Roche

Serum Indices: Reduction of clinical errors in laboratory medicine

Going straight for the answer

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cobas® brand

The **cobas**® brand is the umbrella for products used to complete or expand the screening, diagnostic and monitoring applications of the professional laboratory.

Clinical errors in laboratory medicine

Going straight for the answer

Medical laboratory tests can be affected by endogenous and exogenous constituents in the sample matrix. The automated, objective determination of the interfering substances provides benefits compared with the subjective visual interpretation. These benefits include the traceability, efficiency and effectiveness of the work process.

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Preamble

The aim of the clinical laboratory is to report the true value of a concentration or activity. But the results are often influenced by interfering factors related to the presence of hemoglobin, bilirubin and lipemia, which may be recognized by a colored or turbid appearance of the sample. It is difficult to predict the effect of hemolysis, turbidity (lipemia) and hyperbilirubinemia because each sample must be visually examined immediately after centrifugation and the potential interfering property recorded in the laboratory information system.

At hemoglobin concentrations exceeding 300 mg/l (18.8 mmol/l), hemolysis is visible to the eye by the red color of the plasma. Hemolyzed samples are a rather frequent occurrence in laboratory practice, with a prevalence as high as 3.3 % and accounting for nearly 60% of rejected samples.

Lipemia is defined as turbidity in serum samples which is visible to the naked eye. This is usually observed at triglyceride concentrations above 300 mg/dl (3.4 mmol/l).

The visual recognition of hyperbilirubinemia is often not sufficiently sensitive. Because of the high absorbance of bilirubin within the range 340 to 500 nm and the high background, the linearity range of the method can become a limiting factor for spectrophotometric analysis at these wavelengths.

Of the visible interferences, hemolysis most often affects the major 20 clinical chemistry tests, closely followed by total bilirubin and turbidity. Enzyme tests are hardly affected at all. Certain important tests like creatinine, triglycerides, glucose, cholesterol, phosphorus, uric acid, iron, total protein and bilirubin may be sensitive to the interference of hemoglobin, bilirubin and turbidity.

Serum indices represent the automated determination of potential interferences of hemolysis, hyperbilirubinemia and turbidity (lipemia). Roche has created a tool which makes laboratory professionals aware of interferences, helps to increase the quality of the sample, and minimizes aberrant test results.

"With the **cobas**® 4000, 6000 and 8000 analyzer series, the handling of serum indices has been improved further, thereby simplifying the cross check of data and the identification of affected requests. The work process is thus shorter and safer."

Prof. Lothar Thomas, Frankfurt, Germany

Introduction

A laboratory error may be defined as "any real or potentially negative effect on patient management."

Laboratory reporting has a great influence on clinical decision making. Laboratory medicine requires high performance quality controls, ensured by regulatory authorities and certification procedures.

All laboratories make use of statistical quality control procedures to enhance their analytical quality. Nonetheless, clinical laboratory quality standards and error detection rates still fall below industrial quality standards.

Many studies (1, 2, 3) have shown that the majority of clinical laboratory errors occur in the pre- and post-analytical phases. However, within the analytical phase, where the minority of errors occur (13–32 %), there may be undetected errors due to the way in which these errors can be identified.

Lapworth and Teal (4) reported finding in the literature an overall error rate of approx. 0.3 %, though the authors acknowledged that some errors may have gone unnoticed due to the design of the study. Kalra (5) quotes reported error rates of between 0.1–9.3 %. Many studies of error detection rates do not include erroneous results that were unreported due to the result fitting other clinical data.

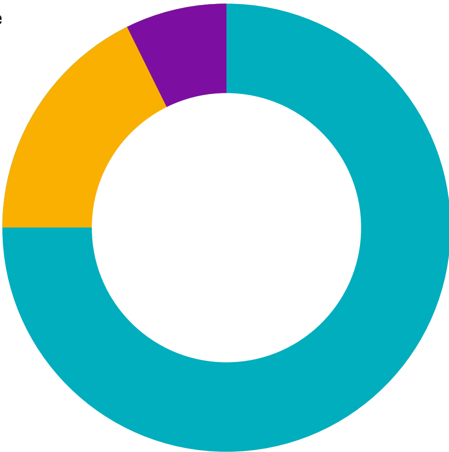
Bonini (6) et al found error rates of 0.60 % in inpatients and 0.039 % in outpatients

Chambers (7) reported an error rate of 0.3 % in a large laboratory and earlier studies by McSwiney and Woodrow (8) found an occurrence of 2.3 %.

