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Feature Story

Lung cancer diagnoses on small samples using minimally invasive techniques

ALSO IN THIS ISSUE:

Lung Cancer Diagnoses on Small Samples Using Minimally Invasive Techniques

By Jordan Reynolds, MD, and Carol Farver, MD

Lung cancer continues to be the leading cause of cancer death in the world, responsible for 1.6 million deaths every year. Non-small cell lung carcinoma (NSCLC) comprises up to 80% of lung cancers. Though patients with early lung cancers, Stage I and 2, have a survival rate of 50-80%, most patients (80%) are diagnosed at an advanced stage with metastases to peripheral sites and mediastinal lymph nodes, accounting for the high mortality rate. The increased use of targeted cancer screening with CT will increase the diagnosis of these tumors at an earlier stage and improve prognosis, as will the improvement in the systemic therapy for advanced disease.

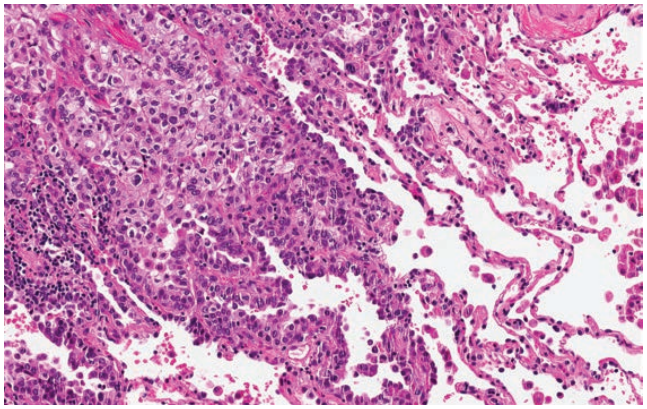
The diagnosis of NSCLC is treated with conventional chemotherapies that have significant debilitating side effects with only limited improvement of survival. However, in the past five to seven years, new molecular drivers for non-small cell lung carcinoma are being discovered leading to the development of more effective therapies that target the mutations specific to each patient's cancer. Because of this new approach, it has become imperative to sample each patient's tumor and have sufficient tissue to perform these diagnostic molecular tests so that the appropriate target therapy is used.

Historically these diagnoses were made on core needle biopsies or surgical resection specimens; however, currently over 50% of diagnoses come from small samples, including cytology samples. Tumors located in the peripheral lung parenchyma may be sampled by CT-guided transthoracic fine needle aspiration biopsies. During this procedure, an interventional radiologist locates the tumor using a CT scan to more accurately localize the needle. With more centrally located lesions an endobronchial ultrasound guided fine needle aspiration may be used. In this setting an interventional pulmonologist uses ultrasound localization to more accurately localize the lesions in real time. The samples, obtained by a transbronchial fine needle technique, are evaluated on site by the cytopathology team and provide information that is vital to patient care. Based on the interpretation of these cytologic smear preparations, the cytopathologist provides feedback regarding adequacy for diagnosis, directs triaging the specimen for appropriate testing and can be helpful to pulmonologists in providing rapid staging information.

In patients with more advanced stage disease, peripheral fine needle aspiration of distant metastases to the skin, subcutaneous tissue or palpable lymph nodes provides an even less invasive method for diagnosis. Finally, patients who do not show evidence of metastatic disease and are healthy enough to undergo surgery may go directly to the operating room for a resection of the tumor. In this scenario, the tissue from the surgically resected tumor will provide the needed tissue for further molecular testing.

Overall, a myriad of procedures is available to procure adequate tissue for appropriate molecular testing in patients regardless of the extent of the disease. From fine needle aspiration of localized and distant metastatic disease, guided by ultrasound or CT imaging, to complete resection of an early stage tumor in the OR, the pathologist must be ready to perform both confirmatory diagnostic testing for tumor type as well as testing for possible molecular targets on small tissue samples.

