

Health Technology Assessment: Concept for designing laboratory instruments

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Summary

Due to the rapid development of new insight into human pathology, novel parameters become available for the clinical laboratory. However, each potential parameter needs scientific assessments on how and where it should be introduced. The need for laboratory testing varies according to the health care setting. However, in addition to medical criteria economical aspects have to be taken into consideration. For this reasons – after the survey of the existing health care settings, laboratory systems and parameter packages available – we propose a scoring and grading system, which helps to decide whether a parameter should be introduced into routine and where it would be the most appropriate.

Five mayor criteria were scored and selected: **time requirements, prevalence of disease, prevalence/frequency of the tested parameter, pre- and post-test probability**, and the **quality of testing**. Further, these parameter-scores can be weighted by needs of different health care settings, or according to its usefulness to one or more groups of disease.

Thus, such a scoring system can be used to decide whether a parameter should be introduced into routine under certain circumstances or not. In addition it can assist the development of new modular POCT systems, adjusted and customized for the different health care requirements.

New laboratory parameters

The rapid development in life science leads to new insight in human pathology. This brings along novel parameters which need to be introduced into the clinical laboratory to become routinely available for the clinicians and their patients. These parameters have an extensive scientific body of evidence, but they need additional assessment on how they should be introduced into routine e.g POCT vs Corelab.

For these reasons, we developed a system which helps to decide whether a parameter should be introduced into routine or not and if yes, where it would be the most appropriate to be introduced. Therefore, we chose several criteria to be taken into consideration for each potential new parameter:

- Epidemiological data
- Reimbursement system
- Time requirements
- Medical speciality (e.g. speciality clinics)
- Bayes Theorem (pre-test- / post-test-probability)
- Evidence based medicine (EBM) data
- Paths/Algorithms for diagnose finding, treatment and monitoring
- Patient self-testing, POCT, ventral laboratory testing

Existing health care settings, lab systems and “parameter packages”

Depending on the different health care settings, the laboratory testing requirements differ intensely. We separate between centralized health care settings, like e.g. in France and Germany, decentralized health care settings, like in the US and Switzerland, and health care settings in the developing countries. Each of these settings has their own claim regarding the performance of the laboratory routine analysis and the question where a parameter should be measured. Laboratory instruments are in use in core labs, physician’s offices, special clinics, private and commercial laboratories, laboratories in university, state and regional hospitals and their intensive care stations (ICU), operation and emergency rooms. In addition, laboratory instruments are necessary for self-testing. Luppa, Schlebusch et al. designed an “application hierarchy of POCT”. It appears that the intensive care stations and the operation rooms have the highest requirement of POCT, especially for critical care testing parameters such as blood gas, electrolytes and lactat, followed by the emergency rooms with emergency parameters, the ambulance with critical care testing parameters, the physician’s office and the patient with survey, exclusion and diagnostic parameters and self monitoring.

Nowadays parameters are mostly ordered individually. Nevertheless, “packages” where several parameters are analysed at the same time may be useful for e.g. HIV-therapy monitoring, thalassemia and hemoglobiopathies, protein profiles, immuno-phenotypical determinations, and so on.

The lab systems and the “parameter packages” are mainly categorized according to the different specialties namely immunology, haematology, clinical chemistry, molecular biology, microbiology and so on. These units may be pooled in a so-called core lab or can also be divided into separated institutes less working as a unity than as specialized centres.

The simple system developed in this work helps answering the following questions: I) Is this novel parameter useful for the decision making of the clinicians? II) Where and how should this parameter be introduced into routine?

Scoring system

We defined five categories - in part they are independent, in part interdependent of each other - representing the most important factors to be taken into account before the introduction of each new parameter. Score-tables were established, allowing an easy rating of the laboratory parameters.

