June 2010 | VOLUME 3 No. 2 | Quarterly Publication

Journal Watch
Summaries of recent topical publications in the medical literature
Full Article ..... pg 2

Test Announcement
Tests now available in the clinical laboratory
Full Article ..... pg 5

Research & Development
The Tumor Biology of Breast Cancer
Continued ..... pg 4

The Laboratorian SM

Clinical Aspects Of Breast Cancer

Author: Shlomo Stemmer, MD

Breast cancer is defined as cancer that forms in the ducts (invasive ductal carcinoma) and lobules (invasive lobular carcinoma) in the breast. It occurs in males and females, although it is rare in males. Breast cancer rates have been declining in recent years; however, it is still a major cause of death among women throughout the world. After lung cancer it is the most common cause of death among women in the United States and it is the most common malignancy after skin cancer. An overall lifetime risk for developing breast cancer is estimated at 12.5%, or 1 in 8. Estimated new cases and death from breast cancer for 2009 are 192,370 and 40,170, respectively.

Factors that increase the relative risk for breast cancer in women are: Increasing age, personal history of breast cancer, family history of breast cancer, inherited genes such as BRCA1 and BRCA2, history of high-dose radiation exposure to the chest, obesity, beginning of menses before age 12, beginning of menopause after age 55, having first term pregnancy after age 35, history of never breastfeeding a child, postmenopausal hormone therapy, personal history of cancer of the endometrium, ovary, or colon, alcohol consumption, and being of Jewish heritage.

Continued.....pg 4

The Tumor Biology of Breast Cancer

Author: Jason Trama, Ph.D.

Breast tissue is particularly sensitive to developing cancer for several reasons. One reason is that breast cells divide rapidly upon hormone and growth factor developmental cues. Cells that divide are at higher risk of acquiring mutations that may contribute to tumorigenesis. It would be impossible to discuss the research of breast cancer tumor biology and its impact on patient care without mentioning findings regarding hormone and growth factor receptors, namely the estrogen receptor (ER), the progesterone receptor (PR) and the human epidermal growth factor receptor (Her2/neu/neu, or ErbB-2). The basic scientific study of these receptors has been critical in understanding cell growth and tumor development, in providing patient prognosis, and in developing anticancer drugs. Herein is discussed the role of these important receptors in breast cancer, how this knowledge has translated to patient management, and areas are identified where more research in breast cancer tumor biology is needed.

As implied by their names, ER, PR, and Her2/neu are receptors that regulate hormone and growth factor signaling in breast cells. These receptors are important biologic factors involved in cell proliferation and survival and are therefore critical in the transition of normal cells to cancer cells. Most breast cancers express ER and PR, which are nuclear receptors. The ER binds its ligand, estrogen (more specifically, estradiol), and the PR binds progesterone. The ligand-receptor complex is then capable of translocating to the nucleus of the cell where the receptor will bind to specific DNA sequences in the promoters of certain genes. Once bound to DNA, the receptor will associate with transcriptional coregulators and consequently control the level of gene transcription. Estrogen acts as a critically important mitogen for breast cells during normal breast development and influences the growth of milk ducts. Estrogen signaling regulates the expression of the PR; therefore, the presence of PR usually indicates a functioning ER pathway. Progesterone is an important factor stimulating the formation of the milk glands. It is the dysregulation of hormone signaling, usually due to increased expression of these receptors, which is associated with uncontrolled cell growth during cancer pathogenesis (Dickson and Lippman, 1988).

