



**Cleveland Clinic**

**Robert J. Tomsich Pathology &  
Laboratory Medicine Institute**

Clinical and Translational

# Pathology Innovations

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Eric Hsi, MD



Feature Story  
DLBCL molecular  
subtyping assay

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## DLBCL molecular subtyping assay

By Eric Hsi, MD, and Angela M.B. Collie, MD, PhD

Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin's lymphoma in the United States, accounting for approximately 40% of cases of non-Hodgkin's lymphoma with 25,000 new cases diagnosed each year. DLBCL is an aggressive malignancy, and treatment with modern immunochemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP)) can result in cure in approximately 70% of patients. However, many patients relapse and ultimately die of their disease.<sup>1</sup> Thus, there is heterogeneity in clinical course. A combination of clinical parameters is currently used to assess a patient's risk profile. However, these prognostic variables are considered to be proxies for the underlying cellular and molecular variations within DLBCL.

Histologically, DLBCL is composed of large B-cells arranged in a diffuse pattern. There are several morphologic variants, and recent advances in molecular genetic research have shown that DLBCL is also a biologically heterogeneous disease.<sup>2</sup>

DLBCL can be classified into two molecular subtypes using microarray gene expression profiling (GEP). These subtypes are based on a putative "cell-of-origin" and are called germinal center B-cell-like (GCB) and activated B-cell-like (ABC).<sup>3</sup> The recognition of DLBCL subtypes has profound biological, prognostic and potentially therapeutic implications, with the ABC subtype having an unfavorable prognosis compared to the GCB subtype, and distinct pathobiology that includes activation of the B-cell receptor and nuclear factor (NF)- $\kappa$ B pathways. Improved molecular diagnostic methods can prospectively identify high-risk patients who may benefit from individualized therapy based on their DLBCL molecular subtype.

In order to support clinical trial needs for an integral biomarker study in which patients are enrolled for therapy targeting ABC DLBCL, and to offer diagnostic information for DLBCL patients on our clinical services, Cleveland Clinic Laboratories developed a DLBCL molecular subtyping assay using real-time multiplex PCR-based expression profiling with the Modaplex System (QIAGEN

Mansfield, Inc., Mansfield, MA, USA). This work was done in collaboration with our colleagues in the Cleveland Clinic Taussig Cancer Institute, including Brian T. Hill, MD, PhD, and John Sweetham, MD, FACP, FRCP, as well as with Qiagen Mansfield.

Although the original classification of DLBCL into germinal center B cell-like (GCB) and activated B cell-like (ABC) subtypes was based on microarray gene expression profiling, this technique is not currently feasible in a clinical setting, primarily because it cannot be performed on formalin-fixed, paraffin-embedded (FFPE) specimens. Surrogate studies to assign classification, such as immunohistochemistry, have shown variability between laboratories and may not yield reliable results.<sup>4, 5, 6</sup>

Therefore, we developed a rapid, accurate gene expression-based DLBCL subclassification on FFPE tissue on the Modaplex platform. The Modaplex integrates a PCR thermal cycler that accommodates a standard 96-well PCR plate, a capillary electrophoresis (CE) system with a replaceable CE cartridge and fluidic pumps with on-board reagents. Since the Modaplex system has two solid-state lasers (488nm and 639nm excitation) and a spectrophotometer with CCD camera, two different fluorescent labels can be detected simultaneously in single well. The system allows detection of multiple fluorescently labeled PCR products with unique sizes by sequential sampling and separation using capillary gel electrophoresis (CE) in real time.

The DLBCL molecular subtyping assay is performed on the Modaplex platform and requires a single 10- $\mu$ m FFPE section. It is based on a 14-gene signature (Table 1), together with housekeeping genes, to provide a subtyping S score that classifies tumors into GCB, ABC or unclassifiable categories.<sup>7</sup> Results are reported as "germinal center expression signature identified" or "activated B-cell expression signature identified." Cases with borderline linear prediction scores are reported as "unclassifiable expression signature identified."