One such set of mutations is on the *ALK* gene. Presence of this oncogenic fusion renders the tumor susceptible to tyrosine kinase inhibitors (TKIs), but is only present in 3-8% of lung adenocarcinomas. The typical patient is younger and is usually a non-smoker. Most mutations involve fusion with a portion of the echinoderm microtubule associated protein like 4 (EML4) gene. ALK-EML4 rearrangements are activating mutations that confer susceptibility to crizotinib, a specific TKI. Other oncogenic fusions such as ROS and RET also confer susceptibility to



Lung adenocarcinoma, H&E stain 20x. (Cover photo is lung adenocarcinoma, Diff-Quik 40x.)

crizotinib. ROS1 encodes a receptor tyrosine kinase that is related to the insulin receptor. These translocations are found in 1.5% of lung adenocarcinomas, also typically in non-smoking younger patients.[1] These mutations also show response to the ALK inhibitor crizotinib. RET rearrangements are identified in ~2% of patients with lung adenocarcinoma, again in young non-smokers. RET rearranged tumors may respond to tyrosine kinase inhibitors such as vandetanib and cabozantinib.

Detection of these oncogenic mutations may be accomplished in many ways. Immunohistochemistry (IHC) can be used, but preanalytic conditions such as fixation time or media (paraffin versus alcohol as typically used in cell blocks) may affect staining. Fluorescence in situ hybridization (FISH) allows for correlation of fusion positive cells with the tumor morphology. This test may be performed on either paraffin-embedded sections or cytology smears.[2, 3] Currently, ALK testing for FISH is performed on the ThinPrep slide on all cytology specimens with sufficient tumor cells. For core biopsies or resections, IHC testing is performed on the paraffin block. For ROS and RET mutations, we offer testing on surgical specimens (core biopsy and resection) using FISH.

EGFR encodes a tyrosine kinase that, when activated, results in cellular growth and survival via the RAS/RAF/MEK and Pi3K/AKT/mTOR pathways. *EGFR* mutations are present in 15-25% of lung adenocarcinomas, and are typically found in females, non-smokers and Asians. Since these mutations involve missense insertions and deletions, sequencing of the tumor with either PCR or next generation sequencing is necessary. Immunohistochemistry testing is not acceptable because while the protein may be expressed on the surface, knowledge of the specific mutation is needed. Most *EGFR* mutations confer susceptibility to the TKIs, but exon 20 insertions and T790M point mutations are associated with resistance to TKIs.[4]

Testing can be performed on surgical specimens as well as cytology samples. With our in-house samples, we are able to readily extract DNA from the residual fluid from each FNA. The advantages of adapting cytology in NSCLC molecular diagnosis is because optimal quality nucleic acids may be reliably isolated. Another benefit is the preservation of the original cytopathology slides. Sparing of the cell block is possible in case future diagnostic testing is needed.

For those DNA samples that were insufficient for NGS libraries, which account for 4% or less liquid-based cytology (LBC) specimens, a reflexive real-time PCR assay can determine the *EGFR* mutation hotspot status in a timely manner.

The main advantage of real-time PCR over NGS is its quick turnaround time (2-3 days), which could be crucial in a clinical setting. Since EGFR-mutated cancers account for 10-35% of NSCLC and may be treatable with TKI, we currently use Therascreen as an alternative to NGS to ensure the timely delivery of actionable molecular results to oncologists.

All patients with small biopsy specimens, resections and cytology samples that demonstrate differentiation of adenocarcinoma should also undergo testing. Small samples may be inconclusive of tumor subtype due to missed sampling of adenocarcinoma (i.e. adenosquamous carcinoma, unsampled adenocarcinoma in a squamous cell carcinoma). Small cell carcinomas or squamous cell carcinoma in the proper clinical context (heavy smokers) should probably not undergo testing.

While there are many targetable genes, the most commonly found are *EGFR* and *ALK*, and these should be prioritized, since these are the most common genes that have a targetable mutation. Knowledge of the presence of

KRAS mutation can be useful, but the priority should go to *EGFR* and *ALK*. Sequencing to detect the specific type of *EGFR* mutation is recommended. *EGFR*, gene copy number or immunohistochemistry staining simply tells the status of the *EGFR* receptor. At Cleveland Clinic, all lung cancer patients that fit into the above criteria undergo next generation sequencing. In the event that the DNA content is insufficient for NGS testing, allele-specific PCR testing for *EGFR* and *KRAS* will be performed.

While paraffin-embedded tissue from surgical specimens has been the classically validated method, cytology smears and cellient cell blocks may also be used to perform sequencing studies. We have found that the residual cytology fluid can be used for next generation sequencing. The supernatant fluid and cell pellet left after the FNA is obtained can be used for DNA extraction and sequencing studies. At our institution, cases that have tumor cellularity greater than 20% on the ThinPrep slide may be selected for NGS on the residual fluid. This is possible because of the willingness of the clinician obtaining the sample to perform additional passes just for testing.

