

The EC4 European Syllabus for Post-Graduate Training in Clinical Chemistry and Laboratory Medicine: version 4 – 2012

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Abstract

Laboratory medicine's practitioners across the European community include medical, scientific and pharmacy trained specialists whose contributions to health and healthcare is in the application of diagnostic tests for screening and early detection of disease, differential diagnosis, monitoring, management and treatment of patients, and their prognostic assessment. In submitting a revised common syllabus for post-graduate education and training across the 27 member states an expectation is set for harmonised, high quality, safe practice. In this regard an extended 'Core knowledge, skills and competencies' division embracing all laboratory medicine disciplines is described. For the first time the syllabus identifies the competencies required to meet clinical leadership demands for defining, directing and assuring the efficiency and effectiveness of laboratory services as well as expectations in translating knowledge and skills into ability to practice. In a 'Specialist knowledge' division, the expectations from the individual disciplines of Clinical Chemistry/Immunology, Haematology/Blood Transfusion, Microbiology/ Virology, Genetics and In Vitro Fertilisation are described. Beyond providing a common platform of knowledge, skills and competency, the syllabus supports the aims of the European Commission in providing safeguards to increasing professional mobility across European borders at a time when demand for highly qualified professionals is increasing and the labour force is declining. It continues to act as a guide for the formulation of national programmes supplemented by the needs of individual country priorities.

Keywords: competence to practice; continuous professional development; education; leadership; quality; specialist in laboratory medicine; training.

Introduction

It has been estimated that up to 70% of all medical decisions are based on data and information provided by laboratory

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medicine (1, 2). It is the clinical specialty that underpins modern medicine's understanding of health and disease. Its contributions include screening and early detection of disease, differential diagnosis, monitoring, management and treatment of patients, and their prognostic assessment. This contribution continues to grow through research and development, technological advances and the increasing knowledge and skills base of its practitioners across the 27 European Union (EU) member states. Central to extending that base is a syllabus for education and training that is fit for purpose in meeting modern medicine's demands for better health and best care.

The European Communities Confederation of Clinical Chemistry's (EC4) syllabus for clinical chemistry and laboratory medicine was first published in 1997 (3). This is its fourth revision. The syllabus describes the level of knowledge and skills required from specialists, who have responsibility for patient care, but recognises that the scope of practice varies across the member states (4), in part depending on whether:

- (a) the specialist is from a medical, scientific or pharmacy background. Medical practitioners comprise about one third of such specialists, their key additional contribution being the provision of direct patient care;
- (b) the specialisation is monovalent (typically clinical chemistry, the largest discipline) or polyvalent (to include one or more of haematology, blood transfusion, microbiology, virology, parasitology, immunology, genetics, reproductive medicine).

The overlap in scope, however, is considerable such that common elements in education and training can be identified in a unified syllabus. Since the last revision was published in 2005 (5), much has changed in terms of the demands placed on the specialist and the service that he/she provides. In part these changes are predicated by individual member states' priorities but, increasingly, common themes emerge in the provision of healthcare across the European Community. Changes include:

- (a) Greater clinical governance expectations for evidence-based protocol-driven care which place new expectations for design of appropriate pathways involving diagnostic tests;
- (b) Increasing demands for professionals to be registered and/or professional practice to be regulated so that the public and patients are protected in the knowledge that safe care is provided by individuals whose competency is maintained through continuous professional development and/or re-validation;
- (c) A shift from voluntary to mandatory accreditation of services that expects standards to be met in areas, such as laboratory management and personnel, premises and environment, technology and information systems, pre-analytical and post-analytical phases, audit, evaluation, quality assurance and its management (6, 7);
- (d) Technological advances in areas, such as proteomics, molecular diagnostics and mass spectrometry. These

advances cross discipline-specific barriers, allowing enhanced diagnostic accuracy, but place new knowledge and skill demands on laboratory services;

- (e) Increasing interest in exploitation of near patient testing as a means of enhancing clinical, financial and organisational outcomes;
- (f) Increasing prioritisation to improving public health as a means of reducing later hospital admissions and costly care.

A syllabus fit for purpose

The changes in professional and clinical expectations are reflected in a revised content and structure of the syllabus – 'Core knowledge, skills and competencies' describes common expectations across laboratory medicine followed by specialist knowledge relating to Clinical Chemistry/Immunology, Haematology/Blood Transfusion, Microbiology/Virology, Genetics and in vitro fertilisation. Amongst the most significant revisions under core knowledge 'Laboratory Management and Quality Assurance' reflects enhanced expectations for direction, leadership, organisation, quality, education/training, safety, legal, ethical and governance considerations; 'Research and Development' has been extensively revised and identifies commitment to audit; enhanced roles in results interpretation and patient intervention are reflected in a revised 'Case-related clinical evaluation of laboratory tests'. The specialist knowledge sections have been retained for this revision.