As a matter of course, not all of the five categories are of the same importance. The time frame in which the result of a parameter’s measurement should be at the doctor’s disposal for example is one of the most important features, certainly more important than e.g. the economical aspect. To take these circumstances into consideration, the five different categories of the scoring system have to be graded themselves by using a factor (1, 1.5, 2, 2.5, 3, 3.5) by which the achieved score of the new parameter will be multiplied.

1. Time requirements

time	score
very urgent (<10 min)	10
urgent (<30 min)	8
rapid (<60 min)	6
normal (>60min – 1d)	4
slow, rare (-1 week)	2

The time frame between order entry and disposal of the result has a high influence on the decision whether a parameter is better tested on a POCT system or in a core laboratory. We defined four time frames: very urgent parameters, where the result is needed in less than 10 minutes, urgent and rapid parameters with a maximum delay of 30 respectively 60 minutes and the so-called “normal” and “slow” parameters, where the

results are needed in >60 minutes to 1 day or up to one week respectively.

2. Prevalence of disease

prevalence of disease	score
very high (1:50)	10
high (1:100)	8
moderate (1:200)	4
low (1:500)	1

According to the world wide distribution of different disease it is evident that not all the available parameters are needed at every location. Therefore it is important to consider the prevalence of the diseases for which the new parameter is needed.

3. Prevalence/Frequency of the tested parameter

Frequency	score
very frequent (1:10)	10
frequent (1:20)	8
rare (1:50)	4
very rare (1:100)	1

Further the prevalence or frequency of the measurement should also be taken into account. This category highly depends on the health care setting: at a doctor's office the high frequent tests are not the same as in an emergency room.

4. Pre-test probability– Post-test probability

To decide whether a new parameter will be implemented into routine or set on a new laboratory instrument, the Bayes' theorem provides assistance. It relates the conditional and marginal (also called unconditional) probabilities of two random events, and it is often used to calculate posterior probabilities, e.g. post-test probability of disease. It permits to calculate e.g. the probability that the proposed diagnosis for a patient is true, due a certain observation or laboratory analyses.

pre-/post-test-probability	score
very high PPV or NPV (> 90%)	10
high PPV or NPV (> 80%)	8
medium PPV or NPV (> 60%)	6
low PPV or NPV (> 40%)	4
very low PPV or NPV (> 20%)	2

The positive predictive value (PPV) is the proportion of patients with positive or negative test results who are correctly diagnosed or excluded. This value is dependant on the prevalence of the disease, which varies between different health care systems. On a collective the PPV is composed of prevalence and sensitivity, whereas the NPV is composed of 100-prevalence and

specifity.

5. Analytical quality

test quality	score
highly robust and simple method	10
robust and simple method	7
rather delicate and complicate method	4
very delicate and complicate method	1

The simpler a test system is, the easier it can be introduced into the routine. Especially for the POCT setting, the method has to be as simple and robust as possible. New potential parameters which can be tested with a highly robust method, with good precision and trueness leading

to high accuracy are favoured to get into the routine diagnostic.

Additional considerations

Tabelle 1 Different locations for laboratory instruments. For each cross a parameter gets, it gets an additional point

	physician's office	special clinics	private / commercial laboratories	regional / university / state hospital	intensive care stations	operation rooms	emergency rooms
Parameter a (total score 127)	x			x			x
Parameter b (total score 76)	x	x	x	x			
Parameter c (total score 65.5)	x						
Parameter d (total score 35)		x	x	x			

Once a potential new parameter got his final score (sum of the scores multiplied by the "factor of importance" reached in the five categories), a basis is created to decide if it should go into routine or not. Afterwards, additional investigations can be done to answer the question in which facility the parameter is of special

interest. This can be done by looking at the different types of locations where laboratory instruments are needed (Table 1) and/or looking at different groups of diseases (Table 2 and 3). The more locations respectively groups of diseases the potential parameter fits in, the more additional points it gets allocated.

Tabelle 2: Groups of diseases. These groups are less based on the geographical distribution of a disease than on the patient population treated in a certain health care system.