Recent research has shown that within minutes estrogen can drive the proliferation of ER-positive breast cancer cells. However, the effects of ER-dependent gene transcription are not seen in the form of newly synthesized proteins for at least 30 minutes to an hour. The discrepancy with the timing of this effect led to the unexpected observation that active ER molecules reside in the outer cell membrane of a subset of tumors, especially those that are Her2/neu positive. The majority of Her2/neu positive tumors are also PR negative, so it is believed that nuclear ER is non-functional, *i.e.* not regulating the transcription of its targets such as the PR. In these cells, the membrane-bound ER directly affects several

Continued.....pg 4

WHAT'S INSIDE

UPCOMING EVENTS

08/6-7	**ACOG:** Florida OB/GYN Society & FL Section American Congress of Obstetricians & Gynecologists Miami Beach, FL
10/8-10	**ACOG:** American Congress of Obstetricians & Gynecologists District I Annual Bar Harbor, ME
10/8-10	**ACOG:** American Congress of Obstetricians & Gynecologists Annual District Meeting (Districts III, & VI) Key Biscayne, FL
10/17-20	**ACOG:** American Congress of Obstetricians & Gynecologists Armed Forces District Annual Meeting San Antonio, TX

Radpour R, Barekati Z, Haghighi M, et al. 2010. Correlation of Telomere Length Shortening With Promoter Methylation Profile of P16/Rb and P53/P21 Pathways in Breast Cancer. *Mod Pathol.* **23**(5):763–72

Telomere shorting is coupled with unregulated cancer cell growth. Therefore scientists measure the telomere length to provide important information on cell replication and proliferation states in cancer tissues. In this report, Radpour R. *et al.* studied relative telomere length and methylation status of the TP53, P21, and P16 promoters in tissues from breast cancer patients. They linked telomere shortening with its potential correlation with down-regulation of cell-cycle regulatory elements. Telomere length was measured in 52 pair-matched breast cancer tissues by quantitative PCR assay. Methylation profiles of selected genes were analyzed in all specimens using a matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI–TOF MS). They found telomere regions were significantly shorter in tumor tissues than in adjacent normal tissues (P<0.001). They also found telomere lengths were significantly shorter in advanced stage cases and in those with higher histological grades (P<0.05). In this report, the researchers successfully correlated the telomere shortening in breast cancer tissues with a different level of hypermethylation in the TP53, P21, and P16 promoters (r=−0.33, P=0.001; r=−0.70, P<0.0001 and r=−0.71, P<0.0001, respectively). These results suggested that p16/Rb and/or p53/p21 pathways inactivation (hypermethylation) are coupled with critical telomere shortening to cause genome instability and ultimately to lead malignant transformation. In summary, telomere shortening and hypermethylation might serve as novel breast cancer biomarkers.

Alley WR, Madera M, Mechref Y, Novotny MV. 2010. Chip-based Reversed-phase Liquid Chromatography−Mass Spectrometry of Permethylated N-Linked Glycans: a Potential Methodology for Cancer-biomarker Discovery. *Anal Chem*, 2010, Epub ahead of print.

In this report, the researchers developed a new method for breast cancer biomarker identification. The protein glycosylation (i.e. glycomic-profile changes) in biological fluids and tissues has been an important marker for a number of diseases including cancer. To quantify glycomic-profile changes, Alley W. *et al.* at Indiana University combined a glycomic sample preparation/solid-phase derivatization of glycoprotein-derived N-linked glycans with their subsequent microchip-based separation and mass-spectrometric (MS) measurements. They first reduced β-elimination for O-linked glycans with ammonia−borane complex to reduce N-linked structures, and then they effectively methylated the N-linked alditol structures in dimethylformamide medium to avoid artifacts in MS measurements. Reversed-phase microfluidic liquid chromatography (LC) of methylated N-linked oligosaccharide alditols resolved some closely related structures into regular retention increments, aiding in their structural assignments. By combining optimized LC gradients together with nanospray MS, the scientists quantitatively measured the N-linked glycans in blood serum: there is significant difference between breast cancer patients and control individuals. Therefore, it is promising to develop a breast cancer diagnostic assay by quantification of permethylated N-linked glycans using chip-based reversed-phase liquid chromatography−mass spectrometry.

Chakravarty D, Nair S, Santhamma B. 2010. Extranuclear Functions of ER Impact Invasive Migration and Metastasis by Breast Cancer Cells**.** *Cancer Res*. **70**:4092-4101.

