

LABORATORY MEDICINE

NOTES ON LECTURES AND SEMINARS
FOR POSTGRADUATE STUDENTS



Gustav Kovac
Anna Porubenová
and

Jozef Glasa, Lubomir Danisovic, Pavel Blazicek, Michal Farkas,
Michal Ondrejcek, Daniel Kuba, Monika Drakulova, Jan Trupl

and

Stefan Keckes, Stanislav Oravec, Ivan Malik, Stefan Matyas, Lucia Hudecova, Eva Zenkova



LABORATORY MEDICINE

NOTES ON LECTURES AND SEMINARS
FOR POSTGRADUATE STUDENTS

**Gustav Kovac
Anna Porubenová
and**

**Jozef Glasa, Lubomir Danisovic, Pavel Blazicek, Michal Farkas, Michal Ondrejcek, Daniel Kuba,
Monika Drakulova, Jan Trupl**

and

Stefan Keckes, Stanislav Oravec, Ivan Malik, Stefan Matyas, Lucia Hudecova, Eva Zenkova

Dr. Josef Raabe Slovakia, s. r. o.

Professional publishing house

Member of the KLETT Group

Heydukova 12 – 14, 811 08 Bratislava

Telephone: 02/32 66 18 40

E-mail address: raabe@raabe.sk

www.raabe.sk

Managing Director: Mgr. Miroslava Bianchi Schrimpelova

Copyright:

© Dr. Josef Raabe Slovensko, s. r. o., 2024

© authors of contributions

All rights reserved.

All rights reserved. No part of this work may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording or by any available transmission of information without the written permission of Dr. Josef Raabe Slovensko, s. r. o., except for reviews, where short passages are quoted for the sake of including the review in magazine, newspaper or broadcast.

Authors:

prof. MUDr. RNDr. Gustav Kovac, CSc., MBA, MUDr. Anna Porubenova, MPH,

prof. MUDr. Jozef Glasa, PhD., doc. RNDr. Lubomír Danisovic, PhD.,

doc. Ing. Pavel Blažicek, PhD., Dipl. Ing. Michal Farkas, doc. MUDr. Michal Ondrejčák, CSc.,

MUDr. Daniel Kuba, PhD., MUDr. Monika Drakulova, prof. RNDr. Jan Trupl, CSc.,

MUDr. Stefan Keckes, prof. MUDr. Stanislav Oravec CSc., prof. PharmDr. Ivan Malik PhD.,

PharmDr. Stefan Matyas PhD., Dipl. Ing. Lucia Hudecova, RNDr. Eva Zenkova PhD.

Reviewer: prof. MUDr. Oliver Racz, CSc.

Project manager. Mgr. Monika Sera

Publication category: university lecture notes

Issue: first

Year of publication: 2024

ISBN: 978-80-8301-033-8

DEDICATION AND THANKS

We dedicate this publication to our teachers

- MUDr. Koloman Pronay, Head of the Department of Internal Medicine of the NsP OUNZ Trnava
- MUDr. Radko Menkyna, Head of the Department of Internal Medicine of the NsP akad. L. Derer and Director of the Institute of Medicine Bratislava
- prof. MUDr. Rastislav Dzurik DrSc., Internist, Nephrologist, Director of the Institute of Clinical and Preventive Medicine in Bratislava

for the efforts made in our education in the spirit of clinical and laboratory collaboration

We would like to thank

- prof. MUDr. Tibor Sagat CSc., Minister of Health of the Slovak Republic
- prof. MUDr. Roman Kovac CSc., Minister of Health of the Slovak Republic
- prof. MUDr. Jan Stencl CSc., Rector of SZU
- Dr. h. c. prof. PhDr. Dana Farkasova CSc., Rector of SZU
- MUDr. Jan Gajdos, Director of the Health Department of the Ministry of Health of the Slovak Republic

for supporting our efforts to establish the new medical specialty of laboratory medicine

Thank you

- Dr. h. c. prof. MUDr. Peter Simko CSc., Rector of SZU
- prof. MUDr. Anna Remkova DrSc, former Dean of the Medical Faculty of SZU
- doc. MUDr. Martin Gajdos CSc, Dean of the Medical Faculty of SZU
- Dr. h. c. prof. PhDr. Dana Farkasova CSc., Dean of the Faculty of Philosophy and Sociology of SZU

for supporting our teaching and publishing activities

Finally, we would like to thank

prof. MUDr. Marian Bernadic CSc.

for professional editing

prof. Lubica Kovacova

for language editing

Mgr. Monika Sera from Raabe publishing house

for technical adjustments

Ing. Vladimir Hudak, Head of Medical Projects Department, Raabe Publishing House

for support with the publication

Working with them has always been, is and will always be a great pleasure

Gustav Kovac

PREFACE

College textbook

- prepared for students of postgraduate specialization studies in laboratory medicine, clinical biochemistry – physicians and laboratory diagnosticians, for whom we provide this study.

Goal

- to create a comprehensive system of knowledge about laboratory diagnostics from the perspective of a physician/laboratory diagnostician working in a clinical laboratory and at the same time collaborating with clinicians.

This requires knowledge and practical skills in

- pathophysiology
 - laboratory methodologies
 - the clinical course and manifestations of diseases
- all from the perspective of the clinical laboratory.

The text is divided into 11 chapters

- Clinical Laboratory
- Molecular pathology
- Clinical Chemistry
- Urine and body fluids
- Cytogenetics
- HLA
- Hematology
- Coagulation
- Clinical Microbiology
- Immunopathology
- Transfusiology

Each chapter is divided into three sections

- Introduction
- Laboratory context
- Clinical context

In the introduction

- we focus on the pathophysiological nature of the problem, we look at the typical pathophysiological features and characteristics of the diseases, so that the student has a clear idea of what we are talking about
- without knowledge of the pathophysiological principles, you can't make any progress in laboratory diagnostics

In a laboratory context

- the range, categories, types and especially the principles of laboratory procedures and methodologies used in the clinical laboratory, including instrumentation and information technology
- the laboratory context is the essence of laboratory diagnostics and is therefore the main focus and concentration on the subject

In a clinical context

- we focus on the symptomatology and syndromology of diseases and their relationship to the results of laboratory tests – i.e. the indication and interpretation of laboratory parameters in the diagnosis, differential diagnosis and monitoring of individual diseases
- we recommend using the clinical context as a basis for clinical consultation. Without ensuring communication between the clinical laboratory and the clinic, there is no reliable laboratory diagnosis

Laboratory diagnostics

- cannot be carried out in isolation,
- but always only in a clinical context – in direct contact in the diagnosis, differential diagnosis, therapy or monitoring of a specific clinical case

This is the problem of physicians and laboratory diagnosticians

who work in the clinical laboratory,

- the clinical laboratory represents the interface (cutting edge) between the clinical and the laboratory,
- providing laboratory results for clinicians is the foundation of a clinical laboratory's existence,
- rational indication and qualified interpretation of laboratory tests is the other side of the coin, without which it is impossible to ensure quality laboratory diagnostics
- bridging this gap between the clinic and the laboratory is the main mission of physicians and laboratory diagnosticians working in the clinical laboratories
- knowledge and experience are essential to master the communication between clinic and laboratory
- the biggest risk in performing this task is the high workload and the resulting slippage into routine

Laboratory medicine

- attempts to bridge the aforementioned issue

In the presented undergraduate textbook

- with a defined focus and scope
- it is not possible to discuss all the tests that can be performed in the clinical laboratory
- nor all aspects of their indication and interpretation

We have drawn on more than 30 years of experience and focused on only the most important ones from our point of view.

In conclusion, we would like to point out that

- errors in laboratory diagnosis whether due to
- non-compliance with a laboratory procedure (faulty laboratory examination)
- incorrect choice of laboratory parameter (indication)
- or its incorrect evaluation (interpretation),

can lead to serious harm to the patient or even death

Gustav Kovac

DEDICATION AND THANKS	3
PREFACE	4
CONTENTS	6
1. CLINICAL LABORATORY	7
2. NOTES ON MOLECULAR PATHOLOGY	50
3. NOTES ON CLINICAL CHEMISTRY	82
4. NOTES ON THE EXAMINATION OF BODY FLUIDS	174
5. NOTES ON CYTOGENETICS	212
6. NOTES ON HLA: MAJOR HISTOCOMPATIBILITY SYSTEM	243
7. NOTES ON HEMATOLOGY	262
8. NOTES ON COAGULATION	320
9. NOTES ON CLINICAL MICROBIOLOGY	340
10. NOTES ON IMMUNOPATHOLOGY	418
11. TRANSFUSIOLOGY	476
CONCLUDING REMARKS	518
LITERATURE	521

1. CLINICAL LABORATORY

**Gustav Kovac
Anna Porubenova
Jozef Glasa**

CONTENTS	PAGE
1.1 Notes on general management principles	8
1.2 Notes on clinical laboratory management	12
1.3 Notes on business management	17
1.4 Notes on safety in the clinical laboratory	27
1.5 Notes on the interpretation of the laboratory result	34
1.6 Notes on laboratory information systems	38
1.7 Notes on ethics in laboratory medicine	42

1.1 NOTES ON GENERAL MANAGEMENT PRINCIPLES

TOPICS

- General management principles
- Fundamentals of clinical laboratory management
- Clinical laboratory business management
- Safety in the clinical laboratory
- Interpretation of laboratory tests
- Information systems in the clinical laboratory
- Ethics in laboratory medicine
- Conclusions to the clinical laboratory

