NEW DIRECTOR OF FINANCE

Martin Lawlor will serve as the next Director of Finance and Administration for the Department of Pathology effective July 1, 2007. Mr. Lawlor received his Bachelor of Science degree in accounting from Loyola Marymount College and is currently the Chief Administrative Officer for the Department of Pathology and Laboratory Medicine at the UCLA School of Medicine. Mr. Lawlor replaces Eugene Napolitan who is retiring after more than 40 years of dedicated service to the Department of Pathology and the University of Michigan.

MICHIGAN MEDICAL GENETICS LAB

The University of Michigan Health System Departments of Pediatrics and Pathology are pleased to announce the opening of the Michigan Medical Genetics Laboratories (MMGL). The new laboratories, which are part of the UMHS Division of Pediatric Genetics, include a Biochemical Genetics Laboratory and a Molecular Genetics Laboratory.

The Biochemical Genetics Laboratory will function to provide rapid, state-of-the-art identification and quantitation of metabolites important in the diagnosis of management of children and adults with inborn errors of metabolism.

Initially, the laboratory will provide analyses of plasma amino acids and urine organic acids, using a Biochrome amino acid analyzer and Agilent GC/MS spectrometer, respectively. These platforms permit the diagnosis of all aminoacidopathies and organic acidemias. They also permit assessment of patient progress and effectiveness of therapy. Some of the familiar diseases in this category include: Urea cycle disorders, organic acidemias, Phenylketonuria (PKU), Maple Syrup Urine Disease, Propionic Acidemia, Tyrosinemia, and approximately 200 other disorders.

Subsequently, a comprehensive menu including plasma carnitine, leukocyte cystine, plasma biotinidase, and other analyses will be offered to enable testing for a wide range of metabolic diseases.

The Molecular Genetics Laboratory will develop and provide cut-edge testing services for a variety of genetic conditions, including rare, orphan and esoteric disorders. The results from these tests will aid in the improved diagnosis and management of children and adults with these disorders. In addition, the lab will work with basic and clinical scientists to design and/or perform assays for clinical research and trials in a CAP/CLIA certified setting.

The Molecular Genetics Laboratory is equipped with a variety of sophisticated instrumentation to detect various types of nucleic acid sequence changes, as well as the accurate quantitation of gene copy number. This instrumentation includes automated fluorescent sequencers, RealTime PCR, a Lumines bhead-array platform, microarray and FISH instrumentation, and liquid handling robots. Initial test offerings will include testing for sensorineural hearing loss (CX26/CX30 gene testing), Prader-Willi and Angelman Syndrome (SNRPN methylation analysis), Noonan Syndrome (PTPN11, SOS1 and KRAS sequencing), Fragile X (repeat copy number analysis), Spinal Muscular Atrophy, Rett Syndrome (MECP2 sequencing), and chromosomal microarray for gene dosage analysis.

Future planned offerings include expanded testing for hearing loss mutations (WFS1, Pendrin/SLC26A4 and mitochondrial mutation analysis), X-linked mental retardation syndromes (ARX gene testing), mutation analysis of ribosy genes (MCI-R sequencing, FTO mutation analysis) and many others. Furthermore, the MMGL will utilize the Biochemical and Molecular Genetics resources and skills acquired within this single organizational entity to establish and provide integrated biochemical and molecular genetics testing for various metabolic disorders.

Added benefits of testing in the MMGL include rapid turn around times and 24/7 availability of laboratory and genetics staff to assist in testing order and result interpretation.

C-Reactive Protein

THE LEAN INFLAMMATION INDICATOR OF CHOICE

Gerald Davis, MPH, MT(ASCP), Senior Clinical Technologist, MLabs Hematology Laboratory

C-reactive protein (CRP) and the Westergren (WEST) erythrocyte sedimentation rate (ESR) are the most widely used tests to measure inflammation and the acute-phase response in the clinical laboratory. These tests are used in diagnosing or evaluating chronic inflammatory disease. Historically the erythrocyte sedimentation rate was introduced to clinical lab medicine first and adopted widely due to ease of measurement, use of a standard specimen container, and relatively low cost. Procedural process improvements and automation of the CRP test have recently made the cost of a CRP test more comparable to that of the WEST.

The WEST is an indirect measurement of plasma proteins initiated by the acute phase inflammatory response. These proteins cause red blood cells to stick together and fall faster when settling in a vertical column of anticoagulated blood under the influence of gravity. Gender, age, pregnancy, temperature, drugs, smoking, anemia, red blood cell size, red blood cell hemoglobin concentration, concentrations of fibrinogen and other plasma proteins can influence the WEST and other erythrocyte sedimentation rate tests. An elevated value remains a nonspecific finding. CRP is a direct measurement of an acute phase protein and is not influenced by the factors listed above for the WEST. In addition, the current CRP test demonstrates better analytical reproducibility than the WEST.