We can perform ALK, ROS and RET testing on all surgical tissue including biopsies and resections. Next generation sequencing can be performed from extraction of DNA from selected blocks. Cytology specimens are currently validated for ALK testing. This can be performed on either the ThinPrep or cell block slide. ROS and RET testing is currently available on surgical specimens, and is undergoing validation and will hopefully be available for testing in the near future. Next generation sequencing can be performed on all cases that have residual fluid remaining in the tumor sample. It may also be performed from scraping tumor cells on slides with greater than 2000 tumor cells (Both Pap or Wright stained slides are commonly used in adequacy assessment). Before sacrificing any slides, we would archive a digital image using our ePathology Department to preserve a record of what was on the slide. In fact, a single FNA can be used to diagnose the tumor, subtype it with immunohistochemistry and provide valuable theranostic information. All of this information can be provided on small samples, using minimally invasive techniques.[5]

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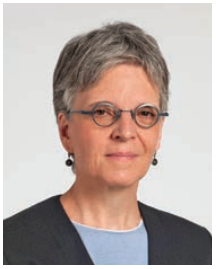

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Cystic Fibrosis: Updates in Diagnosis and Treatment

By Jacquelyn D. Riley, MS, LGC

Cystic fibrosis (CF) is a multisystem genetic disease caused by mutations, also known as pathogenic variants, in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. The gene encodes the CFTR protein, which acts as a chloride channel and regulates ion transport across cell membranes. Defects in the assembly and function of the CFTR protein lead to highly viscous secretions from epithelial cells, causing clinical manifestations in the lungs, pancreas, intestines, liver, sweat glands and male reproductive system.[1] Pulmonary disease is the leading cause of death among individuals with CF, with median predicted survival age of 39 years.[2]

Table 1. CF Carrier Frequency in Different Ethnic Groups

Ethnic Group	Observed Carrier Frequency
African American	1 in 84
Ashkenazi Jewish	1 in 29
Asian	1 in 242
Caucasian	1 in 28
Hispanic	1 in 59
Jewish	1 in 32
Middle Eastern	1 in 91
Native American	1 in 70
South Asian	1 in 118
Other Ethnicity	1 in 111
>1 Ethnicity	1 in 34
Part African American	1 in 56
Part Caucasian	1 in 32
Part Hispanic	1 in 51
Not Provided	1 in 37
All Individuals	1 in 38

Source: Rohlfs EM, Zhou Z, Helm RA, Nagan N, Rosenblum LS, et al. (2011) Cystic fibrosis carrier testing in an ethnically diverse U.S. population. *Clin Chem*. 57: 841-848.

Over 33,000 individuals in the United States have CF and 1,000 new cases are diagnosed each year.[2] It is most common among Caucasians but can affect people of any ethnic or racial background. The condition has autosomal recessive inheritance, meaning that a person develops symptoms only if they are homozygous, that is, they have two *CFTR* gene copies with pathogenic variants. Since heterozygous carriers are unaffected, most people diagnosed with the condition have no known family history. When both partners in a couple are carriers, each of their children has a 25% chance to inherit two variants and be affected with CF. There is also a 50% chance for each child to inherit just one variant and be an unaffected carrier for CF and a 25% chance of being neither affected nor a carrier.

Individuals with CF are now primarily detected at birth through mandatory newborn screening (NBS). CF screening is now included on the NBS panels in all states.[3] In most state programs, immunoreactive trypsinogen (IRT) enzyme testing is performed as the initial screen.[4,5] This screen is sensitive but not specific for CF so when positive, molecular testing of the *CFTR* gene may be performed as a second tier screen prior to reporting results to clinicians and families.

While sweat chloride testing remains the standard diagnostic test for patients with clinical symptoms of CF, genetic testing is routinely performed as confirmation of clinical findings.[6] With the advent of targeted treatment for CF, this confirmation is critical to patient care and management.

New Treatment Options

For many years, the management of CF focused solely on supportive treatment of symptoms, most often of airway obstructions and infections caused by viscous pulmonary secretions. However, in 2012 the FDA approved a medication in a new category that targets defects in the

A Note on Nomenclature

As use of molecular testing has become widespread over the last several years, efforts have been made to standardize the language that is used to describe genomic changes. New discoveries have challenged old assumptions – common variants are not always benign and rare changes are not always harmful. Terms like "mutation" and "polymorphism" have not been clearly or consistently applied and have developed connotations that may be inaccurate.