Emerging evidence suggests that estrogen receptor (ER) mediated extranuclear signaling in response to estrogen results in rapid stimulation of the Src kinase, mitogen-activated protein kinase (MAPK) and phosphatidylinositol-3-kinase(PI3K) in the cytosol. However the molecular mechanisms of ER extranuclear signaling and pathobiology of ER extranuclear action remain unknown.

In this study, the researchers analyzed the role of a proline-, glutamic acid-, and leucine-rich protein-1 (PELP1) in ER mediated extranuclear signaling. PELP1 expression is deregulated in metastatic breast tumors and functions as a potential proto-oncogene and promotes tumor growth in nude mice models. Using estrogen dendrimer conjugate (EDC) that uniquely activate ER extranuclear signaling and by using model cells that stably express PELP1 short hairpin RNA (shRNA), the investigators show that PELP1 is required for optimal activation of ER extranuclear actions. The investigators have identified integrin-linked kinase 1 (ILK1) as a novel PELP1-binding protein. Activation of extranuclear signaling by EDC uniquely enhanced E2-mediated ruffles and filopodia-like structures. Furthermore, estrogen-mediated extranuclear signaling promotes cytoskeleton reorganization through the ER-Src-PELP1-phosphoinositide 3-kinase-ILK1 pathway. Using in vitro Boyden chamber assays and *In vivo* xenograft assays, the researchers found that ER extranuclear actions contribute to cell migration.

Collectively, the data presented in this article suggests that ER extranuclear actions play a role in cell motility/metastasis, establishing for the first time that endogenous PELP1 serves as a critical component of ER extranuclear actions leading to cell motility/invasion and that the ER-Src-PELP1-ILK1 pathway represents a novel therapeutic target for preventing the emergence of ER-positive metastasis.

Lee JH, Jung C, Javadian-Elyaderani P, et al. 2010. Pathways of proliferation and antiapoptosis driven in breast cancer stem cells by stem cell protein Piwil2. 2010. *Cancer Res*. **70**:4569-79

Several studies have confirmed the existence of cancer stem cells which modulate tumor initiation and growth, like that of breast tumors. Stem and progenitor cells are of great interest in cancer research because it is believed that these cells are the initial targets for malignant transformation.

In this study the investigators studied the roles of Piwil2in breast cancer stem cell. In a variety of organisms, Piwil2 has been implicated in multiple roles including stem cell self-renewal, RNA silencing, and translational control. In this study, the researchers documented the specific expression of the stem cell protein Piwil2 in breast cancer with predominant expression in breast cancer stem cells as Piwil 2 expressing cells show higher expression levels of markers specific for pluripotent stem cells like Oct4 and Nanog and show cellular characteristics of stem cells. In breast cancer patients, they determined that 90% of invasive carcinomas and 81% of carcinomas in situ exhibited highest expression of Piwil2. In breast cancer cells, Piwil2 silencing suppressed the expression of signal transducer and activator of transcription 3, a pivotal regulator of Bcl-X(L) and cyclin D1, whose down-regulation paralleled a reduction in cell proliferation and survival.

In conclusion, this study shows that Piwil2 is expressed in breast cancer stem cells modulates the proliferation and anti-apoptotic state of breast cancer cells through the Stat3/Bcl-Xl signaling pathway, suggesting that Piwil2 is a promising candidate for breast cancer diagnosis and a target for breast cancer therapy.

Recent Publications

MEDICAL DIAGNOSTIC LABORATORIES, L.L.C. (MDL)

Abstracts

1. **Chadwick SG, Mordechai E, Adelson ME, Gygax SE.** Susceptibility profiles of Community-Associated MRSA Isolates from Cervicovaginal Swab Samples. 49th Interscience Conference on Antimicrobial Agents & Chemotherapy, San Francisco, CA. September 12-15, 2009.

Peer-Reviewed Papers

2. **Ingvarsdottir K, Blaho J**. 2009. The role of chromatin in the regulation of HSV-1 viral gene expression and replication. *Future Microbiol*. **4**(6):703-12.

