

# **SYLLABUS POSTGRADUATE TRAINING PROGRAM IN CLINICAL BIOCHEMISTRY**

Approved and adopted by the Canadian Academy of Clinical Biochemistry, a body incorporated within the Canadian Society of Clinical Chemists and by the Ordre des chimistes du Québec.

## **REVISED 2013**

### **INTRODUCTION**

#### **Preamble**

This document is a guide:

- 1) To program directors who provide the leadership in organizing local resources for the training of clinical biochemists, and seek to meet and sustain the standards and requirements for Accreditation by the Academy. For a training program to be accredited, it must offer a comprehensive program on the biochemistry and physiology of human disease, with emphasis on the proper use and interpretation of information provided by the clinical chemistry laboratory to the physician. It must also offer training in the technical and analytical components of clinical biochemistry service.
- 2) To postdoctoral trainees, to assist them in their training and as they prepare for the certification examinations of the Academy and of the Ordre des chimistes du Québec. The examinations are based on the syllabus, but may also contain questions on topics pertinent to Clinical Biochemistry beyond the scope of the syllabus.

#### **Required background**

Students entering the post-doctoral training programs must have a PhD (or equivalent degree) in one of the life sciences, or analytical or pure chemistry, demonstrating the ability for independent research and scholarly activity. Knowledge of biochemistry, physiology, analytical chemistry, molecular biology immunology and genetics is required. Exposure to some, or all, of the disciplines of anatomy, pharmacology, pathology, hematology, microbiology, biophysics, and epidemiology and biostatistics is helpful.

#### **General requirements of the training program**

The requirements of an accredited training program in clinical biochemistry are:

- A 24 month program of academic and practical instruction in clinical biochemistry, and associated laboratory specialties as appropriate. Programs should be flexible enough to allow each candidate the opportunity to fill any significant gaps in knowledge or experience, and to explore areas of special interest.
- An adequate number of faculty members with sufficient expertise to provide high quality training in all areas of clinical biochemistry.
- Adequate facilities to ensure that students have access to the laboratories and instruments needed to complete the training requirements.

- Adequate office and study space.
- Adequate access to scholarly material.
- Opportunities for research – basic, applied and developmental.
- Opportunities for clinical experiences, such as rounds, ward visits and patient records.
- Opportunities for students to assume responsibility and leadership in the laboratory, appropriate for their level of training.
- Opportunities to attend local and national meetings.

## **SYLLABUS**

This section describes the theoretical and practical knowledge, and the skills that are required to function as a clinical biochemist. This is based upon the various roles that a clinical biochemist is required to perform in the laboratory and in the wider community. These required competencies are: clinical biochemistry expert, manager, communicator, scholar, collaborator and professional.

### **Clinical Biochemistry Expert**

**Definition:** As experts, clinical biochemists possess the body of scientific and medical knowledge of the field, and integrate this into their practice. This expertise is also reflected in the other required competencies.

#### **Required Competencies**

- Function effectively in directing the laboratory and maintaining high standards of practice.
- Stay familiar and up to date with the newest tests, disease markers and technologies in the field of clinical biochemistry; the lists provided below are not exhaustive.
- Maintain sound knowledge in the theory and operation; and maintenance of instrumentation, methodology, the quality control measures applicable to the modern clinical laboratory, establishment and evaluation of methods, investigation and selection of new instruments and analyzers appropriate for a particular service laboratory.
- Advise the medical staff on the use and interpretation of results and suggest additional chemical diagnostic or monitoring procedures.

#### **Specific Objectives**

### **GENERAL LABORATORY PROCEDURES AND PRINCIPLES**

**Test Ordering:** Methods of generating requests for laboratory tests, requisition forms, computerized order entry, selective requests versus organ system profiles, screening procedures, function tests, pre-arranged batteries of tests or algorithms to answer specific clinical problems.

**Specimen Collection and Processing:** Specimen collection, identification, transport, delivery, preparation and preservation. Patient preparation for tests. Collection from neonates, children and the elderly. Anticoagulants, preservatives and gel separators, coating and cap of collection tubes. Effect of different gel separators and tube type on analysis, especially hormones and drug testing. Regulations and precautions regarding transport of biological specimens.

**Preanalytical Variables and Biological Variations:** Understanding the effect of physiological variables, diurnal and individual variations, rest, exercise, age, sex, fasting, and the effect that drugs may have on test results. Biological variability, reference change values, index of individuality.

**Interference:** Understanding the effects of interference by drugs, hemolysis, lipemia, icterus, heterophilic antibodies and other substances.

**Instruments and Reagents:** Assessing the quality, stability and costs of reagents, commercial "kits", near-patient versus laboratory instruments and analyzers. Laboratory facilities and design: designing laboratories for different types and sizes of institutions, selection of equipment and systems for the laboratory, concepts of workstation consolidation, work flow analysis, concepts in laboratory automation (sample transportation systems, modular systems, and robotics).

**Analytical Evaluation of Methods:** Common errors of laboratory methods, total analytical error and its various components. Calibration techniques: principles of calibration, curve fitting of calibration curve and frequent mathematic models used. Evaluation and comparisons of methods and instruments, precision, accuracy, linearity, analytical measurement range, limits of detection, limit of quantitation. Standardized units (S.I. and conventional). The concepts of definitive and reference methods, standard reference materials, primary and secondary standards, reference materials (international reference materials), reference methods and traceability should be understood.

**Clinical evaluation of methods:** Sensitivity, specificity, ROC curves; likelihood ratios, odds ratios; efficiency. Assessment of the evidence required to bring a test into clinical service. Evidence-based laboratory medicine.

**Establishment of Reference Intervals:** Concept of reference values, clinically significant limits, selection of reference individuals, establishing reference values, therapeutic and toxic levels of drugs.

**Basic Statistics:** Concepts of parametric and non-parametric statistics, probability and significance, standard deviation, confidence limits, t-test, F-test, analysis of variance, Chi-square, linear and other regression, difference plots, non-parametric testing. Cluster discriminant, function and trend analysis.

