**Opinion Paper**

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# Harmonizing the post-analytical phase: focus on the laboratory report

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**Abstract:** The final, post-analytical, phase of laboratory testing is increasingly recognized as a fundamental step in maximizing quality and effectiveness of laboratory information. There is a need to close the loop of the total testing cycle by improving upon the laboratory report, and its notification to users. The harmonization of the post-analytical phase is somewhat complicated, mainly because it calls for communication that involves parties speaking different languages, including laboratorians, physicians, information technology specialists, and patients. Recently, increasing interest has been expressed in integrated diagnostics, defined as convergence of imaging, pathology, and laboratory tests with advanced information technology (IT). In particular, a common laboratory, radiology and pathology diagnostic reporting system that integrates text, sentinel images and molecular diagnostic data to an integrated, coherent interpretation enhances management decisions and improves quality of care.

**Keywords:** post-analytical phase; laboratory report; decision limits; reference change value; interpretative comments; integrated diagnostics

## Introduction

The final, post-analytical, phase of laboratory testing is increasingly recognized as a fundamental step in achieving higher quality and effectiveness of laboratory information. Data reporting, down-stream interpretation of laboratory results and subsequent appropriate action through close relationships between laboratories and clinicians are of crucial importance in the laboratory testing process [1]. Yet these activities are poorly evaluated and monitored, often because the process owner is unidentified, responsibility falling in a no-man's land between the laboratory and clinical departments. Although available evidence highlights that the post-analytical step is a window of opportunity for improvement and harmonization initiatives, it still seems to be a neglected issue.

The ISO 15189:2023 standard for medical laboratory accreditation defines the post-analytical phase as the "processes following the examination, including review of results, formatting, releasing, reporting and retention of examination results, retention and storage of clinical material, the sample and waste disposal" [2]. This definition, however, does not take into consideration the steps (data acknowledgment, interpretation, utilization, follow-up and documentation) taken after the transmission of laboratory reports, and which are crucial to closing the loop. These steps have been grouped in the so-called "post-post-analytical phase" [3]. Even if these final steps of the cycle are not under the direct control of laboratory professionals, they are essential variables that affect both the value of laboratory information, and patient outcome [3].

## From data to information

Data are numbers, magnitudes, entities, and facts, such as in a laboratory test result. However, information is generated when a meaning is given to these data, as data without interpretation are facts without understanding [4]. In the case of laboratory results, numerical data must be accompanied by other parameters, usually defined as "comparators" (mainly, but not only, terminology, units of measurements, reference values, decision limits and interpretative comments) aimed to make the data "actionable". From the user's point of view, whether physician or patient, the conversion of data into useful information is the only thing that counts, as it is that information, not raw analytical results, that affects clinical reasoning and decision making. While laboratory professionals, first and foremost, must assure accuracy and reliability of laboratory results, the notification of analytical results must be accompanied by

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other essential tools that enable the right interpretation and utilization of laboratory information for the clinical decision-making process and patient management. The need to improve the post-analytical phase has been synthesized as "good post-analytical quality makes good laboratory information", recognizing five rights that should be accomplished to ensure that analytical results have meaning and value [3]. Only in this way can laboratory information comply with the ultimate goal of laboratory medicine, which is to improve health outcomes.

## Harmonization of the post-analytical phase: the report

Since it mainly calls for an exercise in communication involving parties (i.e. laboratorians, physicians, information technology specialists, and patients) who speak different languages, post-analytical phase harmonization is a somewhat complicated issue. In particular, the laboratory report is the key to providing users with the right information. In his seminal article of 1976 appearing in the Lancet and entitled "Clinical chemistry reporting. Problems and proposals", Alan M. Bold stressed the need for "standardization of report formats", suggesting that 13 items be reported, 7 of which were defined as "essential" and the remaining 6 as "additional features", as shown in Figure 1. Bold also emphasized that "all reports should include guidance to abnormality, be in cumulative format, and contain a realistic statement of analytical reliability" [5]. Unfortunately, several decades later, available evidence demonstrates poor compliance with the described requirements that, in addition, have received scarce attention in the literature [6]. The requirements for the post-analytical phase, called post-examination processes, are described in subclauses 7.4.1 and 7.4.2 of the International Standard ISO 15189 as "reporting results", "result review and release", "critical result reports", "special consideration for results", "additional information for reports", "amendments to reported results", and "post-examination handling of samples" [2]. A paper by some Working Groups of the European Federation of Laboratory Medicine (EFLM) highlights the need to use ISO 15189 as "a systematic framework to improve the practice of result release to suggest criteria for procedures for obtaining proper result reporting. The result release management should aim to prevent erroneous results without delaying the release of results that are remarkable but correct" [7]. Improved presentation of laboratory information can facilitate speedy interpretation and allow more accurate diagnoses and treatment. However, the report, as presented by most laboratories, "does not hardly reflect the strenuous efforts of laboratories in providing high quality analytics in the shortest amount of time possible, with the lowest error rates throughout medical care. It does not tap the full potential of neither modern information technology solutions nor automated processing for data aggregation. It is like serving Haute Cuisine in a bucket" [8].