3. **Hilbert D, Paulish T, Mordechai E, Adelson ME, Gygax, SE, Trama J**. 2009. Antimicrobial non-susceptibility of cervico-vaginal and rectal *Eschericia coli* isolates is associated with phylogeny and plasmid carriage. *Eur J Clin Microbiol Infect Dis.* In press.

HUMIGEN

Abstracts

1. **Do T, Davis C, Ucisik-Akkaya, E, Morrison B, Dorak MT.** Molecular Mechanism of Sex-specific Association of Interferon Regulatory Factor 4 with Childhood Acute Lymphoblastic Leukemia (ALL). 35th Annual American Society for Histocompatibility and Immunogenetics. San Francisco, CA, November 2-6, 2009.

2. **Ucisik-Akkaya E, Davis C, Do T, Dorak MT.** Immunoregulatory Gene Polymorphisms and Childhood Acute Lymphoblastic Leukemia (ALL) Susceptibility. 35th Annual American Society for Histocompatibility and Immunogenetics. San Francisco, CA, November 2-6, 2009.

3. **Davis C, Ucisik-Akkaya E, Do T, Dorak MT.** Polymorphisms of Iron Regulatory Genes with Immune Functions are Associated with Childhood Acute Lymphoblastic Leukemia (ALL). 35th Annual American Society for Histocompatibility and Immunogenetics San Francisco, CA, November 2-6, 2009.

Peer-Reviewed Papers

1. **Dai J, Megjugorac N, Gallagher GE, and Gallagher G.** 2009. IFNLambda1 (Il-29) inhibits GATA3 expression and suppresses Th2 responses in human naïve and memory T cells. *Blood,* **113**(23):5829-38.

2. **Do T, Ucisik-Akkaya E, Davis C, Morrison B, Dorak MT.** 2009. TP53 R72P and MDM2 SNP309 Polymorphisms in Modification of Childhood Acute Lymphblastic Leukemia Susceptibility, *Cancer Genet Cytogenet*, In press.

Quality Assurance Q&A

Q:Why do I need to list the ethnicity of my patient when ordering Test #1201 Cystic Fibrosis Gene Carrier Screening

A:The incidence and carrier risk for CF varies greatly based upon race or ethnicity. This information is required to complete the result interpretation process.

Table 1. Incidence and Carrier Risk for Cystic Fibrosis Based on Race or Ethnicity (American College of Obstetricians and Gynecologists and American College of Medical Genetics. Preconception and prenatal carrier screening for cystic fibrosis. Clinical and laboratory guidelines. American College of Obstetricians and Gynecologists, Washington, DC 2001).

Racial or Ethnic Group	Incidence of CF	Carrier Risk
Ashkenazi Jewish	1/3,300	1/29
European Caucasian	1/3,300	1/29
Hispanic American	1/8,000 – 9,000	1/46
African American	1/15,300	1/62
Asian American	1/32,100	1/90

If you have a question you would like addressed in future issues, please email your question(s) to QAQ&A@mdlab.com

e-Quiz

1. Which if the following receptors regulate hormone and growth factor signaling in breast cancer:
   a. ER b. PR
   c. Her2/neu d. All of the above

2. The _____ staging System is used to classify breast cancer.
   a. ABC b. 123
   c. TNM d. PET

3. Match the stage of breast cancer with it's 5 year relative survival rate:

Stage I	86%
Stage II	20%
Stage III	100%
Stage IV	57%

4. **True or False:** Clinical features such as patient age, tumor size, nodal status, tumor grade, margin status,and ER/PR/Her2/neu status are currently used to determine the likelihood for recurrence and to guide subsequent treatment options.

5. **True or False:** The current recommendation issued by the US Preventive Services Task Force (USPTF) for breast cancer screening are biennial screening with mammography for women aged 50 to 74 years.

