The implementation of safe and effective high risk result management practices in pathology

Craig Campbell

BAppSc, MSc, MCS

Centre for Health Systems and Safety Research

The Australian Institute of Health Innovation

Faculty of Medicine and Health Sciences

Macquarie University

NSW Australia

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Table of Contents

Dedication

This thesis is dedicated to my late mother Thelma, who sadly passed away in 2018. I miss her love and support, and know that she would be extremely proud of me for completing this work.

Declaration

I certify that the work in this thesis entitled “The implementation of safe and effective high risk result management practices in pathology” has not previously been submitted for a degree nor has it been submitted as part of requirements for a degree to any other university or institution other than Macquarie University. I also certify that the thesis is an original piece of research and it has been written by me. Any help and assistance that I have received in my research work and the preparation of the thesis itself have been appropriately acknowledged.

In addition, I certify that all information sources and literature used are indicated in the thesis.

Some of the research presented in this thesis (Chapter 5) was approved by the human research ethics committee at South Eastern Sydney Health District (HREC/16/POWH/412). This ethics approval was ratified by Macquarie University.

Craig Campbell.

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List of Original Publications

This thesis is based on the following original publications, which are referred to in the text by Roman numbers. Original publications are reproduced with permission from their copyright holders.

I **Campbell CA**, Horvath AR. Harmonization of critical result management in laboratory medicine. *Clin Chim Acta 2014;432:13-47. doi: 10.1016/j.cca.2013.11.004*

II **Campbell CA**, Georgiou A, Westbrook J, Horvath AR. What Alert Thresholds Should Be Used to Identify Critical Risk Results: A Systematic Review of the Evidence. *Clin Chem 2016;62(11):1445-57. doi: 10.1373/clinchem.2016.260638*

III **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(1): 89–94. doi: 10.1515/cclm-2017-1114*

IV **Campbell CA**, Li L, Kotwal S, Georgiou A, Horvath AR, Westbrook J and Endre Z. Under-detection of acute kidney injury in hospitalised patients: a retrospective, multi-site, longitudinal study. *Intern Med J 2019; doi: org/10.1111/imj.14264 (forthcoming)*

Contributors

Supervisor	Professor Andrew Georgiou Centre for Health Systems and Safety Research Australian Institute of Health Innovations Macquarie University
Associate Supervisors	Professor Andrea R Horvath New South Wales Health Pathology Prince of Wales Hospital, Sydney Australia
`	Professor Johanna Westbrook Centre for Health Systems and Safety Research Australian Institute of Health Innovations Macquarie University
	Associate Professor Ling Li Centre for Health Systems and Safety Research Australian Institute of Health Innovations Macquarie University
External Collaborators	Doctor Que Lam Austin Health Heidelberg, Australia
	Doctor Sradha Kotwal Department of Nephrology Prince of Wales Clinical School University of New South Wales, Sydney Australia
	Professor Zoltan Endre Department of Nephrology Prince of Wales Clinical School University of New South Wales, Sydney Australia

Division of Labour in Co-Authored Articles

CC - Craig Campbell; AH – Andrea Horvath; AG – Andrew Georgiou; JW - Johanna Westbrook; QL – Que Lam; LL – Ling Li; SK – Sradha Kotwal; ZE – Zoltan Endre.

	Article I	Article II	Article III	Article IV
Concept and design	CC, AH	CC, AH, AG, JW	CC, AH, QL	CC, SK, ZE, LL, AG, AH, JW
Planning and implementation	CC, AH	CC, AH, AG, JW	CC, AH, QL	CC, SK, ZE, LL, AG, AH, JW
Data collection	CC	CC	CC	CC, LL
Analysis and interpretation	CC, AH	CC, AH	CC	CC,LL
Drafting the article	CC	CC	CC	CC
Article revisions	CC, AH	CC, AH, AG, JW	CC, AH, QL	CC, SK, ZE, LL, AG, AH, JW
Overall responsibility	CC	CC	CC	CC

By signing below, co-authors provide their permission to include co-authored publications in this thesis and indicate their agreement with the description of authorship provided in the table above.

Contributor	Articles	Signature	Date
Andrea Horvath	I, II, III, and IV		
Andrew Georgiou	II and IV		
Johanna Westbrook	II and IV		
Que Lam	III		
Ling Li	IV		
Sradha Kotwal	IV		
Zoltan Endre	IV		

Abbreviations

AACB	Australasian Association of Clinical Biochemists
AKI	Acute kidney injury
CA 19-9	Carbohydrate Antigen 19-9
CLSI	Clinical Laboratory and Standards Institute
EMR	Electronic medical record
IOM	Institute of Medicine
ISO	International Organization for Standardization
IT	Information technology
KDIGO	Kidney disease improving global outcomes
NPAAC	National Pathology Accreditation Advisory Council
RCPA	Royal College of Pathologists of Australasia
UK	United Kingdom
US	United States

Abstract

Numerous national and international patient safety reports have identified failure in the communication of pathology results to the 'clinician responsible for the patient's care' as a significant contributor to unsafe medical care. Although it is standard practice for pathology laboratories to immediately communicate critical results (i.e., results that indicate a high risk of imminent and serious harm to the patient) to the responsible clinician, there is little guidance available to laboratories on how to conduct this task reliably to ensure patient safety. Variations and gaps in critical result management procedures, revealed in international surveys, highlight the importance of and the need for a unified approach. Evidence is also lacking for the thresholds at which pathology results become critical, and due to the differing clinical needs of unique patient populations and settings of care there is no universal consensus on which results should be defined as critical. Some countries have produced "starter" lists of critical result thresholds for laboratories to adapt in collaboration with clinical users to fit their local setting. These starter lists are generally built on expert opinions and state of the art, which make the thresholds difficult to defend when challenged by individual clinicians with contrary views.

