Brigham and Women's Hospital
Clinical Chemistry Resident Manual 2014

Staff - BWH Clinical Chemistry and Adjunct Faculty

Petr Jarolim, MD, PhD Medical Director, Clinical Chemistry, Laboratory Control, and Ambulatory Care Center Clinical Laboratories, BWH Medical Director, Clinical Chemistry and Laboratory Control, DFCI Director, Biomarker Research/TIMI Clinical Trials Laboratory	Office: Ext 2-6672 Pager: 17196
Stacy Melanson, MD, PhD Associate Medical Director, Clinical Chemistry Medical Director, Phlebotomy, Point-of-Care Testing, and Foxborough Laboratory	Office: Ext 5-7237 Pager: 38396
Athena Kantartzis Petrides, PhD Assistant Medical Director, Clinical Chemistry Director of Toxicology	Office: Ext: 2-6790 Pager: 36398
Gail Kinchla, MT, MBA Technical Director, Clinical Chemistry	Office: Ext 2-7410 Pager: 12142
Margaret Lobo Director, Laboratory Support Services	Office: Ext 2-7416 Pager: 11541
Neal Lindeman, MD Director, Center Advanced Molecular Diagnostics Director, Clinical Pathology Residency Training	Office: 857-307-1539 Pager: 39433
Milenko Tanasijevic, MD, MBA Vice-Chair, Director Clinical Laboratories, BWH and DFCI	Office: 2-6360 Pager: 12193
George Mutter, MD Medical Director, Reproductive Endocrinology	Office: 2-6097 Pager: 11191
Peter Schur, MD Medical Director, Immunology	Office: 2-5468 Pager: 11465
Mark Kellogg, PhD Director, Clinical Chemistry, Children's Hospital	Office: 617-355-7484
Sacha Uljon, MD, PhD	Pager:13143
Zara Herskovits, MD, PhD	Office: 617-800-9279 Pager: 15353

Objective

To learn the medical, technical and managerial aspects of clinical chemistry laboratory operations.

Rotation Responsibilities

Laboratory Rotations - The Clinical Chemistry training program consists of focused training at a number of sites, through which the resident rotates during the course of three months. The schedule should be obtained from clinical pathology chief resident, who will coordinate the schedule with each of the participating laboratories. Any specific questions or changes should be addressed with the director(s) of each rotation (contact numbers are provided in each section). The different rotations are

BWH Clinical Chemistry Laboratory
BWH Toxicology Testing
BWH Laboratory Support Services
BWH Point-of-Care Testing
BWH Reproductive Endocrine Laboratory
BWH Clinical Immunology Laboratory
Pediatric Clinical Chemistry at Children's Hospital

Call – The Chemistry residents should be available by pager during the clinical chemistry rotation. Pages should be answered promptly and accurately. A medical and/or technical director will always be available by pager to assist the resident with any questions (see below). The attending call schedule is posted at the chemistry front desk (617-732-7403) as well as the BWH clinical pathology wikipedia website (https://sites.google.com/a/clinpath.bwh.harvard.edu/clinpathwiki/). Do not hesitate to ask for help. Follow up with technical and clinical staff is necessary to promote education, insure appropriate action and prevent recurrent problems.

Dr. Petr Jarolim	17196
Dr. Stacy Melanson	38396
Dr. Athena Petrides	36398
Dr. Milenko Tanasijevic	12193
Dr. Neal Lindeman	39433

a. Types of Calls: Pages are typically received from either clinicians or technical staff in chemistry regarding test-related problems.
   - Suspicious or questionable results: obtain specific information from the patient care area, work with the technical staff to complete the in-lab investigation, report findings to the house-staff in charge of the patient and assess whether and how the mistake(s) can be avoided in the future.
   - Unusual requests: investigate reference laboratory for rare tests, determine appropriate specimen container, processing and storage information and relay information to the laboratory control (see "BWH Laboratory Support Services")

- Consultation: assist with interpreting results, suggest course(s) of action, expedite reports and communicate with physicians
- Specific examples of chemistry calls can be found on BWH clinical pathology wikipedia website (https://sites.google.com/a/clinpath.bwh.harvard.edu/clinpathwiki/)

b. Pager Coverage: During weekends off and vacation, the resident with the help of the chief resident is responsible for finding pager coverage (see Clinical Pathology Residency Manual).

Serum Protein Profile sign-out – The Chemistry residents are responsible for daily interpretation and reporting of protein electrophoresis and immunofixation results. The residents will receive tutorial training from Dr. Petr Jarolim, Dr. Stacy Melanson, Dr. Zara Herskovits or Dr. Sacha Uljon during the initial portion of the Chemistry rotation, after which the residents will be expected to function independently as diagnostic clinical chemists. Attending faculty are always available for consultation and interpretative guidance. Please read the section below (entitled "BWH Serum Protein Profile") for further information.

Laboratory Inspection – The Chemistry residents will inspect the laboratory for compliance with professional guidelines as determined by the College of American Pathologists (CAP), and prepare a written and/or oral report of their findings. The residents will receive guidance from Dr. Stacy Melanson.

Didactic Sessions - The Chemistry residents are expected to participate in daily didactic/discussion sessions with different members of the Clinical Chemistry Faculty. Some of these sessions require advance reading or problem solving in preparation. Please also read the section below, entitled "Didactic sessions".