The assay was validated using a series of paired frozen and FFPE samples from the same DLBCL tumor. Results

patients, for identifying the biologic subtypes of lymphoma that may be useful in clinical trials targeting specific types,

**Table 1. DLBCL Molecular Subtyping Assay Genes**

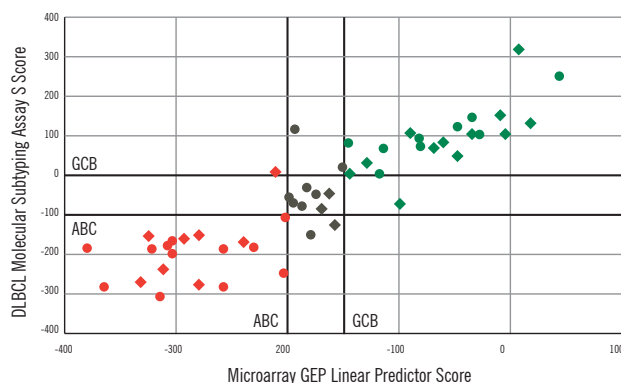
Gene Symbol	Gene Name	Assay Function	Amplicon Size (nt)	Label
ENTPD1	Ectonucleoside triphosphate diphosphohydrolase 1	Classification Algorithm (14 genes)	166	FAM
FUT8	Fucosyltransferase 8		115	FAM
IGHM	Immunoglobulin heavy chain constant region mu		146	TYE
IL16	Interleukin 16		142	FAM
IRF4	Interferon regulatory factor 4		181	FAM
ITPKB	Inositol 1,4,5-triphosphate 3-kinase B		125	TYE
LRMP	Lymphoid-restricted membrane protein		148	FAM
MME	Membrane metalloendopeptidase		160	TYE
MYBL1	V-myb avian myeloblastosis viral oncogene homolog-like 1		129	FAM
PIM1	Oncogene PIM 1		153	FAM
PTPN1	Protein tyrosine phosphatase, non-receptor type 1		125	FAM
CCND2	Cyclin D2		119	FAM
LMO2	Lim Domain only 2		159	FAM
BCL6	B-cell lymphoma 6		133	FAM
TBP	TATA box-binding protein	Housekeeping Genes	175	FAM
TFRC	Transferrin receptor		137	FAM

*Gene targets for the Modaplex DLBCL assay were selected based on the Wright et al. (2003) classification. Template size, amplicon size and fluorescent label for each target are indicated.*

of the DLBCL subtyping assay on FFPE show excellent concordance with global gene expression profiling studies from the matched frozen tissue (Figure 1). There was sensitivity of 95.2% and specificity of 93.8% for assignment of the ABC subtype and sensitivity of 95.2% and specificity was 90.6% for assignment of the GCB subtype for 53 tested samples.<sup>8</sup> Agreement for assignment of ABC subtype was 94.3% and for overall subtype (GCB, ABC or unclassifiable) was 88.7%. In further performance characteristics experiments, the assay showed strong concordance both within and between test runs.

In summary, the DLBCL molecular subtyping assay allows accurate classification of tumors into GCB or ABC molecular subtype using a single 10- $\mu$ m FFPE section. It can be utilized for prognosis based on the prior studies that have shown prognostic differences in R-CHOP treated

**Figure 1.**



*DLBCL subclassification correlation plot between Modaplex DLBCL molecular subtyping assay (FFPE) and GEP microarray (frozen tissue).*

and for clinical immunohistochemistry laboratories as an aid in validating their IHC algorithms in identifying the molecular subtypes.

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Dr. Collie is currently a Dermatopathology Fellow at Cleveland Clinic. She received her bachelor's degree in biomedical engineering from Vanderbilt University, and her PhD in bioengineering and medical degree from the University of Washington. She completed her anatomic and clinical pathology residency at Cleveland Clinic where she was chief resident. Last year, she was a fellow in hematopathology at Cleveland Clinic. Her special interests include general pathology, dermatopathology and hematopathology. She is looking forward to completing her current fellowship in June 2015. Contact Dr. Collie at 216.444.1860 or by email at [colliea@ccf.org](mailto:colliea@ccf.org).