For results to the electronic Epidemiology Quiz, please visit www.mdlab.com and click on the e-Quiz link.

Clinical Aspects Of Breast Cancer

Continued from.....pg 1

Signs and symptoms of breast cancer include:

- A breast lump or thickening that feels different from the surrounding tissue.
- Change in the size or shape of a breast.
- Skin changes such as dimpling, redness or pitting.
- Nipple inversion or bloody nipple discharge.
- Peeling or flaking of the nipple skin.

Any of these signs and symptoms of breast cancer require further testing and possible surgical evaluation. Mammograms are commonly used for screening and diagnosing breast cancer. For younger women with dense breast tissue evaluation may begin with a breast ultrasound. An ultrasound may also be used to determine whether a breast mass is a fluid filled cyst or a breast tumor. A cystic lesion may be aspirated. If the fluid is clear and the cyst disappears, then there is no need for cytological evaluation. If the cyst recurs within 6 weeks or the aspirate is bloody, surgical evaluation with fine needle aspiration (FNA) or biopsy is warranted. A solid, dominant, persistent mass requires tissue diagnosis either by FNA or breast biopsy.

Once breast cancer is diagnosed, to determine the stage of the cancer, one or more of the following tests may be needed. Blood tests such as a CBC, chest x-ray, an extensive mammogram if not already done, breast MRI, bone scan, computed tomography (CT) scan and positron emission tomography (PET) scan. The stage of breast cancer may be based on the results of the physical exam, biopsy, imaging studies and pathological result from surgery. Pathological staging is based on the findings from the breast mass and nearby lymph nodes. The TNM staging system classifies cancer based on their tumor size (T), lymph node (N) involvement and metastasis (M). The five year relative survival rate for stage I is 100%, stage II 86%, stage III 57% and stage IV is only 20%.

Early detection of breast cancer decreases the mortality rate. Current breast screening guidelines are controversial. Last November, the US Preventive Services Task Force (USPTF) issued revised recommendations for breast cancer screening. The task force recommends biennially screening with mammography for women aged 50 to 74 years. These revised recommendations are at odds with the guidelines of the American Cancer Society, American College of Surgeons, National Cancer Institute and American Congress of Obstetricians and Gynecologists (ACOG). They recommend annually or biennially screening beginning at age 40 to 49 and annually thereafter. Breast self examination may detect palpable breast cancer and may be recommended despite inconclusive data for or against. Clinical breast exam is recommended to all women as part of the physical examination. Women with high relative risk for breast cancer such as carrier of the BRCA1 or BRCA1 mutation may benefit from monthly breast self examination, annual or semiannual clinical breast examination beginning at age 25 to 35 years, and annual mammography beginning at age 25 to 35 years.

Breast cancer research has contributed to improvements in early detection and treatment. Survival rates have increased and death rates have been declining. Life style changes such as regular exercise, moderate consumption of alcohol, maintaining a healthy weight, and limiting postmenopausal hormones may further reduce the rates of breast cancer.

The Tumor Biology of Breast Cancer

Continued from.....pg 1

non-nuclear signaling pathways. One non-nuclear target of ER activation is the PI3K-Akt signaling cascade which is involved in cell proliferation and survival. Mitogen-activated protein kinases (MAPK) which direct various cellular activities including proliferation and survival are also a direct target of non-nuclear ER signaling. The activity of both the PI3K-Akt and MAPK pathways are dysregulated in breast cancers causing cells to proliferate without control and allowing them to evade mechanisms that eradicate abnormal cells. Overall, the ER signaling network is complex and pleiotropic. A more detailed understanding of ER biology is necessary to successfully utilize the ER as a diagnostic and therapeutic tool.

