Opinion Paper

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Terminology, units and reporting – how harmonized do we need to be?

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Abstract: Harmonization initiatives in laboratory medicine seek to eliminate or reduce illogical variations in service to patients, clinicians and other healthcare professionals. Significant effort will be required to achieve consistent application of terminology, units and reporting across laboratory testing providers. 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. Clinical terminologies (e.g. SNOMED-CT, LOINC, IFCC/IUPAC NPU) provide a mechanism to correctly identify an analyte or panel of tests within a request for testing and communicate the results back to the clinician or electronic health record (EHR). Electronic systems for requesting and reporting laboratory testing are said to be *interoperable* when reliable connection and communication of content occur. Modern electronic reports and EHRs will provide greater flexibility and functionality, but also require effective guidelines or standards to ensure consistent representation of laboratory data. Programs to harmonize service in these areas require ongoing local, national and international efforts and should incorporate stakeholders from laboratories, medical staff, information technology and informatics specialists, patient representatives and government. The process of identifying harmonized best practice, then ensuring uptake across many laboratory testing providers, is generally iterative rather than “one off”. New opportunities for additional harmonization will be generated as analytical performance, standardization and traceability, and diagnosis and treatment continue to evolve.

Keywords: clinical terminologies; harmonization; laboratory informatics; laboratory testing; total testing process; units of reporting.

Introduction

Requesting and reporting of clinical laboratory testing is an exercise in communication between multiple parties. Successful communication relies on a comprehensive agreed language between all participants.

Dybkaer [1] elegantly described the essentials of this communication over 20 years ago:

“Reliability of clinical laboratory results is obtained through quality assurance in both their production and transmission. The former involves a reference measurement system of reference material and reference measurement procedures with metrological and statistical verification of results. The latter requires that sender and receiver have access to a common terminology.”

At that time, Dybkaer [1] was highlighting the importance of ongoing clinical terminology development through joint efforts of the International Union of Pure and Applied Chemistry (IUPAC) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC). Back then, most laboratory reporting was paper based and electronic messaging in its infancy; however, the fundamentals for unambiguous communication of laboratory data remain just as important now.

In the harmonization-dedicated May 2014 issue of *Clinica Chimica Acta*, Tate et al. [2] emphasized the importance of ongoing harmonization work across the entire “total testing process” (TTP). That is, not just analytical processes but also preanalytical (test selection, sample collection and transport to the laboratory) and postanalytical (reporting back to the clinician, final interpretation and clinical decision making). They also noted that cooperation between a broad range of national and international stakeholders will be required, “including the clinical laboratory community, diagnostics industry, clinicians, professional societies, information technology (IT)

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providers, consumer advocate groups and governmental bodies”.

How much harmonization is necessary? It will be argued that goals should not only target unfounded variation in current practices but also establish foundations for future service requirements that may not yet be revealed. Therefore, laboratory harmonization is rarely a destination but rather an ongoing journey of iterative improvement, where multistakeholder input is essential.

Standardization vs. harmonization

Although the terms “standardization” and “harmonization” are frequently used interchangeably, standardization is more strictly applied where there is a clear specification for a preanalytical, postanalytical or analytical process. Analytical standardization requires the availability and traceability to primary reference material and reference measurement procedures [3, 4]. Harmonization of analytical processes is applicable where primary reference materials and methods are not available and alternative processes for alignment are used.

Beastall [5] has eloquently described standardization as “conformance to an agreed standard, while harmonization is the adoption of consensus agreement where no standard exists”. It is somewhat ironic that the spelling of terms used to communicate testing harmony varies so much around the world. In this paper, both terms have been spelled with a “z” rather than an “s”.

Why is harmonization of terminology, units and reporting necessary?

Plebani [3] and Panteghini [6] have highlighted that patients, clinicians and other clinical stakeholders expect and assume they will receive comparable results from different laboratory providers. They are however frequently surprised and concerned to discover this is not always the case.

Plebani [7] notes that the main drivers for standardization and harmonization projects in laboratory medicine are patient safety and their increasing service expectations, the economics of consolidation and networking of laboratories, clinical governance and advances in IT. There are inefficiency costs and patient risks at all stages of the TTP where inconsistent terminology, units and

Table 1: Issues benefiting from harmonization of terminology, units and reporting.