The aim of this thesis was to establish evidence-based systems for the safe and effective management of critical pathology test results. A narrative review of the current status of international critical result management practices was performed. This review identified the need for a harmonised terminology, highlighted key areas where consistent management practices were necessary and feasible, and offered a conceptual framework and methods for designing evidence-based systems for the timely notification of critical pathology results. A systematic review of critical result thresholds for clinical chemistry, haematology and endocrinology tests was also undertaken to provide an explicit and ranked source of evidence for each of the values. An evidence- and risk-based methodology was developed for the identification and verification of critical result thresholds, which involves reviewing the literature, rating the available evidence, performing a risk analysis (to assess the potential harm associated with use of the proposed threshold), assessing method transferability, considering workload implications and seeking endorsement from stakeholders. A retrospective study across four public hospitals was performed in which critical delta thresholds (for detecting critical change in results) were applied to serum creatinine results in order to identify patients with acute kidney injury (AKI). The value of these critical thresholds was assessed by comparing the incidence of laboratory detected AKI to incidence recorded in the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification diagnosis codes.

This thesis has introduced new terminology (alert threshold and alert list) and inspired the creation of other terms (critical risk result, significant risk result, and high risk result) which have been adopted in Australia and the United States to replace the heterogeneous terminology previously in use. The review of critical result management practices informed recently published recommendations by the Royal College of Pathologists of Australasia (RCPA) and the Australasian Association of Clinical Biochemists (AACB), which provide Australasian laboratories and their users with guidance on how to design shared policies and procedures for the management of high risk results. The National Pathology Accreditation Advisory Council (NPAAC) are drawing from these recommendations in their development of a national standard for the communication of high risk pathology results. The systematic review and risk based methodology for determining 'critical result thresholds' (i.e., alert thresholds) have inspired and contributed to an Australian initiative currently underway to produce an evidence-based national harmonised 'critical result threshold list' (i.e., alert list). The retrospective study that identified acute kidney injury using delta alert thresholds showed the value of an AKI alert system in identification of patients that would otherwise be missed and thus go untreated. The study has provided justification for the introduction of AKI alerting at the four hospitals, with a pilot study involving live AKI alerting currently underway.

Chapter 1

Introduction

Pathology testing involves examination of body tissue or fluid to identify changes that indicate the presence or severity of a health problem (1). It is estimated that around 500 million tests are performed by pathology laboratories each year in Australia (2), providing clinicians with information to support the diagnosis and management of disease and other conditions. The clinician who ordered the test is usually responsible for following up on the result. Depending on the type of test ordered, the result may be available within a few minutes, or may take hours, days or even weeks to produce. When the information systems in pathology and the health care institution are connected, clinicians are able to view the results electronically. In the absence of electronic access, results are usually delivered or faxed by pathology laboratories to the ordering clinician in the form of a paper report.

1.1 Monitoring for Missed Pathology Results

A full-time primary care clinician reviews around one thousand pathology results in a typical week, according to a study conducted in Boston (3). This considerable volume of incoming results needs to be managed to ensure that none are overlooked. Clinicians from 21 primary care practices and a large teaching hospital in South-eastern Michigan were surveyed on their methods for managing and following up on test results, and 83% of respondents reported having a good or excellent method for tracking blood tests ordered to ensure that results had been received (4). Less confidence was expressed in methodology for tracking other types of tests, with 73%, 71% and 68% of respondents rating their methods for tracking PAP smears, mammograms and other X-ray studies as good or excellent. In a survey of primary care clinicians across the Veteran Affairs Midwest Health Care Network, most respondents (55%) relied totally on their electronic medical record (EMR) inbox to avoid missing test results; 34% of respondents used EMR notifications and paper logs, while 8% employed paper logs only (5). Approximately one in five respondents (21%) filtered their inbox to receive only abnormal results, and more than one third (37%) admitted to encountering a patient with a missed result in the prior two weeks. A third clinician survey involving 15 internal medicine practices in Boston revealed that only 32% of respondents had a system for detecting missed results, and 83% reported at least one delay in reviewing results within the previous two months (6).

Missed results are of particular concern when they are abnormal, because failure to consider an abnormal result could see the appearance or progression of a health problem go unnoticed and therefore untreated. Late review of an abnormal result is also of concern as it could lead to the patient not receiving the appropriate treatment in time to prevent harm. Thus delay or failure to review a result is an unacceptable error, and the high incidence of this error observed in clinician surveys suggests that error prevention measures are insufficient or possibly even non-existent. James Reason, an expert in the psychology of human error, argues that the medical profession widely and incorrectly takes the "person" approach to preventing error by directing countermeasures at reducing unwanted variability in human behaviour (7). Blaming the individual for choosing unsafe behaviour is convenient and distances the institution from responsibility, but does not promote an error reporting culture or identify error provoking properties within the system. The medical profession would be better served adopting the "system" approach to error prevention, which is seen in other hazardous industries such as aviation and nuclear power (7). This approach considers errors as consequences of systemic factors, and involves inserting layers of defences, barriers and safeguards into the system to protect potential victims and assets from hazards (7). The goal of the system approach is the development of a comprehensive management programme that targets the individual, the team, the task, the workplace and the institution.

1.2 Medical Error - A Call to Arms

In 1984 and 1992, the impact of medical error was brought to light in a couple of high profile US studies (8, 9). Extrapolation of the results from these studies to all US hospital admissions provides the following estimates: between 44 and 98 thousand patients die in US hospitals each year due to medical error; and the national cost of injury caused by preventable medical error is between 17 and 29 billion US dollars (10). These alarming findings prompted the Institute of Medicine (IOM) to develop a strategy to improve the quality of American health care (10, 11). In order to see their vision become reality, the IOM produced a series of reports to guide the implementation of quality improvements, including a report in 2015 that addresses diagnostic error (12).

1.3 The Diagnostic Process

Diagnosis is a complex process that occurs over time, and involves information gathering, clinical reasoning, collaboration and communication (Figure 1) (12). It may initially involve consideration of a number of diagnostic hypotheses, which are refined and narrowed as new information is obtained. A

diagnosis is verified when the diagnostic team is satisfied that it explains the patient's health problem and is consistent with the information gathered (12). Absolute certainty in diagnosis is unattainable no matter how much information is gathered (13).