Faculty	Day	Time	Location
Jarolim	Tuesday	9-10	Amory 2-215
Melanson	Wednesday	9-10	Amory 2-236a
Petrides	Thursday	10-11	Amory 2-217d
Lindeman	Friday	10-11	Shapiro 5

Conferences –In addition to the daily didactic sessions, the Chemistry residents are expected to participate in the following weekly conferences:

Conference	Day	Time	Location
Call Conference	Monday	9 am	Clinical Lab Conference Room
Path Grand Rounds/ Research Conference	Monday	1:00 pm	Amory 3/BIDMC
Journal Club	Monday	3 pm	Clinical Lab Conference Room
Morning Conference	Wednesday	8 am	Clinical Lab Conference Room
Chemistry Meeting	Wednesday	11 am	Clinical Lab Conference Room
Gross Micro	Thursday	8 am	Pathology Conference Room

CP Conference	Thursday	1 pm	Pathology Conference Room

Teaching

1. *Technologist In-Service or "Tech talks"* – During each month of the rotation, residents should give a 40-minute presentation to the technical staff in clinical chemistry (total of three presentations). The talks should discuss current topics in clinical chemistry and/or interesting cases encountered during the rotation. Please contact Wendy Fuld (Ext 2-5468) to schedule these talks.

2. *Journal Club* – Residents will be responsible for preparing approximately 3 (every month) journal club sessions throughout the rotation. A schedule of these sessions will be received from Dr. Stacy Melanson (617-525-7237). A recent paper related to clinical chemistry should be informally discussed for 30 minutes. The article should be distributed by the Friday prior to the Monday session.

3. *Gross Micro Conference* – Residents may be required to present at the Departmental Gross Micro Conference, as part of the larger requirements of the Clinical Pathology Residency program (see Clinical Pathology Residency Manual).

4. *Medical students* - Residents will be responsible for orienting and teaching any medical students or other visitors rotating through the clinical chemistry laboratory (see Clinical Pathology Residency Manual).

In-depth Projects – Residents are expected to participate in in-depth, longitudinal projects during their rotation. These projects can vary considerably, and could consist of basic investigative science, applied/translational science, development of a new diagnostic method, investigation of existing methods, case investigation and report, or review of an important issue in management or quality control. The Medical Director of Clinical Chemistry will have a list of projects available to the resident at the beginning of the rotation, and the resident may choose among them, or propose a project of his/her own. The projects will be supervised by the clinical chemistry faculty according to their areas of expertise. Longer projects may be continued in a specialized chemistry rotation during the second year of clinical pathology.

Short-term problem solving - In addition to the longitudinal in-depth projects, the residents will be expected to assist with shorter-term projects that may present during the course of the rotation. These projects may require focused efforts of several hours to several days, and will generally be in response to acute, problematic issues in clinical laboratory operation.

Research Projects/Publication Opportunities – There are many ongoing research projects being conducted and published by the Clinical Chemistry attendings. The research interests of the clinical chemistry attendings include, but are not limited to, biomarkers (see Biomarker Research/TIMI Clinical Trials Laboratory below), toxicology, therapeutic drug monitoring, liquid chromatography-tandem mass spectrometry assay

development and laboratory process improvement. Please contact Dr. Petr Jarolim, Dr. Stacy Melanson or Dr. Athena Petrides for more details on ongoing projects and publication opportunities. Some recent studies published by residents rotating through clinical chemistry include:

Melanson SEF, Conrad MJ, **Mosammaparast N**, Jarolim P. Implementation of a highly sensitive cardiac troponin I assay: test volumes, positivity rates and interpretation of results. Clin Chim Acta 2008;395:57-61.

Mahajan VS, Pace CA, Jarolim P: Seroreactivity to HIV antigens in the absence of HIV infection. Clin Chem 2010; 56:1523-6.

Mahajan VS, Jarolim P: How to interpret elevated cardiac troponin levels. Circulation 2011;124:2350-4.

Kelley JM, Watkins J, Jarolim P: Cookie Lover's Crash. Clin Chem 2012;58(6): in press

Kelley JM, Melanson SEF, Snyder ML, Cremers S, Jarolim. Method Comparison of a 25-Hydroxy Vitamin D Enzyme Immunoassay to Liquid Chromatography Tandem Mass Spectrometry. Clin Chem Lab Med 2012;50:1137-8.

Basu SA, Johncilla M, Melanson SE, Jarolim P. Low serum glucose with normal fingerstick glucose. Clin Chem, 2014;60:900.

Biomarker Research/TIMI Clinical Trials Laboratory - The Biomarker Research Laboratory/TIMI Clinical Trials Laboratory (BRL/TCTL) operates within the Department of Pathology, Brigham and Women's Hospital. BRL/TCTL specializes in testing established and novel biomarkers as well as in the storage of serum, plasma, urine and genomic samples for clinical research and clinical trials at all scales from a hundred to a hundred thousand tests or samples.

BRL/TCTL is located in the Thorn Research Building at Brigham and Women's Hospital in Boston, MA. The lab is 2000 sq ft with additional offsite sample storage. The lab is staffed and equipped to process, receive, store and test serum, plasma and urine samples. Testing capabilities include a wide variety of commercially available assays, manual ELISAs and uncommon platforms with cutting edge assays.BRL/TCTL has four full-time Technical Research Assistants and two Medical Technologists as well as a Project Manager and an Administrative Assistant.

