

## HPV DNA Testing of Pap Specimens

Human Papilloma Virus (HPV) is the most common sexually transmitted infection in the United States and has been established as the main cause of cervical cancer and associated precancerous lesions. There are currently more than 50 types of HPV that infect the anogenital area, although only a small portion appears to cause most cervical precancerous lesions and cancers.

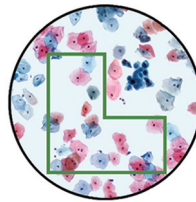
Based on their risk of causing cervical cancer, HPV viruses are grouped into low-risk and high-risk categories. Low-risk types cause genital warts and mild cellular changes. High-risk HPV types, especially when the infection persists for many years, can cause squamous and glandular epithelial cells to become precancerous and possibly cancerous. Pathologists agree that an HPV infection is necessary for the development of precancerous cervical-vaginal disease that may eventually progress to invasive cancer if left untreated.

According to the American Cancer Society, more than 9,000 women were diagnosed with cervical cancer in the United States in 2006, resulting approximately 3,700 deaths. Of note, worldwide cervical cancer

kills approximately 230,000 women annually with the vast majority of deaths occurring in developing countries.

In the U.S., approximately 20 million people—both men and women—are thought to have an active HPV infection at any given time. In fact, 75 percent of sexually active people will be infected with HPV at some point in their lives.

### What is the HPV DNA test?



The HPV DNA test uses advanced molecular technology to determine whether one of the HPV virus types that may cause cancer is present in the cervical and/or vaginal epithelial cells within a liquid-based Pap test or commercially-specified collection media.

Hybrid Capture (HC) technology, developed by the Digene Corporation (recently acquired by Qiagen), is at the time of this writing the only FDA approved technique for HPV DNA testing and is thus the most widely-used methodology in the U.S. HC technology, which includes the first generation Hybrid Capture Tube (HCT) test and the second generation Hybrid Capture II (HC II) assay, uses signal amplification to provide sensitivity comparable to target amplification methods (such as PCR).

The HC II, which detects 13 viral types, is 10 times more sensitive than the prior generation HCT. The HC II assay involves a five-part process:

1. Cervical or vaginal liquid-based Pap tests are combined with an extraction buffer to release and denature the target HPV DNA.
2. The released target DNA hybridize with specific RNA probes to create RNA-DNA hybrids.
3. The hybrids are captured onto a solid phase by a specific antibody.
4. These captured hybrids are tagged with antibody reagents linked to alkaline phosphatase.
5. Finally, a chemiluminescent substrate produces light that is measured on a luminometer in relative light units (RLUs). The amount of RLUs generated is proportional to the amount of target DNA in the original specimen.

Although HPV DNA testing of Pap specimens has been available at Baystate Medical Center since year 2000, a high-throughput rapid capture platform utilizing HC II was implemented January 1, 2007 within the Cytopathology Division of the Department of Pathology at BMC. HPV testing on this platform is performed by cytotechnologists specifically trained and certified in this specific molecular technology, with medical director oversight.

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#### Editorial Information:

BRL News is published biannually by the Baystate Health Department of Pathology and Baystate Reference Laboratories.

Address all communications to the editor: Liron Pantanowitz, MD, Department of Pathology, Baystate Medical Center, 759 Chestnut St., Springfield, MA 01199.

Tel: 413-794-4195 Fax: 413-794-3195  
E-mail: Liron.Pantanowitz@bhs.org

#### Editors:

Liron Pantanowitz, MD

Richard Friedberg, MD, PhD

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## Who should receive the HPV DNA test?

The HPV DNA Test using Hybrid Capture II technology is the only FDA-approved HPV test and is indicated for patient management in the following clinical settings:

1. Primary screening, in conjunction with a morphologic Pap test, of women ages 30 years and older, for combined testing in this age group further increases the sensitivity for detection of precancerous/cancerous lesions, and most importantly, improves negative predictive value. The American Cancer Society (ACS) and the American College of Obstetricians and Gynecologists (ACOG) have both endorsed as an option the primary screening of women  $\geq 30$  with combined testing.
2. Triage of women 21 years and older with ASC-US Pap results, to determine which subgroups (HPV positive patients) should proceed to colposcopy.
3. Post-treatment of the cervix, as a negative HPV test and a normal Pap following treatment of the cervix for a precancerous lesion offers greater negative predictive value than Pap alone.

Having a positive HPV DNA test does not mean the patient has a precancerous or cancerous cervical-vaginal lesion. In fact, most women who are HPV positive will not. The strengths of the test are its sensitivity and negative predictive value. When combined with the Pap test, this makes for a very powerful testing pair. Cervical-vaginal screening and management guidelines have been recently updated by the American

Society for Colposcopy and Cervical Pathology (ASCCP, [www.asccp.org/consensus/cytological.shtml](http://www.asccp.org/consensus/cytological.shtml)), with screening with combination of HPV testing and Pap test acknowledged in clinical guidelines developed by major medical groups.