New guidelines recommend that the term "variant" be used to describe any change in the genomic sequence, with modifiers such as "pathogenic," "benign" or "uncertain significance." There are also detailed guidelines to describe what type of sequence change has occurred, such as nucleotide substitution, deletion or insertion. If you are interested, you can learn more at the Human Genome Variation Society website at http://varnomen.hgvs.org/.

protein function.[7] The first CFTR modulator, called ivacaftor (Kalydeco), was found to be beneficial to individuals with the G551D variant and other *CFTR* gating abnormalities.[8] For these patients, the CFTR protein is correctly assembled and located at the cell membrane but the chloride channel is closed.[9] The medication binds to the protein and restores its function. Patients who took the medication as part of a randomized controlled trial had significantly improved pulmonary function, decreased pulmonary symptoms and increased body weight (patients with CF can be underweight and malnourished due to abnormal intestinal absorption). However, gating variants are present in a minority of CF patients and ivacaftor was not found to be as effective in patients with F508del, which represents 70% of *CFTR* pathogenic variants among Caucasians.[10] F508del interferes with both channel gating and protein folding. In July 2015, the FDA approved a combination drug, lumacaftor-ivacaftor (Orkambi), for patients with homozygous F508del.[11] Patients on this combination CFTR modulator have experienced moderate improvements in pulmonary health.[12] This development represents an exciting application of personalized molecular medicine, where a patient's genotype is used to guide specific treatments. Therefore, molecular testing of the *CFTR* gene in patients with cystic fibrosis is more important than ever.

New *CFTR* Test Platform

Last year, the Cleveland Clinic Molecular Pathology Lab transitioned the *CFTR* mutation assay to a FDA-approved next generation sequencing (NGS) platform. The new test detects 139 variants in the *CFTR* gene, versus 32 variants that were detected with the previous test. The 139 variants were selected from the CFTR2 (Clinical and Functional Translation of CFTR) database as representing the full set of clinically validated variants classified as CF-causing.[13] CFTR2 is a consortium project that gathers clinical and molecular information from patients around the world, which is reviewed by a team of international CF experts. The assay includes all 23 pathogenic variants that are recommended for pan-ethnic carrier screening by the American College of Medical Genetics and the American College of Obstetricians and Gynecologists.[14] Using this set of variants ensures that the test has high sensitivity for both carrier screening and diagnostic testing but minimizes the risk of identifying variants of uncertain significance. Since the NGS technology not only sequences multiple genomic regions across multiple samples at the same time, it also allows for simultaneous sequencing of the same nucleotide multiple times, the test has high accuracy, minimizing the need for repeat testing and ensuring reliable turnaround times. This assay also includes detection of the PolyTG/PolyT intronic region, a repetitive sequence that is challenging to assay. Previously, the region had to be examined separately, an extra step that delayed results. This region can modify the significance of the R117H variant so it is clinically relevant for select patients.

The ability to accurately and quickly obtain molecular diagnosis in patients with cystic fibrosis, coupled with the development of new treatments that target the protein abnormalities caused by specific pathogenic variants, have changed the future for this population of patients. Undoubtedly, they will have better quality of life and longer survival due to these advances in personalized molecular medicine.

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New Multiplex Molecular Detection of Enteric Pathogens

By Susan Harrington, PhD

The World Health Organization estimates that enteric pathogens cause about 1.7 billion cases of diarrheal disease worldwide each year.[1] In the United States diarrheal disease is most commonly associated with consumption of contaminated food, but may also be spread from person-to-person. Centers for Disease Control and Prevention surveillance assessments estimate that 47.8 million food-borne illnesses and 4-17 million episodes of traveler's diarrhea occur annually.[2-4] Although very common, most diarrheal illness lasts only a few days and symptomatic individuals often do not seek medical care, are not treated, and are not tested to determine the etiology of their illness. According to recent guidance from the American College of Gastroenterology, fluid and electrolyte replacement are the most important intervention and mild illness typically resolves without further intervention. Empiric antibiotic therapy is recommended for travelers with moderate to severe illness; and microbiologic assessment is recommended prior to therapy for those with moderate to severe watery diarrhea, those with bloody diarrhea, and individuals with diarrhea lasting more than one week.[2]

