnosis. While the treatment of early stage lung cancer remains surgical resection and close follow up, advanced lung cancer is still a very mortal disease requiring aggressive and toxic treatments. This presents as a

problem in many patients, as they do not have a performance status compatible with the aggressive standard-of-care chemotherapy and radiation regimens. However, many of the existing targeted therapies are better tolerated than standard chemotherapy and this approach may provide more treatment options for these frail patients than currently exist.

Following the human genome project, many genes were implicated in the development of cancer. Continued research into the genetics of lung cancer has led to the discovery of mutations and gene rearrangements influencing oncogenesis also known as, "Driver Mutations." (Table 1) This phenomenon is best described in Non-Small Cell Lung Cancer (NSCLC), specifically adenocarcinoma. As a result, many prognostic tools and medications have been developed. In this review we discuss the most prominent driver mutations and gene rearrangements of NSCLC and the current agents both available and under development which target them.¹

EGFR

EGFR is the most well established driver mutation in NSCLC. Epidermal Growth Factor Receptor is a cell signaling, trans-membrane protein intimately involved in proliferation. Mutations occur in the kinase region and lead to unregulated phosphorylation and activation of cell survival/proliferation pathways. There are multiple therapies available that work against this mutation: Erlotinib and Afatinib are FDA-approved for EGFR mutated tumors.

The incidence is highest in female, non-smokers, with adenocarcinoma histology. Though this gene has multiple known mutations, 90% of those present in adenocarcinoma are of exon 19 and L858R point mutation in exon 21.² This mutation is favored in Asian populations with its frequency reaching 62%,³ as opposed to 10% in US populations.⁴

Table 1. Common Genomic Alterations in NSCLC

	Type of alteration	Frequency	Therapy FDA Approved?	Implications
EGFR	Mutation	10-35%	Yes	Prognostic and Predictive
ALK	Rearrangement	3-7%	Yes	Predictive, Not prognostic
ROS1	Rearrangement	1%	Yes, but for a different mutation	Predictive, Not prognostic
RET	Rearrangement	1%	Yes, but only for other cancers	Not Predictive or Prognostic
BRAF	Mutation	1-3%	Yes, but only for other cancers	Not Predictive or Prognostic
FGFR-1	Amplification	20%	No	Prognostic (Negatively) only
MET	Amplification	2-4%	Yes, but for a different mutation	Prognostic (Negatively) only

NCCN guidelines now recommend routine testing for this mutation for all new cases of metastatic adenocarcinoma, with consideration in squamous cell patients who are never smokers or have mixed histology. Treatment with Erlotinib or Afatinib should be offered as upfront therapy to all patients who harbor this mutation.

It should be noted that insertions to exon 20 have been deemed tyrosine kinase inhibitor (TKI) resistant through clinical trials and EGFR inhibitors will be far less effective in patients with these mutations.⁵ For patients with this insertion, conventional chemotherapy is favored.

A mutation of the 790th amino acid from T to M is found in up to 50% of patients who initially responded to treatment with erlotinib but subsequently progressed despite continued treatment.⁶ T790M can be the sole driver mutation in EGFR mutated cancers; however, this is rare and only accounts for approximately 5% of all EGFR mutated NSCLC.⁷ New TKIs that are mutant specific and can specifically target this mutation are currently under development; rociletinib is furthest along in development but currently there are no approved agents for use against the T790M mutation.⁸

ALK

Anaplastic Lymphoma Kinase, is a CD receptor (CD246) that plays a large role in the development of neurons. The ALK gene products are known to promote cell growth/proliferation and inhibit apoptosis at baseline. Rearrangement and fusion of this gene with EML4 is amplified and leads to a fusion protein product that is produced in an unregulated quantity and subsequently causes excessive cell proliferation. It is found in 5–7% of NSCLC. Again found predominantly in never-smokers and almost exclusively in adenocarcinoma,⁹ this is the second, and only other genetic aberration other to have an FDA-approved therapy in advanced NSCLC.¹⁰ Crizotinib, an ALK inhibitor, was approved for treatment of metastatic NSCLC in 2011 and response rates were comparable to EGFR positive tumors being treated with Erlotinib.

NCCN guidelines now recommend routine testing for this gene fusion (2p23) by FISH for all new diagnoses of metastatic lung adenocarcinoma. (Fig. 2 and 3) Treatment with crizotinib should be offered as upfront therapy to all patients.

In ASCO 2014, Siraj M Ali et al, presented their experience with ALK rearranged lung carcinomas (LC) as detected by a clinical next generation sequencing (NGS)-based assay. Genomic profiling of 1,070 lung carcinomas was performed. Of 1,070 total lung carcinomas profiled, 47 harbored ALK rearrangements (4.4%). Of the 28 ALK rearranged specimens also tested by ALK FISH,⁹ (32%) were negative, and 19 were positive. Twenty-two patients were treated with crizotinib and had response data available; 19 responded by investigator assessment. Of the 9 cases which were negative by FISH, 5 patients responded to crizotinib, 2 patients did not, and

Figure 1. Known mutations to EGFR gene

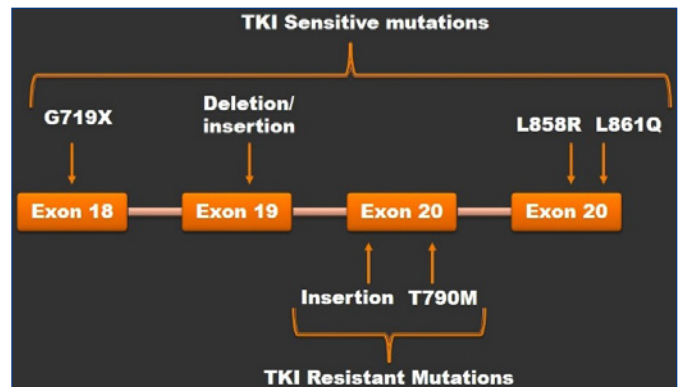


Figure 2. Fluorescence in situ hybridization (FISH) for ALK gene (Arrows indicate wild type)

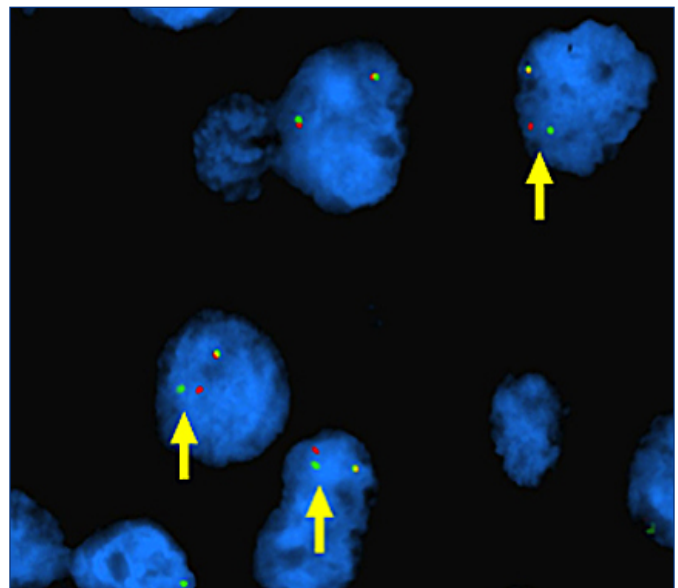
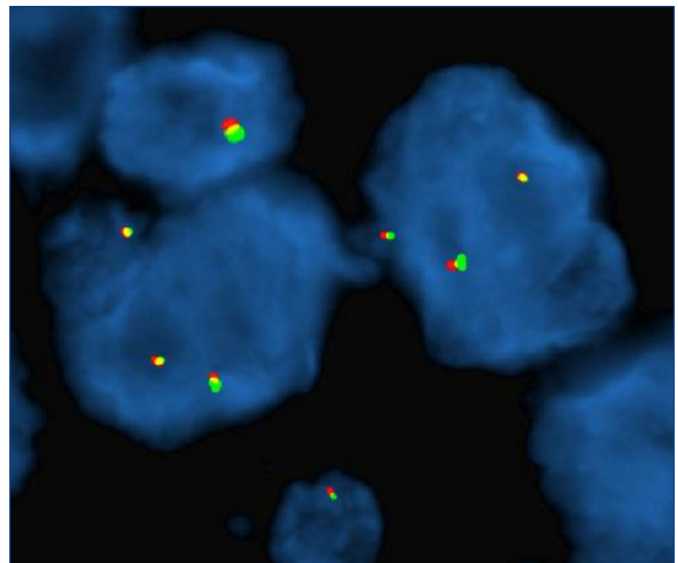


Figure 3. Fluorescence in situ hybridization (FISH) for ALK gene (fusion genes)



the response data for the remaining 2 patients is unavailable. Targeted NGS may be more sensitive for the detection of *ALK* rearrangements than FISH. In light of the responsiveness of *ALK* NGS+/FISH- tumors to crizotinib, the use of FISH as the gold standard for *ALK* detection in LC warrants prospective study.¹¹

Several resistance mutations have been described.¹² In April 2014 a second agent, ceritinib, was approved for treatment of *ALK* positive NSCLC. Ceritinib is a second generation TKI that is approximately 20 times more potent than crizotinib.¹³ Preclinical studies suggested that ceritinib had significant activity against cells that were either sensitive or resistant to crizotinib, including resistant tumors with the most common L1196M and G1269A resistance mutations.¹⁴

ROS1

ROS1 is a tyrosine kinase receptor belonging to the insulin family. Having striking similarity to *ALK*, this gene promotes proliferation and inhibits apoptosis, develops mutations via a rearrangement that leads to unregulated production of fusion proteins which retain the kinase domain,¹⁵ and preferentially affects young, never-smokers with adenocarcinoma. ROS1 translocations are identified by a FISH break-apart assay, again much like *ALK*. Though similar to *ALK* in many respects, the notable difference is the frequency at which ROS1 is found in tumors which is 1–2% of all NSCLC.

Interestingly, this gene rearrangement has increased sensitivity to the well-established *ALK* inhibitor, crizotinib.¹⁶ Retrospective analysis of crizotinib suggest that it may actually be a stronger inhibitor of ROS1 than it is of *ALK*. Initial data is so promising that it is highly likely that this will be the third mutation to be formally included in national guidelines for the treatment of advanced adenocarcinoma of the lung following EGFR and *ALK*.

RET

RET is a proto oncogene that becomes pathologic upon rearrangement with other genes leading to fusion proteins.¹⁷ Normally RET, a tyrosine kinase, responds to growth factors and promotes cell proliferation. RET mutations are present in 1–2 % of lung adenocarcinoma and not found in SCC. This pathway is currently better understood in thyroid cancer and the only FDA-approved agent against this mutation is the multiple kinase inhibitor vandetanib (which targets RET among other kinases).¹⁸ Initial trials of this agent in RET positive NSCLC were disappointing. At this time there are no recommended treatments for RET positive NSCLC patients. Clinical trials with other RET inhibitors are ongoing.

BRAF

BRAF is a member of the Raf kinases which regulate the MAP kinase pathway. Better known for its role in melanoma, BRAF mutations are seen in 1–4% of lung adenocarcinoma.¹⁹ There are several mutations identified,²⁰ of which the most clinically significant is a point mutation, V600E. This mutation causes phosphorylation in the absence of normal signal and unregulated cell growth. V600E accounts for 90% of BRAF positive melanoma, but only accounts for 50% of BRAF positive lung adenocarcinoma. This is problematic as the only two FDA approved BRAF targeting drugs, vemurafenib and dabrafenib, were developed to target this specific mutation. A phase II trial treating V600E positive lung adenocarcinoma with dabrafenib demonstrated clinical efficacy. Responses were relatively durable and the side-effect profile was consistent with what is observed patients with melanoma. This data suggests that current BRAF inhibitors could be as efficacious in V600E positive lung adenocarcinoma as they are in melanoma.

FGFR1

Fibroblast growth factor receptor-1 is another tyrosine kinase which plays a role in cell proliferation. Contrary to other mutations, FGFR1 amplification is associated with smoking and with worse overall survival. This amplification is found in approximately 15–20% of lung squamous cell carcinomas.²¹ Actionable driver mutations are rare in lung SCC compared to adenocarcinoma and there is heightened interest in FGFR1 amplification. Gene copy number is evaluated by fluorescent in situ hybridization, though the number of copies needed for the gene to be significant is not known.²²

TKIs for this mutation are currently under development and in phase I trials. A study of the TKI “BGJ398” in patients with FGFR1-amplified lung SCC showed partial response in 15% of patients. There are no approved FGFR inhibitors at this time.

MET

MET amplification is found in 2-4% of untreated NSCLC but found in up to 20% of EGFR positive cancers that have developed resistance to TKIs.²³ Subsequent studies confirmed that amplification of MET is integral to development of this resistance.²⁴ MET is located on chromosome 7 and amplification can be detected by fluorescent in situ hybridization. In a recent phase I trial, crizotinib showed activity in patients with MET amplified NSCLC and had a response rate of 33%.²⁵ This may evolve into a new second line treatment for TKI resistant EGFR positive patients.

FINAL THOUGHTS

There exist other mutations not mentioned in this article. DDR2, PIK3C, AKT and PTEN mutations are all suspected to be driver mutations and are currently under investigation as well. As yet there are no clear therapies or prognostic implications for tumors positive for these mutations and further development is needed. Additionally, these mutations are found more commonly in squamous cell lung cancer and may offer hope of targeted therapy for a tumor type that currently lacks effective agents.

Although individual rates of mutations are small, when added together they account for a large percentage of new NSCLC diagnoses, particularly in non-smokers with adenocarcinoma. Many new agents offer equivalent or better OS and PFS with less toxicity than chemotherapy. NGS analysis is a useful tool for discovery of these mutations and potential treatments on or off clinical trials. We recommend its use in patients who have progressed through standard therapy but retain a good performance status. Personalized medicine is the future of oncology and genomic analysis will play a large role in cancer prognosis and therapy.

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Primary Care Physicians' Use of Electronic Health Records in Rhode Island: 2009–2014

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ABSTRACT

We used data from the mandatory statewide Rhode Island (RI) Health Information Technology (HIT) Survey to characterize office-based PCPs' adoption and use of EHRs from 2009–2014. We found accelerated adoption of EHRs in the five years since state and federal incentive programs began targeting PCPs' adoption of HIT. There was room for improvement, however; for example, when asked to indicate the proportion of patients with whom they used various functionalities, only 13.4% of office-based PCPs said they "almost always" communicated with patients using secure messaging and 22.3% "almost always" used secure clinical messaging with outside providers. Results suggest uneven use of EHR functionalities, with low rates and slower uptake in some areas. These findings highlight opportunities to increase use of functionalities related to improved patient care and quality-based payment models.

KEYWORDS: Health information technology, electronic health records, primary care physician, quality, meaningful use

INTRODUCTION

Electronic health records (EHRs) may reduce medical errors, increase adherence to clinical guidelines, and improve efficiency and care coordination.¹ Policy efforts to increase EHR use have focused on primary care physicians (PCPs), since PCPs often represent patients' first point of contact with the healthcare system and are responsible for preventive and chronic disease management.