Issue	Examples
Ordering – incorrect or missed test	Intended test is missed or an incorrect test is performed
Misinterpretation of results abnormality	Reference intervals between laboratories can show more inappropriate variation than the actual test results
Misinterpretation of result quantity (units)	Poor communication of units may lead to an incorrect interpretation of the test result
Failure to understand methodological differences in result	Results from different methods may vary from poor traceability or analyte variability
Misinterpretation of chronology	Columnar cumulative reports from different laboratories may have the most recent results at the far left, or at the far right, increasing the risk of misinterpretation by the clinician
Variations in flagging of abnormal results	Different laboratories may use different report flags, in different locations, with or without multilevel flagging that tries to convey the “degree of abnormality”
Economics and appropriate testing	Good terminology can assist with billing, tracking of testing for government reimbursement strategies and help encourage best practice ordering and test utilization
Effective decision support	The provision of relevant and useful commenting on reports can be enhanced by optimal ordering of appropriate tests and test groupings
Implications of electronic health record systems	Illogical variations in reporting between laboratories frustrate both clinicians and patients and reduce the effectiveness of EHRs
Patient benefit	Patients expect user friendly, portable, effective reports and may choose their testing provider on the basis of past performance and intelligibility

reporting are used, and these issues frequently crossover between pre, post and analytical processes in complex ways. Table 1 summarizes the key issues in this area, examined in more detail below.

1. Ordering – incorrect or missed testing

There can be significant variation in the tests offered for routine test panels between laboratories, along with the naming of those panels. An abbreviation for a panel of tests in one city may be widely accepted between testing providers but ambiguous in a wider setting (e.g. national or international). For example, in different parts of the world, liver function test panels may or may not include direct bilirubin, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, iron or cholinesterase [8, 9]. Interpretation becomes more challenging in this setting, and delays may occur while missing tests are reordered. Worse yet, the laboratory may perform the wrong test, or no testing, for an expected analyte.

2. Misinterpretation of results against reference intervals

Widespread adoption of external quality assurance programs (QAPs) has ensured results for many routine automated biochemistry analytes now agree very closely between laboratories. Unfortunately, the variation in quoted reference intervals for a single analyte between laboratories is frequently greater than the variation seen in test results [10].

An erroneous and potentially dangerous solution to this problem is attempting to normalize results based on quoted reference intervals. Consider an example where Lab A and Lab B both report serum lipase from the same analyzer, for the same patient, and agree closely on external QAP:

Lab A lipase=150 U/L (Ref interval 0–100 U/L)
Lab B lipase=145 U/L (Ref interval 0–140 U/L)

If the results are “normalized” according to the quoted upper reference limit, then Lab A’s result would be 150% of the upper limit, whereas Lab B is 104% of the upper reference limit. The analytical imprecision of lipase is generally only a few percent; therefore, for the examples quoted, there is unlikely to have been a significant difference in the results. However, the normalized results suggest a substantial change in lipase levels.

Ideally, there should be little or no variation in reference intervals between laboratories in the same geographic area where analytical methods are well standardized, without some suitable documented explanation.

3. Misinterpretation of results with different units

An analytical result should always be provided with a unit. Communicating a result without a unit assumes 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 they are familiar with from another testing provider.

Often, the magnitude of the result varies greatly for the same analyte quoted in different units, but these differences can sometimes be dangerously subtle. Table 2 shows some common therapeutic drugs quoted in both gravimetric and molar units. For many of the example drugs, there is the potential for a result to be widely misinterpreted against the therapeutic interval. For digoxin, the variation between molar and mass units is subtle, which may make the error more difficult to detect.

The potential for patient harm from incorrect dosing decisions is considerable. Ideally, there should be a national (or international) specification of the recommended unit [11]. Electronic messaging of results between sending and referral laboratories should always include a check that the same unit is used in both sending and receiving computer systems.

4. Failure to understand methodological differences in results

McLawn [12] has noted that clinicians, and sometimes laboratory staff, are frequently unaware of “multifactorial

Table 2: Variation in drug results by molar or mass unit.

Drug	Molar units	Molar to mass factor	Mass units
Digoxin	1.0 nmol/L	0.78	0.8 µg/L
Phenytoin	59.4 µmol/L	0.25	15.0 mg/L
Valproate	69.3 µmol/L	0.14	10.0 mg/L
Methotrexate	2.2 nmol/L	0.45	1.0 µg/L

methodologic differences” in results between analytical methods and laboratory services. Clinical guidelines for diagnosis and monitoring of disease are most likely to be useful where they incorporate input from laboratory professionals, who may highlight these shortcomings and also work to improve comparability of methods.

Notable success stories for improved analytical standardization and harmonization include HbA_{1c} (National Glycohemoglobin Standardization Program [13] and later the IFCC recommendations for standardization and reporting [14, 15]), creatinine (Kidney Disease: Improving Global Outcomes [16]) and cholesterol (National Cholesterol Education Program [17]).