## Medical Kidney Biopsy Interpretation: Applying intricate techniques to complex diseases

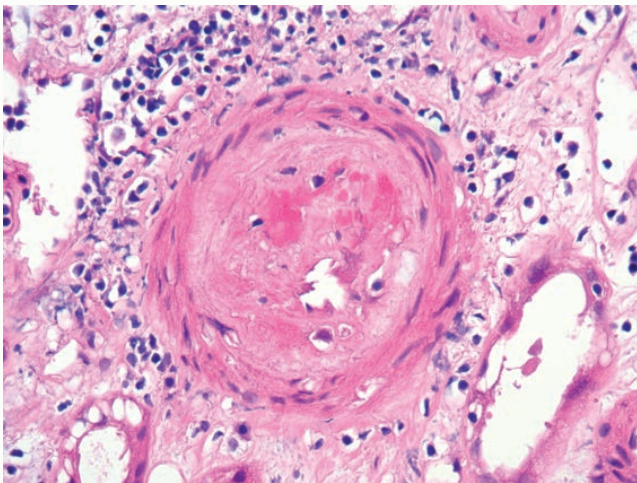
By Leal C. Herlitz, MD

The purpose of performing a renal biopsy is highly variable. If the biopsy is targeted at a mass lesion, evaluation by the pathologist is usually focused on determining what the mass is composed of and whether the lesion is likely to behave in a malignant fashion. In contrast, the “medical kidney biopsy” is taken from a random spot in the kidney and is used to evaluate for the presence of diffuse diseases and systemic medical conditions that may be altering kidney function.

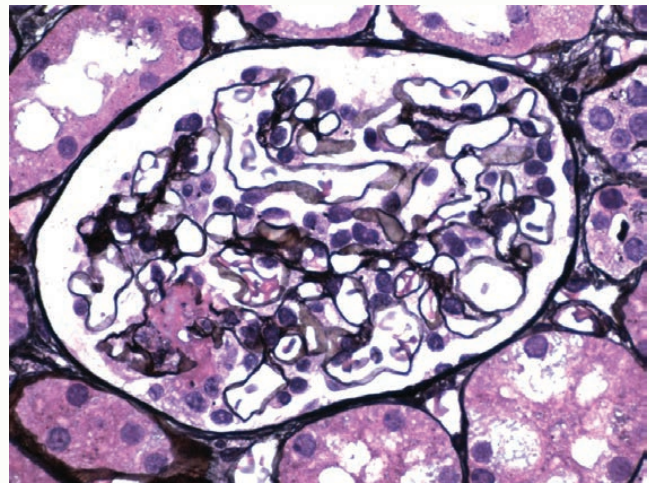
The most common findings that lead to referral for a medical kidney biopsy are the presence of blood or protein in the urine or an unexplained decline in renal function. These abnormalities in kidney function can be caused by numerous conditions, including chronic medical conditions

such as diabetes and hypertension, autoimmune diseases such as lupus, chronic infections such as viral hepatitis, and complications of medical therapies that are directed at treating a variety of medical conditions. If the patient has undergone renal transplantation, biopsy is essential for the diagnosis of rejection, various infections, medication toxicity and recurrence of the patient’s original renal disease. Because treatments for these many types of conditions vary widely, it is often important to establish a tissue diagnosis in order to proceed with the most appropriate therapy.