Goldschmidt and Lent (9) found that 12.5 % of laboratory errors lead to an erroneous medical decision, 75 % of erroneous results were within the reference range and 12.5 % of the erroneous results were implausible. Plebani and Carraro (1) found that 74 % of laboratory errors did not influence patient outcome and 19 % resulted in increased costs and/or further investigations. The authors also commented that 6.4 % of laboratory errors caused inappropriate care or inappropriate changes to therapy.

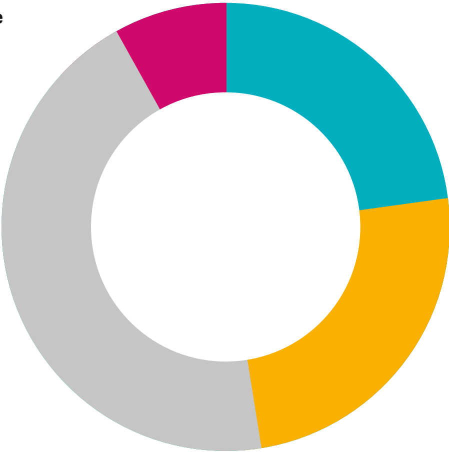
Impact on patient outcome (Plebani and Carraro)

- No influence
- Further investigations
- Inappropriate care



Impact on patient outcome (Goldschmidt)

- Delays
- Potential damage
- None
- Medical intervention



Endogenous interferences in laboratory assays

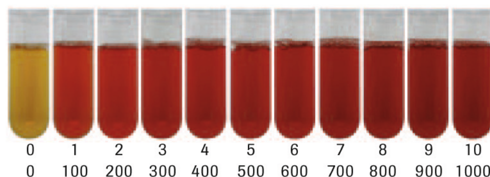
Plebani and Carraro also found that only 13.3 % of total clinical laboratory errors were attributed to the analytical phase. The most common errors here were due to interference or lack of sensitivity of the analytical method.

Some aspects of the testing procedure are often outside the laboratory's control and are outside the bounds of typical analytical process control. These may be differences in biological variation, systematic errors and **interfering substances.**

Kroll and Elin (10) defined interference as "the effect of a substance present in the sample that alters the correct value of the result".

Medical laboratory tests can be affected by endogenous constituents in the sample. Some of these may be recognized by a colored appearance of the sample (hemolysis, icterus and turbidity) but others (drugs) require more detailed information or direct analysis. Interference in an analytical method can produce a false result, which does not reflect the in vivo situation.

Interference by Hemolysis



Dilution-level Tube # n
Index H

Plasma samples with increasing degrees of hemolysis
Differences in the individual appearance is hard to distinguish from level to level; increase of interference level in steps of 100, starting from "zero".

Hemolysis is defined as the release of intracellular components from erythrocytes and other blood cells into the extra cellular fluid and can be caused by many mechanisms.

Hemolysis may be **in vivo** as the result of biochemical, immunological, physical or chemical mechanisms. More commonly hemolysis is **in vitro** and is usually caused by inappropriate or incorrect sample processing. Even if hemolysis is not visible, there may still be discharge of cellular.contents into the serum/plasma.

A study by Carraro and Plebani (1) found that up to 3.3 % of all specimens received by the laboratory were hemolyzed. It is widely accepted that hemolysis can be a source of error in many chemical analyses.

Mechanisms of Interference by hemolysis (11, 12, 13)

Rise of intracellular constituents in the extra-cellular space
Some cell constituents have an intra-cellular concentration 10 times higher than the extra-cellular concentration. Hemolysis in the plasma/serum will cause an increase in concentration of these analytes, for example, potassium, LDH, AST.

Spectral interference
Hemoglobin absorbs light very strongly at its characteristic wavelength of 415 nm. The effect of hemolysis on various analytes measured in clinical chemistry has been thoroughly