Her2/neu is a different kind of cell receptor. Her2/neu is a cell membrane-bound receptor tyrosine kinase and is also normally involved in the signal transduction pathways leading to cell proliferation and survival. Her2/neu is thought to be an orphan receptor, with none of the epidermal growth factor (EGF) family of ligands able to activate it. However, ErbB receptors dimerize on ligand binding, and Her2/neu is the preferential dimerization partner of other members of the ErbB family. Therefore, it is believed that Her2/neu has no ligand of its own, but acts as a coreceptor, enabling heterodimerization and participation in signal transduction in the absence of a specific activating ligand. Like the hormone receptors, Her2/neu is involved in normal breast growth and development, *i.e,.* stimulating lobulo-alveolar development of mammary glands. ErbB/Her2/neu heterodimers are believed to bind EGF ligands for a longer time, increasing the potency of receptor signaling by these receptor combinations. Her2/neu expression is increased in 20 to 30% of breast cancers, usually by a gene amplification, and may be 100 times that seen in normal cells. This overexpression of Her2/neu can disrupt the normal balance of ErB/Her2/neu partnering favoring more potent heterodimers. This increases proliferative and survival signaling, potentially leading to the formation of more aggressive tumor cells (Yarden, 2001).

So how does this information translate to improved patient care? First, breast cancer is a very heterogeneous disease that includes several specific pathological features and biological behaviors that can be identified by analyzing the expression of molecular markers such as ER, PR and Her2/neu. These expression patterns can be used to provide a molecular classification of breast carcinoma that potentially has prognostic and predictive benefits. Clinical features such as patient age, tumor size, nodal status, tumor grade, margin status, and ER / PR / Her2/neu status are currently used to determine the likelihood for recurrence and to guide subsequent treatment options (Menard et al., 2001; Tang et al., 2009). On an individual basis, the intensity of ER expression in normal epithelium is a risk factor for cancer, correlating to a three-fold increase in risk. In epithelial hyperplasia, the expression of ER in conjunction with other markers such as Ki67 correlate with progression to more severe lesions (Gobbi et al., 2005). It has also been suggested that an increase in ER-positive cells in normal lobules adjacent to tumors is associated with increased risk for invasive breast cancer. Similarly, Her2/neu expression in patients with benign breast lesions correlates to a two-fold increased risk of developing breast cancer (Stark et al., 2000). With respect to lobular neoplasia, Her2/

Continued.....pg 5

is elevated in 25% of lobular carcinoma *in situ* (LCIS) (Mohsin et al., 2005). Finally, in ductal carcinoma *in situ* (DCIS) Her2/neu is associated with DCIS of a higher grade. Therefore, ER and Her2/neu are important molecular markers for precursor and preinvasive stage management of breast cancer (Nofech-Mozes et al., 2005).

ER expression profiling in breast cancer patients is also one of the most important determinants of susceptibility to anti-estrogen therapy, of which Tamoxifen (Taxol) is the most widely used. ER status is commonly determined using antibody tests with approximately 70% of breast cancers found to be ER-positive. In general, ER-positive breast cancer patients respond favorably to Tamoxifen therapy (Hanstein et al., 2004; Katzenellenbogen and Frasor, 2004). However, up to 30% of ER-positive patients can be unresponsive to Tamoxifen. The mechanisms of this resistance are not well understood, but may be related to the non-nuclear signaling of the ER as described above, a variant of the ER is not detected by the antibodies used for testing, or another receptor exists for estrogen (Clarke et al., 2001; Normanno et al., 2009). Therapies against Her2/neu have also been developed and have contributed toward improved survival of breast cancer patients. The most significant advances in Her2/neu-targeted therapies are the use of monoclonal antibodies directed against the extracellular domain of Her2/neu. Trastuzumab (which is the tradename Herceptin) is a humanized antibody introduced into practice for patients with metastatic breast cancer. It is suggested that binding of Her2/neu by Trastuzumab may direct Her2/neu to endocytic vesicles in the cell and lead to its degradation, thus reducing the aberrant signaling from the overexpression of the receptor. However, the response rate for HER-positive breast cancer patients can be as low as 30% and little is known about the mechanisms of resistance (Pohlmann et al., 2009). Studying ER and Her2/neu receptor biology, as well as the mechanisms of resistance to the drugs targeting these receptors are warranted and have the potential to directly impact the future of patient management.