## **INSTRUMENTATION AND TECHNIQUES**

For those techniques and instruments essential to the operation of a clinical chemistry laboratory, trainees should have both a theoretical and practical knowledge of suitable examples of each technique, including:

- Understand the principles of analysis.
  - Set up, operate and "troubleshoot" the instruments, know their inherent errors and limitations.
  - Conduct experiments under the direction of a supervisor to demonstrate the precision, accuracy, detection limits and linearity of response, range of application.
  - Understand the criteria for instrument selection including cost-effectiveness.
1. **General Techniques:** Volumetric techniques, weighing, filtration, liquid-liquid and solid-phase extractions, partition coefficients, selection and preparation of buffers, freeze drying, dialysis, concentration, desalting, ultra-filtration, preparation of derivatives.
  2. **General Laboratory Equipment:** Centrifuges, water baths, balances, microscopes, pH meters.
  3. **Water Quality Requirements:** Water purification systems, stills, de-ionizers, reverse osmosis, methods of checking the quality of water.
  4. **Spectrophotometers, Reflectometers and Nephelometers:** Molar absorptivity, spectrophotometer signal detector, reflectance, absorbance, transmittance, fluorometry, fluorescence polarization, bioluminescence, chemiluminescence, electroluminescence, nephelometry and turbidimetry, infrared spectrometry, near infrared spectrometry and phosphorescence.
  5. **Ion Specific Electrodes:** Blood gas instruments and co-oximeters, potentiometry, ion-selective electrodes, voltammetry and amperometry, conductometry, coulometry and biosensors.
  6. **Electrophoresis:** Agarose, capillary, microchip, polyacrylamide, capillary zone, isotachopheresis, isoelectric focusing, immunofixation, two dimensional (2D).
  7. **Automated and Semi-automated Analyzers:** Automatic sampling and pipetting devices, immunologic techniques, chemiluminescence, fluorescence polarization, random access and batch analyzers, reagent cassette and thin film analyzers.
  8. **Clinical Enzymology:** Enzyme and isoenzyme measurement methods (fixed incubation and kinetic methods), standardization and optimization of methods, stability of enzymes. Immobilized enzyme assays (biosensors). Enzyme kinetics, enzymes as reagents, coupled enzymatic reactions, zero-order (enzyme) assays, first-order (substrate) assays.

9. **Immunoassay Techniques**: Preparation, assessment and storage of antisera (polyclonal and monoclonal); methods of assessing analytical sensitivity and specificity (cross-reactivity). Standardization issues. Immunoassays: isotopic and non-isotopic, competitive, non-competitive or immunometric, liquid (homogenous) or solid-phase (non-homogenous).  
Radioreceptor assays: Physical principles of stable and radioactive isotopes, counting techniques and their statistical evaluation, units of radioactivity, concepts of half-life, stable isotope enrichment calculations, laboratory hazards, legal requirements for storage and disposal, problems of purity of labeled compounds, storage and specific activity.  
Immunodiffusion, immunoelectrophoresis, immunoblotting and immunofixation, enzyme-linked immunoassays, nephelometric, turbidimetric, and direct and indirect fluorometric immunoassays.
10. **Chromatography**: Planar vs. column, gas vs. liquid, adsorption, affinity, ion-exchange, partition and size-exclusion techniques, direct and reverse phase liquid chromatography, high performance liquid chromatography, solid phase extraction techniques, gas chromatography.  
Mass Spectrometry: GC-MS, LC-MS, LC-MS-MS, MALDI-TOF, SELDI, ICP-MS. Gas chromatographs with FID, NPD and mass detection.
11. **Osmometers**.
12. **Microscopy**: Phase contrast, polarization (urine and biological fluids).
13. **Small Instruments** for satellite and point-of-care testing.
14. **Flowcytometers**. Urine microscopy; cell markers in hematology.

For those instruments and techniques often found in a clinical laboratory, trainees are expected to develop an understanding of the principles and potential uses for the instruments listed below.

1. Flame photometers (emission and atomic absorption).
2. Fluorometers (conventional and time-gated).
3. Refractometers.
4. **Molecular Diagnostics**: Principles and methods of DNA and RNA isolation, purification, polymerase chain reaction (PCR), DNA probes (radioactive and non-radioactive labels), hybridization, restriction fragment length polymorphism (RFLP), blotting techniques, DNA chips/microarrays, sequencing, real time PCR, fluorescent in situ hybridization (FISH), other methods of genomic analysis.
5. **Proteomics and Protein Arrays**: Qualitative and quantitative methods for proteome characterization such as 2-D gel electrophoresis, SELDI-TOF MS, MALDI-TOF MS, protein profiling, fluorescence resonance energy transfer (FRET), and surface plasmon resonance (SPR).

Trainees should understand the principles, scope and economics of the following.

1. Amino-acid analyzer.
2. Ultracentrifuge (lipoprotein).
3. Fluorescent in situ hybridization (FISH).
4. Biosensors.
5. Oncometers.
6. Tonometers.
7. Infra-red spectrophotometers.
8. Nuclear magnetic resonance.
9. Nanotechnology.
10. Techniques using multiplex beads (ex. Bioplex).

## **ORGAN SYSTEM, METABOLIC AND GENETIC DISEASES**

Trainees should acquire a thorough knowledge of basic human biochemistry and physiology and specific biochemical alterations associated with pathophysiology of diseases of all organ systems.

### **Specific Objectives:**

- Become familiar with the testing strategies and laboratory assays for organ systems, metabolic and genetic diseases.
- Understand the principles and limitations of biochemical analysis including sensitivity, specificity and predictive value of the tests.
- Apply these concepts to the interpretation of results in relation to pathophysiology of disease to clinical application and cost benefits.
- Understand the principles and application of evidence-based medicine in test implementation and patient evaluation.