Dedicated research instruments include:Roche Cobas c6000 (c501 and e601);Roche Cobas e411; Siemens Advia Centaur;Abbott Architect i2000SR; Stago STA-R Evolution; Two Thermo-Scientific BRAHMS Kryptor Compact analyzers; Singulex Erenna / Tecan EVO 150; Tecan EVO 200 #1 (used for automated ELISA testing); Tecan EVO 200 #2 (used for high throughput automated sample preparation); GrifolsTriturus; Dynex DSX; Bio-Rad Bioplex; Waters ACQUITY TQD (anticipated); and a wide variety of manual ELISA Equipment. Additionally, the lab has storage space for nearly 500,000 cryovials at -80°C.

The Lab uses several systems that have been validated and configured to comply with 21 CFR Part 11 to manage the large quantities of data produced in the lab, ensuring that complete and auditable records are being created which meet the FDA's criteria for acceptance of the electronic data in regulatory submissions. These systems are a Laboratory Information System (LIS) which is a customized version of Orchard

Software's Harvest LIS, a Sample Information Management System (SIMS), FreezerWorks, and a Rees Centron temperature monitoring system.
Second and third year Clinical Pathology residents can rotate through BRL/TCTL. This rotation would typically consist of several sessions with the Lab Director and Project Manager and a participation in a small or medium size study.

General References

Burtis CA, Ashwood ER, Bruns David E. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics, 5th edition
Henry JB. Clinical Diagnosis and Management by Laboratory Methods, 20th edition
Kaplan LA, Pesce AJ and Kazmierzcak SC. Clinical Chemistry: Theory, Analysis and Correlation, 4th edition
McClatchey KD. Clinical Laboratory Medicine, 2nd edition
Jacobs DS, DeMott WR and Oxley DK. Jacobs and DeMott Laboratory Test Handbook, 5th edition
Additional reference books for specific areas are also available from staff members.

Didactic Sessions

During the rotation, residents will interact with each faculty member on a weekly basis. Residents are expected to attend and prepare for all didactic sessions. Sessions will last from 45 minutes to two hours. Unless otherwise noted, the sessions will begin on the first week of the rotation. For scheduling changes, please contact the appropriate faculty member.

Weekly sessions

Session time: Tuesday 9 am
Dr. Petr Jarolim
Location: Amory 2-215
Contact Number: Ext 2-6672

1. Preanalytical Artifacts and Analytical Errors and Interferences
2. Laboratory Automation
3. Instrument Selection and Method Validation
4. Reference Ranges and Quality Control
5. Cardiac Markers
6. Hepatitis and HIV
7. FLM, Fetal fibronectin
8. Lipids
9. Mineral and Bone Metabolism

Session time: Wednesday 9 am
Dr. Stacy Melanson
Location: Amory 2-236a
Contact Number: Ext 5-7237

1. Proficiency Testing/Explanation of the mock CAP survey
2. Introduction to Toxicology
3. Clinical Toxicology I and II
4. Therapeutic Drug Monitoring
5. Liver Function and Pancreatitis
6. Clinical Chemistry of Pregnancy
7. Renal Function
8. Endocrine (Pituitary, Adrenal)
9. Endocrine (Pituitary, Adrenal)
10. Point-of-Care Testing/Evaluation of the mock CAP survey

Session time: Thursday 10 am
Dr. Athena Petrides
Location: Amory 2-217d
Contact Number: Ext 2-6790

1. Diabetes
2. Immunoassays and Spectrophotometric Methods (Analytical Tox I)
3. Chromatographic and Mass Spectrometry-based Methods (Analytical Tox II)
4. Pharmacogenetics and Pharmacokinetics
5. Electrolytes, Acid/Base, Blood Gas, Lactate
6. Thyroid
7. Tumor Markers
8. Iron, B12, Folate

Session time: Friday 10 am
Dr. Neal Lindeman
Location: Dr. Lindeman's office, CAMD, 5th floor
Contact Number: 857-307-1540

1. Specimen Processing
2. Analyte Detection: Optical Methods
3. Analyte Detection: Electrochemical Methods
4. Analyte Detection: Chromatography
5. Analyte Detection: Mass Spectrometry
6. Analyte Detection: Immunoassays
7. Management: Test Validation and Performance Characteristics
8. Management: Costs
9. Management: Revenues
[10. Management: Personnel] extra, if time

Additional Didactic Sessions
Additional lectures and/or didactic sessions occur with Dr. Mutter (BWH reproductive endocrine), Dr. Schur (BWH immunology) and Dr. Kellogg (Childrens hospital) during specialized rotations.

BWH Clinical Chemistry Laboratory

Medical Director: Dr. Petr Jarolim
Technical Director: Gail Kinchla
Duration: 3 months
Location: Clinical Chemistry, Amory 2
Contact Number: Ext 2-6672 (Dr. Petr Jarolim)

Introduction: Residents should meet with each of the supervisors below to learn the technical aspects of the instrumentation and methodologies utilized in the clinical chemistry laboratory. These sessions should be scheduled with Wendy Fuld (2-5468). During these sessions the resident should focus on the following: principles of test methodology, pre-analytical variables, assay interferences and troubleshooting, calibration, delta checks, method validation, quality control procedures, and proficiency testing. These sessions may also be used to perform portions of the mock CAP survey (see Laboratory Inspection).

