

Critical risk results – an update on international initiatives

Lam Q.¹, Ajzner E.², Campbell C.A.^{3,4}, Young A.⁵

¹ Austin Pathology, Vic., Australia

² Central Laboratory, Jóna Teaching Hospital of University of Debrecen Medical and Health Science Center, Nyíregyháza, Hungary

³ Department of Clinical Chemistry and Endocrinology, South Eastern Area Laboratory Services, NSW Health Pathology, Australia

⁴ Australian Institute of Health Innovation, Macquarie University, NSW, Australia

⁵ Quest Diagnostics, PA, U.S.A

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Corresponding author:

Dr. Que Lam

Austin Pathology, Austin Health
Studley Rd., Heidelberg, Vic 3084
Australia

E-mail: que.lam@austin.org.au

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ABSTRACT

Direct communication of significant (often life-threatening) results is a universally acknowledged role of the pathology laboratory, and an important contributor to patient safety. Amongst the findings of a recent survey of 871 laboratories from 30 countries by the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM), only 3 tests were noted to be common to 90% of alert lists, and only 48% of laboratories consulted clinicians in developing these alert lists despite ISO15189 recommendations to do so. These findings are similar to previous national surveys demonstrating significant variation worldwide in how critical risk results are managed and also in how these protocols are developed. In order to promote “best practice” and harmonization of critical risk results management, guidelines and recommendations have been published, most recently by Clinical and Laboratory Standards Institute (CLSI) and Australasian Association of Clinical Biochemists (AACB). These statements in particular have placed strong emphasis on patient risk and risk assessment in the management of critical risk results. This focus has resulted in recommendations to adopt new terminology, the

consideration of risk assessment when compiling alert tables, consultative involvement of laboratory users in setting up protocols, and the need for outcome-based evidence to support our practices. With time it is expected that emerging evidence and technological improvements will facilitate the advancement of laboratories down this path to harmonization, best practice, and improve patient safety.



INTRODUCTION

Direct communication of significant (often life-threatening) results which require timely clinical attention is a universally acknowledged role of the pathology laboratory. Accreditation standards formalise the requirement for laboratories to manage these “high risk results” but only offer very general guidance on how this should be achieved. Not surprisingly, there is evidence of wide differences in practice between laboratories both internationally and within the same country. These differences are seen in all aspects of high risk results management including the nomenclature and definitions used; which critical tests and thresholds are included in alert tables; specification of who can receive results and by what mode of communication; what information should be conveyed with the result; how receipt of the result is acknowledged; escalation protocols for failed attempts at communication; and how communication events are recorded. Lack of agreement is evident not only in *what* is contained in laboratory protocols but also in *how* these protocols are developed.

It is now increasingly recognised that successful management of high risk results is an important contributor to patient safety¹. As such, harmonization in this area cannot simply be a matter of shared definitions and procedures, but must involve the determination and implementation

of best practice. The challenge is to define best practice and to obtain the evidence required to support this. This review discusses the work currently being undertaken by a number of professional organisations worldwide to harmonize and bring best practice to the management of high risk results.

WHAT IS THE CURRENT SITUATION?

Existing practices

Information on how laboratories manage high risk results is largely provided by national surveys²⁻¹³, most of which have been questionnaire-based with voluntary participation. Although their findings are limited by the response rate and potential selection bias inherent to this method of data collection, these surveys remain the best source of information we have on existing practices. In 2011, the Australasian Association of Clinical Biochemists (AACB) undertook a survey of laboratories representing a mixture of large private and public pathology networks from key providers in the region, servicing community and hospital patients². Between September 2012 and March 2013, the European Federation of Clinical Chemistry and Laboratory Medicine (ELFM) invited its members, affiliates and provisional member countries to complete a modified version of the Australasian survey, adapted for the European professional environment. Eight hundred and seventy one laboratories from 30 countries responded and these results^{3,4}, in combination with the Australasian findings, have provided a comprehensive insight into international state-of-the-art practice in this area.