The modern era of renal pathology was made possible by the introduction of the percutaneous renal biopsy that came into use in the late 1950’s. Until that time,



*An artery showing severe luminal narrowing with inflammation and fibrinoid necrosis in a patient with a renal transplant. In this setting these changes are diagnostic of grade 3 acute cellular rejection; however similar changes can also be seen in the kidneys of patients with vasculitis due to a variety of autoimmune diseases.*

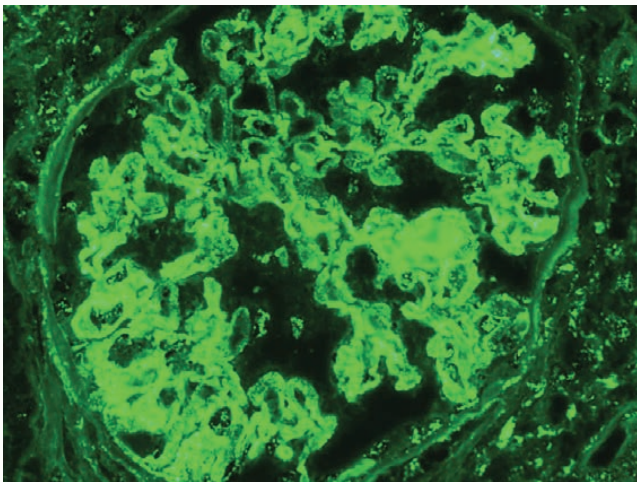


*A Jones methenamine silver stain highlights an early necrotizing lesion in a glomerulus of a patient with anti-neutrophil cytoplasmic antibodies (ANCA). The glomerular basement membrane, stained black, can be seen to be ruptured at 7:00. The accumulation of pink material is fibrinoid necrosis. To see a subtle lesion like this special staining that highlights the contrast between the glomerular basement membrane and other materials is essential.*

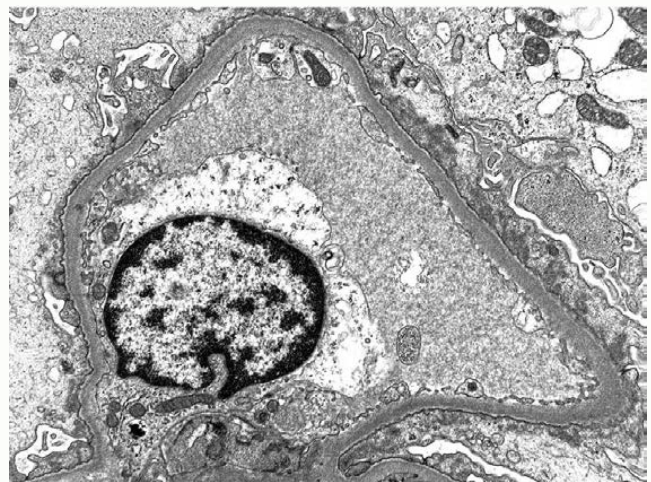
the evaluation of medical kidney disease was largely an autopsy-based practice. The percutaneous biopsy presented the opportunity to evaluate kidney disease in our living patients and use this information to help guide treatment decisions. As with any biopsy, the challenge of diagnosing complex diseases with very limited tissue is ever-present. As interpretation of medical kidney biopsies has been refined, the standard of care has remained the routine performance of light microscopy, immunofluorescence and, in most cases, electron microscopy. The integration of results from each of these modalities, along with detailed clinical-pathologic correlation is essential to the interpretation of medical kidney biopsies.

Because of the variety of diseases being evaluated in the medical kidney biopsy, techniques not routinely used in most subspecialties in anatomic pathology are integral to the art of renal biopsy processing and interpretation. Light microscopy provides the starting point for each case

and helps to determine not only “what” is going wrong, but how active or aggressive the disease process is and how chronic or potentially reversible the damage is. For medical kidney biopsies, “routine” light microscopy consists of examining multiple slides stained with not only hematoxylin and eosin (H&E), but also periodic acid-Schiff (PAS), Masson trichrome and Jones methenamine silver. Each stain highlights different structures that must be individually evaluated in every biopsy. Immunofluorescence is used to identify and localize immunoglobulins and complement components that can be deposited within the kidney in various pathologic states. Both the identity of the immunoglobulin (for example IgG) as well as the intensity of staining and its distribution within the biopsy is important for making the proper diagnosis and assessing how active the disease is. Transmission electron microscopy (EM) is routinely used in medical kidney biopsy interpretation because it is helpful in localizing deposits within the glomerulus, elucidating any substructure that