DEFINITION

Management

- is an activity by which a manager achieves his/her goals through the work of other people

Job description of the manager

by Fayol

- planning
- organising
- motivating
- coordination
- check

by Mintzberg

- decision-making
- informing
- working with people

Stages/process

- strategy – formulation of the intention
- tactics – definition of objectives
- operative – specific tasks

Objectives

- short-term (operational) – days to weeks
- medium-term (tactical) – weeks to months
- long-term (strategic) – months to years

Planning techniques

- milestones – e.g. tasks are set and reviewed weekly – a process suitable for project planning and implementation
- key events – recording them in the calendar (meeting dates) – a process suitable for planning/ recording routine events – as they come
- networked – connecting milestones and key events into one whole – project and current events complement each other

Check

- the process of evaluating inputs, processes and outputs
- based on the feedback loop, we find out whether we have achieved the set goals

Planning
and control

Meeting needs,

which can be arranged hierarchically from the lowest to the highest level

- physiological (hunger)
- security (occupation)
- group (religion/politics)
- leadership (leading place)
- higher order (culture/charity)

Factors of dissatisfaction

- the main function of money is to remove dissatisfaction
- a good salary removes dissatisfaction, but does not motivate you to perform at a high level

Factors of motivation

- career progression
- gaining recognition
- the satisfaction of your own work

Team

- is a group of workers, optimally numbering 5 – 7, working towards a common goal

Stages of team building

- forming (forming)
- storming (confrontation)
- norming (norming)
- performing (activity)

Roles of individual team members

- head
- explorer
- monitor
- worker
- finisher
- maintainer of team spirit

Problems in the team's activities

- *cycling* – poor communication with the environment + concentration on solving own problems + loss of sense of reality
- *scapegoat* – when failures occur, there is a need to personalize the cause of the failure

Drivers of change

- economic
- social
- technological
- political

Change

- occurs when the balance between the driving and braking forces is disturbed
- always provokes resistance

To overcome the change, it is possible to use

- education
- communication
- coercion
- support
- handling
- negotiation
- Engaging

Motivation

Team

Change management

It is important to evaluate

- where we came from
- where have we got to
- how we got there

**Selection
of staff**

Staff shall be selected on the basis of

- analysis and job description
- specifications of personal characteristics
- questionnaires (indicative selection)
- by personal interview

Once a worker has been selected, it is essential in the long term to pay attention to

- development – education and training
- performance evaluation – feedback

**Leadership
and management
styles**

A leader

- motivates
- innovates
- introduces changes
- changing the organisation's activities for the better

The manager is the administrator

- maintains the status and activities of the organisation at a high level

Management styles

Autocratic

- the leader decides alone

Democratic

- the head decides on the basis of majority

Laissez fair

- the manager shall leave the staff to their own discretion and, if necessary, shall intervene as they see fit

No management style can be said to be ideal

- it's more about adapting the style to the specific circumstances
- if tasks need to be completed quickly or workers are not very educated, an autocratic style prevails
- if there is enough time and the workers are educated, the democratic style prevails

**Organisational
structure**

Organisational structure ("organisational spider")

- represents the division of the organisation into individual departments and divisions
- reflects the nature of the organisation's activities

Division of the organisation

- is conditional on the division and description of work

There is always a natural conflict embedded in the organisational structure between

- centralisation (where the ultimate consequence of this trend is cost reduction)
- and decentralisation (where the ultimate consequence is an increase in quality) of activities, products and services
- ultimately, it is a question of finding the right balance between centralisation and decentralisation for the specific situation

**Organisational
culture**

Organisational culture

- is the sharing of the values, beliefs and traditions that prevail in the organization
- it's about relationships – how things are done and how problems are solved

Types of organisational cultures

- *centralist* – a web with one centre – the chairman decides – an example is a political party

- *bureaucratic* – the structure of a power pyramid where everyone has a place, rights and responsibilities – an example is the government and ministries
- *matrix* – there is a blending of management structures in the soap of the “x” and “y” axes – an example is a university hospital – the x-axis follows the hierarchy of teaching, the y-axis follows the hierarchy of the provision of curative and preventive activities (this culture is the most suitable for development, but suffers from the problem of loyalty)
- *club-like* – there is no superiority and subordination – everything works on the basis of the principle of chance – examples are artists and scientists

Outdoor environment

- the space in which individuals and organisations are found (the internal environment)

**Outdoor
environment*****External environmental factors***

- competition
- market
- Sociology
- technology
- policy
- economy

Their basic characteristic is that

- we cannot determine them,
- but we have to adapt to them

1.2 NOTES ON CLINICAL LABORATORY MANAGEMENT

1.1.2 NOTES ON COSTS

- *Strategies*
- *Fiscal system*

Strategies

- outdoor and indoor environment

Fiscal system

- financial decision-making
- outsourcing vs buying, leasing reagent rental analytical equipment

The role of the laboratory diagnostician

- Medical priorities, planning, management/control, anticipation (technology and external environment)

Problems

Fundamental problems

- regulation
- hidden costs
- information system

Cost control

- Automation
- prevention of additional costs
- eficiencia
- Budget

Laboratory costs

Direct costs

- wages
- reagents
- blood (unpredictable nature of costs + costs of communicable disease testing)
- tests that cannot be carried out in the laboratory due to the absence of an analyst or expert
- capital investments: purchase, leasing, rental, special contracts

Indirect costs

- indirect (material, wages, other) = overhead
- marketing
- Administration

Fiscal system

Chart of accounts

Results

- $\text{assets} = \text{liabilities} + \text{principal}$
- $\text{income} - \text{expenditure} = \text{net income (profit or contribution)}$

NOTES TO PROFIT AND LOSS

Contributional margin

- the difference between the price of the examination and the variable cost of the examination

Contribution and profit margin

- profit (net income) = income – expenses
- contribution = income derived from tests produced by the laboratory – costs for which the laboratory is responsible

Impact of “contribution” on the pricing process

- competition, government regulations, other restrictions, treaty restrictions

Managerial responsibility and “contribution margin”

- for market expansion, select only those examinations that will have the most positive impact on the “contributinal margin”

BUDGET NOTES**Principles**

Financial plan in EUR + targets

- projection of the strategy into the operational plan
- operational plan and budget

Projection:

- workload
- estimation of resources
- estimate of direct costs
- calculation of indirect costs
- Balance of income and costs

Budget analysis

- where resources are consumed
- how quickly resources are consumed
- estimation of the causes and their link to the place where the costs are incurred

Departmental budget analysis and allocation of costs to individual sections

- allocation of costs of general functions between posts
- laboratory department budget
- laboratory example

NOTES ON THE CLINICAL CONTEXT**Definitions**

- the role of accounting is to measure, report and control the inputs and outputs of the laboratory

Financial accounting

- presents a point of view for the purpose of presentation to the external environment of the company

Management accounting

- (“responsibility accounting” = responsibility for costs incurred per unit of output = viewpoint from “inside” the firm)
- The smallest unit that can be costed is the product (product)

Cost categories for determining operational costs

- variable, fixed, semi-fixed
- direct, indirect

Accounting for examination and laboratory services

- wages
- Material
- indirect costs

Accounting focused on diagnosis categories

- allows you to calculate the cost of each category of diagnosis
- the basis is the cost of 1 test for each spectrum test provided by the laboratory

Activity-based accounting

- linking the consumption of fiscal resources to the places where the costs are generated
- direct costs
- indirect costs

The role of accounting in variance analysis

- a comparison of the actual variation (deviation) from the planned budget
- explanation (identification of the cause) of the deviation
- corrective measures

Pricing of examinations: a “buy or sell” decision

Strategies

- communication at all levels
- comparative strategy
- cost strategy
- strategy based on intuition
- knowledge and understanding of the market, regulation and competition
- large companies: pricing leaders
- ethics must prevail in some situations

Economic basis for setting prices or charges

- example of price analysis

Selling price

- covering direct costs
- covering a realistic estimate of indirect costs
- the provision of a satisfactory profit

Billable examination

- only if it is reimbursed, it generates income

Methods of calculating prices or charges

- profit maximisation
- return on invested capital
- conversion costs
- contribution margin
- standard costs
- direct costs
- total costs
- relative value

Make or buy decision

- consider the quality of the examination offered
- compare the cost of in-house testing with the cost of outsourcing
- medically necessary TAT statute
- evaluate consultation skills and clinical insight
- estimate logistics problems

The breaking point

- break-even point = fixed expenses + expected profits/revenue – variable expenses

“Management and prevention” of costs

Causes

- Prerequisites
- the output of the examinations is directly proportional to the clinical requirements
- costs are directly proportional to the output of the laboratory tests, provided that the maximum efficiency point is not exceeded and compliance with regulatory and quality requirements does not require additional procedures
- constant indication of inputs without reduction of outputs escalates the cost of the examination

- lack of information on clinical needs
- lack of education on rational indication
- increasing workload
- how to reduce unnecessary costs

Notes on solutions

Adequate education

- providing assessments of the quality and adequacy of the indication

Pareto principle (80/20 rule)

- focus on the most frequently indicated examinations

Managerial control through interpretive commenting on results

- cumulative findings, educational comments

Managerial control of the indication of optimized diagnostic clusters

- fewer resources used on the one hand and unchanged quality of outputs on the other

Management control using the support of “indicator leaders”

- clinical leaders influence indication behaviour

Reducing the importance of the indication of “multitest profiles”