### **Fluid and Electrolyte Disorders**

#### **Concepts:**

- Extracellular and intracellular fluid volumes
- Hormonal control of fluid and electrolyte balance (renin, angiotensin, aldosterone, ADH)
- Principles of correcting fluid losses
- Clinical assessment of ECF volume

#### **Causes, Clinical Signs/Symptoms of and Laboratory Findings Consistent with and/or Used in the Management of:**

- Hyponatremia and pseudohyponatremia (electrolyte exclusion effect) :
- Hypernatremia
- Hypokalemia
- Hyperkalemia and pseudohyperkalemia
- SIADH
- ECF volume loss
- Diabetes insipidus
- Dehydration
- Shock

#### **Specific Laboratory Tests:**

- Electrolytes (sodium, potassium, chloride)
- Serum and urine osmolality
- Urine and fecal electrolytes

### **Acid-Base and Respiratory Function**

#### **Concepts:**

- Henderson-Hasselbach equation
- Control of respiration
- Compensation for acidosis and alkalosis
- Systematic approach to investigating acid-base disturbances
- Hemoglobin dissociation curves and limitations of calculated oxygen saturation
- Osmolal gap
- Anion gap (elevated and decreased)

#### **Causes, Clinical Signs/Symptoms of and Laboratory Findings Consistent with and/or Used in the Management of:**

- Metabolic acidosis
- Metabolic alkalosis

- Respiratory acidosis
- Respiratory alkalosis
- Carbon monoxide poisoning
- Renal tubular acidosis

**Specific Laboratory Tests:**

- Blood gas measurements
- Co-oximetry (carboxyhemoglobin and methemoglobin)
- Calculated blood gas parameters – limitations
- Ketones (urine and serum)
- Lactate
- Alcohols (ethanol, methanol, ethylene glycol, isopropanol)
- Salicylate
- Anion gap
- Osmolar gap
- Osmolality
- Urine anion gap

**Disorders of Kidney and Urinary Tract**

**Concepts:**

- Clearance (creatinine, cystatin C, inulin)
- eGFR calculations
- Creatinine standardization
- Steady state
- Proteinuria; glomerular permeability, tubular proteinuria
- Formation of renal calculi
- Endocrine functions of the kidney
- Hemodialysis
- Peritoneal dialysis
- Transplant biochemistry

**Causes, Clinical Signs/Symptoms of and Laboratory Findings Consistent with and/or Used in the Management of:**

- Chronic kidney disease
- Acute kidney injury
- Renal tubular acidosis
- Uremia
- Glomerulonephritis
- Nephritic syndrome
- Nephrotic syndrome

**Specific Laboratory Tests:**

- Creatinine (serum and urine)
- Urea and urea kinetics
- Urine dip stick analysis
- Urine microscopic analysis
- Examination and identification of renal calculi
- Urine albumin
- Measurement of immunosuppressant (cyclosporine, tacrolimus, sirolimus)
- Cystatin C
- Urine anion gap

- B-2 microglobulin
- Phosphate, calcium and magnesium

### **Cardiovascular Disorders and Hypertension**

#### **Concepts:**

- Acute coronary syndrome
- Myocardial infarction

#### **Causes, Clinical Signs/Symptoms of and Laboratory Findings Consistent with and/or Used in the Management of:**

- Myocardial infarction
- Stable angina
- Unstable angina
- Atherosclerosis
- Congestive heart failure
- Hypertension

#### **Specific Laboratory Tests:**

- Troponin and high-sensitivity troponin
- High-sensitivity CRP
- Natriuretic peptides

### **Hematologic Disorders**

#### **Concepts:**

- Iron absorption, transport and storage
- Heme biosynthesis
- Iron deficiency
- Iron overload
- Heme metabolism

#### **Causes, Clinical Signs/Symptoms of and Laboratory Findings Consistent with and/or Used in the Management of:**

- Iron deficient anemia
- Hemochromatosis
- Thalassemia
- Hemoglobinopathies
- Glucose-6-phosphate dehydrogenase (G6PD) deficiency
- Acute porphyria
- Chronic porphyria
- Intravascular hemolysis

#### **Specific Laboratory Tests:**

- Iron
- Total iron binding capacity
- Transferrin
- Transferrin saturation
- Ferritin
- Soluble transferrin receptor
- Complete blood count
- Delta-aminolevulinic acid (ALA)
- Porphobilinogen (PBG)
- Porphyrins

- Hemoglobin and hemoglobin forms
- G6PD
- Haptoglobin
- Hemopexin

### **Hepatobiliary Disorders**

#### **Concepts:**

- Origin, metabolism and transport of bilirubin
- Liver cirrhosis
- Chronic hepatitis
- Acute hepatitis
- Liver function – metabolic, biochemical
- Exudates vs. transudates

#### **Causes, Clinical Signs/Symptoms of and Laboratory Findings Consistent with and/or Used in the Management of:**

- Acute hepatitis
- Chronic hepatitis
- Cirrhosis
- Elevated bilirubin levels: conjugated, unconjugated and total
- Elevated neonatal bilirubin levels
- Biliary damage and dysfunction

#### **Specific Laboratory Tests:**

- Bilirubin – conjugated, unconjugated, delta, total, transcutaneous
- Liver enzymes: ALT, AST, LD
- ALP
- GGT
- AFP
- Ceruloplasmin
- Albumin (blood and ascites)
- Criteria for classifying fluids as exudates or transudates
- PT-INR
- Hepatitis serology
- Ammonia
- Bile acids
- Iron

### **Gastrointestinal and Pancreatic Disorders**

#### **Concepts:**

- Acute and chronic pancreatitis
- Vitamin B12 absorption
- Causes of gastric ulcer
- Etiology of Celiac disease
- Etiology of Crohn's disease
- Intestinal absorption of proteins, fats and carbohydrates
- Endocrine and exocrine functions of the pancreas
- Neuroendocrine Tumors



**Causes, Clinical Signs/Symptoms of and Laboratory Findings Consistent with and/or Used in the Management of:**

- Acute and chronic pancreatitis
- Pernicious anemia
- Zollinger-Ellison syndrome
- *H. pylori* infection
- Neuroendocrine tumors
- Colon cancer
- Intestinal malabsorption, lactose intolerance and Celiac disease

**Specific Laboratory Tests:**

- Amylase and macroamylase
- Lipase
- Elastase
- <sup>14</sup>CO<sub>2</sub> urea breath test for *H. pylori*
- Transglutaminase autoantibodies
- Gliadin autoantibodies
- Fecal calprotectin
- Fecal occult blood
- Hydrogen breath test for lactose intolerance
- Xylose absorption test
- Carcinoembryonic antigen
- Serotonin and 5 HIAA
- Chromogranin A
- CA 19-9

**Endocrine Disorders**

**Concepts:**

- Hypothalamic-pituitary axis
  - Hypothalamic hormones
  - Anterior pituitary hormones
  - Posterior pituitary hormones
  - Inhibitory hormones
- Communication between pituitary and hypothalamus – anterior vs. posterior
- Stimulation tests
- Suppression tests
- Steroid biosynthesis pathway
- Renin-angiotensinogen-aldosterone pathway
- Hirsutism and virilization
- Primary vs. secondary causes

