

CLINICAL-LABORATORY CORRELATIONS AND COMMUNICATION DIAGNOSTIC PROCESS

KLINIČKO LABORATORIJSKE KORELACIJE I KOMUNIKACIJSKO DIJAGNOSTIČKI PROCES

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Abstract

Clinical-laboratory correlations are the most important part of everyday practice in the era of modern clinical medicine. It is based on the successful functioning of the patient-physician (clinician)-laboratory triangle. Laboratory or other diagnostic tests do not define specific clinical entity or disease; however, they are very useful to make decision related to complicated diagnostic procedures and therapies. Each clinical diagnostic process begins with medical history and physical examination where the doctor uses professional and communication skills. This is followed by setting of the working diagnosis and differential diagnosis. Finally, laboratory tests should help in successful diagnosis and treatment. Daily communication between clinicians and laboratory professionals is very important, and teamwork guidelines are based on modern technological achievements, which is the main postulate for effective diagnostic procedures and treatment. Translational medicine has been developed rapidly in the past ten years, representing a two-way communication between basic science and clinical practice. Discovery of biomarkers and different new molecular pathways in the pathogenesis of disease has enabled early detection of disease when it could not be detected by other standard diagnostic methods. This should lead to more successful diagnosis and treatment.

Sažetak

U modernoj medicini kliničko laboratorijske korelacije dio su svakodnevne prakse i temelje se na uspješnom funkcioniranju trokuta bolesnik-lijječnik-laboratorij. Laboratorijsko-dijagnostičke pretrage ne definiraju pojedini klinički entitet, ali pomažu kliničaru u donošenju daljnjih složenijih dijagnostičkih procedura i terapijskih odluka. Svaki kliničko-dijagnostički proces započinje anamnezom i fizikalnim pregledom gdje se liječnik koristi stručnim i komunikacijskim vještinama. Nakon stvaranja radne dijagnoze i diferencijalnih dijagnoza odabiru se laboratorijske pretrage koje trebaju pomoći u što bržem i uspješnijem dijagnosticiranju bolesnikovog problema – bolesti. Svakodnevna komunikacija kliničara i laboratorijskih stručnjaka, donošenje smjernica timskim radom utemeljenih na suvremenim tehnološkim dostignućima preduvjet su uspješnog dijagnostičkog procesa i liječenja. Translacijska medicina se razvija zadnjih desetak godina i predstavlja dvosmjernu komunikaciju između bazičnih znanosti i kliničkih struka. Otkriće biomarkera i molekularnih puteva u nastanku bolesti omogućava ranije otkrivanje bolesti kada se ne može otkriti standardnim metodama. To bi trebalo pripomoći u uspješnijem dijagnosticiranju bolesti i liječenju oboljelih.

1. Introduction

The main goal of modern medicine is extension of human life and improvement of life quality. In this regard, it is necessary to raise awareness of

the importance of the well-functioning patient-physician-laboratory triangle. Clinical and laboratory medicine primarily are aimed at the patient, which is the basic determinant of the World

Health Organization (WHO) definition of health ("Health is a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity") /1/. We use clinical and

laboratory procedures to diagnose the patient's problem in a faster and more efficient way (Fig. 1).