One finding common to all surveys has been the lack of uniformity in alert lists, both in their contents and how they are compiled. Only 41% of Australasian and 48% of European laboratories consulted clinicians in this process despite the recommendation within ISO 15189 that

clinical agreement be sought. However, this rate varied between nations with Norway and the Netherlands reporting high consultation rates (72% and 88% respectively) comparable to the 73% of U.S. laboratories previously described¹⁰. It is known from other national surveys that clinical consultation rates can be significantly lower^{12,13}. Alert lists solely derived from the laboratory run the risk of being detached from clinical practice. A Canadian laboratory found that when their laboratory-derived alert lists were presented to their hospital physicians, only 36% of adult and 61.5% of paediatric alert thresholds were considered acceptable and did not require modification^{14,15}. "Published literature" is another commonly cited source of critical thresholds (listed by 59% of Australasian and 66% of European laboratories) but what laboratories interpret this term to mean is often not explored. A previous survey of UK laboratories found that only 2 out of 94 laboratories actually quoted literature to support the thresholds in their alert table⁶.

Surveys have consistently highlighted variation in the content of alert lists. In Europe, only 3 tests (potassium, glucose and sodium) were common to the alert lists of more than 90% of survey respondents. In comparison, a U.S. report found 8 common tests (potassium, sodium, calcium, platelets, hemoglobin, activated partial thromboplastin time, white blood count and prothrombin time), again shared by more than 90% of the surveyed laboratories⁷. How many tests should we expect to be common on alert lists is not clear. The answer is likely to be complicated when considering the patient population serviced by individual laboratories, the tests performed and whether there is evidence of clinical risk from outcome studies.

When the numerical alert thresholds used are compared between laboratories, the findings are varied. Some analyte thresholds do show harmonization probably as a consequence of the wide adoption of thresholds from a single

source (e.g. guidelines), rather than consensus regarding clinical risk. This can be seen amongst laboratories measuring the drug carbamazepine. In the Australasian survey, 22 out of 26 laboratories reported a high critical threshold for this drug, the median of which was 15 mg/L (range 9-20). This same median high threshold (15 mg/L) was found in a US survey of 36 internet-published alert lists for therapeutic drugs (range 11-20)¹⁶. Fifteen mg/L was also the mean high threshold (range 10-20) found in a survey of UK laboratories⁶. In contrast, there is little agreement with C-reactive protein thresholds in adults. Its inclusion in alert lists can be seen in 28% of Australasian alert lists with a median value of 100 mg/L (range 80-300) and in 30% and 43% of European adult and pediatric alert lists, respectively. Forty-three percent of Norwegian laboratories use CRP on their alert lists¹⁷ with a median applied alert threshold of 200 (10 and 90 percentiles; 50-200) mg/L. Of interest, only 35% of responding general practitioners actually wanted to be alerted of CRP values above 120 mg/L (10 and 90 percentiles of responses were 50 and 200mg/L, respectively). Further variation in alert list content has been described as a result of some laboratories using customized thresholds and modified policies based on the patient age, location, individual provider or practice group requesting the test, or the disease type where known⁷. Sixty-one percent of European laboratories use children-specific alert thresholds, and 19% apply unique thresholds for specialist wards.

Many surveys also described diversity in the communication policies around high risk results. Around 65% of European and 80% of Australasian laboratories would not actively communicate a critical risk result if it was not significantly different from a previously delivered result for that patient. In U.S., only 36% laboratories had a policy allowing for these repeat critical results not to be called¹⁸. Furthermore, a

College of Pathologist Q-Tracks study suggested that reporting all critical values, including repeat ones, was actually valuable as it may indicate a higher degree of vigilance in the critical value reporting system¹⁹.