**Causes, Clinical Signs/Symptoms of and Laboratory Findings Consistent with and/or Used in the Management of:**

- Acromegaly/gigantism
- Growth hormone deficiency
- Cushing's syndrome and Cushing's disease
- Addison's syndrome
- Adrenal insufficiency
- Hyperaldosteronism
- Polycystic ovarian syndrome
- Premature ovarian failure
- Congenital adrenal hyperplasia

- Hypothyroidism
- Hyperthyroidism
- Thyroid cancer
- Pheochromocytoma
- Male infertility
- Female infertility
- Hyperprolactinemia
- Sheehan's syndrome

**Specific Laboratory Tests:**

- Growth hormone
- Insulin-like growth factor 1 (IGF-1)
- Growth hormone suppression test (OGTT)
- Cortisol – serum, urine, salivary
- Dexamethasone suppression test
- ACTH
- Aldosterone, renin and ratio
- Angiotensin converting enzyme (ACE)
- LH
- FSH
- Androstenedione
- DHEAS
- Testosterone – total, free, bioavailable
- SHBG
- Estradiol
- Progesterone
- 17 hydroxyprogesterone
- TSH
- Total T3, total T4
- Free T3, free T4
- Anti-thyroid peroxidase antibodies
- TSH receptor antibodies
- Catecholamines (plasma and urine)
- Metanephrines (plasma and urine)
- Prolactin and macroprolactin
- ADH
- Thyroglobulin, anti-thyroglobulin antibodies

**Musculoskeletal Arthritic and Rheumatic Disorders**

**Concepts:**

- Autoimmune testing – limitations
- Muscle function

**Causes, Clinical Signs/Symptoms of and Laboratory Findings Consistent with and/or Used in the Management of:**

- Osteoarthritis
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Vasculitis
- Goodpasture's syndrome
- Rhabdomyolitis

**Specific Laboratory Tests:**

- Rheumatoid factor
- Anti-CCP antibodies
- Anti-ds DNA
- Anti-nuclear antibodies (ANA and specific antibodies SSA, SSB, Sm, RNP)
- Anti neutrophilic cytoplasmic antibodies (ANCA)
- Serum creatine kinase

**Neurologic and Psychiatric Disorders****Concepts:**

- Paraneoplastic syndromes
- Blood brain barrier

**Causes, Clinical Signs/Symptoms of and Laboratory Findings Consistent with and/or Used in the Management of:**

- Multiple sclerosis
- Paraneoplastic syndrome
- Meningitis
- Myasthenia gravis
- Alzheimer's disease
- Epilepsy
- Acute porphyria's

**Specific Laboratory Tests:**

- Paraneoplastic antibodies
- Anti-Hu, Anti-Yo antibodies
- CSF glucose
- CSF protein
- CSF beta-2-transferrin in rhinorrhea and otorrhea (fistula)
- Examination of synovial fluid
- Oligoclonal banding (isoelectric focusing)
- Anti-acetylcholine receptor antibodies
- Porphyrins (urine, feces, serum)
- Porphobilinogen (PBG)
- Aminolevulinic acid (ALA)

**Diabetes Mellitus****Concepts:**

- Etiology of Type I vs. Type 2 vs. gestational diabetes
- HbA1c standardization
- Complications of diabetes (microvascular, macrovascular)
- Self-monitoring of blood glucose
- Diabetic ketoacidosis
- Non-ketotic hyperosmolar coma
- CDA Guidelines – screening, diagnosis and monitoring of diabetes

**Causes, Clinical Signs/Symptoms of and Laboratory Findings Consistent with and/or Used in the Management of:**

- Type 1 diabetes
- Type 2 diabetes
- Gestational diabetes

- Diabetic ketoacidosis
- Non-ketotic hyperosmolar coma
- Hypoglycemia
- Metabolic syndrome

**Specific Laboratory Tests:**

- HbA1c
- Glucose
- Glucose challenge and glucose tolerance tests
- Ketones, ( $\beta$ -hydroxy butyrate)
- Insulin
- C-peptide
- Glucagon
- Microalbumin
- Fructosamine
- Anti-glutamic acid decarboxylase (GAD) antibodies

**Lipids and Lipoprotein Disorders**

**Concepts:**

- Lipid absorption, transport and metabolism
- Lipoprotein metabolism: endogenous and exogenous pathways
- Fatty acid transport and oxidation
- Apolipoproteins: functions, receptors (e.g. LDL-R)
- Cardiovascular disease risk calculation and evaluation: Framingham risk score, Reynolds risk score, Canadian Cardiovascular Society guidelines, cost-effectiveness of lipid screening strategies.

**Causes, Clinical Signs/Symptoms of and Laboratory Findings Consistent with and/or Used in the Management of:**

- Atherosclerosis
- Hyperlipidemia
  - Inherited disorders
  - Non-inherited disorders
- Hypercholesterolemia
- Metabolic syndrome

**Specific Laboratory Tests:**

- Total cholesterol
- Triglycerides
- LDL cholesterol – direct and calculated methods
- HDL cholesterol
- Non-HDL cholesterol (calculated)
- Apolipoprotein A and B
- Lp(a)
- High sensitive CRP
- Genotyping of ApoE, LDL receptor and LPL
- Lipoprotein ultracentrifugation

## **Calcium, Phosphorus, Magnesium, Parathyroid and Bone Diseases**

### **Concepts:**

- Regulation of calcium and phosphate levels
- Metabolism of vitamin D
- Markers of bone resorption and bone formation
- Primary versus secondary hyper/hypo calcemia
- Circulating forms of calcium

### **Causes, Clinical Signs/Symptoms of and Laboratory Findings Consistent with and/or Used in the Management of:**

- Hypocalcemia
- Hypercalcemia
- Hyperparathyroidism
- Hypoparathyroidism
- Pseudohypoparathyroidism
- Osteoporosis
- Osteogenesis imperfecta
- Paget's disease
- Hypophosphatemia
- Hyperphosphatemia
- Hypermagnesemia
- Hypomagnesemia

### **Specific Laboratory Tests:**

- PTH
- PTHrp
- Calcium – total and ionized
- Phosphate
- 25 hydroxy vitamin D
- 1, 25 di-hydroxy vitamin D
- Magnesium
- Osteocalcin
- Pyridinolines
- Bone-specific ALP
- C- and N-telopeptides