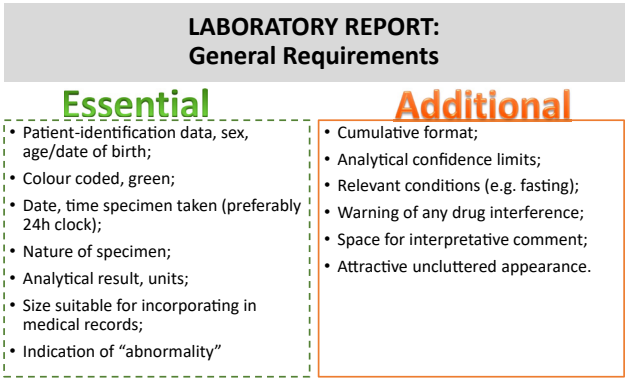


**Figure 1:** General requirements of laboratory reports. From ref. [5], modified.

## Main requirements of a laboratory report

The laboratory report should contain, at least, patient identity, sample receipt time, measurement units, reference intervals and/or clinical decision limits if available, therapeutic range for drugs, and interpretive comments, when needed. According to Robert Flatman "those basics include test names, and abbreviated names, units of measure, derivation and display of reference intervals, flagging and report layout (e.g. left/right vs. right/left issue for columnar reporting of historical results" [9]). The requirements for reports, described in ISO 15189, in the 7.4 "post-examination processes" and the 7.2 "pre-examination processes" clauses, include important requirements concerning the need for "unequivocal traceability of the patient to the request and sample, identity and contact information of requester, identification of the examination(s) requested" [2]. Importantly, the international standard recommends that "examination results shall be reported accurately, clearly, unambiguously and in accordance with any specific instructions in the examination procedure", thus highlighting the interrelationships between the different phases of the testing process. The standard emphasizes the importance of the term "unambiguous identification", as it states that "Logical Observation Identifiers of Names and Codes

(LOINC) and Nomenclature for Properties and Units (NPU, NGC) and SNOMED CT are examples of electronic identification. Terminology in the report should be harmonized to internationally agreed systems (e.g., Logical Observation Identifiers Names and Codes (LOINC) or Nomenclature for Properties and Units (NPU) systems) and use of International System of Units (SI) promoted" [2]. The issue of terminology is described in article 11 of the recent publication by the eHealth Network entitled "Laboratory Results guidelines" [10], in which it is stressed that "sharing of laboratory results between different healthcare providers requires standardized terminology used to clearly identify the laboratory test (such as "culture of bacteria"), examined properties (kind of property such as "mass concentration of albumin in blood plasma"), types of specimens (for example arterial blood, 24 h urine collection, cerebrospinal fluid), anatomical location of sample (e.g. sample from skin of left knee) as well as the analytes (components or elements such as sodium, alanine transaminase, Brucella antibody), kind of measured property (e.g., mass concentration, volume, number fraction, rate, frequency, mass, etc.) results for nominal or ordinal result values, and the units by which the value is presented (for quantitative result values)". The document also recommends that "as member states use different laboratory coding systems, not only the code and a test name but also additional constituents of the test specification and result should be taken into consideration" [10]. Therefore, harmonization is clearly needed in the post-analytical phase for cross-border care, crucial to ensuring consistency and obviating fragmentation and duplication of test requests, but the same consistency should be guaranteed at local, regional, national and international levels. Yet, according to Robert Flatman "current variations in practice for nomenclature, reference intervals, flagging, units, standardization and traceability between analytical methods, and presentation of cumulative result data are inefficient and inconvenient, or worse yet, patient safety risks. All aspects of laboratory service across the total testing process ultimately depend on concise, reliable communication". The Author also reports a challenging risk of error in current report formats, including "misinterpretation with different units, against reference intervals and of chronobiology, failure to understand method differences in results, and variation in flagging of abnormal results" [9]. While it is clear that an analytical result should always be provided with a unit, the communication of a result without a unit is based on the assumption that the receiver knows the correct unit. Although this may rarely be an issue locally for routine analytes, many drug and hormone assays are frequently quoted in different units between laboratories, states and countries. Where a unit is provided, the clinician may still inadvertently assume use of the unit from another testing provider that they are familiar with. The magnitude of the result often varies greatly for the same analyte quoted in different units and these differences can sometimes be dangerously subtle and/or incur a risk to patient safety. This has been described, for example, for hemoglobin results sometimes not expressed in g/L (the right units), but in g/dL (a 10-fold difference) [11].

Even if variations in laboratory reports emerged during the "paper era", some factors are now compromising the reliability of the newer electronic systems, which should assure functional interoperability (communication and reception of the actual message between hardware, software and people) and semantic interoperability (successful coding and decoding of the transmitted information) [12]. Moreover, electronic reports should assure "flexibility to display results accessible and intelligible to medical staff and patients, functionality for showing additional information, options to filter complexity, access to laboratory performance data, functionality to clarify where grouping or separation of results is appropriate, and graphical presentation of cumulative results" [12].