A review of current ordering practices at the University of Michigan Health System reveals that CRP and WEST are ordered together concurrently on the same patient more than 68% of the time. When comparing normal, high and low results, correlation between the two test values is greater than 93% and the outlier study showing discordance is more often than not, evidenced by an increased WEST due to anemia. Since both tests measure the same response, there is little clinical evidence to support ordering both tests concurrently.
CRP and WEST are both used to detect inflammation but are non-specific for any disease condition. Only CRP directly measures an inflammatory protein, is specific for inflammation, and shows a more rapid response to infection and/or inflammation in the initial phases of the acute-phase response (see figure 1 above). CRP is more reproducible, and is a much quicker test to perform than the often lengthy and often compromised WEST. CRP has been shown to be a better indicator of inflammation and is a preferred test for diagnosing and monitoring inflammatory disease states.

REFERENCES


3. Hussain TM, Kim DH. C-Reactive Protein and Erythrocyte Sedimentation Rate, Orthopaedics, 2002, 15: 13-16


The MLabs Chemical Pathology Laboratory performs the C-Reactive Protein assay using an Immunoturbidimetric methodology:

**Collection Instructions:** Collect specimen in an SST tube. Centrifuge, aliquot 0.5 mL (minimum 0.25 mL) of serum into a plastic vial and refrigerate up to 1 week or freeze for longer storage. Excessive hemolysis or lipemic serum are unacceptable.

**Reference Range:** 0.0 - 0.6 mg/dL

Test Updates

New Tests

**IMMUNOGLOBULIN FREE LIGHT CHAINS, SERUM**

Beginning March 6, 2007, Serum Immunoglobulin Free Light Chain testing is offered in-house in the Immunology section of the MLabs Chemistry Laboratory using a nephelometry methodology.

**Collection Instructions:** Collect specimen in a red top or SST tube. Centrifuge, aliquot 0.1 mL (minimum 0.05 mL) of serum into a plastic vial and refrigerate.

**Reference Range:**
- Kappa Free Light Chain: 0.33 - 1.94 mg/dL
- Lambda Free Light Chain: 0.57 - 2.63 mg/dL
- Kappa/Lambda FLC Ratio: 0.26 - 1.65

**MICROSATELLITE INSTABILITY ANALYSIS**

The MLabs Molecular Diagnostics Laboratory began performing Microsatellite Instability (MSI) Analysis by multiplex polymerase chain reaction (PCR) with capillary electrophoresis in-house effective February 1, 2007. Testing is performed Monday – Friday with results available within 48 to 72 hours.

Microsatellite instability (MSI) is the change in length of a microsatellite allele due to either insertion or deletion of repeating units and a failure of the DNA mismatch repair (MMR) system to repair these replication errors. This genomic instability arises in a variety of human neoplasms where tumor cells have a decreased ability to faithfully replicate DNA. MSI is particularly associated with colorectal cancer, where 15-20% of sporadic tumors show MSI, in contrast to the more common chromosomal instability (CIN) phenotype, with MSI status being an independent prognostic indicator. MSI analysis is also clinically useful in identifying patients at increased risk of hereditary nonpolyposis colorectal cancer (HNPCC), Lynch Syndrome, where a germline mutation of a MMR gene causes a familial predisposition to colorectal cancer.

**Collection Instructions:** Both normal and tumor tissue are required for the analysis. Send formalin-fixed paraffin-embedded tissue stored at room temperature. Please include any pertinent clinical history.

**ADENOVIRUS ANTIBODY**

Effective March 22, 2007, due to unavailability of reagents, Mayo Medical Laboratories Adenovirus IgG and IgM assay is no longer available. Requests for this assay are now sent to Focus Diagnostics. Note that the Focus assay includes a total antibody titer without differentiation between IgG and IgM.

**Collection Instructions:** Collect specimen in a red top or SST tube. Centrifuge, aliquot 1 mL (minimum 0.2 mL) of serum into a plastic vial and refrigerate.

**Reference Range:** <1:8. Single titers >=1:64 are indicative of recent or current infection. Titers of 1:8 - 1:32 may be indicative of either past or recent infection, since CF antibody levels persist for only a few months. A four-fold or greater increase in titer between acute and convalescent specimens confirms the diagnosis.

**VITAMIN D, 25-HYDROXY**

Beginning February 21, 2007, 25-hydroxy Vitamin D testing is performed in-house by the MLabs Chemical Pathology Laboratory using a chemiluminescence methodology.

**Collection Instructions:** Collect specimen in a red top or SST tube. Centrifuge, aliquot 0.7 mL of serum into a plastic vial, and freeze. Specimen may be stored refrigerated if received by MLabs within 48 hours of collection.

**Reference Range:** 25-80 ng/mL

**Interpretation:**
- Optimal: 25-80 ng/mL
- Deficiency: < 10 ng/mL
- Toxicity: > 150 ng/mL

Note that the MLabs assay provides a total 25-hydroxy Vitamin D result. There is no clinical significance to fractionation into 25-hydroxy D2 and D3; it is only important that the assay measure both forms equally, which the MLabs assay does.

