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Critical review of laboratory investigations in clinical practice guidelines: proposals for the description of investigation

Abstract

Background: Correct information provided by guidelines may reduce laboratory test related errors during the pre-analytical, analytical and post-analytical phase and increase the quality of laboratory results.

Methods: Twelve clinical practice guidelines were reviewed regarding inclusion of important laboratory investigations. Based on the results and the authors' experience, two checklists were developed: one comprehensive list including topics that authors of guidelines may consider and one consisting of minimal standards that should be covered for all laboratory tests recommended in clinical practice guidelines. The number of topics addressed by the guidelines was related to involvement of laboratory medicine specialists in the guideline development process.

Results: The comprehensive list suggests 33 pre-analytical, 37 analytical and 10 post-analytical items. The mean percentage of topics dealt with by the guidelines was 33% (median 30%, range 17%–55%) and inclusion of a laboratory medicine specialist in the guideline committee significantly increased the number of topics addressed. Information about patient status, biological and analytical interferences and sample handling were scarce in most guidelines even if the inclusion of a laboratory medicine specialist in the development process seemingly led to increased focus on, e.g., sample type, sample handling and analytical variation. Examples underlining the importance of including laboratory items are given.

Conclusions: Inclusion of laboratory medicine specialist in the guideline development process may increase the focus on important laboratory related items even if this information is usually limited. Two checklists are suggested to help guideline developers to cover all important topics related to laboratory testing.

Keywords: clinical chemistry tests; guideline; laboratory personnel; quality improvement.

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Introduction

Laboratory testing is an important and integral part of medical decision-making. It is widely reported that 60%–70% of all medical decisions are influenced by results of laboratory analysis [1, 2] and most clinical practice guidelines include recommendations for the use of laboratory tests. However, the success and cost-effectiveness of preventive or therapeutic interventions are highly dependent on the use of the most appropriate diagnostic tests and their correct interpretation. The quality of laboratory test results may be reduced by errors occurring during the three phases of analytic handling: pre-analytical, analytical and post-analytical.

Laboratories have worked steadily and quite successfully over the past decades to reduce within laboratory analytical errors. These errors are now considered to be less of a problem compared to those errors of test selection and interpretation which are largely outside the control of the laboratories; and these errors account for more than 80% of mistakes within the total testing procedure [3]. The most frequent errors are caused by inappropriate choice of laboratory tests or panel of tests (pre-pre-analytical errors) and inappropriate interpretation and utilization of laboratory results (post-post-analytical errors) [3]. These mistakes cannot be reduced without collaborative efforts between the laboratory and the users of the laboratory, i.e., the clinicians. Creation of clinical practice guidelines recommending use of laboratory tests without involving a laboratory medicine specialist may lead to uncertainty in the description of laboratory tests [4]. To reduce the number of errors during the total testing procedure, the European Federation of Clinical Chemistry and Laboratory Medicine and the European Union of Medical Specialists joint working group on Guidelines suggests establishing closer co-operation between laboratory professionals and clinicians in the development of clinical practice guidelines. This article proposes two checklists for relevant laboratory issues that should be considered or included during development of clinical practice guidelines. These may act as a facilitator for increasing knowledge about laboratory tests among clinicians and the production of improved clinical practice guidelines in the laboratory.