- repeated examinations, reflex testing

Providing higher efficiency in automated areas of the laboratory

- ill-considered choice of automatic analysers

Stricter budget monitoring

- 80% of the most commonly used tests are underestimated

Acquisition of eligible chapter equipment

- purchase – leasing – response rental – special terms and conditions
- Workflow optimization is the main reason for the acquisition of automated analyzers
- A new analyzer in the context of legacy workflows is not an asset
- Consolidation of jobs
- Reduction of downtime
- Replacement of existing equipment
- Reduction of staff
- Cost of the examination carried out
- Cost of a new instrument

Workflow notes

Cost analysis

Purchase***Key factors***

- the benefit of each capital expenditure
- net future increases in profits/savings (cash flow)
- the useful life of the investment (depreciation)

Important factors

- the number of patients who will benefit
- degree of benefit to patients
- the demographic characteristics of the patients who will benefit
- benefit for the “parent” organisation

Analytical technique and equipment

Key elements

- duration of the project
- original capital investment
- annual operating costs
- present value of expenditure
- average annual savings

- number of patients examined
- age of patients examined
- average cost per patient examined
- intangible benefit

Lease/rental agreement

- a remedy against technological obsolescence
- depreciation is calculated on the basis of historical cost

Cost of 1 contracted examination (reagent rental)

- the analytical technology provider provides: reagents, consumables automated data processing, installation, training, maintenance and other requirements – excluding manpower
- the owner is burdened with the cost of labour
- the analytical technology provider shall establish a fixed cost per test including control materials and calibrators
- advantage: avoiding depreciation as well as fixing fixed and variable costs for a period of 5 years
- cost-benefit analysis

Conclusions

Measuring laboratory productivity

- productivity types

Types of laboratory productivity

- worker productivity
- productivity of automatic equipment
- clinical productivity
- workload productivity

Improving fiscal productivity

- in most cases it covers wages and overemployment

1.3 NOTES ON BUSINESS MANAGEMENT

TOPICS

- Diagnostic specialisations
- The clash of medical culture with technological innovation
- The impact of medical technologies
- Flexibility, adaptability and alternatives
- Merging and merger shock
- Management skills
- Legislative factors
- Government inaction
- Compliance
- Balance medicine and business
- Supporting the value of the laboratory
- Managing patient outcomes
- Case reports: evidence-based medicine and rational indication
- Significance: pathological and normal results
- Specificity and sensitivity
- Diseases
- Lege artis
- Leadership, relationships , business
- Information management
- Total cost management
- Managerial responsibilities and profit
- Utilisation
- Productivity
- Revenue
- Profit
- Price
- Risk
- Reimbursement management
- Summary and conclusions

INTRODUCTORY REMARKS

Overview

- the health care system may have forgotten , perhaps never realised and appreciated the importance of the diagnostic laboratory to health care
- medical diagnostic technologies are the method of choice
- physical examination and other subjective methods are replaced by quantitative measurements
- new generation POCT
- Medical technology segment: laboratory medicine and other clinical in vitro diagnostic technologies generated the largest volume of sales in medical technology in 1988
- interacting forces: ambulatory care, prevention and reliance on objective data

Outpatient care and prevention requires more laboratory tests

- decentralisation: transfer of care from hospitals to outpatient clinics
- diagnostic support for specialisations
- costly medical diagnostic laboratories
- increasing obligation for preventive examinations in chronically ill elderly patients

Emphasising primary care

- the decline in the importance of medical specialties and the rise in the importance of primary care
- compulsory preventive screening for diabetes, prostate cancer and breast cancer

Diagnostic specialisations

Providers increasingly trust objective findings (medical technology) more than clinical findings

- the average doctor's time per patient is 20 minutes or less
- medical decisions need to be made immediately
- Laboratory support cannot be remote but must be fast, easy and reliable (POCT)
- reliance on objective data
- a culture shift in the delivery of medical care
- the value of a medical and diagnostic laboratory
- new and dynamic technologies with research support
- medical diagnostic technologies increase the cost but also the speed of the diagnostic process
- however, these are necessary steps in making medical decisions

Marketing dynamics

- Medical diagnostic technologies represent the largest segment within the medical hospital cost industry
- the average cost of a laboratory test is: 0.03 – 0.05 USD
- but the use of its result by providers affects : 0,7 – 0,8 USD
- the following health care
- 80% objective patient data
- laboratory testing with the highest possible diagnostic specificity and sensitivity is a prerequisite for good medical practice
- this has an impact on costs
- research is part of the medical diagnostic technology industry

Delaying reimbursement for new examinations

- FDA approval 1 – 2 years
- waiting for AMA recognition 1 – 2 years
- current list of examinations: eligible examinations (CPT-4 letter) 1 – 2 years

Payments are controlled by a third party

- insurance companies
- Payers
- healthcare management organisations

Experts are worth something

- 90 000 Kč (Germany for a doctor starting out)
- 60 000 CZK (CR specialist)
- 30 000 CZK (Czech starting doctor)
- during chaos, a leader must have more than one strategy to ensure survival in the noise and confusion of battle: flexibility and adaptability

Mission is no longer a determinant of cost

- altruism no longer has an effect

Diagnostic laboratory in the role of a competitor

- the hospital's expertise is based on a professional and time basis
- continuous erosion of the median price of a single test by out-of-hospital laboratories: \$28 – \$23
- esoteric examinations become routine
- complexity is increasing
- the practice of global accounting is eliminated

Integrated delivery systems, decentralisation and networks

- the need to reduce costs and increase value and quality of care
- coordination, integration and consolidation is the answer
- educational initiatives: explaining why this is necessary
- some (not all) of the staff want to be involved in planning and decision-making

Creative directors and managers face these barriers:

- lack of understanding that a new external environment has been created
- lack of understanding and merit of integration

- fear of loss of influence after integration
- constant emphasis on the central operating unit as a decisive factor

Lack of understanding in the central operating unit of the objectives of integrated health care delivery

- loss of geographical concentration of the operational unit
- lack of qualified staff
- failure to identify key moments of integration
- inappropriate information systems
- lack of demographic data on the population receiving care and their needs
- the key elements necessary for building an integrated system
- in integration, the integrated organisation remains intact
- in mergers and amalgamations, one entity absorbs the other with fundamental changes in organisational structure, culture
- the reason for changes in the laboratory are changes in market requirements in regulations
- the dual role of a leader: business and medicine

Key considerations for transformation management

- Supporting staff in implementing the necessary steps in the shift
- managing people in the context of transformation
- encouraging new ways of thinking

Technomanagement

- traditional management methods rely on manipulation: getting people to do what management wants
- technimanagement focuses on the needs of the individual and
- Management skills consist of selecting the means and preparing the environment within which each staff member will align his or her own goals with those of the organization
- The organization gains control of the process by providing staff who express interest with the opportunity to integrate their personal goals with organizational goals, extend this to co-workers, and present this group as an example that gives reassurance to the staff, the organization (financially), and at the same time improves the quality of health care
- success in the management of a complex medical technology organisation lies in the recognition of appropriate methods as well as existing constraints
- management cannot be squeezed into one equation

Balanced Budget Act 1997

- negative implications and operational changes for laboratories
- medical necessities
- decrease in reimbursements
- invitations to tender for the provision of examinations
- screening: diabetes, cervical, prostate, breast cancer

Clinical Laboratory Improvement Act

- massive organisational changes in laboratories within healthcare management organisations
- occupational medicine and occupational safety protection
- regulations
- training
- overview
- cost
- fraud prevention
- reimbursements
- the government rejected the position of clinical laboratories that they cannot be held responsible for the rational indication of laboratory tests

The greed and misjudgment of a minority has caused the federal government to be unstoppably hyper-reactive in preventing and detecting fraud:

- crime
- audits
- programs
- officials

Shock of change of owners and mergers

Management skills

Legislation

The inaction of the government (of the USA, but also of ours)

Compliance

Balance: medicine
and business

- additional administrative costs
- laboratory directors need to plan for the additional costs of providing the above
- health care becomes significant and visible
- 100,000 deaths are caused by medical failures annually in the US, according to a National Academies finding
- electronic information link between the laboratory and the provider is the most important factor influencing the safety of healthcare
- efforts should be made to be a partner to clinicians and government
- the future of the laboratory depends on how valuable clinicians and the government consider it to be
- the clinical laboratory must be involved in programs that increase value with clinicians and government

Supporting the value
of the laboratory

NOTES ON THE LABORATORY CONTEXT

Leadership,
relationships,
business

- the external environment of the laboratory – the clinical interface area is based on 4 basic pillars that the medical director must consider and master

Leadership

- transforming external and internal changes, trends and forces into daily practice: how to get subordinates to do it

Motivate subordinates to participate in training activities that address this

- be familiar and knowledgeable with experts in legislation
- look for information beyond the usual references

Communication

- a laboratory professional is traditionally considered a scientist, less so a manager or politician
- for a business professional, conflict and conflict of interest is a normal part of his professional practice
- laboratory management requires a new quality based on the hybridisation of medical and business knowledge and skills

Policy

- negative view: a politician is a person who gains power and influence by using methods that discredit the value system
- a positive view: the art and practice of managing public affairs
- the laboratory leader must realize that he or she lives in a political system and must behave in a way that ensures compensation for himself, the laboratory and the laboratory staff
- it is necessary to manage both inward policy (integration and consolidation) and outward policy (public funds) and their acquisition

The laboratory professional must be skilled in

- protecting patient rights
- forming alliances with other laboratory professionals
- be a vocal and effective advocate for the highest quality healthcare