Supervisor	Instrumentation
Arthur Cassidy	Siemens RapidLab 1265
Maria Fernandes	Siemens Centaur, Cobas 4, Waters Xevo, Beckman AU480
Marcia Niland	Cobas c501/e601
Elizabeth (Beth) Glidden	Helena Spife, Ortho Vitros 3600, Abbott TDx, Waters Xevo, Beckman Access 2, Osmometer
Wendy Fuld	Cobas c501/e601, Porphyria, FFN
Humberto (Bert) Loayza	Night Shift Supervisor
Louis (Erick) Kilham	Weekend Evening and Weekend Senior
Lisa Bernhard	Immunology Supervisor

Supervisor: Arthur Cassidy
Siemens RapidLab 1265 - Blood gas and co-oximeter measurements

Supervisor: Maria Fernandes
Siemens Centaur – Immunoanalyzer performing multiple tests, including anemia tests (folate, B12, ferritin) and tumor markers (CA125, CEA).
Cobas 4 -25 OH-Vitamin D, insulin, TgAb, IgA, IgG, IgM, free light chains
Beckman AU480 – Qualitative urine drug screens for pain management
Waters Xevo – Liquid chromatography tandem mass spectrometery (LC-MS/MS) used for therapeutic drug monitoring (cyclosporine, tacrolimus, sirolimus) and Quantitative toxicology testing (opioids, benzodiazepines)

Supervisor: Marcia Niland and Wendy Fuld

Cobas c501 – Photometric/colorimetric and electrochemical analyzer, performing high volume chemistry tests such as electrolytes (Na, K, Cl, CO_2), enzymes (AST, ALT, GGT, alkaline phosphatase, LDH, lipase, amylase, creatine kinase), lipid/cholesterol profiles, tumor markers (PSA), selected small molecules (creatinine, BUN, uric acid, ammonia, lactate) and proteins (total protein, albumin, globulin, prealbumin, C-reactive protein), therapeutic drug monitoring and drug of abuse screening, and testing of urine and other fluids.

Cobas e601 - Immunoanalyzer performing multiple tests, including cardiac tests (NTproBNP, CK-MB, cTNT), thyroid tests (T3, T4, TSH), anemia tests (iron, UIBC), pregnancy testing (HCG), and other miscellaneous tests (PTH, homocysteine and cortisol)

Thermo Porphyria Assay – Porphobilinogen

TLi$_{IQ}$ fetal fibronectin (fFN) meter – fFN

Supervisor: Elizabeth (Beth) Glidden

Helena Spife - Protein Electrophoresis and Immunofixation (see Serum Protein Profiles)

Ortho Vitros 3600 – Hepatitis A, B and C serologies, HIV

Abbott TDx – Methotrexate

Waters Xevo – Liquid chromatography tandem mass spectrometry (LC-MS/MS) used for therapeutic drug monitoring (cyclosporine, tacrolimus, sirolimus) and Quantitative toxicology testing (opioids, benzodiazepines)

Beckman Access 2 –thyroglobulin

Osmometer – Osmolarity

BWH Serum Protein Profile

Dr. Petr Jarolim, Dr. Stacy Melanson, Dr. Zara Herskovits and Dr. Sacha Uljon
Supervisor: Elizabeth Glidden
Duration: 3 months
Location: Amory 3
Contact Number: 617-525-7237 (Dr. Stacy Melanson)

1. Serum Protein Electrophoresis (SPE)
    a. Principle
    High Resolution SPE is intended for the qualitative separation of protein fractions in serum, using agarose gel electrophoresis.
    Proteins are large molecules composed of covalently linked amino acids. Proteins can be either polar or nonpolar at a given pH depending on electron distributions resulting from covalent or ionic bonding of structural subgroups. In the procedure used in the laboratory, proteins are separated according to their respective electrical charges on agarose gel using both the electrophoretic and electroendosmotic forces present in the system. The separations are stained with a protein sensitive stain.

    b. Indications

SPE should be done when multiple myeloma, Waldenstrom's macroglobulinemia, primary amyloidosis, or a related disorder is suspected. In addition, SPE is indicated in any patient with unexpected weakness or fatigue, anemia, elevation or erythrocyte sedimentation rate, unexplained back pain, osteoporosis, osteolytic lesions or fractures, hypercalcemia, Bence Jones proteinuria, renal insufficiency, or recurrent infections. It is also performed in adults with any clinical evidence that suggests primary amyloidosis, such as unexplained sensorimotor peripheral neuropathy, carpal tunnel syndrome, refractory congestive heart failure, nephritic syndrome or renal insufficiency, or malabsorption.

2. Urine Protein Electrophoresis (UPEP)

    a. Principle
    Same as SPE.

    b. Indications
    Patients with a serum monoclonal protein should have electrophoresis of an aliquot from a 24-hour urine collection. It is essential that all patients with a monoclonal light chain in serum (Bence Jones proteinemia) have electrophoresis of a 24-hour urine specimen.

3. Immunofixation of serum or urine

    a. Principle
    Immunofixation electrophoresis (IFE) is intended for the qualitativeidentification of monoclonal gammopathies in serum or urine using protein electrophoresis and immunofixation procedures. IFE is a two-stage procedure using agarose gel high-resolution electrophoresis in the first stage and immunoprecipitation in the second. Proteins are first resolved by electrophoresis. In the second stage, the soluble antigen and antibody are allowed to react. The resultant antigen-antibody complex(es) may become insoluble (as long as the antibody is in slight excess or near equivalency) and precipitate. The precipitation rate depends on the proportions of the reactants, temperature, salt concentration and the pH of the solution. The unreacted proteins are removed by a washing step and the antigen-antibody complex (which might be visible as a white cloudy band in the unstained gel against a dark background), is visualized by staining. The bands in the protein separation are compared with the precipitin bands obtained with IFE.

    b. Indications
    IFE should be performed when a sharp peak or band is found in the agarose gel or when multiple myeloma, or a related disorder is suspected. IFE is critical for the differentiation of a monoclonal from a polyclonal increase in immunoglobulins. Initially, IFE should be performed with IgG, IgA, IgM, kappa and lambda antisera. In all patients with only a monoclonal light chain

detected, the possibility of IgD and IgE monoclonal proteins must be excluded.