*Immunofluorescence staining with IgG in a patient with lupus nephritis. The glomerulus pictured shows a bright green signal in the locations where IgG has been deposited. These deposits of IgG can attract inflammatory cells that will damage the glomerulus. Integrating the immunofluorescence staining shown here with the light microscopic findings is essential to accurately grading the activity and chronicity of renal involvement in patients with lupus.*



*Electron microscopic findings in a patient who presented with severe edema. Light microscopy and immunofluorescence were both within normal limits, however, electron microscopy reveals the diffuse fusion of podocyte foot processes that normally invest the outside of the glomerular basement membrane. These podocyte processes are essential for normal function of the glomerular filtration barrier. This change, which can only be appreciated with electron microscopy, is associated with the development of profound leakage of protein into the urine.*

deposits may have, documenting textural alterations in basement membranes and showing structural changes that can be critical to the proper function of cells such as podocytes that form a key component of the glomerular filtration barrier.

The reliance on specialized techniques such as immunofluorescence and electron microscopy, which require costly equipment and considerable technical expertise, makes it difficult for most hospitals to offer these services economically. There is the additional need for interpretation of the biopsy material by a pathologist with expertise in medical kidney pathology. The typical exposure of pathologists-in-training to medical kidney pathology is no more than a month, which is not nearly enough time to become proficient at interpretation of these somewhat obscure specimens. As it is difficult to effectively process the relatively low volume of renal biopsies received in most practice settings, most medical kidney biopsies are sent to referral centers, such as Cleveland Clinic, for processing and interpretation.

While the medical kidney biopsies processed and interpreted at Cleveland Clinic may have originated in a medical center that is thousands of miles away, detailed communication between the pathologist and the nephrologist is essential for getting the most information possible from each biopsy. The renal pathologist requires a thorough understanding of renal disease and the wide spectrum of histologic manifestations. As in much of medicine, any given abnormality can have a variety of etiologies. The pathologic changes, while very helpful in forming a differential diagnosis, can show considerable overlap in numerous conditions. For this reason, medical kidney biopsies must be interpreted by integrating the light microscopy, immunofluorescence, electron microscopy and a detailed clinical history in order to arrive at the proper diagnosis.

The collaboration between the pathologist and the treating physician is as essential for proper diagnosis as any of the specialized techniques used in the laboratory. Often, the most important nuances used to arrive at the correct diagnosis and guide appropriate therapy become apparent not at the microscope, but in the telephone conversation about the biopsy findings.

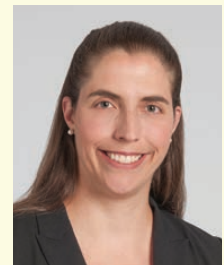
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## CDC recommends enhanced HIV testing strategy to improve diagnosis of early HIV infection and HIV2 disease

By M. Qasim Ansari, MD

In 1981 the first report of five cases of HIV disease in previously healthy young men was published in the CDC's *Morbidity and Mortality Weekly Report (MMWR)*. In quick order the causative organism was identified and a diagnostic test to detect HIV antibodies was described. The CDC quickly established a strategy whereby a repeatedly positive screening test was followed by a confirmatory test – a western blot (WB) or immunofluorescent (IFA) assay – to establish a diagnosis of HIV disease.

Tests for HIV disease have considerably improved, as each successive generation has led to better sensitivity, specificity and accuracy. The advent of molecular testing by PCR and other techniques and their use in the blood transfusion community has led to virtual elimination of transfusion-associated HIV disease. In addition, the FDA has approved numerous point-of-care rapid tests to facilitate early and immediate testing for diagnosis in the ED and obstetrics wards.

The viral load PCR assay has become an extremely sensitive and specific test that is easy to perform, is automated and commonly used for determining prognosis of patients along with the enumeration of the CD4+ T-cells in the peripheral blood. The CDC and the WHO continued to stress the initial basic model, namely a positive screening antibody test followed by another confirmatory antibody test, to establish diagnosis. This was usually an EIA screen followed by a western blot or IFA confirmatory assay. After diagnosis, prognosis was monitored by the HIV viral load assay and the CD4 helper T-cell counts by flow cytometry.