## Measurement uncertainty

Measurement uncertainty (MU) is an inherent property of any quantitative measurement result which expresses the lack of knowledge of the true value of the result and incorporates the factors known to influence it. As stated by the Guide to the Expression of Uncertainty in Measurement "the result of a measurement is only an approximation or estimate of the value of the measurand and thus is completed only when accompanied by a statement of the uncertainty of that estimate" [13]. As variability of laboratory results is unavoidable, "the result of any measurement represents an approximation or estimate of the value of a measurand and thus is complete only when accompanied by a statement of the uncertainty of that estimate". MU is not only a quantification of doubt concerning the measurement result and a valuable indicator of the result quality, but is essential information without which measurement results should not be meaningfully interpreted. For laboratory professionals, MU yields information on the quality of measurements, providing evidence of the compliance with analytical performance characteristics (e.g. expression of imprecision and bias of the analytical system) and monitoring these performances over time. Moreover, it should be used for comparing the metrological quality either of different clinical laboratories or of different analytical methods as well as the various platforms [14]. For physicians (and patients) it should facilitate the interpretation of

measurement results, providing objective information. However, the notification of MU to the users is still under debate. The rationale for its inclusion in laboratory reports is that "diagnostic uncertainty may derive from incomplete information in laboratory reports, leading to an increased risk of inappropriate interpretation of laboratory data" [15]. According to the ISO 15189 (subclause 7.3.4) "MU information shall be made available to laboratory users on request" [2] and, therefore, even if the MU is not included in the report attributes and cannot be considered a definite post-analytical requirement, it is recommended as information that should facilitate appropriate interpretation of quantitative results (quantity values). In fact, for many laboratory tests, the analytical quality (based on established performance specifications) may vary over time and should be improved thanks to better diagnostic systems and/or higher compliance with analytical performance specifications (APS). Therefore, correct interpretation is possible only on the basis of knowledge of the uncertainty of laboratory results, which derives from both analytical (e.g. bias and imprecision), and other possible sources of uncertainty (e.g. pre-analytical issues). In our view, the ISO 15189 subclause cited appears ambiguous, as the inclusion of MU "on request" is first and foremost very challenging from a practical viewpoint, and, second, it does not allow many users to receive information that can enhance the interpretation of laboratory data. For the past decade we, in the Department of Laboratory Medicine of Padova University-Hospital, have included in the laboratory reports information on total analytical error (TAE) error and RCV (reference change value) for measurands more commonly used for patient monitoring, after involving the clinicians in a discussion on the usefulness of this information. More recently, in a paper dealing with the reporting of MU in the laboratory report, we proposed replacing the TAE with MU in order to comply with the current state-of-the-art, as shown in Figure 2 [15].

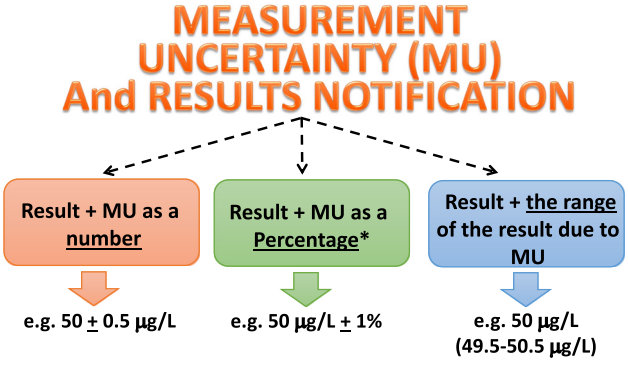


**Figure 2:** Notification of MU in laboratory reports. From ref. [15], modified.

## Reference intervals (RI) and decision limits

Reference intervals (RI) and decision limits (DL) are a valuable tool for results interpretation and are therefore a relevant part of the laboratory report, and the most commonly used comparison tool in laboratory medicine. RIs, statistical confidence limits for the typical spread of results to be found in a healthy reference population, are designed to confirm health (*absence* of *any* disease) with a high specificity (typically 95 %) [16]. There are some special forms of reference limits for substances not normally found in healthy people, such as therapeutic ranges for drug levels, detection limits for toxins (or drugs of abuse), legal limits such as for alcohol.

RI establishment using "direct methods" involves defining and sampling a reference population, sample collection, analytical measurement, and statistical analysis. Statistical methods have been described for several aspects of RI establishment, including appropriate outlier detection and removal, partitioning RIs by covariates (e.g., age and sex), and calculating confidence intervals (CIs) around reference limits [17]. Ideally, RIs should be influenced only by the population served and not by the analytical systems used, provided they are sufficiently harmonized/standardized [18]. In the era of big data, the so-called "indirect approach", which relies on the use of large amounts of data already stored in the laboratory databases for the definition and/or verification of RI, has been advocated to replace the direct approach. Indeed, it seems to offer several advantages over the conventional direct approach, including reduced costs and easier application in specific age groups and many indirect algorithms have been developed to define RI. However, Ceriotti and Vidali have recently emphasized the limitations and critical aspects of the indirect approach, briefly summarized as: (a) contamination of big data with results from diseased individuals; (b) lack of control of pre-analytical variables such as fasting vs. non-fasting, serum vs. plasma, sample pretreatment, etc.; and, lack of standardization and/or selectivity of the analytical methods used [19]. For many measurands, the use of big data may provide a complementary approach to the traditional method for defining common RI, which is often hindered by theoretical and practical issues. However, the true question is about the choice between RI and DL. Decision limits are more clinically focused, as they are related to a specific clinical condition, and generally aim to confirm the *presence* of *a particular* disease or clinical risk with appropriately high sensitivity. Ceriotti identified some indicators for the extra-analytical phase of laboratory testing and in particular on the