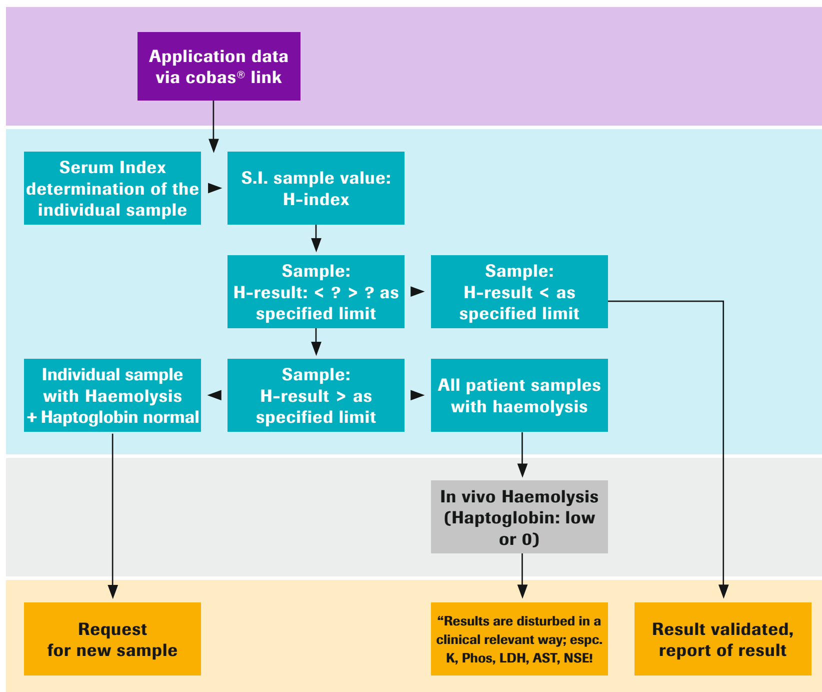
investigated. The observed increase or decrease of a result by hemoglobin has been found to be dependent on the method and analyte concentration.

Chemical Interference

Blood cell constituents can interfere directly or indirectly in the measurement of analytes. Adenylate kinase released from erythrocytes may cause an increase of creatine kinase and CK-MB activity.

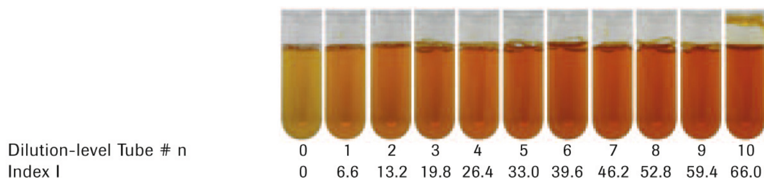
Free hemoglobin with its pseudo-peroxidase activity interferes in the bilirubin procedure of Jendrassik and Grof by inhibiting the diazonium color formation. Proteases released from blood cells reduce the activity of coagulation factors and fibrin split product formation may increase.

Hemoglobin may also interfere by reacting with one or more constituents of the reagent and the interference may differ with different reagent sources.



Hemolytic Interference?! – Sample operation with interference check on cobas® 6000 analyzer series; Prof. L. Thomas

Interference by Icterus



Plasma samples with increasing degrees of icterus
Retrievable differentiation can be performed with an automated process. To distinguish the individual appearance can potentially classify the sample in another level; increase of interference level in steps of 6.6, starting from “zero”.

Elevated concentrations of bilirubin are another source of endogenous interference. Such elevations can be found in a variety of conditions including acute and chronic liver disease, biliary cirrhosis, alcoholism or as a physiological response to many drugs.

Mechanisms of bilirubin interference (11, 12)

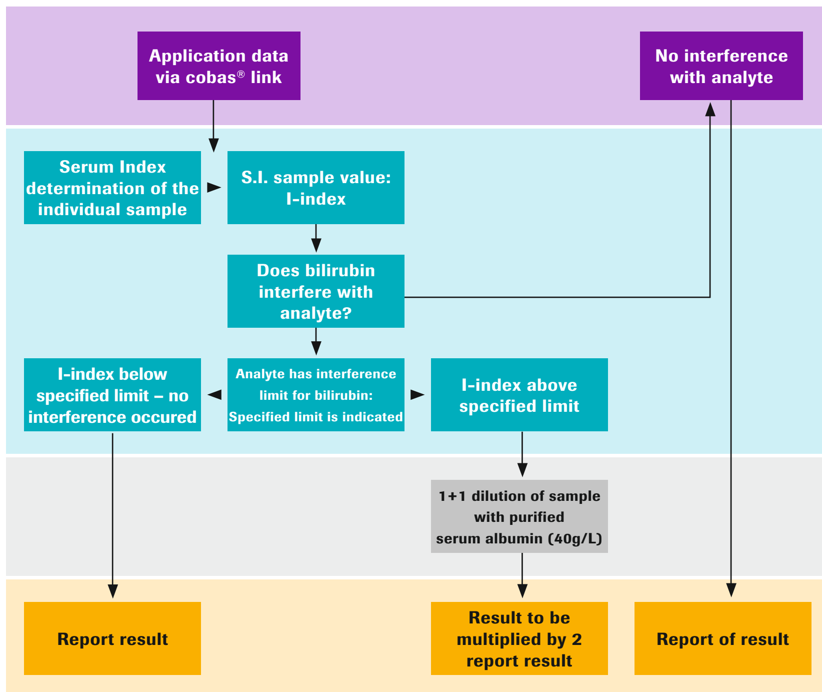
Spectral interference
Bilirubin absorbs strongly between 340 nm and 500 nm wavelengths and the high background absorbance can lead to absorbance readings in excess of the linearity of spectrophotometric procedures.