Materials and methods

Twelve clinical practice guidelines dealing with common laboratory medicine tests were critically reviewed (Table 1). As inclusion criteria the guidelines should have been published since 2000 and should address a medical question where results of one or more laboratory tests play an important role in the diagnostic, monitoring or therapeutic process [e.g., brain natriuretic peptide (BNP) in heart failure and prothrombin time-international normalized ratio (PT-INR) in warfarin monitoring] or were part of the diagnostic definition of a disease (e.g., troponin in acute myocardial infarction and lupus anticoagulant testing in antiphospholipid syndrome). Clinical practice guidelines including the following topics were explored: nephrology, dyslipidemia, heart failure, myocardial infarction, diabetes, thyroid disease, prostate cancer, monoclonal gammopathy of undetermined significance, coagulation, hematology, immunology and microbiology [5–16]. The authors developed a list of items relevant for laboratory testing and the number of items addressed for the relevant laboratory test(s) in a guideline was recorded by some of the authors (K.M.A., M.R.L., J.W. and W.P.O.). If one item was considered not relevant for the particular test evaluated this was recorded. The list was supplied with relevant items acknowledged during the evaluation. As a result of the work two checklists were developed: one comprehensive list including topics that authors of clinical practice guidelines should consider (and discuss when relevant) when recommendations for use of a laboratory test is included in a guideline (Table 2) and one consisting of minimal standards that should be covered for all laboratory tests recommended in clinical practice guidelines (Table 3). Differences in the number of topics addressed by the 12 guidelines were related to involvement of laboratory medicine specialist in the guideline development process and evaluated using independent Student's t-test. Fisher's exact test was used for analyzing the correlation between laboratory medicine specialists' involvement and the likelihood of a single checklist item to be included in a guideline. SPSS 18.0 (IBM Corporation, New York, NY, USA) was used for statistical analysis.

Results

An overview of the clinical practice guidelines evaluated and number of laboratory related items included in each guideline is shown in Table 1. The comprehensive checklist and percentage of guidelines dealing with the topics enlisted is shown in Table 2. The mean percentage of topics dealt with by the guidelines was 33% (median 30%, range 17%–55%) and inclusion of a laboratory medicine specialist in the guideline committee significantly increased the number of topics addressed (mean 43% vs. 28%; p=0.04). Overall, clinical practice guidelines commonly presented information regarding target population, diagnostic characteristics and recommended method used. Information about patient status, biological and analytical interferences and sample handling were scarce in most guidelines but the inclusion of a laboratory medicine specialist in the development of the guidelines seemingly led to an increased focus on some traditional headlines within laboratory medicine (Table 4), e.g., sample type, sample handling and analytical variation. To underline the relevance of laboratory related information in clinical practice guidelines, examples are given of important topics included and excluded in some of the guidelines (see below). Finally, a basic checklist is proposed which suggests topics which we feel should be considered to be mandatory components of all clinical practice guidelines when laboratory testing is recommended (Table 3).

Chronic kidney disease [6]

The guideline on chronic kidney disease is the most comprehensive regarding laboratory issues and includes considerable information regarding pre-analytical (e.g., influence of food intake, circadian rhythm, centrifugation and transport), analytical [e.g., standardization and

Guideline	Laboratory test(s) evaluated	Percentage of relevant laboratory items included
National Collaborating Centre for Chronic Conditions. Chronic kidney disease: national guideline for early identification and management in adults in primary and secondary care [6]	Creatinine/eGFR	55 (45/82)
ESC/EAS guidelines for the management of dyslipidaemias The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) [9]	Total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, apolipoprotein B	49 (42/85)
ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM) [14]	BNP, NT-proBNP	24 (21/86)
Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC) [10]	Troponin I, troponin T	24 (21/88)
American Diabetes Association. Standards of medical care in diabetes – 2011 [7]	HbA_{1c}, glucose	35 (31/89)
American Thyroid Association guidelines for detection of thyroid dysfunction [11]	TSH, FT4, FT3	15 (17/90)
National Collaborating Centre for Chronic Conditions. Prostate cancer. Diagnosis and treatment [12]	PSA	24 (20/83)
UK Myeloma Forum (UKMF) and Nordic Myeloma Study Group (NMSG): guidelines for the investigation of newly detected M-proteins and the management of monoclonal gammopathy of undetermined significance (MGUS) [13]	Serum protein electrophoresis	37 (29/78)
SIGN 122: prevention and management of venous thromboembolism [8]	INR	22 (15/69)
ICSH recommendations for identification, diagnostic value and quantitation of schistocytes [16]	Schistocytes count	48 (41/85)
International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS) [5]	Lupus anticoagulant	29 (24/82)
Guidelines for the laboratory diagnosis of mycoplasma genitalium infections in East European countries [15]	Nucleic acid amplification tests	31 (27/86)