Test Methodology, Reference Range, and Specimen Handling Changes
Figure 1: CRP and ESR patterns of response (bpacnz better medicine)(1)

CRP and WEST are both used to detect inflammation but are non-specific for any disease condition. Only CRP directly measures an inflammatory protein, is specific for inflammation, and shows a more rapid response to infection and/or inflammation in the initial phases of the acute-phase response (see figure 1 above). CRP is more reproducible, and is a much quicker test to perform than the often lengthy and often compromised WEST. CRP has an improved clinical utility over the ESR.

REFERENCES
3. Hussain TM, Kim DH. C-Reactive Protein and Erythrocyte Sedimentation Rate, Orthopaedics, 2002, 15: 13-16

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Collection Instructions: Collect specimen in an SST tube. Centrifuge, aliquot 0.5 mL (minimum 0.25 mL) of serum into a plastic vial and refrigerate up to 1 week or freeze for longer storage. Excessive hemolysis or lipemic serum are unacceptable.

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Reference Range:
- Kappa Free Light Chain: 0.33 - 1.94 mg/dL
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- Kappa/Lambda FLC Ratio: 0.26 - 1.55

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Collection Instructions: Both normal and tumor tissue are required for the analysis. Send formalin-fixed paraffin-embedded tissue stored at room temperature. Please include any pertinent clinical history.

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Collection Instructions: Collect specimen in a red top or SST tube. Centrifuge, aliquot 0.7 mL of serum into a plastic vial, and freeze. Specimen may be stored refrigerated if received by MLabs within 48 hours of collection.

Reference Range: 25 - 80 ng/mL

Interpretation:
- Optimal: 25 - 80 ng/mL
- Deficiency: < 10 ng/mL
- Toxicity: > 150 ng/mL

Note that the MLabs assay provides a total 25-hydroxy Vitamin D result. There is no clinical significance to fractionation into 25-hydroxy D2 and D3; it is only important that the assay measure both forms equally, which the MLabs assay does.

Test Methodology, Reference Range, and Specimen Handling Changes

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Collection Instructions: Collect specimen in a red top or SST tube. Centrifuge, aliquot 1 mL (minimum 0.2 mL) of serum into a plastic vial and refrigerate.

Reference Range: <1:8. Single titers >=1:64 are indicative of recent or current infection. Titers of 1:8 - 1:32 may be indicative of either past or recent infection, since CF antibody levels persist for only a few months. A four-fold or greater increase in titer between acute and convalescent specimens confirms the diagnosis.
ALPHA-1 ANTRITRYPsin PHENOTYPE
To optimize testing for Alpha-1 Antitrypsin deficiencies, Mayo Medical Laboratories began offering an Alpha-1 Antitrypsin Deficiency Profile (test #89050) effective March 1, 2007. The Alpha-1 Phenotype assay is available as a separately orderable assay (test #26953).

The Alpha-1 Antitrypsin Deficiency Profile features genotype testing and protein quantitation for Alpha-1 Antitrypsin deficiency. Genotyping is a less variable and more specific than phenotype testing. Phenotyping will be performed as a reflex at an additional charge if the genotype and quantitation are discordant.

Collection Instructions: This test requires both whole blood and serum specimens. BLOOD: Collect specimen in a lavender top (EDTA) or yellow top (ACD) tube. Send 5 mL intact whole blood at room temperature. SERUM: Collect specimen in a red top or SST tube. Centrifuge, aliquot 1 mL of serum into a plastic vial and refrigerate.

AMINO ACIDS, QUANTITATIVE, PLASMA
Effective April 25, 2007, Quantitative Plasma Amino Acids are now performed by the MLabs Michigan Medical Genetics Laboratory using a HPLC methodology. This test is used for assessment of metabolic defects resulting in abnormal amino acid metabolism.

Collection Instructions: Collect specimen in a green top tube from a fasting patient (12 hour fast). Centrifuge, aliquot 3 mL (minimum 1 mL) of plasma into plastic vial, and freeze. Whole blood specimens may be stored refrigerated up to 24 hours prior to aliquoting. Include the patient’s family history, clinical condition (asymptomatic or acute), diet, and a list of current medications with the test requisition.

Reference Range: Age specific reference ranges provided with report. An interpretive report will be provided.

DIGOXIN
Effective May 1, 2007, the Digoxin assay reference range and interpretation have been adjusted. This change is at the request of University of Michigan Health System cardiologists due to concern that patients with acute heart failure may be under dosed when using the previous reference range of 0.5 - 1.2 ng/mL. The reference range is now 0.5 - 1.5 ng/mL. The interpretation reads as follows:

Note that in the setting of chronic heart failure, retrospective analysis of data from a randomized clinical trial revealed the following associations between serum digoxin concentrations and all-cause mortality: 0.5 to 0.8 ng/mL, lower risk than placebo 0.9 - 1.1 ng/mL, similar risk to placebo 1.2 and above, higher risk than placebo.

DIHYDROTESTOSTERONE
Mayo Medical Laboratories has resumed the Dihydrotestosterone assay with a new method and reference values effective March 6, 2007.