Where results are successfully conveyed by verbal communication, the procedure of asking recipients to “read-back” results to confirm successful transmission was practiced inconsistently between countries^{2,5,7,11}; only 46 % of laboratories surveyed both in France and Australasia compared to 79% of U.K. laboratories. Rates at which this “read back” was formally documented and records kept also varied between nations; 10% of Australasian and 23% of European laboratories.

There is also diversity in escalation policies when a responsible clinician cannot be contacted. Only 38% of responding laboratories in the European survey had an existing formal protocol. Some laboratories contact the patient either directly (64% of French and 23% of Australasian laboratories) or via the police or ambulance service (15% of Australasian laboratories). Thirty four percent of European and 39% of Australasian laboratories formally documented occurrences where delivery of a critical result had to be abandoned. Information regarding the average time to abandonment of communication attempts is sparse but has previously been reported amongst U.S laboratories to be 20.2 minutes for inpatients and 46.3 minutes for outpatients¹⁰.

Available evidence

For patient safety, laboratories should follow procedures that are considered best practice and based on high level evidence. However, in most aspects of high risk results management, the evidence required is often lacking. Contributing to this problem is the inconsistency in terminology and definitions used in the

literature. There has been disagreement on terminology since the original phrase “panic values” was first coined by Lundberg²⁰. Commonly used terms including “critical”, “significantly abnormal”, “life-threatening” and “urgent” have all been criticised because of their inability to include all results that require timely notification, and because of the ambiguity caused by their use in other areas of medicine and everyday language. Their generic use creates a problem when these phrases are used as search terms; searching the NIH PubMed website (accessed 4/11/2015) with “laboratory AND critical AND results” yielded over 22,500 articles, the top 50 of which were not relevant to our intention. Likewise, use of the term “value” itself has also been discouraged as it seemingly excludes semi-quantitative or non-quantitative results such as microbiological cultures²¹.

Failure to distinguish “critical tests” from “critical test result” also creates confusion. A “critical test” is a laboratory test that influences clinically urgent patient management decisions irrespective of whether the result is normal, abnormal or critical. Thus any result for a critical test should be rapidly communicated. It is distinct from a “critical test result” which refers to a test result that requires timely communication only because it falls outside a pre-defined risk alert threshold. If critical tests are not clearly defined, the lack of associated thresholds to assist in their identification may lead to results being overlooked and therefore not communicated nor acted upon.

Recent discussion around the evidence required for alert list design has suggested that alert thresholds should be considered “clinical decision limits” given that their purpose extends beyond merely indicating illness, but to trigger clinical action. A modified Stockholm Hierarchy has been proposed for clinical decision limits which assigns Level 1 evidence as “clinical outcomes in specific clinical settings”²². Such evidence is best attained with randomised

control trials as they explicitly investigate the relationship between an exposure (e.g., a critical risk result) and an outcome (e.g., mortality or serious morbidity) and enable calculation of the outcome risk specifically associated with that exposure. However, even if it were possible to induce a pathological state to generate critical risk results within a random selection of subjects, it certainly would not be ethical. Consequently, the critical risk result outcome studies reported in the literature are generally retrospective observational studies. The main, and often impossible, challenge in the design of such studies is separating the contribution to the risk of adverse outcome posed by confounding variables (characteristics of the study subjects other than the critical risk result) in order to assess the independent effect of the critical risk result.

A further limitation of retrospective observational studies is that they typically have not been designed for the purpose of identifying the optimal alert threshold. A number of retrospective observational studies published for serum potassium show relatively congruous results with increased mortality risk observed when potassium concentrations are below 3.0-4.1 mmol/L or above 4.3-4.5 mmol/L, despite diverse study populations (general hospital, patients with chronic kidney disease, acute myocardial infarction, head trauma or on peritoneal dialysis) and varying timeframes observed for mortality (during inpatient admission, 1 year or longer term)²³⁻²⁷. However, these thresholds cross into commonly quoted reference intervals for potassium and therefore would be impractical for laboratory alert lists. While studies that explore the continuous relationship between test result values and outcome are important, a decision must be made as to when the risk of adverse outcome becomes unacceptable and hence where clinical action should be taken. Unlike potassium (and sodium), only a small

number of studies addressing clinical decision limits exist for many other analytes. This likely reflects the difficulty of studying analytes with assay-related variations in measurement and where a clearly associated clinical outcome has not been identified.