HUMAN RESOURCES

Information
management

Primary(active databases

- the interface between the clinic and the laboratory should be provided electronically
- database connectivity

Secondary (passive) databases

- workload
- codes
- verification of the provider's diagnosis
- financial accounting
- compliance
- accreditation

Networks

- intranet
- internet
- total costs represent the direct and indirect costs of producing the product or providing the service

Total cost management

Expectations

- estimates of hidden costs
- regulatory and legislative support
- be flexible to the unexpected
- be aware of macro- and turnover variations
- management information
- the inevitability of redesigning the process if necessary
- revenue must outweigh costs
- the choice of examinations and services for future expansion will have a major impact on the company's future profits

Managerial responsibilities and profit

High cost areas of the laboratory*Esoteric examinations: high costs, low numbers***Example**

- very sensitive and specific but very expensive screening test
- small number of patients but high workload

Solution

- evidence based medicine: validation
- the refund rule
- make or buy

Make or buy (break even analysis)

- to resolve issues of: quality, cost, consultation and logistics

Decision to make: when to start

- criteria identifying the laboratory's spare capacity and opportunities to increase revenue by adding new tests

Decision to buy: when to stop

- evaluating the potential gains and losses in a strategic decision to expand

Event costing

- a spreadsheet to determine the costs and benefits of a single examination
- no possibility of estimation: to be calculated

Cost management in transfusion medicine

- high cost: expensive
- management costs
- estimation of profits/revenues
- if costs exceed revenues, a decision must be taken
- it is about managing the efficiency of services, tests and the whole laboratory diagnostic process
- in the medical care process, the manufacturing process is the laboratory's response to the requirements of providers
- the absence of immediate, continuous and direct communication between the requester and the provider implies a certain control of the process

Efficiency

Definition of diagnostic economics

- economics: efficient and economical use of resources to achieve a defined objective

Diagnosis

- a careful and critical study of the nature and meaning of a phenomenon (Webster)
- the art or acts of identifying a disease from its signs and symptoms

Productivity

- diagnostic economy = careful and critical
- the previous generation of doctors had no idea or need for knowledge about the costs of the examinations they require

Productivity

can be determined at the level of

- workstations
- section
- department
- departments

Knowledge of allocated costs is essential to:

Benchmarking

- Benchmarking is the process of setting standards based on past, present data and an estimate of future trends

Areas monitored

- daily workload
- quality
- Productivity
- achieving the right goals/achieving goals in the right way
- the need to improve production and cost management
- productivity management is based on measuring daily productivity and comparing it to a “gold standard”
- There is no “national benchmarking producer” that sets targets (gold standard) for productivity, efficiency and laboratory staff
- therefore, the role of the medical director is to set these objectives: namely, the standards, the rhythm and the direction to be followed towards achieving the equivalence of high quality and high profits

Operational productivity

- $\text{productivity} = \text{output/input} = \text{profit/cost} = \text{examinations/resources}$
- total booked calculations/FTE
- increasing the ratio is a desirable trend

Rule 4C + 1I

(Consolidation, Constriction, Constraint, Cross training + Integration)

- the pressure to reduce costs has a major impact on the way examinations are carried out.
- the answer is to consolidate small laboratories into regional laboratories.
- hospital laboratories are focusing on reducing and outsourcing low-volume testing to laboratories where the sentiment to provide it is justified
- such measures are necessary in order to achieve both efficiency and a shortage of skilled labour
- mergers take place at the level of corporations such as hospitals, airlines and others
- the translation of the process into the laboratory sector is the integration and consolidation of small laboratories into regional laboratories and of individual sections within a large laboratory into larger sections
- a prerequisite for the success of the project is the achievement of win/win outcomes for management, staff and patients
- a real threat to this idea is the level of staff willingness to collaborate: the existing culture “eats” strategic planning for every “breakfast”

Consolidation, constriction, constraint, cross training and integration

- staff involvement is crucial
- Adequate preparation begins with informing staff and requesting participation

Current trends in internal reorganisation

- chemistry + hematology = chematology
- one order – one result similar workflow pattern

- the basis of consolidation is to achieve a more intensive and efficient use of working time
- differences in the complexity of testing between sections and departments of the laboratory

Current trends for external reorganisation

- the process of laboratory networking within a country or region is considerably less controllable

Transfusion, infusion, pheresis (TIP) service

- the area of highest operational costs, which requires consolidation:
- consolidation of similar activities + reduction of locations + reduction of functions
- the closure of decentralised sites
- creation of centres

The Equation

- $\text{profit} = \text{income} - \text{expense}$
- $\text{expected revenue} = \text{billable volume of examinations} \times \text{price (price, rate, charge, fee)}$

The unwritten rule

- add new revenue streams
- avoid revenue losses
- reduce operating costs

Organisational rules

- never go over budget
- plan for unexpected situations
- never ask for new money in the same year

PROFIT

Profit (margin)

- is a term used to refer to the amount of money that remains after deducting the cost of income earned from reimbursements or other activities of a company
- can be used for distribution to owners or for the development of the company
- anatomy of a billable test
- “positive” profit requirements

PRICE (CHARGE, RATE, FEE)

Price

- what must be provided for the exchange
- the value of expected future income
- the amount of money that will provide revenues above the break-even point

Charge/fee

- the same as the price

Rate/dose/value

- the amount of money per unit specified in the contract for a period of time

Fee/fee

- the concept used to value professional services – it may or may not be precisely defined
- $\text{price (charge, rate, fee)} = \text{direct production costs} + \text{indirect production costs} + \text{indirect costs of the corporation} + \text{profit}$

RISK

Risks for the laboratory

- loss of accreditation and contracts
- risk management is the process of loss prevention
- DRG charges for hospital laboratory diagnostics

Reimbursement
management

- CPT (Current Procedure Terminology) for outpatient laboratory diagnostics
- the medical director's voice must be heard loudly when setting conditions, otherwise there is a risk that conditions are set by financiers who do not understand the issues and create risk

Characteristics of success

- control over the volume of examinations (the more examinations, the less control)
- Targeted infrastructure management (utilisation management and local knowledge)
- strong relationships between doctors and staff
- knowledge of costs (productivity)
- Bargaining (market power: willingness to accept 20% higher costs for a test that costs more than income from the payer)
- correct completion of requests for reimbursement

Documentation

- what is not documented does not exist
- meet all the requirements of professional accounting

Code system

CPT Codes

- biggest shortcoming: terminology
- New examinations (2 years delay in reimbursement)
- slow phasing out of obsolete examinations

ICD-9 Codes

- alphabetical order and Arabic numerals

Invoice management

- correct completion
- correct diagnosis and correct code
- certification of medical necessity
- licensed applicant

Management of compliance with conditions/requirements

Prevention of abuse and embezzlement

- overflow audits
- rational indication
- records kept correctly

Legislation

- safety and quality
- accreditation

Summary and conclusion

- balance and playfulness of team players in a business where experience, education leads to success
- the only non-negotiable plan is the budget
- the clinical laboratory must be proficient in scientific and business practices
- however, medical knowledge is key
- basic management knowledge and skills are the key to survival in the uncertain world of laboratory diagnostics

NOTES ON THE CLINICAL CONTEXT

Managing patient
outcomes

Lab workers

- must defend not only patients but also themselves against accusations

Problems

- too much diagnostic information
- there is no universal grading system to assess the relevance of the tests to the patient
- patient outcomes are enhanced by the classification, evaluation and interpretation of diagnostic tests applied to specific clinical cases

A physician's approach to laboratory investigations***The role of logic, memory and intuition***

- medical intuition
- medical logic is based on syllogisms, strategies and evaluations programmed into short-term, long-term and subconscious memory
- pressing the right button: the inner logic and natural intelligence of the doctor
- the database is transformed into a list of problems
- information is filtered and a meaningful cluster of problems is assembled

The role of experience***Clinical judgement***

- an experienced physician forms early hypotheses, focuses on the essentials, forms clusters, creates triads and tetrads, thinks differentially in a diagnostically correct way, observes only a significant part of the database and quickly arrives at a diagnosis

Recognition of significant abnormalities

- clustering, sorting, matching
- ranking and evaluating
- the important (value) group of related tests to a patient's expected outcome

Integration of clinical findings***With clinically significant laboratory test abnormalities***

- the value of the laboratory lies in condensing the laboratory finding and placing it in the context of the physical findings and history
- databases can be used to correlate laboratory findings with clinical findings
- it is essential to find a suitable format that allows the laboratory professional to make the above conclusions
- decision analysis is the most important tool

Incentives/obstacles***Integrating clinical and laboratory findings***

- lack of economic incentives to scrap unsuitable and obsolete software

Medical necessity***Other standard federal regulations***

- federal regulations require the prevention of redundancies
- information systems

Information systems***That support user interaction***

- data manipulation
- interpretation of results
- interpretative comments
- graphs, trends, isolation of significant abnormalities

The number of non-medical providers is increasing

- catalogue of examinations
- laboratory professionals represent a group of prepared experts
- interpretation of laboratory findings and comments on significant abnormalities can significantly improve the quality of laboratory diagnosis
- electronic interface

Non-medical providers

- misuse or inappropriate use of laboratory tests
- laboratory experts to have support and consultation mechanisms for clinicians

Case reports:
evidence-based
medicine

Diagnostic
situations:

Specificity
and sensitivity

Disease
management

Definition
of provider

**What is essential
for proper disease
management**

Team approach

- interaction and cooperation
- one doctor rarely takes responsibility

Interpretation

Significant abnormalities for non-physicians

- professional expertise needs to be transposed

Direct consultation

Laboratory specialists with clinicians

- how to teach the user to exploit potential and economics within a rational indication

Providing information

Current costs of services and laboratory tests

- providers are unaware of the economic consequences of their decisions

Evidence-based case reports

Useful to narrow down the indication schemes

- evidence-based medicine focuses on the exclusion of subjective opinion, practical experience and intuition in the medical process
- it is a style that provides a basis for good decision-making

Clinical Information Interface Management

- immediate and direct consultation by any means: in person, by phone, electronically can save a life

1.4 NOTES ON SAFETY IN THE CLINICAL LABORATORY

Topics

- Definition
- Patient safety
- Clothing
- Proper laboratory hygiene
- Premises and ventilation
- Order
- Personal protection barriers
- Warning alarm
- Chemical risk
- Gases
- Microbiological risk
- Radiation risk
- Fire protection
- Safety programme
- Electrical risk
- Special equipment
- Waste
- Acute conditions
- Improving

INTRODUCTORY REMARKS

Reagents

Toxic, samples are infectious, analytical technique may not work, technology may not be understood

- all of the above processes put the operator at risk
- each clinical laboratory poses a risk

Therefore

Safety should be part of the culture of the laboratory and it is essential to create

- policy
- plan (scope, objectives, personal responsibility)
- safety programme
- manuals (preparation of biological media, collection of biological material)
- a committee (composed of experienced representatives for each discipline)
- the person responsible (technician)

Threat risk minimisation programme

- represents a systematic and continuous effort to reduce worker exposure to the minimum acceptable level

Activities

- Threat/risk management focuses on measures to ensure that the threat is minimised

Introducing

- control systems
- facilities
- personal protective equipment
- other equipment

Definitions

NOTES ON THE LABORATORY CONTEXT

Proper laboratory hygiene

Measures

- hand washing
- detergents
- ban on eating and drinking
- special measures

Attention

- contact lenses

Space and ventilation

Measures

- plenty of space
- lighting
- air conditioning

Attention

- disabled workers
- Purity
- Retrieved from
- Neatness
- System
- Culture

Order

Personal protective equipment

Gloves

- most often
- rubber, latex, vinyl, heat-resistant, “wallpapered”

Uppers

- buttoned coats
- dress
- parts of clothing

Eye and face protection

- glasses
- shields

Respiratory protection

- masks
- respirators

Warning alarm

Regulatory and support systems

- Information signalling for the purpose of hazard prevention: the Office of Occupational Safety

Red

- hazards

Yellow

- attention

Green

- recommendation
- good laboratory practice includes labels on reagent containers indicating the date of opening

Chemical risk

Hygiene plan

- reagents
- strategic document

Corrosives

- ability to eat away steel
- store on the ground or below eye level

- gloves and aprons
- pouring and pipetting
- couples

Inflammability***Class Flash point Boiling point***

- IA: 23 °C 38
(most incendiary)
- IB 23 8
- IC 23 38
- IIA 38 60
- IIB 60 93
- IIC 93
- (least flammable)
- room for incendiaries

Instability

- decomposition at normal temperature
- hydrazines, sodium

Poison

- factors: quantity and biological effect
- short-term: irritants, allergens, asphyxiants
- long-term: mutagens, carcinogens, tumorigens
- LD 50: oral, dermal , inhalation
- access: strictly limited
- institution: hygienist
- materials used in spillage: sand, soda, ash
- literature: toxins

Risk

- explosion, toxicity, flammability

Bombs

- marked, do not roll, do not pull

Valves

- high pressure, low pressure

Incendiary gases

- minimum quantity, storage facility: secure room, no incendiary materials in the vicinity, empty bombs returned to supplier

Home

- all biological samples are potentially infectious (HIV, hepatitis B, C)
- exposure control plan and corrective measures
- oral, parenteral (abrasions), inhalation

Biosecurity/need for separation (cabinetry)***Class I***

- vacuum and air velocity 75 ft/min. High efficiency purifier filters

Class II

- vertical airflow and internal filter recirculation

Class III

- most virulent agents, completely closed, handling only in rubber gloves, autoclaves (TB, systemic mycoses, HIV)

Gases

Microbiological risk

Biosafety levels

I: teaching laboratories

- generally non-infectious to humans: pipetting, wiping up spills, daily disinfection, regular waste removal

II: clinical laboratories

- limited access, routine bacteriology

III: life-threatening danger after inhalation

- full protective laboratory clothing

General measures

- design, control of work procedures, personal protective equipment: shields to protect against infectious materials in the blood
- HBV (DNA virus) more dangerous, HIV 1,II (RNA viruses) less dangerous
- hepatitis C, malaria, syphilis, babesiosis, brucellosis, leptospirosis, arboviruses, borreliosis, Jacob Creutzfeldt, CMV, viral haemorrhagic fever, human T lymphotropic virus
- gloves, waterproof clothing, vests, face protection, frequent hand washing
- containers and plastic bags
- spilled blood
- decontamination after each shift
- warning labels
- special procedure for tissues and necropsy: containers and full range of PPE
- Jacob Creutzfeldt: resistant to formalin, aldehyde, alcohol, heat. Only sodium hydroxide or sodium hypochlorite and exposure to a temperature of 132 °C for 1 hour are effective

Decontamination

Germicides

- generic name for pathogen-killing agents

Sterilants

- All

Disinfection

- Selective

Sanitation

- reducing the level of risk considered safe
- sodium hypochlorite, iodine tincture, aldehydes
- decontaminant and the spectrum of their effectiveness

Accidental threats and immunisation

Vaccination

- HBV, anthrax, tularemia, Q fever, polio, yellow fever, equine encephalitis

Injury/prophylaxis

- Hepatitis B (immune globulin) HIV (zidovudine, lamivudine)

Seroconversion monitoring

- 6 months

Acute

- lymphocytosis, bone marrow attenuation skin and epithelial damage

Long term

- germinal and somatic tissues

Radionuclides

- markers: as normal reagents
- prevention of ingestion
- beta emitters: H,C,P,S

Administration

- and delivery

Dosimeters

- 200 disintegrations per minute per cm²

Spill and cleanse

- PPE
- cleansing

Radiation risk

- washing
- dosimetric control

Incendiary materials in the laboratory

- flammable liquids, flammable gases, paper, wood construction material

Extinguishing and evacuation

- as quickly as possible

Walls

- protection: 60 minutes, door 45 minutes

Warning alarm

Portable fire extinguishing vessels***Class A***

- Wood and paper (organic, halogen)

Class B

- flammable liquids (CO₂)

Class C

- electrical equipment (dry chemicals)

Training and practice***Disclosure***

- hardest

Check

- at least once a year

Cables and plugs

- grounding

TRAINING***Centrifuges***

- large rotors

Autoclaves

- steam under pressure

Cryogenic fluids

- boiling point (liquid nitrogen)

Cell sorting equipment

- droplet infection

NOTES ON THE CLINICAL CONTEXT***Measures***

- restricted access to the laboratory (only staff allowed)
- collection of biological material in a separate room
- gloves

Attention

- allergy to iodine
- spilled blood: detergents

Personal protective equipment (PPE)

- uniform

Fire protection

Electrical safety

Special equipment

Patient safety

Clothing

Notes on safety in the clinical laboratory

- coat, dress, trousers, shirt, gloves
- shoes with rubber soles

Necropsy

- cut resistant gloves

Attention

- hair and jewellery

Hazardous waste

Factors

- waste dissolved, incinerated, transformed
- flammability, corrosives reactants toxicity
- not to be confused
- ventilation
- on site: neutralisation, distillation

Infectious waste

- cultures, human blood, veterinary medicine
- integrated packages with red labels
- storage in a separate room
- autoclaving and sterilisation before removal

Radioactive waste

- regulation, licensing, segregation

Sharp materials

- needles, scalpels, pipettes, capillaries
- into fixed containers

Waste disposal

- the perpetrator is responsible for personal damage and damage to the external environment
- incineration in licensed incineration plants

Waste minimisation

- reduction programme: substitution, reduction, recycling, redistribution

Conditional/pragmatic planning

- spill, fire, explosion

Records

- completed and preserved

Prevention of acute threats

Definition of measures

- in laboratory policy manuals

Power outage

- emergency lighting, cooling, air conditioning

Fire

- prevention, fire extinguishers and training

Natural disasters

- tornadoes, floods, earthquakes: building, wiring, damaged containers

Cleaning up spills

- awareness of the threat of infection, radiation, poisons

Medical acute conditions

- clinical crises: cardiopulmonary resuscitation, electric shock, infection

Bomb threat

- take the warning seriously: call the police and security services

Scope

- applies to all staff

Table of Contents

- security policy, selected risks, procedures

Targeted Audience

all employees

Methods

- lectures, practices

Documentation

- date, title, summary, attendance list

Monitoring and evaluation

- testing in an objective manner
- Regular security audits
- Effectiveness of the Security Committee
- External auditors' reports
- Prioritisation of remediation of identified deficiencies
- Suitable training programme
- Working groups setting safety standards

Training

Improving
safety levels

1.5 NOTES ON THE INTERPRETATION OF THE LABORATORY RESULT

Topics

- Diagnostic cycle
- Variability within the clinical laboratory
- Analytical variation is only part of the total variation
- Analytical and clinical aspects
- Reference values