A variety of bacterial, viral and parasitic pathogens may cause gastroenteritis and microbiologic analysis has traditionally involved several test formats including bacterial culture, enzyme immunoassays for organisms or toxins, microscopy and, more recently, polymerase chain reaction (PCR). Performing all of these methods to detect the causative pathogen(s) requires many hours of technical time and a number of different media and laboratory reagents or kits. These traditional test methods have been shown to lack sensitivity and an etiology is often not determined despite significant effort.[5-8] Importantly, the time to achieve all of these results is typically two or three days. By this time, decisions about therapy may have been determined based upon symptoms, duration of illness and patient history, not based on microbiologic data.

Detection of enteric pathogens is the ideal laboratory setting for application of a molecular test. A distinct set of etiologic agents can be defined and traditional tests are slow, insensitive, and not inexpensive if multiple tests are ordered. The FilmArray™ Gastrointestinal (GI) Panel (Biofire Diagnostics, Inc. Salt Lake City, UT) is a comprehensive, molecular test that has been approved by the Food and Drug Administration for use in diagnostic laboratories. The panel detects 13 bacterial species, four parasites and five viruses using the PCR method *(Table 1)*. Test components are contained in a single test "pouch" to which a hydration

Table 1. Enteric pathogens detected by the FilmArray GI Panel

Campylobacter (jejuni, coli, & upsaliensis)	*Yersinia enterocolitica*	*Cyclospora cayatenensis*
Salmonella spp.	*Plesiomonas shigelloides*	Norovirus
Shigella spp./EIEC	Vibrio spp. (parahemolyticus, vulnificus, cholerae)	Rotavirus A
Shiga toxins (STEC)	*V. cholerae*	Adenovirus 40/41
E. coli 0157	*C. difficile* toxin A/B	Astrovirus
ETEC (LT/ST)	*Giardia duodenalis*	Sapovirus
EPEC	Cryptosporidium spp.	
EAEC	*Entamoeba. histolytica*	

Table 2. Guidance for testing for enteric pathogens[a]

Testing not indicated:
Community-acquired, watery diarrhea for < 7 days duration, with no or low-grade fever
Diagnostic assessment with FilmArray is recommended:
dysentery
moderate-to-severe illness[b] and fever >72 hrs
diarrhea symptoms >7 days
severe abdominal pain or dehydration, hospitalization
immunocompromised state
C. difficile toxin assay is recommended:
health care-associate diarrhea
recent antibotics

[a] Guidance derived from reference #2
[b] Moderate illness: forced change in activities; Severe illness: total disability

solution and the sample are added prior to insertion into the FilmArray instrument. DNA or RNA extraction, purification, reverse transcription, nested PCR and detection are all performed inside the test pouch. Results are available from the instrument in one hour. PCR products are contained within the pouch, minimizing the risk of cross-contamination within the laboratory. To improve throughput, up to 12 instrument units can be combined to achieve rapid detection of pathogens with high sensitivity and specificity.[6, 8]

Ease of specimen collection and ordering is another advantage of testing with the FilmArray GI panel. After passing the specimen into a clean container, it should be transferred to Cary Blair transport medium for submission to the laboratory. Only the FilmArray GI test needs to be ordered. Although this test will be more expensive than individual tests for viral, parasitic or bacterial pathogens, savings may be achieved with fewer test orders and rapid results.

We recommend testing with the FilmArray GI panel based upon guidance derived from the American College of Gastroenterology.[2] Patients with community-acquired, watery diarrhea of less than seven days duration, with no or low-grade fever do not need to be tested. Diagnostic assessment is recommended for those with dysentery, moderate-to-severe disease and symptoms lasting more than seven days. FilmArray testing is also appropriate for those with severe abdominal pain, dehydration, hospitalization or immunocompromised state. Separate testing for *Clostridium difficile* toxin is recommended for health care-associated diarrhea and for patients who have recently received antibiotics.

The FilmArray panel has a few limitations. *Aeromonas species* are not included. Stool culture for *Aeromonas* spp. may be ordered if FilmArray is negative. Similarly, diarrheal disease in immunocompromised patients may be due to microsporidia and microscopic examination for microsporidium requires a special stain that is ordered separately. Although the FilmArray detects the most common parasitic pathogens in the United States, an ova and parasite microscopic examination for helminths and modified acid fast staining for Cystoisospora, Cyclospora and Cryptosporidium may be helpful if FilmArray does not detect a pathogen or for those with traveler's diarrhea. Intermittent shedding of parasites may require testing of multiple specimens with specific tests.