There are now more than 35 million HIV-positive patients worldwide and over 1.2 million in the U.S. The CDC estimates that 20% of HIV patients are undiagnosed and responsible for the majority of the estimated 56,000

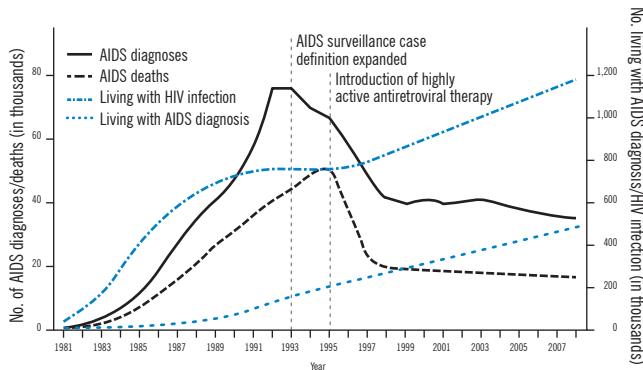
new cases seen annually in the U.S. Therefore, a major push was directed at screening for and finding these undiagnosed HIV patients by testing many susceptible groups of the population. To prevent newborn infants from getting HIV, a similar robust effort was directed at testing all pregnant women.

The race was on to diagnose all undiagnosed patients, to prevent new infections and decrease the incidence of disease. The recently approved fourth generation assays used at Cleveland Clinic Laboratories detect the p24 antigen in addition to the HIV antibody. This new combo (antigen + antibody) is more sensitive, shortens the "window period" (time between the start of disease and the appearance of positive test results) and is more specific than the previous generation test. It is run on an automated random access analyzer that is interfaced with the hospital computer system. The assay can run virtually 24/7 with a short turnaround time.

In Figure 2 from a *New England Journal of Medicine*<sup>4</sup> article, the sensitivity of different clinical laboratory tests compared to the HIV RNA is shown. The RNA appears first chronologically. As can be seen the p24 antigen and the ELISA HIV antibodies appear within a few days of the RNA, but the western blot assays have a long window period and may not be positive many weeks after disease. This could lead to missed diagnosis of acute HIV infections.

Major strides also have been made in treating HIV diseases with numerous classes of drugs that make survival possible for decades with greatly reduced morbidity and mortality. Recent CDC data shows this remarkable decrease in the number of people dying of HIV disease and the surge of people living with HIV infection. (*figure 1*)





**Figure 1. Estimated number of AIDS diagnoses and deaths and estimated number of persons living with AIDS diagnosis\* and living with diagnosed or undiagnosed HIV infection† among persons aged ≥13 years – United States, 1981–2008**

**ABBREVIATIONS:**

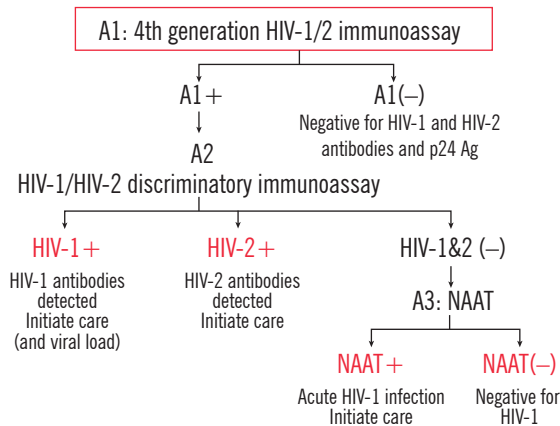
**AIDS** – acquired immunodeficiency syndrome

**HIV** – human immunodeficiency virus

\*Yearly AIDS estimates were obtained by statistically adjusting national surveillance data reported through June 2010 for reporting delays, but not for incomplete reporting