The 2009 Health Information Technology for Economic and Clinical Health (HITECH) Act created Medicare and Medicaid EHR incentive payment programs targeting PCPs.² By 2012, nearly three-quarters of office-based physicians reported having EHRs, a twofold increase since 2007, but only 18% of all office-based physicians met requirements to qualify for federal incentives.³ Despite increased adoption of EHRs, gaps remain in the use of functionalities that may improve patients' experience and care coordination, such as providing patients access to their records, sending summary-of-care documents, and securely transmitting information between providers.⁴

Capitalizing on EHRs' potential requires understanding which functionalities PCPs use and why. In 2008, the Rhode Island Department of Health became the first state to require all practicing physicians to respond to an annual survey about their health information technology (HIT) adoption. In this analysis, we use the Rhode Island (RI) HIT Survey to characterize how RI PCPs use EHRs and to examine trends in the use of specific functionalities over time.

METHODS

Sample

The RI HIT Survey targets all licensed independent practitioners (LIPs), including physicians, licensed in RI, in active practice, and providing direct patient care in RI or an adjacent state. We classified respondents as PCPs if they were office-based physicians who identified their specialty as: internal medicine (general), geriatrics, family medicine, or pediatrics. We classified respondents as hospital- or office-based based on their self-reported main practice location. This analysis was limited to PCPs in active practice.

Survey Instrument and Administration

The Department of Health's efforts to create the RI HIT survey with its quality reporting contractor, Healthcentric Advisors, are described elsewhere,⁵ but the instrument draws upon efforts in Massachusetts⁶ and nationally.⁷ It was piloted in 2008 and is updated annually to incorporate feedback and reflect changes in HIT and related policy. Results have been publicly reported annually since 2009.⁸

The survey aims to measure not only the presence or absence of an EHR, but LIPs' use of EHRs. To do so, it asks respondents to indicate how often they use EHR functionalities in eight domains: demographics, clinical documentation, decision support, interoperability, order management, patient support, reporting, and results management. It also asks about use of RI's health information exchange, CurrentCare, and prescription monitoring program, a database of controlled substance prescriptions filled at the state's pharmacies. Respondents indicate the percentage of patients with whom they use each specific EHR functionality and program: "Don't Have," "0% of patients" (Never), "<30% of patients" (Sometimes), "30–60% of patients" (Often), and ">60% of patients" (Almost Always). We reference the labels "never," "sometimes," "often," and "almost always."

In 2014, the RI HIT Survey was administered electronically (via SurveyMonkey) from April–June. All physicians with active RI licenses received mailed notices; the subset with available email addresses also received an email notification and up to two reminders. The survey incorporated skip patterns that excluded respondents who did not meet eligibility criteria and limited questions to those relevant to each respondent.

Data Analysis

We obtained a dataset with merged survey and licensure data for 2009–2014 under a data use agreement. Because these data do not contain any identifiers, the Brown University Institutional Review Board determined that this analysis did not constitute human subjects research.

We conducted all analyses using STATA 13 (College Station, TX). For descriptive analyses of 2014 data, we stratified responses by the presence or absence of an EHR in the respondents' main practice and defined an EHR as "an integrated electronic information system that tracks patient health data, and may include such functions as visit notes, prescriptions, lab orders, etc." For longitudinal analyses of 2009–2014 data, we chose "almost always" to capture physicians' routine use of various EHR functionalities in typical practice and a cutoff of 40% to identify physicians who consistently interact with Medicaid and uninsured patients.

RESULTS

In 2014, the response rate was 62.3% among all physicians and 89.5% among all PCPs; this includes 698 office-based PCPs, our population of interest (Table 1). Within this population, use of EHRs was higher among those <60 years old and in practices with ≥5 clinicians; it did not vary considerably by the proportion of Medicaid or uninsured patients. 89.5% of PCPs reported having an EHR in 2014, up from 25.1% in 2009. The largest growth occurred between 2009 and 2010, when rates of EHR use increased from 25.1% of PCPs to 72.5%.

The vast majority of PCPs (~90%) reported using patient demographics, clinical documentation, and drug interaction warning functionalities "almost always" (Table 2). A large majority (>70%) also reported using lab and radiology order entry functionalities "almost always." Adoption of other functionalities was lower; only 13.4% and 22.3% "almost always" communicated with patients using secure messaging and used clinical messaging with outside providers, respectively.

Use of EHRs increased more than threefold from 2009 to 2014 (25.1% to 89.5%), with most of the increase between 2009 and 2010 (25.1% to 72.5%). The proportion of PCPs using each functionality increased across the board, although the increase varied from a modest 0.5% for scanning results of labs to a 25.8% for generating

Table 1. Office-Based Primary Care Physician Respondents' Characteristics, 2014 (N=698)

Characteristic	With EHRs* (N=625)	Without EHRs (N=73)
	n (%)	
Age, years		
<44	159 (25.4)	7 (9.6)
45-59	308 (49.3)	21 (28.8)
≥60	158 (25.3)	45 (61.6)
Practice size†		
<5 clinicians	276 (44.3)	64 (88.9)
5-10 clinicians	205 (32.9)	6 (8.3)
>10 clinicians	142 (22.8)	2 (2.8)
Use of e-prescribing	579 (92.6)	11 (15.1)
Patient population		
≥40% Medicaid	164 (26.2)	15 (20.6)
≥40% uninsured	59 (9.4)	6 (8.2)

*Defined by question, "Does your main practice have EHR components? By 'EHR components,' we mean an integrated electronic information system that tracks patient health data, and may include such functions as visit notes, prescriptions, lab orders, etc. (This is also known as an electronic medical record or EMR.)"

†Defined by question, "Altogether, approximately how large is your main practice? Please consider physicians, nurse practitioners, and physician assistants."

Table 2. Percentage of Office-Based Primary Care Physicians Using EHR Functionalities "Almost Always," 2014 (N=625)*

Functionality	Use "Almost Always"
Patient demographics	582 (94.2)
Clinical documentation	
Write visit notes	569 (91.3)
Document patient medications	585 (94.1)
Document problem lists	573 (92.1)
Order management	
Lab order entry	470 (75.6)
Radiology order entry	445 (71.5)
Results management	
Results direct from lab	401 (64.5)
Scan paper lab results	215 (34.8)
Radiology results direct from facility	294 (47.3)
Scan paper radiology reports	247 (40.0)
Interoperability	
Generate referrals	430 (69.5)
Clinical messaging to outside providers	138 (22.3)
Generate clinical summaries for referrals/transfers	384 (61.8)
Decision support	
Drug interaction warnings	554 (89.1)
Reminders of indicated/overdue care	335 (53.8)
Recommended care prompts	312 (50.2)
Identify patients with condition or risk factor	325 (52.9)
Patient support tools	
Accept prescription refill requests	503 (83.1)
Communicate with patients with secure messaging	82 (13.4)
Provide patient-specific educational resources	194 (31.1)
Provide patients with test results	251 (40.6)
Schedule patient appointments	407 (66.8)
Provide clinical summaries to patients	412 (66.6)
Reporting	
Report clinical quality measures	377 (60.8)
Identify patients out of compliance with guidelines	323 (52.1)

*Due to missing data, the denominator varies by question and ranges from 605-623.

referrals through the EHR (**Figure 1**).

In 2014, more than half of PCPs (51.5%) reported using the prescription monitoring program with any frequency, but only one in 10 (9.8%) used it “almost always.” About a quarter of PCPs used CurrentCare with any frequency (25.1%); just 3.1% reported using it “almost always.”

DISCUSSION

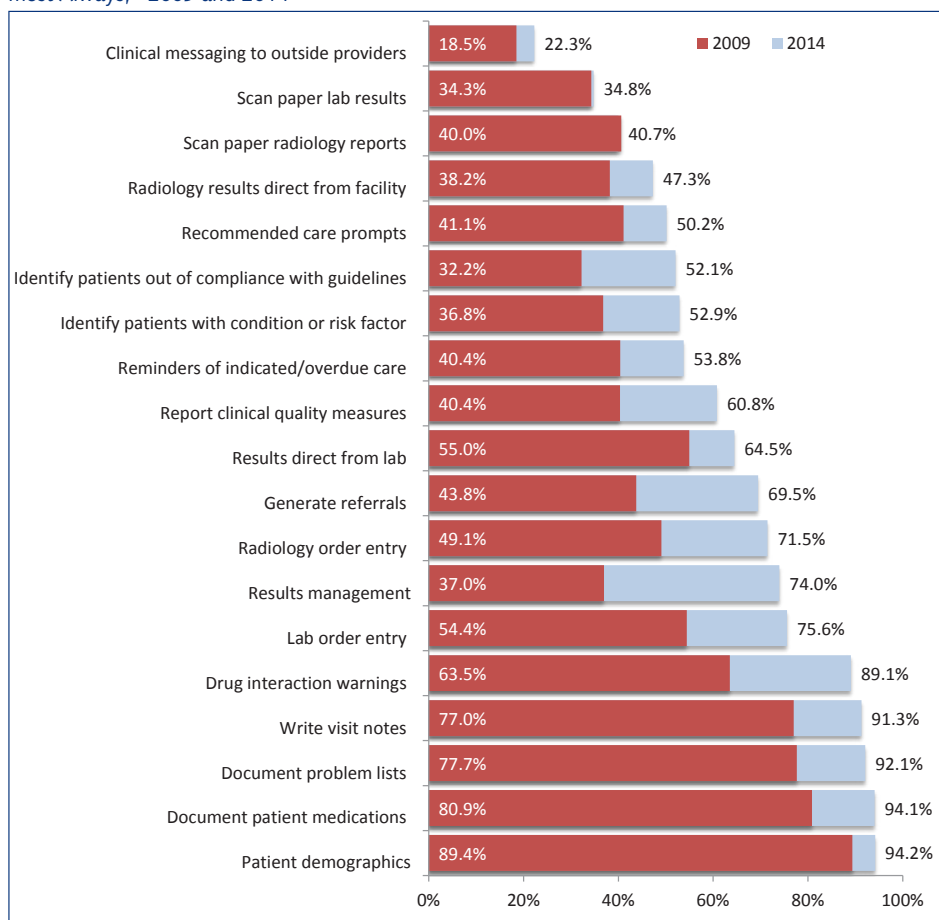
In this statewide analysis, we found increasing adoption and use of EHRs among PCPs over five years. PCPs’ use of EHRs to generate referrals, order tests, and report quality measures increased markedly, perhaps because EHRs make these activities easier⁹ and incentive programs specify quality reporting goals.¹⁰ However, quality reporting did not become commonplace. It was higher in practices with >10 vs. <5 clinicians (71% vs. 50% “almost always,” respectively). This may be due to the complexity of extracting and analyzing EHR data¹¹ or the infrastructure and personnel needed to perform these tasks.

The 2014 data highlight other opportunities to further support PCPs’ use of many EHR functionalities, particularly those dependent on interoperability; that is, the ability of independent HIT systems to communicate and exchange data. Emerging payment models, such as accountable care organizations, will require effective cross-setting communication, particularly between PCPs and other providers.¹² Yet in our analysis, fewer than one in four PCPs used secure clinical messaging, consistent with national data.^{13,14} Although providers may communicate in other ways, low use of EHR communication functionalities suggests the need to address barriers, e.g., interoperability^{15,16} and concerns regarding secure transmission of patient data.¹⁷

Our findings support previous analyses showing that younger physicians in larger practices are most likely to have EHRs and that use of some functionalities is increasing more slowly than others.¹⁸ In contrast to earlier studies,^{19,20} we found no evidence of a “digital divide”: RI PCPs who care for large proportions of Medicaid or uninsured patients adopted EHRs at similar rates as those who care for less vulnerable patient populations.

The state’s health information exchange, CurrentCare, and prescription monitoring program both have the potential to improve patient safety and cross-setting communication. Yet PCPs’ use of these programs is low, perhaps in part because of perceived workflow inefficiencies, such

Figure 1. Percentage of Office-Based Primary Care Physicians Using EHR Functionalities “Almost Always,” 2009 and 2014



as having to switch from the EHR and login to a separate Internet-based system,²¹ documented in previous qualitative work.²² Incorporation of these programs into existing EHR interfaces or the use of single sign-on technology may increase uptake.²³

We note several limitations to this descriptive analysis. First, physicians with EHRs may be more likely to respond to the RI HIT Survey, both because of greater interest in the topic and because they are likely to have the technical capacity. Second, responses are self-reported and thus may be subject to response bias, although this may be mitigated by the fact that the Department of Health mandates participation. Third, we classified physicians as PCPs using survey responses (for respondents) and licensure data (for non-respondents); physicians may be subject to misclassification.

In conclusion, we found accelerated adoption of EHRs in the five years since state and federal incentive programs began targeting PCPs’ adoption of HIT, but also note ongoing opportunities to support further uptake of various functionalities, particularly those that require interoperability. These findings reinforce the fact that EHR implementation does not inevitably lead to optimal use of functionalities linked to improved patient care. We call for policies that address

barriers to EHR use, including core technical standards for EHRs and national certification programs to ensure EHR vendors are selling technology that can seamlessly exchange information with other health systems.^{24,25} Such policies, combined with research examining the barriers to EHR use, will better enable PCPs to maximize EHRs' potential and to improve the experience of both patients and providers.

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Recurrent Mixed Cryoglobulinemia (MCS): A Case Report and Literature Review

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ABSTRACT

We report a case of recurrent mixed type II cryoglobulinemia with difficult diagnosis and treatment dilemma and uncertain prognosis in view of limited studies. A 60-year-old male with history of essential mixed cryoglobulinemia 12 years ago treated successfully with six months of cyclophosphamide and prednisone presented with bilateral lower extremity purpuric rash and swelling. He was found to have proteinuria, hematuria, RBC casts, low serum complement levels, and acute kidney injury (AKI). Initial therapy with methylprednisone and oral cyclophosphamide was ineffective (patient developed respiratory failure due to alveolar hemorrhage). Additional labs revealed positive type II cryoglobulins, high free Kappa/Lambda, UPEP with minimal urine protein, SPEP with marked hypogammaglobulinemia, and negative tests for HIV, HCV, ANA, and ANCA. More aggressive therapy with daily plasmapheresis and rituximab was instituted with very good clinical response. He achieved clinical remission but developed another flare 8 months later. Kidney biopsy showed membranoproliferative glomerulonephritis with cryoglobulin deposits. Flow cytometry and biopsy of bone marrow was consistent with lymphoplasmacytic lymphoma. His diagnosis was eventually confirmed and responded clinically to another course of rituximab and plasmapheresis, but prognosis is yet to be seen.