In a strongly acidic solution the absorption of conjugated bilirubin shifts to the UV wavelengths. Therefore, bilirubin interferes in the determination of some analytes that use these wavelengths. Under alkaline conditions bilirubin is oxidized and loses some of its absorption properties.

Chemical interference

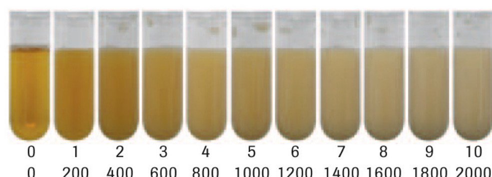
Bilirubin may interfere by acting as a reducing substance because it is easily oxidized to biliverdin and bilipurpurin with a reduction in absorbance. Assays that utilize oxidase/peroxidase based reactions to produce hydrogen peroxide, may produce lower results because bilirubin reacts with the H_2O_2 formed in the test system. The reduction in H_2O_2 is relative to the concentration of bilirubin present. This is true for enzymatic procedures that are used for the measurement of glucose, cholesterol, triglycerides and uric acid.

In albumin assays that employ dye binding, bilirubin can competitively bind to the dye and produce lower albumin results.



Icteric Interference?! – Sample operation with interference check on cobas® 6000 analyzer series; Prof. L. Thomas

Interference by Lipemia



Dilution-level Tube # n	0	1	2	3	4	5	6	7	8	9	10
Index L	0	200	400	600	800	1000	1200	1400	1600	1800	2000

Plasma samples with increasing degrees of turbidity
Any changes in the individual appearance from level to level may barely be distinguishable; increase of interference level in steps of 200, starting from “zero”.

Lipemia is defined as turbidity in samples which is visible to the naked eye. The most common cause of turbidity is an increased concentration of triglycerides. Lipemic samples cannot be avoided as increased concentration of lipids is often secondary to other disease states such as: diabetes mellitus, ethanol use, chronic renal failure and pancreatitis etc.

Mechanisms of Lipemic interference (11, 12, 14, 15)

Spectral interference
The interference caused by lipemia is fundamentally different from the interference from hemolysis and icterus. Lipemia interferes by scattering the light and absorbing the transmission of light through the reaction mixture. In lipemia there is a number of lipid components that can scatter light to produce a milky appearance or turbidity. The degree of light scattering depends on the number, size and refractive index of the suspended lipid particles. As patient serum samples are a mixture of various particle sizes, the sample appears white because the light is scattered at all angles.

Larger lipid entities such as chylomicrons and VLDL cause light to be scattered to the greatest degree. Chylomicrons constitute a diverse group of particles with varying sizes and vary from individual to individual. VLDL particles are a heterogeneous mixture of sizes and lipid content and the number of VLDL particles can be increased in various disease states.

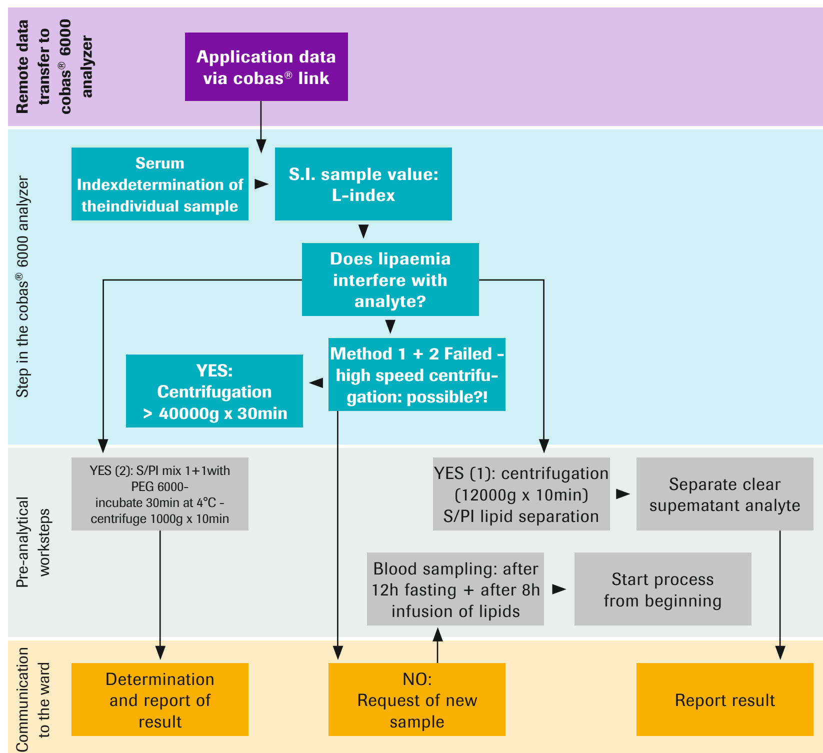
The interference can be either positive or negative depending on the blanking procedure of the assay. At high turbidity, no measurement may be possible due to the limits of the linearity of the spectrophotometer.