5. Misinterpretation of chronology

Cumulative historical results are frequently presented in columnar format, however there is no accepted standard for which side of the report should display the most recent results. Laboratory A may show newest episodes in the rightmost columns, whereas Laboratory B chooses to do the reverse. It may even be the case that onscreen display of results varies from the order presented on paper reports.

The clinician’s assessment of disease progression will be adversely affected if the report chronology is misinterpreted. For example, an acute deterioration of renal function might be incorrectly interpreted as a successful intervention if the order of renal function tests was read incorrectly. The Australian RCPA PITUS (Pathology Information, Terminology and Units Standardisation) project has recommended that the most recent results should ideally be highlighted to reduce this interpretive risk (e.g. surrounded by a bold, rectangular box) [18, 19].

6. Variations in flagging of abnormal results

Flagging of abnormal results often varies between testing providers [20]. Examples include the following:

1. **Location of reference intervals on the report** – most laboratories will display this information to the right of the test result on numerical reports; however, the use of parentheses and positioning of the unit field will frequently vary between providers. The text heading for reference intervals frequently varies (e.g. “Normal”, “Reference Intervals”, “Intervals”, “Reference”).
2. **The source and applicability of the reference intervals.** Laboratories frequently use historical intervals that have been “transferred” between generations of

analytical technology. Harmonization studies often show greater variation in reference intervals for routine analytes than the known total accuracy and precision for those methods on QAPs [10].

3. **Variation in the character(s) applied for flagging.** Printed reports often use special characters to highlight abnormal values (e.g. asterisks, L, H, shading, colored fonts). Variation in the type of flagging and choice of characters increases the likelihood of mis-translation between systems. Medical staff may incorrectly read a flag character as part of a numerical result. Color flagging can be misleading on electronic or paper reports if the user has impaired color vision, or if the report is duplicated.
4. **Multilevel flagging** is used by some laboratories to denote a scale of abnormality for numerical results (e.g. L, LL, LLL flags to denote increasingly abnormal low results). As previously described, there can be large unfounded variation in reference intervals between laboratories, and this variation is likely to be much greater for any additional multilevel ranges and flags without a coordinating harmonization process. Although reference intervals are generally derived mathematically (e.g. 95% confidence interval), multilevel flagging is frequently chosen arbitrarily to denote increasing abnormality, increasing the likelihood of inter-laboratory variability. Flagging of critical risk results is a particular challenge. Most laboratory systems still do not specifically flag critically significant results on reports, preferring to rely on escalation to an additional urgent notification system (e.g. telephone or text message to clinician). Campbell and Horvath [21] have highlighted a great need for laboratories to harmonize their policies and procedures for critical risk results. Electronic reporting systems of the future may incorporate additional mechanisms for highlighting these results in parallel with traditional report flags.

7. Economics of billing, reimbursement, appropriate testing and demand management

Consistent use of test terminology can also prove beneficial for financial systems. Individual laboratory information systems typically use their own internal codes for test panels and results. Shared billing information, such as government reimbursement models, can be more consistently applied where global or regionally recognized terminology is used.

Effective reimbursement models may also foster productive reviews of test ordering, although effective test utilization may sometimes require an increase in testing. Clinical pathways recommending consistent testing appropriate for suspected disease may reduce unnecessary testing or inappropriate frequency of testing. Lang [22] has described the benefits of an evidence-based approach for demand management of appropriate laboratory testing in the UK National Health Service.

8. Effective decision support

Effective evidence-based ordering through clinical pathways enables more powerful decision support. Interpretive commenting on reports can be more powerful if the most useful results are available. Interpretation may be suboptimal, or even misleading, if the most relevant tests are not performed.

9. Implications of electronic health record systems

Users of electronic health records (EHRs) expect consistency in all of the potentially problematic areas listed above. Beastall [23] has noted effective EHRs are not only reliant on suitable hardware and software, but in the arena of laboratory medicine also reliant on “harmonisation of minimum data sets, reference ranges, and the creation of a national electronic handbook for laboratory medicine”.

Addressing these issues to achieve harmonization takes time, money and resources. Laboratories should ideally be planning for changes in their requesting, reporting and financial systems before EHR users question illogical variations between providers. Tenders for new laboratory information systems should include a review of the proposed implementation model against local or international informatics standards.

10. Patient empowerment

Patients expect modern healthcare systems to be transparent, portable and intelligible. Laboratory professionals are generally well aware of how differences in testing and reporting evolved, and the significant amount of work required to rectify these issues. Patients, clinicians and other customers of the laboratory’s services are likely to find illogical variations in service frustrating and expect prompt rectification.

Testing providers that fall behind in their obligations for harmonized requesting and reporting may at best suffer loss of reputation, or at worse substantial financial disadvantage.