KEYWORDS: Cryoglobulinemia, Lymphoplasmacytic Lymphoma, Hepatitis C, Rituximab, Cyclophosphamide, Plasmapheresis

BACKGROUND

The paucity of available data and lack of clear clinical guidelines pose diagnostic and therapeutic dilemma in patients with recurrent noninfectious MCS. In this report, we present a patient who was diagnosed with essential MCS 12 years ago, treated successfully with cyclophosphamide and prednisone. After more than a decade of complete remission he had recurrence of disease when he presented with skin purpura and acute kidney injury complicated by life-threatening pulmonary hemorrhage that was effectively treated with rituximab and plasmapheresis and a tapering course of oral prednisone. A month later after discontinuation of oral prednisone and following a dental procedure (removal of six teeth)

he experienced another recurrence with skin and AKI. At that time a bone marrow and flow cytometry was performed. This case represents a rare cause of cryoglobulinemia, and the diagnostic and treatment dilemma associated with it.

CASE PRESENTATION

A 60-year-old male originally from Argentina with history of essential MCS diagnosed 12 years ago and successfully treated with six months of cyclophosphamide and prednisone presented with bilateral lower extremity purpuric skin rash and ankle swelling. Exam findings were significant for elevated BP, 169/89 mmHg, bilateral lower extremity purpura, and trace edema. Laboratory tests revealed serum creatinine at 2 mg/dL (baseline 1 mg/dL); C3 at 35 mg/dL (reference range 79-152 mg/dL) and C4 at <10 mg/dL (reference range 16-38 mg/dL). The urinalysis revealed proteinuria (spot protein/creatinine: 1.5 mcg/gr creatinine), hematuria, and RBC casts. Haptoglobin was <5.8 mg/dL (reference range 36-195 mg/dL), LDH 449 IU/L (reference range <171 IU/L), hemoglobin 11.2 gm/dL, and peripheral blood smear showed no evidence of schistocytes. He was initially treated with intravenous solumedrol 1 gm daily for 3 days. However, he developed respiratory distress, decreased pulse oxygenation (83% on room air) on day 3 of admission. Chest X-ray showed diffuse bilateral airspace consolidation along with drop in hemoglobin level, concerning for diffuse alveolar hemorrhage. His therapy was switched to combination oral cyclophosphamide 100 mg/day and daily plasmapheresis. Additional laboratory findings showed presence of type II cryoglobulins, rheumatoid factor (RF) at 115 IU/mL (reference range <20 IU/mL), free Kappa/Lambda at 3.53, urine protein electrophoresis (UPEP) with minimal urine protein, serum protein electrophoresis (SPEP) with marked hypogammaglobulinemia; and serological tests negative for HIV, HCV PCR, antinuclear antibody (ANA), and anti-neutrophil cytoplasmic antibody (ANCA). On Day 7 of hospitalization, patient required intubation for progressive respiratory failure although creatinine had improved from 2.2 to 1.3 mg/dL. Because of recurrent disease involving lungs, kidneys, and skin with light chain abnormalities and rapidly deteriorating course, his treatment regimen was switched to daily plasmapheresis and rituximab 375 mg/m²/week. There was remarkable improvement in clinical course with discontinuation of ventilatory support eight days later. Subsequent

three additional doses of rituximab administered one week apart (total of 4 doses) were completed as outpatient. Follow-up laboratory studies five months post-hospital discharge revealed creatinine at 1 mg/dL, urinalysis with trace proteinuria (urine protein/creatinine: 0.15 gm/day), non-dysmorphic RBCs and absent casts, C3 at 121 mg/dL, C4 at 14 mg/dL, free Kappa/Lambda at 0.83 and absent cryoglobulins. Monoclonal protein was absent on serum immunofixation. The prednisone therapy had been tapered to 10 mg/day with excellent clinical and biochemical remission.

He represented 8 months later with similar complaints consistent with mixed cryoglobulinemia flare. By that time, he was off oral prednisone for a month. Following a dental procedure (removal of six teeth) he experienced another flare-up with purpuric skin rash and AKI. A repeat kidney biopsy

showed recurrent type II membranoproliferative glomerulonephritis with cryoglobulinemia deposits (**Figures 1–5**). Bone marrow biopsy showed hypocellular (25%) marrow with kappa-positive mild plasmacytosis (4%). Flow cytometric immunophenotypic analysis of bone marrow demonstrated less than 1% of CD19+, CD20-, kappa-restricted B cells consistent with low level B-cell lymphoplasmacytic lymphoma. Bone marrow chromosomal analysis did not reveal any numerical or structural abnormalities. CT scan of chest, abdomen, and pelvis excluded occult lymphadenopathy. Treatment with Rituximab and plasmapheresis, due to previous life-threatening presentation was instituted. His clinical condition improved and was subsequently discharged from the hospital. His last serum creatinine has normalized and he is now on oral cyclophosphamide at 50 mg/day.

Figure 1. Mesangiocapillary proliferation and cryoglobulin thrombi (H&E stain at 400x)

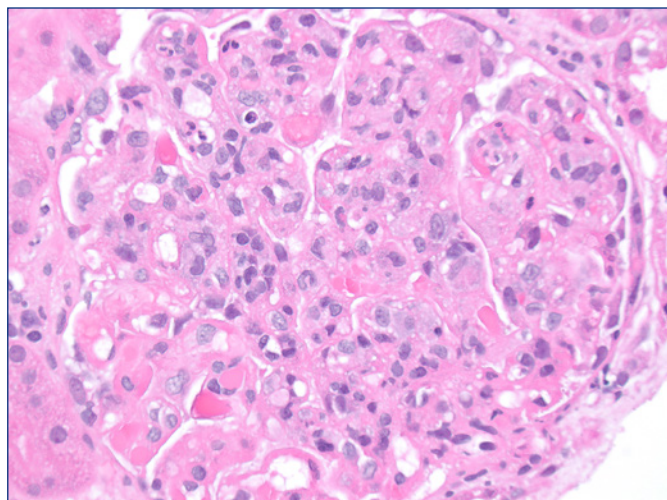


Figure 2. Cryoglobulin thrombi is present in upper right (PAS stain at 400x)

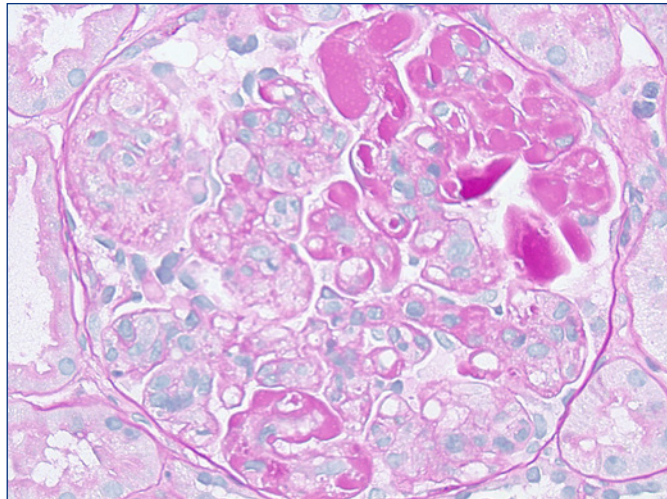


Figure 3. Cryoglobulin thrombi is seen in lower right and glomerular basement membrane deposits are stained throughout the glomerulus (IgM immunoperoxidase stain at 400x)

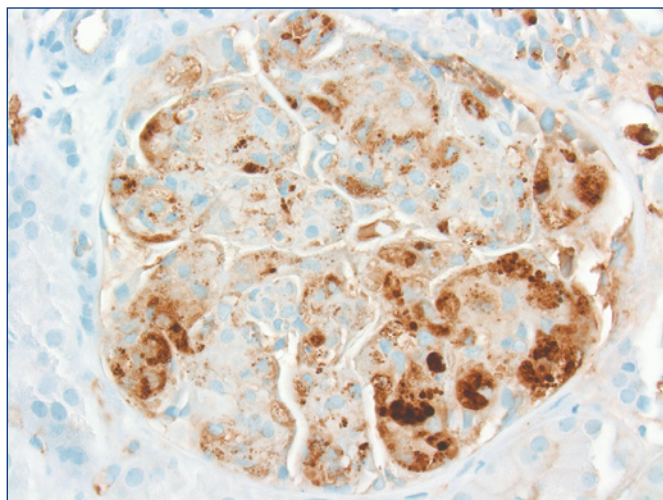


Figure 4. Cryoglobulin thrombus is seen in the capillary loop with double contoured glomerular basement membrane. There are proximal tubule protein resorption droplets seen in left upper quadrant (Jones silver stain at 400x)

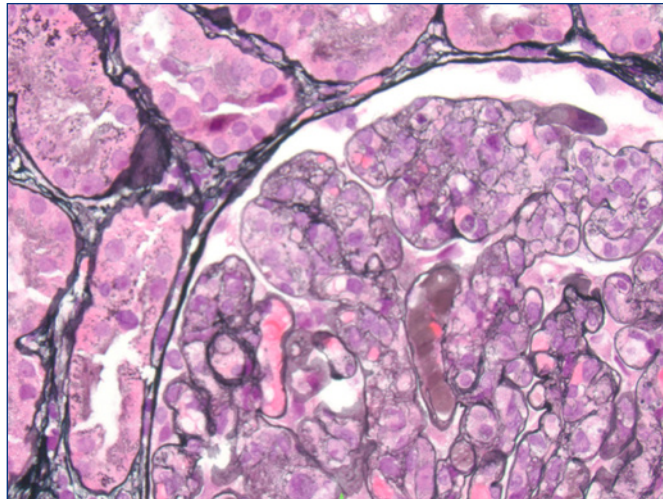
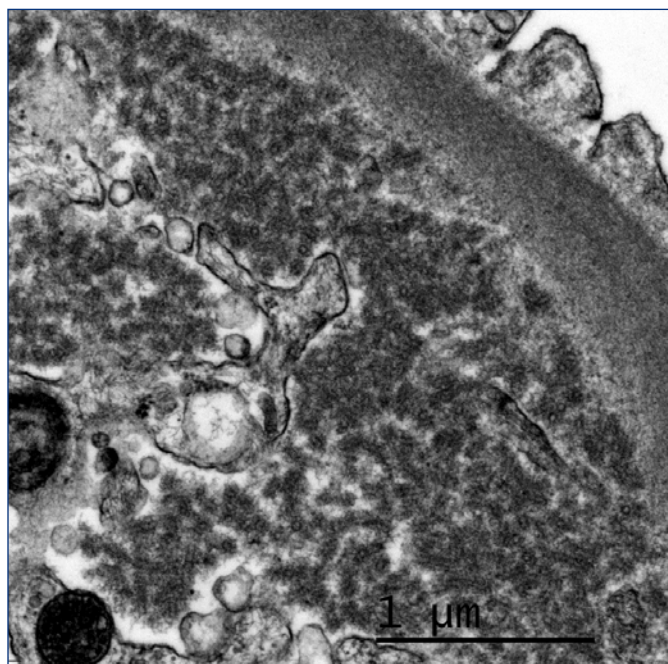


Figure 5. Cryoglobulin deposits are seen in the endothelium (EM at 30kx)



DISCUSSION

Cryoglobulins are serum immunoglobulins that precipitate with cooling ($<37^{\circ}\text{C}$) and redissolve upon rewarming. Meltzer et al identified mixed cryoglobulins in 1966¹, then Brouet et al, in 1974, classified cryoglobulins into three different biochemical types.² Type I cryoglobulin consists of monoclonal immunoglobulin (Ig), either IgG or IgM, usually seen in Multiple Myeloma (MM) and Waldenstrom's Macroglobulinemia (WM). Type II cryoglobulins imply monoclonal IgM RF against polyclonal IgG, more commonly associated with HCV infection, and less commonly with hepatitis B (HBV) and Epstein-Barr virus (EBV). Type III cryoglobulins are polyclonal IgM RF against IgG, seen in autoimmune diseases (systemic lupus nephritis (SLE) and Systemic Sclerosis (SS)) and Lymphoproliferative diseases (LPD). Reported incidence of type I, II, and III cryoglobulins are 6%, 62%, and 32%, respectively.³ Mixed cryoglobulinemia connotes the presence of type II or type III cryoglobulins in the blood sample and 'essential' means obscure cause, therefore eMCS indicates absence of identifiable cause of type II or III cryoglobulinemia.

Recurrence risk of eMCS after complete remission is unpredictable. Our patient presented with skin purpura which constitutes 81% of presenting feature in MCS.⁴ It may present with weakness and fatigue (80%), arthralgia (72%), and frank arthritis (8%). Renal involvement in the form of glomerulonephritis (GN) is evident on presentation in 20% of MCS patients. The most frequent renal presentation is microscopic hematuria and proteinuria. Beddhu et al reported type I MPGN as the predominant histologic pattern, followed by focal and mesangioproliferative GN in a series

of 17 patients with cryoglobulinemia and renal disease.⁵ In the same report, HCV positive, as compared to HCV negative, cryoglobulinemia was more commonly associated with progression to end stage renal disease (ESRD) attributable to less immunosuppressive usage in the former group. Rapidly progressive course is infrequent but when present signals poor prognosis.

The detailed work-up and treatment should be tailored to the clinical presentation. HCV infection is frequently associated with the presence of type II or type III cryoglobulins without obvious vasculitis symptoms, thus the utility of checking cryoglobulin level in the absence of vasculitis symptoms is unhelpful as it would not alter the treatment plan. Conversely, strong clinical suspicion should be raised and pertinent work-up pursued if patients present with purpura or arthralgia with the evidence of positive RF titer and hypocomplementemia. It was necessary to investigate deeply in our patient in view of multi-organ involvement. Approximately 30–40% of type II and some type III MCS have undetectable cryoglobulins on presentation. In such scenario, improper handling of specimen (specimen collection at temperature below 37°C) has to be ruled out by carefully reviewing the entire procedure and cryoglobulin level be repeated if clinical suspicion is very high. Failure to maintain warm temperature results in precipitation of cryoglobulin to the bottom of the collection tube and the supernatant serum would not yield any cryoglobulins leading to false negative result. The cryocrit is percentage of packed cryoglobulins and it is frequently used measure to report cryoglobulins by the most laboratories. The normal cryocrit level should be close to zero in the absence of MCS and level $>1\%$ is clinically significant. The cryocrit level between 1–3% is seen in Type III and 2–7% is seen in Type II MCS. Normal cryoglobulin level is 2–5 mg/dL. Approximately, 95% of MCS are associated with HCV infection^{6,9}; this clinical correlation was unknown before the early 1990s, prior to discovery of HCV. Detailed work-up to delineate the cause of cryoglobulinemia must include HCV, HBV, HIV, MM, WM, LPD, SLE, SS, and Sjogren's syndrome as the primary goal is to treat the underlying cause of cryoglobulinemia. Presence of severe hypogammaglobulinemia, abnormal kappa/lambda ratio, IgM kappa monoclonal protein in our case during recurrence, responding to rituximab, initially suggested underlying chronic low-grade lymphoproliferative disorder precipitating the recurrent events which was eventually proven by bone marrow biopsy and flow cytometry.