Overarching the new structure is the identification of competencies as measures of fitness to practice and provide clinical leadership in defining a service, identifying the resources required to support efficiency and effectiveness whilst meeting national medico-legal and regulatory requirements. The competencies identified here complement those identified by Beastall et al. (8) and Gurr et al. (9) as being appropriate for, respectively, 'consultant' and 'specialist' level practise. They are broken down to be associated with the individual sections. In identifying competencies the distinct contribution of the specialist in ensuring high quality, safe practice is underlined. They provide the standards of proficiency that must be met, e.g., for registration and regulation purposes. They can also provide the cornerstone measures for individual appraisal and personal development.

Recognising professional qualifications

To date, the European Register of Specialists in Clinical Chemistry and Laboratory Medicine (10) has recognised over 2500 individuals across the EU as being able to demonstrate:

- (a) At least 9 years of undergraduate and post-graduate study;
- (b) A minimum of 5 years specialist training in an approved laboratory to a level at least equivalent to that in the European syllabus;

- (c) Inclusion on a professional register in their home country;
- (d) Participation in continuous professional development activities.

Since its inception in 1997, registrants have held the title European Specialist in Clinical Chemistry and Laboratory Medicine (*EurClinChem*). The Register is a key facilitator in disseminating high quality practice and extending recognition of the profession. The weight of its argument comes from the growing numbers of specialists wishing to join it, the quality of its argument from the standards it sets (11, 12). Potentially the Register acts as a key inventory item for establishing a common mechanism for automatic recognition of professional qualifications across Europe for the two thirds of specialists with a pharmacy or science training background (13). Currently only medically qualified specialists enjoy the automatic recognition that allows professional mobility across European borders. Such mobility is important in supporting individual choice and encouraging a more equitable distribution of human resources and expertise across the EU at a time when demand for highly qualified professionals is increasing whilst the labour force is declining (14, 15). The identification of competencies in the revised syllabus hence takes on additional significance in allowing practitioners to demonstrate their ability to deliver common expectations for high quality, safe practice across European borders.

In 2007 EC4 merged with the Forum of European Societies of Clinical Chemistry and Laboratory Medicine (FESCC) to form the European Federation of Clinical Chemistry and Laboratory Medicine (EFCC) (16). A key initiative in 2011 of the newly formed organisation has been to replace the 1997 *EurClinChem* title with the term Specialist in Laboratory Medicine. In unifying previous descriptors the new term provides a common theme to the profession as well as clarity to the general public. Its adoption also brings individual disciplines and their national societies together under a common umbrella of influence to enhance high quality practice across the EU.

This paper is the report of a working group which has been endorsed by the Executive Board of EFCC after two rounds of consultation with national society representatives on the EC4 Register Commission who commented on manuscripts and contributed with examples of their national education and training programmes. The outcome is a framework that is capable of interpretation by governments and national societies in individual EU countries to help deliver a common approach to education and training.

Laboratory medicine: core knowledge, skills and competencies

I. Basic knowledge requirements

1. Knowledge of the structure and function of the cell.
2. Understanding of the chemical, cellular and tissue level of organisation of the body.

3. Understanding of normal anatomy, physiology and pathology of the body across the integumentary, skeletal, nervous, cardiovascular (including blood, blood vessels and lymphatic system), respiratory, endocrine, renal, gastrointestinal (including nutrition), urinary system, reproductive system.
4. Knowledge of the process by which embryonic development occurs from conception to birth.
5. Knowledge of the principles of inheritance, DNA and genetics including carrier status, genetic crosses/pedigree/punnet squares/cross diagrams.
6. Knowledge of the cellular, tissue and systems responses to disease including cell death, inflammation, neoplasia, hypertrophy, hyperplasia, tissue responses to injury and repair.
7. Describe the pathophysiology of disease development in common diseases across the body systems.
8. Understand the basic principles of microbiology including infection control, bacteria, recognition of extracellular pathogens, virus types and structures, viral infection and replication.
9. Understand the basic principles of immunology, natural defences, B and T cell-mediated immune responses.
10. Understand the basic principles of clinical biochemistry and metabolism in physiological, homeostatic and pathophysiological processes.
11. Understand the basic principles of haematology including anaemias, haematological malignancies, blood clotting disorders.
12. Understand the basic principles of histology including microscopic and staining techniques.

Competencies

- Thorough knowledge of all aspects of clinical laboratory sciences relevant to the discipline practiced.
- Broad knowledge of, and insight into, biochemical processes in human health and disease on a general and patient-specific level.

II. Indications for laboratory medicine procedures

1. In the early detection of disease or disease susceptibility, screening, and in epidemiology.
2. In disease related diagnosis.
3. In organ related diagnosis.
4. In monitoring vital functions and predicting disease outcome.
5. In treatment targeting, predicting and monitoring the response to therapy.
6. Indications for subsequent specialised examinations.
7. Indications for functional tests.
8. Prognostic assessment.

Competencies

- Appreciation of developments in science and technology and in the understanding of disease in order to ensure the appropriate use of laboratory investigations.

III. Influence of collection and storage of specimens

1. Place and time of sample collection, preservation, influence of nutrition, drugs, posture, fasting state, etc.
2. Choice and correct use of anticoagulants and transport media, order of draw, tourniquet effects.
3. Care of the specimens, patient identification, transport, storage, stability of analytes, influence of temperature, freezing/thawing.