Table 1 Clinical practical guidelines included in the evaluation and percentage of relevant laboratory items included in the guidelines. Total number of laboratory items evaluated was 91 (a few general topics were evaluated in addition to the very specific topics enlisted in the comprehensive list, e.g., overall information on target population was evaluated in addition to an assessment if any specific information such as age, gender, etc. was given for the target population). If one topic was not relevant for the test evaluated the nominator was reduced. Absolute numbers (included/relevant) are given in parentheses.

traceability of creatinine measurements and estimating glomerular filtration rate (eGFR)] and post-analytical topics (e.g., clinical meaningful changes in eGFR based on patient outcome studies). Data on biological variation for creatinine is presented but may be difficult to interpret because reference change values are not calculated nor for creatinine or eGFR. Another important issue that is not discussed in the guideline is commenting on eGFR results. Studies have shown such commenting to be beneficial when eGFR reporting is implemented [17].

Dyslipidemia [9]

In the 2011 European Atherosclerosis Society/European Society of Cardiology (EAS/ESC) guidelines for management of dyslipidemia, characteristics of the target population are very well described and even incorporated in the risk calculation system (age, gender, diabetes). Test indication is clear for all lipid tests, e.g., risk calculation or therapeutic target, but concrete data on sensitivity, specificity and predictive value are missing. With the exception

Pre-analytical phase	Target population for use		Included in guideline, %
		Age	73
		Gender	78
		Diabetes	75
		Specific diseases	72
	Indication for using the test		
		Monitoring	73
		Frequency of testing	64
		Diagnosis	92
		Prognosis	82
		Screening	67
		Self-monitoring	25
	Clinical performance		
		Sensitivity	64
		Specificity	64
		ROC curve	18
		Added value of the test	70
		Comparison with related diagnostic tests	82
		Post-test probability of diagnosis	27
		Positive outcome of testing	75
		Negative outcome of testing	67
	Multimarker approach		
		Included in a multimarker panel	70
		Sensitivity (panel)	11
		Specificity (panel)	11
		ROC curve (panel)	11
		Added value of the panel	56
	Sampling procedures		
		Fasting required	27
		Time from clinical event	27
		Patient position	0
		Circadian rhythm	14
		Sample type	25
		Sample transportation	17
		Centrifugation	10
		Sample pre-treatment (maximum delay)	17
		Maximum storage time (at specified temperature)	17
		Maximum number of freezing/thawing cycles	9
Analytical phase	Methodology		
		Recommended method	91
		Standardization	70
		Traceability to reference method	33
		Biomarker heterogeneity	27
		Detection limit	27
	Analytical interferences		
		Lipemia	9
		Hemolysis	0
		Bilirubin	0
		Monoclonal paraproteins	0
		Heterophilic antibodies	11
		Endogenous autoantibodies	0
		Rheumatoid factor	0
		Other relevant	17
		Define actions when analytical interference is suspected	8
	Biological interferences		
		Age	33
		Gender	9
		Acute illness	17
		Acute phase	17

(**Table 2** Continued)

Pre-analytical phase	Target population for use		Included in guideline, %
		Food intake	18
		Medication	25
		Smoking	8
		Alcohol	8
		Pregnancy	27
		(Post) menopausal status	0
		Obesity	17
		Physical activity	8
		Genetic factors	17
		Ethnicity	25
		Geographical region	8
		Other	73
	Quality issues		
		Analytical variation	33
		External quality assessment	25
		Internal quality assessment	17
		Performance goals (MAPS)	8
		Allowable bias, imprecision and total error	8
		Accreditation	8
		Special training or expertise necessary	25
		Turnaround time	9
Post-analytical phase			
		Qualitative or quantitative results	67
		Unit used	64
		Recommended to comment on reported results	17
		Reference interval (method specific)	50 (63)
		Diagnostic cut-off value (method specific)	100 (46)
		Therapeutic target	40
		Biological variation	25
		Information about clinical meaningful changes	50
		Changes interpreted based on reference change values	8
		Changes interpreted based on outcome studies	25