INITIATIVES

Terminology

The need for harmonization and the implementation of best practice in high risk results management is now widely acknowledged and has provided a common goal for laboratories and pathology organisations worldwide. Addressing the variation in terminology has been an important first step. It is vital that the language used must not only be common but it must correctly convey the intention so that there is shared understanding of the concepts underlying the process.

Recently, the term “high-risk results” has been proposed as an umbrella term to include “critical-risk results”; results requiring immediate medical attention and action because they indicate a high risk of imminent death or major patient harm, and “significant-risk results”; results that are not imminently life-threatening, but signify significant risk to patient well-being and therefore require medical attention and follow-up action within a clinically justified time limit²⁸. Emphasising the clinical *risk* to the patient rather than the timeframe required for notification or the need to initiate clinical action, is an important distinction. It underscores the need for clinicians to assess and consider the risk of harm in an individual patient with a particular result, and to then decide on an appropriate course of action. Although it might be argued that this change in terminology is purely cosmetic, it reminds us that critical values are not “one-size-fits-all”; that results notification is a *trigger* for clinical assessment. Common use

of this terminology in clinical trials and publications would facilitate the transferability of findings as well as helping to collate evidence in a more systematic manner.

CLSI GUIDELINES

The terminology and concepts of “critical-risk” and “significant-risk” have already been adopted by some professional bodies in their guidance documents^{29,30}. The Clinical and Laboratory Standards Institute (CLSI) in its recently released guideline for management of laboratory results that indicate risk for patient safety²⁹ has introduced these terms to emphasize that the appropriate steps for reporting a laboratory result can be defined by the degree of risk for adverse patient outcome. Degree of risk in this context is differentiated by immediacy, probability and/or severity of potential patient harm, as well as likelihood of harm due to undetected breakdowns in communication. “Critical-risk” results signify probable, immediate risk of major adverse outcomes in the absence of urgent clinical evaluation. The guidelines stress that such results should be actively communicated to responsible caregivers without delay, and that there should be documentation that the caregivers received this information accurately. “Significant-risk” results indicate risk of important adverse outcomes that can be mitigated by timely clinical evaluation (although the risks are not necessarily immediate, highly probable or life-threatening). Unless routine reporting systems have safeguards against breakdowns in communication, significant-risk results should also be actively reported to responsible caregivers with documentation of successful and accurate communication. However, the time frame(s) for reporting such results do not need to be the same as for critical-risk results, as long as they permit appropriately timely clinical evaluation.