Wherever possible, laboratories should actively track their performance in the areas described above using dedicated quality indicators [24] and publically share those indicators. Recognizing and documenting failures throughout the TTP not only provides valuable data for the laboratory’s own improvement programs but also provides a valuable resource for prioritizing work programs within national or international laboratory harmonization initiatives.

Clinical terminologies – the key to good communication throughout the TTP

Legg [25] has described the ordering of laboratory testing as a clinical “question” and the report as the “answer”. Central to the successful execution of this cycle is the requirement for concise, reliable communication. Although clinical disciplines such as biochemistry and hematology lend themselves to a straight-forward question-answer pair (e.g. serum sodium request and result), other disciplines such as microbiology and molecular pathology may require a more complex narrative in response, requiring specialized information constructs to organize the “answer”.

Clinical terminologies have evolved to provide a language for the naming of laboratory analyses, requesting of testing and reporting of results. Some go further and aim to classify the entire medical history and treatment of the patient. Examples of clinical terminologies include SNOMED-CT [26], LOINC [27], NPU [28] and ICD [29]. A sound clinical terminology is not simply a set of rules for encoding textual information but provides a model and framework for describing key categories and relationships in the data. That is, it operates within an *ontology* for describing and organizing the information. Dybkaer [30] has detailed an ontology for clinical properties in physical, chemical and biological systems, which forms the basis for the NPU terminology [28]. Those seeking to better understand the attributes of a good terminology should refer to Legg [25] and Cimino [31]. Legg has summarized those key criteria as follows:

1. Appropriate to the clinical setting
2. Implementable within existing systems

3. Understandable by stakeholders
4. Acceptable to clinicians
5. Acceptable to software developers
6. Acceptable for statistical reporting
7. Customizable to meet current and future needs

Achieving and balancing these ideals is challenging; however, all stakeholders need to be reminded of their applicability and agree on how they will be prioritized in real world projects.

Interoperability

Successful communication and exchange of information between IT and medical systems requires both *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) [25, 32]. Good semantic interoperability is generally reliant on logical agreed data sets for reporting, requiring ongoing harmonization effort (e.g. of test names, units, reference intervals, etc.).

A key benefit of interoperable systems is a reduction in the number of interfaces required between participants. Harmonized electronic requesting and reporting frequently allows use of the same interface for many providers with little or no customization. This is against the alternative of writing and maintaining interfaces for every health provider or customer that communicates with the laboratory, a proposition that rapidly becomes untenable for more than a few such interfaces [32].

Electronic health messaging is generally conveyed via the Health Layer Seven (HL7) [33] standard, which includes fields for patient demographics, clinical terminology, test orders, atomic and formatted test results, and much more. Those wishing to learn more about EHR communications could refer to ISO 13606 (Health Informatics – Electronic Health Record Communication) [34].

Specification of units

Newcomers to clinical terminology are often surprised that the unit of measure for the analyte of interest is not necessarily specified by the terminology code. The type of unit (e.g. mass, substance, ratio) may be given, but this requires further harmonization between labs on the preferred unit to be used (e.g. $\mu\text{mol/L}$ and mmol/L are both substance creatinine units). Some terminologies, such as the IFCC NPU system [28], specify the kind of quantity and unit of measurement explicitly within the analyte's concept definition.

The Unified Code for Units of Measure [35] is a coding system designed to unambiguously communicate units in both electronic and human readable form. There is generally greater long-term benefit in basing harmonization decisions on a unit defined from physical properties (e.g. most SI units [36]) rather than arbitrary definitions dependent on preparation with an expiry date limitation (e.g. "International units").

The harmonization process for terminology, units and reporting

It is beyond the scope of this paper to describe all the excellent initiatives in progress around the world aiming to enhance laboratory harmonization. Tate and Myers [37] have given an excellent overview of many national and international harmonization initiatives across the TTP, and indeed many of these involve work on terminology (both for requesting and reporting), report formatting, reference intervals, units and flagging, and commenting or decision support.

Achieving harmonization throughout the TTP requires improvement in both horizontal and vertical integration of processes and communication between key stakeholders [38, 39]. When these stakeholders meet to determine and mandate harmonization initiatives, it should never be assumed that all parties understand the actual process of reaching and approving consensus. The principles below are not always obvious or easily grasped by newcomers to harmonization meetings, and so it can be advantageous to ensure these basic principles are communicated before engaging in any group effort to pursue harmonization. More specific examples relating to terminology, units and reporting have been used to illustrate these general harmonization concepts (Table 3).