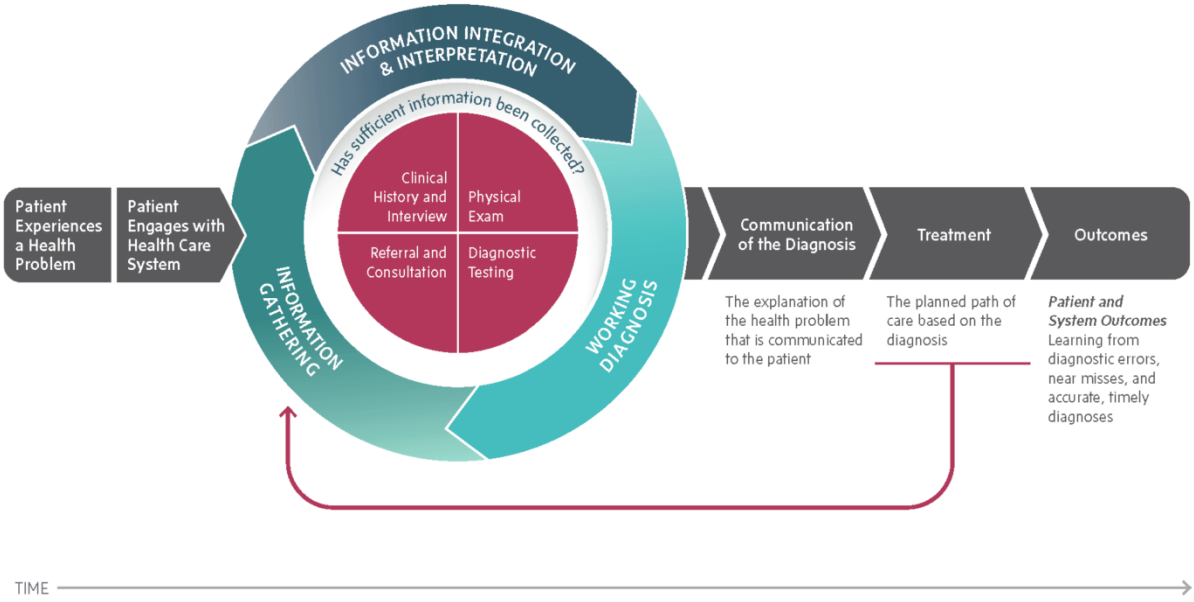

Figure 1: The diagnostic process. *Republished with permission of National Academies Press, from "Institute of Medicine. Improving Diagnosis in Health Care. National Academies Press, Washington 2015."; permission conveyed through Copyright Clearance Center, Inc.*

1.4 Diagnostic Error

A diagnostic error is a mistake or failure in the diagnostic process that leads to a misdiagnosis, missed diagnosis or delayed diagnosis (14). Evidence suggests that diagnostic errors account for six to seventeen percent of adverse hospital events (8, 9, 15), ten percent of patient deaths (16), and the highest proportion of medical malpractice claims and payments (17). According to the IOM report, diagnostic error is a largely unappreciated quality and patient safety issue that will likely worsen without a dedicated focus on improving diagnosis (12). The report recommends changes to the diagnostic process to make it less prone to error, through more effective teamwork among health care professionals and patients, enhanced education and training, capable IT support, supportive work system and culture, diagnostic error detection and reporting, and dedicated funding for research.

1.4.1 Errors in Diagnostic Testing

Diagnostic testing occurs in the information gathering stage of the diagnostic process (Figure 1), and may be performed in multiple rounds of the information gathering, integration and interpretation cycle as the diagnosis is refined (12). It involves ordering a test(s), analysis/measurement to produce a test result, and interpretation of the result. The analysis/measurement is usually performed by pathology or radiology. Due to the growing number and complexity of diagnostic tests available, clinicians should consult with pathologists and radiologists for advice on appropriate test selection and implications of test results (12). Mistakes or failures during diagnostic testing that may lead to diagnostic errors include: i) delay or failure to order needed test(s), ii) ordering the wrong test(s), iii) mislabelled sample (i.e., wrong patient), iv) technical errors in sample processing, v) erroneous measurement of the test result (analytical error), vi) delay or failure in reporting the result to the clinician, vi) delay or failure in the follow up of an abnormal test result, and viii) error in clinician interpretation of the result (14). A survey, in which 310 clinicians from 22 institutions across the United States provided details on 583 cases of diagnostic error, revealed that most errors were due to failures within the diagnostic testing phase (44%) (14).

1.4.1.1 Errors in Laboratory Analysis/Measurement (Analytical Error)

For many years, pathology laboratories have focussed on the prevention of analytical errors. Since the early 1950s, laboratories have performed regular testing of control material (internal quality control) to ensure that their measurements are within a permissible analytical error (18, 19). Proficiency testing (external quality assurance) was established by the College of American Pathologists in the early 1960s, which enabled laboratories to regularly compare their performance against their peers at measuring the constituents of the provided sample material (20). Today, most developed countries have well established national external quality assurance programmes for laboratories to participate in (21). Automation of laboratory testing together with regulatory requirements for laboratory quality control systems has seen a reduction in analytical error from 16.2% in 1947 (22) to 1.4% in 1996 (23). However, certain types of pathology tests are still prone to analytical error. Immunoassays in particular, suffer from interference that is difficult to identify, and the limitations of these assays should be considered before clinical decisions are made (24).

1.4.1.2 Pre- and Post-Analytical Error

Accreditation standards require pathology laboratories to maintain a quality management system containing procedures for all operations of the laboratory, including acquisition and processing of the sample to be tested (pre-analytical) and reporting of results (post-analytical) (25, 26). A study by Plebani and Carraro, in which 359 questionable pathology results (identified by clinicians) were investigated, revealed that the majority of laboratory errors (68.2%) occurred in the pre-analytical

phase of testing (27). Analytical error accounted for only 13.3% of laboratory errors, while post-analytical error (most commonly involving a lack of communication between the laboratory and clinicians) contributed 18.5%. A literature review of laboratory errors revealed that even with different study designs, the distribution of error between the phases of testing was similar (28). Medians calculated across the seven studies reviewed, for the proportion of error occurring in each phase, were: 56% pre-analytical, 19% analytical and 19% post-analytical. These findings highlight the need for laboratories to widen their focus on error prevention to pre- and post-analytical processes.