Competencies

- Recognition of pre-analytical factors that influence the validity of the analytical process;
- Ability to deliver the pre-analytical requirements of a laboratory medicine service.

IV. Analytical principles and techniques

1. Separation techniques
 - i. Chromatography – liquid, gas, thin layer, column, high pressure, affinity.
 - ii. Electrophoresis – gel, capillary zone, iso-electric focussing.
 - iii. Dialysis.
 - iv. Centrifugation – ultracentrifugation.
2. Standard analytical techniques
 - i. Titrimetry.
 - ii. Osmometry.
3. Photometric methods
 - i. Spectrophotometry – ultra violet, visible.
 - ii. Atomic absorption.
 - iii. Turbidimetry.
 - iv. Nephelometry.
 - v. Fluorimetry.
 - vi. Flame emission.
 - vii. Reflectometry.
4. Spectrometric methods
 - i. Mass spectrometry, tandem mass spectrometry.
 - ii. Nuclear magnetic resonance.
 - iii. Infra-red.
5. Electrochemical techniques
 - i. Ion selective electrodes.
 - ii. Biosensors.
 - iii. Impedance (cell counting).
6. Nucleic acid analysis
 - i. Extraction and preparation of DNA and RNA.
 - ii. Polymerase chain reaction (PCR) and reverse PCR.
 - iii. Quantitative PCR.
 - iv. Techniques for point mutation detection.
 - v. Techniques for detecting more complex genetic variation.
 - vi. Cytogenetic analysis.
 - vii. Array technology, DNA sequencing, FISH.
7. Immunological techniques
 - i. Principles of Ag-Ab reactions, immunoassay design.
 - ii. Competitive immunoassay.
 - iii. Non-competitive immunoassay.
 - iv. Homogeneous and heterogeneous assays.
 - v. Interference.

- vi. Signal detection systems – use of radioisotopes, colorimetric/fluorimetric labels.
- vii. Immuno-precipitation – immunoelectrophoresis, immunofixation, immuno-turbidimetry, immunonephelometry.
- viii. Agglutination techniques.
8. Enzymes
 - i. Analytical techniques – reaction rate, end point analyses.
 - ii. Enzymes as reagents.
 - iii. Enzyme kinetics, inhibitors, allosteric behaviour.
9. Microscopy – light, brightfield, phase-contrast, polarising, interference contrast, darkfield, fluorescence microscopy.
10. Haematological cell staining techniques and preparation of smears, slides or films.
11. Flow cytometry
 - i. Cell counting, cell markers detection and fluorochromes.
 - ii. Subsystems: fluidics, optics and electronics.
12. Rheology.
13. Culture and sensitivity: microbial culturing, selection of media, incubation conditions, organism identification techniques, antibiotic sensitivity testing.
14. Microbial cell staining techniques – microbe, virus, parasite and fungus identification (including principal differential characteristics).

Competencies

- Knowledge of, and insight into, the use of technology and analytical techniques relevant to the field of specialisation, an active appreciation of developments, and an attitude of innovation and creativity in their implementation.

V. Analytical evaluation of laboratory methods

1. Precision, accuracy, sensitivity, specificity.
2. Interference.
3. Analytical and clinical ranges, limits of detection, carry over.
4. Internal quality assurance and external quality assessment.
5. Statistical comparison of methods.
6. Definitive methods, reference methods, primary and secondary calibrants, traceability.
7. Laboratory and population data: sampling, reference values.
8. Negative and positive predictive values of results; diagnostic sensitivity and specificity, diagnostic accuracy; likelihood ratios.
9. Confidence intervals.

Competencies

- Ability to determine the essential parameters required to evaluate a laboratory method.
- Ability to conduct an evaluation using appropriate statistical tools, computer-aided spreadsheets and databases.
- Ability to determine the clinical significance of the outcome of a laboratory method evaluation.

VI. Clinical evaluation of laboratory methods

1. Reference intervals and biological variability. Genetic influences, environmental influences, age, sex, nutrition, season and time of day, influence of therapeutic agents.

2. Clinical sensitivity, specificity and predictive value of analytical methods.
3. Diagnostic strategies and analytical goals in the use of clinical chemistry tests.

Competencies

- Ability to obtain, explore, and employ knowledge and methods of investigation in the interests of health care and humankind.
- Ability to take responsibility for the data and information produced, including knowledge of the influence of variation (biological as well as analytical) on interpretation of data.

VII. Case-related medical evaluation of laboratory tests

The specialist in laboratory medicine in a consultative role requires a working knowledge of the subject underlying the choice of tests and interpretation of results.

1. Evaluation of individual results (identifying extreme values, recognition of significance of previous results, recognition of combinations of findings typical of diseases).
2. Use of reference values: influence of age, genetics, sex, lifestyle, interfering factors, effect of therapeutic agents, biological and analytical variation.
3. Longitudinal evaluation of critical differences during disease course, e.g., in long-term conditions, cancer, during therapeutic drug monitoring and as a result of treatment regimen changes.
4. Recommended testing strategies in response to clinical demand for intervention and guidance.
5. Independent initiation and/or recommendation of further investigations, reflective testing.
6. The laboratory report – provision of evaluation, guidance and interpretive comments.

