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8. Discussion

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One main purpose of this NORDKEM project has been to combine the efforts and results from the two previous NORDKEM-projects on "Assessing quality requirements in clinical chemistry" (13), and "Quality control in clinical chemistry - efforts to find an efficient strategy" (3), in order to establish a more relevant basis for analytical quality management in laboratory medicine. In order to obtain a broad and reliable basis for the evaluation, a number of mostly Scandinavian experts were invited for critical comments and ideas in a two day meeting (The Friibergh Herrgård Seminar), from which a report has been published (2). One conclusion was that the project group should describe and summarize the most significant knowledge of analytical goals/analytical quality specifications and analytical quality control, and invite a number of scientists, who were involved in clinical and analytical projects. From these projects aspects on analytical goals/quality specifications and control could be extracted in order to obtain contributions to approaches presented in the final report. These *associated projects* were chosen according to the participants knowledge about current projects within the field. Representatives from the associated projects were invited two years later to another two-day meeting for information and coordination, whereafter reports have been prepared within the individual projects.

A uniform terminology is essential in order to communicate in an effective way and great efforts have been made to collect and suggest suitable terms and abbreviations.
Two major projects, dealing with transferability of laboratory data and reference intervals, have all the time been an integral part of the total project.

8.1. TERMINOLOGY

There is a pronounced lack of internationally accepted terminology within this area. To avoid undefined concepts and expressions René Dybkær has participated in the project group and prepared two documents: a more general one about 'Truth, Accuracy, Error, and Uncertainty' (8), and a 'Vocabulary for describing the metrological quality of a measurement procedure' (7). The concepts and expressions have been defined according to internationally accepted authorities or organizations such as BIPM, ISO, IUPAC, IFCC, etc. Some terms, which we find necessary to use in this report, lack generally accepted definitions. We have collected these separately under the headline 'Explanation of some other Concepts and Terms Used in this Report' (5). It is our expectation that these terms - usually collected from authorities and organization on a high hierarchical level - should be accepted by the clinical laboratory community. It is a risk that less well authorized concepts and terms may intimidate the laboratory people from their use. In such cases it is more important to start the quantitative characterization of goals and procedures of measurement and quality assurance than to wait for more fancy concepts and terms.

8.2. TRANSFERABILITY OF LABORATORY DATA

It is easy to recognize a prolonged trend from the tendency of the practitioners and the physicians to use their own, in practical work acquired, "database" for reference values towards the use of scientifically acquired "databases" which use methodologies including reference method technology, statistical techniques and multicentre studies. This new tendency makes it important to try to reduce between-laboratory analytical variation (s_{bL}) or, expressed in other words, to urge the laboratories to reduce their long term bias. Although our experiences are limited to a regional study including creatinine and urate in 17 laboratories for three 14-week periods (18) and a Nordic study including creatinine, calcium and cholesterol in 7 laboratories for a 4-week period and a later 2-week period (Chapter 5.2) (11, 12), it is justified to conclude that application of a carefully selected bias assessment and correction procedure is motivated for several analytical methods. The alternatives may be to try to reduce the *random* error to an unrealistic extent and to instal new measurement procedures which may be more expensive and less practical.

8.3. EXTERNAL QUALITY ASSURANCE FOR PROTEINS

The Nordic Protein Project includes all the three elements of analytical quality in a structured combination: i) specification of analytical quality ii) creation of analytical quality iii) control of analytical quality. Thereby it comes close to a model for total analytical quality management, with planning, implementation, registration, control, and evaluation.