INTRODUCTORY REMARKS

Table of Contents

- Biological variation
- Reference values
- Clinical efficacy characteristics

NOTES ON THE LABORATORY CONTEXT

Home

- root cause: biorhythms
- factors influencing biological variation

Biological rhythms

Circadian

- 24 hour (Na, K, glucose, P, urea, cholesterol, bilirubin, GGT, TSH, blood cells, urine – volume, density)

Ultradianne

- less than 24 h: testosterone

Infradianne

- more than 24 h: gonadotropins

Constitutive factors

Gender

- for most parameters, but clinically largely insignificant

Age

- newborns, children, adults, old

Genetic heterogeneity

- whites, blacks, yellows, reds

External factors

Location

- fluid shift, renin

Exercise

- plasma and urine composition, electrolytes, coagulation

Food

- cholesterol, glucose, triglycerides

Caffeine

- diuresis, adrenal glands, gastrin, lipid metabolism

Medicines

- Interference

Biological
variation

Alcohol

- acute: triglycerides, osmolality
- chronic: GGT, enzymes

Oral contraceptives

- binding globulins, clotting factors

Pregnancy

- plasma volume expansion, increased plasma protein concentration

Intercurrent diseases

- shock, malnutrition, fever

NOTES ON THE CLINICAL CONTEXT***The basis for***

- a scientific basis for the interpretation of laboratory tests

Development of standardised nomenclature

- old: normal, physiological
- new: values obtained by measuring defined variables in defined individuals

Types

- reference individuals, population, samples, (values, distribution, limits, intervals) – observed values can be compared

Accreditation requirements

- JCAHO, CAP, CLIA, NCCLS

Principles for setting benchmarks*Specification*

- characteristics of the reference population

Literary research

- the first step and a basic prerequisite

Criteria for inclusion and exclusion

- biological rhythms, constitutive factors, extrinsic factors

Selection of the reference sample

- prospective/retrospective
- 30 – 700
- 2.5 – 97.5 percentiles

Subject preparation, sample collection and analysis

- standard procedure

Data analysis

- parametric and non-parametric methods
- Gaussian and non-Gaussian distribution

Setting reference limits: some examples

- start – breakdown – distribution – distribution – deviations – Gaussian = parametric – non-Gaussian = non-parametric – transformation

Non-parametric methods

- sort in ascending order and determine the 95 % distribution

Parametric methods

- steepness, width – 95 % of the values obtained

Transformation

- Monte Carlo, statistical analysis

Reference values

Multidimensional RV

- $P = (1 - 0,95)^n$

Individual RH

Individuality of biological rhythms

- Individuality index: $I = (CVi^2 + CVa^2)/CVg$

Reference change value

- $RC = 2.77 (CVa^2 + CVi^2)^{1/2}$

Clinically significant difference

- RHs are compared in the setting of other relevant clinical information such as history, prognosis, consequences of misinterpretation
- all this affects the reference range, which may expand or contract as a result of the above

RV presentation

- as illustrative as possible

CLINICAL PERFORMANCE CHARACTERISTICS

Rating

- the added value of laboratory tests

Determination of clinical performance characteristics

- forming in Phase II and III clinical trials according to the FDA
- gold standard – healthy and sick population – calculation for all parameters – comparison of diagnostic reliability

Specificity and sensitivity

- Binary table : TP true positives, TN true negatives, FP false positives, FN false negatives

Calculation of specificity and sensitivity

- Sensitivity = $TP / (TP + FN)$ (all sick) Specificity = $TN / (TN + FP)$ (all healthy)

Predictive value and Bayes' theorem

- $PV+ = TP / (TP + FP)$ (all positive) $PV- = TN / (TN + FN)$ (all negative)
- Bayes' theorem: $PV+ = (Se)(prevalence) / ((Se)(prevalence) + (1 - Se)(1 - prevalence))$

Likelihood ratios: probability fractions

- $LH+ = Se / (1 - Sp) = TP \text{ count} / FP \text{ count}$
- $LH- = (1 - Se) / Sp = FN \text{ count} / TN \text{ count}$

Working with LHR

- if we know the pre-test likelihood (Se and Sp) this allows us to know the post-test likelihood
- odds = probability / (1 - probability)
- pretest odds x LHR = posttest odds

Nomogram allowing estimation of posttest probabilities

- Fagan

Estimation of LHRs from ROC curves

- evaluation of the ROC steepness curve (tangent/directive)

ROC

Receiver Operating Characteristic Curves

- graphical method for determining the most appropriate/effective decision threshold
- comparison of relative clinical reliability in specific clinical situations
- the perfect laboratory test is a myth: specificity = 1 sensitivity = 1 this condition allowing 100% differentiation between sick and healthy does not exist

- real situation: overlap: decision criteria need to be established
- Y axis: sensitivity
- X axis: $1 - \text{specificity}$

Creating ROC curves

- hyperbola consisting of multiple decision points : the most effective values to allow the distinction between sick and healthy

Summary of the ROC analysis

- sensitivity and $1 - \text{specificity}$ for the most effective decision threshold from each study is plotted as 1 point on the meta-analytic curve

1.6 NOTES ON LABORATORY INFORMATION SYSTEMS

Topics

- History
- Basic concepts
- Department of Informatics and Clinical Laboratory
- Clinical pathology and the wider context
- Laboratory information systems
- LIS project team
- Search for information
- Development of requirements
- Choice of supplier
- LIS Management

INTRODUCTORY REMARKS

What does information technology (IT) mean for the clinical laboratory (CL)?

- opportunity
- change
- a new level of communication

History

1950

- FORTRAN (formula – translation)
- COBOL (common business-oriented language)

Drivers

- technology: miniaturisation
- Expertise: of technologists and users
- Economics: efficient and effective administration and record-keeping
- increased data production: automation of processes
- information requirements: government and insurance companies
- CPU (central processing unit)
- ROM (read only memory)
- RAM (random access memory = read and write memory)
- bit: 0 or 1
- nibble: 4 bits
- byte: 8 bits
- MG (megabyte): 1 000 000 dwellings
- GB (gigabyte) 1 000 MG
- TB (terabyte) 10 000 MG
- 32 or 64 bit architecture
- 90-550 MHz (rate of replacement of 1 number by another)
- 28 points per inch (sharpness)
- Running speed: 286, 385, 486 (Pentium, Pentium II, Pentium III)
- computer components: input/output port, current, clock, RAM, CPU, ROM
- personal computer components : system drive, disk, monitor, keyboard, modem, printer

Basic concepts

NOTES ON THE LABORATORY CONTEXT

LIS project team

Core

- clinical laboratory staff

Share

- staff outside the laboratory

LIS design process

- definition: the closure of a traditional development
- Design and construction: understanding
- installation: gaps
- maintenance: gaps

4 sources

- exchange of personal experiences
- professional societies
- suppliers
- professional events

Key elements

- laboratory profile
- system functionality requirements
- technical requirements
- training requirements
- implementation requirements
- financial considerations
- supplier profile
- selection conditions
- evaluation criteria
- timetable for decision-making

Key objectives

- obtaining information about the supplier
- analysis of current activities in the LIS Unit laboratory
- a long-term and strategic automation plan
- reasons for purchase
- consensus with the team and a formal plan for staff

Analysis of current laboratory operations

- evaluation of information processing
- specific lab documentation loop closures
- analysis of the laboratory in terms of: input, process, control, output
- flow diagrams

Purchase of LIS with sufficient capacity

- current laboratory workload
- annual numbers of ambulances
- numbers of acute cases
- workload measurement
- expected increase

Criteria for supplier selection**Criteria**

- meets the requirements of the system ?
- is the supplier financially sound ?
- Documentation
- location of the supplier
- product development
- contract modules
- possibility of adapting LIS modules to the laboratory cycle
- interfaces
- information from other workplaces

Acquisition
of informationDevelopment
of requirements

Choice of supplier

- training and installation
- the supplier's market position

Methods

- education/estimation
- costs only
- the easy way out
- aspects of elimination (elimination method)
- scores and weights

Site visit/supplier/selection

- the biggest threats of LIS failure
- poor matching of LIS and laboratory interfaces
- poor design of LIS
- poor acceptance
- non-acceptable delay time
- insufficient training
- weak leader chip
- poor support from the supplier
- an ambitious implementation plan

Purchase of LIS

- project team
- obtaining information
- information analysis
- development of requirements
- evaluation of offers
- supplier selection
- negotiation with the supplier
- training and preparation
- hardware installation
- parallel runs
- sharp
- at full power
- evaluation and monitoring

NOTES ON THE CLINICAL CONTEXT

Department of Information and Clinical Laboratory

- administrative component
- PC support

Applications and integrated databases

- patient database

Disease management system

- outpatients – inpatients – laboratories – radiology – clinics
- reception – outpatient clinics – inpatient services – laboratories – clinics
- clerk – primary – nurse – laboratory diagnostician – clinical staff

Impact of clinical pathology

- doctor – researcher – patient – pathologist

Reporting

- communication between clinical pathologist and clinician

Workflow

- improvement

Department
of Information and
Clinical Laboratory

Laboratory
information
system

Productivity

- increases by computer and email

Choosing a system

- Strengths: speed + memory
- weaknesses: “stupidity” + interfaces
- benefit: automation of repeatable tasks

- Pathological anatomy
- Clinical pathology
- Radiology
- Radiation oncology
- Nuclear medicine
- Pharmacy
- Home care
- Clinical integration