Test Methodology: Liquid Chromatography Tandem Mass Spectrometry (LC/MS/MS).

Reference Range:

<table>
<thead>
<tr>
<th>Test Methodology:</th>
<th>Liquid Chromatography Tandem Mass Spectrometry (LC/MS/MS).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Males</strong></td>
<td></td>
</tr>
<tr>
<td>Cord blood:</td>
<td>&lt;=100 pg/mL</td>
</tr>
<tr>
<td>&lt;=&lt;6 months:</td>
<td>&lt;=1200 pg/mL</td>
</tr>
<tr>
<td>Tanner Stage</td>
<td>Mean Age</td>
</tr>
<tr>
<td>Stage I</td>
<td>7.1</td>
</tr>
<tr>
<td>Stage II</td>
<td>12.1</td>
</tr>
<tr>
<td>Stage III</td>
<td>13.6</td>
</tr>
<tr>
<td>Stage IV</td>
<td>15.1</td>
</tr>
<tr>
<td>Stage V</td>
<td>19.0</td>
</tr>
<tr>
<td>&gt;=19 years:</td>
<td>11.2 - 855 pg/mL</td>
</tr>
</tbody>
</table>

| Females          |                                                          |
| Cord blood:       | <=50 pg/mL                                               |
| <=<6 months:      | <=1200 pg/mL                                              |
| Tanner Stage      | Mean Age | Value                  |
| Stage I           | 7.1       | <=50 pg/mL             |
| Stage II          | 10.5      | <=50 pg/mL             |
| Stage III         | 11.6      | <=300 pg/mL            |
| Stage IV          | 12.3      | <=300 pg/mL            |
| Stage V           | 14.5      | <=300 pg/mL            |
| >=20-55 years:    | <=300 pg/mL                                              |
| >55 years:        | >=128 pg/mL                                              |

Guidelines for comparing current specimen results with previous results (only results from identical specimen types can be compared):

For low – moderate positives (<20 ng/mL):
- > 5 ng/mL increase in antigen: Probable treatment failure/rerese
- <3 ng/mL decrease in antigen: Possible treatment failure
- > 3 ng/mL decrease in antigen: Probable treatment response

For high positives (>=20 ng/mL):
- > 15% increase in antigen: Probable treatment failure/rerese
- <15% decrease in antigen: Possible treatment failure
- > 15% decrease in antigen: Probable treatment response

HIV TYPE 1 RNA QUANTITATION
The MLabs Microbiology Laboratory began using the Roche Amplicon instrument on April 3, 2007, for specimen processing for the HIV-1 Quantitative Assay and the HIV-1 Ultrasensitive Quantitative Assay. Specimen collection and handling requirements and reference ranges have changed as follows:

**HIV-1 QUANTITATION BY PCR**

Collection Instructions: Collect specimen in lavender top (EDTA) tube. Centrifuge and aliquot at least 1 mL of plasma into a polypropylene plastic vial within 6 hours of collection. Freeze. Specimens submitted in polystyrene tubes are not acceptable.

Note that ACD tubes will no longer be accepted for this test.
Note that in the setting of chronic heart failure, retrospective analysis of data from a randomized clinical trial revealed the following associations between serum digoxin concentrations and all-cause mortality: 0.5 to 0.8 ng/mL, lower risk than placebo; 0.9 - 1.1 ng/mL, similar risk to placebo; 1.2 and above, higher risk than placebo.

DIHYDROTESTOSTERONE
Mayo Medical Laboratories has Resume the Dihydrotestosterone assay with a new method and reference values effective March 6, 2007.

Test Methodology: Liquid Chromatography-Tandem Mass Spectrometry (LC/MS/MS).

Reference Range:

<table>
<thead>
<tr>
<th>Reference Range</th>
<th>Male: Correlation Coefficient</th>
<th>Interpretation</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.6 - 3.9 ng/mL</td>
<td>0.125</td>
<td>Positive, low</td>
<td>Results reported as &lt;0.6 ng/mL are positive but below the lowest calibrator and cannot be quantified.</td>
</tr>
<tr>
<td>4.0 - 19.9 ng/mL</td>
<td>0.6</td>
<td>Positive, moderate</td>
<td>Quantitation is most accurate in this area of the calibration curve.</td>
</tr>
<tr>
<td>20.0 - &gt;39 ng/mL</td>
<td>0.6</td>
<td>Positive, high</td>
<td>Results &gt;39 ng/mL are above the highest calibrator and cannot be quantified. Suggest monitoring antigenemia if antigenuria &gt;29 ng/mL.</td>
</tr>
</tbody>
</table>

Guidelines for comparing current specimen results with previous results (only results from identical specimen types can be compared):

- For low – moderate positives (<20 ng/mL):
  - < 3 ng/mL increase in antigen: Probable treatment failure/relapse
  - >= 3 ng/mL decrease in antigen: Possible treatment failure

- For high positives (>=20 ng/mL):
  - > 15% increase in antigen: Probable treatment failure/relapse
  - <= 15% decrease in antigen: Possible treatment failure
  - > 15% decrease in antigen: Probable treatment response

HIV TYPE 1 RNA QUANTITATION
The MLabs Microbiology Laboratory began using the Roche Ampliciprep instrument on April 3, 2007, for specimen processing for the HIV-1 Quantitative Assay and the HIV-1 Ultrasensitive Quantitative Assay. Specimen collection and handling requirements and reference ranges have changed as follows:

HIV-1 QUANTITATION BY PCR

Collection Instructions: Collect specimen in lavender top (EDTA) tube. Centrifuge and aliquot at least 1 mL of plasma into a polypropylene plastic vial within 6 hours of collection. Freeze. Specimens submitted in polystyrene tubes are not acceptable.