The basis for analytical quality specifications, however, is not clinical but rather biological. This choice relates to several considerations: i) it is very difficult to find clinical situations for all the proteins where the result is determining ii) the use of specific proteins varies from country to country iii) the need for common reference intervals seems to be considerable. Moreover, the projects on reference intervals in Denmark and Finland made the concept of quality specifications for sharing common reference intervals most relevant. Creation of analytical quality relates to the analytical procedures and the basis for standardization. As evaluation of analytical procedures, equipments, and reagents are performed mainly by industry, it is difficult to influence on this directly. Guidelines are, however, given in the project for improving performance or for choosing better methods. The need for common calibration was eminent in the project and solved by use of the Nordic calibrator. This is further improved by transferring values from the IFCC reference preparation, whereby the traceability is secured.
Finally, the project designs a control system which challenges trueness of measurements by controlling the calibration with use of optimal (clear) control samples, and identical samples, except for turbidity. Furthermore, the presentation of data relates directly to differences, both for estimation of bias related to calibration (measured minus conventional true value) and unspecific signals from turbidity (turbid minus clear sample).

8.4. ETHICAL ASPECTS

According to our opinion it is unethical to provide an analytical service and sell it without stating its 'analytical quality' and 'service quality'. See Chapter 1, Fig. 1.1 (4). This question was considered similarly in the General Scandinavian Recommendations on Quality Control and Quality Assurance in Clinical Chemistry issued by the Board of the Scandinavian Society for Clinical Chemistry in 1990 (21). How the analytical quality should

be presented to the customers in practice is another problem. As stated by prof. Doumas, President of AACC, in a recent discussion (6) it seems to be be most practical to provide this information in the 'Laboratory Guide for Physicians' from the laboratory.

Certification and accreditation are procedures through which the management of the laboratory tries to guarantee that the AQSpecs are followed. It involves stated activities to ascertain the traceability of the methods and to implement internal and external quality control and quality assurance systems. Clinical goals and AQSpecs are essential elements in these activities.

8.5. ECONOMICAL ASPECTS

In the attempts by ISO and its national standardization organizations to advertise their ISO Guides for Quality it is stressed that the characterization of the quality of a product or a service is important for its marketing and selling. This is a truth that has been known for decades in industry and it seems now to spread slowly to clinical laboratories along with the introduction of market economy within the health care sector. It is natural that for analyses with lower systematic and random errors, higher analytical specificity, lower detection limits and shorter turnaround time (19) a higher price could be charged. This requires, however, massive information and motivation from the laboratories directed towards the clinicians, the practitoners, their staff, and the adminitrators within health care. NORDKEM has recently carried out a project about 'Cost Management in Clinical Chemistry Laboratories' (16). Unfortunately, in this phase of that project, the relation between cost and quality was not discussed.

8.6. THE ASSOCIATED PROJECTS

In general the participants in the associated projects found it easy to grasp the concept of influence of analytical quality on the outcome of a clinical strategy. The process of assessing this influence was, however, a critical point, and especially the concrete assessment, where analytical disturbances were assumed or simulated, seemed to be rather difficult. In addition to the calculations, the approach of splitting up the process in clinical problems, biological variation, and analytical variation (considering both trueness and precision), was a hard nut to crack. Some of the associated projects did not succeed in the total process of combining all the elements, partly because the basic problem was too

complicated for a clear and straight forward evaluation, and partly because the process was too cumbersome. The associated projects provided, however, valuable approaches to the problems - and the variety of approaches has widened the whole concept of the project. In order to demonstrate that there are many aspects on clinical goals and AQSpecs all the associated projects have been included in this report.
Fig. 8.1 illustrates what has been achieved by the associated projects. This scheme shows that the involved projects cover the whole spectrum of aspects related to quality specification. Some of the projects are more detailed and therefore difficult to give a place between the boxes. The scheme provides, however, some indications of the expansion of the concept as it has been extended considerably compared to the original scheme in Chapter 1. (Fig. 1.1)

The associated projects can be incorporated in different kinds of schemes or structures. In the list of contents of this book they have been order according to Table 8.1.

Table 8.1. The Associated Projects, Structure

6.1 *Approaches from clinical situations*
6.1.1 New approaches
6.1.2 Known approaches
6.1.3 Other approaches
6.2 *Approaches from biological and methodological data*
6.3 *Other projects*

In order to provide *another type of overview* the associated projects have been listed in Fig. 8.2 in a scheme comparable to Fig. 4.3.1. Contributions covering more than one approach of goal setting are listed accordingly. It is further seen that the fraction of bimodal approaches is comparatively smaller and that the 'Time series' are represented only by one single project. In contrast, the approach 'Other situations' covers a broad spectrum from 'Decision models', 'Selection of measurement', and 'Definition of measurand' over 'Contamination' and 'Detection limit' to 'Technical' approaches as well as 'Quality improvement'. All are not listed in Fig. 8.2 but presented under different headlines in Table 8.2.

