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6.1.1.7 Quality Specifications in the Clinical Laboratory: How Good are Our Methods, and What are They Good For?

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The technical performance of laboratory techniques can be clearly defined and documented in terms of precision, accuracy, detection limits etc. At present, much interest focuses on how to define clinical requirements for assay performance in order to obtain an optimal combination of analytical quality, accessibility, simplicity, speed of operation and economy in our laboratories (e g 1, 2). From such considerations it is possible to describe how good our methods are. However, quality specifications in a broader sense also require that we define and explain to our customers what our analyses are good for, and how they may, or may not, be helpful in various clinical settings (Fig 1).

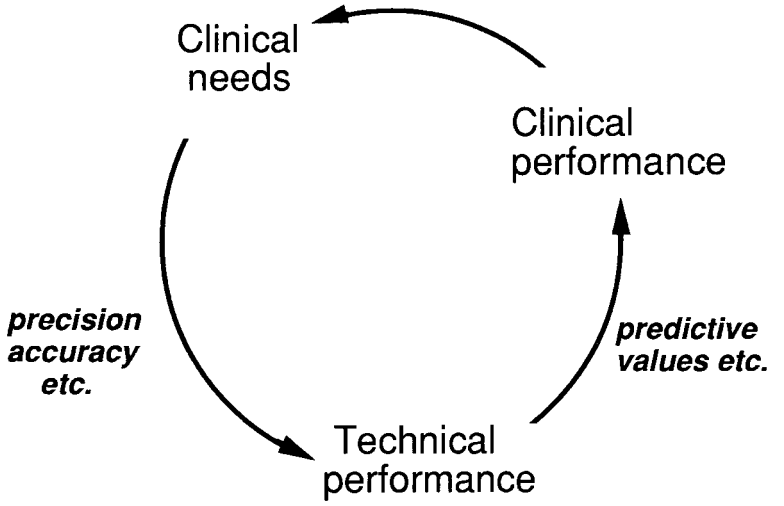


Figure 1. Interactions between clinical specialities and the laboratory in defining analytical quality specifications and assessing the clinical usefulness of laboratory measurements.

Lack of such information does not necessarily mean that the analyses in question loose their market or popularity. Rather, the risk is that the clinical use of a method is influenced or even governed by information or concepts which are not relevant for or directly applicable in medical practice. The "cholesterol debate" provides us with a recent example.

Different perspectives of medical problems

For health authorities, health economists and colleagues engaged in occupational medicine and pharmaceutical industries, epidemiological concepts such as (biochemical) risk factors, risk ratios and relative risk are crucial to describe the health situation in a population and analyze needs for activities or intervention on the national, community or local level. For those engaged in medical practice, however, these concepts offer little guidance in the assessment of the individual patient's situation and treatment. In this situation, the ability of laboratory tests to differentiate between normal and abnormal, to predict prognosis, to monitor the development of disease and to document the effects of treatment are of prime importance. Thus, information related to biological variation, diagnostic sensitivity and specificity and, especially, the predictive values of laboratory data is in focus.

If these different perspectives are not recognized, laboratory services may be used inefficiently. An important didactic task for clinical laboratories is to provide easily accessible, clear background information to illustrate the usefulness of various analyses in different clinical situations, i e what different measurements are good for.

The cholesterol debate

During the last decade, intervention programmes of various designs (including general screening programmes for plasma cholesterol) have been advocated to lower plasma cholesterol levels in the population in order to remedy the high incidence of cardiovascular disease in Western countries. In general terms, the arguments for such programmes have been that the plasma cholesterol level is a major risk factor for cardiovascular disease, that cholesterol concentrations can be lowered by non-pharmaceutical or pharmaceutical means, and that such lipid lowering does indeed prevent manifestations of atherosclerosis. Let us scrutinize the underlying information.