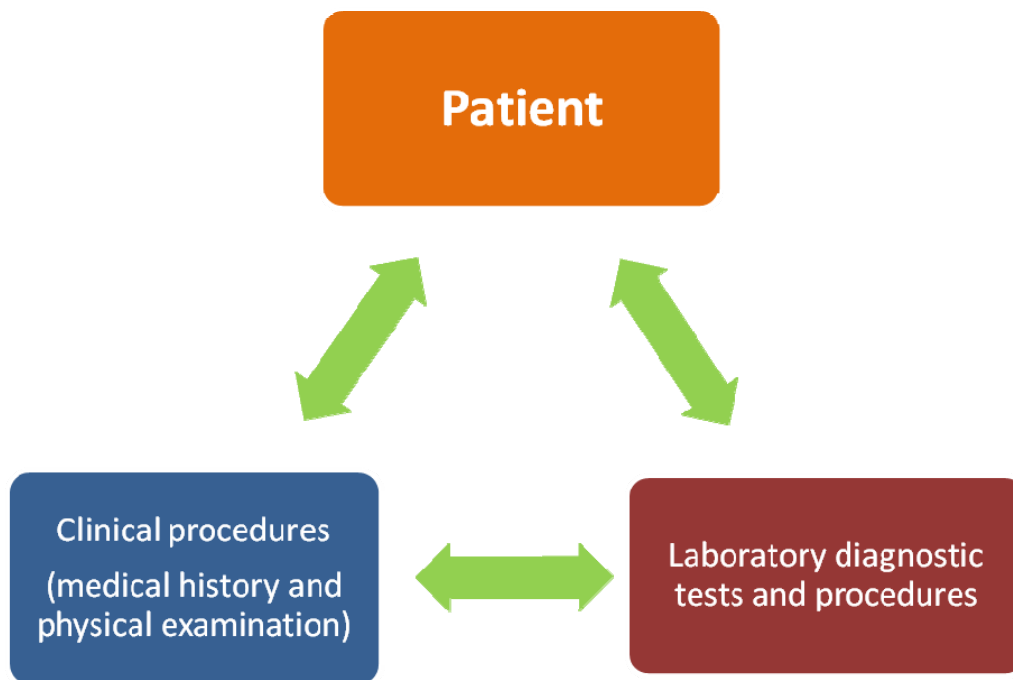


Figure 1. Triangle of interdependence between physicians who perform clinical diagnosis (medical history, physical examination), laboratories (different diagnostic tests) and patient, which is of great importance for successful diagnosis and treatment.

On the other hand studies tend to translate many discoveries from laboratory and basic sciences into clinical practice, which results in the development of translational medicine.

Diagnostic process begins and ends with the patient who has a problem or different symptoms, and is expected to confirm the diagnosis and successful treatment. It begins with taking medical history.

Medical history includes a set of patient data, circumstances, and states or other diseases preceding current illness or disease/2/. These data are collected from the patient or by hetero history (family, relatives) and together with the data obtained during physical examination and laboratory tests are recorded in a special form called medical history. Medical history should be well structured and contain the key information that could help in defining the working diagnosis and other differential diagnoses. Medical history is the essential and most important part of the diagnostic process. Many diseases can be diagnosed or suspected after taking thorough case thoroughly.

Physical examination or 'clinical status' is a procedure in which the doctor recognizes the signs of disease. Physical examination and medical history play a major role in setting the diagnosis /3/. The doctor uses his communication skills, which are important for faster and better history taking. It is important because patients who had direct communication *via* web with their doctors were more satisfied and decisions related to treatment were made easier. It is especially important in hematologic patients who are treated over a long period of time, which is generally associated with a number of possible complications /4/.

Laboratory is the third part of this triangle that helps in diagnostic process. Technological development and modern laboratory tests have provided better and faster diagnosis in a situation when different diseases have similar symptoms and signs. Based on these discoveries, new clinical entities have been identified.

2. Clinical diagnosis

Clinical diagnosis is the first and of ten the most important part of the diagnostic process; it reveals and defines the patient's problem or disease. The patient is admitted because of some problems (symptoms such as chest pain, abdominal pain,

dysuria, headache, neck swelling, etc.), followed by clinical diagnosis with history taking, physical examination and laboratory testing. Therapy or treatment is the final step of the clinical procedure (Fig. 2).

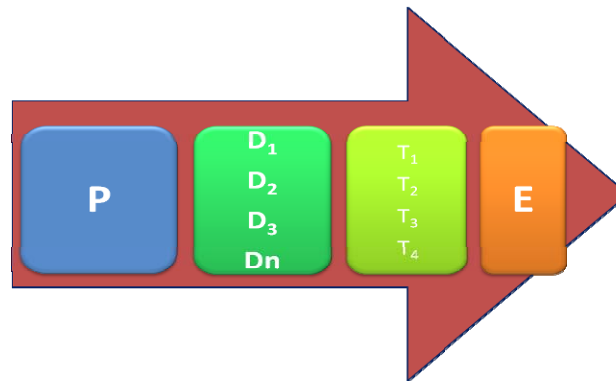


Figure 2. Clinical diagnosis and practice: P = appearance of problem (sign, symptom, or some laboratory findings); D = definition of problem, working diagnosis and differential diagnosis; followed by T = treatment or therapy; and E = evaluation of therapy or treatment.

The patient should be in the center of diagnostic process. This requires development of clinical research,

improvement, training and evaluation of diagnostic procedures and tests (Table 1).