Competencies

- Provision of interpretive, advisory and intervention guidance in the application of laboratory tests, as appropriate.
- Ability to communicate the value of laboratory investigations to service users.

VIII. Clinical training

Training requires exposure to clinical environments where laboratory medicine impacts on patient care. Examples include accident and emergency, critical care, and applications of point of care testing. Participation in ward rounds, provision of direct clinical care (as appropriate) as a member of the clinical team and other contact with the users of the laboratory is key to achieving clinical competency. Participating and leading seminars, case discussions also provide valuable experience.

Competencies

- Ability to work in a multi-disciplinary environment and function as a consulting advisor to his/her clinical

colleagues and liaise with them in the choice of tests and the interpretation of laboratory results.

- Understanding of the registrant's responsibility in the practice of his/her profession to the well-being and personal safety of patients, colleagues, co-workers, the community, and the environment.
- Ability to provide direct clinical care, as appropriate.

IX. Research and development; audit

As laboratory medicine is continually and rapidly evolving, research and development of both the laboratory aspects and their clinical application are indispensable. The specialist in laboratory medicine must maintain up to date knowledge in all relevant diagnostic procedures. Special attention must be paid to the following:

1. Development and improvement in technologies, techniques and methodologies; with special emphasis on new developments in areas such as molecular biology, proteomics, mass spectrometry.
2. Procedures to test and evaluate the steps of a method and the components of an instrument.
3. Initiation, conduct and evaluation of laboratory-based and clinical research and development based on best evidence of practice.
4. Initiation, conduct and evaluation of clinical and laboratory audit to ensure quality, governance and patients' needs continue to be met.
5. Generating outcomes of research and development, audit and service improvement programmes using recognised scientific and statistical techniques.

Competencies

- Ability to conduct research, either basic or applied, in order to further knowledge in the field of clinical chemistry and laboratory medicine.
- Ability to undertake literature/systematic reviews and design quantitative and qualitative programmes for research, development, audit and service improvement based on best evidence.
- Ability to appraise the need and set priorities for research, development, audit and service improvement programmes.
- Understanding of research governance, ethical and legal frameworks, funding streams, the influence of regulatory and healthcare-related organisations in local settings.
- Ability to design and conduct the required experiments to ensure objectives are met.
- The application of statistical and biostatistical procedures to evaluate quantitative and qualitative information and data.
- Ability to appraise and translate outcomes to enhance activities, as appropriate.
- Ability to communicate orally and in writing, including the production of clear, cogent reports and publications in international scientific journals.

X. Laboratory management and quality assurance

Depending on the working environment the consultant should be familiar with some or all aspects of the responsibilities listed below. Some may be led on an organisation-wide basis, some fall within the remit of the lead consultant, some may also be delegated.

1. Laboratory direction and leadership
 - i. Specifying requirements.
 - ii. Setting strategy and establishing policy.
 - iii. Formulating laboratory plans.
 - iv. Assessing resource requirements – staff, space, equipment.
 - v. Analysing costings (efficiency) and cost-benefits (effectiveness).
2. Laboratory organisation
 - i. Design and utilisation of space and facilities.
 - ii. Selection of methodologies and equipment.
 - iii. Selection of information management and technology systems.
 - iv. Recruiting and managing a staff/skill mix appropriate for the service.
 - v. Establishing pre-analytical, analytical and post-analytical processes.
 - vi. Preparing protocols, procedures, guidelines.
 - vii. Budgetary responsibilities (contracting, performance management, financial controls).
 - viii. Design of request and report forms.
3. Quality
 - i. Medical laboratory and point of care testing accreditation systems.
 - ii. Requirements for a quality management system – quality assurance, governance, monitoring of planned actions.
 - iii. Managing internal quality control and external quality assessment performance.
 - iv. Data management: use of medical informatics, data processing, spread sheets/databases, electronic/telecommunications.
4. Education/training/continuous professional development
 - i. Ensuring skills, competencies and motivation of staff meet service requirements.
 - ii. Ensuring staff access education and training programmes appropriate for service needs.
 - iii. Participation, as appropriate, in staff education, training and appraisal.
 - iv. Ensuring staff remain up to date by participation in continuous professional development (CPD).
 - v. Ensuring own training, education, appraisal and CPD needs are maintained.
5. Laboratory safety
 - i. Handling of potentially infectious samples (e.g., HIV and hepatitis), handling of noxious chemicals and isotopes, mechanical and electrical safety, fire precautions, dealing with an accident, accident prevention and hygiene regulations, occupational diseases.
 - ii. Alert systems, incident reporting.
6. Legal, ethical and governance considerations
 - i. Laws, regulations, guidelines and recommendations on work in clinical laboratories: in particular requirements for accreditation of services, education and training,

health and safety, infection control, buildings, employment law, regulation and registration of staff.

- ii. Ethical aspects and conventions on production, interpretation, reporting and use of medical laboratory data. Confidentiality, data protection and security.
- iii. Clinical and research governance expectations of government, health care-related organisations and employers for high quality, evidence-based care.