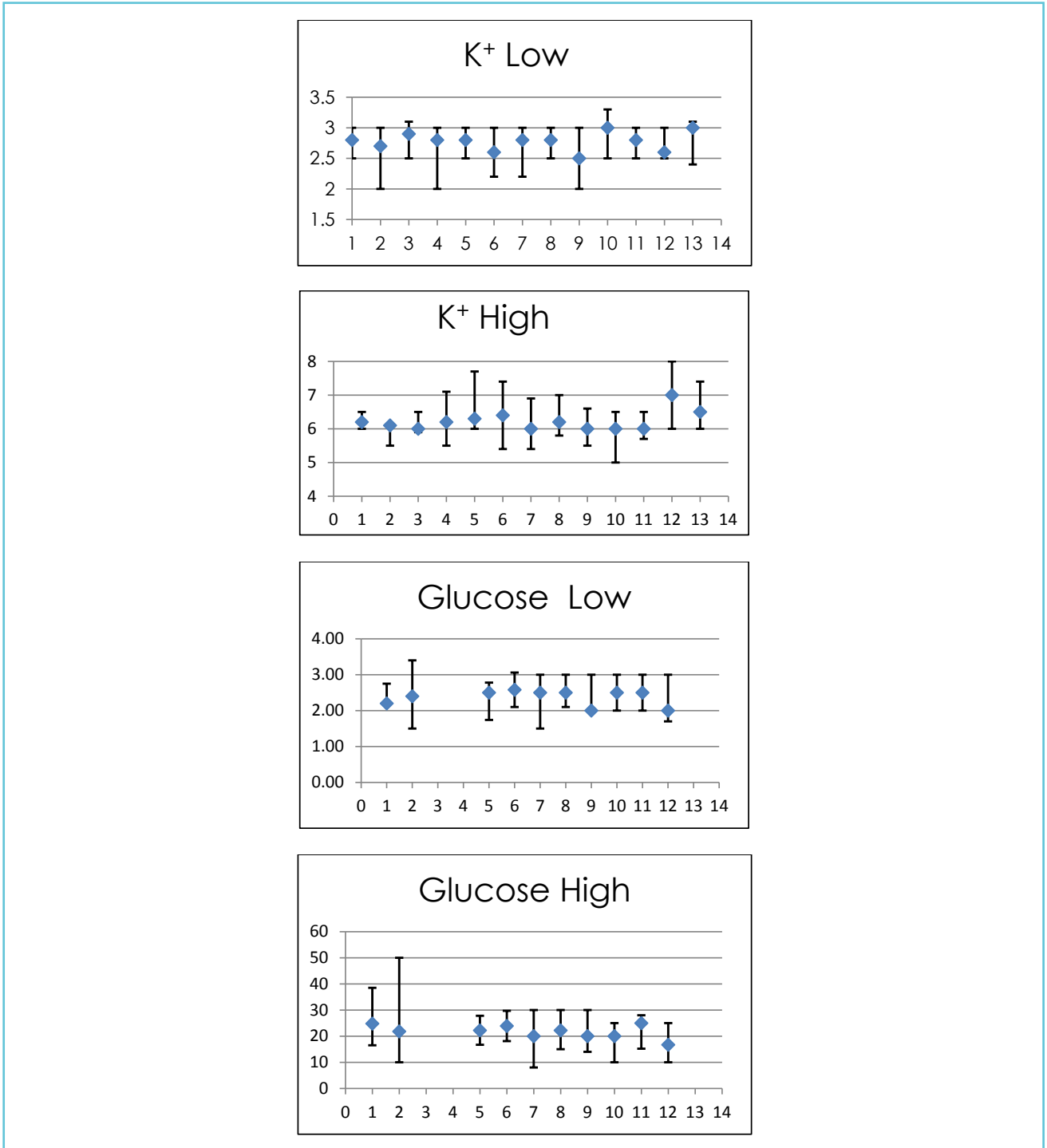
The CLSI guideline recommends that a laboratory or healthcare organization conduct local risk analysis to determine which laboratory results should be defined as “critical-risk” or “significant-risk”. In addition, risk analysis should determine the most reliable processes to communicate results to responsible caregivers, and how to monitor these processes for effectiveness. The analysis should focus on the following initial questions:

1. Do the laboratory results indicate a significant risk for adverse patient outcome?
2. Can the caregiver act on these results to significantly reduce patient risk?
3. Will active communication from laboratory to caregiver reduce patient risk or promote better care?

To address these questions, organizations should consult with local laboratory and medical staff leadership, and review locally applicable regulations and accreditation standards. In addition, the organization can refer to the growing number of international surveys on the reporting of abnormal laboratory results. The surveys, while revealing substantial practice variations, have identified a core list of results that the majority of peer institutions define as “critical-risk”; these results would likely be applicable for the organization, with modification as needed based on local risk analysis or feedback from laboratory and medical staff. Examples of common critical-risk results include very abnormal potassium or glucose concentrations in serum/plasma (See Figure 1), or cell counts in whole blood.