The future of breast cancer management will not only see a greater integration of the current molecular markers such as ER, PR, and Her2/neu status within clinical assessments, but also a translation of the current basic tumor biology research to biomarkers and drug targets. As the details of ER and Her2/neu function and activity are examined, such information may have a direct impact on the classification and treatment of breast cancer. For example, like other receptor tyrosine kinases, Her2/neu requires phosphorylation on certain tyrosine residues to transmit extracellular growth signals to the cell. Determination of the phosphorylation pattern of the Her2/neu receptor at certain tyrosine residues has been shown to correlate to poor survival in ER/PR-positive patients receiving Tamoxifen treatment. Therefore, in hormone receptor-positive breast cancer, determining the phosphorylation status of Her2/neu yields additional prognostic information compared to traditional measuring of Her2/neu expression alone. As such discoveries become more rapid and robust, the responsibility of today's cancer scientists in bridging research and patient management is two-fold. Of course we must strive to understand tumor biology on its fundamental level, but we must also be creative and explore new ways to increase the effectiveness of detection methods and to reduce the complexity and cost of testing. Then, developing biomarker assays like ones measuring Her2/neu phosphorylation or developing drugs that specifically target Her2/neu phosphorylation will bring personalized medicine closer to a reality for the diagnostic laboratory and clinic.

REFERENCES:

1. **Clarke R, Leonessa F, Welch JN, Skaar TC**. 2001. Cellular and molecular pharmacology of antiestrogen action and resistance. *Pharmacol Rev.* **53**(1):25-71.
2. **Dickson RB, Lippman ME.** 1988. Control of human breast cancer by estrogen, growth factors, and oncogenes. *Cancer Treat Res;* **40**:119-65.
3. **Gobbi H, Dupont WD, Parl FF, Schuyler PA, Plummer WD, Olson SJ, Page DL.** 2005. Breast cancer risk associated with estrogen receptor expression in epithelial hyperplasia lacking atypia and adjacent lobular units. *Int J Cancer;* **113**(5):857-9.
4. **Hanstein B, Djahansouzi S, Dall P, Beckmann MW, Bender HG.** 2004. Insights into the molecular biology of the estrogen receptor define novel therapeutic targets for breast cancer. *Eur J Endocrinol*; **150**(3):243-55.
5. **Katzenellenbogen BS, Frasor J.** 2004. Therapeutic targeting in the estrogen receptor hormonal pathway. *Semin Oncol;* **31**(1 Suppl 3):28-38.
6. **Menard S, Fortis S, Castiglioni F, Agresti R, Balsari A**. 2001. HER2 as a prognostic factor in breast cancer. *Oncology;* **61** Suppl 2(67-72.
7. **Mohsin SK, O'Connell P, Allred DC, Libby AL**. 2005. Biomarker profile and genetic abnormalities in lobular carcinoma in situ. *Breast Cancer Res Treat;* **90**(3):249-56.
8. Nofech-Mozes S, Spayne J, Rakovitch E and Hanna W. Prognostic and predictive molecular markers in DCIS: a review. *Adv Anat Pathol* 2005;12(5):256-64.
9. **Normanno N, Morabito A, De Luca A, Piccirillo MC, Gallo M, Maiello MR, Perrone F**. 2009. Target-based therapies in breast cancer: current status and future perspectives. *Endocr Relat Cancer;* **16**(3):675-702.
10. **Pohlmann PR, Mayer IA, Mernaugh R**. 2009. Resistance to Trastuzumab in Breast Cancer. *Clin Cancer Res;* **15**(24):7479-7491.
11. **Stark A, Hulka BS, Joens S, Novotny D, Thor AD, Wold LE, Schell MJ, Melton LJ, 3rd, Liu ET, Conway K**. 2000. HER-2/neu amplification in benign breast disease and the risk of subsequent breast cancer. *J Clin Oncol;* **18**(2):267-74.
12. **Tang P, Skinner KA, Hicks DG**. 2009. Molecular classification of breast carcinomas by immunohistochemical analysis: are we ready? *Diagn Mol Pathol;* **18**(3):125-32.
13. **Yarden Y.** 2001. Biology of HER2 and its importance in breast cancer. *Oncology;* **61** Suppl 2(1-13.