- high quality

Routine operations***Guidelines***

- physical location and security
- backup and restoration to service
- software and database security
- electric current: fluctuations and stability assurance

Backup and restoration to service

- Establishing a clear work schedule/procedure (expected time intervals)
- losses and time losses
- revitalisation and re-entry

System security

- basic prerequisites: ability to continue laboratory investigation
- Stability

Imaging and voice

- telepathology and telemedicine
- transcription of read/spoken text

Reporting on the internet

- customisation of information from available databases and libraries
- databases of patient outcomes

Clinical pathology
and the wider context

LIS Management

1.7 NOTES ON ETHICS IN LABORATORY MEDICINE

Topics

- **Introductory remarks**
- **Why do we need ethics ?**
- **Basic principles of bioethics (biomedical ethics)**
- **Notes on the laboratory context**
- **Notes on the clinical context**
- **Notes on codes of ethics**

INTRODUCTORY REMARKS

Definitions

Incorrect (erroneous, negligent, poor quality) laboratory examination

- usually leads to an incorrect outcome that is inconsistent with the patient's reality ('truth') and may lead to an erroneous clinical decision by the doctor, nurse or other healthcare professional
- the same applies to an incorrectly (mis)interpreted laboratory test result
- improper (erroneous, negligent, poor quality) laboratory testing does not benefit but rather endangers the patient's life or health

Occupation (profession) of laboratory diagnostician – physician

- or other health professional is defined by two basic pillars:
 - a) specific knowledge, skills and abilities of the field laboratory medicine
 - b) ethical requirements of professional ethics in laboratory medicine
- the work of the laboratory diagnostician is governed by relevant legislation and ethical requirements in addition to professionally defined ('standard') laboratory medicine procedures
- there is a close relationship between the quality of the work of a laboratory diagnostician and adherence to professional ethics (morality)

Morality

- the totality of respected beliefs, opinions, attitudes in relation to the moral evaluation of a person's actions or behaviour (morally good/bad, right/wrong, etc.)

Ethics

- a philosophical discipline, "moral theory", examines a person's actions in terms of their ethical evaluation (ethically good/bad, right/wrong, etc.)
- legislation – enforced by state power
- moral requirements – their observance is achieved by the mechanism of moral condemnation or moral evaluation by the environment or society

Professional code of ethics (deontological code)

- contains an inventory of the duties of the profession(s) defined on the basis of the relevant professional ethics
- the professional and ethical competence of the health professional is assessed by the relevant professional chamber (they are a condition of membership, licensing, etc.)

Doctor

- a registered and appropriately trained healthcare provider

Laboratory diagnostician

- a registered and appropriately trained health care provider who is a doctor or other health professional

Laboratory – laboratory medicine workplace

- a professional unit, department, institution (e.g. private company) providing laboratory services = carries out examinations

Ethical practice

- complies with relevant ethical requirements (e.g. in terms of the code of ethics of the profession, workplace, institution)

WHY DO WE NEED ETHICS?**Reasons**

- the need to ensure the proper practice of the profession of laboratory diagnostician, laboratory technician (including compliance with standards)
- the need to protect and promote the compelling legitimate interests of the individual, the group and society (up to the level of human and civil rights – e.g. the right to health and healthcare of adequate quality, etc.) that are relevant to the exercise of the profession/profession in question
- the need to protect significant values (material, social, etc.) entrusted to the use/management of the profession/profession
- it is not enough to formally regulate actions/behaviour by laws or other regulations
- ethical reasons – the “ethos” of a given society, group of people (family, company, nation, etc.) – are the basis and content of the relevant legislation (laws, decrees, ordinances)
- ethical (moral) principles, norms and rules are the regulators of human interactions and actions/behaviour in society, including patient-doctor/lab diagnostician/other health professionals, health professionals-doctors/lab diagnosticians/lab professionals, etc.
- the new possibilities in laboratory medicine brought by the development of sciences and the latest technologies and their application to humans – the need to make a qualified assessment from an ethical (moral) point of view: is it a good/bad, right/wrong option, or: is it right/good to allow/approve/restrict/prohibit a given option (e.g. human cloning, human genome sequencing, human genome alterations, etc.)?

Asymmetries in relationships

- information and knowledge asymmetry in the doctor-patient relationship
- asymmetry of influence/power in the doctor-patient relationship
- asymmetry of power in the relationship doctor/laboratory diagnostician/laboratory/laboratory services company – payer (separately – health insurance companies)

BASIC PRINCIPLES OF BIOMEDICAL ETHICS**CLASSIC (*Prima facie*)**

- are based on principled approach to ethical problem solving – good/correct is that which meets the requirements of predetermined principles
- the specific content of each principle is crucial (e.g. what is good, what is harmless, what supports autonomy, what is fair)
- the first and the second are based on the *Hippocratic Oath*

Beneficence (*Beneficiencia*)

- to do good
- duty to act in the best interests of the patient
- “Patient health is the supreme law!”
- concerns the individual, but also the group, organisation/institution, society, etc.

Harmlessness (*Non-maleficencia*)

- Avoid doing evil, harming the patient/person/workplace/organisation etc.
- “Above all, do no harm!”

Autonomy

- respect the patient’s ability and opportunity to make decisions about everything that concerns him or her

Justice

- to give everyone what is due to them according to established criteria of fair treatment
- the most common criteria:
- depending on what they are entitled to (e.g. by law, health insurance)

- by merit (e.g. good/better person good/better, bad/worse person not, but – problem, assessment, problem of correction)
- according to what is urgently needed (dealing with an urgent condition (cyto examination) versus a chronic, non-urgent condition (routine examination))
- according to the consequences/consequences of the action/non-action (e.g. triage and prioritisation of assistance to the injured in mass casualty incidents)

OTHER - ADDITIONAL

Caution

- to avoid actions/behaviours that involve undue risk

Subsidiarity

- address the problem at the lowest possible level of management/organisation

Transparency

- making available reasonably comprehensible information on the reasons for and mechanisms for decision-making in matters of public interest
- declaring and managing conflicts of interest

Responsibility

- to act/act/behave “to the best of one’s knowledge and conscience” when making decisions/actions/behaviour

THE PROCEDURE FOR SOLVING AN ETHICAL DILEMMA

- recognise/determine that there may be an ethical dilemma
- ethical dilemma: a decision-making situation where two or more alternatives with different ethical (moral) judgements are available (e.g. to perform or not to perform a given laboratory test in specific circumstances – e.g. emergency situation and poorly calibrated/unreliable instrument; different opinion of the attending physician – laboratory diagnostician – other health professional – patient – patient’s relatives – health insurer on whether or not to perform a given test, etc.).
- define and invite all parties involved in the problem/decision to the solution
- clarify the facts of the case (medical, laboratory)
- ensure the integrity and proper storage of data (laboratory test results)
- name the ethical issues that exist in a given problem
- define the assumptions and options for addressing the ethical issues identified
- consensus – the resulting solution fully satisfies all parties involved
- compromise – the resulting solution does not fully satisfy all parties involved, but is acceptable to them
- an authoritative decision by a responsible person (e.g. treating physician, clinical (chief)/laboratory manager, director of the organisation, court, etc.)
- take a decision
- record the decision
- communicate (in an appropriate manner) the decision to all parties involved
- evaluation of the decision taken with time – education

NOTES ON THE LABORATORY CONTEXT

Responsibility

- towards the patient: quality
- towards colleagues and the profession: dignity and honesty, reputation, acceptance
- towards society: the common good, quality of healthcare, utility – medical, social and economic (accessibility, sustainability, etc.)

Sampling and obtaining health information

- informed consent to the sampling, collection, recording, storage (processing) of health data
- Justification
- justification for sampling/obtaining health data (legitimate objective)

- adherence to correct/standard procedures
- data protection, confidentiality

Implementation of examinations

- adherence to correct/standard procedures, quality assurance
- data protection, confidentiality

Issuing results

- each laboratory test result constitutes
- sensitive personal data and must be adequately protected against disclosure to unauthorised persons (disclosure is a serious offence, sometimes even a criminal offence)
- adherence to correct/standard procedures,
- ensuring quality of communication, confidentiality, timeliness, etc.
- data protection, confidentiality
- authorisation to take delivery of the result
- telephone notification of results
- electronic transmission of results
- who is authorised to inform the patient, relatives and close persons (the attending physician, not a nurse or other health professional)

Keeping medical records (results of laboratory tests)

- the requirements are set by law and other generally binding legislation (usually by the provider), the prescribed time limits
- the responsibility of the laboratory site manager and all authorised persons

Maintaining quality assurance documentation

- the requirements are mandated by law and other generally binding legislation, or are part of the laboratory's established standard operating procedures
- the responsibilities of the laboratory site manager and all authorised persons
- inspection, audit needs

Access to medical records

- regulated by law (in particular Act 576/2004 Coll. on health care)
- attending physician, patient, laboratory personnel, other authorised persons (within the scope of the specific authorisation)
- the requirements are laid down by law and other generally binding legislation

Financial and organisational matters

- professional independence in professional and professional decision-making
- dealing with conflicts of interest
- civic virtues applied to oneself (self-control)
- bad/good relations between people in the workplace are a sign of a wrong-bad/right-good organisation of work and the working environment

NOTES ON THE CLINICAL CONTEXT

Autopsies – Autopsies

- post mortem examination of the patient, clarification of the cause(s) of death
- educational importance for attending physicians (inadequate legislation has virtually eliminated this possibility of an important “conscience of medicine” in the Slovak Republic)
- medical autopsy – especially for deaths in hospital, family members may request that the patient not be autopsied
- forensic autopsy – indicated by the examining physician in the case of a suspected crime/crime