Note that ACD tubes will no longer be accepted for this test.
Questions assumed by Duane W. Newton, Ph.D., D(ABMM), Director, MLabs Clinical Microbiology & Virology Laboratories

**QUESTION:** Hepatitis C Antibody on patient is reported as positive (reactive); RIBA testing is not performed. Hepatitis C Virus RNA Quantitation by PCR is performed and is negative. What, if any testing should the clinician request next?

**ANSWER:** The CDC has reported that samples with high signal/cutoff ratios in Hepatitis C Antibody screening test almost always confirm [MMWR 2003;52(No. RR-3)]. The appropriate ratio to use depends on the assay, so the clinician may be able to determine whether the result is a true positive using this ratio. That said, false positives do occur when testing low prevalence populations. Since most testing is performed on patients with evidence of liver disease, the false positive rate is very low because these assays have very high sensitivities and specificities. However, the significance of a single HCV RNA negative result with a “positive” screen is unknown; in a truly infected individual it does not differentiate between a person who is exhibiting intermittent viremia or who has resolved their infection. So, the main issue is to determine whether this patient is truly infected. MLabs would recommend:

Collect three separate samples for repeat testing:

- SST or redtop to repeat the screen
- SST or redtop for RIBA testing
- SST, red top, or lavender top for HCV RNA testing

Separate specimens are best to rule-out cross contamination or specimen mix-up as a consideration. MLabs would also recommend waiting to conduct this testing until 3-4 weeks have passed from the initial testing in case the patient was in the process of seroconversion.

Reference:
Centers for Disease Control and Prevention. Guidelines for laboratory testing and result reporting of antibody to hepatitis C virus. MMWR 2003;52(No. RR-3).

**QUESTION:** Regarding Herpes simplex Virus (HSV) Types 1 & 2 – what is the clinical significance of knowing the type? Is the patient treatment different?

**ANSWER:** Distinguishing between HSV 1 and 2 can be important because treatment options can vary. It is also important to recognize both HSV-1 and HSV-2 can cause genital herpes. However, recurrences and asymptomatic shedding are more frequent with HSV-2. On the other hand, making a diagnosis of genital herpes purely on clinical grounds is very difficult because not all patients present with obvious ulcerative lesions. Type-specific testing can be accomplished, though, in two ways:

1. Culture of non-crusted lesions is very good at recovering the virus, which can be typed at the request of the ordering physician or
2. Type specific serology has made changes to specimen requirements for their Insulin-Like Growth Factor Binding Protein 3 (IGFBP-3), Serum and IGFBP-3 Growth Panel assays:

Collection Instructions:
Collect a trough specimen in SST tube. Centrifuge, aliquot 0.5 mL serum into a plastic vial and freeze.

Reference Range:
IGFBP-3: 4.0 - 40.0 ng/mL; critical value: 50.0 ng/mL. Low-dose therapeutic range: 1.0 - 2.25 ng/mL.

**MLabs Q & A**

**Collection Instructions:** Collect specimen in lavender top (EDTA) tube. Centrifuge and aliquot at least 1.5 mL of plasma into a polypropylene plastic vial within 6 hours of collection. Freeze. Specimens submitted in polyestrene tubes are not acceptable.

Note that ACD tubes will no longer be accepted for this test.

Reference Range: <50 HIV-1 RNA copies/mL (Log10: -1.70). A result of <50 copies/mL does not rule out the presence of HIV-1 RNA. A positive result indicates the presence of viral RNA, reported as the number of HIV-1 RNA copies/mL of plasma. The linear range of this assay is 50,000 HIV-1 RNA copies/mL. If the actual viral load level is needed, please contact the MLabs Client Services Center. These samples can be assayed using the companion HIV Type 1 RNA Quantitation test (QHIV) which can determine viral load levels up to 750,000 HIV-1 RNA copies/mL. There is an additional charge for this quantitation.

**IGF-1 AND IGFBP-3 GROWTH PANEL AND IGFBP-3 ASSAY**

Effective February 22, 2007, Mayo Medical Laboratories has made changes to specimen requirements for their Insulin-Like Growth Factor Binding Protein 3 (IGFBP-3), Serum and IGF 1 and IGFBP-3 Growth Panel assays:

Collection Instructions:
Collect specimen in a red top or SST tube. Centrifuge, aliquot 0.5 mL serum into a plastic vial and freeze.