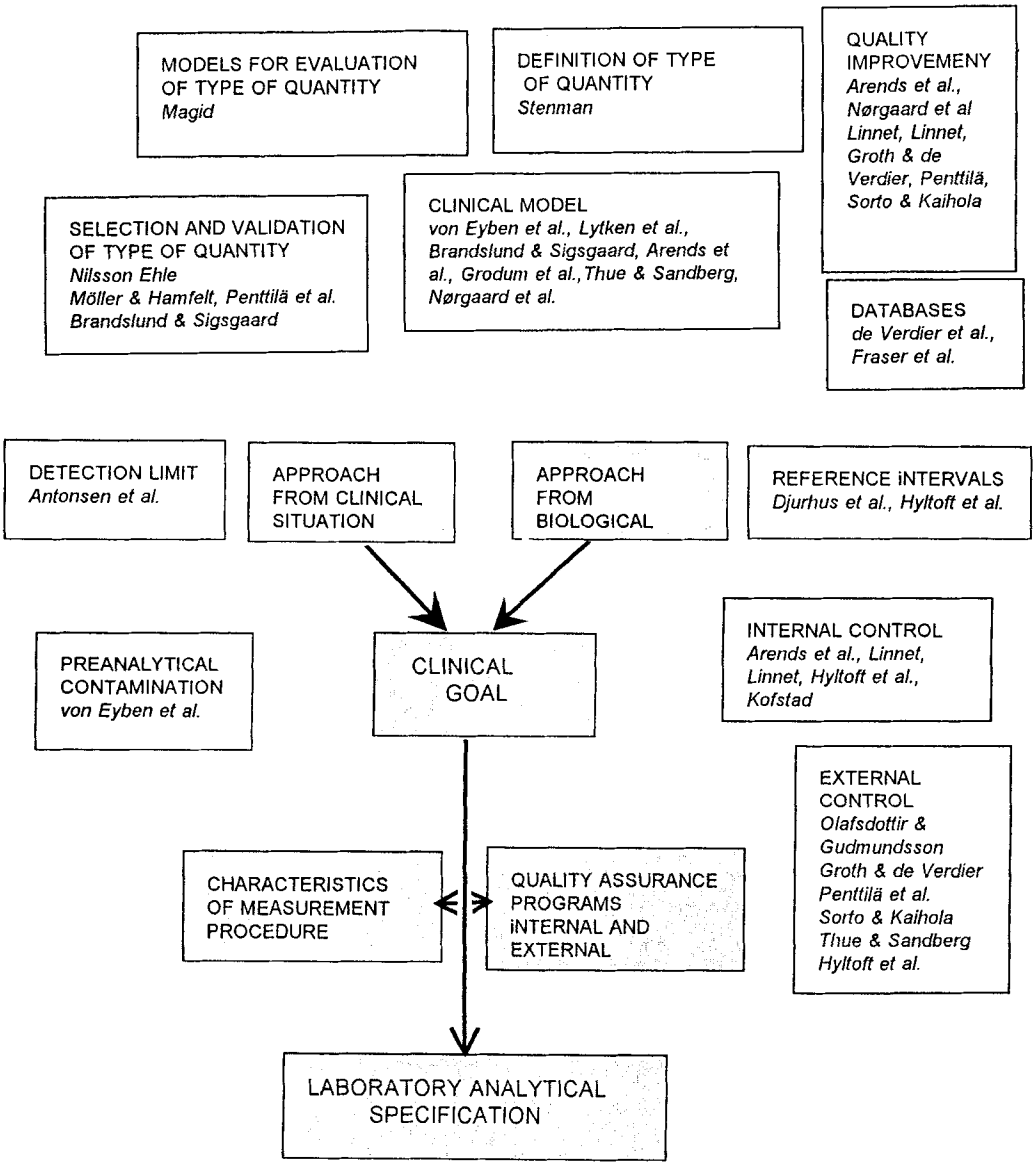

Fig. 8.1. A scheme describing the various associated projects in relation to the structure presented in Fig. 1.1. The boxes taken over from Fig. 1.1 are shadowed. The scheme illustrates that the associated projects cover the whole spectrum of aspects related to clinical goals and AQSpecs.