Consent to autopsy/dissection

- currently, the legitimacy of autopsy is more or less unquestioned in cultural countries and societies – but there may be different attitudes for religious or cultural reasons

**Selected
fields/activities**

Histopathology, cytology, clinical pathology

- results relevant to the diagnosis and treatment and monitoring of treatment of serious diseases
- significant technological advances in sample collection, processing, sample evaluation and interpretation of test results
- sometimes the need to obtain a result in a time crunch (examination during surgery)
- high demands on expertise and quality of work
- multiple experts/workplaces often work together to evaluate the same sample
- the costliness of modern techniques/technologies

Reproductive medicine and assisted reproductive procedures

- a range of practices – significant medical, technical, technological and ethical differences
- laboratory worker involvement (direct, indirect)
- a number of serious ethical issues
- significant cultural and religious influence in their solution
- reservation of conscience

Transfusion medicine***Voluntary blood donors and their protection***

- medically preferred group of donors (paid – increased risk of transmission of infectious diseases)
- voluntary, free of charge (reimbursement of travel expenses, refreshment allowance, time off work, etc. are admissible)
- provision of the necessary medical care (pre-collection testing, follow-up care when findings are found outside the reference range or directly disease – e.g. hepatitis virus infection, etc.)
- moral award

Protection of the recipient

- informed consent to transfusion (there are those who refuse transfusion because of religious beliefs – e.g. members of the Jehovah's Witnesses)
- detailed laboratory examination of the blood collected before it is admitted for transfusion
- determination of blood group(s), pre-administration cross-examination – at the patient's bedside
- patient monitoring – early recognition and treatment of transfusion events and complications (relatively rare if standard procedure is followed)
- proper quality assurance

Geneva Declaration of the World Medical Association (WMA)

- developed by the WHO in 1948 as an updated version of the Hippocratic Oath, written in non-archaic, contemporary language, defines the most important duties of a physician – to the patient, to colleagues and medicine, to society, and to oneself, for example
- service to humanity
- respect for your teachers
- conscientiousness in practice
- putting the patient's welfare first
- care provided is guided by medical considerations, without unfair discrimination
- strict confidentiality (even after the death of the patient)
- preserving the respect and best traditions of the medical profession
- respect for and protection of human life
- last update in 2017

International Code of Medical Ethics

- developed by WHO in 1949, last updated in 2006
- International Code of Medical Deontology, a brief elaboration of the WHO Geneva Declaration
- defines the most important duties of a doctor – towards the patient, towards colleagues and medicine, towards society and towards oneself, e.g.

Codes of ethics in blood donation and transfusiology

- developed and amended by international organisations, adopted by consensus
- are not legally binding, but represent an important ethical/moral standard that is widely recognised and respected

- the protection of the welfare and legitimate interests of all stakeholders, especially the donor and the recipient, includes the ethical obligations of health professionals, institutions and organisations
- include practical expression of ethical standards in blood donation and transfusion medicine, such as voluntariness, respect for donor selection criteria, indication criteria for the use of blood, blood derivatives and other transfusion products, adequate education and training of personnel, accountability, prohibition of profiting from the provision of human blood, etc.

1.8 CONCLUSION TO THE CLINICAL LABORATORY

Innovation and change

The main challenge today is to manage innovation and change.

This requires courage and creativity. But this is only the beginning. Having an idea is easy. Having a good idea is harder. But the hardest part is turning a good idea into a practical result. You need to offer a tangible outcome – either a better product, or a better service, or a new structure, or even a change in strategy or a shift in culture. You will always encounter obstacles in this endeavour.

We often create our own barriers with our approach and attitudes. While there are a bunch of great ideas out there, we often take an immediately hostile attitude towards them if someone wants to apply them and put them into practice.

Barriers also exist at the organisational level. The process of innovation and change is often not understood. New ideas are not generated within the system, but on an ad hoc basis. This has consequences: creative individuals are not taken into account and the views of customers and clients are ignored. To the detriment of the organisation.

Managing the process

We are often unable to manage the process of innovation and change ourselves.

We lack knowledge and skills, sometimes we lack courage and sometimes we lack both. In the existing chaos, this is not a task for one, albeit excellent individual, but for the whole team. It is a matter of finding a balance in a coalition between the bearers of original ideas, the leaders who set the direction and the so-called silent majority who provide stability. Without mutual trust and support, we will not overcome the Berlin walls that exist within our profession. To overcome them, it is necessary to recognise the frameworks and create a supportive environment.

Ideas may develop in a collective, but they are born in one brain. The change champion is a key part of this equation. It represents the driving force behind the process. Often it is not a good manager, but a troubled person with extraordinary qualities.

The framework for change

The framework for change is created by personalities who have a sense of context.

They understand the obstacles that exist in the organisation. They don't consider themselves overly creative, but they are able to create an environment in which ideas flash like electric sparks. Environment and framework are key in the process of creating a balance between structure and improvisation, set goals and freedom to maneuver.

It is increasingly acknowledged that complex processes cannot be solved by an individual, but only by mutual cooperation. The knowledge of the specific environment that the rank and file knows is just as important as the strategic skills of the director. It is possible to trace a path from the originator of an idea to shared responsibility.

Two extremes

It is one thing to generate new ideas,

well-intentioned advice and generalisations, which are mostly produced in the silence of university offices or similar ivory towers. Let us be aware of the risks of applying these recommendations: well-meaning advice, when not applied in the right setting and at the right time, is useless.

The other extreme is to implement change directly in the workplace,

in the harsh reality of uncertainty, conflict and confrontation, where fear is the father of aggression, and where decisions are often made in an atmosphere of hatred. The vision can remain misunderstood. Personal motivation can slip into destructive aggression. Creativity can degenerate into anarchy. The structure of the organization can crumble. Such a scenario is also possible.

Principles

Principles may be distorted by practice,

but that does not discredit them at all. To warn of risks is to arm oneself against them. It is crucial to compare the principles with the actual situation, to evaluate their interactions carefully and to weigh the decisions honestly.

Most creative activities are doomed.

New ideas in an uncertain and often hostile environment are easily vulnerable. Out of a hundred proposals, perhaps one will begin to be realistically considered. And out of a thousand proposals, perhaps one will be successful. Probability works against you.

T

his statement does not fill you with pessimism.

Take a neutral attitude to this fact, because that is the way of the world. Concentrate all the more on the quality of new ideas and proposals. A good manager must distinguish the good from the bad. If you are convinced that the idea you have decided on is a good one, then you need persistence and nerve. The persistence to see it through to the winning end, and the nerve to be able to start again if it fails.

2. NOTES ON MOLECULAR PATHOLOGY

**Gustav Kovac
Anna Porubenova
Lubomir Danisovic
Stefan Keckes**

CONTENTS	PAGE
2.1 Notes on introduction to molecular diagnostics	51
2.2 Notes on the molecular biology of inherited disorders	57
2.3 Notes on the molecular biology of solid tumours	61
2.4 Notes on the molecular biology of infectious diseases	65
2.5 Notes on clinical applications of molecular biology in diseases of the haemopoietic system	70
2.6 Notes for the seminar on molecular pathology	74
2.7 Notes on the polymerase chain reaction (PCR)	78

2.1 NOTES ON INTRODUCTION TO MOLECULAR DIAGNOSTICS

2.1.1 INTRODUCTORY REMARKS

Topics

- Overview of nucleic acid biochemistry
- Nucleic acid probe technology
- Nucleic acid probe signal amplification technology
- Automation and technological advances in molecular diagnostics

Genetic diseases and malignancies are increasingly diagnosed using molecular genetics methods

- molecular pathology deals with gene organization, hereditary, oncological, microbiological diseases as well as diseases of the hemopoietic system with particular attention to lympho- and myeloproliferation, where it provides important therapeutic and prognostic information
- new information on genes and proteins is rapidly blurring the boundaries that exist between traditional disciplines
- a framework for molecular o biological diagnostics creates the detection of changes in nucleic acids and the biological processes that are their consequence

Molecular
pathology

OVERVIEW OF NUCLEIC ACID BIOCHEMISTRY

Nitrogen base, pentose, phosphate

- A – T/G – C
- double-stranded DNA molecule
- 3' – 5'-phosphodiester bonds
- the distance between two consecutive bases is 0.34 nm
- thread size is 3.4 nm

Structure
of nucleic acids

Genetic material

- is found in both the nucleus and the mitochondria

Genome
and replication

DNA

- is organised into a chromosome containing 30 000 000 000 nucleotide base pairs

Chromosomes

- there are 23 pairs (22 pairs of autosomes, 1 pair of gonosomes)

Two strands of DNA

- can be separated by helicase

Isolated DNA strand

- forms a template for RNA, which is synthesized by RNA polymerase

Replication

- two identical daughter molecules are formed from the parent DNA molecule
- by the action of helicase, the DNA molecule is split into two strands (a replication fork is formed)
- via primase, a primer is bound to which the 3'-OH group is added by the DNA polymerase deoxyribonucleotides
- in the case of the leading strand, the DNA polymerase proceeds in the 5' → 3' direction
- in the case of a delayed chain, replication takes place in small fragments (called Okazaki fragments), which are cleaved by DNA ligase

Gene

- is the smallest functional unit of genetic information
- encodes a functional product: an RNA or protein

Gene
and expression