Groups of disease	Including following examples
infection disease	general bacterial and viral infections, HIV, Herpes, Hepatitis, fungal and parasite infections
bleeding	severe bleeding
Anemia	ACD, microcytic, macrocytic, normocytic, dimorphic anemia, Heinz Body anemia
hematologic disease	chronic and acute lymphatic and myeloid leucemias, Hodgkin and non-Hodgkin Lymphoma
thrombotic disease	DVT, HIT, TTP
rheumatic disease	rheumatoid arthritis, collagenosis (Sjörger-Syndrom, systemic lupus erythematodes, ...), vasculitis, arthrosis
autoimmune reaction	Multiple sclerosis, morbus Bechterew, morbus Crohn, celiac disease, ...
heart and circulation disease	atherosclerosis, coronary disease, shoke
vascular disease	raynaud syndrome, phlebothrombosis, varicosis
respiratory disease	sracoidosis, pleuritis, bronchitis, pneumonia
gastrointestinal disease	mouth-, oesophagus-, stomach-, intestine-, liver-disease
oncological disease	sarcoma, melanoma, carcinoma
endocrine disease	thyroid disease, gonad disease, adrenal disease
renal disease	glomerulonephritis, nephropathies (diabetic, chronic or toxic), prostatitis

Tabelle 3: Different groups of diseases. Each cross a parameter gets, the parameter receives an additional point

	Infection	Bleeding	Anemia	Hematologic disease	Thrombotic disease	Rheumatic disease	Autoimmune reaction	Vascular disease	Gastrointestinal disease	Oncological disease	Endocrine disease	Renal disease
Parameter a (total score 127)				x								x
Parameter b (total score 76)							x	x		x		
Parameter c (total score 65.5)		x	x	x			x	x		x		
Parameter d (total score 35)		x	x	x								

Taken together, scientific basic knowledge is needed in order to select high quality parameters. However, a clinically appropriate and economic use of candidate parameters is important as well. For this reasons – after the survey of the existing health care settings, laboratory systems and parameter packages available – we designed a scoring and grading system with five mayor criteria differentially weighted, to decide whether a parameter should be introduced into routine and where it would be the most appropriate. Further this system may also be useful for the development of new modular POCT systems and their adjustment and customization depending on their future location.

Calculation example: Which of the two potential parameters is more important to be introduced into a physician's office POCT system?

Parameter b:

In this case test frequency is the most important factor (x3), followed by the prevalence of disease (x2.5), test quality (x2) and PPV (x1.5) and time (x1). The disease for which the parameter would be used is highly prevalent in Switzerland (8), so the test would be done frequently (8). The PPV of this parameter is high (8) and the test is simple to perform (7), but one hour is needed for the analysis (6).

Final score for parameter b = $3 \times 8 + 2.5 \times 8 + 2 \times 7 + 1.5 \times 8 + 1 \times 6 = 76$

Parameter c:

For parameter c, time is the most important factor (x 3), followed by test frequency (x2.5), prevalence of disease (x2), PPV (x1.5) and test quality (x1). The disease for which the parameter would be used is moderately prevalent in Switzerland (4), the test would be done very rarely (1). The PPV of this parameter is very high (10), the test is highly robust (10), and very rapidly performed (10).

Final score for parameter c = $3 \times 10 + 2.5 \times 1 + 2 \times 4 + 1.5 \times 10 + 1 \times 10 = 65.5$

Additional considerations:

As the place of the POCT system is already certain, there is no need to asses the different type of locations, but it may be interesting to check, for which other groups of diseases the parameter d and c could although of use.

Parameter b and c are both useful for the analysis of autoimmune reactions, vascular diseases and oncological diseases, whereas parameter c can further be used for the investigation of bleeding, anemia and hematologic diseases. Therefore parameter b gets 3 additional points, parameter c 6.

Parameter b = $76 + 3 = 79$

Parameter c = $65.5 + 6 = 71.5$

→ The introduction of parameter b is more urgent than the one of parameter c.