4. CSF Protein Electrophoresis (CSF)
    a. Principle
    Same as SPE

    b. Indications
    The main indication for analysis of protein in CSF is during the diagnostic work-up of Multiple Sclerosis (MS). Oligoclonal bands (more than one band) in the gamma region are observed in approximately 60-80% of patients with MS. The presence of oligoclonal bands in CSF is not specific for MS. Other disorders including inflammatory and infectious (bacterial, viral or parasitic) diseases can be associated with oligoclonal bands. Since a monoclonal protein crosses the blood-brain barrier, one must perform IFE of the serum as well. Rarely, one finds a monoclonal immunoglobulin in the cerebrospinal fluid and none in the serum. In this setting, the possibility of central nervous system lymphoma or, more rarely, plasmacytoma should be considered. Careful cytological examination of the CSF is critical in this situation.

5. Expectations
    Serum protein electrophoresis is performed Monday through Friday during the day shift when requested by a physician.
    New residents are trained for the first 2-3 weeks of the rotation on the sign-out procedure by Dr. Jarolim, Melanson or Uljon. During this time, the resident reviews and comments on cases with the attending on a daily basis. After the training period, residents are expected to sign-out the cases by themselves. Interesting cases and questions about particular cases can be discussed at any time with the attending on-call and/or presented at the PEP rally every 4th Tuesday at 12pm in the clinical laboratory conference room.

6. Recommended Readings
    a. Keren DF, et al. Guidelines for Clinical and Laboratory Evaluation of Patients with Monoclonal Gammopathies. Arch Pathol Lab Med, 1999; 123:106.
    b. Kyle RA. Sequence of Testing for Monoclonal Gammophathies. Arch Pathol Lab Med, 1999; 123:114.
    c. Alexanian R, et al. Differential Diagnosis of Monoclonal Gammopathies. Arch Pathol Lab Med, 1999; 123:108.
    d. Bataille R, et al. Multiple Myeloma. N Eng J Med, 1997; 336:1657.

BWH Mass Spectrometry and Toxicology Testing

Director: Dr. Athena Petrides
Supervisor: Elizabeth Glidden and Maria Fernandes
Duration: 1 week
Location: Amory 2

Contact Number: Ext 2-6790

Overview

The Toxicology Laboratory provides urine toxicology testing for both drugs-of-abuse and agents deployed for pain management, such as chronic opioid therapy. Immunoassay-based drug screens and liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods are deployed for this in-house testing. LC-MS/MS is also used in the BWH chemistry laboratory for immunosuppressant drug monitoring of cyclosporine A, tacrolimus (FK-506) and sirolimus (rapamycin).

Residents will learn the analytical techniques and principles associated with these toxicology tests. The rotation will include instruction from the technologist as they perform these assays. A comprehensive review of opioid and benzodiazepine metabolism will be required as the residents will be expected to interpret patient confirmation test results for these drug classes. The toxicology rotation will be supported by resident didactic sessions describing; Immunoassays and Spectrophotometric Methods (Analytical Tox I) and Chromatographic and Mass Spectrometry-based Methods (Analytical Tox II) prior to the rotation.

Toxicology Testing

Urine toxicology testing for drugs relevant to the management of pain is performed in the BWH chemistry laboratory and our reference laboratory. These tests are ordered by the physician using the name; Pain Toxicology Panel. For most of the drugs included in this panel, their respective presence in a specimen is initially screened for with a competitive homogeneous immunoassay manufactured by Microgenics, Lin-Zhi or Immunalysis. A Beckman AU480 automated platform is used to perform this testing.

If a drug is found to be present in the specimen, at a level above their defined positive/negative concentration threshold or cut-off, an aliquot of the specimen may then be referred to our reference lab (Mayo Clinic) for confirmation testing by a more sensitive and specific method. Gas chromatography-mass spectrometry (GC-MS) or LC-MS/MS are the two analytical platforms typically used for this confirmatory testing.

Opioids and benzodiazepines are an exception to this protocol as specimens are not screened for these drugs by immunoassays; instead all specimens are tested in the BWH chemistry laboratory by LC-MS/MS. A Waters Acquity LC system and a Waters Xevo triple quadruple tandem mass spectrometer are used for this testing. The following metabolites are quantified by our in-house LC-MS/MS urine opioid method: codeine, hydrocodone, hydromorphone, morphine, oxymorphone and oxycodone. 7-amino-clonazepam, α-hydroxy-alprazolam, lorazepam, nordiazepam, oxazepam and temazepam are respectively quantified by our in-house LC-MS/MS urine benzodiazepine method.

The Table below summarizes the testing associated with our Pain Toxicology Panel. The respective positive/negative cut-off concentration for both the immunoassay screens and the confirmation testing is provided. The respective protocols for when and where the confirmatory testing is performed are also included.