Volume depletion effect

Lipoproteins have a "solvent displacing effect" on sampling by reducing the available water of the sample volume. Most analytes are dissolved in the aqueous phase of the plasma/serum. Thus, the effect is to decrease the apparent concentration of the analyte because the volume occupied by lipoproteins in plasma or serum is included in the calculation of the analyte concentration. For analytes that are lipid soluble, including certain drugs that are taken up by lipoproteins, there is an apparent increase in concentration.

Physico-chemical effects

An analyte that is soluble in lipids may not be accessible to the reagent for reactivity. Similarly, electrophoretic and chromatographic procedures may be affected by lipoproteins present in the matrix.



Lipemic Interference?! – Sample operation with interference check on cobas® 6000 analyzer series; Prof. L. Thomas

Endogenous interferences in immunoassays

Immunoassays may be susceptible to the same endogenous interferences as mentioned above if the measuring system used is photometric such as for enzyme linked immunoassay or fluorescence immunoassay.

Roche analyzers have a measuring system that employs electro-chemiluminescence (ECL), which is less prone to these interferences, although some immunoassays may still have interference from unusual serum constituents.

Immunoassays employ antibodies to specific proteins and rely on the binding of these antibodies to the antigen. Unusual proteins in the patient sera, for example, endogenous heterophilic antibodies such as rheumatoid factor, anti-animal antibodies or other non-specific antibodies may interfere in the binding process.

Hemolysis interference in immunoassays may be caused by constituents of red blood cells being released into the serum/plasma. These constituents may influence antibody-antigen binding and produce lower or higher results depending on where they interfere in the reaction.

Interference from **Icterus** in immunoassays is not common because the wavelengths employed in chemiluminescent technology are well separated from the absorbance maxima of bilirubin.

Lipemia interference in immunoassays relates to the solubility of the antigen to be measured in lipid and is therefore no longer available to bind with the antibody.

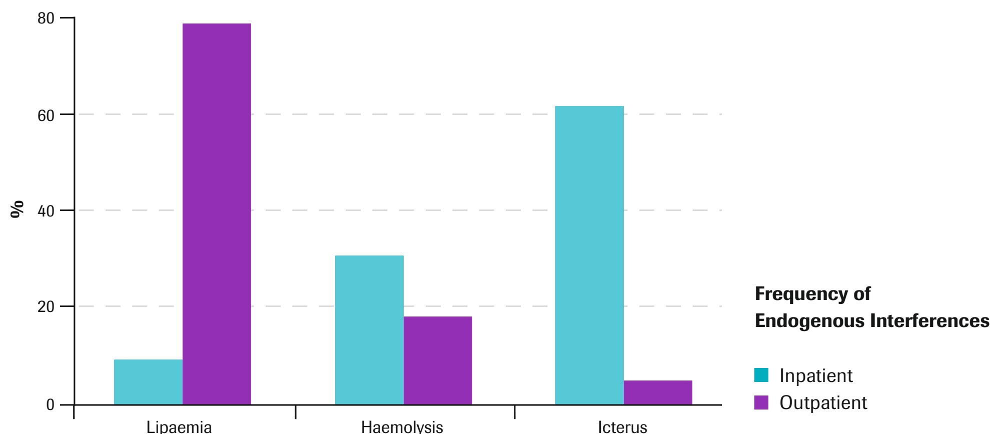
Identifying Clinical Errors

It is the responsibility of the laboratory to produce precise and accurate results and to minimize or avoid producing results with a real or potentially significant negative effect on a patient's health.

Because laboratory errors caused by interferences are random, it is difficult to detect and prevent them from being reported. Many errors may not necessarily produce detectable abnormal results or raise questions for the clinician. Errors caused by interfering substances cannot be detected or prevented by the use of statistical QC procedures. Such procedures can only control analytical variations. Results released from "in-control" runs may contain spurious results that are not detected.