**ORGANIC ACIDS, QUALITATIVE, URINE**

Effective April 25, 2007, Qualitative Urine Organic Acids will be performed by the MLabs Michigan Medical Genetics Laboratory using a GCMS methodology. This test is used for diagnosis of suspected organic acidurian.

Collection Instructions:
Collect 10 mL (minimum 5 mL) random urine specimen and refrigerate for up to 1 week or freeze for longer storage. Freeze specimen if multiple collections are needed to reach the minimum volume. Include the patient’s family history, clinical condition (asymptomatic or acute), diet, and a list of current medications with the test requisition.

Reference Range: An interpretive report will be provided.

**PLASMINOGEN ANTIGEN**

Effective March 1, 2007, the MLabs Coagulation Laboratory has discontinued the Plasminogen Antigen assay. Requests for this test will be forwarded to Esoterix Coagulation.

Collection Instructions:
Collect specimen in blue top (citrate) tube. Centrifuge, aliquot 1 mL (minimum 0.5 mL) of plasma into a plastic vial and freeze.

Reference Range: 7.5 – 15.5 mg/dL.

**PROTOPORPHRINS, FRACTIONATION, ERYTHROCYTES**

Effective April 10, 2007, there was a change to the reference range for the erythrocyte protoporphyrin fractionation assay referred to Mayo Medical Laboratories.

Collection Instructions:
Free Protoporphyrin: <20 pg/dL packed cells; Zinc-complexed Protoporphyrin: <50 pg/dL packed cells.

**TRIFLUOPERAZINE, SERUM**

Due to assay technical issues and low utilization, Mayo Medical Laboratories has discontinued performing their Trifluoperazine assay effective February 2, 2007. Requests for this test will be forwarded to MedTox.

**TRIFLUOPERAZINE, SERUM**

Collection Instructions:
Collect a trough specimen in a red or green top tube; do not use SST tube. Centrifuge, aliquot 3 mL serum or plasma into a plastic vial and refrigerate or freeze. Protect specimen from light.

Reference Range: 4.0 - 40.0 ng/mL; critical value: 50.0 ng/mL. Low-dose therapeutic range: 1.0 - 2.25 ng/mL.

**HERPES SIMPLEX VIRUS (HSV) TYPES 1 & 2 – WHAT IS THE CLINICAL SIGNIFICANCE OF KNOWING THE TYPE? IS THE PATIENT TREATMENT DIFFERENT?**

**ANSWER:** Type-specific HSV serologic assays might be useful in the following scenarios: 1) recurrent genital symptoms or atypical symptoms with negative HSV cultures; 2) a clinical diagnosis of genital herpes without laboratory confirmation; and 3) a partner with genital herpes. Some specialists believe that HSV serologic testing should be included in a comprehensive evaluation for STDs among persons with multiple sex partners, HIV infection, and among MSM [men who have sex with men] at increased risk for HIV acquisition. Screening for HSV-1 or HSV-2 in the general population is not indicated.” [MMWR 2005;54(No. RR-12)]

Detection of only HSV-1 antibodies is not helpful because it could indicate asymptomatic oral infection. Since recurrences are more frequent and often more severe with HSV-2, some patients and clinicians opt for episodic treatment regimens rather than episodic treatment regimens. The frequency and dosing are different for each and are described in the STD guidelines from the CDC.

Reference:
**HIV-1 QUANTITATION BY PCR, ULTRASENSITIVE**

**Collection Instructions:** Collect specimen in lavender top (EDTA) tube. Centrifuge and aliquot at least 1.5 mL of plasma into a polypropylene plastic vial within 6 hours of collection. Freeze. Specimens submitted in polystyrene tubes are not acceptable.

Note that ACD tubes will not be accepted for this test.

**Reference Range:** <50 HIV-1 RNA copies/mL (Log10: <1.70). A result of >50 copies/mL does not rule out the presence of HIV-1 RNA. A positive result indicates the presence of viral RNA, reported as the number of HIV-1 RNA copies/mL of plasma. The linear range of this assay is 50 - 100,000 HIV-1 RNA copies/mL (Log10: 1.70 - 4.88).

**Additional Information:** Results above 100,000 HIV-1 RNA copies/mL fall outside the upper limit of the linear range of the assay and will be reported as >100,000 HIV-1 copies/mL detected. If the actual viral load level is needed, please contact the MLabs Client Services Center. These samples can be assayed using the companion HIV Type 1 RNA Quantitation test (QHIV) which can determine viral load levels up to 750,000 HIV-1 RNA copies/mL. There is an additional charge for this quantitation.

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**Collection Instructions:** Collect 10 mL (minimum 5 mL) random urine specimen and refrigerate for up to 1 week or freeze for longer storage. Freeze specimen if multiple collections are needed to reach the minimum volume. Include the patient’s family history, clinical condition (asymptomatic or acute), diet, and a list of current medications with the test requisition.

**FREE PROTOPORPHYRINS, FRACTIONATION, ERYTHROCYTES**

Effective April 10, 2007, there was a change to the reference range for the erythrocyte protoporphyrin fractionation assay referred to Mayo Medical Laboratories.