usefulness of reporting RI and/or DL, as follows: (a) correct use of RI vs. DL, (b) common vs. laboratory specific RI, (c) correct use of gender-related reference interval, and (d) correct use of age-related reference intervals [18]. The debate is ongoing, but I believe the right solution is for reference intervals to be used as a comparator in the laboratory report only when decision limits or therapeutic targets are unavailable. The advantages of DL, particularly in complying with clinical practice guidelines and defining analytical goals, have been proven in the case of, for example, total and LDL cholesterol in dyslipidemia, glucose and HbA1C in diabetes, and cardiac troponin in acute coronary disease. The complexity of the laboratory report and of the dilemma between RI and DL, is evident and a further current challenge is the management of transgender patient data both in test requesting and results reporting [20].

## Reference change value

For serial results monitoring, a body of evidence indicates that the so-called reference change value (RCV) should be recommended as a more effective comparator than RI and DL. This simple tool for use in monitoring serial results from an individual is based on the assumption that, for a change to be significant, the difference in serial results must be greater than the inherent variation, in terms of both biological and analytical variability [21]. The availability of reliable biological variation (BV) data is important for defining analytical performance specifications (APS), and necessary for establishing the reference change value (RCV). The European Biological Variation Study (EuBIVAS), which has been developed over the last few years, and is still in progress thanks to the efforts of the EFLM Working Group on BV (WG-BV), has provided evidence-based data on BV, thus allowing clinical laboratories to safely include RCV in their reports [22]. The advantages of reporting RCV in patient monitoring has been demonstrated in many diseases and for many measurands, including tumor and bone markers, and in evaluating the success and compliance of therapeutic measures [23–25].

## Critical results reporting

One of the main issues pertaining to post-analytical activity is the notification of critical results (CRs) which, by definition, indicate a life-threatening condition with a significant adverse outcome for the patient if immediate, life-saving action is not promptly undertaken, as originally stated by GD Lundberg [26]. Still used today, the development of a CRs policy has become a quality practice in procedures of medical laboratories, many of which have implemented systems for the notification of CRs. Accordingly, the issue has been included as a requirement in many accreditation standards. In particular, ISO 15189 has specified three requirements for critical results reporting: (1) the user or other authorized person is notified as soon as relevant, based on clinical information available; (2) actions taken are documented, including data (obtained), time, responsible person, person notified, results conveyed, verification of accuracy of communication, and any difficulties encountered in notification; and (3) the laboratory must have an escalation procedure for laboratory personnel when a responsible person cannot be contacted [2]. The first requirement is based on the evidence that a result showing a risk of a life-threatening condition is considered a critical-risk result and should be reported to authorized staff as soon as possible (no more than 1 h later), while a result indicating potential adverse outcome, considered a significant-risk result, can have a longer reporting time. Whatever the case, the laboratory should have a process in place to report critical results with in the shortest possible time-frame by means of reliable and timely notification systems to ensure timely communication. While a telephone call is traditionally used for communication, call centers, secure text messaging, and automated notifications systems combining all communication routes may be effective alternatives enabling a reduction in turnaround time [27].

However, the different terminologies used, and variations in practices and policies described in the literature, indicate the need for a more harmonized and systematic approach in notifying critical results. Harmonization initiatives should take into consideration the following: (a) reliable value limits should be chosen for true “life-threatening” analytes, according to the definition; (b) critical values should be formulated while considering patients’ characteristics (i.e. age, gender and ethnic origin); (c) notification should be made with the most efficient reporting and communication tools; (d) policies should be laid down to identify the person to be in charge of notifying critical values, and the caregiver to be responsible for receiving these values; and (e) technological tools should allow for the acknowledgment of critical values, facilitate feedback and data recording, and ensure that the indicators control and monitor the critical value process [27]. We recently highlighted that the value of critical results notification has been clearly demonstrated, their notification leading to a change of treatment in 98 % of patients admitted to surgical, and in 90.6 % of those admitted to medical, wards. Clinicians made an additional evaluation of new complications and conditions in 70 and 60.4 % of patients, in

surgical and medical wards, respectively, and took further steps in inpatient care following the critical value notification. A closer monitoring of patients' clinical condition was made in 26 % and in 25.5 % of cases in surgical and medical wards, respectively [28]. Clinicians reported that critical values were unexpected findings in 42.3 % of patients admitted to surgical, and 43.0 % of those admitted to medical wards [28], thus stressing the key role played by critical results notification in improving quality of care and patient safety. Projects designed to harmonize the notification of critical results have been undertaken in the USA, Australia and New Zealand [29, 30], but further efforts are needed.

## Interpretative comments

The provision of interpretative advice on laboratory results, a post-analytic activity, is an integral part of clinical laboratory services since the correct clinical interpretation of laboratory results is the desired outcome of laboratory services. The brain-to-brain loop cannot be closed until the laboratory information is captured by the physician's brain, and the right interpretation is used to enable the correct diagnosis and treatment.