In a study conducted by Glick (16) in an acute care hospital, the frequency with which turbidity, hemolysis or icterus was encountered in serum samples was determined. 32 % of all samples were found to have more than trace concentrations of an interferent. Of these, approximately 63 % were icteric, 29 % hemolyzed and 8 % lipemic.

Ryder (17) studied serum from outpatients and found that 9.7 % of specimens received contained at least one visible interferent. Of these, 76 % were lipemic, probably due to non-fasting, 16.5 % were hemolyzed and 5.5 % were icteric.



Therefore, to prevent the reporting of erroneous results, every sample should be evaluated for the possibility of interference. The benefit is the improvement of the quality of the service provided, as well as improvements in patient care by reducing inaccurate results that can occur from interferences.

Within the manufacturing industry, Shingo (18) showed that the random nature of errors can only be controlled with 100 % inspection, but this must be both easy and inexpensive. He also reported that the inspection must be upstream of the product before it causes an error, which is before the result is released.

Hinkley (19) observed that human inspection methods failed to detect most errors. Glick (16) found that the visual interpretation of hemolysis, lipemia and icterus showed very little agreement to the actual concentration of interferent. Even when comparison samples are used, visual grading was still problematic. He noted that because of this inconsistency, an unbiased method is required to quantitate the level of interference.

Serum Indices

Serum indices are calculations of absorbance measurements that provide a semi-quantitative representation of levels of icterus, hemolysis, or lipemia present in unknown samples. Thus the quality of the sample is assessed at the same time as the sample is processed.

Roche analyzers have been capable of semi-quantitative measurement and reporting of the Serum-Indices since the early 1980s, using 0.9 % NaCl as reagent.

The bichromatic wavelength pairs used for serum index measurement are
480 nm and 505 nm (range 1)
570 nm and 600 nm (range 2)
660 nm and 700 nm (range 3)

Calculation formulas include corrections to compensate for the spectral overlap.

How accurate are the Serum Indices?

Lipemia and Intralipid®
The Lipemic Index L is measured in lipemia units and is based on the optical behaviour of the lipid substitute Intralipid. L units are linear up to 2000 mg/dL. The Lipemic Index provides an estimate of sample turbidity, **not** the concentration of triglycerides. This is because the lipemic Index is a measure of light scatter, which is dependent on particle size.

Hemolysis and hemoglobin
Recovery of the Hemolysis Index correlates approximately with the hemoglobin concentration in the patient's sample depending on the method used to measure Hb.

Icterus and bilirubin
Recovery of the Icteric Index correlates approximately with the bilirubin concentration in the patient's sample.

Serum Indices – How are they done on cobas c analyzers?

Serum indexes are calculations of absorbance measurements that provide a semi-quantitative representation of levels of icterus, hemolysis or lipemia (turbidity) present in patient samples.

A quantification of these interfering materials is possible with the Serum Index Gen. 2 (SI2) application which can be installed on all **cobas c** systems. When measuring Serum Indices, the analyzer takes an aliquot of the patient sample, dilutes it with 0.9 % NaCl, and then measures the absorbances at three pairs of wavelengths:

1. For measurement of lipemia (L), wavelengths 700/660 nm are used because this range is free from influence by hemolysis and icterus (see figure page 18).
2. Hemolysis (H) is measured at 600/570 nm and correction is made for absorption due to lipemia.
3. Icterus (I) is measured at 505/480 nm and correction is made for absorption due to lipemia and hemolysis.

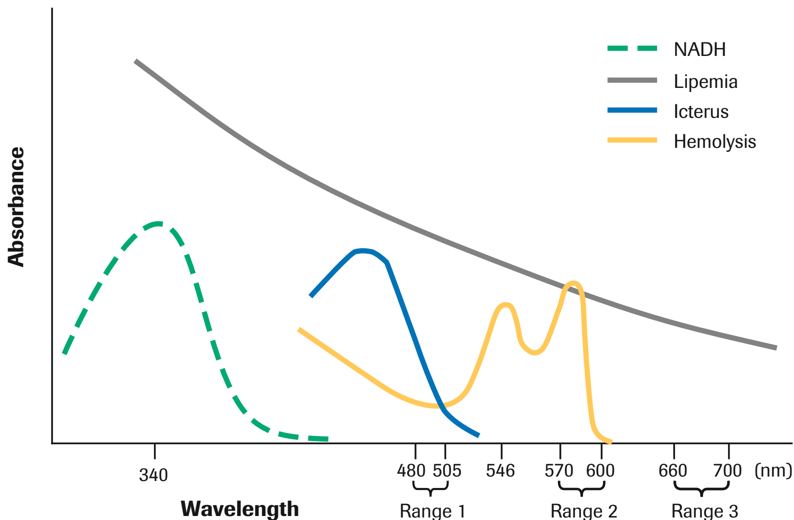
Performing a Serum Index check on the **cobas c** analyzer is very easy. The analyzer operator needs to perform some simple steps:

- download Serum Index (SI2) application
- cross-link SI2 application with pre-installed H, I and L applications
- calibrate SI2
- request SI2 together with other test requests for a serum sample

Serum indices can be programmed in either conventional or SI units.