**Reference Range:** Free Protoporphyrin: <20 pg/dL packed cells; Zinc-complexed Protoporphyrin: <60 pg/dL packed cells.

**TRIFLUOPERAZINE, SERUM**

Due to assay technical issues and low utilization, Mayo Medical Laboratories has discontinued performing their Trifluoperazine assay effective February 2, 2007. Requests for this test will be forwarded to MedTroc.

**Collection Instructions:** Collect a trough specimen in a red or green top tube; do not use SST tube. Centrifuge, aliquot 3 mL serum or plasma into a plastic vial and refrigerate or freeze. Protect specimen from light.

**Reference Range:** 4.0 - 40.0 ng/mL; critical value: 50.0 ng/mL. Low-dose therapeutic range: 1.0 - 2.25 ng/mL.

**PROTOPORPHYRINS, FRACTIONATION, ERYTHROCYTES**

Effective March 1, 2007, the MLabs Coagulation Laboratory has discontinued the Plasminogen Antigen assay. Requests for this test will be forwarded to Esoterix Coagulation.

**Collection Instructions:** Collect specimen in blue top (citrate) tube. Centrifuge, aliquot 1 mL (minimum 0.5 mL) of plasma into a plastic vial and freeze.

**Reference Range:** 7.5 – 15.5 mg/dL

**QUESTION**

Reference Range:

Note that ACD tubes will no longer be accepted for this test.

**Effective March 1, 2007, the MLabs Coagulation Laboratory has discontinued the Plasminogen Antigen assay. Requests for this test will be forwarded to Esoterix Coagulation.**

**ANSWER**

Collect three separate samples for repeat testing:

- **SST or red-top to repeat the screen**
- **SST and red-top for RIBA testing**
- **SST, red-top, or lavender top for HCV RNA testing**

Separate specimens are best to rule-out cross contamination or specimen mix-up as a consideration. MLabs would also recommend waiting to conduct this testing until 3-4 weeks have passed from the initial testing in case the patient was in the process of seroconversion.

**Reference:**

Centers for Disease Control and Prevention. Guidelines for laboratory testing and result reporting of antibody to hepatitis C virus. MMWR 2003;52(No. RR-3).

**QUESTION:**

Regarding Herpes simplex Virus (HSV) Types 1 & 2 – what is the clinical significance of knowing the type? Is the patient treatment different?

**ANSWER:**

Distinguishing between HSV 1 and 2 can be important because treatment options can vary. It is also important to recognize that both HSV-1 and HSV-2 can cause genital herps. However, recurrences and asymptomatic shedding are more frequent with HSV-2. On the other hand, making a diagnosis of genital herpes purely on clinical grounds is very difficult because not all patients present with obvious ulcerative lesions. Type-specific testing can be accomplished, though, in two ways: 1) culture of non-crusted lesions is very good at recovering the virus, which can be typed at the request of the ordering physician or 2) type specific serology testing is also available (sent to Mayo Medical Laboratories); this is different from the HSV 1/2 testing that MLabs offers in-house that does not discriminate between types. The sensitivity of type-specific testing for HSV-2 is 80%+, and since nearly all HSV-2 infections are sexually transmitted, presence of HSV-2 antibodies implies anogenital infection, but MLabs recommends being very careful in how this testing is applied and would never use this testing to resolve issues of marital infidelity for example. The CDC only suggests (not recommended) testing as follows:

- “Type-specific HSV serologic assays might be useful in the following scenarios: 1) recurrent genital symptoms or atypical symptoms with negative HSV cultures, 2) a clinical diagnosis of genital herps without laboratory confirmation, and 3) a partner with genital herpes. Some specialists believe that HSV serologic testing should be included in a comprehensive evaluation for STDs among persons with multiple sex partners, HIV infection, and among MSM [men who have sex with men] at increased risk for HIV acquisition. Screening for HSV-1 or HSV-2 in the general population is not indicated.” [MMWR 2006;55(No. RR-11)].

Detection of only HSV-1 antibodies is not helpful because it could indicate asymptomatic oral infection. Since recurrences are more frequent and often more severe with HSV-2, some patients and clinicians opt for suppressive treatment regimens rather than episodic treatment regimens. The frequency and dosing are different for each and are described in the STD guidelines from the CDC.

**Reference:**

NEW DIRECTOR OF FINANCE

Martin Lawlor will serve as the next Director of Finance and Administration for the Department of Pathology effective July 1, 2007. Mr. Lawlor received his Bachelor of Science degree in accounting from Loyola Marymount College and is currently the Chief Administrative Officer for the Department of Pathology and Laboratory at the UCLA School of Medicine. Mr. Lawlor replaces Eugene Napolitan who is retiring after more than 40 years of dedicated service to the Department of Pathology and the University of Michigan.