Competencies

- Ability to safeguard and protect the public against misuse of medical laboratory investigations.
- Knowledge of the principles of management leading to satisfactory direction, supervision, and organisation of a laboratory department in a public or private hospital or in any other healthcare environment resulting in the provision of a competent service as laid down in a laboratory quality manual, based on good laboratory services as defined in EN-ISO document 15189 and the EC4 Essential Criteria.
- Ability to determine the optimum distribution of resources across central laboratories, peripheral sites and near patient testing settings.
- Ability to assess conflicting and various technical, financial, and human considerations (e.g., care, quality, safety, cost, and time scales) both in the short- and long-term, and to find the optimal solution in relation to patient care.
- Ability to apply current techniques in human resource management.
- Execution of judgment and leadership.

Laboratory medicine disciplines: specialist knowledge

Clinical chemistry/immunology

1. Carbohydrates
 - Glucose metabolism and regulation.
 - Metabolism and regulation of other carbohydrates (e.g., galactose, lactose, glycogen).
 - Type 1 and type 2 diabetes mellitus. Hypoglycaemic states.
 - Other hereditary and acquired metabolic disorders (e.g., lactose intolerance, galactosaemia, storage diseases).
 - Ketogenesis.
2. Lipids and lipoproteins
 - Metabolism.
 - Hereditary and acquired disorders. Storage diseases hypercholesterolaemia. Hypo- and hyper-lipoproteinaemia; characterisation by classical methodology; apolipoproteins; lipoprotein lipase.
3. Proteins and amino acids
 - Metabolism.
 - Important plasma proteins (albumin, immunoglobulin, haptoglobin, transferrin, C reactive protein, etc.).
 - Dysproteinaemia, monoclonal components.
 - Tumour associated proteins.
 - Hereditary and acquired disorders of amino acid metabolism.
 - Urine proteins and proteinurias.

4. Nucleic acids and purines
 - Metabolism.
 - Gout.
 - Other hereditary and acquired disorders of purine metabolism.
5. Porphyrins and haem pigments
 - Metabolism.
 - Porphyrias.
6. Biogenic amines
 - Metabolism.
 - Catecholamines, serotonin and their breakdown products.
7. Water and electrolytes
 - Metabolism.
 - Sodium, potassium, chloride abnormalities.
 - Osmolality.
 - Overhydration, dehydration.
 - Oedema, ascites.
8. Acid-base, blood gases
 - Acid-base balance and disorders; buffer systems (bicarbonate, phosphate, haemoglobin, protein); Henderson-Hasselbalch equation; acidosis and alkalosis.
 - Renal regulation systems.
 - Pulmonary gas exchange; oxygen metabolism.
9. Iron metabolism
10. Vitamins and trace elements
11. Immune system
 - Functions of the humoral and cellular immune systems and their regulation; cytokines; inflammation; acute phase proteins.
 - Surface antigens.
 - Hereditary and acquired disorders.
 - Immunoglobulin deficiency and overproduction, monoclonal and polyclonal immunopathies.
 - Major histocompatibility complex.
 - Autoimmune diseases; allergy.
 - Complement factors.
 - Inflammation; cytokines; acute phase proteins.
12. Enzymes
 - Induction, synthesis and elimination.
 - Enzyme patterns in various tissues and body compartments; isoenzymes; diagnostic significance.
13. Cerebrospinal fluid (CSF)
 - CSF synthesis and circulation.
 - Composition of CSF in comparison to serum.
 - Hereditary and acquired disorders of CSF homeostasis.
14. Body fluids other than CSF – saliva, gastric juice, ascites, chyle etc..
 - Composition.
 - Appropriate analyses.
15. Digestive tract
 - Digestive enzymes in the various sections of the digestive system including the exocrine functions of the liver and pancreas.
 - Hydrochloric acid, bicarbonate and bile secretion.
 - Fluid and electrolyte secretion.
- Absorption.
- Gastrointestinal hormones.
- Hereditary and acquired disorders of the digestive system.
- Malabsorption including vitamin malabsorption.
16. Exocrine functions of the pancreas
 - Acute pancreatitis.
 - Chronic pancreatitis.
17. Liver and biliary tract
 - Physiology; normal and disturbed functions of the liver; metabolism, synthesis, biotransformation, excretion.
 - Enterohepatic circulation; metabolism of bilirubin and bile acids.
 - Hepatitis, cirrhosis, cholestasis, necrosis.
18. Kidneys and urinary tract
 - Physiology; normal and disturbed renal function.
 - Excretory substances in the plasma and urine. Glomerular filtration rate and clearance. Activity and effects of diuretics; free water clearance.
 - Proteinuria.
 - Acute and chronic renal insufficiency, nephritis, nephrotic syndrome.
19. Heart and circulatory system
 - Normal and disturbed circulation.
 - Myocardial infarction and shock; marker proteins; fluid balance.
 - Hypertension.
 - Heart failure, blood markers.
20. Skeletal and locomotor system
 - Function and metabolism of muscles, bones, cartilage, synovial and connective tissues (fasciae, tendons).
 - Hereditary and acquired disorders, especially of calcium and phosphate metabolism, vitamin D, collagen and proteopolysaccharide metabolism.
21. Endocrine system
 - Physiology biosynthesis and catabolism of hormones.
 - Hormonal regulation, hormone transport, receptor systems.
 - Functional disorders of the thyroid gland, the parathyroid glands, the adrenal cortex, the adrenal medulla, the endocrine part of the pancreas, the gonads, the placenta, the pituitary-hypothalamus system.
22. Pregnancy, perinatal laboratory analysis
 - Hormone analyses; in vitro fertilisation.
 - Molecular biology of hereditary disorders.
 - Inherited metabolic disease.
 - Pre-natal screening for foetal abnormalities (first trimester, second trimester).
23. Drug monitoring
 - Pharmacokinetics, pharmacodynamics and bioavailability of drugs, pharmacogenetics.
 - Therapeutic range.
 - Individual determinations for the most important drugs: digoxin, theophylline, anticonvulsants, immunosuppressants.