Therapeutic management of MCS is based on the severity of disease and the underlying disorder. Presence of cryoglobulins in the absence of clinical symptoms warrants close monitoring. Addition of low to moderate doses of steroids relieves mild symptoms like purpura and arthralgia. Cold exposure should be avoided to prevent cryoglobulin precipitation. Angiotensin converting enzyme inhibitor is prescribed to reduce intraglomerular filtration pressure and proteinuria, if present. Limited data is available on colchicine

and low antigen diet to restore saturated mononuclear phagocytic system and spare steroid use.¹⁰ Prompt therapeutic intervention with combined immunosuppressive therapy (Rituximab or, if unavailable, Cyclophosphamide) and pulse steroid, to prevent new cryoglobulins production, is mandated in life threatening or rapidly progressive disease including pulmonary hemorrhage, CNS vasculitis, GI hemorrhage, and skin necrosis to stabilize disease. This patient's renal function improved after 3 doses, total of 3 grams, of methylprednisolone but clinical course deteriorated, despite upgraded therapy with cyclophosphamide, until rituximab was added. Modest dose of rituximab can deplete CD20+ B cells in the peripheral blood at 24–72 hours with the effect lasting at least 2–3 months.¹¹ Plasmapheresis, although controversial, may be added in such a situation.¹² Replacement fluid for plasmapheresis should be warmed to prevent precipitation of cryoglobulins.¹³ Once the disease is stabilized the underlying cause must be identified and treated. The exception to this rule is HIV and HBV infection which must be treated before or at the same time of aggressive therapy with immunosuppressants and plasmapheresis in order to prevent enhanced viral replication. In MCS related to viral etiology presenting with mild symptoms, the goal should be focused on the eradication of the virus. HCV infection, with the exception of decompensated cirrhosis, is treated with pegylated IF and Rituximab.¹⁴ Rituximab is an effective therapy in severe cryoglobulinemic vasculitis.¹⁵ It has steroid sparing effect as well. In HCV-related MCS it inhibits auto-reactive antibodies produced by oligoclonal or polyclonal B lymphocyte expansion related to chronic HCV infection. Complete remission in MCS secondary to non-infectious etiology is higher with rituximab plus glucocorticoids compared to glucocorticoids alone but associated with increased risk of infection, especially when a higher steroid dose is used.¹⁶ In the same study combined cyclophosphamide and glucocorticoid therapy was not associated with better outcome compared to glucocorticoid alone. One small study on low-dose rituximab 250 mg/m² in the treatment of MCS was less effective in achieving one-year remission.¹⁷ Clinical response is determined based on improvement of clinical picture (improvement of ulcers, respiratory failure), serum creatinine and proteinuria. Serum concentration of cryoglobulin (cryocrit) is not a marker of severity of disease or a response to the therapy.¹⁸ The tapering of steroids and total duration of course depends on the disease response. The duration of antiviral therapy is the same for HCV infection with or without cryoglobulinemia. Treatment of lymphoplasmacytic lymphoma is challenging in the absence of strong data. For the treatment of recurrent disease like in our case, combination therapy with rituximab and bendamustine or fludarabine can be administered in patients older than 70 years; however, there is no comparison data between these two regimens. In patients younger than 70 years, combination therapy with cyclophosphamide, fludarabine, and rituximab has been suggested by the Italian Society of

Hematology to minimize the toxicity of fludarabine in the absence of comorbidities.

Prognosis in MCS does not rely on presence or absence of viral infection; absence of infection in fact may have a worse prognosis. In a cohort of HCV-infected patients treated with appropriate anti-HCV therapy, overall survival was more than 80% at a median of 15 years regardless of presence or absence of MCS.¹⁹ Patient survival in non-infectious MCS at 1, 2, 5, and 10 years are 91, 89, 79, and 65%, respectively.²⁰ Lymphoplasmacytic lymphoma usually has an indolent clinical course and some have an aggressive course with median survival of 5 to 7 years. This case had an indolent course for a decade followed by an aggressive course. Overall one-year survival with the manifestation of acute pulmonary hemorrhage, CNS vasculitis, intestinal vasculitis with gastrointestinal bleeding/ischemia, rapidly progressive glomerulonephritis, and cardiac vasculitis are 22%, 66%, 67%, 79%, and 100%, respectively.^{21, 22} Recurrence rate of MCS after renal transplantation has been reported between 50–70% even with clinical and serologic remission during transplantation but most patients do not lose graft from recurrent disease.²³

SUMMARY

In summary, 12 years ago our patient presented with eMCS and completely responded to Cyclophosphamide and prednisone. He was admitted with an identical cryoglobulin profile with a rapid deterioration failing high-dose steroids, plasmapheresis and cyclophosphamide. After a single dose of rituximab his clinical condition dramatically improved allowing him to be extubated and have his therapy completed as an outpatient. Patients with low-grade NHL commonly go into a complete remission with an alkylating agent and corticosteroid therapy and commonly recur years later. As our patient had a monoclonal protein detected in the serum separate from the cryoglobulin, we postulated that he had all along suffered from a low-grade LPD which secretes an IgM Kappa monoclonal protein with the biophysical properties to instigate the development of the aforementioned type II mixed cryoglobulinemia. This diagnosis was confirmed on his second recurrence with flow cytometry and biopsy of bone marrow. His recurrent flares have been controlled with rituximab therapy and plasmapheresis. He subsequently has been started on oral cyclophosphamide with fair tolerance. His future treatment will be challenging due to his recurrence while on rituximab therapy.

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Understanding the Disparities of Citizen Health Preparedness – Can Providers Help Close the Gaps?

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Health equity means everyone has an equal opportunity to take advantage of resources that will help them live a long, healthy life.¹ Health security is a state in which a community and its people are prepared for, protected from, and resilient in the face of incidents with health consequences.² The two are intrinsically linked.

Disparities in health outcomes are commonly explored with respect to traditional public health prevention and promotion programs and result in a more insightful understanding of the burden of infant mortality rates, complications from diabetes, and hospitalization rates.³ More uncommon, however, is the application of such analysis to determine potential outcomes and indicators of public health preparedness. Such application may further define a given subset of the community's vulnerability to an emergency or large-scale disaster. With a renewed focus in Rhode Island on achieving health equity and reducing the inequities caused by social and environmental determinants of health, dialogue between the public health and healthcare sectors about addressing the gaps in health preparedness can be catalyzed. Access to adequate food, water, shelter, clothing, and proper medical care are often noted by the world community as basic human rights (i.e., decent standard of living) and therefore, also as elements needed to ensure health equity.⁴ Should this same concept not apply during emergency times as well?

Public health preparedness is a relatively new discipline, with a generally limited evidence base.⁵ Unlike other health promotion programs, health preparedness lacks best practices pertaining to the provider-patient role. According to a Federal Emergency Management Agency study, only 19% of American families reported being very prepared for an emergency.⁶ In essence, 81% of American families lack essential components to being prepared, such as a three-day supply of food, water, and medications or plans for appropriate sheltering.

METHODS

The Behavioral Risk Factor Surveillance System (BRFSS) is a national telephone survey of randomly selected adults ages 18 and older. The surveillance system monitors behavioral health risks, access to health care, and health conditions that contribute to the leading causes of disease and death among adults in the United States. From January through December 2013, the RI BRFSS conducted random-digit dialed

telephone interviews with 6,531 non-institutional adults in Rhode Island. An eight-question module was developed by the CDC and asked within the 2013 RI BRFSS. Four of the eight emergency preparedness questions are reported in **Table 1**. Two measures each were used to create combined indicators for "Being Prepared" and "Willingness to Follow Orders." Respondents were defined as "being prepared" if they answered "yes" to both questions (1) and (2). Respondents were defined as "willing to follow orders" if they answered "yes" to both questions (3) and (4). Respondents answered "yes", "no", "don't know", or "refused" to these four questions:

Having a disability was defined as described in Table 1. Health behaviors and health conditions were used as variables to identify the role, if any, that health status might have in citizen health preparedness. Optimal health behaviors (i.e., always wearing a seatbelt, obtaining influenza vaccination) were chosen from BRFSS data with high sample size. Having been diagnosed with diabetes was selected to compare individuals with a pre-existing health condition to those without using this same selection method. Having social support was analyzed by grouping always/usually

Table 1. Emergency Preparedness Indicators and Questions

INDICATOR	QUESTIONS MEASURED
"Being Prepared"	(1) Does your household have a written disaster evacuation plan for how you will leave your home and communicate with your family in the case of a large-scale disaster or emergency that requires evacuation?
	(2) Does your household have a 3-day supply of water, nonperishable food, and 3-day supply of prescription medication for everyone who lives there? A 3-day supply of water is 1 gallon of water per person per day.
"Willingness to Follow Orders"	(3) If public authorities announced a mandatory evacuation from your community due to a large-scale disaster or emergency, would you evacuate?
	(4) Some emergencies could be due to an infectious disease. If you were instructed to go to a public facility, such as a school, to get medication to fight a very infectious disease, would you go?
Note – Having a disability was defined by respondents answering yes to either of the following questions: Are you limited in any way in any activities because of physical, mental, or emotional problems? and/or Do you now have any health problem that requires you to use special equipment?	

having sufficient social support versus less than always/usually having sufficient social support. This variable was chosen to explore the relationship of social cohesion within citizen preparedness. When the two preparedness indicators were examined using income as a variable, a total of 30.2% and 29.0% of missing observations were present. No other variable had more than 20.1% missing observations. Bivariate analyses were conducted and confidence intervals (CI) were reviewed. A 95% CI reflects the stability of an estimate of prevalence. If the 95% CI do not overlap, a statistically significant difference between groups exists. To account for the complex sampling design, data were analyzed using SAS ® 9.3.

RESULTS

Figure 1 illustrates the disparities associated with being prepared. Overall, only 19.9% of the population met both measures associated with being prepared while 25.6% met neither measure. Of the two measures associated with being prepared, 23% of households had a written evacuation plan and 72% of households reported having a three-day supply of water, food, and medication for the household (data not shown). Age was identified as a predominant factor in determining one's level of being prepared. Older adults (ages 65 or older) were the most prepared (29.9% met both measures) with a significant disparity seen between this group and both categories under 65 years of age. Sex was observed, given very small CI overlap, to be a factor in the disparity seen among those being unprepared, with females reporting to have not met either measure more frequently (27.8%) compared to males (23.2%).

Having a disability resulted in a higher proportion of individuals meeting both measures of being prepared (25.1%) compared to those without (18.3%); however, all groups were similarly unprepared. Individuals who reported being diagnosed with diabetes were seen to be both less likely to be unprepared (19.7%) and more likely to meet both measures of being prepared (26.2%). This same trend was also observed with individuals who received an influenza vaccine and individuals who always wear a seatbelt. Individuals who were not married/coupled (e.g., widowed, separated, divorced, or never married) were more likely (22.6%) to meet both measures of being prepared. Individuals who reported not having social support available were more likely (32.4%) to have not met either measure of being prepared. Two observations can be made about housing type and income. Those

Figure 1. Disparities Observed with “Being Prepared” among Rhode Island Adults, 2013

“BEING PREPARED”		Met NEITHER Measure		Met BOTH Measures	
		Wght %	(95% CI)	Wght %	(95% CI)
Overall Prevalence	N=5289	25.6	23.9-27.2	19.9	18.4-21.4
Age	18-45	32.0	28.8-35.2	16.4	13.7-19.1
	45-64	24.3	22.1-26.6	18.2	16.2-20.2
	65 and Older	14.8	12.7-16.8	29.9	27.0-32.8
Sex	Male	23.2	20.7-25.6*	19.8	17.4-22.2
	Female	27.8	25.5-30.0*	19.9	18.0-21.7
Income Level	Less than \$25,000	26.1	22.4-29.8	27.4	23.9-30.9
	\$25,000-\$49,999	24.3	20.9-27.6	21.7	18.5-24.9
	\$50,000-\$74,999	26.1	21.8-30.3	15.9	12.0-19.7
	\$75,000 and Greater	26.2	23.2-29.2	13.4	11.0-15.7
Housing Type	Own	23.6	21.8-25.5	18.4	16.7-20.1
	Rent/Other	29.8	26.6-33.1	22.9	19.9-25.9
Marital Status	Married/Coupled	25.0	23.0-27.0	17.5	15.8-19.2
	Not Married/Coupled	26.2	23.5-29.0	22.6	20.0-25.1
Social Support	Always/Usually	23.5	21.7-25.3	20.0	18.3-21.6
	Some/Rare/Never	32.4	28.6-36.2	19.7	16.3-23.0
Disability	Yes	25.7	22.5-29.0	25.1	22.1-28.2
	No	25.4	23.5-27.3	18.3	16.6-20.0
Diabetes	Yes	19.7	15.1-24.2	26.2	21.8-30.7
	No	26.2	24.4-27.9	19.2	17.6-20.8
Flu Vaccine	Yes	22.8	20.7-24.9	20.6	18.6-22.6
	No	28.0	25.5-30.4	19.1	16.9-21.2
Seatbelt Use (Always)	Yes	24.5	22.8-26.2	20.7	19.1-22.3
	No	32.2	26.5-37.9	14.6	10.6-18.7

Wght %: weighted percent; CI: confidence interval

*CI overlap exaggerated due to rounding convention.

reporting the smallest household income were the most prepared while those who rent or have another arrangement were the most unprepared.

Figure 2 depicts results of the population's willingness to follow orders. A total of 78.3% of the population met both measures of willingness to follow orders with 21.7% having not met both measures. When looking at the specific questions associated with willingness to follow orders, 93% of households would evacuate if public authorities mandated evacuation during an emergency. Similarly, 92% of households reported that in the event of an emergency due to an infectious disease, the household would go to a public facility to get treatment (data not shown). Figure 2 showed that sex was again a factor, with males more likely (25.3%) to not or to be unsure if they would follow orders. Similarly, the same disparity was observed between those who did not practice optimal health behaviors, those who were not married/coupled, and those with suboptimal social support. Income varied significantly only between the two bipolar groups. No difference was observed by age, disability, health condition, or housing type.