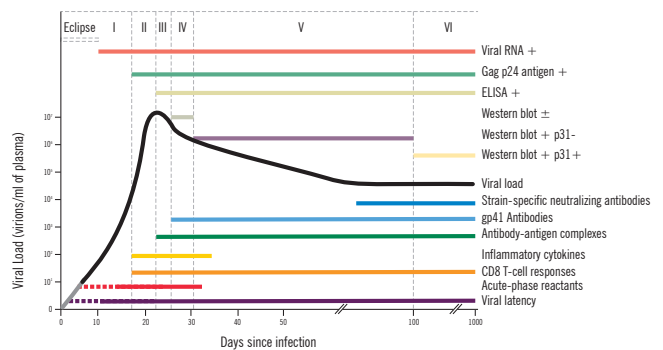
† HIV prevalence estimates were based on national HIV surveillance data reported through June 2010 using extended back-calculation

The CDC has recently released a new algorithm of HIV testing (figure 3). They recommend a screening antibody test by a fourth generation assay to detect both HIV1/HIV2 antibody and the p24 antigen. No further testing is done if this initial test is negative.



**Figure 3. HIV Confirmation Algorithm (proposed by the CDC at 2010 HIV)**

Repeatedly positive results by the screening “combo” assay (A1) necessitates that a subsequent “differentiation” assay (A2), called a multispot test, be performed for confirmation. This simple and rapid point-of-care test differentiates between HIV1 and HIV2 disease (figure 4). A positive sample may be positive for HIV1, indicating HIV1 disease; positive for HIV 2, indicating the rare HIV2 disease; or, in very rare cases, positive for both HIV 1 and 2.



**Figure 2. Natural history and immunopathogenesis of HIV-1 infection**

If antibodies to neither HIV1 or HIV2 are evident by the multispot test, a negative result is reported and, according to the CDC model (figure 3), a NAAT (molecular) (A3) test is advised to rule out acute HIV infection. This test is recommended because antibodies may not have had time to develop in the acute HIV infection phase, resulting in a “false negative” result by the multispot. The NAAT test will indicate a positive result even before the p24 antigen in the combo assay, and is recommended to rule out acute HIV disease. A positive NAAT result indicates an acute HIV infection, which is in a very dangerous phase with high levels of highly infective viruses. A negative result rules out the presence of HIV disease.



**Figure 4. A Multispot test positive for HIV 1**  
**The first spot on the left represents positive control and two spots on the right indicate positive HIV 1 disease.**

The only diagnostic HIV molecular assay approved by the FDA is the HIV RNA test by transcription-mediated amplification (TMA). All of these tests – with the exception of the TMA assay (which is sent out) – are performed at Cleveland Clinic Laboratories.

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## About the Author

### M. Qasim Ansari, MD

Dr. Ansari joined the Department of Clinical Pathology at Cleveland Clinic in 2013. He is board certified in anatomic pathology, clinical pathology, immunopathology and hematology. His interests include immune-related disorders, autoimmune diseases and lymphoid neoplasias. Dr. Ansari is a graduate of Dow Medical College, Karachi, Pakistan. He completed his residency training in Pathology (AP/CP) at Baylor Medical College in Houston, and a fellowship in immunopathology at UT Southwestern Medical Center in Dallas. He is a professor of pathology and teaches pathology residents and fellows. He has published 51 scientific papers in peer-reviewed journals, several book chapters and given numerous presentations at national meetings. Contact Dr. Ansari at 216.445.2056 or by email at [ansarim@ccf.org](mailto:ansarim@ccf.org).



## Alumni Connect

Dear Alumnus,

This is the third edition of our commitment to provide you with regular alumni communication.

As noted previously, exciting educational activities are happening within the Robert J. Tomsich Pathology and Laboratory Medicine Institute (RT-PLMI). With every correspondence, we will provide information on upcoming conferences, educational events and publications. This issue of *Pathology Innovations* is one of several important initiatives highlighting our scientific updates.