Molecular methods detect DNA and/or RNA. They will detect dead organisms and free nucleic acids from toxins or organisms. In general tests of cure are not recommended – instead resolution of clinical symptoms should be monitored. In the limited settings when a test of cure is needed, molecular methods should not be used due to detection of nonviable DNA. Culture would be preferred. Similarly, a specific test for a bacterial, viral or parasitic pathogen may be ordered if the differential is known to be limited such as if a patient is involved in an outbreak or has a specific exposure.

With detection of many different pathogens comes the need to interpret complex and possibly, unexpected results. Of note is the presence of the *C. difficile* toxin target on the FilmArray panels. Toxigenic *C. difficile* may colonize the human host, especially children less than two years old. Positive results determined from patients not recently exposed to antibiotics should be interpreted with caution. The FilmArray GI panel incorporates a number of lesser known targets such as pathogenic *E. coli* (enteroaggregative *E. coli* (EAEC), enteroinvasive *E. coli* (EIEC), enteropathogenic *E. coli* (EPEC), enterotoxigenic *E. coli* (ETEC)), astrovirus and sapovirus. Although associated with outbreaks and known to be present in patients in developed countries, pathogenic *E. coli*, other than Shiga-toxin producing strains, are mostly associated with diarrhea in children in the developing world.[9] Until

Table 3. Supplemental tests for specific enteric pathogens:

Bacteria:
Culture for *Salmonella, Shigella, Campylobacter,* Shiga Toxins (Stool culture) (STCUL)
Culture for *Vibrio* spp. (VIBCUL)
Culture for *Yersinia* spp. (YERCUL)
Culture for *Aeromonas/Plesiomonas* spp. (AERPLE)
C. difficile Toxin PCR (CDPCR)

Parasites:
Cryptosporidium & Giardia Antigens by EIA (OVAPSC)
Cystoisospora/*Cryptosporidium/Cyclospora* examination (CRYSPO)
Ova and Parasite (microscopic) Examination (OVAP)

Fungi:
Microsporidia examination (MICSPO) Test performed in parasitology.

Virus:
Rotavirus Antigen Detection (EROTA)
Rotavirus and Adenovirus 40/41 Antigens (ROTAD)
Norovirus Group 1 and 2 Detection by PCR (NORPCR)

recently, detection of these pathogens was limited to research laboratories and epidemiological assessments. Relevance in clinical samples in the U.S. is uncertain and hasn't been well-studied with this new generation of multiplex assays, such as the FilmArray. In a small study of 230 specimens collected prospectively in the United States Khare, *et al*. found 33% of samples to be positive by FilmArray, but only 8% by conventional test methods (8). The most common pathogens detected were *Clostridium difficile* toxin (14%), norovirus (6%) and sapovirus (6%). A few samples each were positive for *Campylobacter* spp., *Salmonella* spp., *Shigella* spp., adenovirus and astrovirus, as well as, EAEC, EPEC and ETEC. Pathogenic *E. coli* were among the most common species detected by FilmArray in a study conducted among ten European countries and were frequently found in mixed infections.[10] As expected, other prevalent infecting species determined were *Campylobacter* spp., *C. difficile*, norovirus, rotavirus and *Salmonella* spp. Another interesting finding from this study was variability from country to country with regard to the most common pathogens detected. Thus, regional differences may impact test ordering or empiric therapy as data on circulating pathogens are compiled.

The impact of multiplex molecular testing for enteric pathogens on the diagnosis and treatment of diarrheal disease remains to be seen, but the prospect is intriguing. Certainly, an etiologic agent will be identified more frequently than might have been with conventional testing. This should lead to appropriate therapy directed at the pathogen(s) detected and is likely to result in a reduction in inappropriate antibiotic therapy for infections with viral pathogens and some bacterial species. Investigation of the clinical relevance of mixed infections and pathogenic *E. coli* in patients in the U.S. is needed, but is now possible with comprehensive molecular panels. Knowing the pathogen quickly may lead to other benefits such as a reduction in phone calls and office visits and an increase in satisfaction for both the patient and provider. If utilized in the appropriate patient population, the information gained should help bring an overall improvement in patient care.