## How often should I perform the HPV DNA test?

An appropriate and endorsed option for women 30 years of age or older is to have combined screening with the high-risk HPV DNA test and a morphologic Pap test. If both tests are negative, it is highly unlikely that a woman has precancerous changes or cancer. Because cervical cancer develops so slowly, when both tests are negative, routine screening in this age group does not need to be repeated for three years. If the Pap test is negative and the HPV DNA test is positive, both tests should be repeated in 6 to 12 months. The testing and management algorithms for all potential test results in combination are nicely delineated in the ASCCP Guidelines, at the above web-link.

The HPV DNA test is available Monday through Friday at Baystate Reference Laboratories, with a turnaround time of two to three working days after the morphologic interpretation of the Pap test has been performed. If the specimen is collected for ThinPrep Pap test (PreservCyt, available through Client Service 322-4000), no additional collection is needed.

For more information or clarification, please contact Q. Jackie Cao, MD, PhD, director of Molecular Cytopathology, or Bob Goulart, MD, director of Cytopathology Services, at 413-794-4594.

## Meet Mary M. Zakhary, MD Director, Pathology Department, Baystate Franklin Medical Center

Dr. Zakhary received her medical degree in Cairo, Egypt, and completed her combined anatomic and clinical pathology residency training at Brown University Affiliated Hospitals in Providence, RI. She also completed a one year surgical pathology fellowship and served as chief resident at the then New England Deaconess Hospital in Boston. Dr. Zakhary's primary interest is surgical pathology, with a particular interest in breast and genitourinary pathology.

"Working at Baystate Franklin Medical Center, a community hospital, provides me with a great opportunity to get to know all of our physicians

well, which makes communication easy and results in delivering a better quality of care to our patients," says Dr. Zakhary. "I strive to render the most accurate diagnosis in the shortest time possible."

Baystate Franklin Medical Center offers a full service laboratory that provides testing in hematology, clinical chemistry, urinalysis, blood banking, diagnostic immunology, and anatomic pathology. The laboratory maintains accreditation with the College of American Pathologists (CAP) and the American Association of Blood Banks (AABB).

Integration with Baystate Reference Laboratories enables the pathology lab at Baystate Franklin Medical Center to provide consistency in test methodologies and reference ranges across the health system, as well as share expertise and an integrated laboratory information system.

Dr. Mary Zakhary can be reached by phone at 413-773-2218 or by email at [mary.zakhary@baystatehealth.org](mailto:mary.zakhary@baystatehealth.org).



One of the core missions of Baystate Reference Laboratories (BRL) is to provide accurate and timely information to our clinical colleagues, allowing you to give your patients the best possible care. We face many emerging challenges, such as patient safety and error reduction, as well as adoption of the Electronic Health Record. In order to meet these challenges, BRL has leveraged its advanced information systems and skilled information services staff, and embraced novel technologies.

**Electronic Health Record:** Our team has been an active participant in developing and maintaining our Electronic Medical Record (EMR) at Baystate Health. We have advanced laboratory computerized order entry and have strived to consistently deliver secure, accurate, and real-time pathology results in the EMR. BRL is also currently working with several regional physician practices that have their own EMR systems to develop a direct link to match the clinician's orders with BRL laboratory results. This will allow a lab test ordered in the physician office's EMR to be seamlessly transmitted to Baystate Health. The results for that order will then automatically post into the requesting office's EMR.

**Automation/Autoverification:** We are strong proponents for automation. Most blood specimens received in our laboratories are within minutes placed onto an automated platform for analysis and subsequent testing. To further improve turn-around times for lab results, reduce errors, and improve patient care, we have activated a system to immediately release accurate lab results upon analysis by an instrument. This process is called autoverification, and was established between our instrument and laboratory computer systems. Logic rules with self checking mechanisms are consistency applied across all shifts at all times. Consequently, once a result passes all of our logic rules, it takes literally seconds for it to electronically transfer from an analyzer into the EMR.

**Patient & Specimen Identification:** To keep patient safety at the forefront of care, BRL is investing in the latest systems to reduce potential patient and specimen identification errors. We have collaborated with the nursing phlebotomy

team on a new endeavor to produce blood specimen collection labels at the patients' bedside. Our phlebotomists are now using a special PDA to read patients' wristbands for Positive Patient Identification (PPID). This PDA automatically links to our laboratory computer system via a secure wireless connection, displaying in real-time any blood draw orders. At the same time, labels for these blood specimens are printed directly at the bedside, virtually eliminating any potential for mislabeling. Similar steps are underway in the histology laboratory to implement an advanced bar coding and tracking (AB&T) system to safely manage all patients' surgical and biopsy specimens coming through our laboratory.