Figure 2. Disparities Observed with “Willingness to Follow Orders” among Rhode Island Adults, 2013

“WILLINGNESS TO FOLLOW ORDERS”		DID NOT Meet BOTH Measures		Met BOTH Measures	
		Wght %	(95% CI)	Wght %	(95% CI)
Overall Prevalence	N=5409	21.7	20.1-23.3	78.3	76.7-79.9
Age	18-45	21.7	18.7-24.7	78.3	75.3-81.3
	45-64	21.4	19.2-23.6	78.6	76.4-80.8
	65 and Older	21.7	19.2-24.1	78.3	75.9-80.8
Sex	Male	25.3	22.6-27.9	74.7	72.1-77.4
	Female	18.5	16.6-20.3	81.5	79.7-83.4
Income Level	Less than \$25,000	25.4	21.8-28.9	74.6	71.1-78.2
	\$25,000-\$49,999	18.7	15.5-21.8	81.3	78.2-84.5
	\$50,000-\$74,999	21.9	17.8-25.9	78.1	74.1-82.2
	\$75,000 and Greater	18.2	15.4-21.0	81.8	79.0-84.6
Housing Type	Own	21.1	19.2-22.9	78.9	77.1-80.8
	Rent/Other	23.1	20.1-26.2	76.9	73.8-79.9
Marital Status	Married/Coupled	19.4	17.5-21.2	80.6	78.8-82.5
	Not Married/Coupled	24.2	21.6-26.9	75.8	73.1-78.4
Social Support	Always/Usually	18.7	17.1-20.4	81.3	79.6-82.9
	Some/Rare/Never	29.4	25.6-33.3	70.6	66.7-74.4
Disability	Yes	24.2	21.1-27.3	75.8	72.7-78.9
	No	20.8	19.0-22.7	79.2	77.3-81.0
Diabetes	Yes	23.2	18.6-27.7	76.8	72.3-81.4
	No	21.6	19.9-23.3	78.4	76.7-80.1
Flu Vaccine	Yes	18.4	16.4-20.4	81.6	79.6-83.6
	No	24.3	22.0-26.7	75.7	73.3-78.0
Seatbelt Use (Always)	Yes	20.5	18.8-22.1	79.5	77.9-81.2
	No	29.2	23.6-34.8	70.8	65.2-76.4

Wght %: weighted percent; CI: confidence interval

DISCUSSION

Age was observed to have a significant role in health preparedness when both measures of the “Being Prepared” indicator were met, congruent with previous findings.^{7,8} The data illustrated that while age is a driver, life stages do not correlate with one’s level of preparedness. Uncertainty remains as to whether or not today’s disaster experiences influence tomorrow’s preparedness, indicative of the life-course approach.¹ Whether or not an individual’s innate awareness of the risks of being caught unprepared is linked to age remains to be seen.⁹ Perhaps messaging shifts linking preparedness to common, relatable experiences are needed to engage younger generations.

Gender was observed to also have a role in health preparedness,⁷ with females more likely to be unprepared (i.e., met neither measure) and males less likely to follow orders. With respect to the social and environmental determinants of health, neither metropolitan area of residence nor education were observed to have led to any distinct disparities within the population’s levels of being prepared or willingness to

follow orders. Geographic location has previously been identified as having a limited role in personal preparedness,¹⁰ while education has been cited as having a role previously, despite this study’s findings^{7,8} to the contrary. Understanding the roles of income (i.e., why less money resulted in an increased frequency of being prepared but decreased willingness to follow orders) and housing type⁸ (i.e., why home ownership alone resulted in decreased frequency of being unprepared) remains important. Exploring how socio-economic status and the housing environment might influence household preparedness requires further study.

Inadequate social support may influence the frequency of both being unprepared and unwilling to follow orders compared to adequate support. Social connectedness has been identified as a core component to community preparedness, from both a self-sufficiency and resident safety perspective.¹¹ These results highlight an opportunity for the healthcare sector to intervene as service-providing organizations within the community, particularly for those with health conditions. While those with diabetes were more likely to be prepared, the fact remains that only 26.2% of diabetics met both measures, increasing the vulnerability of an already at-risk population during an emergency.¹²

There are a few study limitations. The survey questions used in this study were state-added, and therefore subjected to end of survey drop-off. Using only one year of available data from a self-report survey resulted in limitations on sample size. Race/ethnicity was not examined

for this reason. The number of children per household was excluded due to limitations with this variable, as it was only available on landline surveys. Despite these limitations, the study provides baseline data to better understand populations at-risk of being caught unprepared and to refine studies on the barriers associated with preparedness behavior.

Moving Forward

Reducing the age, gender, and housing disparities seen with citizen preparedness levels remains a future focus at the Rhode Island Department of Health (RIDOH). More research is needed through surveys, focus groups, or based on data from clinician-initiated conversations to further understand the age-preparedness level relationship. Factors to explore with greater sample size and with age include race/ethnicity¹³ and religion. Once these relationships are defined, personal preparedness programs can be reframed or redesigned, especially if life experience is the predominant factor for the age disparity and whether or not aspects of culture play an equal or greater role.^{12,13}

The Community Health Resilience Project at RIDOH is examining how community-clinical linkages lacking within health preparedness can be built. Inviting the healthcare community to help drive these conversations is critical. While differences in emergency kits for a child versus an adult have been promoted by a variety of audiences (e.g., community leaders), those for individuals with specific health needs have not. Success in increasing the overall population's level of preparedness, especially for those with disabilities, health conditions (e.g., diabetes, cardiovascular disease,⁹ general health status¹⁰), and other risk factors is a shared role between community sectors.

The healthcare and public health systems ultimately maintain responsibility for assuring an individuals' or families' preparedness level is high enough before an emergency at least to have basic nutritional, medical, and sheltering needs met. How might the public health and medical communities learn from each other to collectively define roles for the assurance of basic needs, regardless of a routine or emergent situation?

For example, diabetes maintenance recommends insulin be used if refrigerated properly with the use of a clean needle (e.g., good health behavior). Before an emergency happens, who is telling the individual with diabetes that using unrefrigerated insulin (and, in some cases, that using the same, unshared needle) is okay to do when displaced or isolated during an emergency? Who should that messenger be? How about nutritional alterations needed for emergency food kits or receiving an extra three-day prescription supply? If general guidance pertaining to the needs of a diabetic patient is primarily addressed by providers, should the community deviate from this approach for emergency preparations? Should current infrastructure be expanded to address patient-specific preparations before an emergency?

These questions need answers, and getting answers necessitates community consensus. RIDOH has begun to explore the intricacies of preparedness behaviors in an attempt to illustrate the disparities of citizen health preparedness and engage the provider community in helping assure a basic level of preparedness among the patient community. Increased integration with academia is needed to explore the relationship between attitudes, perceptions, knowledge, and beliefs to both personal health preparedness and overall health-seeking/health risk-taking behaviors on an iterative basis. Doing this can inform strategies aimed to promote health equity and health security by identifying root causes of preparedness inequities within the Rhode Island population.

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**VITAL STATISTICS**

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Rhode Island Monthly Vital Statistics Report

Provisional Occurrence Data from the Division of Vital Records

VITAL EVENTS	REPORTING PERIOD		
	APRIL 2015	12 MONTHS ENDING WITH APRIL 2015	
	Number	Number	Rates
Live Births	940	11,446	10.8*
Deaths	861	10,237	9.7*
Infant Deaths	6	61	5.3#
Neonatal Deaths	5	49	4.3#
Marriages	338	6,849	6.5*
Divorces	259	3,012	2.9*
Induced Terminations	239	2,796	244.3#
Spontaneous Fetal Deaths	61	618	54.0#
Under 20 weeks gestation	56	559	54.6#
20+ weeks gestation	5	59	5.2#

* Rates per 1,000 estimated population

Rates per 1,000 live births

Underlying Cause of Death Category	REPORTING PERIOD			
	OCTOBER 2014	12 MONTHS ENDING WITH OCTOBER 2014		
	Number (a)	Number (a)	Rates (b)	YPLL (c)
Diseases of the Heart	191	2,316	219.9	3,321.5
Malignant Neoplasms	186	2,340	222.2	6,292.0
Cerebrovascular Disease	46	393	37.3	460.0
Injuries (Accident/Suicide/Homicide)	65	774	73.5	11,678.5
COPD	40	505	47.9	487.5

(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 1,055,173 (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.

It's a new day.

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RIMS and Coverys announce new partnership

In October 2014, the Medical Society entered into a new strategic partnership with Coverys, the 40 year-old medical liability insurance giant headquartered in Boston.

Coverys and RIMS have pledged to combine and coordinate their complementary strengths for the purpose of enhancing patient safety. The two organizations share the conviction that safety is fundamental to promoting and maintaining the kind of professional liability environment that everyone wants for Rhode Island: one that is stable and responsive to the needs of the medical profession and the public. RIMS and Coverys are uniquely positioned to support each other in this endeavor.

Key elements of the new collaboration will be peer review, risk management and continuing education. RIMS' peer review prowess is well established, particularly in the highly sensitive and all-important area of physician health. In addition, RIMS is recognized by the American Council for Continuing Medical Education (ACCME) as the agency responsible for accrediting the CME programs of all the hospitals within the state of Rhode Island. RIMS has been a consistent star nationally in earning an unbroken string of long-term recognitions from ACCME.

For its part, Coverys is one of a tiny number of medical professional insurers that have devoted the necessary and substantial resources to gaining and maintaining full accreditation by the ACCME as a source of Category 1 CME credits for physicians. RIMS regards this extraordinary commitment to CME as particularly meaningful and praiseworthy in an insurance company. Of course, medical peer review and continuing medical education, each in its own way, provide targeted risk management and serve to enhance quality and safety.



RIMS has also agreed to advise Coverys and to offer the company additional eyes and ears focused on the evolving insurance market, the medical practice environment and the medical liability climate, as each of these is affected by legislative, regulatory, judicial, economic, demographic and political developments in the Ocean State. In recognition of their strong relationship and mutual support, RIMS and Coverys will also engage in joint marketing.

Coverys is the sixth largest medical liability insurer in the nation. It protects more than 32,000 physicians, dentists and other health professionals nationally, as well as over 500 hospitals, health centers and clinics. It is rated A ("excellent") by A.M. Best. It writes over \$400 million in premium, has net assets of \$3.5 billion, and maintained a policyholder surplus of \$1.5 billion as of the end of last year. Member companies include Medical Professional Mutual Insurance Company ("ProMutual") and the ProSelect Insurance Company.

Coverys is the dominant insurer of physicians and surgeons in Rhode Island. The Rhode Island Medical Society Insurance Brokerage Corporation (RIMS-IBC) is proud to have been appointed as an agent for Coverys three years ago. The RIMS-IBC is a full-service agency that specializes in medical professional liability.



Robert A. Anderson, Jr, Director of the IBC, can be reached at 401-272-1050.

CONVIVIUM

On September 26, RIMS members gathered at the waterfront Save the Bay center at Field's Point in Providence for the second annual Convivium. Those who arrived early had the opportunity to take a guided tour of Narragansett Bay aboard Save the Bay's 46-foot bio-diesel fueled M/V Elizabeth Morris. On shore, Convivium participants mingled and dined, and enjoyed music by the Be Bop Docs.

A brief speaking program included the inaugural presentation of RIMS' newly established Stanley M. Aronson Award for humanism in medicine. Dr. Aronson is remembered for many things, including teaching his students that medicine is the most humanistic of the sciences and the most scientific of the humanities. The first recipient of the Aronson Award was **HERBERT RAKATANSKY, MD**.

RIMS' Charles L. Hill Award for outstanding service was presented to **PETER A. HOLLMANN, MD**.

The Herbert Rakatansky Award for professionalism in medicine was presented to **CHARLES B. "BUD" KAHN, MD**.

The John Clarke Award for distinguished public service was presented to **U.S. SEN. SHELDON WHITEHOUSE**. (The Award is named for Dr. John Clarke, 1609–1676, who negotiated and secured Rhode Island's radically liberal Royal Charter of 1663.)

RUSSELL SETTIPANE, MD succeeded **PETER KARCZMAR, MD** as President of the Rhode Island Medical Society. **SARAH FESSLER, MD** became President-Elect of the Society. **BRADLEY COLLINS, MD**, **CHRISTINE BROUSSEAU, MD**, and **JOSE POLANCO, MD** were installed as Vice President, Secretary and Treasurer, respectively.

View the photo album:
www.rimed.org/photos-annual-meeting.asp



Award recipients: Herbert Rakatansky, MD; US Senator Sheldon Whitehouse; Charles B. "Bud" Kahn, MD; Peter A. Hollmann, MD



Newly inaugurated 2015–2016 RIMS Officers: Treasurer Jose Polanco, MD; Vice President Bradley Collins, MD; President Russell Settipane, MD; President-Elect Sarah Fessler, MD; Secretary Christine Brousseau, MD.

Working for You: RIMS advocacy activities

September 1, Tuesday

Physician Health Committee,
Herbert Rakatansky, MD, Chair
CMS conference call regarding
alternative payment models
AMA Advocacy Resource Center
conference call regarding federal
licensure and interstate compact

September 2, Wednesday

State Innovation Model (SIM)
Measurement Harmonization Working
Committee, Peter A. Hollmann, MD,
and staff

September 3, Thursday

AMA ARC conference call with Directors
of Department of Health and Department
of Behavioral Health, Developmental
Disabilities, and Hospitals (BHDDH)
regarding grant from US Substance Abuse,
Mental Health Services Administration
(SAMHSA), RIMS staff

September 8, Tuesday

AMA conference call regarding no-fault
medical liability Department of Health
Primary Care Physician

September 9, Wednesday

Board of Medical Licensure and
Discipline, Presentation by RIMS
Physician Health Program, Dr. Herbert
Rakatansky, Kathleen Boyd.
Meeting of RI Governor's Overdose
Prevention & Intervention Task Force
Meeting with Board of RI ACEP regarding
legislation and political fundraising
Employment 101 Seminar, Peter
Hollmann, MD; Robert A. Anderson;
Jeffrey Chase-Lubitz, Esq., and staff

September 10, Thursday

Meeting with OHIC regarding RIMS
representation on care transformation
working committees
Meeting of Good Samaritan allies
regarding General Assembly special
session
Public Hearing on BMLD regulations
SIM Board Meeting,
Peter A. Hollmann, MD

September 11–13, Friday–Saturday

Attendance at Maine Medical Association
Annual Session

September 15, Tuesday

Alliance for Healthy RI meeting regarding
obesity prevention legislation
September 16, Wednesday
Primary Physician Advisory Committee,
Department of Health
Health Care Planning and Accountability
Advisory Council

September 17–18, Thursday–Friday

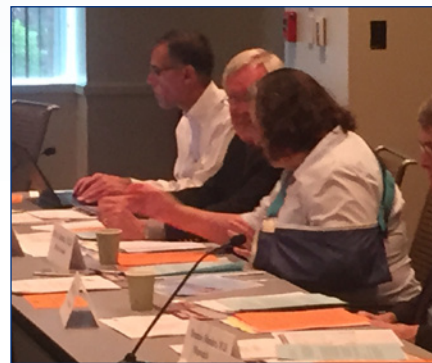
AMPAC State Federation Meeting,
Washington, DC; meetings with
Congressional offices regarding
meaningful use, Health IT, IPAB
(Independent Payment Advisory Board),
and other topics; Michael E. Migliori, MD,
and staff

September 19, Saturday

AMA New England Delegation Meeting,
Peter Hollmann, MD, Alyn Adrain, MD;
RIMS Staff Newell Warde and Steve
DeToy attending

September 21, Monday

Meeting with New Jersey-based opioid
addiction prevention coalition, Josiah
Rich, MD, and staff
RIMS Finance Committee, Jose R.
Polanco, MD, Chair



AMA New England Delegation Meeting

On September 19, RIMS' **Peter Hollmann, MD**, RIMS' Senior AMA Delegate; RIMS' Executive Director, **Newell Warde, PhD** and **Alyn Adrain, MD**, AMA Delegate attended the fall meeting of the New England Delegation at the headquarters of the Massachusetts Medical Society in Waltham, Massachusetts. RIMS' trio joined their colleagues from the other New England states to discuss the upcoming interim meeting of the AMA House of Delegates.