## **Proteins, Disorders of Protein Metabolism and Nutrition**

### **Concepts:**

- Serum fractions by electrophoresis
- Acute phase reaction
- Total parenteral nutrition and monitoring
- Monitoring nutritional status
- Monoclonal gammopathies

### **Causes, Clinical Signs/Symptoms of and Laboratory Findings Consistent with and/or Used in the Management of:**

- Multiple myeloma
  - Smoldering
  - Symptomatic
- Light chain myeloma
- Amyloidosis
- MGUS

- Waldenström's macroglobulinemia
- Immunodeficiency (hypogammaglobulinemia, IgA deficiency, etc.)
- Acute inflammation
- Alpha-1-antitrypsin deficiency
- Malnutrition
- Positive or negative nitrogen balance
- Cryoglobulinemia
- Lymphoma

**Specific Laboratory Tests:**

- Serum protein electrophoresis
- Urine protein electrophoresis
- Capillary electrophoresis
- Immunofixation electrophoresis
- Immunosubstraction
- Serum free light chains
- Immunoglobulins (IgA, IgG, IgM, IgE, IgD)
- CRP
- Albumin
- Prealbumin
- Haptoglobin
- B-2-microglobulin

**Disorders of Purine and Pyrimidine Metabolism**

**Causes, Clinical Signs/Symptoms of and Laboratory Findings Consistent with and/or Used in the Management of:**

- Gout
- Uricemia
- Renal calculi - types
- Lesch-Nyhan syndrome

**Specific Laboratory Tests:**

- Uric acid
- Analysis of renal calculi

**Inherited Disorders of Metabolism**

**Concepts:**

- Diseases appropriate for newborn screening – characteristics
- Challenges with newborn screening
- Newborn screening process

**Causes, Clinical Signs/Symptoms of and Laboratory Findings Consistent with and/or Used in the Management of:**

- Phenylketonuria
- Congenital hypothyroidism
- Tyrosinemia
- Maple syrup urine disease
- Homocystinuria
- Fatty acid oxidation disorders: short, medium, long and very long chain
- Lysosomal disease, glycogen storage diseases: lipidoses, hexosaminidases, Fabry disease

- Enzyme deficiencies: biotinidase, galactokinase
- Hemoglobinopathies
- Cystic fibrosis

**Specific Laboratory Tests:**

- Amino acids
- Organic acids
- Acylcarnitines
- Specific enzyme testing (e.g., biotinidase, galactokinase)
- Alpha-1-antitrypsin genotyping
- Hemoglobin electrophoresis
- Immunoreactive trypsinogen
- Sweat chloride

**Pregnancy, Prenatal Diagnosis, Assessment and Monitoring of High Risk Pregnancy**

**Concepts:**

- Maternal serum screening – purpose, limitations, screen vs. definitive testing
  - First trimester screening
  - Second trimester screening
  - Integrated screening
- Changes in analyte levels throughout pregnancy
  - Multiples of the median
- Fetal lung maturity
- Biochemical, hematological and endocrine changes during pregnancy
- Rh isoimmunization
- hCG forms
- hCG doubling time
- Premature rupture of membranes and pre-term labor

**Causes, Clinical Signs/Symptoms of and Laboratory Findings Consistent with and/or Used in the Management of:**

- Trisomy 21, 18 and 13
- Open neural tube defects
- Ectopic pregnancy
- Pre-eclampsia, HELLP syndrome
- Gestational diabetes
- Rh isoimmunization
- Molar pregnancy
- Trophoblastic disease
- Choriocarcinoma

**Specific Laboratory Tests:**

- hCG
- PAPP
- Unconjugated estriol
- Inhibin A
- AFP
- Tests using amniotic fluid
  - Acetylcholinesterase
  - AFP
  - Karyotype
  - Bilirubin – absorbance at 450 nm

- Methods for assessing fetal lung maturity
- Fetal fibronectin

### **Immune System**

#### **Concepts:**

- Monoclonal vs. polyclonal antibodies
- Complement system
- HLA system
- Transplant biochemistry
- Allergens

#### **Causes, Clinical Signs/Symptoms of and Laboratory Findings Consistent with and/or Used in the Management of:**

- Viral hepatitis – A, B, C
- HIV infection, AIDS
- Complement disorders

#### **Specific Laboratory Tests:**

- Complement C3, C4
- CH50
- C1 esterase inhibitor
- Hepatitis A, B and C serology
- HIV serology
- IgE allergen specific tests

### **Molecular Diagnosis of Genetic Defects**

#### **Concepts:**

- DNA sequencing, mRNA amplification
- Restriction enzyme digests
- Restriction fragment length polymorphism (RFLP)
- Polymerase chain reaction (PCR)
- Quantitative RT-PCR
- Southern blotting
- DNA melting temperature
- Reverse transcription

#### **Causes, Clinical Signs/Symptoms of and Laboratory Findings Consistent with and/or Used in the Management of:**

- Cystic fibrosis
- Hemochromatosis
- Thalassemia
- Wilson's Disease
- Sickle cell disease
- Inherited cancers

#### **Specific Laboratory Tests:**

- Sweat chloride
- Hemoglobin electrophoresis
- Ceruloplasmin
- Serum/urine copper
- HFE, CFTR genotyping



## **Biochemical Aspects of Oncology**

### **Concepts:**

- Characteristics of an ideal tumor marker
- Uses of tumor markers: screening, diagnosis, prognosis, monitoring, recurrence
- Uses and limitations of current tumor markers

### **Specific Laboratory Tests:**

- PTHrp
- HER2/Neu
- CEA
- AFP
- hCG
- PSA (total and free)
- CA 19-9
- CA 15-3
- CA 125
- ALP isoenzymes
- LD isoenzymes
- Calcitonin
- Thyroglobulin, anti-thyroglobulin antibodies

## **Pharmacology/Toxicology/Therapeutic Drug Monitoring**

### **Concepts:**

- Pharmacokinetics
  - Compliance
  - Bioavailability
  - Absorption
  - Distribution
  - Metabolism
  - Excretion
- Pharmacodynamics
- Pharmacogenetics
- Drugs appropriate for TDM
- Free drugs
- Steady state
- Peak vs. trough drug levels
- Drug screens vs. confirmatory tests for drugs of abuse
- Anti-epileptic drugs
- Anti-psychotic drugs
- Cardioactive drugs
- Antibiotics
- Antidepressants
- Lithium
- Methotrexate and rescue
- Thiopurines
- Immunosuppressants
- Carbon monoxide poisoning
- Common drugs of abuse