The relationship between plasma cholesterol and cardiovascular disease

There is ample documentation that the plasma cholesterol level is one of the three major risk factors for premature cardiovascular disease, as is frequently demonstrated in diagrams of relative risk vs. cholesterol concentrations (Fig 2 a). Nevertheless, less than 50% of myocardial infarctions in Sweden occur in subjects with plasma cholesterol levels > 6,5 mmol/L (Fig 2 b), the limit recommended for active intervention by authorities in most countries (4, 5). Thus, screening for and successful intervention against S-Cholesterol concentrations above 6,5 mmol/L may at best prevent a minority of cases of e g myocardial infarction.

When a variable expressing absolute rather than relative risk is introduced, the impact of isolated hypercholesterolemia on cardiovascular disease is considerably less impressive. Fig 2 c illustrates "cardiovascular survival" vs. plasma cholesterol concentrations. Its message is that most middle-aged men, even those with moderately elevated cholesterol levels, will not suffer from cardiovascular disease during the next 5 - 10 years. Expressed in other terms, the incidence of cardiovascular manifestations is only about 5% over the observation period. Consequently, the predictive value of elevated S-Cholesterol concentrations for cardiovascular disease is extremely low.

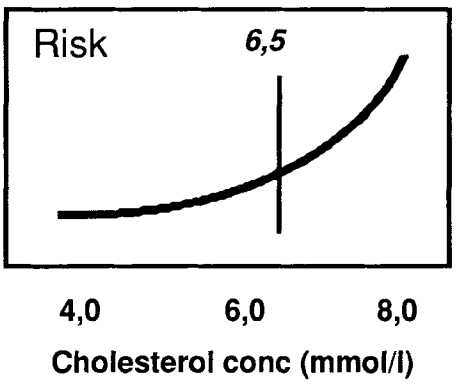


Figure 2a.

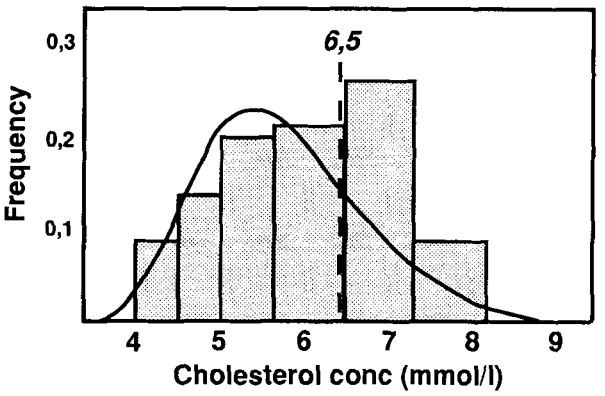


Figure 2b.

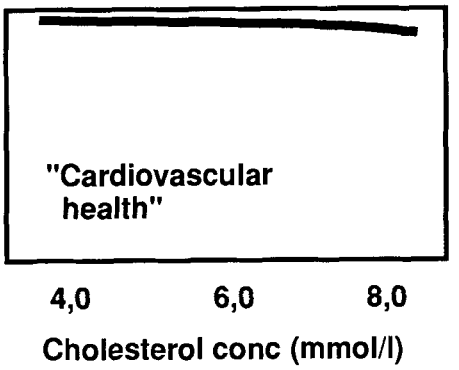


Figure 2c.

Figure 2. Schematic representations of the relationships between plasma cholesterol levels and cardiovascular disease expressed as (a) relative risk vs cholesterol concentrations, (b) incidence of myocardial infarctions in cholesterol concentration intervals (bars) as compared to the frequency distribution of cholesterol concentrations in the general population, and (c) percentage of middle-aged men with moderate hypercholesterolemia who did not develop serious cardiovascular symptoms during a 5 year follow up.
Figs 3 a and b are modified from ref 3 and 5, and Fig 3 c is based on data from refs 3 and 6.

Effects of lipid-lowering therapy

A number of large-scale intervention studies have demonstrated that efficient lipid-lowering therapy is indeed associated with a lowered incidence of atherosclerotic manifestations. The results are generally expressed as a 20 - 40% reduction of cardiovascular

events. Fig 3 shows schematically two popular, and strongly suggestive, illustrations of the effects of intervention.