AMPAC Federation Meeting

On September 17, **Michael E. Migliori, MD**, Chair of RIMS Public Laws Committee, and **Steve DeToy**, RIMS Director of Government and Public Affairs (not pictured) met with RI Representative David Cicilline and other members of the RI Delegation in Washington, DC.

September 22, Tuesday

Meeting with Blue Cross Blue Shield of RI
regarding Health Services Council
September 24, Thursday
Healthy Kids in Schools Coalition
Breakfast
State Innovation Model (SIM)
Measurement Harmonization Working
Committee, Peter A. Hollmann, MD, and
staff

September 25, Friday

Primary care/behavioral health summit
September 26, Saturday
RIMS Convivium, Save the Bay,
Providence; Awards Ceremony and
Installation of New Officers

September 28, Monday

Meeting with Blue Cross Blue Shield of RI,
Russell A. Settignano, MD; Sarah J. Fessler,
MD; staff

September 29, Tuesday

Meeting of EOHHS Provider Advisory
Committee; RI Medical Society office

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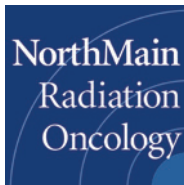
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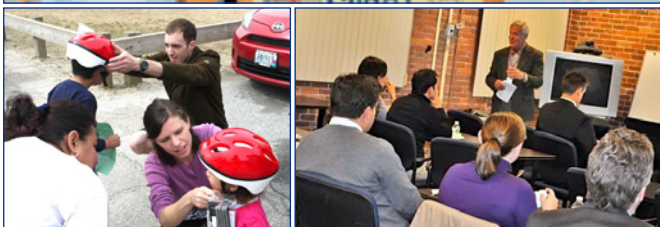
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Brown to launch Hassenfeld Child Health Innovation Institute

Brown will match Hassenfeld family donation of \$12.5M to target asthma, obesity and autism

MARY KORR

RIMJ MANAGING EDITOR



Alan Hassenfeld, former Hasbro, Inc. Chairman and CEO, announced the \$12.5 million donation at the State House this week, along with Brown President Christina Paxson, Gov. Gina Raimondo and Thomas J. Tisch, Brown Chancellor.

PROVIDENCE — **ALAN HASSENFELD**, former Hasbro, Inc. Chairman and CEO and his family have donated \$12.5 million to create the Hassenfeld Child Health Innovation Institute, to be launched by Brown University in collaboration with Hasbro Children's Hospital and Women & Infants Hospital. Researchers from other institutions, such as Bradley and Butler hospitals, will also be partnering in what is hoped to be a transformative initiative in the lives and health of Rhode Island's children and families, as well as nationally and globally.

The gift was announced at the State House on Monday, Sept. 28. In opening remarks, Brown's President **CHRISTINA PAXSON** said the university will begin a fundraising effort to match that amount. The Institute will initially target three areas: asthma, obesity and autism, in the pregnancy through young adulthood populations.

"A single act of generosity can have an impact on generations," Paxson said of the Hassenfeld donation.

She recognized **DEAN TERRIE FOX**

WETLE of Brown's School of Public Health and **DEAN JACK ELIAS** of the Warren Alpert Medical School as instrumental in forging hospital and health-care systems partnerships that will contribute to the Institute's success.

Gov. Gina Raimondo pledged the support of the Dept. of Health and the Dept. of Human Services to provide the statewide data needed for research, and cited the launch as a model of a "high level of innovation which will help ignite the economy and contribute to the 21st century jobs we need here," she said.

"Children are our greatest natural resource," said Hassenfeld, a former Brown trustee, in his remarks. "We are all inspired by a common purpose. Our future is something we create, not that we inherit."

In a press statement, he further elaborated on his vision for the Institute. "My greatest hope is that when we look back 10, 20, 30 years, we will have created global solutions to alleviating some of these child health conditions. I know we can't remove them, but at

least we can put the dollars behind research that will develop innovative approaches that help us truly move the needle in significant ways."

The Institute will officially launch in 2016, led by Hasbro's pediatrician-in-chief and newcomer to the state, **DR. PHYLLIS DENNERY**, the Sylvia K. Hassenfeld Professor and Chair of Pediatrics at Brown; **DR. MAUREEN PHIPPS**, the Chace-Joukowsky Professor of Obstetrics and Gynecology at Brown, chair of the Department of Obstetrics and Gynecology, and executive chief of obstetrics and gynecology at Women & Infants Hospital; and **DR. PATRICK VIVIER**, the Royce Family Associate Professor of Teaching Excellence, associate professor of health services, policy and practice and of pediatrics at Brown, and director of general pediatrics and community health at Hasbro.

According to a Brown statement, the team will build a core research and evaluation unit with all the statistical, bioinformatic, genomic, epidemiologic, and medical expertise needed to conduct rigorous and effective studies of childhood health issues.

"The collaboration, partnerships, focus, dedication, and resources brought together to develop this initiative have set the stage for having a lasting, positive impact on the lives of children, families, and communities in Rhode Island," Dr. Phipps said.

"These initiatives are at the heart of pediatric health," Dr. Dennery said. "We have seen epidemics in all three areas and can attribute these in part to environmental factors facing vulnerable children and families. Clearly, the issues we have identified can be better addressed through targeted therapies and interventions. The institute will seamlessly coordinate our collective system-wide efforts to address these challenges." ♦

MICHAEL COHEA/BROWN UNIVERSITY

Grant funds jail suicide intervention

Brown University and Michigan State University will share a \$6.8 million federal grant to test an intervention to reduce suicides among people being released from jail.

PROVIDENCE— Suicide risk is high among people in jail and even higher during the transition when they return home. With a new \$6.8-million grant, researchers at Brown University and Michigan State University will test whether a new intervention can help preserve the lives of people who are going through the system, often with mental health and substance abuse difficulties.

In the Suicide Prevention for at-Risk Individuals in Transition – SPIRIT – trial, the researchers plan to enroll 800 detainees as they leave either the Rhode Island Department of Corrections jail in Cranston or the Genesee County Jail in Flint, Mich. Participants will randomly be assigned to either standard care or the Safety Planning Intervention, conducted by trained community mental health center providers. Among people receiving both types of care, researchers will track improvements in suicidal behavior and psychiatric and substance abuse outcomes, as well as their use of community services and their re-arrest rates.

LAUREN M. WEINSTOCK, PHD, associate professor (research) of psychiatry and human behavior in the Alpert Medical School of Brown University, and **JENNIFER**

E. JOHNSON, the C.S. Mott Endowed Professor of Public Health at MSU's College of Human Medicine, are co-principal investigators on the study. Johnson is also an adjunct associate professor at Brown.

"We will be evaluating the effectiveness and cost-effectiveness of a Safety Planning Intervention, with telephone follow-up to problem-solve around stressors and to promote safety and community service utilization during the post-release period," said Weinstock, a clinical psychologist at Butler Hospital. "Given that roughly 10 percent of all suicides in the United States with known circumstances occur in the context of a recent criminal legal stressor, reducing suicide risk in the year after jail detention could have a noticeable impact on national suicide rates."

The four-year grant comes from the National Institute of Mental Health, the National Institutes of Health Office of Behavioral and Social Sciences Research, and the National Institute of Justice. ❖



Lauren M. Weinstock, PhD

BROWN UNIVERSITY

Southcoast targets region's high AFib rate with prevention program

NEW BEDFORD, MASSACHUSETTS — Southcoast® Health recently launched a comprehensive Atrial Fibrillation Wellness and Stroke Prevention Program, designed to help identify high-risk patients and streamline their access to care, while offering them the tools to help prevent risk factors through education, exercise and lifestyle changes, and social supports.

The population of the South Coast region has a particularly high rate of AFib, said **NITESH A. SOOD, MD**, electrophysiologist at Southcoast Health.

The program aims to educate patients and the local physician community – including emergency department doctors and primary care physicians – to quickly diagnose and treat risk factors in patients and streamline a patient's referral to a cardiologist.

Because AFib can increase a patient's risk of stroke, the Atrial Fibrillation

Wellness and Stroke Prevention Program will assess patients' stroke risk and offer appropriate preventative medication or therapy, such as blood thinners. Additionally, Southcoast is among the first hospitals in New England to offer a new treatment option, the WATCHMAN Device. WATCHMAN is implanted in the heart as an alternative to blood thinners, for patients who may be experiencing problems with bleeding or who don't want to be on anticoagulants long-term.

Southcoast Health also performs advanced procedures to treat AFib – such as Cryo-ablation and Convergent Hybrid Ablation – but early identification is important. "The longer Atrial Fibrillation goes untreated, the worse it gets," Dr. Sood said. "If you are a candidate for the procedure, it should be done as soon as possible."

"While we have these procedures,

what really needs to happen is lifestyle modification to help with outcomes or to prevent patients from coming to us later needing these procedures," he added.

The patients in the Atrial Fibrillation Wellness and Stroke Prevention Program receive a three-month supervised fitness and exercise program at a minimal cost. The wellness initiative also includes:

- Regular support groups and a social media platform to share experiences
- Yoga and meditation classes
- Nutrition and cooking classes
- Access to a physician on call, 24/7

Additionally, Southcoast Health will collaborate with a sleep apnea program. "We will be able to have a sleep study done within 48 hours of a patient being seen in our program, to quickly diagnose and treat people with sleep apnea," Dr. Sood said. ❖

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Pictured from left to right are: Mary Brown, 104; Sarah Phillips, MD, a third-year resident, Department of Family Medicine at Memorial Hospital; and Anna Testa, age 100. Both women are residents of Jeanne Jugan Residence in Pawtucket.

Memorial's geriatric program prepares residents for expanding aging population

RI has the highest percentage of adults 85 years of age and older in the US

PAWTUCKET— Mary Brown, 104, a former World War II Army Corps nurse and public health official, who lives at the Jeanne Jugan Residence in Pawtucket, is just one of the older adults **SARAH PHILLIPS, MD**, has cared for in her three years of her family medicine residency at Memorial Hospital's Department of Family Medicine.

The curriculum in geriatrics includes clinical rotations in the acute care setting, assisted living, nursing and rehabilitation facilities as well as in the home setting. Family resident physicians conduct monthly home visits to older adults who have difficulty leaving their homes for primary medical care.

Family medicine and internal medicine residents also take part in interprofessional clinical team seminars in geriatric assessment which bring together health professional students in nursing, pharmacy, physical therapy and nutrition from the University of Rhode Island (URI), as well as social work and nursing students from Rhode Island College (RIC).

In Rhode Island – which has the highest percentage of adults 85 years of age and older in the country (U.S. Census, 2010) and ranked ninth for the proportion of those 65 and older (15.5%) in 2012 – the impact is exacerbated by

shortages of health care professionals including physicians, nurses, pharmacists, social workers and allied health professionals. Growth of the state's geriatrics population is outpacing the number of specialists equipped to address their needs.

With recent funding from the Health Resources & Services Administration (HRSA) Geriatric Workforce Enhancement Program, Memorial's interprofessional geriatric education program and clinical geriatrics program will expand to include other Care New England's operating units, URI, RIC, state primary care networks and community-based agencies.

PHILIP CLARK, ScD, a URI professor and director of the Rhode Island Geriatric Education Center, will lead the efforts to establish a statewide model of interprofessional team training in geriatric care to improve the quality of care of the state's older adults. **ALICIA CURTIN, PhD**, director of Geriatrics of Memorial's Department of Family Medicine, states, "We are excited about collaborating in this statewide initiative to meet the critical need of preparing health care professionals, caregivers, families and patients to care for our aging population." ❖

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Denise Coppa, PhD, URI nursing professor, awarded \$1.6M grant to partner with health agencies

Key goals: graduate 109 new nurse practitioners, build faculty capacity

KINGSTON – University of Rhode Island Nursing Professor **DENISE COPPA, PhD, RNP**, has been awarded a \$1.6 million federal grant to establish academic and clinical partnerships with two Rhode Island community health centers.

URI was one of 21 schools chosen from the 300 that applied nationally.

The federal Health Resources and Services Administration grant will support collaboration between URI's College of Nursing and Providence Community Health Centers and Thundermist Health Centers to improve advanced nursing practice and primary care access for medically underserved individuals, many of whom live in poverty. The centers will use clinical faculty from the College of Nursing to partner with their own nurse practitioners to mentor students in their agencies and patient homes. This mentoring will improve students' readiness to practice upon graduation.

The project also calls for the URI College of Nursing's Nurse Practitioner Programs, in partnership with these agencies, to prepare 109 family nurse practitioner and adult/gerontological nurse practitioner students over three years at either the master's degree or doctoral levels. Twenty-five percent of those enrolled will be from diverse and disadvantaged backgrounds.

At URI, nurse practitioner students are prepared at the master's degree or doctoral levels, and are eligible to become licensed primary care providers authorized to: order, perform and

interpret diagnostic tests such as lab work and X-rays; diagnose and treat acute and chronic conditions such as diabetes, high blood pressure, infections, and injuries; prescribe medications and other treatments and manage patients' overall care.

"This is an endorsement of our program," Coppa said. "All URI nurse practitioner students will be prepared to a high level of safe, quality, culturally fluent health care within the complex practice-based environment of the nation's evolving health care system. This grant project is a direct result of the Affordable Care Act, which is calling for new models that address access to primary care by underrepresented groups. We should be proud that URI is a leader in educating advanced practice nurses to provide this critical, comprehensive care, in collaboration with two well respected community health centers."

Since URI must demonstrate the effectiveness of the project to the federal government, Coppa and her team will be researching patient satisfaction with care, preceptor satisfaction, the level of competency among nurse practitioner students, patient outcomes, workforce development and enhancement of nurse practitioner clinical education.

The need for primary care is great



Denise Coppa, PhD, RNP

right now, as 70,000 Rhode Islanders have been added to the state Health Exchange, and there are still individuals without health insurance. Both groups are potential patients at the centers participating in the project.

The grant allows URI to hire four new nurse practitioner faculty members, two of whom will be assigned to Thundermist. Through

the Woonsocket branch, the faculty members will provide primary care in patients' homes and oversee nurse practitioner candidates who will gain clinical proficiency during those visits. The other two will provide primary care and oversee students at the Providence Community Health Centers.

"The home visits resemble the public health models of the 1940s when nurses visited families in their homes and assessed the entire environment—health of family members, sanitation and home conditions," Coppa said.