**Causes, Clinical Signs/Symptoms of and Laboratory Findings Consistent with and/or Used in the Management of:**

- Acetaminophen toxicity
- Salicylate toxicity
- Ethanol, alcohol toxicity
- Carbon monoxide poisoning
- Organophosphate poisoning

**Specific Laboratory Tests:**

- Acetaminophen
- Salicylates
- Ethanol
- Methanol
- Ethylene glycol
- Isopropanol
- Osmolality
- Cyclosporine
- Tacrolimus
- Sirolimus
- Mycophenolic acid (MPA)
- Carbon monoxide – carboxyhemoglobin
- Cholinesterase and pseudocholinesterase
- Point-of-care drug screens – limitations

**Vitamins, Trace Elements and Environmental Toxins**

**Concepts:**

- Essential and non-essential metals
- Toxic and non-toxic metals
- Vitamin B12 absorption, metabolism and function
- Folate metabolism and function
- General understanding of vitamin A, carotene, vitamin E, vitamin K, vitamin B6, thiamine, riboflavin, biotin, niacin and vitamin C function and metabolism

**Causes, Clinical Signs/Symptoms of and Laboratory Findings Consistent with and/or Used in the Management of:**

- Vitamin B12 deficiency
- Folate deficiency
- Copper deficiency/excess
- Lead poisoning
- Mercury poisoning
- Iron poisoning
- Cadmium poisoning
- Vitamin deficiencies

**Specific Laboratory Tests:**

- Vitamin B12
- Folate
- Homocysteine
- Methylmalonic Acid
- Intrinsic factor antibody
- Serum/urinary copper

- Ceruloplasmin
- Serum/urine lead
- Delta amino levulinic acid (ALA)
- Serum/urinary mercury
- Serum/urinary iron
- Serum/urinary cadmium
- Other vitamins

### **Pediatric Clinical Biochemistry**

#### **Concepts:**

- Sample volume and collection issues
- Issues with capillary specimens
- How to collect heel prick samples
- Pediatric reference intervals – dynamic changes with growth, development and puberty

### **Geriatric Clinical Biochemistry**

#### **Concepts:**

- Changes in analyte values with aging

### **Hematology**

#### **Concepts:**

- General knowledge of blood components
  - Major cell types
  - Blood formed elements
- General knowledge of coagulation

#### **Specific Laboratory Tests:**

- Complete blood count (CBC) and differential
- Basic coagulation assays
- PT-INR
- PTT

### **Microbiology**

#### **Concepts:**

- General understanding of the techniques used and the logistics of activities in a routine clinical microbiology laboratory including specimen handling, aseptic techniques, precautions for CSF culture

#### **Specific Laboratory Tests:**

- C-reactive protein
- Pro-calcitonin

### **Pathology**

#### **Concepts:**

- General understanding of the techniques used and the logistics of activities in a routine clinical pathology laboratory

## Manager

**Definition:** Clinical biochemists are an integral part of laboratory medicine and health care organizations. They are competent in assisting laboratory administration in ensuring cost-effectiveness, providing quality services, making decisions for capital equipment, allocating of resources and contributing to the effectiveness of healthcare facilities.

### Required Competencies

- Demonstrate management skills related to budgets, costs, and personnel.
- Demonstrate ethics of medicine and science.
- Demonstrate good knowledge about quality management systems.
- Chair or participate effectively in committees and meetings, develop good collegial relationship with laboratory and medical staff.

### Specific Objectives

#### LABORATORY MANAGEMENT ORGANIZATION AND OPERATION

**Principles of leadership and organization:** Concepts of Total Quality Management, Lean, Six Sigma. Interactions between the laboratory service and clients that are served by the laboratory.

**Professional ethics:** Professional responsibilities as a leader in laboratory medicine and research.

**General aspects of financial management of laboratories:** Cost-analysis (tests and instruments), decision analysis for instrumentation, delegation of budget responsibilities, work load statistics. Billing and reimbursement concepts where applicable.

**Quality management:** Total quality management; Laboratory errors; control of pre-analytical, analytical and post analytical variables; development and monitoring of performance indicators; quality control standards and practices; QC material limitations; control of analytical quality using patient data. Elements of quality assurance. External quality assessments and proficiency testing programs. Accreditation requirements.

**Laboratory reporting systems:** Need for information to reach the attending physician within a time-frame for appropriate action. Attention to abnormal results, and critical values. Clinical interpretation. Sample identification and tracking (e.g. bar code systems).

**General aspects of system design:** Central vs. stand-alone systems. Laboratory information systems (LIS), hospital information systems (HIS), electronic data transfer and instrument interfacing, data-base structure, data-mining SQL (data extraction for statistical analysis or quality management reports). Security of data storage and transmission.

**Medico-legal requirements:** Confidentiality, record keeping, knowledge of relevant provincial legislation, personal liability, chain of custody.

**Procedures:** Preparation and maintenance of proper laboratory manuals, standard operating procedures.

**Training of technical staff:** Familiarity with the syllabi of various training programs, knowledge of the teaching requirements and level of knowledge of medical technologists.

**Laboratory Information Systems (LIS):** Required features and desired or ideal features of an LIS.

**Selection of reference laboratories:** Requirement of a referral lab (lab license, evidence of method evaluation, quality control and quality assurance). Logistical aspects of sending specimens to a referral lab.

**Point of Care Testing (POCT):** Aspects of quality management in POCT, challenges facing POCT in terms of regulatory and accreditation requirements and compliance, selection of POCT instruments, limitations of POCT.

## **LABORATORY SAFETY**

- Fire, chemical, radiation and infection control.
- Waste disposal regulations.
- Blood and body fluids precautions.
- WHMIS and Globally Harmonized System of classification and labeling of chemicals (GHS); Material Safety Data Sheets interpretations.
- Any additional laboratory or institutional safety practices.

## **Communicator**

**Definition:** Clinical Biochemists are effective communicators with laboratory personnel, clinicians, administrators and the public. They have ability to elicit and transmit accurate information and to reach a common understanding is important.