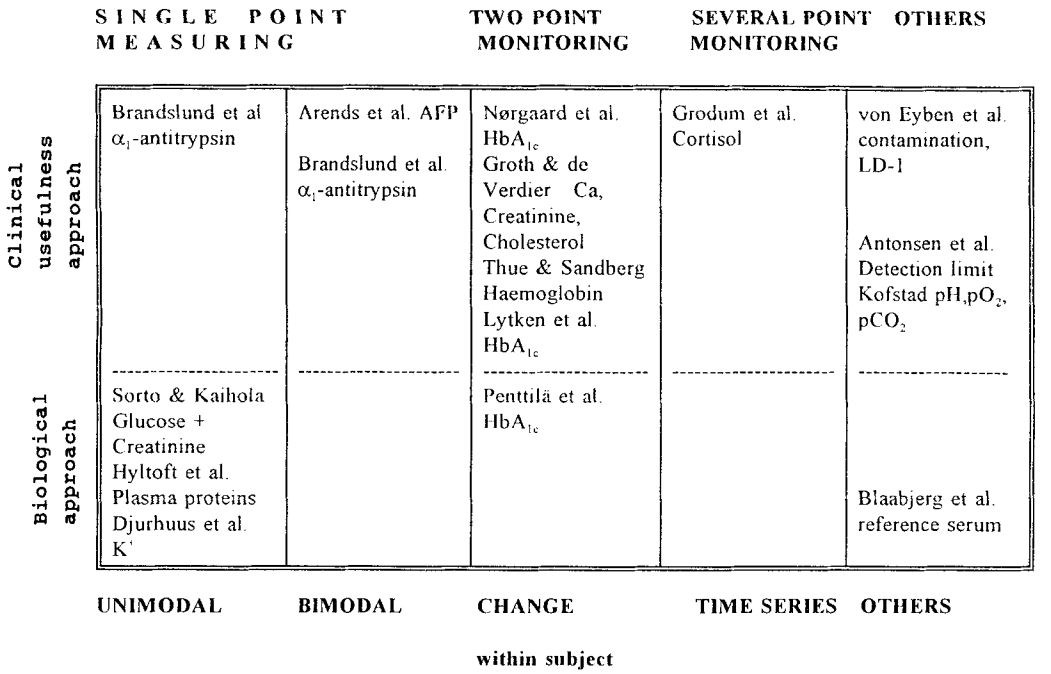

Fig. 8.2. This figure shows the associated projects in a structure comparable to Fig. 4.3.1

Table 8.2. The table demonstrates different associated projects and how they can be distributed under six specified headlines.

Decision models	**Selection and validation of measurements**	**Definition of components**	**AQSpecs for External Quality Assessment**	**Nomenclature & Terminology**	**Databases**
Magid: General models	*Nilsson-Ehle: Cholesterol Möller & Hamfelt: Myoglobin Penttilä et al. AFP +hCG Brandslund et al.: α_1-A*	*Stenman: Specificity, hCG*	*Olafsdottir & Gudmundsson: Cholesterol Groth & de Verdier: Ca, Cholesterol, Creatinine Sorto & Kaihola: Glucose, Creatinine*	*Dybkœr: Terminology de Verdier et al.: Explanation of some concepts*	*de Verdier et al.:Biology + control Fraser: Biology*

In the majority of involved projects the link has been obtained between goals/quality specifications and quality control, whether established or only indicated. Thereby, the purpose of the project has been fulfilled and it has also been confirmed that it is possible within a broad area.