Table 2 Comprehensive checklist including 80 topics that should be considered for all laboratory tests included in a clinical practice guideline.
Percentage of guidelines (n=12) that included information on the items are shown in the last column. If one topic was not relevant for evaluation in one particular guideline the nominator was adjusted when calculating the percentages.

of a recommendation for fasting blood sampling, pre-analytical issues are lacking in the guideline. There are no data on potential interferences in the tests except for the rare condition of hyperglycerolemia that may cause falsely high triglycerides in assays without glycerol blanking, and information on biological interferences are summarized for triglycerides only. The use of direct low-density lipoprotein (LDL) methods is recommended in cases of invalid LDL calculation with the Friedewald equation but problems related to standardization of LDL and high-density lipoprotein (HDL) assays are not addressed. Risk- and gender-related cut points and therapeutic target values are clearly given. Intra-individual variation data are given for total cholesterol and triglycerides with a recommendation for repeat testing but a clinical meaningful change is only given for on-treatment LDL target to achieve a 50% relative reduction from baseline LDL.

Heart failure [14]

Both BNP and N-terminal pro-brain natriuretic peptide (NT-proBNP) tests can be used according to a flow chart for the diagnosis of heart failure in the ESC guideline. Pre-analytical and analytical recommendations are not included. A comparison of BNP vs. NT-proBNP testing advantages and disadvantages is lacking. Diagnostic cut-off values (decision limits) are provided and conditions other than heart failure associated with elevated natriuretic peptides are listed.

Pre-analytical phase	Target population for use	All relevant information (Table 2) should be included
	Indication for using the test	All relevant information (Table 2) should be included
	Clinical performance	Sensitivity
		Specificity
		Positive outcome of testing
		Negative outcome of testing
	Sampling procedures	Fasting required
		Time from clinical event
Analytical phase	Methodology	Recommended method
	Biological interferences	All relevant information (Table 2) should be included
	Quality issues	Allowable bias, imprecision and total error
Post-analytical phase		Commenting on reported results
		Diagnostic cut-off value
		Therapeutic target (if relevant)
		Information about clinical meaningful changes based on RCVs and clinical outcome studies when available

Table 3 Laboratory issues that should be addressed in all clinical practice guidelines when laboratory testing is recommended.

Myocardial infarction [10]

The cardiac troponins play a central role in the 2011 ESC guidelines for management of patients with suspected acute coronary syndrome (ACS). There are clear indications for testing to establish the diagnosis, stratify risk and distinguish between non-ST-elevation myocardial infarction and unstable angina. The guideline states that troponin tests are preferred because they are more specific and sensitive than creatine kinase, creatine kinase-MB and myoglobin. A comprehensive table with non-ACS causes of troponin elevation is provided. There is only a recommendation to use high-sensitive troponin assays but there are no concrete methodological recommendations such as standardization and analytical performance goals. The diagnostic cut-off value for myocardial infarction is defined as the 99th percentile of a normal reference population using an assay with imprecision (coefficient of variation) of ≤10% at the upper reference limit. The use of point-of-care tests for troponin is recommended when a laboratory cannot consistently provide test results within 60 min (maximum turnaround time).