Clinical, technical and financial catalysts have brought about the current demand for interpretative comments and their desirability. Clinical drivers include patient safety, value of interpretative comments, quality requirement in international standards for laboratory accreditation, physician's satisfaction, new and complex laboratory tests, and the doctor's education; technical drivers include lack of harmonization of laboratory information and increased electronic data communication; financial drivers are the competition between clinical laboratories and cost-reduction initiatives. In many cases, the value of a laboratory result can be considerably enhanced by an accompanying interpretative comment; examples include unexpected results due to an interference (e.g. from heterophile antibodies in immunoassays), particular findings discovered by the laboratory (e.g. macroprolactin or macroamylase), or an extension of the clinician's original request by reflexive or reflective testing (e.g., the identification of a monoclonal peak in serum electrophoresis). The introduction of new and complex tests into routine practice is a further major driver for the inclusion of interpretative comments in the laboratory report. This is particularly true in some diagnostic areas such as coagulation, autoimmunity, allergy testing, and molecular diagnostics, which are major challenges since they call for advanced expertise in correctly interpreting the laboratory data. In addition, interpretative comments are increasingly welcomed by the requesting physicians, particularly when they provide clinical advice on "what to do next" [31]. The IFCC WG "Harmonization of Quality Assessment of Interpretative Comments" has published a seminal paper dealing with the main requirements of Interpretative Comments, including the need for education, training, appropriate professional qualifications and expertise in providing interpretative comments. Moreover, the importance of specific external quality assessment (EQA) schemes has been highlighted to facilitate improved quality of comments and, ultimately, patient outcomes [32]. A recent paper has demonstrated the value of interpretative comments in modifying patient management and improving clinical outcomes [33]. Interpretative comments should be viewed as a fundamental part of a strategy dedicated to improving the post-analytical phase of laboratory testing, but recently reported data also emphasize the need for further initiatives aiming to assure quality, harmonization and monitoring of interpretative comments [34].

## Intended recipients of the laboratory report

Laboratory tests are usually ordered by a health care provider, reports being reviewed by physicians in order to diagnose and/or treat their patients. The optimal presentation of laboratory test results in these cases depends greatly on the specific medical situation and most recommendations, requirements and information to be included in the laboratory report have been developed while taking into consideration this type of recipient. However, apart from physicians, laboratory reports may also be presented to patients. The few available studies aiming to define formats meeting patients' needs and capabilities show that results in such reports must be summarized and that their meaning must be provided in a clear, understandable, and accessible, 'non-medical' language. As health systems move towards providing each person with full access to their own health-related data, people are increasingly able to access their laboratory results via patient portals. The potential benefits of this access include a reduction in patient burden and improvement in patient satisfaction, disease management, and medical decision making, but also come hand in hand with concerns about issues such as results causing confusion or anxiety among patients. In fact, access alone cannot confer the full benefits of such data and information, and an erroneous interpretation of laboratory results can cause the patient anxiety, potentially leading to patient harm.

Witteman and Zikmund-Fisher [35] have defined 10 recommendations to support people in converting the potentially meaningless data of results into meaningful information and actionable knowledge, as follows: (1) whenever possible, provide a clear takeaway message for each result; (2) signal whether differences are meaningful or not; (3) when feasible, provide thresholds for concern and action; (4) individualize the frame of reference by allowing custom reference ranges; (5) ensure the system is accessible; (6) provide conversion tools along with results; (7) design in collaboration with users; (8) design for both new and experienced users; (9) make it easy for people to use the data as they wish; (10) collaborate with experts from relevant fields. In their conclusion, the authors emphasized that by "using best practices to present laboratory results in ways that help people understand and use them, we can support people in making informed health decisions and managing their health" [35].

It has been reported that the use of even the simplest number line graphics instead of tables to represent test results can decrease the patient's perception of urgency about values near the standard range and therefore increase sensitivity to variations in test values Graphical visual displays can increase the meaningfulness of test results by clearly defining possible values and leveraging color cues and evaluative labels: this type of data reporting, which is increasing the ability of patients to directly access and view laboratory test results, is justified by the concept that, thanks to "patient empowerment" [36, 37], patients will be able to translate access to test results into a better preparation for clinical visits, and gain better disease self-management, as shown in Figure 3. In conclusion, the issue of different recipients of laboratory reports, an additional variable, influences the complexity of harmonization of the post-analytical phase and, in particular, that of the laboratory report.