1. Clarify what is not harmonized and could be improved

It should be possible to demonstrate improved value where harmonization is applied, in terms of reduced patient risk, improved service for the patient and clinical stakeholders, without incurring unreasonable cost. For example, the standardization of creatinine testing to isotope dilution mass spectrometry reference methods together with the use of standardized equations for estimated glomerular filtration rate resulted in improved detection and treatment of chronic kidney disease [40].

Table 3: Key harmonization elements requiring stakeholder understanding and commitment.

Harmonization issue	Related issues
Clarify what is problematic and what could be improved	Stakeholders should debate, clarify, then commit, to priority issues that would generate benefit from harmonization
Harmonization is generally an iterative process of improvement	Stakeholders should anticipate the need for ongoing maintenance and future further improvements. Failure to achieve immediate total harmonization is not an acceptable reason to avoid changes that would bring partial benefit
Harmonization relies on continuous improvement throughout the TTP	Harmonization is frequently difficult to achieve without ancillary work in many areas including test availability, performance, traceability, QA and clinical pathways
Laboratory and information technology continue to evolve	Future technology may make harmonization easier or require examination of past recommendations
Harmonization should be evidence based	Expert opinions and stakeholder review are valuable but where possible must be quantitative and evidence based

2. Harmonization is usually an iterative process of improvement

It is rarely possible to agree on a single “one off” initiative that will resolve all existing variability. This process can be challenging for scientists and clinicians used to assembling all available evidence, then committing to the single best course of action. Stakeholders must agree from the outset on the principle of incremental improvement. Where unacceptable risk has been identified, then that at least some minimal harmonization improvement should be implemented, rather than walking away to await postulated future solutions.

This principle is illustrated in Figure 1 which, shows the uptake of recommended harmonized intervals for Australian laboratories, since their publication in 2014 (Arrow “A”) [10]. The percentage of analytes from each laboratory meeting the recommendations was surveyed by the Royal College of Pathologists of Australasia external Quality Assurance Program (RCPA QAP) each year. Over many years, publications, workshop meetings and other initiatives have gradually seen an increased uptake of the recommendations; however, much work remains to further increase the percentage of harmonized reporting.

3. Harmonization generally relies on improvements in multiple areas through the TTP

Reaching harmonization in one area of laboratory practice is frequently dependent on preceding developments in many other areas.

For example, 20 years ago, there was significant interlaboratory variation in the accuracy and precision of reported HbA_{1c} measurements [41]. In order to improve the quality of results and better harmonize reporting, advances in the following areas were required:

1. Implementation of harmonization programs (National Glycohemoglobin Standardization Program – NGSP [13])
2. Improved analytical performance and accuracy
3. Definition of analyte and unit of measure [14]
4. Availability of suitable reference material
5. Definition of reference method
6. Traceability of field methods to reference material and method
7. Migration to SI units for reporting
8. Improved understanding of clinical decision points for HbA_{1c} diagnosis and treatment based on the scientific literature
9. Improved interpretive reporting based on revised clinical decision point
10. Availability of suitable and commutable QAP and QC materials

Improvements in HbA_{1c} analysis and clinical utility occurred over an extended period, and any attempt to harmonize reporting terminology and units over that period could only proceed as far as developments in each of these key areas allowed. The founders of the NGSP program laid foundations for huge improvements in the utility of HbA_{1c} long before the fundamental definition of HbA_{1c} and identification of reference methods and material for traceable standardization. Adoption of SI units has not become universal, but the process of defining improved reference material and measurement procedures has also improved the utility of HbA_{1c} around the world.

Figure 1: Percentage of reported analytes from surveyed Australian laboratories meeting published harmonized reference interval recommendations.

Arrow A, time of release of initial recommendations, Arrow B, time of follow-up recommendations. Courtesy Dr. Graham Jones, with permission RCPA QAP.

4. Laboratory and information technology continue to evolve

Harmonization recommendations must evolve as new technologies and clinical research becomes available. Efforts to improve methodologies and traceability require cooperation with *in vitro* device (IVD) and reagent manufacturers.

For example, modern thyroid assays are more sensitive than ever before but could further benefit from work on standardization of results and reference intervals between manufacturers. Reaching compromises and improving performance is however costly for manufacturers, who need assurance of the benefits and long-term stability of thyroid harmonization initiatives [42, 43].

5. Harmonization should be evidence-based

Successful harmonization relies on evidence-based knowledge along with systems to monitor and maintain the implementation, benefits and problems resulting from the harmonization [44]. Plebani [7] has noted a hierarchy of three levels of responsibility for harmonization – local initiatives (e.g. laboratory professionals and local physicians), national (e.g. national societies, EQAs and professional bodies) and international (e.g. international federations, IVD manufacturers, standards and accreditation organizations).

Harmonization of terminology, units and reporting is therefore an ongoing multistage process benefiting from a systematic and evidence-based approach [45].