Medical Diagnostic Laboratories, L.L.C.

New Tests Announcement

Now available on the ***OneSwab***®

166 Bacterial Vaginosis Panel by Real-Time PCR [*Atopobium vaginae,* BVAB2*, Gardnerella vaginalis, Megasphaera* species (Type 1 and Type 2*)*]

164 Bacterial Vaginosis Associated Bacteria 2 (BVAB2) by Real-Time PCR

165 *Megasphaera* species (Type 1 and Type 2) by Real-Time PCR

167 *Neisseria gonorrhoeae* by Real-Time PCR (Reflex to Antibiotic Resistance by Bio-Plex Analysis)

Tests Discontinued…

Test Number	Test Name	Date Discontinued
145	*Neisseria gonorrhoeae* by Real-Time PCR (Reflex to Ciprofloxacin Resistance by Pyrosequencing)	June 21, 2010
133	Bacterial Vaginosis Panel by Real-Time PCR *(Bacteroides fragilis, Mobiluncus mulieris* and *M. curtisii, Gardnerella vaginalis)*	September 7, 2010

Tests Replaced…

As of June 21, 2010 requests received for Test 145 shall be replaced with:

167 *Neisseria gonorrhoeae* by Real-Time PCR (Reflex to Antibiotic Resistance by Bio-Plex Analysis)

Medical Diagnostic Laboratories, L.L.C.
2439 Kuser Road
Hamilton, NJ 08690

Presorted
First-Class Mail
U.S. Postage
PAID
Trenton, NJ
Permit 348

Journal Watch
Summaries of recent topical publications in the medical literature
Full Article ..... pg 2

Test Announcement
Tests now available in the clinical laboratory
Full Article ..... pg 5

Research & Development
The Tumor Biology of Breast Cancer
Continued ..... pg 4

The Laboratorian SM

WorldWide Medical Products, Inc.

Item Number - 14001003
Small Vaginal Speculum, Indiv. Wrapped
10/pack - $37.95

Item Number - 14001004
Medium Vaginal Speculum, Indiv. Wrapped
10/pack - $39.95

Item Number - 14001005
Large Vaginal Speculum, Indiv. Wrapped
10/pack - $41.95

Item Number - 71011000
Powder-Free Nitrile Gloves
1000/case - $54.95

Item Number - 71011010
Powder-Free Latex Gloves
1000/case - $48.95

BioExcell

Item Number - 14011002
Exam Table Rolls, Crepe, 21" x 125',
White 12/case - $24.92

Item Number - 14011006
Exam Table Rolls, Smooth, 21" x 125',
White10/pack - $35.76

Item Number - 31031000
3" Cotton Tipped Applicator
1000/box - $3.15

Item Number - 31031001
6" Cotton Tipped Applicator
1000/box - $4.49

Item Number - 31031005
51/2" Tongue Depressors Sterile
1000/case - $32.95

Item Number - 31031006
6" Tongue Depressors Sterile
1000/case - $32.95

41021159	10x75- Borosilicate Disposable Culture Tubes- 1000/cs	34.50
41021160	12x75- Borosilicate Disposable Culture Tubes- 1000/cs	38.75
41021161	13x100- Borosilicate Disposable Culture Tubes- 1000/cs	49.25
41021164	16x125- Borosilicate Disposable Culture Tubes- 1000/cs	79.50
41021165	16x150- Borosilicate Disposable Culture Tubes- 1000/cs	85.50

866.889.WWMP(9967) • FAX: 609.570.1110 • **WWW.WWMPONLINE.COM**
For information on placing a classified advertisement, please email sthompson@mdlab.com.