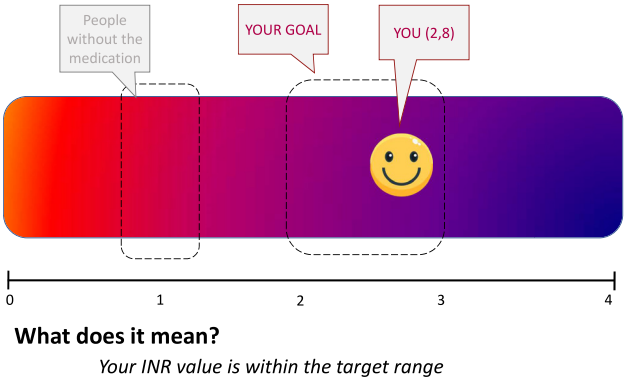


**Figure 3:** Graphic representation of laboratory results. From ref. [6], modified.

## Integrative diagnostics and integrated report

According to the World Health Organization (WHO), health services should be "managed and delivered so that people receive a continuum of health promotion, disease prevention, diagnosis, treatment, disease-management, rehabilitation and palliative care services, coordinated across the different levels and sites of care within and beyond the health sector, and according to their needs throughout the life course" [38]. "Integrated diagnostics" (ID) has been defined as "convergence of imaging, pathology, and laboratory tests with advanced information technology (IT)" [39]. Indeed, diagnoses depend on multiple components that include not only imaging, but also clinical observation, pathology, laboratory, and genomic tests. Radiology, clinical laboratories, and pathology departments, which perform the preponderance of diagnostic tests, currently play a central role in medical diagnostics. However, these disciplines are not working as an integrated unit. Rather, they are "islands of vast data and extraordinary intradisciplinary expertise separated from one another and from our clinical colleagues by informatics, physical, and specialty barriers" [40]. To date, there is too little coordination between the medical specialties responsible for ordering and performing these tests, and nor is enough consideration given to optimal ordering and reporting of tests. This will change in a world of integrated diagnostics, where, instead of relying on individual provider bias in the selection of tests, data from diverse sources will be used to determine the most efficient diagnostic algorithms. Imaging will be incorporated judiciously into these integrated diagnostic algorithms, complementing other diagnostic techniques in order to maximize efficiency and minimize waste. This, in turn, may allow a more rapid, efficient and accurate clinical decision-making process, which should ultimately assure better clinical and cost-effective outcomes. Irrespective of clinical and environmental scenarios, several lines of evidence now attest to the role that so-called "integrated diagnostics" will play in the foreseeable future, allowing not only earlier and more accurate diagnoses, but also saving considerable human and economic resources [41]. In their seminal paper on integrative diagnostics, Beauchamp et al. stress that "clinical questions can be addressed by "*in vivo*" and "*in vitro*" diagnostic medicine, with different disciplines integrating their respective data and reporting interpreted results to other providers and patients in a combined report" [40]. Integrated reports aggregating numerical data from clinical laboratories with pathology and imaging data may facilitate the right interpretation and utilization of diagnostic

information. A shared laboratory, radiology and pathology diagnostic reporting system that integrates text, sentinel images and molecular diagnostic data in a coherent interpretation would better inform management decisions. While several bottlenecks still exist, an integrated report should be based on and, in turn encourage, standardization: multidisciplinary collaborations foster the use of controlled terminologies and standardized reporting structures, making evaluation across multiple patient cohorts possible [42]. Clinical laboratory-pathology-radiology integration workflows must ensure effective communication, the flow of communications, and link structured diagnostic results from laboratorians and pathologists with those of radiologists. ID can also bring further human and computational resources to bear on these essentially raw data thus yielding information useful for diagnosing and treating individual patients, for addressing disease in a given population, and for improving upon health management [42, 43].

## Artificial intelligence in the post-analytical phase

We recently highlighted that "advances in the understanding of biology, pathophysiology of diseases and molecular medicine combined with technological developments have given laboratory medicine a central role, ranging from maintaining well-being to disease prevention, early detection, prognosis, monitoring and guiding personalized therapy" [44]. It is time to appropriately manage the interpretation and use of the huge amount of data generated daily by clinical laboratories in order to enhance patient care. Decision algorithm models for reporting results, clinical decision support systems and artificial intelligence (AI) are increasingly recognized as fundamental tools for achieving this goal. Computerized Clinical Decision Support Systems (CDSS), which represent a paradigm shift in current healthcare, are employed to aid clinicians in their complex decision-making processes and can be useful in laboratory testing and interpretation [45]. Providing clinical decision support for clinicians and general practitioners will result in a comprehensive interpretation of all, even complex, diagnostic procedures in the individual patient context, thus allowing a stratified therapeutic decision to be made [46].

Interactive machine learning tools have been developed to improve data aggregation, interpretation and results reporting [47]. The field, generically termed AI, but which includes different systems such as machine learning and artificial neural networking, is currently receiving increasing attention and will certainly yield new insights on, and improvement to, the value of laboratory information [48–50]. However, if laboratory results and information are not standardized and harmonized, the use of machine learning, big data and, in general, artificial intelligence may not only be toxic for many researchers in medicine, but may also compromise the reliability of diagnoses, and the efficacy of patient treatment.

## Conclusions

In the last few decades, the focus on the analytical phase has enabled laboratory medicine to improve upon quality and quality assurance. However, a body of evidence collected demonstrates that the extra-analytical phases are vulnerable to error, including those at risk of translating into diagnostic errors and patient harm [51, 52]. Numerous efforts have been made to improve upon the pre-analytical phase, whereas the post-analytical phase appears to be a neglected issue. However, this final phase of laboratory testing is increasingly being recognized as a fundamental step in enhancing the quality and effectiveness of laboratory information: there is still a need to close the loop of the total testing cycle by improving both the laboratory report and its communication to users.