Future directions in reporting: the need for a strong harmonized foundation

Initiatives to harmonize reporting of laboratory tests must ensure the basics of content and formatting are formalized before more complex work on commenting and decision support can be tackled. 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). Essentially, these are variations that emerged during the “paper era” of laboratory reporting, but they must be dealt with satisfactorily to ensure the basics are in place not just for paper-based systems, but the newer electronic systems that are emerging to supplement and replace them.

It is always difficult to predict which innovations will become commonplace in the future; however, some areas where traditional reporting will need to evolve are described below.

1. Electronic reports – opportunities for additional functionality

As laboratory results from many laboratories are compiled for a single patient, graphical displays of results vs. time are more likely to contain results from different laboratories and testing methodologies. Issues and functionality that become more important include the following:

1. Flexibility to display results on multiple electronic formats that are accessible and intelligible to medical staff and patients (e.g. portable devices including phones and tablets)
2. Functionality for showing additional information such as source laboratory, terminology codes and method/analyzer (e.g. during “mouse over” movements by the user)
3. Options to filter complexity (e.g. patients may prefer a more fully specified report with links to additional online interpretive resources, whereas a busy clinician may prefer a streamlined report format)
4. Access to laboratory performance data (e.g. measurement uncertainty values)
5. Functionality to clarify where grouping or separation of results between methods is appropriate
6. Graphical presentation of cumulative results

Decisions regarding point 5 can be challenging. Terminology codes should be chosen to distinguish results that cannot be combined on cumulative reports; however, confirming comparability between methods is challenging, often requiring expert review of QA performance, commutability of QA material, clinical decision goals and specificity of methodologies. The Australian PITUS project attempted to develop three “traffic light” comparability categories for important analytes, classifying methods as either “Red – unsafe to combine”, “Green – safe to combine”, or “Yellow – unknown – not safe to combine” [25, 38].

2. Improved integration between requesting and reporting

We have previously seen that modern requesting systems will increasingly incorporate evidence-based clinical pathways that aim to improve the relevance of testing and reduce inappropriate ordering. Reporting systems will likewise need to incorporate clearer interpretation of risk against clinical guidelines appropriate for the recommended clinical pathway. Critically abnormal results, which were rarely flagged on traditional reports, should be prioritized on

review queues and ideally be communicated securely to handheld devices allowing clinician acknowledgement.

3. Multianalyte risk and display

Traditional reporting for clinical disciplines is heavily based on single analyte values flagged against a reference interval or “normal range”. Clinical pathways recommending multi-analyte testing will likely benefit from innovative graphical or result grouping strategies in addition to showing results separately. Chronic kidney disease prognosis based on calculated glomerular filtration rate and albuminuria for example can be plotted graphically to quickly categorize risk assessment [46]. Rapidly evolving disciplines such as genomics and proteomics will require innovative reporting and storage solutions for large multi-dimensional data sets.

4. Greater dependence on external QAPs

Clinical laboratories are generally required to enroll in external QAPs to monitor analytical performance. This close and regular relationship between the laboratory and the QAP provider offers opportunities for future harmonization initiatives, including the following:

1. Acting as “clearing houses” for checks on interoperability and messaging conformance against standards (e.g. check terminology, HL7 format, requesting, reporting and then provide feedback to laboratory)
2. Provision of coding frameworks for specimen type, reagent, instrument and method classification. External QAPs generally have preexisting systems for coding this information for submitted results. As harmonization initiatives proceed past basic formatting standards, these data could provide valuable additional granularity over and above analyte terminology codes. Future epidemiological reviews of EHR databases could be more powerful if this additional information was available to qualify the source of results.

Storing this methodology information in some agreed standardized form could also empower “combine/do-not-combine” decisions, or allow EHR displays to be filtered based on coded methodologies, rather than simplistic text method descriptions.

3. External QAP performance data sets for many laboratories and analytical methods are a valuable resource for harmonization programs and IVD manufacturers seeking to prioritize and scope future projects, by highlighting those analytes that would most benefit from standardization and traceability initiatives.

EQA programs may therefore be invaluable facilitators for future healthcare interoperability, along with their more traditional role of underpinning analytical performance [47, 48].

5. Multidisciplinary consistency and cooperation

Harmonization initiatives need to use consistent evidence-based processes across scientific disciplines. Patients and clinicians expect a consistent interface from the laboratory across all of its services. Ideally, harmonization initiatives should be governed by multidisciplinary pathologist, scientist, administrator, programmer, clinician and patient advocacy groups [18].