In order to drive quality improvement, a list of quality indicators for pathology laboratories to monitor their pre-, intra- and post-analytical performance has been compiled by a working group of the International Federation of Clinical Chemistry and Laboratory Medicine (29). Performance data is being collected from laboratories around the world so that benchmarks can be set for each of these indicators. Initiatives such as these will improve the reliability of laboratory results, but efforts in the prevention of error must go beyond the walls of the laboratory in order to minimise failures in diagnostic testing. The number and complexity of pathology tests is constantly growing, making it increasingly difficult for clinicians to select the right test and correctly interpret the results. Evidence suggests that including a pathologist in the diagnostic team results in a reduction in the number of tests ordered and the prevention of misdiagnosis due to incorrect result interpretation (30, 31). In the United States, the main barrier to collaboration between clinicians and pathologists appears to be a fee-for-service payment system that lacks financial incentives for clinicians to collaborate with other health care professionals by rewarding procedural care over cognitive care (12). Another barrier (in the United States) is that many pathologists currently lack the confidence or skills to provide interpretations to clinicians asking diagnostic questions, due to their history of nonparticipation in the diagnostic process (32).

1.4.1.3 Timeliness of Diagnostic Testing

Time is an important factor in the diagnostic process. Most diseases evolve over time, and diagnosis may take days, weeks, or even months to establish (12). Some health problems need to be identified very quickly, when immediate medical action is required to prevent serious harm. In such circumstances, it is imperative that diagnostic testing is performed expeditiously to prevent delayed diagnosis. Missed diagnosis may occur if a test result is not available to a health care provider in time for a follow up appointment with a patient, or before the patient is discharged from hospital. Thus the timeframe in which diagnostic testing is performed (turnaround time) should be closely monitored and kept to a minimum.

Many pathology laboratories measure turnaround time based on the time interval between arrival of the test sample to the laboratory and release of the test result, as this period is within the

laboratory's control (33). From a clinician's (and patient's) point of view, the turnaround time is the time between the decision to order a test and the action taken in response to the test result. In 1975, Lundberg modelled the clinician's view of turnaround time in his "brain-to-brain turnaround time loop" (Figure 2), a nine step process for performing a laboratory test that starts and ends inside the clinician's brain (34). He reasoned that since clinicians typically lay blame for delayed results entirely on the laboratory, laboratories should take management control of or exert influence in each of the nine steps to ensure that the loop is closed promptly and efficiently. Three years earlier, Lundberg published his laboratory's novel, patient-focused approach for reporting "critical results" (i.e., results that represent an immediately life-threatening state unless clinical action is taken) (35). A short list of critical result thresholds was defined, and upon measurement of a critical result, laboratory staff immediately delivered the result by telephone to a clinician responsible for the patient. This approach ensured swift closure of the brain-to-brain loop in situations where even the slightest delay in diagnosis could have dire consequences. Lundberg's critical result reporting system was well-received by pathology, which soon led to its incorporation into laboratory accreditation standards (36).

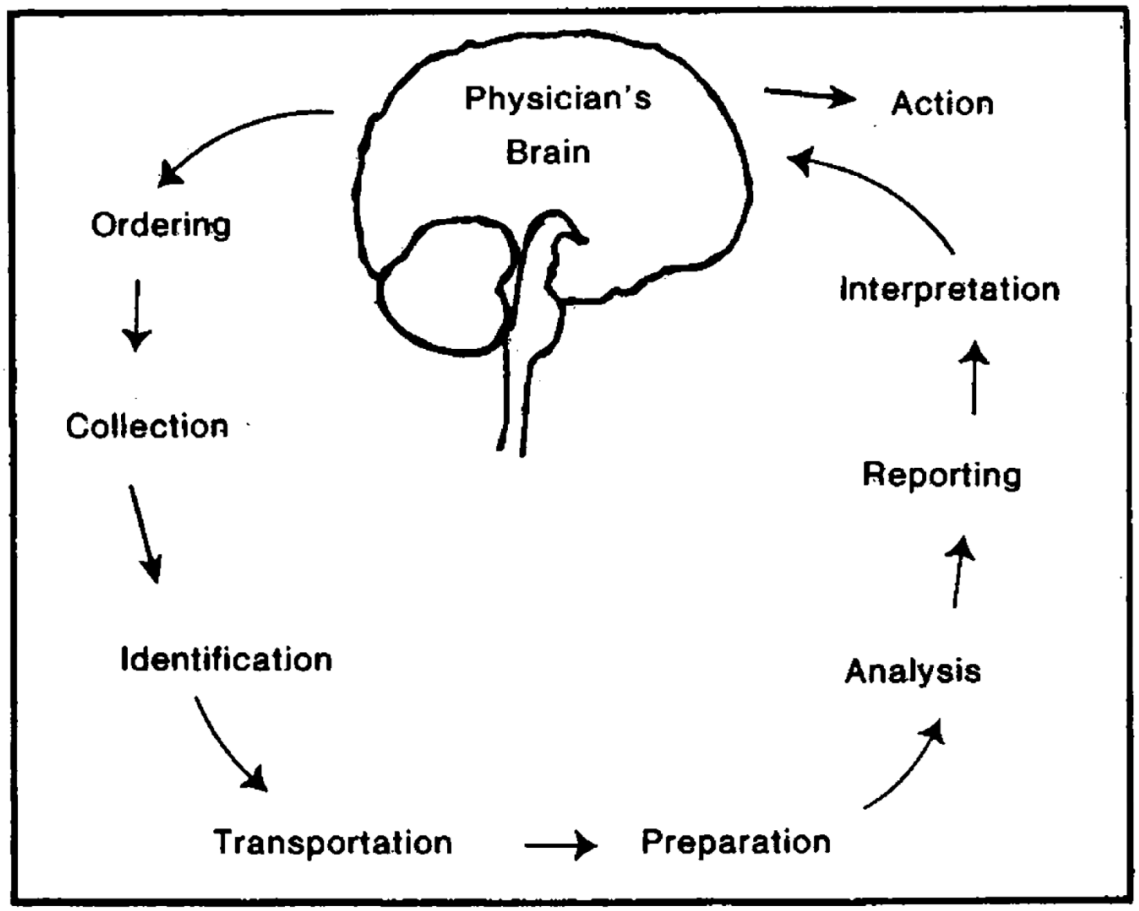

Figure 2: The brain-to-brain turnaround time loop. *Republished with permission of American Medical Association, from "Lundberg GD. Acting on significant laboratory results. JAMA 1981;245:1762-3."; permission conveyed through Copyright Clearance Center, Inc.*

1.5 Laboratory Management of Critical Results

From the outside, one would expect that communication of critical pathology results would be a straightforward, trouble-free task. However, due to a lack of consensus on which results to define as critical, difficulties in identifying and locating a clinician responsible for a patient, confusion over test follow up responsibilities across clinical handovers, and information overload for clinicians due to the vast number of results produced by the laboratory, failure to communicate and follow up on critical results is recognised as a global issue (37-41). Formal procedures for handling critical results are needed both within the laboratory and at the point of care, to ensure that critical results are reliably communicated and acted upon in a timely manner.