Analyte	Immunoassay Screen Positive/Negative Cut-off Concentration (ng/mL)	Confirmations Associated with Pain Toxicology Panel (Testing Lab)	Confirmation Positive/Negative Cut-off Concentration (ng/mL)
6-monoacetylmorphine (6-MAM, primary heroin metabolite)	10 Screens are only performed when the specimen has a morphine level >2000 ng/mL	All positive screen specimens (Mayo Clinic)	5
Amphetamines	1000	All positive screen specimens (Mayo Clinic)	50
Barbiturates	200	By request only (Mayo Clinic)	100
Benzodiazepines	N/A	All specimens (BWH)	50
Buprenorphine	5	All positive screen specimens (Mayo Clinic)	2.5
Cannabinoids	20	All positive screen specimens (Mayo Clinic)	3
Cocaine	150	All positive screen specimens (Mayo Clinic)	50
EDDP (primary methadone metabolite)	100	Only positive specimens with discrepant methadone screen results (Mayo Clinic)	100
Fentanyl	2	All positive screen specimens (Mayo Clinic)	1
Methadone	300	Only positive specimens with discrepant EDDP screen results (Mayo Clinic)	100
Opioids	N/A	All specimens (BWH)	100
Tramadol	200	By request only (Mayo Clinic)	20

Pain Toxicology Panel testing is performed every Tuesday and Thursday on the day-shift. On the following day all opioid and benzodiazepine confirmation results are reviewed by the Technician, Technical Specialist and/or Supervisor. During this review any questionable results are flagged for further examination by a Director prior to their reporting.

Immunosuppressant Drug Monitoring

The risk of post-transplant organ rejection, due to insufficient suppression of the patient's immune system, combined with the narrow therapeutic window for immunosuppressant drugs necessitates that the clinical laboratory perform whole blood immunosuppressant testing daily. Accurate, rapid and precise results are necessary for optimal clinical care both immediately post-transplant and long-term. The immunosuppressant drugs, cyclosporine A, tacrolimus (FK-506) and sirolimus (rapamycin), are currently quantified in the BWH chemistry laboratory by LC-MS/MS. Therapeutic ranges of these agents are based on their concentrations within specimens that are drawn at trough drug levels (i.e., immediately before a scheduled dose). Concentration dependent adverse effects are observed for these therapies and each drugs preferred therapeutic ranges may vary by transplant type, protocol, and co-medications. A Waters Acquity LC system and a Waters Xevo triple quadruple tandem mass spectrometer are deployed for this testing which occurs on the day-shift every day of the week.

BWH Laboratory Support Services

Director: Margaret Lobo
Supervisor: Remia Onario
Duration: 30 minute tour
Location: Amory 2
Contact Number: Ext 2-7416

Lab Control

Lab Control is the central processing area for the Clinical Laboratory; serving the Departments of Chemistry, Hematology, Immunology, and Reproductive Endocrinology. Approximately 3000 sets of patient lab orders are processed each day, comprising, on average, 15,000 tests. Most specimens arrive with a BWH Laboratory Requisition or an order-entry label, in a sealed plastic biohazard bag. Upon arrival, the samples are processed according to individual testing requirements and each collection container (i.e., tube type) is assigned a 7 character alpha-numeric unique specimen identifier (USI) that is used to identify the sample going forward.

The Lab Control staff handles all telephone inquiries, problems with specimens or questions about patient orders. The Department of Lab Control currently employs four "Coordinators"; two on the day shift, one on the evening and one on weekend eve/nights. These individuals are responsible for the smooth flow of work through the lab and its daily operation in the absence of the Supervisor. They are also responsible for responding

to the majority of inquiries into the laboratory and ensuring that all problems are resolved in a timely manner. Coordinators are experienced, senior lab control employees that are available to help with any questions you may have. They are able to cover all workstations and assist with administrative duties and training. They can also be paged 24/7 at beeper 30344. Current Coordinators are:

- Yohannes Gebremichael: day shift
- Shauna Charles-Beye: day shift
- Marie Pierre-Charles: evening shift
- Henry Tham: weekend evening/nights

Additionally, all tests sent out to commercial labs or other hospitals (Reference Testing) are processed in Lab Control. All new tests or tests that are designated "Restricted" require advance approval. When tests in this category are requested, the technician covering send outs or Keith Camara, the Medical Technologist overseeing reference testing, will page or email the Clinical Pathology Resident to approve the test and/or review the appropriateness of the order with the requesting physician. Keith Camara will submit a "New Test Request" form to the ordering clinician. Keith is available to assist you with the approval process and can be reached at 617-525-7954 or via email at kcamara@partners.org The policy covering new and/or restricted sendouts can be found in the following shared drive: \\Sfa17\clinpath$\chemistry.

Most common Reference Laboratories

ARUP	800-242-2787	www.aruplab.com
Athena	800-394-4493	www.athenadiagnostics.com
FOCUS	800-445-4032	www.focustechnologies.com
Genzyme Genetics	508-539-3521	www.genzymegenetics.com
Mayo (Primary Vendor)	800-533-1710	www.mayoreferenceservices.org
Prometheus	888-423-5227	www.prometheuslabs.com
Quest Diagnostics	617-547-8900	www.questdiagnostics.com

BWH Point-of-Care Testing (POCT)

Medical Director: Dr. Stacy Melanson
Director of Operations, Compliance and Quality Assurance: Ellen Goonan
POCT Coordinator: Larisa Fiman and Pamela Wakefield
Duration: 2 hours
Location: Amory 2
Contact Number: Ext. 2-7459 (Larisa Fiman); Ext. 5-7237 (Dr. Stacy Melanson); Ext 3-3587 (Ellen Goonan)

POCT is testing that is performed outside a central laboratory environment, generally nearer to, or at the site of, the patient.

The Point of Care testing program at BWH comprises the Clinical Laboratories, Center for Nursing Excellence, Hospital Compliance, alternate testing sites outside the Clinical Laboratories, and a POCT Advisory Committee.