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About the Author

Susan Harrington, PhD

Susan Harrington, PhD, is a staff microbiologist at the Cleveland Clinic Pathology and Laboratory Medicine Institute. She directs the Mycobacteriology and Specimen Processing sections of the main campus laboratory and serves to integrate microbiology services across the Cleveland Clinic Health System. She is actively involved in teaching Medical Laboratory Science students, residents, medical students and fellows and is the medical director for the Cleveland Clinic School of Medical Laboratory Science. Her research interests include molecular detection of enteric pathogens, the diagnosis and susceptibility testing of mycobacteria and optimization of specimen processing procedures.

Dr. Harrington received her undergraduate degree from the University of Pittsburgh and completed a master's degree in public health at the Johns Hopkins Bloomberg School of Public Health. She earned a PhD in bacterial pathogenesis at the University of Maryland and completed a clinical microbiology fellowship at the NIH Clinical Center. Her first position as a laboratory director was at Albany Medical Center in Albany, NY.

Dr. Harrington serves on the Board of Governors for the ASCP Board of Certification, and actively participates on committees for the Board of Certification. She has been a member of the American Society for Microbiology (ASM) since 1984 and currently volunteers on the editorial board of the *Journal of Clinical Microbiology*. Dr. Harrington speaks at regional meetings and has authored many peer-reviewed journal articles. She is certified as a diplomate of the American Board of Medical Microbiology.

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Alumni Connect

We are thrilled to feature one of our distinguished alumni, James Richard, DO, in this installment of Alumni Connect. Dr. Richard graduated medical school from Ohio University College of Osteopathic Medicine and did a rotating internship at Grandview Hospital in Dayton, Ohio. He was a resident in anatomic and clinical pathology at Cleveland Clinic from 1983 to 1987 and then joined the medical staff at Doctors Hospital in Massillon, Ohio, near his hometown. Dr. Richard moved to Lansing, Michigan, in 1991 for a staff pathologist position at Sparrow Hospital. In 1996 he founded CAP-Lab, a private practice AP laboratory serving various hospitals and physician offices in mid-Michigan. He was laboratory director of McLaren Medical Center in Lansing from 2000 to 2010 and served on that hospital's board of directors for 10 years. In 2014, Sparrow purchased CAP-Lab and Dr. Richard returned to Sparrow to begin his next adventure as chairman of the Pathology Department and laboratory director of their laboratories. He continues to serve in that capacity.

Dr. Richard and Robin, his wife of 40 years, reside in the Greater Lansing area and their three children live in Texas, Ohio and North Carolina. Their eight grandchildren are a great source of joy for them, not to mention a great source of stories with adventures of their own.

We invited Dr. Richard to tell us about his current position, reflect on his training at Cleveland Clinic, and provide current residents and fellows with valuable advice:

> "While at Cleveland Clinic I was encouraged to pursue my passion in Pathology, wherever it may lead me. I was not told what I could or could not attempt. Some of my choices raised eyebrows, like when I chose to do malpractice in pathology as my grand rounds talk. But I was always encouraged to do my best. The wonderful professional staff were a great resource to my practice even after I completed my residency. They were there for me, both during and after training. During my second year of residency I was having a challenge of faith about whether or not I was cut out to be a pathologist. When I went to the staff member in charge of the residents, I was told to stick it out a little longer, as I was performing as an average pathology resident. Nothing motivated me more than being told I was "average!" Later in practice, I got tired of being told I was "just a doctor and really didn't understand business," so I got an MBA to speak the administrators' language and effectively communicate my value as a pathologist to the health care system. We, as pathologists, do much more to contribute to patient care than reading slides and managing the laboratory. Our role on hospital committees, such as blood bank utilization and infection control, leads to better care for all hospital patients.
>
> During my third year of residency, I was elected president of the Clinic house staff, and that catalyzed my efforts to become involved in organized medicine. I was later elected county medical society president, and then served on the board of the state medical society and the board of the hospital. I also served as state pathology society president and delegate to the CAP House of Delegates, and I am currently serving as Speaker of the House of Delegates for the CAP. Get involved as a pathologist and stay with it. You can make a difference in our specialty. Every time I heard it was somebody else's job to do, I just figured that I was that somebody else.
>
> I have been a laboratory director of small hospitals, large hospitals, publicly traded reference labs, and have owned and operated

"We, as pathologists, do much more to contribute to patient care than reading slides and managing the laboratory. Our role ... leads to better care for all hospital patients."

my own AP lab with 50 employees. I have been an employee and a private practice partner. I even put together a mobile frozen section lab in the back of an old ambulance to service plastic surgeons operating at a surgery center. Use your training and your imagination to be able to bring something to the table. I have held a number of professional positions over the years, but each time I went in with the attitude that I had something they needed – even if I had to convince them of it.