24. Poisoning

- Pathomechanisms of the most important types of poisoning.
- Knowledge of the preparation and preservation of specimens, regulations for examination, documentation of examinations, chain of custody.
- Knowledge of strategies for group recognition of poisons by extraction, isolation and identification.
- Individual determinations for the most important types of poisoning, e.g., ethylalcohol, carbon monoxide, barbiturates, benzodiazepines, tricyclic antidepressants, methaemoglobin, methylalcohol, ethyleneglycol, benzene, toluene, etc... Cholinesterase in the case of organic phosphate intoxications.
- Tests for drugs of abuse.
- Radioactive isotope toxicology.
- Toxicology: drugs, opiates, cannabis, cocaine.
- Professional and environmental toxicology.

25. Prenatal diagnosis of inborn errors of metabolism.

26. Oncogenes/tumour markers.

Haematology/blood transfusion (including cells, transfusion serology, coagulation, and cellular immunology)

1. Basic haematology

- General morphology and blood cell counting.
- Determination of erythrocyte sedimentation rate. Determination of haemoglobin concentration, haematocrit, cell counts and knowledge of haematological parameters (MCV, MCH, MCHC, RDW).
- Preparation and staining of blood smears, with microscopical evaluation.
- Investigation of haemolysis.
- Flow cytometry and leucocyte sub-grouping.

2. General haemostasis

- Coagulation tests.
- Determination of coagulation factors. Control of anticoagulation factors, supervision of all treatments.
- Investigation of fibrinolysis.
- Determination of antithrombin III and heparin.

3. Immuno-haematology

- Blood group typing, ABO and Rh(D); D-variant determination, Kell.
- Detection of irregular antibodies.
- Cross matching of blood samples for transfusion. Indirect antiglobin test, direct antiglobin test.
- Rhesus- and ABO-antagonism.

4. Haematological biochemistry of erythrocytes

- Detection and measurement of variant and minor (Hb A2 and HbF) haemoglobins.
- Red blood cell enzymes.

5. Theoretical and clinical background

- Haemoglobinopathies and thalassaemias.
- Vitamin B12 and folic acid deficiencies; iron status.
- Kinetics of blood cells and platelets.
- Enzymology of blood cells and platelets.
- Haemato-oncological abnormalities (leukaemias, lymphomas, polycythaemias).

- Possible causes and background of anaemias.
- TTP, HELLP, DIC.
- Immunological determination of coagulation factors and knowledge of coagulation abnormalities (factor deficiency, increased fibrinolytic activity) and regulation and monitoring of thrombosis and disseminated intravascular coagulation. The use of anticoagulant drugs.
- Blood group antigens and other antigen systems as considered in blood transfusion (including genetics).
- Selection criteria of donors for blood transfusion.
- Several types of transfusion reactions, foetal maternal bleeding.
- Medical applications, clinical relevance and indications for the administration of blood and blood components.
- Haematopoiesis and haemostasis physiology.

6. Morphology and haematopoiesis

- Morphological investigation of bone marrow smears including different staining procedures. PAS staining for intracellular glycogen, Sudan black staining for lipids, iron staining, acid phosphatase, esterase and peroxidase staining.
- Investigation of cellular characteristics and abnormalities by flow cytometry.
- Haemoglobinopathies. Haemoglobin electrophoresis on cellulose acetate, in agar gel. Foetal haemoglobin testing (Kleihauer, flow cytometric HbF determination). Molecular diagnostic approaches.
- Investigation of anaemias, both congenital and acquired. Ham test and sucrose test.
- Detection of abnormal haemoglobin derivatives: spectrophotometric analysis.
- Haemato-oncology, including cytogenetic and molecular diagnostic alterations of haematological malignancies.
- Myelodysplasia.
- Ganglion exploration.
- Lymphoid system pathology.