Most projects are related to external control where six of these are established in external quality assessment schemes. It may be mentioned that the HbA_{1c} projects (Nørgaard *et al.*; Penttilä *et al.*) are restricted by lack of ideal control materials and that the project on contamination (von Eyben *et al.*) does not recommend traditional control but rather a correction procedure. HbA_{1c} is an analyte of great importance for the guidance of treatment of diabetes. It also provides an excellent example of how bias and imprecision can be combined in a two-dimensional plot illustrating their contributions to the total error. Fig. 8.3 presents results achieved from the three associated projects dealing with this problem.

Additional comments on the associated projects

* *Applicability*

The well known approaches and models are applicable in a series of clinical situations where a single quantity is determining for a medical decision. The clearest applications are the bimodal model in pure screening situations, *e.g.* TSH- and PKU-screenings. The same model may also be relevant in diagnostic situations where there is a clear distinction between the two classification groups. In screenings and decisions where the basic concept is purely unimodal, *e.g.* cholesterol screening (Nilsson-Ehle), the unimodal model is relevant. Which concept should be applied must be thoroughly investigated *prior to* the assessment.

For a predetermined change in a quantity the assessment is quite clear, whereas, there are actions of clinicians on change in test results that are more doubtful. Do they indicate how the clinicians think that they are expected to answer or how they really use the data?

* *New approaches to goal setting*

The associated projects have revealed that various approaches are possible and relevant in order to derive AQSpecs. Here, it becomes clear that decision models for assessment of clinical strategies, definition of the quantity to be measured, and the selection and validation of the right quantity to measure (Fig. 8.1) are prerequisites for the outcome. Furthermore, the preanalytical problems must be assessed and compensated for when