Although it is standard practice for laboratories to immediately communicate critical results to a clinician (or other authorised health professional) (25), there is little guidance available on how to design safe and reliable procedures for managing critical results. National surveys of laboratories reveal variations and gaps in critical result management practices including: how critical result threshold lists are compiled, acceptable modes of result communication, who is qualified to deliver the results, who is qualified to receive results, acknowledging receipt of results, handling results similar to previous, and record keeping (42-49). Harmonisation of critical result management is required to ensure that all laboratories follow best practice. This is most easily achieved at a national or provincial level through pre-existing professional relationships between laboratories. Recommendations for designing safe critical result management procedures have been produced in a few countries to promote local harmonisation (50-53).

The ”International Organization for Standardization” accreditation standard for pathology laboratories (ISO 15189) requires laboratories to determine their own list of critical result thresholds (25). Laboratories typically refer to the literature, their own experience and data, recommendations from their test manufacturers, and thresholds used by their peers when compiling their list (42, 45, 46, 48, 49). Most laboratories outside of the United States do not consult with their clinician users regarding the suitability of selected thresholds (42, 45, 46, 48, 49). This lack of engagement is at odds with the first recommendation of the IOM report addressing diagnostic error, which calls for enhanced collaboration between pathology and clinicians in order to improve diagnostic testing processes (12). It is interesting to note that the previous edition of the ISO 15189 standard required the laboratory to determine its list of critical result thresholds “in agreement with clinicians using the laboratory” (54). The removal of the need for clinician involvement in the current version of the standard was likely in acknowledgement of the difficulty laboratories face in reaching consensus between clinical users, who often have opposing views on which results require immediate communication.

Well-designed outcome studies associating test result concentrations with critical pathological responses would reduce grounds for disagreement over critical result thresholds. A threshold list built on such evidence could conceivably achieve universal consensus. Unfortunately, there is a lack of outcome data associated with critical results in the literature (42, 55, 56). The clinical significance of abnormal pathology results can vary in different patient populations and clinical settings, further complicating the ambition for a universal critical result threshold list. Some countries have produced "starter" lists of critical result thresholds for laboratories to adapt in collaboration with clinical users to fit their local setting (50, 53, 57). These starter lists are generally built on expert opinions and state of the art, which make the thresholds difficult to defend when challenged by individual clinicians with contrary views.

Critical results are most commonly defined based on their magnitude of difference from what is considered normal within a healthy population. This method of identification is easy to apply, but does not account for the fact that grossly abnormal pathology results are often seen in chronically ill patients who do not require medical attention as their condition is stable. A more reliable approach would be to monitor for deterioration in a patient's condition through the detection of sudden changes in laboratory results. However, for most tests the magnitude and timescale of change needed for a result to be critical is difficult to define due to a lack of outcome evidence or a lack of understanding of the pathophysiology of the change. Determining the baseline result for the delta calculation can also be challenging as patients most often present after they become ill, too late to provide a baseline measurement. Also, some laboratory information systems do not have the capability to perform time-factored delta checks; without consideration of the time interval, the suddenness of a change and the urgency for medical intervention is unknown.

The UK National Health Service standardised algorithm for detecting acute kidney injury provides an example approach for determining delta baselines (58). The baseline calculation in this algorithm determines the lowest serum creatinine measured in the previous seven days, and also considers the median serum creatinine over the previous year in case the seven day history is absent or only contains creatinine measurements post-acute impairment. Including the yearly history compromises specificity in order to improve sensitivity, as chronic kidney disease may be falsely identified as acute kidney injury.

1.6 Thesis Aims

The aim of this thesis was to establish evidence-based systems for the safe and effective management of critical pathology test results. To achieve this aim my research focused on four objectives:

1. To review the current status of international critical result management practices and highlight key areas where consistent management practices are necessary and feasible.

2. To systematically review the critical result thresholds used for clinical chemistry, haematology and endocrinology tests, and provide an explicit and ranked source of evidence for each of the values.

3. To develop an evidence- and risk-based methodology for the identification and verification of critical result thresholds.

4. To assess the value of using serum creatinine critical delta thresholds to identify patients with acute kidney injury across four public hospitals in the in the South-Eastern Sydney/Illawarra regions of New South Wales, Australia.

1.7 Thesis Structure

This thesis is comprised of four peer reviewed journal articles, of which three have been published and the fourth has been accepted for publication. The first article, presented in chapter two, contains a narrative review of current international critical result management practices, highlights key areas where consistent management practices are needed, and offers a conceptual framework for designing evidence-based critical result management systems. Chapter three provides the second article, a systematic review of critical result thresholds with an explicit and ranked source of evidence for each of the values. The third article, a risk-based methodology for the identification and verification of critical result thresholds, is shown in Chapter four. The fourth article, contained in chapter five, presents a retrospective study across four public hospitals in which serum creatinine critical delta thresholds were applied in order to identify patients with AKI. Chapter six provides an overall discussion of what was achieved in the thesis, the impact of the work on pathology laboratories, and the implications for health care in Australia.

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Chapter 2

The current status of international critical result management practices

2.1 Chapter Background

The International Organization for Standardization (ISO) and the accreditation standards of the College of American Pathologists require pathology laboratories to have a system in place to manage critical results (1, 2). However, at the time the article in this chapter was published, there was no guidance for laboratories on how this management system should be constructed or what features it should possess (with the exception of a small number of local safe practice recommendations used within a few countries (3-6)). Laboratory surveys conducted in a number of countries reveal large variations and gaps in critical result management practices (7-13). These findings highlight the need for a standardised and harmonised approach to critical result management in order to improve patient safety.