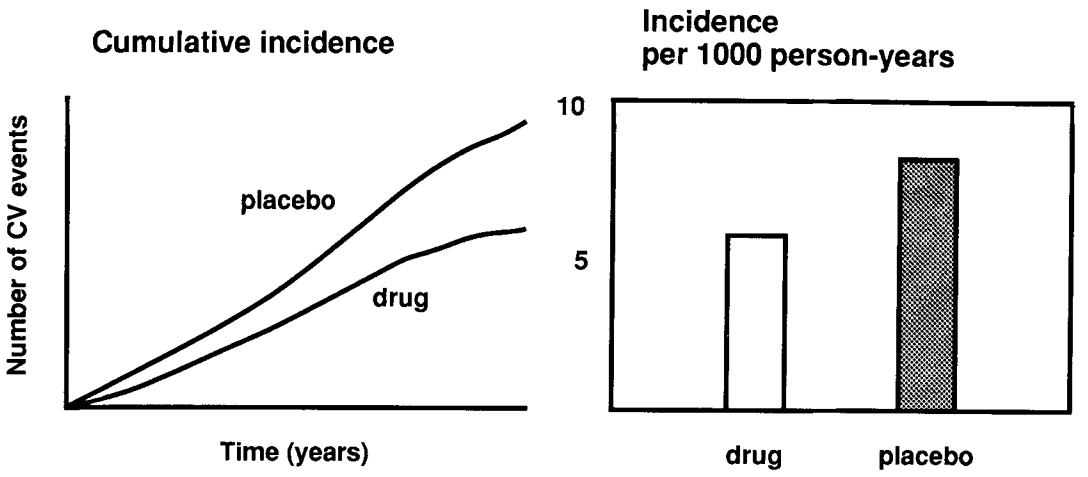


Figure 3. Schematic representations of the effects of intervention on cardiovascular morbidity and mortality in middle-aged men with hypercholesterolemia. Based on data from ref 6.

Again, however, presentation of the overall results may convey a different message. Fig 4 a shows 100 middle-aged men with elevated cholesterol levels. Given the incidence of cardiovascular manifestations in this particular group, five of them will suffer from a cardiovascular event over an observation period of 5 years (Fig 4 b). If all 100 men are treated with an efficient lipid-lowering drug (Fig 4 c), cardiovascular events will be registered in tree subjects. Thus, the program has resulted in the prevention of cardiovascular events in two subjects (40% therapeutic efficacy). The therapeutic gain, consequently, is around one case per 250 treatment years.

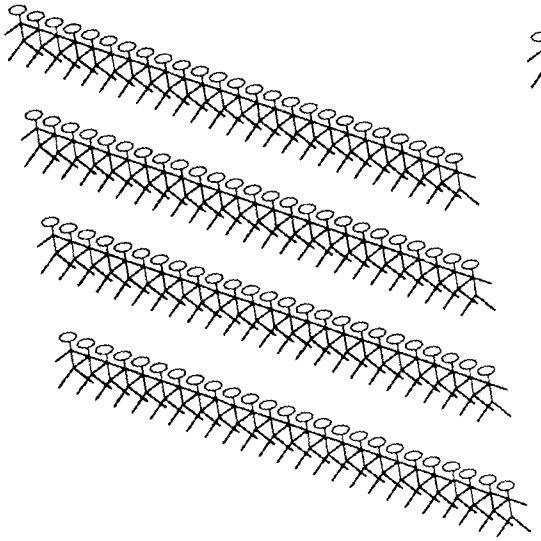
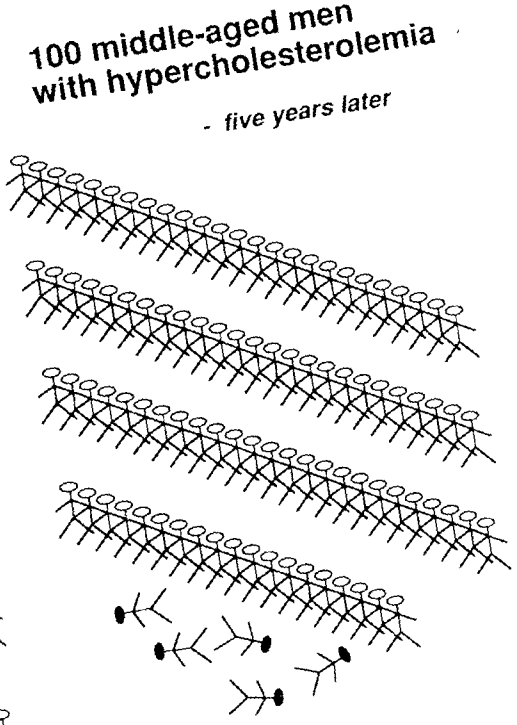