### **Required Competencies**

- Communicate in a clear and effective way with the professional personnel of the laboratory.
- Develop teaching skills in Clinical Biochemistry at levels of complexity appropriate for the audience, including residents, technologists and other health professionals.
- Offer advice on methods and instruments when requested by laboratories lacking a clinical biochemist, serving on inspection and accreditation teams, assist with research protocols.
- Discuss appropriate test ordering with clinicians, suggest confirmatory tests; provide clinical interpretation when appropriate. In consultation with the responsible physician and where it is warranted, monitor the clinical action taken on the basis of laboratory data provided to the physician and the consequences for the patient.

## **Collaborator**

**Definition:** Clinical Biochemists work with other members of the laboratory and health care team to provide accurate and timely information that will assist in the provision of optimal patient care.

### **Required Competencies**

- Describe clearly their roles and responsibilities to other members of the health care team.
- Recognize the roles and responsibilities of other members of the health care team.
- Contribute effectively to interdisciplinary team activities. This may include activities at the laboratory management level, involvement and participation in committees at various levels, research, teaching pre and post graduates. Demonstrate leadership in a health care team where appropriate.

## **Scholar**

**Definition:** Clinical Biochemists demonstrate lifelong commitment to reflective learning as well as the creation and dissemination of knowledge.

### **Required Competencies**

**Continuing Education:** Develop, implement and monitor a personal continuing education strategy. Participate in continuing education and maintenance of competence programs. Keep pace with changes in all areas of laboratory medicine in order to understand, apply and develop new technologies as may be required. Assist the clinical staff in practicing effective laboratory utilization; take the initiative in introducing new laboratory tests and effective utilization. Participate in the education and training of clinical biochemists, medical students, interns, residents, technologists, and other health professionals.

**Research:** For those Clinical Biochemists working in academic/university hospital settings carry out independent research projects. Collaborate with members of the clinical staff when occasions present themselves in clinical research programs.

## **Professional**

**Definition:** Clinical Biochemists are committed to the provision of the highest quality of laboratory services. They adhere to the principles of ethical practice, professional regulation and high professional standards of behavior.

### **Required Competencies**

- Demonstrate Professional behaviors including, honesty, integrity, commitment.
- Demonstrate a commitment to delivering the highest quality laboratory services.
- Commit to and participate in maintenance of competence.
- Maintain appropriate relationships with co-workers and learners, especially relationships involving an imbalance of power.
- Recognize and adhere to requirements of confidentiality.
- Recognize and manage conflicts of interest.
- Recognize and respond appropriately to unprofessional, unethical or inappropriate behavior in others.
- Demonstrate accountability to appropriate regulatory and legal bodies.

## APPENDIX 1

### **SPECIFIC ANALYTICAL METHODS**

Analytes specific to organ systems and clinical disorders appear in their respective sections. Provided here are three lists of analytes to aid students in ensuring completeness and appropriate depth of coverage for analytes found in the clinical biochemistry laboratory. These lists are not exhaustive. Remember also, that analytes will increase or diminish in their importance as science advances. Thus, analytes not listed below may become important for students to know and understand.

**List 1 includes analytes** for which trainees must have detailed knowledge of the analytical principle(s), factors that govern the choice of method, specimen type(s), interferences, clinical application and interpretation.

1. Ammonia.
2. Bilirubin: Total, conjugated (direct), micro (pediatric).
3. Blood gases and pH, carboxyhemoglobin, CO, Met Hb, O<sub>2</sub> saturation.
4. Cardiac Markers: troponins I&T, CRP, myoglobin, natriuretic peptides.
5. Creatinine.
6. Drug analysis: Acetaminophen, aminoglycosides, phenobarbital, phenytoin, salicylates, carbamazepine, ethanol, methanol, isopropyl alcohol, ethylene glycol theophylline, digoxin, lithium, valproic acid, amphetamines, cocaine, opiates, cannabinoids, PCP, barbiturates, benzodiazepines, tricyclic antidepressants, screening for drugs of abuse.
7. Electrolytes: Sodium, potassium, chloride, CO<sub>2</sub> (HCO<sub>3</sub><sup>-</sup>), total and ionized calcium, phosphorus (inorg.), magnesium.
8. Enzymes: Alkaline phosphatase (ALP), amylase, creatine kinase (CK), gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LD), lipase; prothrombin time (clotting time) or INR.
9. Fecal occult blood.
10. Glucose.
11. Glycated proteins: HbA1c, fructosamine.
12. Hormone tests, including, but not limited to: hCG screen (pregnancy test) and quantitative hCG, thyroxin (T4) and free thyroxin, thyrotropin (TSH), triiodothyronine (Total T3) and free T3, anti-TPO, anti-TG, thyroglobulin, cortisol (plasma and urinary free), estradiol, testosterone, dehydroepiandrosterone sulfate (DHEA-S), progesterone, follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), growth hormone (hGH), insulin, PTH, , 25-OH Vitamin D.
13. Iron: Serum, iron binding capacity, iron saturation, transferrin, ferritin.
14. Ketones: Blood and urine.
15. Lactate.
16. Lipids: Cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol, apolipoproteins A and B.
17. Metanephrines, catecholamines, VMA.
18. Osmolality.
19. Porphyrins: (qualitative).
20. Proteins, including but not limited to: Serum total, albumin, electrophoresis, monoclonal gammopathies, immunoglobulins (IgG, IgA, IgM), complement, urinary microalbumin, C-reactive protein.
21. Spinal fluid: Glucose, protein, oligoclonal bands.
22. Tumor markers, including but not limited to: Prostate specific antigen (PSA) total, free, complexed. Carcinoembryonic antigen (CEA), CA-125, alpha-fetoprotein (AFP), chorionic gonadotropin (CG), 5-HIAA, CA 19-9, CA 15-3, thyroglobulin.
23. Urea.
24. Uric acid.
25. Urinalysis (including microscopy).
26. Vitamins: Vitamin B12, folate.

**List 2 includes analytes** for which trainees should understand the theoretical basis of the tests, and the clinical interpretation. If the tests are performed at the training facility, the trainees should gain practical experience with as many of them as possible.