Each report on laboratory findings should contain a notation characterizing the sample's appearance. If lipemia or a relevant color is found, the cobas c analyzer will indicate, in each case, the type of finding (L)-index "lipemic", (H)-index "hemolytic" and (I), index "icteric".

The diagram shows an example absorption spectra of a turbid serum, a hemolytic solution, and a bilirubin solution.



Once the serum indexes are determined, **cobas c** analyzers compare them with the H, I and L limits given in each individual test application. The limits are indications below which potential interference is considered clinically irrelevant.

If measured values are higher than specified limits of the individual test, the analyzer issues alarms for the measured results. The benefit for the user: if the results are affected by endogenous sample interference – there is no need to manually crosscheck the Roche instructions for use for the index level nor is an additional LIS check needed.

Serum index limits are provided as a part of the application. Application data is downloaded electronically via the **cobas**® link. Potential updates are provided on a daily basis. No manual interaction, such as typing in application data from an application sheet, is required. The user initiates the download of the data from **cobas**® link to the analyzer.

Serum index results are very useful for monitoring the degree of potential interference due to lipemia (turbidity), hemolysis and icterus (bilirubin) and therefore

- *improves the quality of reported results:* 100 % of samples are checked
- *in almost no time:* One simple pipetting step in the analytical phase replaces both the visual check in the pre-analytical phase and the retrieval of suspicious samples in the post-analytical phase
- *with minimal cost:* only the use of a simple NaCl solution compared to manually intensive tasks in the pre and post-analytic phases
- *improved handling of pediatric samples:* enabling efficient and reliable handling of very small sample volumes

Advantages of Automated Serum Indices

Advances in technology allow Roche to incorporate an automated feature into their analytical instruments to verify the quality of the specimen at the same time as the result is produced.

Up to now, medical laboratories have taken a "judgment inspection" approach to endogenous interferences; the operator decides whether the sample is appropriate or not. If an abnormal result is obtained, the sample is inspected for visible interferences. Thus judgment inspections can only detect errors after they have been made and identified.

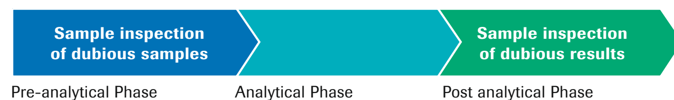
Decreased Turnaround Time (TAT)

Manual inspection may be performed on every specimen before analysis (pre-analytical) or inspecting specimens that produce "suspect" results (post-analytical). This is very time consuming and produces very inconsistent results. In addition, a falsely "normal" result may go undetected.

When Serum Indices are generated by the analyzer, consistent evaluations are made and remove the potential for human error and save operator time.

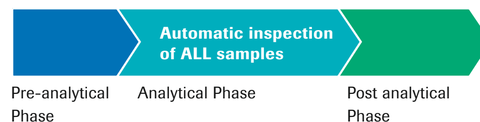
Turn Around Time

(A) Manual Sample Inspection in Pre/Post-Analytical Phase



Pre-analytical Phase Analytical Phase Post analytical Phase

(B) Serum Index incorporated into Analytical Phase



Pre-analytical Phase Analytical Phase Post analytical Phase

(B) a slight increase in analytical time but a large decrease in pre- and/or post-analytical time = reduced overall TAT