Table 1. Relationship and association among the symptoms experienced by patients, signs discovered by physical examination, and differential diagnosis or working diagnosis

MEDICAL HISTORY (SYMPTOMS)	PHYSICAL EXAMINATION(SIGNS)
Neck tumefaction or swelling	Enlarged lymph node, palpable tumor (size, consistence), additional signs (fever, weight loss). (diff. dg. lymphoma (NHL, Hodgkin's lymphoma, metastasis, inflammation (phlegmona, folliculitis)
Chills, cough(dry, productive), chest pain	Fever, impaired breathing, sound auscultation phenomena, rales/crepitation(diff. dg. pneumonia, bronchitis, pleurisy, etc.)
Abdominal pain in right upper quadrant, yellow skin	Hepatomegaly, painful tense wall, jaundice(diff. dg. cholecystitis, gallstones, hepatitis, cholangitis, obstruction of biliary tree)
Discomfort and dullness in left upper quadrant	Splenomegaly (diff. dg. portal hypertension, myeloproliferative neoplasms, CML, myelofibrosis), lymphoproliferative neoplasms
Nocturnal dyspnea, chest pain, shortness of breath, rest dyspnea	Impaired breathing sound, rales, crackles heart murmur, blood pressure (diff dg. Cardiac failure, myocardial infarction, valvular disease, myocarditis, pericarditis, etc.)
Dysuria, discomfort during micturition, chills, fever, hematuria	Lumbar succussion, pain localization, fever (diff. dg. urolithiasis, pyelonephritis, prostatitis, cystitis)

Diagnosis defined as identification of diseases that should answer the following questions: 1) which system is affected?; 2) what are structural

changes and their localization?; 3) what is the nature of the process (benign or malignant)?; 4) does the disease cause or lead to functional im-

pairment?; 5) is there a known cause of the disease – etiology?; and 6) outcome of disease – prognosis /5/.

The role of clinician

The clinician is responsible for conducting the clinical process, primarily for the implementation of diagnostic procedures and diagnosing the patient's problem. The clinician collaborates with experts from various fields (e.g., microbiologists, cytologists, pathologists, immunologists, medical biochemists and hematologists, radiologists, etc.). It is crucial to decide what data/information should be collected, what laboratory and diagnostic tests should be looked for, how to interpret the information from the tests and examinations requested, and eventually to prescribed appropriate therapy/treatment.

The clinician collects information on the patient and his disease based on: 1) medical history, 2) physical examination (status), 3) laboratory and diagnostic tests (hematology, biochemistry, coagulation, molecular, cytology, immunology, histology, cytogenetics, endoscopy, electrophysiology, functional, radiology, etc.). Defining medical problem should be made in each patient individually.

Diagnostic process is not always easy despite clinical and laboratory diagnosis; however, it can be exhausting for both the patient and the clinician. Definitive diagnosis is set after developing a number of different hypotheses or differential diagnoses that explain the problems, which can cause the disease. The final or the most likely diagnosis is defined in the process by eliminating or confirming differential diagnosis /6/, /7/ (Fig. 3)

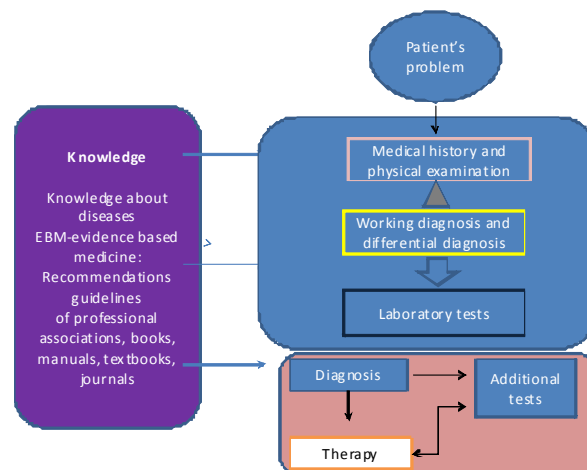


Figure 3. Clinical and diagnostic process: the patient presents to physician (clinician) because of problems (symptoms, signs of disease). Laboratory diagnostic tests and procedures can be performed after data collection from the patient (medical history, physical examination), based on working diagnosis and differential diagnosis. The following step in the process is diagnostic-therapeutic decision, definitive diagnosis and treatment/therapy. Additional data/information should be obtained by other diagnostic tests if the problem (disease) cannot be diagnosed. Knowledge represents data on the diseases, symptoms, signs or tests which are disease-specific; EBM = evidence based medicine

Evidence-based medicine (EBM) (sometimes called evidence-based health care or EBHC) has been defined as "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients⁶. The five steps of EBM in practice were first described in 1992/8/:

1. Translation of uncertainty to an answerable question and includes critical questioning, study design and levels of evidence/9/
2. Systematic retrieval of best evidence available /10/

3. Critical appraisal of evidence for internal validity that can be broken down into aspects regarding /11/

- systematic errors as a result of selection bias, information bias and confounding
- quantitative aspects of diagnosis and treatment
- the effect size and aspects regarding its precision
- clinical importance of results
- external validity or generalizability
- Application of results in practice /12/

Evaluation of performance

All created algorithms, protocols or recommendations for the selection of necessary tests for the most common cases are based on EBM postulates and clinical studies. Algorithm is a step-by-step method of solving a problem or making decisions, as in making a diagnosis. Algorithms and other recommendations for treatment are published and supported by professional associations, and should be accepted by the health ministry, authorities and health insurance. Recommendations are general and should be critically applied to indi-

3. Laboratory diagnostic tests

Simple diagnostic tests are used in each treatment routinely and some of them almost daily, e.g., erythrocyte sedimentation rate (ESR), complete blood count (CBC), glucose, urea, creatinine, potassium, sodium, etc. The second group consists of tests that are used weekly, e.g., bilirubin, liver

enzymes aspartate transferase (AST), alanine transferase (ALT), gamma glutamyltransferase (γ GT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), total proteins, C-reactive protein (CRP), protein electrophoresis, prothrombin time (PT) and international sensitivity ratio (International Normalized Ratio, INR) (Table 2).

vidual cases; what is more, sometimes it requires some deviation /13/. The physician (clinician) who is responsible for the patient takes responsibility for the whole diagnostic process and treatment. Physician in charge often contacts and requires consultant physicians of other specialties, sharing in this way responsibility for planning, implementation and evaluation of the diagnostic procedures proposed /14/.

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Table 2. Common laboratory tests that indicate some common diseases

Laboratory test	Disease/condition
Glucose tolerance test (glycemia)	Diabetes, hyperglycemia, hypoglycemia, glucose intolerance
Creatinine and urea	Renal failure (acute, chronic)
Complete blood count	Anemia, leukemia, leukocytosis, thrombocytopenia, etc.
Lactate dehydrogenase (LDH)	Anemia (megaloblastic, hemolytic), malignancies, pulmonary embolism, acute pancreatitis, pneumonia, myocardial infarction
Liver enzymes (ALT, AST, γ GT, ALP)	Hepatocellular damage (viral hepatitis, autoimmune hepatitis, ischemia), cholestasis (primary biliary cirrhosis, bile duct diseases)
Prothrombin time (PT) and international normalized ratio (INR)	Liver cirrhosis, end stage liver disease, anticoagulants (warfarin), disseminated intravascular coagulation (DIC)
C-reactive protein (CRP)	Infections, noninfectious inflammatory diseases, autoimmune diseases, malignancies

These tests are standard and in more than two-thirds of cases can indicate possible pathologies. Besides blood tests, other diagnostic procedures often include electrocardiogram (ECG), chest x-

ray, and blood type in case of urgent surgery or severe bleeding or hemorrhagic diathesis /15/, /16/. In addition to these tests, screening tests (such as tumor markers) are aimed at the most common

diseases in the population, e.g., prostate specific antigen (PSA), carcinoembryonic antigen (CEA), Papanicolaou smear cytology (Pap test), thyroid

stimulating hormone (TSH), alpha fetoprotein (AFP), etc. (Table 3).

Table 3. Laboratory screening tests for diseases posing public health problems

Laboratory/diagnostic test	Disease
Breast ultrasound, mammography	Early detection of breast cancer
Thyroid-stimulating hormone (TSH)	Hypo/hyperthyroidism
Prostate-specific antigen (PSA)	Early detection of prostate cancer
Carcinoembryonic antigen (CEA)	Detection of colorectal carcinoma
Alpha-fetoprotein (AFP)	Liver cirrhosis, hepatitis, hepatocellular carcinoma
Papanicolaou test (Pap test)	Early detection of cervical carcinoma
Ferritin	Sideropenic anemia

Screening tests may be universal (general population) or selective (different groups at a high risk of a specific disease). A large number of these tests have false-negative or false-positive value /17/, /18/.