Diabetes mellitus [7]

Laboratory items of hemoglobin A_{1c} (HbA_{1c}) and glucose testing are satisfactorily incorporated in the American Diabetes Association (ADA) guidelines for diagnosis and care of diabetes mellitus. Target populations, test indications, diagnostic criteria and frequency of testing are well described. Sensitivity and specificity of HbA_{1c} compared with glucose testing are described in a separate ADA position statement paper [18]. It is recommended to use an HbA_{1c} method that is certified by the National Glycohemoglobin Standardization Program (NGSP) and standardized or traceable to the Diabetes Control and Complications Trial (DCCT) reference assay. The different standardizations (i.e., International Federation of Clinical Chemistry international standard and NGSP) and units used for reporting results (i.e., mmol/mol and %) that are utilized for this assay is not explained and this may lead to confusion. Analytical performance goals and maximum turnaround time are not given, but the use of point-of-care HbA_{1c} assays is discouraged because they are not sufficiently accurate. For HbA_{1c}, there is a clear warning of analytical interference by hemoglobin variants and biological interference of clinical conditions with abnormal red cell turnover.

Prostate cancer [12]

Recommendations for prostate-specific antigen (PSA) testing are insufficient in the 2008 National Institute for Health and Clinical Excellence (NICE) guidelines for prostate cancer diagnosis and treatment, and laboratory aspects of PSA are restricted to a small one-page appendix to the guidelines. Target populations and indications for PSA testing are well described. PSA is recommended to be combined with digital rectal examination for prostate cancer diagnosis. The role and frequency of PSA testing for follow-up and risk stratification are clearly described. Pre-analytical and analytical issues are totally omitted; there is only a recommendation to use the same assay for serial PSA testing. Post-analytical interpretation is supported

Topic	Laboratory medicine specialist involved	Laboratory medicine specialist not involved	p-Value of difference
Sample type	3/4	0/8	0.02
Sample transportation	2/4	0/8	0.09
Sample pre-treatment (maximum delay)	2/4	0/8	0.09
Analytical variation	3/4	1/8	0.07
Maximum storage time (at specified temperature)	2/4	0/8	0.09
Recommended to comment on reported results	2/4	0/8	0.09

Table 4 Number of guidelines that included information about a topic stratified according to involvement of laboratory medicine specialist in the development process (n=12).

with the concept of age-adjusted PSA cut-off values and false-positive PSA values due to benign prostate hypertrophy or prostatitis; other biological interferences such as digital rectal examination are not mentioned. Total PSA testing combined with free PSA (fPSA) or complexed PSA (cPSA) is proposed to increase test specificity but without methodological recommendations (e.g., use of equimolar assays). Clinically meaningful changes are provided for "PSA velocity" (the absolute rate of PSA change over time) and "PSA doubling time" (the time taken for PSA concentration to double) to predict a more aggressive tumor course.

Monoclonal gammopathy of undetermined significance [13]

Serum protein electrophoresis is used for monitoring patients with monoclonal gammopathy of undetermined significance. It is reassuring that the high inter-laboratory variability in quantification of M-protein is acknowledged but even so no suggestions are given for allowable bias, imprecision and total error, nor is there a recommendation for the use of internal or external quality assessment. The inclusion of such information would have been a signal from clinicians to laboratory professionals and manufacturers that the current situation is not satisfactory. The guideline states that a 25% increase (5 g/L) is indicative of a clinically significant change but the background for this recommendation (e.g., clinical outcome studies or reference change values) is not stated.

Monitoring PT-INR [8]

The use of warfarin and monitoring by measuring PT-INR is described in this guideline addressing the prevention and management of venous thromboembolism. The guideline does suggest INR values that indicate higher bleeding risk but does not give any information on reference change values (i.e., changes that may be seen in stable patients and that should not lead to changes in warfarin therapy) or biological interference that may affect PT-INR values (e.g., food intake). This must be considered a clear limitation because warfarin treatment is well known to induce frequent and serious side effects.

Identification, diagnostic value and quantitation of schistocytes [16]

Some important items of the checklist, e.g., pre-analytical factors, seem to be completely missing in the guideline. However, a personal communication with the corresponding author of these guidelines reveals that many of the missing items could very well be taken into account in the future editions of these schistocytes guidelines.