MICHIGAN MEDICAL GENETICS LAB

The University of Michigan Health System Departments of Pediatrics and Pathology are pleased to announce the opening of the Michigan Medical Genetics Laboratories (MMGL). The new laboratories, which are part of the UMHS Division of Pediatric Genetics, include a Biochemical Genetics Laboratory and a Molecular Genetics Laboratory.

The Biochemical Genetics Laboratory will function to provide rapid, state-of-the-art identification and quantification of metabolites important in the diagnosis of management of children and adults with inborn errors of metabolism.

Initially, the laboratory will provide analyses of plasma amino acids and urine organic acids, using a Biochrome amino acid analyzer and Agilent GC/MS spectrometer, respectively. These platforms permit the diagnosis of all aminocacidopathies and organic acidaemias. They also permit assessment of patient progress and effectiveness of therapy. Some of the familiar diseases in this category include: Urea cycle disorders, organic acidaemias, Phenylketonuria (PKU), Maple Syrup Urine Disease, Propionic Acidemia, Tyrosinemia, and approximately 200 other disorders.

Subsequently, a comprehensive menu including plasma carnitine, leucovorin cytochrome, plasma biotinidase, and other analyses will be offered to enable testing for a wide range of metabolic diseases.

The Molecular Genetics Laboratory will develop and provide cutting-edge testing services for a variety of genetic conditions, including rare, orphan and esoteric disorders. The results from these tests will aid in the improved diagnosis and management of children and adults with these disorders. In addition, the lab will still work with basic and clinical scientists to design and/or perform assays for clinical research and trials in a CAP/CLIA certified setting.

The Molecular Genetics Laboratory is equipped with a variety of sophisticated instrumentation to detect various types of nucleic acid sequence changes, as well as the accurate quantitation of gene copy number. This instrumentation includes automated fluorescent sequencers, RealTime PCR, a Luminox bead-array platform, microarray and FISH instrumentation, and liquid handling robots. Initial test offerings will include testing for sensorineural hearing loss (CX26, CX30 gene testing), Prader-Willi and Angelman Syndrome (SNRPN methylation analysis), Noonan Syndrome (PTPN1, SOS1 and KRAS sequencing), Fragile X (repeat copy number analysis), Spinal Muscular Atrophy, Rett Syndrome (MECP2 sequencing), and chromosomal microarray for gene dosage analysis.

Future planned offerings include expanded testing for hearing loss mutations (WSFI, Pendrin, SLC26A4 and mitochondrial mutation analysis), X-linked mental retardation syndromes (ARX mutation analysis), mutation analysis of obesity genes (MC4R sequencing, FTO mutation analysis) and many others. Furthermore, the MMGL will utilize the Biochemical and Molecular Genetics resources and skills provided within this single organizational entity to establish and provide integrated biochemical and molecular genetics testing for various metabolic disorders.

Added benefits of testing in the MMGL include rapid turn round times and 24/7 availability of laboratory and genetics staff to assist in test ordering and result interpretation.

** MLabs News **

C-Reactive Protein

THE LEAN INFLAMMATION INDICATOR OF CHOICE

Gerald Davis, MPH, MT/ASCP, Senior Clinical Technology, MLabs Hematology Laboratory

C-reactive protein (CRP) and the Westergren (WEST) erythrocyte sedimentation rate (ESR) are the most widely used tests to measure inflammation and the acute-phase response in the clinical laboratory. These tests are used in diagnosing or evaluating chronic inflammatory disease. Historically the erythrocyte sedimentation rate was introduced to clinical lab medicine first and adopted widely due to ease of measurement, use of a standard specimen container, and relatively low cost. Procedural process improvements and automation of the CRP test have recently made the cost of testing a CRP test more comparable to that of the WEST.

The WEST is an indirect measurement of plasma proteins initiated by the acute phase inflammatory response. These proteins cause red blood cells to stick together and fall faster when settling in a vertical column of anticoagulated blood under the influence of gravity. Gender, age, pregnancy, temperature, drugs, smoking, anemia, red blood cell size, red blood cell hemoglobin concentration, concentrations of fibrinogen and other plasma proteins can influence the WEST and other erythrocyte sedimentation rate tests. An elevated value finding is a nonspecific result. CRP is a direct measurement of an acute phase protein and is not influenced by the factors listed above for WEST. In addition, the current CRP test demonstrates better analytical reproducibility than the WEST.

A review of current ordering practices at the University of Michigan Health System reveals that CRP and WEST are ordered together concurrently on the same patient more than 68% of the time. When comparing normal, high and low results, correlation between the two test values is greater than 93% and the outlier study showing discordance is more often than not, evidenced by an increased WEST due to anemia. Since both tests measure the same response, there is little clinical evidence to support ordering both tests concurrently.

** MLabs News**

NEW DIRECTOR OF FINANCE

For additional clarification concerning any of the information contained in this Spectra, please contact the MLabs Client Services Center at 734-936-2398 (local) or 800-802-7294.

Address correspondence to:

NEW DIRECTOR OF FINANCE

To keep our Spectrum circulation records accurate and up to date, please send any name or address changes, corrections, additions or deletions to the address listed above. Thank you.

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