Access to routine laboratory processing must be logical and rational, based on clinical procedures of medical history and physical examination (status). Laboratory or diagnostic targeted approach should contain a set of tests that hold the key findings important for diagnosis. Physicians (clinicians) use tests attempting to confirm the working diagnosis and to make definitive diagnosis. Abnormal laboratory findings detected incidentally maybe the beginning of further diagnostic process /19/, /20/. A properly taken medical history and physical examination are a cornerstone for further diagnostic process, however, they cannot explain abnormal laboratory test. Use of faster, simpler, less expensive or less unpleasant tests/procedures is justified if it satisfies the principle of targeted approach. It is important to weigh the cost and benefit of aggressive and invasive procedures against the possible complications. Any significant deviation of laboratory findings, especially when it is not expected, should be discussed with laboratory expert who performed the test /21/. Modern medicine should be based on teamwork because contact and collaboration between clinicians and laboratory experts help avoid misunderstandings, mistakes and unnecessary diagnostic tests that can be potentially harmful.

4. Translational research and clinical practice

Translational research is scientific research and facilitates the translation of findings from basic science to practical applications that enhance human health and well-being. Biomedical science

has opened a new period after discovering the genome and proteome function, and it is expected that the development of novel drugs and targeted molecular therapies will help in the treatment of malignancies and chronic diseases. Development of new drugs has become more complex because of the increasing need of integration of different segments of biomedical disciplines, which are aimed at improvement of treatment, while reducing the time elapsed from the basic drug research to clinical trials and practice. Translational research refers to two distinct domains: T1 research, the 'bench-to-bedside' process of translating knowledge from basic sciences to the development of new treatments; and T2 research translating the findings from clinical trials to everyday practice /22/, /23/.

Translational medicine provides new opportunities in the development of targeted research projects that result in a more efficient research followed by rapid and successful development of new drugs. One of the greatest contributions of translational science is a new reclassification of diseases based on the well-known molecular characteristics of diseases, for example, the new classification of acute leukemias /24/. This approach has great potential to detect disease before the onset of symptoms, based on the knowledge of the specific interaction of molecular pathways that lead to the symptoms. Such a progress could reduce the cost of treatment and follow-up of patients.

Translational medicine is based on translational science, which is derived from the association of public research institutions, academia, health care institutions, and industry (e.g., pharmaceuticals). The main prerequisite is integration of basic research and clinical medicine, and the main goal is to identify novel drugs that should be easily accessible /25/. Translational science is based on two-

way communication between basic researchers and clinicians because clinicians can provide feedback and samples for basic researchers/26/. Biomarkers (biologic markers) have helped researchers and clinicians in conducting research and monitoring therapeutic response to novel drugs. Biomarkers are indicators of early response to treatment; they assist in defining the drug dose, and can predict the possible drug toxicity. Translational science based on biomarkers can be a reliable tool for clinical experimental models to reduce the length of phase II clinical trials (investigation) /27/. In this stage, the new drug is administered for the first time and the results obtained can prove the efficacy and preliminary safety of a new drug (therapy). Phase II is significantly shorter because multicenter trials are conducted after the drug has been tested in phase I. This would reduce the time of drug development for several years, as well as the number of high-quality and valuable molecules that take part in the final stages of testing; eventually, they would be more readily applicable in clinical practice.

Translational studies are applicable in many areas of biological sciences and medicine, first of all they have shown special interest and benefit in oncology and chronic diseases addressed by various public health activities (i.e. prevention of obesity) /28/.

The molecular basis of disease and targeted therapies

Translation of knowledge from molecular basis to clinical treatment of disease according to patient individualized treatment protocol is found in oncology and hematology. It is considered that cancer and tumors of hematopoietic tissue are due to molecular disorders that cause the disease, therefore these diseases require treatment with targeted therapies that specifically act upon molecular disorder. Using biomarkers and sophisticated diagnostic scan help in conducting targeted therapy, either with biologic drugs (proteins, peptides, antibodies) or with small chemical molecules. We mention the following examples: the type of *K-RAS* mutation is necessary for good clinical response of antibodies against the epidermal growth factor (EGF) receptor in colorectal cancer. Overexpression of the *HER2* receptor is required for good clinical response to treatment with Herceptin in breast cancer. Furthermore, the expression of estrogen receptors in breast cancer predicts response to therapy with selective

estrogen antagonists, such as tamoxifen /29/. Expression of the CD20 positive receptor on lymphoma cells, primarily B giant cell lymphoma and follicular lymphoma, is important for treatment with the anti-CD20 antibody rituximab, which has finally increased survival and curability/30/.