The article in this chapter provides a narrative review of existing international laboratory practices in the management of critical results. The need for clearly defined and harmonised terminology within management policies and procedures is emphasised. The wide variety of alternative terms currently used to describe the results and thresholds are assessed for their literal relevance, and new, more explicit terminology is proposed. Current international practices are described for each component of a critical result management system; and steps within the procedure that pose a high risk to patient safety when not strictly followed, are identified as requiring harmonisation. Recommendations are provided to assist laboratories with the creation of their critical result threshold list, including: the need to consult with clinicians and refer to treatment protocols when deciding which tests belong on the list; and, the need for selected critical result thresholds to be traceable to their source. An evidence based approach for selecting alert thresholds of the highest quality is described.

This was an invited article, which was peer reviewed and published in a special issue of *Clinica Chimica Acta* on global activities in the harmonisation of laboratory testing. It directly addresses objective one of the thesis, by reviewing the current status of international critical result management practices and highlighting key areas where consistent management practices are

necessary and feasible. The article also introduces concepts and the foundations of methodology for: a systematic review of critical result thresholds with an explicit and ranked source of evidence for each of the values (objective two); and an evidence-based approach for the identification and verification of critical result thresholds (objective three).

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2.3 Article I - Harmonization of Critical Result Management in Laboratory Medicine

Harmonization of critical result management in laboratory medicine

CA Campbell[1], AR Horvath[1,2,3]

[1]SEALS Department of Clinical Chemistry, Prince of Wales Hospital, [2]Screening and Test Evaluation Program, School of Public Health, University of Sydney, and [3]School of Medical Sciences, University of New South Wales, Sydney, NSW 2031, Australia

Abstract

Unsafe medical care is a major source of disabling injuries and death throughout the world. The failure to notify, follow up, and action critical results, which signify life threatening situations, are of particular concern and may cause avoidable morbidity and mortality. International accreditation standards require pathology laboratories to have a system for the timely and reliable communication of critical results to clinical personnel responsible for patient care. In response, various practices and a number of different terminologies have been described in the literature. Increased attention to patient safety standards and multinational surveys, however, highlighted shortcomings and inefficiencies in existing communication systems. These failures and variations in practice call for clear guidance and harmonization of approaches in order to improve communications and to provide safer patient care. The objectives of this review are to create a harmonized terminology and to learn from international practices by systematically reviewing the best available evidence on existing

approaches. Based on literature review findings we highlight key areas where harmonization is necessary and feasible and offer a conceptual framework and methods for designing better and more evidence-based systems for the timely notification of laboratory results that represent potential patient safety hazards.

Key words: alert result; critical result; laboratory medicine; patient safety

Abbreviations: Clinical Laboratory Improvement Amendments: CLIA; European Federation of Clinical Chemistry and Laboratory Medicine: EFLM; ISO: International Organization for Standardization; United States of America: USA or US; United Kingdom: UK; World Health Organization: WHO

Introduction

Medical tests should only be requested if the results of the tests will be used to influence subsequent management decisions of the patient. As trivial as it may sound, laboratory professionals all over the world know too well that many of the test results that are released to clinicians in vast numbers with rapid turn-around times are not followed up in a timely manner and may have no beneficial impact on patient management. This is of particular concern when critical results are involved, as they signify situations which may be life threatening or lead to irreversible damage or harm to the patient and which therefore require immediate or timely medical intervention. Unsafe medical care is a major source of disabling injuries and death throughout the world. In 2008 a report, published by the World Health Organization World Alliance for Patient Safety, identified poor test follow up as one of 23 topics that have a substantial impact on the safety of medical care *(1).* The rate of test follow up was found to be suboptimal across the globe, with communication of test results between the laboratory and physicians being one area that needs improving. A systematic literature review of evidence between 1990 and 2010 revealed a lack of test follow up for up to 60% of hospital inpatients, and up to 75% for patients treated in the emergency department *(2).* Critical test results were identified as one area where problems were particularly evident. In the United States the National Quality Forum's list of serious reportable events in 2011 included two new laboratory-related errors leading to serious injury or death of patients. One of these reportable errors was due to the failure to follow up or communicate laboratory, pathology or radiology results *(3).* In 2010, the Clinical Excellence Commission Patient Safety Team analysed data collected from the New South Wales Incident Information Management System to review and identify how access and follow up of diagnostic test results affected patient outcomes *(4).* Findings of the review indicated that failure in processes associated with obtaining and using diagnostic test results have the potential to seriously compromise patient safety. Issues identified included timeframes for test reporting being poorly defined and unrelated to clinical urgency; pending results that are potentially critical never being reviewed by the treating team; no consistent mechanisms exist for clinicians to identify critical results which have not been reviewed; and considerable variability in the process for communicating unexpected or significantly abnormal results.

Automation and information technology revolutionized the delivery of laboratory services and we have almost limitless opportunities to communicate test results on various devices faster and closer to the clinician and patient than ever before. Paradoxically, the vast amount and rapid flow of data contribute to information overload and communication breakdowns and, as a consequence, to increasing medical error rates. Therefore laboratories have even greater responsibility of controlling post-analytical and post-post-analytical processes and offering solutions that help to reduce medical error rates and improve the effectiveness and timeliness of medical decisions *(5).*

It was over 40 years ago that Dr George D. Lundberg reported the implementation of the first formal critical result communication system in Pathology at the Los Angeles County USC Medical Center. Lundberg coined the term of 'critical result' as a laboratory test result representing a pathophysiologic state so abnormal that it is life-threatening if action is not taken quickly and for which an effective action is possible *(6)*. A short list of critical limits (i.e., upper and/or lower

thresholds for a test outside of which a result would be critical) was compiled, and once a critical result was recognised by a laboratory technologist, it became the responsibility of the laboratory to urgently and personally communicate it to the physician responsible for the patient. Although not initially published in a peer-reviewed journal, the critical result system gained rapid acceptance *(7).* It was widely implemented in a very short time and soon became a laboratory accreditation requirement *(8-11)*. Lundberg claims that the rapid success of his critical result system was largely due to the initial critical list only containing limits that were clearly life threatening *(7).* Subsequently, Lundberg proposed that laboratories should also have a system for communicating important (according to his terminology "vital") but less urgently reportable results *(12).*

Since Lundberg's pioneering work and in response to accreditation requirements, many laboratories have implemented critical result communication systems. Various practices and a number of different terminologies have been described in the literature, while increased attention to patient safety standards highlighted shortcomings and inefficiencies in existing communication systems. These failures and variations in practice triggered a number of national organizations to investigate their current practices and, based on findings, formulate recommendations for a more harmonized and systematic approach for notifying clinicians about abnormal test results that need urgent or timely medical attention. These published multinational surveys and recommendations provide the backbone of this review. We will discuss in more detail below what can be learnt from the synthesis of the evidence and how that information can support global harmonization initiatives in this area.