I found Cleveland Clinic to be a great place to train and came away with good memories and a sense of purpose. I feel that I have the opportunity to make a difference every day, whether at the microscope, in the clinical laboratory, or in the various meetings and efforts I make to help the patients and physicians we serve. I am proud to be a member of the Cleveland Clinic family."

We want to hear from you

Please send us your news and accomplishments to be featured in this "Alumni Connect" section in future issues of *Pathology Today*. If you prefer to receive an electronic version, please let us know by providing your preferred email address to ClientServices@ccf.org.

Fadi W. Abdul-Karim, MD, MEd
Vice-Chair, RT-PLMI
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Jonathan L. Myles, MD
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Medicine Specialty Director

Alumni Connect Steering Commitee
Fadi Abdul-Karim, MD, MEd, Jonathan Myles, MD, Karl Theil, MD, Paul Suchy, PhD, Daniel Kelly and Kathy Leonhardt

Cleveland Clinic Multispecialty Symposium in Las Vegas

The second annual Multispecialty Pathology Symposium will be held at the Monte Carlo in Las Vegas Jan. 20-22, 2017. Hosted by John Goldblum, MD, and Cristina Magi-Galluzzi, MD, PhD, the program will feature 2½ days of the expert analysis in the fields of soft tissue, GI, GU, head and neck, cytology and lung.

This symposium will help practicing pathologists, fellows and residents maintain, develop,and increase their knowledge, competence, and professional performance with the intent to improve patient care and reduce disease impact.

For more information and registration, visit www.ccfcme.org/Pathology2017.

New Staff

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Pathology Today
offers information from the medical staff in the Cleveland Clinic's Robert J. Tomsich Pathology & Laboratory Medicine Institute about its research, services and laboratory technology.

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News

Cleveland Clinic well represented at USCAP

The 2016 USCAP Annual Meeting, the largest gathering of pathologists in the world, was held in Seattle from March 12-18. As usual, the residents, fellows and faculty members from the Robert Tomsich Pathology & Laboratory Medicine Institute (RT-PLMI) made an enormous impact on this meeting.

Ninety-three abstracts were presented from Cleveland Clinic residents, fellows and faculty. In the vast majority of abstracts, RT-PLMI residents and fellows served as the first author for these outstanding presentations. Several abstracts were honored, including first-author abstracts by Alana Donaldson, MD, and Sarah Falzarano, MD, each of whom was awarded Best Abstracts by the International Society of Breast Pathology and International Society of Urological Pathology, respectively.

In addition to the strong presence in the poster and platform sessions, no other institution was as strongly represented in the large number of educational activities presented at this meeting. Numerous Cleveland Clinic faculty served as short course directors, moderators or presenters at Evening Specialty Conferences; moderators or presenters at the various companion society meetings; and scientific platform moderators. A number of faculty also served as interactive microscopy directors, an activity which was under the leadership of Steven Billings, MD. Carol

Farver, MD, served as course director and presenter for one of the USCAP Special Courses entitled, "Leadership, Collaboration and Change in Healthcare, A Residents' Workshop for Essential Skills."

Several individuals also hold key positions with the USCAP or related companion societies. John Goldblum, MD, served as President of the USCAP and Chairman of the USCAP Executive Committee/Board of Directors. Dr. Billings serves as the Short Course Coordinator for the USCAP Education Committee, Dr. Farver is also a member of the Education Committee. Cristina Magi-Galluzzi, MD, PhD, is a member of the Membership Committee, and Brian Rubin, MD, PhD, is a member of the Publications Committee. Deborah Chute, MD, serves as a member of the committee that awards the Stowell-Orbison awards, and Dr. Rubin serves on a similar committee that awards the Vogel award. Finally, Ben Calhoun, MD, PhD, serves as a member of the Resident Advisory Committee.

The Institute is proud of its residents, fellows and faculty members who contributed to the success of this most prestigious meeting, and we look forward to similar success for the 2017 annual meeting in San Antonio.

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