7. Haemostasis

- Investigation of platelet function. PFA, thromboelastography. Influence on platelet aggregation by ADP-adrenaline, collagen, ristocetin, ADP, ATP, arachidonic acid. Determination of serotonin. Spontaneous aggregation. Clot retraction. Platelet factor III determination, glass pearl test.
- Use of chromogenic substrates for the determination of coagulation factors.
- Detection of circulating inhibitors, thrombo test diluted curve, cephalin dilution curve.
- Protein S, protein C.
- VWD: VWag, VWric, ADAMTS13.
- Theoretical background and clinical background and knowledge of the following subjects: prekallikrein, high molecular kininogen determination, plasminogen, antiplasmin, plasminogen activators.
- Thrombophilia testing (FV Leiden, FII, PAI, MTHFR), (LAC testing: anti cardiolip etc).

- Thrombin activation: TAT, protrombin fragments F1+2, D-dimer.
 - Knowledge of anticoagulant treatment as well in clinical as in outpatient conditions.
 - Acute vascular diseases TTP, HUS, DIS. Place of plasmapheresis in treatment.
8. Immuno-haematology and blood banking
- Typing of irregular (auto) antibodies; determination of antibody titre.
 - Extended blood group typing (beyond ABO, Rhesus D and Kell).
 - Investigation of transfusion reactions.
 - Preparation and application of blood components.
 - Organisation of blood banking.
 - Typing of B and T lymphocytes.
 - Platelet antibodies.
 - Typing of leucocytes and tissue antigens.
 - Recognition of cell markers using monoclonal antibodies.
 - The application of plasmapheresis both in donors and in patients.

Microbiology/virology (bacteriology, parasitology, and mycology)

1. General aspects

The investigation of biological samples in infectious diseases is different from the other specialities in that it requires general knowledge of pathogenic agents (bacteria or viruses) and of host reaction.

- Definition of infection and infectious disease: natural bacteriological ecosystem.
- Pathogenicity of bacteria and viruses; disinfection.
- General epidemiology of infection and infectious diseases.

2. Diagnostic procedures

- Specimen selection and collection (blood, urine, sputum, faeces, others).
- Specimen processing: smears, staining, cultures including cell cultures, susceptibility testing, antigen detection.
- Usual techniques for microbe and virus identification (including principal differential characteristics).
- Molecular biology techniques for characterisation of microbes and viral agents.
- Bacteriological and viral serology.

3. Bacteria and viruses

Succinct description of responsible bacteria and viruses in bacteriological and viral syndromes or diseases (including principal differential characteristics):

- Bacteria: *Neisseria gonorrhoeae* and *N. meningitidis*, *Staphylococcus aureus*, *Streptococcus pyogenes*, (especially *S. agalactiae* and *S. pneumoniae*), *Escherichia coli*, *Salmonella*, *Shigella* and other enterobacteriaceae, *Vibrio cholerae*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Clostridium perfringens*, *C. tetani*, *Bacteroides* spp, *Listeria monocytogenes*, *Legionella*, *Mycobacterium tuberculosis* and others, *Treponema pallidum*, *Chlamydiae*, *Mycoplasma* etc.

- Viruses: Herpes (herpes simplex, herpes varicellae, cytomegalovirus, Epstein-Barr virus), hepatitis A, B, C, D, E, human immunodeficiency virus, enteroviruses (poliovirus), rubella, mumps, measles, parvovirus B19, RSV, myxovirus, rhinovirus, coronavirus, adenovirus, rotavirus, papillomavirus, rabies etc.

4. Bacteriological and viral syndromes or diseases

Epidemiology, main clinical signs, basis for biological diagnosis, treatment:

- Meninged syndrome.
- Septicaemic syndrome.
- Urinary and genital infections.
- Bacteriological and viral diarrhoeas.
- Respiratory infections.
- Human acquired immunodeficiency syndrome.
- Sexually transmitted diseases.
- Hepatic virus infections.
- Cytomegalovirus infections.

5. Antibiotics and antiviral agents

- Basic knowledge of antibiotics and antimicrobiological therapy.
- Antibiotic and antiviral sensitivity test.
- Antibiotic and antiviral resistant mechanisms.

6. Medical parasitology (including mycology)

6.1. Epidemiology, main clinical signs, basis for biological diagnosis (including a succinct description of parasites and fungi without biochemical characteristics), treatment.

- Amoebiasis: *Entamoeba histolytica*.
- Giardiasis, cryptosporidiosis and uro-genital trichomoniasis.
- Malaria.
- Toxoplasmosis.
- Intestinal, hepatic and urinary helminthiasis: strongyloidiasis, ancylostomiasis, enterobiasis, ascariasis, schistosomiasis (*Schistosoma mansoni* et *S. haematobium*) fascioliasis (*Fasciola hepatica*) taeniasis (*Taenia saginata*).
- Fungal infections (*Candida albicans*, *Cryptococcus neoformans* etc).
- Aspergillus infections (*Aspergillus fumigatus*).
- Dermatophyte infections (*Microsporum canis*, *Epidermophyton floccosum*, *Trichophyton rubrum*, *Trichophyton mentagrophytes*).
- Leishmaniasis.
- Echinococcosis.
- Pneumocystosis.
- Filariasis.