The objectives of this review are to 1/ create a harmonized terminology; and 2/ reflect on the current status of international practices. Based on findings of the review of the literature we 3/ highlight key areas where harmonization is necessary and feasible; and 4/ offer a conceptual framework and methods for designing better and more evidence-based systems for the timely notification of laboratory results that represent potential patient safety hazards.

Need for Harmonized Terms and Definitions

Singh and Vij have made eight very useful practical recommendations for policies and practices of communicating abnormal test results *(13).* Their first recommendation emphasizes the importance of clear definitions in order to provide credibility to the policy and to ensure a common understanding across a broad range of users. For clarity and harmonization of terminology we present currently used and published definitions together with their most common alternative synonyms and our proposed terms (Table 1).

Current patient safety goals require timely communication and follow-up of abnormal diagnostic test results to avoid medical errors, adverse events, and liability claims *(13).* There is significant confusion in this area of what type of laboratory tests and results should be communicated to clinicians and how one should define the various categories of abnormal test results that need urgent or timely clinical notification. Due to differing clinical significance and priority, similarly to a number of authors *(12,13)*, we highlight the importance of clearly differentiating life-threatening *critical results* from non-life threatening *significantly abnormal results. Critical results* may signify a pathophysiologic state that is potentially life threatening or that could result in significant patient morbidity or irreversible harm or mortality and therefore requires urgent medical attention and action *(6,10,13-16). Significantly abnormal results* are not life threatening but they require medical attention and follow up action within a medically justified timescale, and for which timing is not as crucial as for critical results (Table 1) *(12,13).* We suggest that no terms that refer to 'values' (i.e. critical, panic, crisis, alarm value) are used as not all laboratory results that need notification have quantitative values (e.g. microbiological cultures or semiquantitative tests are reported as positive or negative). We also propose that terms such as 'panic' or 'crisis' or 'alarm' are avoided because they suggest that no systems are in place for managing such results in a professional manner.

A simple umbrella term for these various categories of notification priorities would be helpful but no terms in the literature seem to be appropriate so far. The various meanings of the term 'alert' may

Table 1: Key definitions

Commonly used term	**Alternative terms**	***Published term*/definition**	**Source**	***Proposed term*/definition**
Critical result	– critical value – panic value – crisis value – critical alarm – alarm value	A *critical (or panic) laboratory value* is a laboratory test result that represents a pathophysiologic state at such variance with normal as to be life-threatening if an action is not taken quickly and for which an effective action is possible.	*(6)*	*Critical result:* A test result which may signify a pathophysiological state that is potentially life threatening or that could result in significant patient morbidity or irreversible harm or mortality and therefore requires urgent medical attention and action.
		Critical result: Any result or finding that may be considered life threatening or that could result in severe morbidity and require urgent or emergent clinical attention	*(13)*	
		A *critical test result* is defined as those values or interpretations that, if left untreated, could be life threatening or place the patient at serious risk.	*(14)*	
		Critical test results: any values/interpretations for which delays in reporting can result in serious adverse outcomes for patients.	*(15)*	
		Alert or critical values are those results that may require rapid clinical attention to avert significant patient morbidity or mortality.	*(10)*	
		Markedly abnormal laboratory test result: a result that may signify a pathophysiological state that may be life-threatening or of immediate clinical significance and that requires urgent action.	*(16)*	
Significantly abnormal result	– vital result – life-altering result – alert value – markedly abnormal result of medical significance	A *vital value* is a laboratory result just as important as a critical value, but one for which timing is not as crucial.	*(12)*	*Significantly abnormal result:* A test result that is not life threatening but that requires a timely medical attention and follow up action within a medically justified timescale.
		Significantly abnormal result: No-emergent, non-life-threatening results that need attention and follow-up action as soon as possible, but for which timing is not as crucial as critical results.	*(13)*	
Critical test		*Critical test:* Tests that require rapid communication of results, whether normal, abnormal, or critical	*(13)*	*Critical test:* A test that requires rapid communication of the result irrespective whether it is normal, significantly abnormal or critical.
Critical limit	– critical value limit – alarm limit – alert limit – action limit – critical or alert interval or range – critical decision limit or threshold	*Critical limits* define the lower and upper boundary values of diagnostic test results that represent life-threatening and also actionable knowledge for clinical therapeutic decisions.	*(17)*	*Alert thresholds:* The upper and/or lower threshold of a test result or the magnitude of change in a test result within a critical or clinically significant time scale beyond which the finding is considered to be a medical priority warranting urgent or timely action.
		Critical limits reflect medical thresholds for emergency patient evaluation and optimization decision points for critical care	*(17)*	
		Critical or alert limits are the values of laboratory measurements that are regarded as requiring urgent clinical attention and should be communicated to a clinician urgently.	*(19)*	
Critical list				*Alert list:* A list of laboratory tests, including critical tests and non-critical tests with alert thresholds for critical and/or significantly abnormal results that reflect an agreed policy between laboratory and clinical staff for rapid communication within a pre-specified time frame and according to a procedure.

probably be more suitable as this term describes in the broadest sense the actual problem and the typical actions that follow. In addition, this word can be used as a noun, adjective and verb and provides flexibility in describing subsequent definitions discussed below. According to various dictionaries the noun 'alert' refers to i) a signal that warns of danger; ii) a condition or period of heightened watchfulness or preparation for action. As an adjective it means i) vigilantly attentive, watchful; ii) mentally responsive and perceptive; iii) quick (http://www.thefreedictionary.com/alert); iv) watchful and prompt to meet danger or emergency; or v) quick to perceive and act (http://www.merriam-webster.com/dictionary/alert). As a verb it means to alarm, forewarn, inform, notify, signal, or warn someone (http://dictionary.reverso.net/english-synonyms/alert). We propose using the umbrella term of *alert results* and in this review we will also refer to this term when we discuss policies and practices related to both critical and significantly abnormal laboratory results. We propose retaining the well-embedded terms of 'critical results' and 'significantly abnormal results', when reference is specifically made to such scenarios and practices.