Antiphospholipid syndrome [5]

Testing for lupus anticoagulant is mandatory when diagnosing antiphospholipid syndrome. The guideline describes the poor standardization of the tests and gives recommendations to reduce this but does not give advice regarding pre-analytical concerns (e.g., centrifugation procedures, transportation and storing conditions) well known to be important to obtain correct results [19, 20]. Because sampling may be conducted in primary care offices or small laboratories and thereafter mailed to larger centers performing the assay such information would have been useful. There is no information about narrative commenting even if studies indicate that commenting results of complex coagulation assays would facilitate more adequate use and interpretation of the results [21].

Discussion

The clinical practice guidelines we have studied typically describe the target population, indications and frequency of testing and give the diagnostic performance characteristics (sensitivity, specificity) and diagnostic cut-off values of the appropriate laboratory tests. However, the more laboratory focused aspects such as methods and standardization are not emphasized. The inclusion of laboratory medicine specialists in the development committees of the guidelines seemingly lead to a general increase in attention to the laboratory related aspects and especially those related to pre-analytical requirements.

Do laboratories need clinical practice guidelines?

The role of laboratory medicine specialists has changed in recent years. In the past, the main role was in the analytic phase, whereas now the emphasis needs to move to creating clinical added value services (more than data production). This consists of guiding appropriate test ordering and ensuring optimal test interpretation. Clinical practice guidelines are an appropriate route to achieve this aim. However, despite this, studies have shown laboratory medicine specialists to have limited knowledge of the clinical use of the tests their laboratory offer [22–24]. Our study shows that this information is commonly included in clinical practice guidelines and laboratory medicine specialists would therefore benefit from larger familiarity with such information sources. Joint clinical and laboratory guidelines could be a tool to increase knowledge on clinical use of tests within the laboratories and make laboratory professionals able to play a more active role in reducing number of wrongly requested or interpreted laboratory tests [25].

Do clinicians need knowledge about laboratory specific topics?

The proposed list is very comprehensive and it could be argued that some topics suggested are the responsibility of the laboratory rather than clinicians and should, therefore, not be included in clinical practice guidelines. However, the data and examples show that clinicians commonly need specialized laboratory related information to be able to obtain a correct result and to reach a correct interpretation of the result. The need for sufficient description of laboratory methods in clinical studies is also emphasized in a recent paper written by the editors of nine laboratory medicine journals [26]. Furthermore, it has been shown that primary care physicians find it difficult to become familiar with the use and interpretation of new tests [27, 28], and similar findings should also be expected among specialized physicians regarding tests that are not specific to their specialty. As even more complex testing becomes available (e.g., genomic and proteomic testing, nanotechnologies), pre- and post-analytical errors may even further lead to reduced quality of disease management and increased healthcare costs.

Suggestion of checklists for implementation of laboratory investigations in guidelines

One-third of the clinical practical guidelines studied in this report included a laboratory medicine specialist in the development process and our evaluation shows that this involvement increased the focus on the relevant laboratory issues. However, not all topics were covered even when a laboratory medicine specialist was involved and the checklist (Table 2) may therefore serve as a tool to ensure that all laboratory issues are considered in a structured way. The information suggested in Table 3 is proposed as a minimum list and should be included for all tests recommended but the comprehensive checklist might be used more selectively as applicable. It may be best to consider including the detailed laboratory information as an appendix rather than by inclusion in the main guideline document. The topics included in such checklists will always be a matter of debate and our suggestions may be changed according to feedback or discussion within the relevant clinical chemistry or clinical societies. An important purpose of the checklist is to facilitate interaction between laboratory professionals and clinicians in order to write optimal guidelines and help both disciplines increase their knowledge of each other. Moreover, joint documents may possibly also enhance the implementation of clinical practice guidelines because they seemingly are read by more people (e.g., both laboratory professionals and clinicians). The working group therefore suggests that these two checklists are used as tools to ensure that structured information related to pre-analytic, analytic and post-analytic errors are included in all clinical practice guidelines to the benefit of patients, society, laboratory professionals and clinicians.

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