In a recently published paper, Favaloro and Colleagues have emphasized the importance of improving the post-analytical phase to avoid the risk of misinterpretation of hemostasis tests, related diagnostic errors and adverse clinical events, suggesting the standardization/harmonization of reported measurement units and reference ranges, as well as the inclusion on laboratory reports of interpretative comments and timely reporting of critical results [53]. Since harmonization plays a fundamental role in improving the post-analytical phase, laboratory professionals, national and international scientific societies and federations should strengthen their efforts to provide valuable guidelines and recommendations designed to improve upon both the laboratory report and its communication to the user.

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## References


1. Plebani M. Harmonization in laboratory medicine: requests, samples, measurements and reports. Crit Rev Clin Lab Sci 2016;53:184–96.
2. ISO 15189:2022. Medical laboratories – requirements for quality and competence. Geneva, Switzerland: International Organization for Standardization; 2012.
3. Plebani M. Towards a new paradigm in laboratory medicine: the five rights. Clin Chem Lab Med 2016;54:1881–91.
4. Goldschmidt HM. Postanalytical factors and their influence on analytical quality specifications. Scand J Clin Lab Invest 1999;59:551–4.
5. Bold AM. Clinical chemistry reporting. Problems and proposals. Lancet 1976;1:951–5.
6. Cadamuro J, Hillarp A, Unger A, von Meyer A, Bauçà JM, Plekhanova O, et al. Presentation and formatting of laboratory results: a narrative review on behalf of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) Working Group “postanalytical phase” (WG-POST). Crit Rev Clin Lab Sci 2021;58:329–53.
7. Can Çubukçu H, Vanstapel F, Thelen M, Bernabeu-Andreu FA, van SchrojensteinLantman M, Brugnoni D, et al. European federation of clinical chemistry, laboratory medicine EFLM working group accreditation, ISO/CEN standards WG-A/ISO. Improving the laboratory result release process in the light of ISO 15189:2012 standard. Clin Chim Acta 2021;522:167–73.
8. Cadamuro J, Winzer J, Perkhofer L, von Meyer A, Bauça JM, Plekhanova O, et al. Efficiency, efficacy and subjective user satisfaction of alternative laboratory report formats. An investigation on behalf of the Working Group for Postanalytical Phase (WG-POST), of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM). Clin Chem Lab Med 2022;60:1356–64.
9. Flatman R. Terminology, units and reporting – how harmonized do we need to be? Clin Chem Lab Med 2018;57:1–11.
10. eHN Laboratory Result Guidelines. https://health.ec.europa.eu/publications/ehn-laboratory-resultguidelines_en [Accessed 25 Nov 2023].
11. De la Salle B. Pre- and postanalytical errors in haematology. Int J Lab Hematol 2019;41(1 Suppl):170–6.
12. Legg M. Standardization of test requesting and reporting for the electronic health record. Clin Chim Acta 2014;432:148–56.
13. JCGM 100:2008, evaluation of measurement data – Guide to the expression of uncertainty in measurement (GUM). www.bipm.org [Accessed 2 Oct 2023].
14. Padoan A, Sciacovelli L, Aita A, Antonelli G, Plebani M. Measurement uncertainty in laboratory reports: a tool for improving the interpretation of test results. Clin Biochem 2018;57:41–7.
15. Plebani M, Sciacovelli L, Bernardi D, Aita A, Antonelli G, Padoan A. What information on measurement uncertainty should be communicated to clinicians, and how? Clin Biochem 2018;57:18–22.
16. Sikaris K. Performance criteria of the post-analytical phase. Clin Chem Lab Med 2015;53:949–58.
17. Higgins V, Asgari S, Adeli K. Choosing the best statistical method for reference interval estimation. Clin Biochem 2019;71:14–16.
18. Ceriotti F. Quality specifications for the extra-analytical phase of laboratory testing: reference intervals and decision limits. Clin Biochem 2017;50:595–8.
19. Ceriotti F, Vidali M. Reference interval harmonization: will big data provide a solution? Clin Chem 2023;69:945–7.
20. Hepburn S, Buchanan D, Costelloe SJ. Current practice and recommendations for managing transgender patient data in clinical laboratories in the United Kingdom and Republic of Ireland. Ann Clin Biochem 2023:45632231195484. https://doi.org/10.1177/00045632231195484.
21. Fraser CG. Reference change values. Clin Chem Lab Med 2011;50:807–12.
22. Sandberg S, Carobene A, Bartlett B, Coskun A, Fernandez-Calle P, Jonker N, et al. Biological variation: recent development and future challenges. Clin Chem Lab Med 2022;61:741–50.
23. Bozkurt Yavuz H, Bildirici MA, Yaman H, Karahan SC, Aliyazıcıoğlu Y, Örem A. Reference change value and measurement uncertainty in the evaluation of tumor markers. Scand J Clin Lab Invest 2021;81:601–5.
24. Plebani M, Bernardi D, Meneghetti MF, Ujka F, Zaninotto M. Biological variability in assessing the clinical value of biochemical markers of bone turnover. Clin Chim Acta 2000;299:77–86.
25. Clerico A, Padoan A, Zaninotto M, Passino C, Plebani M. Clinical relevance of biological variation of cardiac troponins. Clin Chem Lab Med 2020;59:641–65.
26. Lundberg GD. When to panic over abnormal values. MLO Med Lab Obs 1972;4:47–54.
27. Piva E, Plebani M, Doering TA, Crawford JM, Plapp F. Laboratory critical values should support effective clinical decision making. Am J Clin Pathol 2016;145:142–3.
28. Piva E, Sciacovelli L, Pelloso M, Plebani M. Performance specifications of critical results management. Clin Biochem 2017;50:617–21.
29. Hashim IA, Cuthbert JA. For the Critical Values Working Group. Establishing, harmonizing and analyzing critical values in a large academic health center. Clin Chem Lab Med 2014;52:1129–35.
30. Campbell CA, Lam Q, Horvath AR. An evidence- and risk-based approach to a harmonized laboratory alert list in Australia and New Zealand. Clin Chem Lab Med 2019;57:89–94.
31. Plebani M. Interpretative commenting: a tool for improving the laboratory-clinical interface. Clin Chim Acta 2009;404:46–51.
32. Vasikaran S, Sikaris K, Kilpatrick E, French J, Badrick T, Osypiw J, et al. IFCC WG Harmonization of Quality Assessment of Interpretative Comments. Assuring the quality of interpretative comments in clinical chemistry. Clin Chem Lab Med 2016;54:1901–11.
33. Wilkinson B, Whitehead SJ, George E, Horton S, Bellaby J, Mohamed S, et al. Do reflex comments on laboratory reports alter patient management? Ann Clin Biochem 2020;57:312–15.
34. Rimac V, Podolar S, Jokic A, Vlasic Tanaskovic J, Honovic L, LenicekKrleza J. Interpretative comments – need for harmonization? Results of the Croatian survey by the Working Group for Post-analytics. Biochem Med 2022;32:010901.
35. Witteman HO, Zikmund-Fisher BJ. Communicating laboratory results to patients and families. Clin Chem Lab Med 2019;57:359–64.
36. O’Connor JD. Reducing post analytical error: perspectives on new formats for the blood sciences pathology report. Clin Biochem Rev 2015;36:7–20.
37. Zikmund-Fisher B, Scherer AM, Witteman HO, Solomon JB, Exe N, Tetal TB, et al. Graphics help patients distinguish between urgent and non-urgent deviations in laboratory test results. J Am Med Inf Assoc 2017;24:520–8.
38. WHO. Framework on integrated people-centred health services, Report by the secretariat (document A69/39). Geneva: Sixty-ninth World Health Assembly; 2016. 23–28 May 2016. https://apps.who.int/gb/ebwha/pdf_fles/WHA69/A69_39-en.pdf [Accessed 28 Dec 2022].
39. Krestin GP, Grenier PA, Hricak H, Jackson VP, Khong PL, Miller JC, et al. Integrated diagnostics: proceedings from the 9th biennial symposium of the international society for strategic studies in radiology. Eur Radiol 2012;22:228394.