Other major goals of the program are:

- Increasing by 36 percent the number of clinical placements for URI nurse practitioner programs due to a larger pool of experienced preceptors, allowing the College of Nursing to accept more students.
- Increasing the ability of the agencies to recruit nurse practitioner candidates in their last semester of study to participate in pre-graduate fellowships. ❖



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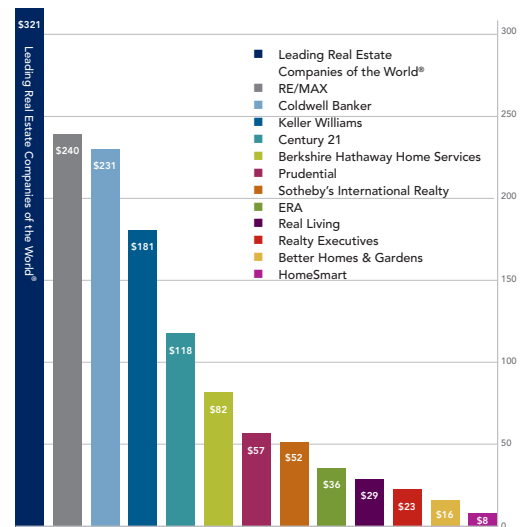
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Recognition

Hasbro's Phyllis A. Dennery, MD, honored with Distinguished Alumni Award by Howard University

PROVIDENCE – **PHYLLIS A. DENNERY, MD**, pediatrician-in-chief at Hasbro Children's Hospital, has been awarded the Distinguished Alumni Award from the Office of the Dean of the Howard University College of Medicine. She received the honor for



HASBRO

"distinction in leadership, teaching, clinical care and research." Dr. Dennery was presented with the award at the recent Howard University College of Medicine 40th Annual Distinguished Alumni Award Dinner in Detroit, as part of the National Medical Association annual meeting.

Dr. Dennery, an '84 alumna of the Howard University College of Medicine, joined Hasbro Children's Hospital in April

2015, bringing more than 20 years of experience in pediatric care, teaching and research. In addition to her role as pediatrician-in-chief and medical director, she is also the Sylvia Kay Hassenfeld Chair of Pediatrics at the Warren Alpert School of Medicine of Brown University and a professor of Molecular Biology, Cell Biology and Biochemistry at Brown University.

At Hasbro Children's Hospital, Dr. Dennery oversees all pediatric clinical programs, such as centers and clinics for pediatric imaging, hematology/oncology, asthma and allergies, neurodevelopment and cardiology.

Previously, Dr. Dennery served as the chief of the division of neonatology and newborn services at Children's Hospital of Philadelphia and the University of Pennsylvania.

Dr. Dennery is a member of the National Academy of Medicine (formerly Institute of Medicine), the Society for Pediatric Research, and the American Pediatric Society, among many others and also serves as an associate editor of the journal *Pediatrics*. She was recently elected to the Association of American Physicians, one of the highest honors in academic medicine. ❖

Angelita Hensman, MS, named Robert Wood Johnson Foundation Future of Nursing Scholar

PROVIDENCE – **ANGELITA HENSMAN, MS, RNC-NIC**, of Providence, is among 46 nurses from around the country this year to receive the *Future of Nursing Scholars* Program Award to support her doctorate study at the University of Rhode Island's (URI) College of Nursing. The *Future of Nursing Scholars* program began last year with an inaugural cohort of 16 scholars. This new cohort brings the number of nurses it is supporting to 62.

Hensman's scholarship is funded by a Rhode Island Foundation grant totaling \$75,000 and a \$50,000 scholarship from URI. The university selected her for the nursing scholars program.



WOMEN & INFANTS

Hensman began her career as a staff nurse in the neonatal intensive care unit (NICU) at Women & Infants Hospital after receiving her bachelor of science degree in nursing from URI in 1985. She went on to become a research nurse and since 1991, has been the research coordinator for the National Institute of Child Health and Human Development's Neonatal Research Network at Women & Infants. She is also a research manager in the Pediatrics Department at the hospital, a role she has had since 2004, managing and coordinating all Neonatal Research Network trials – more than 60 studies to date – at Women & Infants.

"It is a tremendous honor to receive this scholarship," said Hensman. "I have wanted to go back to school for a long time. When I graduated from nursing school we were encouraged to get practice experience before we began graduate studies. However, when you are working and raising a family, it is more difficult to stop working to attend school full time. I am very excited and humbled by this award, and I look forward to giving back to nursing and Rhode Island. I see teaching, research and scholarship as an integral part of my role in the future as a PhD prepared nurse."

Her doctoral studies will focus on patient safety in the NICU, and she will be working with URI nursing professor Debra Erickson-Owens, CNM, PhD, who is a co-principal investigator on a federal grant looking into the benefits of delayed cord clamping for full-term infants. ❖

Recognition

Women's Medicine Collaborative earns Level 3 Patient-Centered Medical Home recognition

Highest designation for care coordination, communication awarded by the National Committee for Quality Assurance

PROVIDENCE – The Women's Medicine Collaborative primary care team has been designated a Level 3 Patient-Centered Medical Home (PCMH) by the National Committee for Quality Assurance (NCQA). The patient-centered medical home model of care emphasizes using coordination and communication to transform primary care to accommodate patients' needs. Having a nurse care manager work one on one with high-risk patients who have chronic conditions leads to a higher quality, better patient experience and reduced costs. Level 3 is NCQA's highest designation in its recognition program.

"Since the Women's Medicine Collaborative opened its doors in 2011, our primary care team has been focused on achieving this important designation," says **PEG MILLER, MD**, director of the Women's Medicine Collaborative. "Our patients at the Women's Medicine Collaborative expect personal, sensitive, individualized care, something everyone on our team focuses on each and every day. This designation recognizes those efforts and showcases our group as a model for delivering health with care."

To earn NCQA recognition, practices must meet rigorous standards for addressing patient needs, including:

- Patient-centered access: accommodating patients' needs during and after hours, providing medical home information, and offering team-based care
- Team-based care – engaging all practice team members by providing patients comprehensive care and meeting cultural and linguistic patient needs
- Population health management – collecting and using data to help improve the care of our group of patients
- Care management and support – using evidence-based guidelines for preventive, acute care, and chronic care management and helping patients reach their health goals with the support of our nurse care manager
- Care coordination and care transitions – tracking and coordinating tests, referrals, and care transitions
- Performance measurement and quality improvement – tracking and using medical data for continuous improvement in the quality of our care

"The medical home model aims to meet patients' individual health needs by providing comprehensive, coordinated and accessible care that is focused on quality and safety," says **IRIS TONG, MD, FACP**, director of Women's Primary Care at the Women's Medicine Collaborative. "This team-based care model involves patients, primary care providers, medical assistants, patient service representatives and the nurse care manager, and as part of the Women's Medicine Collaborative, Women's Primary Care takes a team approach to all the care we provide – from assisting in coordinating appointments with specialists to guiding patients through the health care system."

"In today's world, it's refreshing to be part of a medical organization that looks at the patient as a full package and truly cares about all aspects of the person," DeAngelis says. "I believe that the Women's Medicine Collaborative wants all of its patients to be happy and healthy." ❖

David Edmonson, MD, helps pioneer new approach to breast cancer treatment at W&I

Among first to adopt new device that can improve radiation treatment and cosmetic outcome after surgery

PROVIDENCE – A surgeon with the Breast Health Center at Women & Infants Hospital is among the first in New England to adopt an innovative new device that improves the treatment of breast cancer by more precisely targeting radiation treatment and providing for better follow-up exams.



DAVID EDMONSON, MD, has helped pioneer the use of the BioZorb™ marker, a three-dimensional device that is placed in the breast during a lumpectomy, the conservation surgery performed to remove only the cancer and not the entire breast. The BioZorb marker is the first device that identifies in a fixed, 3D manner where the tumor was removed, helping the radiation oncologist more reliably determine where to aim the radiation in follow-up treatments.

The marker consists of a spiral made of a bioabsorbable material that holds six titanium clips. The spiral slowly dissolves in the body over the course of a year or more, leaving the tiny marker clips in place so the surgical site can be viewed for long-term monitoring.

"We've now used the marker with more than 100 patients, and we've found it is useful with a wide variety of patients," said Dr. Edmonson. "The marker has also allowed some women who would not previously have been candidates for breast conservation treatment to have a lumpectomy. This device helps us achieve better cosmetic outcomes and improves our communication with the radiation oncologist about the specific area of the breast to target with follow-up radiation."

"Before the Biozorb device was available, we had to rely on techniques that gave us an inexact idea of where to aim the radiation," said Darlene Gabeau, MD, PhD, medical director at 21st Century Oncology. "The new device is sutured right to the involved site providing a three-dimensional representation of the tumor bed allowing more precise treatments." ❖

University Orthopedics proudly welcomes three outstanding surgeons.



Valentin Antoci, MD

Dr. Antoci is a Harvard fellowship trained orthopedic surgeon with a focus in adult reconstruction, hip and knee joint replacement, and a special interest in unicompartmental partial knee replacement, minimally invasive surgery, complex

reconstructions, failed total joints, preservation techniques, and trauma.



Alan Daniels, MD

Dr. Daniels is a Brown University fellowship trained spine surgeon who specializes in complex spinal disorders. His practice focuses on patients who suffer from scoliosis, kyphosis, flatback syndrome, revision spinal surgery, degenerative spinal

disease, as well as spinal trauma and spinal tumors in adult and pediatric patients.



Aristides Cruz, Jr., MD

Dr. Cruz is a board-certified orthopedic surgeon, specializing in the treatment of orthopedic conditions in children and adolescents. He completed a Pediatric Sports Fellowship from Children's Hospital of Philadelphia.

His areas of interest include

traumatic injuries and fracture care, treatment of pediatric and adolescent sports related conditions, and general pediatric orthopedics.

All three surgeons are on the faculty of the Alpert Medical School of Brown University and will perform surgery at Rhode Island Hospital, The Miriam Hospital, Newport Hospital and Hasbro Children's Hospital.

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Appointments

Kamran Manzoor, MD, appointed to Memorial Hospital

PAWTUCKET – Memorial Hospital of Rhode Island recently appointed **KAMRAN MANZOOR, MD**, to its medical staff in the Department of Pulmonary and Critical Care. Dr. Manzoor is a member of Affinity Physicians and will work out of Memorial Hospital.

Dr. Manzoor earned his medical degree from Nishtar Medical College, Multan, Pakistan. He completed his residency in Internal Medicine at Mount Sinai School of Medicine, New York at the James J. Peters VA Medical Center / Mount Sinai Medical Center. He also served as chief resident in his final year. Dr. Manzoor went on to complete a fellowship in pulmonary medicine from the University of Tennessee Medical Center, Knoxville, TN and a fellowship in Critical Care Medicine from Dartmouth Hitchcock Medical Center, Lebanon, NH.

Dr. Manzoor is a member of the American College of Physicians, American Thoracic Society and American College of Chest Physicians. His clinical and research interests include: Sepsis, Endothelial dysfunction, inflammatory cell markers and ARDS. He is fluent in Urdu and Hindi. ❖

Beth Cronin, MD, selected for Apgo Scholars and Leaders Program

PROVIDENCE – **BETH CRONIN, MD**, of Providence, a physician in the Department of Obstetrics and Gynecology at Women & Infants Hospital, and assistant professor in the Department of Obstetrics and Gynecology at The Warren Alpert Medical School of Brown University, has been accepted into the Association of Professors of Gynecology and Obstetrics' (APGO) Scholars and Leaders Program. The Program is an initiative to enhance education

in obstetrics and gynecology by preparing and equipping the physicians with the necessary skills and knowledge to be outstanding teachers and administrators in the field.

Starting January 2016, Dr. Cronin will begin the 15-month program that focuses on curriculum design, instructional theory, group instruction, clinical instruction, evaluation of teaching, feedback on performance, assessment of simulated and workplace clinical skills, educational research designs, management/leadership skills, team building, and organization change and conflict management.

Dr. Cronin's selection was based on her leadership position at the institution, scholarship in education, current educational activities, teaching recognition, APGO participation, mentoring and advising roles, and departmental support.

Dr. Cronin received her medical degree from the University of Vermont College of Medicine and completed her residency at Women & Infants Hospital and Brown University. Currently, Dr. Cronin serves as the co-director of the Women's Dysplasia Program and director of the Pelvic Pain Program at the Women's Primary Care Center of Women & Infants. ❖



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Lauren Goddard, MD, joins Newport Hospital



NEWPORT HOSPITAL

NEWPORT— Newport Hospital announced that **LAUREN GODDARD, MD**, has joined the Newport Hospital medical staff as part of Jamestown Family Practice and NHCC Medical Associates. She began seeing patients on September 9.

Dr. Goddard received her medical degree from The Warren Alpert Medical School of Brown University and completed her family medicine residency at Memorial

Hospital of Rhode Island. She is board eligible and a member of the American Academy of Family Physicians.

"I'm really looking forward to working one on one with a diverse group of area residents and providing them and their families with coordinated, comprehensive health care tailored to their individual health needs – whether that is pediatrics or geriatrics," said Dr. Goddard. ❖

Appointments

Cedric J. Priebe, MD, named Lifespan senior vice president and chief information officer

PROVIDENCE – **CEDRIC J. PRIEBE, MD**, has been appointed senior vice president and chief information officer of Lifespan, effective November 1, 2015.

Dr. Priebe joins Lifespan from Partners HealthCare – Massachusetts' largest health care system – where



LIFESPAN

he served as vice president and chief information officer for Brigham and Women's Hospital and Brigham and Women's Faulkner Hospital, as well as provided oversight for IT at the Dana-Farber Cancer Institute.

While at Partners, Dr. Priebe successfully implemented its new electronic health record system at Brigham and Women's Hospital, Brigham and Women's Faulkner Hospital, Partners HealthCare at Home and at the Dana-Farber Cancer Institute. The system, called Partners eCare, is an Epic-based electronic health record system similar to Lifespan's recently launched LifeChart.

Prior to his role at Partners, he was senior vice president and CIO at Care New England, where he led major clinical information system initiatives for Women & Infants, Kent and Butler hospitals.

Dr. Priebe will direct the planning and implementation of IT systems in support of Lifespan's strategic plan and business needs. He will be responsible for all aspects of the organization's information technology and systems, as well as for ensuring that the highest level of effective and cost-beneficial technology service is provided to the organization, its clinicians and employees.

As a medical researcher, Dr. Priebe has focused on the impact clinical information software and networks have on the quality of care being delivered, as well as the influence it has on medical education.

During his tenure with Care New England, he was active and well known within Rhode Island's health care and IT sectors. He was instrumental in the early work that led to the creation of Rhode Island's health information exchange, CurrentCare.

Dr. Priebe earned his medical degree from Harvard Medical School. A pediatrician, he plans to have a clinical role at Hasbro Children's Hospital. ❖

Mary Elizabeth Hanley, DO, appointed director of Kent's Undersea and Hyperbaric Medicine Fellowship program

WARWICK – Kent Hospital has appointed **MARY ELIZABETH HANLEY, DO**, as director of its Undersea and Hyperbaric Medicine Fellowship program.

Dr. Hanley was Kent Hospital's first Undersea and Hyperbaric Medicine fellow, after completing a family medicine residency at Kent Hospital from 2009-2011, and served as chief resident from 2010-2011. Prior to coming to Kent Hospital, Dr. Hanley completed her first residency in Anesthesiology and Critical Care Medicine at The Johns Hopkins Hospital in Baltimore, Maryland where she was also chief resident. She was then appointed to the faculty of The Johns Hopkins Hospital School of Medicine. Dr. Hanley also served as medical director of the Narragansett Indian Health Center in Charlestown, RI, from 2012–2013.