### Article of the Week

Hopefully you are now receiving “Article of the Week” by email. Five have been sent so far. These articles are mailed to all our residents, faculty and affiliates, and will now include our esteemed alumni. From your initial feedback, this initiative has been well received as part of staying current with literature, general education and sharing of relevant information. We encourage you to submit articles that would be of educational interest to your colleagues.

### L Building renovations to increase efficiency, productivity and capacity

The first floor renovation is complete and includes a new Education Suite that will house all the residents, fellows, MT and Cytology Schools, a library with a multiheaded scope and a large conference room. Hematopathology has relocated to the newly remodeled third floor. Pictures of all the renovated areas in the L Building will appear in the next Alumni Connect.

### Sixth Annual Continuing Education Conference: Looking Beyond the Lab

Our Sixth Annual Education Conference, “Looking beyond the Laboratory,” will be held on Saturday, April 18, at the Cleveland Clinic Lyndhurst Campus and is open to all pathologists, laboratory professionals, managers and supervisors. We would appreciate it if you would forward this invitation to your respective laboratories across the region and neighboring states. This conference will be an opportunity for laboratory professionals to learn, *continued on back page*

## Fellow Attends CAP Leadership Academy

*Shelley Odronic, MD, a cytopathology fellow in the Robert J. Tomsich Pathology & Laboratory Medicine Institute, was invited to attend the College of American Pathologists’ Engaged Leadership Academy in Chicago. During the two-and-a-half day workshop, she worked with*



*CAP President Gene Herbek, MD, FCAP, to strengthen the communication and leadership skills necessary to expand the visibility of pathology and laboratory medicine at a national level.*

## New Staff

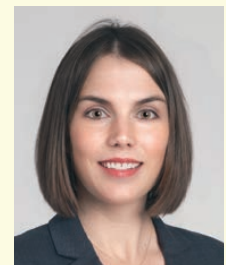
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### **Pathology Innovations**

**Magazine** 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.

Thomas Daly, MD  
*Medical Editor*  
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## Alumni Connect (continued from page 11)

interact with colleagues, and obtain up to 6 hours of PACE credit. For additional information and online registration please visit: <http://my.clevelandclinic.org/services/pathology-laboratory-medicine/for-medical-professionals>.

### **Consultation services at CCL**

You are already familiar with Cleveland Clinic Laboratories and many of its highly accomplished pathologists. As the Pathology Department continues to expand its outreach services, it recruits additional experts in their respective fields. Our Pathology Department offers second opinion consultations for surgical pathology, cytology and hematopathology cases. Specimens for consultations are forwarded to one of our subspecialty teams that is comprised of nationally and internationally renowned pathologists with a high level of diagnostic expertise in their specific fields. It will be our privilege to serve the consultation needs of our esteemed alumni. Our aim is to guarantee you superior quality consults and rapid turnaround times. To request a consultation, please visit our website at [clevelandcliniclabs.com/subspecialty-consultative-services](http://clevelandcliniclabs.com/subspecialty-consultative-services) for required information. Or contact Client Services at 800.628.6816, 24 hours-a-day, seven days-a-week.

### **RT-PLMI at USCAP**

The faculty of the Robert J. Tomsich Pathology and Laboratory Medicine Institute (RT-PLMI) were prominently involved in presenting at USCAP's Companion Society Meetings, Evening Specialty Conferences, Short Courses, Special Courses and Standalone Meeting Session, as well as being moderators and committee members. We also sponsored a fellowship booth exhibit and reception. Please stop by and visit us at our booth at an upcoming conference.

### **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 Innovations*. If you prefer to receive an electronic version, please let us know by providing your preferred email address to [ClientServices@ccf.org](mailto:ClientServices@ccf.org).

#### **Fadi W. Abdul-Karim, MD, MMEd**

Vice-Chair, RT-PLMI  
Center for Pathology Education

#### **Jonathan L. Myles, MD**

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#### *Alumni Connect Steering Committee:*

Drs. Abdul-Karim and Myles, Daniel Kelly, Kathy Leonhardt, Emily Lopick, Paul Suchy, PhD, and Karl Theil, MD



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