**Digital Imaging:** Digital images are playing an ever increasing role in the field of pathology. At BRL, we welcomed this new technology early on and have a well established image management system integrated with our anatomical pathology laboratory information system. This allows us to save digital pathology images with our patient's records, allowing pathologists to include images in their surgical pathology reports. We support live, interactive telepathology using robotic microscope stages that are remotely operated at both Baystate Medical Center and Baystate Franklin Medical Center. We will soon implement whole slide imaging (i.e. entirely digitized slides). Also, we plan to start using computer assisted image analysis of digital images to provide precise, reproducible, and accurate breast proteomics (e.g. ER, PR & HER-2/neu results).

These are some of the examples that place Baystate Reference Laboratories at the cutting edge of technology, ensuring that our clients receive the best possible service and our patients the highest level of care.

**Liron Pantanowitz, MD**  
Director of Pathology  
Informatics

**William Lareau**  
Manager of Laboratory  
Information Systems

For more information contact Dr. Pantanowitz at telephone 413-794-4195.

# Baystate Reference Laboratories Patient Service Centers

## Amherst

Amherst Family Practice  
413-549-0291  
29C Cottage Street  
Monday-Friday,  
8 am-12:30 pm, 1:30-4:30 pm

## Belchertown

Baystate Mary Lane Outpatient Laboratory  
413-967-2535  
95 Sargent Street  
Monday-Thursday, 7 am-7:00 pm  
Friday 7 am-6 pm, Saturday 7 am-12 pm

## East Longmeadow

Medical/Dental Building  
413-322-4000  
294 North Main Street, First Floor  
Monday-Friday, 8 am-5 pm

## Greenfield

Baystate Franklin Medical Center  
Outpatient Laboratory  
413-773-2606  
164 High Street  
Monday-Friday, 7 am-5 pm

Greenfield Outpatient Laboratory  
413-773-2241  
48 Sanderson Street  
Monday-Friday, 8 am-5 pm

## Longmeadow

\*Longmeadow Professional Building  
413-787-5160  
167 Dwight Road, Suite 100  
Monday-Friday, 7 am-12:30 pm, 1:30-5 pm

## Northampton

\*Pioneer Valley Family Medicine Building  
413-582-0107  
118 Conz Street  
Monday-Friday 7:30 am-5 pm

## South Hadley

\*The Raymond Center  
413-322-4000  
470 Granby Road  
Monday-Friday, 8 am-5 pm

## Springfield

\*Baystate Health Building  
413-787-5407  
3550 Main Street, Suite 202  
(GTT center 2-3 hr)  
Monday-Friday, 8:30 am-5 pm

Birnie Avenue Professional Building  
413-794-2357  
300 Birnie Avenue, Third Floor  
Monday-Friday, 8 am-5 pm

Carew Medical Building  
413-785-1078  
222 Carew Street, First Floor  
Monday-Friday, 8 am-5 pm

Liberty Medical Arts Building  
413-787-5151  
125 Liberty Street, Basement Level  
Monday-Friday, 8 am-12:30 pm, 1:30-5 pm

\*Medical Office Building  
413-794-8522  
2 Medical Center Drive, Suite 105  
Monday-Friday, 7 am-6 pm  
Saturday-Sunday, 7:30 am-4 pm

North Main Medical Center  
413-794-8933  
3455 Main Street, B Level  
Monday-Friday, 8 am-5 pm

Baystate Outpatient Laboratory  
413-794-2585  
140 High Street, C Level  
Monday-Friday, 8 am-5:30 pm

Baystate Outpatient Testing Laboratory  
413-794-7014  
3300 Main Street  
Monday-Friday, 7 am-5:30 pm

\*Women and Infants' Laboratory  
413-794-5374  
759 Chestnut Street,  
Wesson Building, Ground Floor  
Monday-Friday,  
8 am-8 pm

## Ware

Baystate Mary Lane Hospital Laboratory  
413-967-2182  
85 South Street, First Floor  
Monday-Friday, 7:30 am-5 pm,  
Saturday, 7:30 am-12 pm

## West Springfield

Baystate Ob/Gyn  
413-794-5768  
50 Union Street  
Monday-Friday 8 am-12 pm, 1-4:30 pm

\*Daggett Place  
413-794-3399  
46 Daggett Drive, Third Floor  
Monday-Friday, 8 am-5 pm

## Westfield

\*Pioneer Valley Professional Center  
413-568-6391  
65 Springfield Road, Ground Level  
Monday-Friday  
8:30 am-12:30 pm, 1:30-5 pm

## Wilbraham

\*Boston Road Medical Building  
413-794-0154  
2377 Boston Road, Second Floor  
Monday-Friday, 8 am-5 pm

\* Glucose Tolerance Tests (GTTs) are performed at these locations. Please call Diagnostic Scheduling at 413-794-2222 to book appointment for this test.

For further information, contact Jacki Stack-Rossi, Business Development, Baystate Reference Laboratories, 361 Whitney Ave, Holyoke, MA. Tel: 413-322-4093. Email: Jacki.Stack-Rossi@baystatehealth.org



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