Kent Hospital's Undersea and Hyperbaric Medicine fellowship was established in 2010.

The Wound Recovery and Hyperbaric Medicine Center at Kent is regional referral center that treats diabetic ulcers, surgical wounds, osteomy problems, bone infections and other chronic concerns. The center's nationally accredited advanced hyperbaric oxygen chambers are available 24-hours a day for emergency referrals needing immediate intervention. ❖



KENT HOSPITAL

Betty Sadaniantz, DNP, RN, named Dean of St. Joseph School of Nursing

NORTH PROVIDENCE – **BETTY SADANIANZ, DNP, RN**, has been named the Dean of the St. Joseph School of Nursing. She has been a full-time faculty member of the School of Nursing since 2009 and freshman level chairperson since 2013, where her teaching responsibilities included nursing diagnosis, legal aspects of nursing care, and pharmacology.



Sadaniantz brings experience in management, education, publishing, and clinical practice to the role of Dean. She has served on numerous national and regional boards, including the American Organization of Nurse Executives, the American Association of Critical Care Nurses, and the American Heart Association. Her diverse clinical practice experience has been in the areas of intensive care, coronary care, and medical-surgical nursing, as well as labor and delivery.

A graduate of RI College, she received her Doctor of Nursing Practice (DNP) degree from the University of Rhode Island. Sadaniantz earned her Master of Science in Nursing in nursing administration from the Medical University of South Carolina. She has made numerous publications and presentations on topics related to nursing, health care, and leadership.

Sadaniantz focused her DNP clinical hours and capstone project on the Institute of Medicine Report of 2011: *The Future of Nursing: Leading Change, Advancing Health*. She has been involved in the implementation of these IOM recommendations for the transformation of health care through work with the Rhode Island Action Coalition of the Robert Wood Johnson Foundation Campaign for Action and as Project Director for the Rhode Island Center for Nursing Excellence. ❖

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Appointments

Dr. Raymond O. Powrie named Chief of Medicine at Women & Infants Hospital

PROVIDENCE – **RAYMOND O. PORIE, MD, FRCP(C), FACP**, of Brookline, MA, has been named chief of medicine at Women & Infants Hospital, and will also be taking on a new role as the hospital's senior vice president for population health. Dr. Powrie is also chief medical quality officer for Care New England, is an attending physician on Women & Infants' obstetric and consultative medicine service, and is a professor of medicine and obstetrics and gynecology at The Warren Alpert Medical School of Brown University.

Dr. Powrie has served as interim chief of medicine since 2012, overseeing the clinical and academic work of the Department of Medicine, which includes primary care, women's behavioral health, women's gastrointestinal health, and obstetric and consultative medicine. Under his leadership, the Department of Medicine experienced tremendous growth, including the recruiting of world-class physicians and providers, the introduction of New England's only Integrated Program for High-Risk Pregnancy in coordination with the Department of Maternal-Fetal Medicine, and the development of an Obesity in Pregnancy Program.

Dr. Powrie earned his medical degree from the University of Alberta, Faculty of Medicine in Edmonton, Canada, where he also completed his residency in internal medicine. He completed his fellowship in obstetric and consultative medicine at Women & Infants Hospital. Board certified in internal medicine, Dr. Powrie is also an instructor for the Faculty of Medicine at Harvard Medical School. He is a fellow of the American College of Physicians and the Royal College of Physicians and Surgeons of Canada, as well as a founding leader of the International Society of Obstetric Medicine.

Dr. Powrie has published numerous articles and a textbook, has been the recipient of local and national teaching awards, and has an international reputation as a leader in the field of medical illness in pregnancy. His research and clinical interests include education, quality and safety, medical problems in pregnancy, and perioperative consultation. ❖



Nancy Fogarty named Director of Quality for CharterCARE Health Partners

PROVIDENCE – **NANCY FOGARTY** has been named Director of Quality and Performance Improvement for CharterCARE Health Partners. Since 2003, she has served in a similar role at Roger Williams Medical Center, a CharterCARE affiliate. She previously held quality assurance and management roles for St. Joseph Health Services and Lifespan.

A graduate of Providence College with a BS in Health Services Administration, Fogarty is professionally certified in healthcare quality and electronic medical records. She is a member of the Rhode Island chapter of the National Association for Health Care Quality, having previously served in a number of leadership roles including president.

In this new system-level position, Fogarty will be responsible for coordinating performance improvement and quality initiatives supporting operational goals. She will also work with the hospital presidents to develop and implement Joint Commission and other regulatory agency guidelines to promote compliance with performance and quality improvement requirements. ❖



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Not Just Clowning Around: Patch Adams, MD, speaks at URI Honors Colloquium on humor, health

MARY KORR
RIMJ MANAGING EDITOR

KINGSTON – **PATCH ADAMS, MD**, 70, dressed in billowy bloomers with blue-streaked hair which he hasn't cut in decades, addressed a full house on the power of humor and friendship at the URI Honors Colloquium Sept. 22.

A graduate of Georgetown University and the Virginia Commonwealth University School of Medicine in 1971, he was the inspiration for the 1998 film "Patch Adams" starring the late Robin Williams.

"Friendship is the best medicine, the strongest human possibility – humor is a good grease," he said. "The most revolutionary act one can commit in our world," he added, "is to be happy." He said he dresses the way he does to "break down barriers between people."

A graduate of Georgetown University and the Virginia Commonwealth University School of Medicine in 1971,

he was the inspiration for the 1998 film "Patch Adams" starring the late Robin Williams.

Born in Washington, DC, he grew up on military bases throughout the world. His father was a career US Army officer, until his untimely death at age 52. Patch's mother, a teacher, returned to the states with her family. Patch was 16 at the time. He shared episodes of being bullied and beaten up in high school,

his sense of isolation after his father's death, and his multiple hospitalizations for mental health issues.

After being released from a psychiatric facility for the third time, he says he decided to "never have another bad day, to live in a mindful, intentional way, to be happy all the time." Describing himself as an extreme extrovert, "humor gave me back my life. I decided to be happy, funny, loving, cooperative, creative and thoughtful – I am only going to be those qualities."

He said it took him his college years to achieve this, and at age 22, he entered medical school to use the profession as a vehicle for social change. His primary interest was in studying health-care delivery systems and putting the care back in health. Upon graduation, he founded the Gesundheit Institute to improve medical care. (Gesundheit means "good health" in German.)

During the talk he described the concept of the communal hospital he and several like-minded physicians and their families opened in a large, six-bedroom house, offering free care, room and board for all, with no malpractice or health insurance.

"We had anywhere from 1,000 to 3,000 'guests' a month, many of whom had profound mental illnesses," he said.

His philosophy, and those of his colleagues, was that "medicine is an art not a science." Jokes, play, theatrics



Prior to his talk at URI on Sept. 22, Dr. Patch Adams, comedian, author, social activist and clown, paid a visit to patients at Kent Hospital with URI students.

were all part of the compassionate care they offered.

The facility, which he called the first "silly hospital in the world," lasted for 12 years. "We made living funny and dying funny." He added: "I never made money in 45 years as a doctor and that is why I am a happy physician."

Currently, he's working on building a "model health care community" on 310 acres in Pocahontas County, West Virginia. The site will also have a theater and arts and crafts shops, as well as horticulture and vocational therapy.

More than five years ago, Dr. Adams stopped seeing patients so he could raise money to build the hospital. He now travels the world with his clown-clad entourage, visiting clinics, hospitals, refugee camps, and making speeches to raise money for his hospital.

He invited those present, students, physicians and academicians to join him on his bi-monthly clown-care tours, no experience necessary. For more information, visit patchadams.org. ❖



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110 years ago: Oysters Anyone? Not if Harvested from Providence River

MARY KORR
RIMJ MANAGING EDITOR

More than a century ago, Rhode Island oysters were famous. In 1903, it should be noted, a report by the RI Commission of Shell Fisheries reported income from the 5,000 leased oyster beds totaled \$45,000. It was a good time for the oystermen of the Ocean State.

But were these bivalves safe to eat in the days before the state tested the areas for pollution? That was the question **CALEB A. FULLER**, a Brown University doctoral student, posed in his thesis. In 1901–1902, he sampled oysters from the Providence River, and Narragansett and Mt. Hope Bays for *Bacillus coli communis*.

The 1904–1905 edition of the *Providence Medical Journal*, precursor to the *Rhode Island Medical Journal*, reported the results of his analysis, which was carried out at the Brown Anatomical Laboratory under **PROF. F.P. GORHAM** and **DR. A.D. MEAD**, as well as **DR. H.C. BUMPUS**, director of the American Museum of Natural History.

What the PhD student found in one sampling from the Providence River was not appetizing: “When opened the specimens

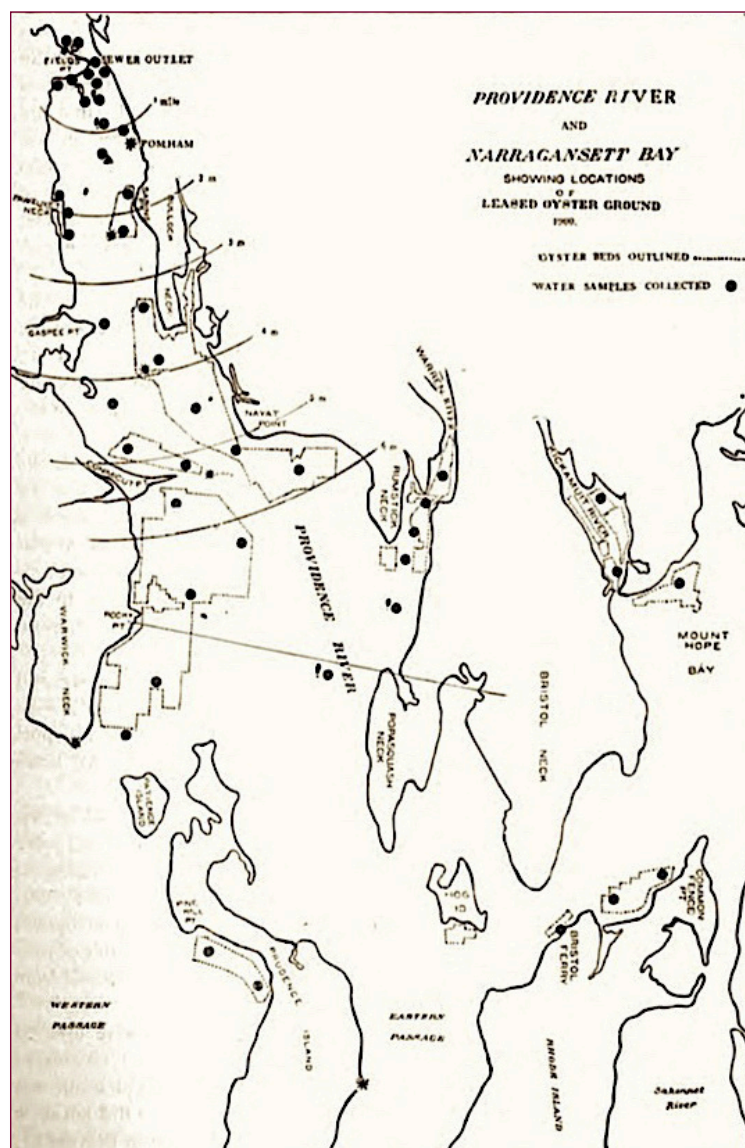
were seen to be lean and unhealthy. The bodies were a very dark green, and the mantle folds bright green in color...*B. coli* was present in every specimen examined. It was found in the juice of all ten oysters and in the intestines of nine.”

When opened the specimens were seen to be lean and unhealthy. The bodies were a very dark green, and the mantle folds bright green in color

This should come as no surprise to scientists then and now. At the time, Providence, Pawtucket and neighboring Fall River were major manufacturing cities, with waste from metal refineries, bleacheries and dye houses discharged into the area’s rivers and bays. In addition, the Journal report stated, 14,000,000 gallons of raw sewage was pumped daily through the Fields Point sewer into the Providence River.

Among Fuller’s findings reported in the Journal and other publications were the following:

- “*B. coli* was abundant, not only in the water about Fields Point, but was readily isolated from samples of sand taken from the beaches near by; also oysters collected from these highly polluted waters, and clams and mussels from the shores within half a mile from the sewer outlet, without exception, contained *B. coli*, and in many cases other sewage bacteria, within their shells.
- “The Providence River above Conimicut Point is a sewage-polluted body of water, but below this point the water of the river and the headwaters of Narragansett Bay are free from contamination.
- “The presence of sewage may also be detected in the Warren River.



A 1900 map which accompanied the article on the infection of oysters in Providence River shows a considerable portion of the leased oyster area lies within the zone of contamination from fecal organisms.

- “That section of Mount Hope Bay in which the oyster ground is situated appears to be entirely free from pollution.”

It was not pollution, however, which quelled the RI oyster industry a century ago. Mother Nature intervened with the Great Hurricane in 1938, which destroyed most of the oyster harvesting grounds for decades to come. ❖

Original Communications.

OYSTERS AND SEWAGE IN NARRAGANSETT BAY.

By C. A. FULLER, Ph.D.

Providence.

In 1900 the State of Rhode Island leased three thousand acres of land for oyster culture in the Providence River and Narragansett Bay. The accompanying map shows the locations of these oyster grounds as given in the plan published with the report of the Rhode Island Commissioners of Shell Fisheries for 1900. The areas occupied by the beds are outlined in dotted lines. It will be seen that the most extensive oyster grounds are in the Providence River, between Warwick Neck and Bullock Neck. There is, however, one small cultivated bed farther up the river nearer the city. This bed is the first one we come upon passing down stream from Providence. It is planted on the eastern side of the river just off Sabins Point, its southern limit reaching to Sabins Point Light. The stakes marking the northern boundary of these layings are about two miles below the outlet of the Providence sewer. About a mile below the Sabins Point bed we find the northern limits of the extensive layings which extend from Bullock Neck nearly to Rumstick Neck. These beds follow the eastern shore of the river without a break for nearly three miles. The third oyster bed lies directly across the river, off the northern shore of Conimicut Point about five miles below the city sewer outlet. Above Conimicut the river is scarcely one mile wide, but below this point it broadens abruptly to twice that distance. In this larger water are the most extensive oyster layings in the Providence River. They form a continuous area of over a thousand acres, extending from a short distance below Conimicut Point Light, on the western side of the ship channel to the lower end of Warwick Neck. A strong tide sweeps the western shore of the river causing a constant circulation of water over these beds. Turning again to the eastern shore of the river, we find there are extensive beds in the Warren River. These beds occupy ground off the south shore of Rumstick Neck and reach up the Warren river almost to the town of Warren. The northern areas of these layings extend from bank to bank, occupying the channel as well as the shallower water of the river.