Decreased Costs

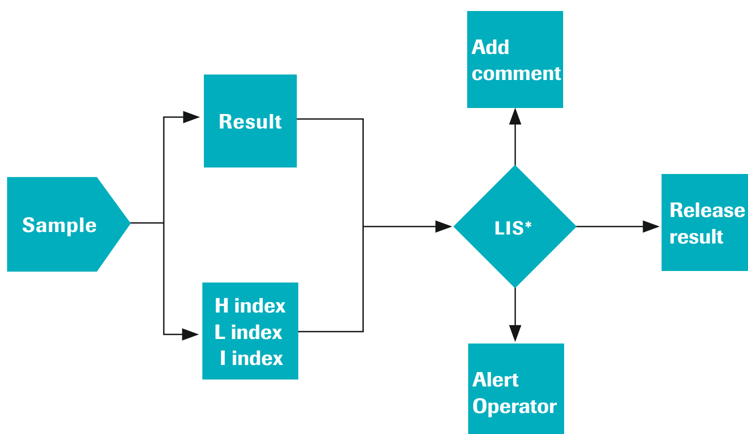
With less operator time involved in examining suspicious samples, not only is the TAT decreased, but also the costs involved in repeating "out of limit" results due to interferences. The serum index result reported simultaneously with the test result enables the operator to acknowledge the presence of interfering substances as the potential cause of the abnormal result. This removes the need to rerun the sample, thus reducing costs.

Improved Result Quality and Patient Care

In 2005, Vermeer (20) reported on improvements in patient results with respect to endogenous interferences with the introduction of an automated detection and reporting system. The laboratory information system (LIS) used a rule-based algorithm to assess the effect of interference on each analyte measured.

Test-specific serum index decision thresholds were used to:

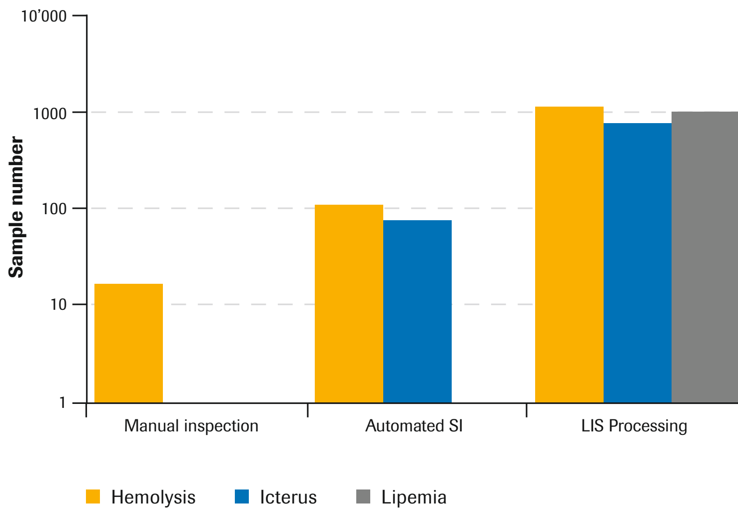
- Detect interference
- Alert the operator
- Add appropriate comments
- Reject a result where necessary



The laboratory found that by introducing the rule-based system, the detection rate of clinically significant hemolysis increased approximately 70 fold, icterus 10 fold and lipemia over 1000 fold.

Glick (22, 23) interferographs are produced for all Roche clinical chemistry assays. This is an easily understandable graphical display of the interference data showing the deviation from the original result caused by the interferent. The level of interference producing a clinically significant difference is indicated in the Roche instructions for use.

Effect of Serum Index and LIS



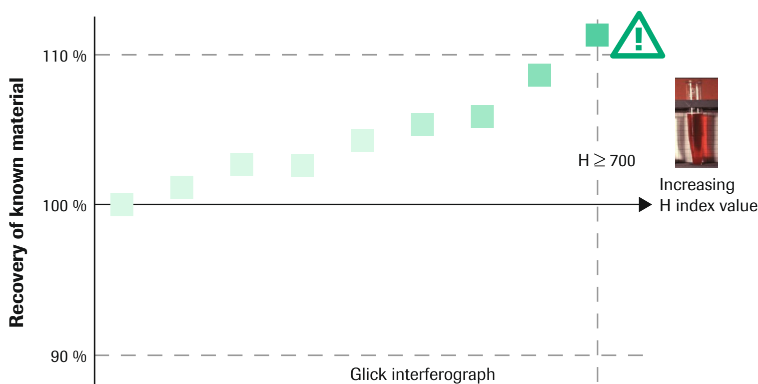
What does this really mean?

Of all the samples received by the laboratory, as many as 22 % may be influenced by endogenous interferences. The chance of identifying a possible visible interferent is greatly decreased when primary tubes are covered with several labels which prevent the clear inspection of the sample.

A serum index result generated simultaneously with the sample result ensures that all samples are correctly identified.

Reporting results that acknowledge the effect of interferences improves the clinical usefulness of the result. This allows better clinical decisions and better patient care.

The FDA and IVD directives oblige manufacturers of instruments and analytical methods to provide details of the degree of interference for each assay. Roche conducts the interference studies according to the guidelines of the NCCLS (EP7-P).



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Notes

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