In the hospital, measurement of blood glucose accounts for the majority of POCT. There are 400 glucose meters (glucometers) in the hospital and ~4000 operators. Other POCT includes coagulation tests, urine tests (microscopy, pregnancy), guaiac for occult blood (stool, gastric fluid), KOH for fungi and rapid strep.

POCT is performed at ambulatory practices; alternate test site laboratories associated with BWH, and patient care areas. The Clinical Laboratories evaluates and determines the kits, test methods and procedures that are used in these areas to ensure that all POCT enhances the quality of patient care and is consistent throughout the institution.

Testing performed outside the Clinical Laboratories is subject to the regulatory requirements of the Joint Commission, the State Department of Public Health, the Clinical Laboratory Improvement Act of 1988 (CLIA), and applicable Clinical Laboratories Administrative Policies and Procedures.

The following is a list of test and methods that are being used at Point of Care Testing locations.

Test	Methods
Blood Glucose	*Precision XceedPro*
Urine Pregnancy	*Sure Vue*
Urinalysis	*Bayer Multistix 8 SG*
Occult Blood	*Hemocult SENSA*
Gastric Occult Blood	*Gastrocult*
H. Pylori	*CLOtest*
PH	*Nitrazine Paper/Amniotest*
Rapid Strep	*Sure-Vue Strep A Test Kit*
Hemoglobin A1C	*Siemens DCA Vantage*
Blood gas	*Siemens Rapidpoint 400*
Activate Clotting Time	*Hemochron Jr and Medtronics ACT plus*
Provider Performed Microscopy	*Wet preps, KOH, fern testing, joint fluid and urine sediment examination*

Each testing area outside the clinical laboratories has a separate CLIA license. The type of testing performed dictates the type of required licensure (Certificate of Waiver, Certificate of Provider Performed Microscopy or Certificate of Accreditation). Laboratory Administration coordinates the application process.

The Clinical Laboratories also maintain a list of all licensed alternate test site laboratories associated with BWH, and the staff serve as advisors to the testing sites in the development and implementation of laboratory policies and procedures.

The Clinical Laboratory Technical Director for QA and Compliance, conducts periodic visits to all testing sites to ensure compliance to regulatory standards. The visits are intended for the purpose of advice and consultation.

The role of the Point of Care Testing Advisory Committee is to recommend improvements to current POCT protocols and procedures, review applications for introduction of new POCT and to recommend meritorious new POCT to the Laboratory Director and Hospital Administration for consideration for implementation.

The contact person in the Point of Care Testing area is Larisa Fiman (extension 2-7459). The residents will be given an overview of the POCT program and will visit a location where the Point of Care Testing is performed.

Residents will learn how quality control, quality assurance and compliance for POCT are evaluated and monitored in the central laboratory with Dr. Stacy Melanson. In addition, training will provide an understanding of the principles of the assays, procedures for introducing new instruments and tracking patient results.

BWH Reproductive Endocrinology Laboratory

Medical Director: Dr. George Mutter
Technical Director: Gail Kinchla
Supervisor: Barbara Pereira
Duration: 1 week
Location: Amory 3
Contact Number: Ext 2-6097, BWH beeper 11191 (Dr. George Mutter)

Overview

The Reproductive Endocrinology Laboratory provides andrology, and steroid hormone testing services. Diagnostic andrology testing includes computerized (image analysis) and manual semen analysis. Therapeutic semen washing for intrauterine insemination (IUI), and non-donor sperm banking is also performed in the laboratory.

Testing Programs

Semen Analysis:

Computer assisted semen analysis (CASA) is part of all routine semen examinations. Specialized procedures include morphologic and histochemical characterization of non-sperm components (inflammatory cells) in whole semen.

Semen Preparation for Intrauterine Insemination (IUI):

Semen inseminated into the uterine cavity must be free of seminal plasma and ideally free of potentially adverse components such as white blood cells and abnormal sperm forms. We use a Percoll step gradient for isolation of sperm from seminal plasma.

Sperm Banking:

Semen is cryopreserved for sole use by the depositor (non-donor). Preliminary trial post-thaw analysis is followed by generation of deposit requirements estimated for the individual. Common indications include anticipated infertility (chemotherapy), absence of the male partner during ART, and pooling of ejaculates which individually are suboptimal.

Hormone assays:

A wide spectrum of hormones relevant to reproductive function are quantitated by immunoassay. These include estrogens (E2, E3), testosterone, progesterone, DHEA, and DHEA-SO_4.

Research Opportunities

Research opportunities involving endometrial carcinogenesis are available in Dr. Mutter's research laboratory. There is also a research program within the diagnostic Reproductive Endocrinology Laboratory. This includes evaluation of new methods for fertility assessment, such as an ongoing study of the ability of computerized morphometric analysis of sperm morphology in predicting IVF outcome.

Trainees may participate in a full range of laboratory activities, within the context of a defined sub project. These activities may include application of molecular biomarkers for early diagnosis of premalignant endometrial disease, or evaluation of new diagnostic modalities in reproductive medicine. Trainees may also work with laboratory staff to learn about routine diagnostic procedures currently in place.

BWH Clinical Immunology Laboratory

Medical Director: Dr. Peter H. Schur
Technical Director: Lisa Bernhard
Duration: 1 week
Location: 221 Longwood Avenue
Contact Number: Ext 2-5468 (Lisa Bernhard); Ext 2-5350 (Dr. Peter Schur)

Immunology Tests

For the following tests, residents should gain a full understanding of the principles and purpose of each test, the methodology, the normal values, the possible test interferents, the interpretation of results and the clinical significance of abnormal results. In addition,

residents should become familiar with immunofluorescence, nephelometry, immunodiffusion, hemolytic and ELISA assays.