40. Beauchamp NJ, Bryan RN, Bui MM, Krestin GP, McGinty GB, Meltzer CC, et al. Integrative diagnostics: the time is now – A report from the international society for strategic studies in radiology. J Am Coll Radiol 2023;20:455–66.
41. Lippi G, Plebani M. Integrated diagnostics: the future of laboratory medicine? Biochem Med 2020;30:010501.
42. Sorace J, Aberle DR, Elimam D, Lawvere S, Tawfik O, Wallace WD. Integrating pathology and radiology disciplines: an emerging opportunity? BMC Med 2012;10:100.
43. Association of State and Territorial Health Officials. Public health informatics. https://www.astho.org/Health-Systems-Transformation/Medicaid-and-Public-Health-Partnerships/Learning-Series/Public-Health-Informatics/ [Accessed 15 Nov 2023].
44. Plebani M, Laposata M, Lippi G. Driving the route of laboratory medicine: a manifesto for the future. Internet Emerg Med 2019;14:337–40.
45. Sutton RT, Pincock D, Baumgart DC, Sadowski DC, Fedorak RN, Kroeker KI. An overview of clinical decision support systems: benefits, risks, and strategies for success. NPJ Digit Med 2020;3:17.
46. Haselmann V, Schoenberg SO, Neumaier M, Froelich MF. Integrated diagnostics. Radiol 2022;62(1 Suppl):11–6.
47. Fillmore N, Do N, Brophy M, Zimolzak A. Interactive machine learning for laboratory data integration. Stud Health Technol Inf 2019;264:133–7.
48. Padoan A, Plebani M. Artificial intelligence: is it the right time for clinical laboratories? Clin Chem Lab Med 2022;60:1859–61.
49. Padoan A, Plebani M. Flowing through laboratory clinical data: the role of artificial intelligence and big data. Clin Chem Lab Med 2022;60:1875–80.
50. Demirci F, Akan P, Kume T, Sisman AR, Erbayraktar Z, Sevinc S. Artificial neural Network approach in laboratory test reporting: learning algorithms. Am J Clin Pathol 2016;146:227–37.
51. Plebani M. The detection and prevention of errors in laboratory medicine. Ann Clin Biochem 2010;47:101–10.
52. Plebani M. System-related and cognitive errors in laboratory medicine. Diagnosis 2018;5:191–6.
53. Favaloro EJ, Gosselin RC, Pasalic L, Lippi G. Post-analytical issues in hemostasis and thrombosis testing: an update. Methods Mol Biol 2023;2663:787–811.