In contrast to critical-risk results, significant-risk laboratory results are not specifically addressed in regulatory and accreditation standards, and there are few published surveys for reporting these results. Therefore, the organization’s reporting procedure can be determined by local risk analyses. To use a specific example,

Figure 1 Alert thresholds of the two most frequent blood parameters on adult alert lists in different surveys



Surveys included: 1. US 2002 Median (p10-p90), 2. UK 2003 Mean (range), 3. US 2007 Median (p5-p95), 4. Italy 2010 Median (p10-p90), 5. Spain 2010 Median (p10-p90), 6. Thailand 2010 Mean (\pm SD), 7. Australia 2012 Median (range), 8. China 2013 Median (p5-p95), 9. Norway Median (range), 10. Norway GP's Median (range), 11. EU adult Median (p10-p90), 12. EU paediatrics Median (p10-p90), 13. EU dialysis Median (p10-p90), 14. EU obstetrics Median (p10-p90).

the organization might consider how to report unexpected, early-stage adenocarcinoma in a routine appendectomy specimen. This result is significant for prognosis and therapy, but does not indicate immediate risk of severe adverse events, and does not require immediate clinical intervention for appropriate care. However, a delay in recognition and treatment could result in a significantly worse outcome for the patient. Therefore, this result might meet criteria for “significant-risk” depending on an organizational risk analysis. If routine pathology reports cannot be verified for receipt and acknowledgment, the organization should classify the unexpected finding of malignancy as a significant-risk result, and require the pathology laboratory to actively notify caregivers in a clinically appropriate time frame (for example, within 24 hours). On the other hand, if routine pathology reports are monitored to verify acknowledgment by responsible caregivers within an appropriate time frame, the organization might choose to rely on standard reporting in this situation.

Policies and procedures for reporting critical-risk and significant-risk laboratory results should include the following:

1. The definition of critical-risk and significant-risk results, and timeframes for reporting. These should be established through consensus between laboratory, medical and administrative personnel.
2. The laboratory should identify personnel responsible for reporting critical-risk and significant-risk results.
3. The organization should identify caregivers authorized to receive reports of critical-risk and significant-risk results. Final recipients should be responsible clinicians who can direct patient care based on the laboratory results. It may be reasonable for the laboratory to report results to intermediaries, who relay the report to the responsible clinician. However, the

accuracy and timeliness of the communication must remain appropriate for patient care.

4. Reports of critical-risk and significant-risk results should be documented to identify the patient or patient’s sample, the laboratory result, the reporter and recipient, the time of report, and verification of accurate communication. If intermediary personnel are involved in the report, each leg of communication should be documented.
5. The reporting of critical-risk and significant-risk results should be continually monitored for effectiveness. Root cause analyses should be conducted if performance targets are not met, in order to identify potential sources of risk.

AUSTRALASIAN RECOMMENDATIONS

A guidance document on the communication and management of high risk results has also been recently published by the AACB in conjunction with the Royal College of Pathologists of Australasia (RCPA)³⁰. It contains recommendations which reflect “best practice” based, where possible, on available literature but ultimately reflects the consensus view of a specifically formed working party comprising of pathologists and laboratory scientists with interest and expertise in this area. The statement has been written in a general manner so as to be able to be applied to all disciplines within pathology. Before publication, an open invitation to comment on the draft was sent to the wider laboratory community, clinicians and patient interest groups. This wide consultative process acknowledged the importance of agreement amongst these three groups in order for the successful management of high risk results.

The document features 8 key recommendations for laboratories, namely to:

1. compile an alert list(s) in consultation with its users;

2. have procedures to ensure that high risk results are reliably identified;
3. specify, in agreement with its users, the modes of transmission for the communication of high risk results;
4. specify, in agreement with its users, who is authorised to receive high risk results;
5. define what data needs to be communicated to the recipients of high risk results;
6. develop a system for the acknowledgement of the receipt of high risk results to confirm that results were accurately and effectively communicated;
7. ensure that every high risk result notification is appropriately documented;
8. have procedures that involve its users in maintaining and monitoring the outcomes of its high risk result management practices.