Antinuclear Antibodies
Anti-Double Stranded DNA (dsDNA)
Antibodies to Extractable Nuclear Antigens (ENA)
Anti-Scl-70
Lyme Antibodies
CH50 (Total Hemolytic Complement)
Complement Components
Cryoglobulin
Haptoglobin, Ceruloplasmin, Alpha-1-anti-trypsin
BNII
Rheumatoid Factors, anti-CCP, Immunoglobulins and IgG Subclasses
Anti Cardiolipin Antibodies
Allergy Testing
Anti-Beta 2 Glycoprotein
Anti Prothrombin Antibodies
Galactomannan
Syphilis
ANCA

Pediatric Clinical Chemistry at Children's Hospital

Medical Director: Dr. Mark Kellogg
Technical Directors: Tricia Hoover & Terry Law
Duration: 1 week
Location: Childrens Hospital Chemistry Laboratory, Farley Building 7th floor, Room 765
Contact Number: 617-355-7319 (Tricia Hoover) or 617-355-7484 (Dr. Kellogg)

Typical schedule:

Monday:	Observe acylcarnitine and Organic Acid extractions
Tuesday :	Amino acids extraction/readings and organic readings 11am meeting with Dr. Mark Kellogg for lab tour and discussion of pediatric issues 1pm: Weekly metabolism service review (Farley 7 conference room)
Wednesday:	Acylglycine extraction, Atomic absorption spectroscopy
Thursday:	Acylglycine readings
Friday:	Follow up and review of abnormals

NOTE: days begin at 7am. Please plan your schedule accordingly.

Clinical Chemistry Competency

The following is a list of specific knowledge and skills that residents are expected to acquire during the Clinical Chemistry rotation. The competency criteria were developed in 1994 under the auspices of the Conjoint Intersociety Task Force on Clinical Pathology Residency Training (ACLPS, APC, APF, ASCP and CAP).

Analytical/Technical:

1) Be knowledgeable about the influence of pre-analytical factors, analytical variables, specimen variables, effects of age, sex, race, method, timing, or patient diagnosis, etc. on the interpretation of common test results.
2) Know what is involved in developing, validating, implementing, and maintaining a clinical test.
3) Derive and evaluate basic statistics and metrics in chemistry, including:
    a. Linearity, precision, accuracy, sensitivity, specificity
    b. Reference ranges
    c. Bias, concordance, correlation
    d. Sensitivity, specificity, and predictive values;
    e. Quality control charts and metrics
4) Understand and solve problems of analytical devices, sample collection and processing, labor and personnel.
5) Be able to evaluate laboratory instrumentation based on assessment of the technical merits of the analyzer, its capability to meet the needs of the laboratory, and the financial implications.
6) Understand the regulations and requirements of various accrediting agencies and overseers with regards to all aspects of clinical laboratory operations.
7) Analyze and optimize patterns of laboratory utilization, sample flow through, workforce allocation, information management, and resource consumption.
8) Have research experience in Laboratory Medicine including:
    a. How to collect, organize and analyze data;
    b. How to convey results of research
9) Be able to critically evaluate method comparisons in the medical literature.
10) Have specific knowledge of laboratory testing methods, to include:
    a. Clinical Indications and Interpretation
    b. Methodologic Information
        i. Precision and accuracy
        ii. Sensitivity and specificity
        iii. Preanalytical variables
        iv. Sample requirements
        v. Specimen tracking
        vi. Throughput and turnaround time
        vii. Interferences
        viii. Human error
        ix. Quality control and assurance

c. Financial considerations

11) Be familiar with the principles of operation of instruments and analytical methods:
    a. Immunochemistry
    b. Electrophoresis and chromatography
    c. Spectrophotometry
    d. Electrochemistry
    e. Molecular Diagnostics
    f. Mass spectrometry

Consultation:

1) Have a thorough understanding of basic biochemistry and physiology, and their alteration in disease.
2) Be able to advise clinical physicians on proper test strategy and interpretation of laboratory tests for diagnosis of a patient's disorder or monitoring of treatment, including:
    a. Clinical interpretations of selected tests;
    b. Consultative interpretative reporting including integrating multiple laboratory parameters;
    c. Interpretative reporting including clinical or technical context as appropriate;
    d. Establishing laboratory guidelines to identify possible assay or clinical problems and seek opportunities to assist clinicians in evaluation of patients.
3) Be able to serve as a liaison between clinical (medical and nursing) staff and the Clinical Chemistry laboratory for lab-related and test-related problems.
4) Be able to participate in hospital-wide educational activities on laboratory utilization.
5) Be able to set limits for clinical chemistry test utilization where appropriate.
6) Be able to establish priorities for tests and allocate labor and resources appropriately
7) Be facile and comfortable in making educational presentations to varied audiences.
8) Be able to advise clinicians on point-of-care testing.
9) Be adept at evaluating publications related to chemistry.
10) Be able to evaluate appropriate algorithms for testing (AMI, thyroid, etc.).
11) Have a broad understanding of the following topics and the associated tests:
    a. Liver function
    b. Lipids and lipoproteins
    c. Renal function
    d. GI function
    e. Tumor markers
    f. Endocrinology and metabolism
    g. Therapeutic drug monitoring
    h. Pregnancy
    i. Hematology

j. Toxicology