Informatics and harmonization education

Harmonization initiatives for terminology, reporting and units must adapt as laboratory testing technology evolves. The adaption process is most likely to be successful with the combined input of all the clinical, IT, patient and laboratory stakeholders relying on laboratory services. It makes sense to include both experienced and student stakeholders in these reengineering processes. Professional societies are generally highly dependent on volunteered time from their members. Graduate, postgraduate and professional fellowship candidates can assist harmonization committees through projects to conduct literature searches, data mining of laboratory databases, terminology mapping and consultation with clinical colleagues. Educational curricula for laboratory professionals should therefore include harmonization-specific material, including

1. Informatics (including electronic messaging, terminology, archetypes)
2. Standardization, traceability, reference materials and methods, metrology and units, terminology
3. The evidence-based process of harmonization and consensus over the TTP.

Education, mentoring and encouraging the next generation of laboratory professionals to become active in this space requires planning now. All laboratory staff should develop basic skills in IT literacy, informatics and statistics to better support emerging electronic health initiatives and also assist with harmonization and best practice for those systems [49].

Conclusions

In recent years, many exciting harmonization initiatives have focused on improving the quality and consistency of laboratory testing. Many of these programs include, or depend on, efforts to harmonize the content of both requests for testing and the electronic and paper reporting of results. There is an urgent need for much more terminology and reporting harmonization, and that work will best succeed with diverse stakeholder engagement including laboratory professionals, clinicians, patients, software vendors and government.

EHR systems will continue to drive the need for vertical and horizontal coordination between laboratories, and the clinicians and patients depending on their services. As a service industry, laboratories must ensure they provide a consistent and useful product of value to their customers, not just what laboratory professionals believe is best.

Investing in initiatives for harmonization of terminology, units and reporting will lay foundations for stronger healthcare systems in the future, by reducing errors and inefficiency and improving patient benefit from laboratory services.

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References

1. Dybkaer R. Reference materials and reference measurement systems in laboratory medicine. Harmonization of nomenclature and definitions in reference measurement systems. *Eur J Clin Chem Clin Biochem* 1995;33:995–8.
2. Tate J, Johnson R, Barth J, Panteghini M. Harmonization of laboratory testing – current achievements and future strategies. *Clin Chim Acta* 2014;432:4–7.