Further details of how each recommendation should be achieved, including some examples, are explored within the body of the paper.

The consensus statement aims to incorporate a number of important concepts for harmonization and best practice. Laboratories are encouraged to adopt the newly proposed international terminology and are also encouraged not to develop their procedures in isolation but instead to collaborate with their laboratory users (that is, medical practitioners, nurses and other health care professionals directly involved in patient care). Although the guidance document represents what is considered best practice, it recognises that individual laboratories, due to unique circumstances, may struggle with some recommendations. To address this, the terms “needs to”, “should” and “may” are purposely used to give an indication of the strength of each recommendation, providing laboratories with an understanding of which recommendations must be adhered to, and which can be viewed as suggestions. It is also important that

laboratories see the management of high risk results as a dynamic process requiring monitoring and updating in light of changing circumstances and technology.

These recommendations are an initial step towards harmonization. The working party hopes to compile a “starter” alert list with thresholds based on outcome studies and expert opinion, framed by the risk assessment model proposed by the CSLI. Laboratories could expect to use this list as a foundation for discussion with their clinical users.

FUTURE DIRECTIONS

Future directions in the area of high risk results management will be influenced by emerging evidence and advances in technology. There is a clear need for more outcome studies. These studies should use consensus terminology and be designed to not only demonstrate where the risk of harm to patients starts but also determine the threshold level(s) where clinical action can eliminate or diminish this risk. With stronger evidence will come harmonization of alert thresholds and protocols for laboratories and their users. Studies should also look at specific populations or scenarios to allow for alert lists to better cater for individuals thus generating less false positive clinical notifications. While having more exceptions or rules seems unmanageable today, it is reasonable to expect improvements in technology that will assist the way we identify and communicate high risk results.

Laboratories will also need to adapt their procedures and protocols as new opportunities are presented by improving technology. Already, the use of electronic text messaging as an alternative form of communication to the traditional phone call has been described with success^{31,32}. Further advances in the way laboratories identify high risk results and notify clinicians are certain. However, it is important that

the underlying principles of best practice remain, so that in the example of text messaging, receipt of the result must be acknowledged and documented and where this does not occur, an escalation procedure implemented.

CONCLUSION

High risk results management is recognised as an important contributor to patient safety. Wide variation in laboratory practices worldwide has been identified, and the need for harmonization is universally acknowledged. Recent initiatives towards harmonization have focussed on patient risk and risk assessment. This approach has framed proposed new terminology, discussions around the design of alert tables, the need for outcome-based evidence and best practice recommendations for laboratory procedures. With time it is expected that emerging evidence and technological improvements will further advance laboratories down this path to harmonization and best practice, and improve patient safety.

DEFINITIONS

Critical test: A test that requires immediate communication of the result irrespective of whether it is normal, significantly abnormal or critical.

Critical risk result: Results requiring immediate medical attention and action because they indicate a high risk of imminent death or major patient harm.

Significant risk result: Results that are not imminently life-threatening, but signify significant risk to patient well-being and therefore require medical attention and follow-up action within a clinically justified time limit.

High risk results: A collective term used to denote results that require communication in a timely manner; i.e. critical risk results, significant risk results and results of critical tests.

Alert threshold: The upper and/or lower threshold of a test result or the magnitude of change (delta) in a test result within a clinically significant time period, beyond which the finding is considered to be a medical priority warranting timely action.

Alert list: A list of critical tests and tests with alert thresholds for high risk results ideally reflecting an agreed policy between the laboratory and its users for rapid communication within a pre-specified time frame and according to a procedure.

Escalation procedure: An ordered list of alternative steps to be followed when the appropriate recipient(s) of a high risk result cannot be reached in a clinically appropriate time frame.

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