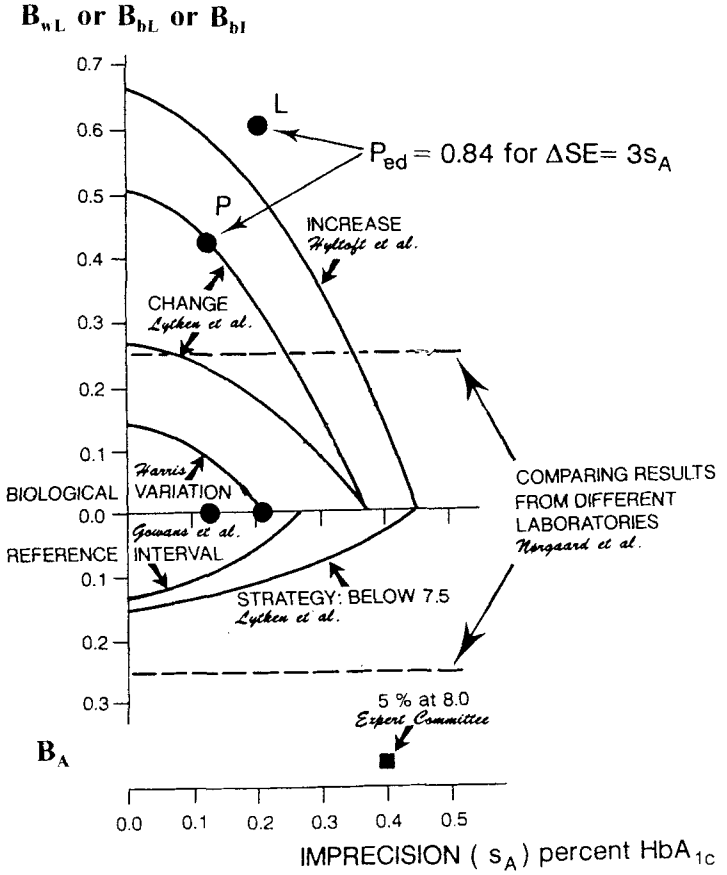

Fig. 8.3. Comparison between different quality specifications for the measurement of HbA_{1c} combining imprecision (s_A) along the abscissa with bias along the ordinate. The part of the figure *above* the upper abscissa describes the clinical situation, where an increase of per cent HbA_{1c} of 1 or 2 between two samplings is considered. Here the measurements are considered to be made in the same laboratory (Bias = B_{wL}) or between two instruments (B_{bI}) or between laboratories (B_{bL}). The part of the figure *below* the upper abscissa is related directly to the bias (B_A) in each individual laboratory. Here the measurements are considered to be made in different laboratories (Bias = B_{bL}).
The four upwards convex curves illustrate: i) the clinical goal suggested by Harris (15), ii) Lytken Larsen *et al.* with Δ per cent HbA_{1c} = 1, bidirectional change and 0.80 confidence level (9,15), iii) Lytken Larsen *et al.* with Δ per cent HbA_{1c} = 2, bidirectional change and 0.99 confidence level (15) and iv) Hyltoft Petersen *et al.* with Δ per cent HbA_{1c} = 2, unidirectional change and 0.99 confidence level (14).
The two downwards convex curves illustrate:i) quality specifications calculated from data obtained from the reference interval (10) and from a clinical strategy assuming that the clinician reacts for increase above per cent HbA_{1c} 7.5.
The two horizontal hatched lines demonstrate the maximal allowable limits for B_{bI} or B_{wI} (17).
The two dots (●) along the upper abscissa indicate published values for actual measured value of s_A. The lower value is published by Penttilä *et al.* (20) and the higher by Lytken Larsen *et al.* (15). The two similar upper dots marked P and L correspond, respectively, to a situation where the same s_A-values are combined with a systematic errors (ΔSE) = 3 s_A. With the control rule: 1_{3s} this gives a probability for error detection (P_{ed}) = 0.84 (22).
The filled square (■) at the bottom of the of the figure indicates the recommendation for s_A by a US expert committee (1).

possible, and the aspects of limit of detection must be considered. Validation of the use of laboratory data is necessary (Hamfelt, Nilsson-Ehle). The problems related to selection of the right classification (uni- and bimodal) is demonstrated for α_1-Antitrypsin, where choice of the bimodal concept may lead to the recommendation of typing of z-types instead of measuring S--α_1-Antitrypsin (Brandslund).

* *New models for assessment of quality specifications*

Two models are principally new (Grodum, Nørgaard) but one of them is a transformation of time-series data to a simple bimodal concept leaving only one new model (Nørgaard). Here the problem of transferability is very concrete, as the patients are judged according to the same decision limits but may be classified differently due to divergencies between two (or more) measurement procedures. The assessment model is very simple, as the clinical outcome is the degree of disagreement between the results.

* *Proposals for creation of better analytical quality*

Arends *et al.* have proposed internal reference material, Nørgaard *et al.* materials for calibration and control and Linnet finally reference methods.

8.7. STRATEGIC APPROACHES TOWARDS LABORATORY AQSpecs

Our experiences during these four project years have tought us that there are no simple solutions to how the laboratory AQSpecs should be settled. Clinical goals must be the origin, either they come from a description of the clinical situation - which is preferred - or are estimated from data on 'biological variation'. The laboratory has to investigate what can be achieved with the present analytical equipment or with other equipments possible to procure. The internal quality control system and the external quality assurance system have to be selected and they should eliminate most erroneous analytical results (give high error detection and low false rejection). It is thus obvious that the three elements: clinical goals, characteristics of the measurement procedure, and quality control/assurance must be involved in the calculations. In Chapter 7 we have tried to collect data from a few illustrative laboratory investigations. The important thing is not to try to find the most correct way of doing it but to start to provide documented laboratory AQSpecs in order to gain experiences.

At the recent AACC Forum on "Accuracy and Precision Goals in Clinical Chemistry Testing: Can they be defined by medical relevance?" (6) Prof. B. T. Doumas, president of AACC, asked if it is feasible to set such goals and if it is the right approach. The joint answer from AACC, CAP, and NCCLS was yes. This is also the answer from the NORDKEM PROJECT group 5/89. There are still many difficulties and much work has to be done but the advantages with acquiring and using AQSpecs are considerable.

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