Figure 4 a.



Firgure 4 b.

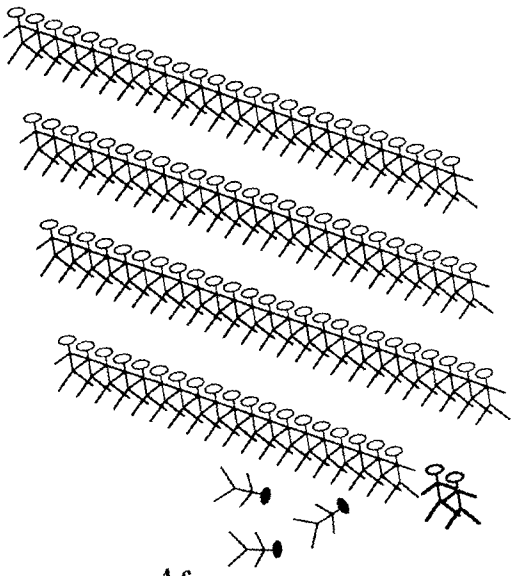


Figure 4 c.

Figure 4. Outcome of an intervention program in middle-aged men with hypercholesterolemia. Figures represent 100 participants at the start of the program (a), and after 5 years in the control group taking placebo (b) and in the intervention group on active medication (c). Based on data from ref 6.

In a couple of these studies there has been an excess mortality from apparently unrelated causes such as suicide, accidents etc. Although it has been suggested that this may represent a side effect of cholesterol lowering, the general pattern (relation to dose, time frame etc) is not typical of a traditional drug side effect.

The clinical situation

The individual patient's attitude and inclination to adopt a specific therapy is largely governed by the information and advice given by his physician. The message of elevated S-Cholesterol to a middle-aged man with isolated, moderate hypercholesterolemia can, depending upon which perspective is in focus, be phrased in two ways:

- "Your cholesterol is elevated, and you run a 3 - 4 fold increased risk to develop a cardiac condition. With diet and drugs, we can reduce that risk by almost 50%".
- "Your cholesterol is elevated, but your chances to escape cardiac trouble over the next 5 - 10 years is still about 95%. With diet and drugs, those chances will increase to 97%. Hopefully, there will be no side effects of the treatment".

Although neither is incorrect, it is quite conceivable that these messages will result in different schemes of management.

Conclusions

Technical specifications of the performance of chemical analyses and documentation of the different sources of variation are basic components of quality assurance programmes. Information on the usefulness of laboratory data in different clinical settings is another important aspect of providing laboratory services of high quality. Predictive values of positive and negative tests are informative, but may be difficult to use efficiently in our relation with clinicians. New efforts and initiatives in this area would promote the rational use of laboratory resources. These considerations are especially important as the technical development now allows a large number of analyses to be performed outside the major hospital laboratories.

Some possibilities to simplify and clarify available information in order to make it relevant

for the typical clinical situation have been illustrated using plasma cholesterol measurements as an example. The analysis demonstrates that screening programmes in the general population would be costly and ineffective mainly because the incidence of cardiovascular events in subjects with isolated, moderate hypercholesterolemia is low. It should be pointed out that determination of cholesterol (and HDL and triglycerides) is recommended in subjects presenting additional risk factors such as genetic disposition, smoking, hypertension, obesity, diabetes etc. In these cases, the overall relative risk may be increased 30-fold, and the incidence of cardiovascular disease is high enough to warrant an integrated assessment of the risk profile as a base for intervention.

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