5. Clinical approach to laboratory tests and the importance of teamwork

Laboratory medicine has been developing rapidly in the last few decades. New discoveries and the application of modern and precise laboratory tests change the guidelines for diagnosis and treatment, which is obvious in internal medicine /31/. Technological advances are quickly implemented in laboratory tests, thus facilitating and accelerating diagnostic process. Clinicians are aware of such developments in daily work, as demonstrated by the implementation of new laboratory methods (molecular biology, cytogenetics, and radiological imaging methods such as magnetic resonance imaging (MRI) and positron emission tomography (PET)) that provide valuable diagnostic and therapeutic information while reducing adverse effects, such as ionizing radiation. Conventional glucometer can be replaced by a glucometer using infrared radiation, rapid test of buccal smear for detection of HIV, proteomics, etc. /32/, /33/, /34/.

The accuracy, specificity and sensitivity of laboratory tests have been increased significantly, but clinicians define definitive diagnosis through a complex process that is based on medical history, physical examination, laboratory and other tests, their own knowledge and experience. Communication and close cooperation between clinicians and different laboratories are necessary in daily work, and modern diagnostic process is based on teamwork. All team members should stream to the same goal and each member should know the basic work principles of all other members, restrictions and difficulties in work within the team. The team develops recommendations and guidelines, determines the tests to be done in specific situations as to rationalize the utilization of health resources and limit excessive and unjustified use of tests. Every physician-clinician should know what is expected from each laboratory test because finding does not mean diagnosis. Laboratory tests are a link between medical history and physical examination. Clinicians and laboratory

professionals should know the limitations of tests, clinical validity and test value (sensitivity, specificity, positive and negative predictive value) /35/, /36/.

Considering healthcare system financial limits and need of rationalization, pharmacoeconomic analysis should be performed to define necessary tests, patient groups where these tests are diagnostic, prognostic, and financially feasible. Laboratory receives loads of biological materials (blood, urine, stool, effusions, ascites, aspiration, swabs, cerebrospinal fluid, etc.) on a daily basis. Each sample should be delivered in optimal medium and within appropriate time window, taking care of the interval between sampling, storage and analysis. The physician-clinician should write the diagnosis on each referral. Some important laboratory and clinical findings should be highlighted if cytologic or histopathologic tests are requested /37/, /38/. Clinicians and laboratory experts communicate daily by telephone or electronic media (web), which facilitates routine work on the ward, in out patient clinic and in emergency department. It is important to know numerical value, test ranges and standard deviations because such a positive test could deviate an original plan of initial diagnostic procedure. Laboratory experts play a dominant role in providing the physician with information on the possible errors in particular tests.

The main task of laboratory medicine is the interaction between laboratory professionals and clinicians in choosing the best selection of diagnostic tests and upgrading their interpretation, thus improving the efficiency of clinical diagnosis. Laboratory and diagnostic tests are a significant source of additional information on the patient. Laboratory tests are not therapeutic; however, these tests have a great value only in combination with medical history and physical examination to confirm the diagnosis. They provide important information on the patient's therapeutic response /39/, /40/, /41/. Before each sampling and performing laboratory tests or diagnostic procedures, the clinician should know what kind of test is performed and explain to the patient in an understandable way the indications, contraindications and the possible side effects of the test or examination. The patient should sign an informed consent form if the test may be associated with some complications, side effects or adverse effects. The procedure should first be explained in detail (e.g., pleural puncture, cerebrospinal fluid puncture,

bone biopsy, etc.), considering the ethical and legal framework. The clinician must know how to handle the material during diagnostic procedures (e.g., tissue sample for histopathologic analysis), what clinical implications and further investigations are required after pathologic test results or interventions. Eventually, the clinician should know the factors that can yield false-positive or false-negative result. Each test or investigation requires clinical interpretation. The physician-clinician should think of the next steps in diagnostic process, patient monitoring, and decisions about therapy (conservative, surgery) or further follow-up.

6. Conclusion

In modern medicine, clinical laboratory correlations are part of everyday practice. Every clinical diagnostic process begins with the patient. None of the tests and investigations by itself can define a specific clinical entity or disease. Therefore, constant communication between clinicians and laboratory professionals, exchange of information and opinions should facilitate diagnostic process and improve patient treatment. In the last decade, translational medicine has been developing based on transitional research, which is a two-way communication between basic science and clinical expertise. Discovery of biomarkers, different molecular pathways in the pathogenesis should detect disease before the onset of clinical symptoms or signs, which should certainly contribute to earlier successful diagnosis, better treatment and cure, which is the main determinant of clinical laboratory correlations.

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