1. Amniotic fluid: Bilirubin, alpha-fetoprotein.
2. Calculi (renal).
3. Chloride (sweat test cystic fibrosis).
4. Drugs and TDM screen and/or quantitative: Quinidine, alkaloids, amphetamine, barbiturates fractionation, phenothiazines, diazepam, chlorthalidone; ethosuximide, primidone, lidocaine, methotrexate, free drugs, procainamide and NAPA, cyclosporin, tacrolimus.
5. Enzymes: Acetylcholinesterase, angiotensin converting enzyme (ACE), pseudocholinesterase, glucose-6-phosphate dehydrogenase (GPD) and other red cell enzymes, CK isoforms, immunoreactive trypsinogen (IRT) and chymotrypsin, amylase isoenzymes, macroamylases, isoenzymes (CK, LD, ALP).
6. Fecal fat analysis.
7. Hormone Tests: 17-hydroxyprogesterone, 11-deoxycortisol, corticotropin (ACTH), aldosterone, gastrin, renin, C-peptide, glucagon, sex hormone binding globulin (SHBG), androstenedione, unconjugated estradiol.
8. Lipids: Lipoprotein(a), apolipoprotein E.
9. Metals: Copper, lead, mercury, zinc, aluminum.
10. Oxalate, porphyrins (quantitative), porphobilinogen, delta-aminolevulinic acid.
11. Proteins, including but not limited to: Alpha-1-antitrypsin, ceruloplasmin, fibrinogen, cryoglobulin, haptoglobin, immunoglobulin IgE, allergen specific IgE, hepatitis A, B and C, AIDS serology, beta-2-microglobulin.
12. Hemoglobins: Sulfhemoglobin, hemoglobin separation techniques, molecular diagnosis.
13. Pyruvate.
14. Sugars: Galactose, lactose, urine chromatography.
15. Viscosity: Serum, blood.
16. Vitamins: A, E and carotenoids, 25-hydroxyvitamin D, 1, 25-dihydroxyvitamin D.
17. Bone markers: Pyridinoline cross-links, alkaline phosphatase (bone specific).
18. Xylose.

**List 3 includes analytes** not commonly requested in Biochemistry. General knowledge is required regarding the clinical utility and the analytical approach.

1. Ascorbic acid.
2. Amino acids chromatography: Cysteine/cystine, phenylalanine/tyrosine (PKU), hydroxyproline, branched chain aminoacidemia, etc.
3. Antibodies, including but not limited to: Anti-ds-DNA, anti-nuclear antibodies by immunofluorescence, specific anti-nuclear antibodies (SS-A, SS-B, Sm, RNP), anti-TPO (anti-microsomal) and anti-thyroglobulin, anti-glomerular basement membrane, anti-insulin, anti-smooth muscle, anti-neutrophil cytoplasmic antibodies, anti-cardiolipin antibodies, anti-transglutaminase and antigliadin antibodies.
4. Bile acid analysis by liquid chromatography/mass spectrometry.
5. Breath tests: Hydrogen (jejunal disaccharidases),  $^{14}\text{CO}_2$  (bile acids),  $^{13}\text{CO}_2$  (*Helicobacter pylori*).
6. Enzymes: Hexosaminidase (Tay Sachs), sphingomyelinase (Niemann Pick), macroenzymes, lysozyme pseudocholinesterase phenotyping, pyruvate kinase.
7. Gastric analysis.
8. Hormone tests: Thyroglobulin, cAMP, reverse T3, TSH-receptor antibody, cGMP, calcitonin, corticotropin releasing hormone (CRH/CRF), prostaglandins, endorphins, estrogen and progesterone receptors, somatostatins, somatomedins, atrial natriuretic peptide, TSH receptor antibody, islet-cell antibodies, antidiuretic hormone (ADH), growth hormone measurement and stimulation tests, IGF-1 and IGF-BP3, insulin tolerance test, saline infusion test for hyperaldosteronism.
9. Lipids: Lipoprotein electrophoresis.
10. Metals: Arsenic, chromium.
11. Oncotic pressure.



12. Proteins: Immunoglobulin IgD, circulating immune complexes, soluble transferrin receptor.
13. Tumor markers: PTHrp, NSE, Her2/Neu.
14. Vitamins: K (prothrombin).
15. Genotyping for susceptibility of hemostatic diseases (Leiden Factor V, MTHFR).
16. Immune system: Cytokines and lymphokines.

## **APPENDIX 2**

### **RECOMMENDED REFERENCE MATERIAL**

#### **Biochemistry**

Biochemistry: A Case-Oriented Approach. Montgomery, R. et al., 6th ed. Mosby, 1996.  
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Harper's Biochemistry. Harper's Illustrated Biochemistry Murray, R.K., Granner, D.K., Mayes, P.A., Rodwell, V.W. (Eds.), 29th ed. Lange, 2012.

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Review of Medical Physiology. Ganong, W.F., 23rd ed. Lange, 2010.  
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#### **General**

Robbins and Cotran Pathologic Basis of Disease Professional Edition. Kumar V, Abbas A.K., Fausto N. and Aster J. 8th ed. Saunders Elsevier 2010.  
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Greenspan's Basic and Clinical Endocrinology. Gardner D.G and Shoback D. (Eds.), 9th McGraw-Hill, 2011.

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Clinical Guide to Laboratory Tests. Tietz, N. (Ed.), 4th ed. Saunders, 2006.  
Clinical Diagnosis and Management by Laboratory Methods. Henry, J.B., 22th ed., Saunders 2012.

#### **CLINICAL BIOCHEMISTRY**

Textbook of Biochemistry with Clinical Correlations, Devlin T.M., (Ed), 6th ed, Wiley-Liss, 2010  
Biochemical and Molecular Basis of Pediatric Disease. Dietzen D.J., Bennett M.J. and Wong M.C.C., 4th ed, American Association for Clinical Chemistry, 2010.  
Cases in Chemical Pathology: A Diagnostic Approach. Walmsley, R.N., Watkinson, L.R., Kain H.J., 4th ed. World Scientific, 2004

#### **Journals**

American Journal of Clinical Pathology  
Annals of Clinical Biochemistry  
Annals of Internal Medicine  
British Medical Journal  
Clinical Biochemistry  
Clinica Chimica Acta  
Clinical Chemistry

Clinics in Endocrinology and Metabolism  
Clinics in Laboratory Medicine  
Critical Reviews in Clinical Laboratory Sciences  
Current Clinical Chemistry  
Endocrinology  
Journal of Bone and Mineral Research  
Journal of Clinical Chemistry and Clinical Biochemistry  
Journal of Clinical Endocrinology and Metabolism  
Journal of Clinical Pathology  
Lancet  
New England Journal of Medicine  
Pediatric Research  
The Clinical Biochemist Reviews  
Therapeutic Drug Monitoring  
Scandinavian Journal of Clinical and Laboratory Investigation  
Science.