6.2. Usual techniques for parasite and fungus identification.

6.3. Immunological and molecular diagnosis of parasitic and mycologic diseases.

Genetics, in vitro fertilisation

Biological genetics includes cytogenetics and molecular genetics

1. Cytogenetics

At the end of his/her training, the clinical chemist must be able to appreciate the relevance of the prescription, evaluate the cohesiveness of the results, to perform and supervise the realisation of a karyotype and an in situ hybridisation.

1.1. Karyotype

- To know the different analysable materials and the culture requirements.
- To know the culture conditions according to the sample and the indications (medium, support, culture time).
- To perform chromosomal preparations as directed.
- To master the acquisition of the principal types of chromosomal bands.
- To perform high resolution karyotypes (replication bands).
- To perform microscopic examination, display capture on analyser and karyotype classification.
- To know how to supervise and critically analyse: the quality of the chromosomal preparations and the resolution level of the chromosomal bands.
- To appreciate the validity criteria of chromosomal analysis.

2. Molecular cytogenetics

- To know how to perform in situ hybridisation fluorescent technique: centromeric probe, chromosome painting probe, specific probe of a locus on metaphase or interphase.
- To acquire the necessary knowledge to perform comparative genomic hybridisation on microarrays.
- To appreciate the validity criteria of molecular cytogenetics assays.

To be able to describe the analysis strategy of the under-listed abnormalities and to recognise their diagnostic, prognosis and/or therapeutic interest:

- Chromosome number abnormalities.
- Mosaicism.
- Structure abnormalities in equilibrium and disequilibrium.
- Chromosomal microrearrangement.
- Identification of a chromosomal marker.
- Identification of chromosomal variants.
- Chromosome fragility and chromosome breakage syndromes.

3. Molecular genetics

At the end of his training, the clinical chemist must be able to appreciate the prescription relevance, evaluate the cohesiveness of the results, perform and supervise the carrying out of molecular genetics analysis.

3.1. Molecular genetics procedures

- To perform the different procedures of nucleic acid extraction (genomic DNA, RNA, RNApolyA+).
- To perform the different identification methods of point mutations.
- To perform the different identification methods of genomic mutations.
- To perform the different methods of study of DNA polymorphisms (SNP, microsatellites).
- To perform the different nucleic acid quantification methods.

- To perform the different methods of gene expression study at RNA level.
- To acquire the necessary notions to perform and interpret the DNA or cDNA microarrays techniques.
- To appreciate the validity criteria of molecular genetics analysis.

3.2. To be able to describe the analysis strategy of the following pathological types and to recognise their diagnostic, prognosis and/or therapeutic interest:

- Monogenic disorders (autosomal dominant, autosomal recessive, X-linked recessive, X-linked dominant).
- Oligo- and polygenic disorders.
- Mitochondrial disorders.

4. Reproductive medicine

4.1. Basic knowledge

- Sperm count.
- Sperm vitality and motility.
- Sperm morphology: normal spermatozoa and cells other than spermatozoa.
- Antibody coating of spermatozoa.
- Sperm preparation test.
- Interaction tests between spermatozoa and cervical mucus.

4.2. Extended knowledge

- Biochemical assay for accessory sex organ function.
- Computer-aided sperm analysis.
- Assessment of sperm DNA fragmentation and decondensation.
- Knowledge of the WHO criteria for sperm analysis.

5. In vitro fertilisation

- Sperm preparation for fertilisation with frozen sperm or from testicular or epidymal biopsy.
- Fertilisation by conventional IVF.
- Fertilisation by ICSI technic and/or high magnification (IMSI).
- In vitro maturation of the oocytes.
- Oocyte quality.
- Embryo culture from day 1 (pronuclei) to day 6 (blastocysts).
- Embryo quality.
- Blastocyst quality.
- Embryo biopsy.
- Embryo preparation for transfer.

6. Cryopreservation of gametes (sperm and oocyte) and embryos (day 1 to 6).

- Slow cooling.
- Vitrification.

Examples of scientific and medical literature

1. Example textbooks

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Lotze MT, Thomson AW. *Measuring immunity. Basic science and clinical practice*. Amsterdam, Boston: Elsevier Academic Press, 2005.

Doucette LJ. *Mathematics for the clinical laboratory*, 2nd ed. Philadelphia, PA: Saunders Co., 2011.

2. Scientific and medical journals

- Annals of Clinical Biochemistry
- Antimicrobial Agents and Chemotherapy
- Biochemia Medica (<http://www.biochemia-medica.com/>)
- British Medical Journal
- Clinical Chemistry
- Clinical Chemistry and Laboratory Medicine
- Clinica Chimica Acta
- Current Advances in Clinical Chemistry
- European Journal of Clinical Microbiology and Infectious Diseases
- Journal of Biological Chemistry
- Journal of Clinical Endocrinology and Metabolism
- Journal of Clinical Microbiology
- Nature
- New England Journal of Medicine
- Scandinavian Journal of Clinical & Laboratory Investigation
- Science
- The Lancet

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15. CEDEFOP study. Accessed 9 November 2011. Available from: http://cedefop.europa.eu/EN/Files/9021_en.pdf.
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