3. Plebani M. Harmonization in laboratory medicine: requests, samples, measurements and reports. *Crit Rev Clin Lab Sci* 2016;53:184–96.
4. Muller M. Implementation of reference systems in laboratory medicine. *Clin Chem* 2000;46:12.
5. Beastall G. Adding value to laboratory medicine: a professional responsibility. *Clin Chem Lab Med* 2013;51:221–7.
6. Panteghini M. Implementation of standardization in clinical practice; not always an easy task. *Clin Chem Lab Med* 2012;50:1237–41.
7. Plebani M. Harmonization in laboratory medicine: the complete picture. *Clin Chem Lab Med* 2013;51:741–51.
8. Badrick T, Turner P. Review and recommendations for the component tests in the liver function test profile. *Ind J Clin Biochem* 2016;31:21–9.
9. Tatsumi N, Hino M, Nakamura H, Tsuda I, Konda H. Current status of liver function tests in Japan. *Southeast Asian J Trop Med Public Health* 1999;30(Suppl 3):99–104.
10. Tate J, Sikaris K, Jones G, Yen T, Koerbin G, Ryan J, et al. Harmonising adult and paediatric reference intervals in Australia and New Zealand: an evidence-based approach for establishing a first panel of chemistry analytes. *Clin Biochem Rev* 2014;35:213–35.
11. Jones G, Bryant S, Fullinlaw R, Ilett K, Miners J, Morris R, et al. Mass or molar? Recommendations for reporting concentrations of therapeutic drugs. *Med J Aust* 2013;198:368–9.
12. McLawhon R. Patient safety and clinical effectiveness as imperatives for achieving harmonization inside and outside the clinical laboratory. *Clin Chem* 2011;57:936–8.
13. National Glycohemoglobin Standardization Program (NGSP). Available at: www.ngsp.org.
14. Nordin G, Dybkaer R. Recommendation for term and measurement unit for “HbA1c”. *Clin Chem Lab Med* 2007;45:1081–2.
15. Jeppsson J, Kobold U, Barr J, Finke A, Hoelzel W, Hoshino T, et al. Approved IFCC reference method for the measurement of HbA1c in human blood. *Clin Chem Lab Med* 2002;40:78–89.
16. Khwala A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract* 2012;120:c179–84.
17. National Cholesterol Education Program (NCEP). Available at: <http://www.nhlbi.nih.gov/about>.
18. RCPA Pathology Terminology and Information Standardisation. Available at: <https://www.rcpa.edu.au/Library/Practising-Pathology/PTIS>.
19. Standards for Pathology Informatics in Australia (SPIA) V3.0. The Royal College of Pathologists of Australasia. RCPA. Available at: <https://www.rcpa.edu.au/Library/Practising-Pathology/PTIS/APUTS-Downloads>.
20. Flatman R, Legg M, Jones GR, Graham P, Moore D, Tate J, et al. Recommendations for reporting and flagging of reference limits on pathology reports. *Clin Biochem Rev* 2014;35:199–202.
21. Campbell C, Horvath A. Harmonization of critical result management in laboratory medicine. *Clin Chim Acta* 2014;432:135–47.
22. Lang T. Laboratory demand management of repetitive testing – time for harmonisation and an evidenced based approach. *Clin Chem Lab Med* 2013;51:1139–40.
23. Beastall G. The modernisation of pathology and laboratory medicine in the UK: networking into the future. *Clin Biochem Rev* 2008;29:3–10.
24. Plebani M, Chiozza ML, Sciacovelli L. Towards harmonization of quality indicators in laboratory medicine. *Clin Chem Lab Med* 2013;51:187–95.
25. Legg M. Standardisation of test requesting and reporting for the electronic health record. *Clin Chim Acta* 2014;432:148–56.
26. SNOMED CT. Available at: <http://www.snomed.org/snomed-ct>.
27. LOINC. Available at: <https://loinc.org/>.
28. NPU Terminology. Available at: <http://www.npu-terminology.org/>.
29. WHO ICD. Available at: <http://www.who.int/classifications/icd/en/>.
30. Dybkaer R. An ontology on property, for physical, chemical and biological systems. IUPAC online: <http://ontology.iupac.org/ontology.pdf>.
31. Cimino J. Desiderata for controlled medical vocabularies in the twenty-first century. *Methods Info Med* 1998;37:394–403.
32. Flatman R. Coding for pathology tests – strengths and weaknesses. *Clin Biochem Rev* 2012;33:109–13.
33. Health Layer Seven International. Available at: www.hl7.org.
34. ISO 13606 – Health Informatics – Electronic Health Record Communication (EN 13606). Available at: www.en13606.org & also at: <https://www.iso.org/standard/40784.html>.
35. The Unified Code for Units of Measure. Available at: <http://unitsofmeasure.org/trac>.
36. Bureau International des Poids et Mesures (BIPM), Le Système International d’Unités, (known in English as the International System of Units) (SI). Eighth ed. 2006, updated 2014. Available at: <https://www.bipm.org/en/publications/si-brochure/>.
37. Tate J, Myers G. Harmonization of clinical laboratory test results. *eJIFCC* 2016;27:5–14.
38. Legg M, Swanepoel C. The Australian Pathology Units and Terminology Standardisation Project – an overview. *Clin Biochem Rev* 2012;33:103–8.
39. Berg J, Lane V. Pathology harmony; a pragmatic and scientific approach to unfounded variation in the clinical laboratory. *Ann Clin Biochem* 2011;48:195–7.
40. Quinn M, Rainey A, Cairns KJ, Marshall AH, Savage G, Kee F, et al. The practical implications of using standardized estimation equations in calculating the prevalence of chronic kidney disease. *Neph Dial Trans* 2008;23:1–2.
41. John WG, Mosca A, Weykamp C, Goodall I. HbA1c Standardisation: history, science and politics. *Clin Biochem Rev* 2007;28:163–8.
42. Thienpont L, Van Uytendaele K, De Grande L, Reynders D, Das B, Faix J, et al. Harmonization of serum thyroid-stimulating hormone measurements paves the way for the adoption of a more uniform reference interval. *Clin Chem* 2017;63:1248–60.
43. Klee G. Harmonization and standardization of thyroid function tests. *Clin Chem* 2010;56:879–80.
44. Aarsand A, Sandberg S. How to achieve harmonisation of laboratory testing – the complete picture. *Clin Chim Acta* 2014;432:8–14.
45. Tate J. Harmonisation in laboratory medicine. *EFLM EuroLab-News Issue 3/2017*:1–2.
46. Jones G. The New International Recommendations for chronic Kidney Disease. *AACC Clinical Lab News*. Oct 2014. Available at: <https://www.aacc.org/publications/cln/articles/2014/october/kidney-disease>.
47. Jones G. The role of EQA in harmonization in laboratory medicine – a global effort. *Biochem Med* 2017;27:23–9.
48. Miller G. The role of proficiency testing in achieving standardization and harmonization between laboratories. *Clin Biochem* 2009;42:232–5.
49. Jones RG, Johnson OA, Batstone G. Informatics and the clinical laboratory. *Clin Biochem Rev* 2014;35:177–92.