Critical test refers to a test that requires rapid communication of the result to guide further management decisions of medical urgency irrespective whether it is normal, significantly abnormal or critical *(13)* – e.g. Troponin results in all requests from the emergency department, paracetamol results in suspected overdose cases, haematology and coagulation results in suspected disseminated intravascular coagulation, xanthochromia results in suspected subarachnoid haemorrhage, methotrexate results to guide the optimal timing of leucovorin rescue, or tests in cerebrospinal fluid when meningitis is investigated.

Kost and Hale define *critical limit*s as the lower and upper boundary values of diagnostic test results that represent life-threatening and also actionable knowledge for clinical therapeutic decisions *(17-19)*. This term has many synonyms, such as critical value limit, alarm or alert limit, critical or alert interval or range, critical decision limit or threshold, etc (Table 1). Some authors propose the term, 'action limits' *(16),* but we (would prefer to) believe that all laboratory results requested, irrespective of their degree of abnormality, will lead to some form of medical decisions or actions, even if the decision or action is only watchful waiting or monitoring. In our view none of these alternative terms encapsulate the current requirements of achieving better patient safety goals by notifying not just life-threatening (i.e. critical) but also medically important, non-life-threatening (i.e. significantly abnormal) results. Another shortcoming of the current definitions is that they refer to single critical limits and do not include rapid changes in test results which could also be critical or significantly abnormal requiring timely medical intervention. Therefore we propose broadening this term to *alert threshold*s which define the upper and/or lower thresholds of a test result or the magnitude of change in a test result within a critical or clinically significant time scale beyond which the finding is considered to be a medical priority warranting urgent or timely action. We prefer using the word threshold rather than limit as, according to the Oxford Dictionary, threshold refers to the "magnitude or intensity that must be exceeded for a certain reaction, phenomenon, result or condition to be manifested" (http://oxforddictionaries.com/definition/english/threshold). This generic definition encapsulates the impact on test results and the consequences in patient's condition once a threshold is exceeded. In the same dictionary, *threshold level* is defined as "the level at which one starts to feel or react to something". Again, we find that this definition covers both how the patient may be affected and how the laboratory personnel and clinician should react when alert threshold levels of certain laboratory tests are reached or passed. Different alert thresholds applicable to critical and significantly abnormal results and for different clinical scenarios and settings, as well as allocating different priorities and timescales to their communication will be discussed in later chapters.

In the same vein, we propose the use of the broader term of alert list to replace the term of *critical list.* In the context of laboratory medicine, *alert list* refers to a list of laboratory tests, including critical and non-critical tests with alert thresholds for critical and/or significantly abnormal results that reflect an agreed policy between laboratory and clinical staff for rapid communication within a pre-specified time frame and according to a procedure.

Need for Harmonized Policies and Procedures

As mentioned earlier, international accreditation and patient safety standards require pathology laboratories to have a system for the timely and reliable communication of alert results to clinical personnel responsible for patient care *(8-11).* Such systems should address the following issues:

- who should define alert lists;
- what should be defined in alert lists;
- how alert results are verified;
- what is the timeframe of communication;
- what communication channels are used for delivering alert results;
- who should deliver and receive the results;
- how is receipt of the results acknowledged;
- what communication details need to be recorded;
- what escalation procedures are in place when communication is unsuccessful;
- how to assess performance and impact on patient outcome and safety?

Two paragraphs of the most commonly used accreditation standard, ISO 15189 indicate that "the laboratory shall have procedures for the immediate notification of a physician (or other clinical personnel responsible for patient care) when examination results for critical properties fall within established 'alert' or 'critical' intervals; and that the laboratory shall determine its critical properties and the 'alert'/'critical' intervals in agreement with the users of the laboratory" *(8)*. By definition, the ISO standards are usually brief and nonspecific and leave much room for interpretations. Some countries therefore developed explanatory notes or guidance documents to the ISO 15189 accreditation standard. Under the umbrella of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) we have surveyed 38 European countries in order to find out if they had any specific interpretations of the above mentioned two paragraphs in the standards. Out of 29 respondents (response rate 76%) only three countries, Hungary, Israel and the UK reported the availability of such additional guidance. It comes by no surprise then that national surveys run in various countries have shown significant inconsistencies and variations in alert thresholds defined by laboratories and in alert result notification practices *(19-29)*. Table 2 summarizes published survey findings of various management approaches and point to significant heterogeneity in practice both within and between countries *(22-29)*.

Who should define alert lists?

Communication of critical and significantly abnormal results should represent a shared policy between the laboratory and medical care providers. In spite of the mentioned requirements in ISO 15189, in most countries laboratory professionals are still often the sole stakeholders in determining which tests and what alert thresholds should be on their list. Consultation with clinicians in compiling alert lists was shown to be more widespread in the United States (USA) *(22)*. Alert lists are often defined solely on empirical, anecdotal, and commercial basis, or based on guideline or other literature sources. For a selection of common tests, one third of laboratories surveyed in the USA used published literature as the primary source for their alert thresholds, while another third used non-laboratory medical staff recommendations *(21)*. An Italian national survey revealed that 57% of laboratories used data from the literature to compile their alert lists, 37% adopted the recommendations published by Italian laboratory medical societies *(30),* and 21% based their alert thresholds on opinions from clinicians at their institutions *(25).* According to an Australian survey, resources used by laboratories to compile their alert lists include the laboratories' professional experience (62%), published literature (59%), international guidelines (41%), and consultation with doctors (41%) *(28)*. A survey conducted in Spain found that 52% of laboratories used their own data to establish their alert thresholds, 48% used the literature, and only 10% formed consensus with clinicians *(26).* Similarly low clinical consultation rates (13%) were found in the most recently

Table 2: National surveys on critical result management practices

Procedures	National Surveys							
	US 2002 *(22)* **(n=623)**	**US 2008***(23)* **(n=121)**	**US 2008** *(24)* **(n=731)**	**Italy 2010** *(25)* **(n=90)**	**Spain 2010** *(26)* **(n=157)**	**Thailand 2010** *(27)* **(n=242)**	**Australia 2012** *(28)* **(n=58)**	**China 2013** *(29)* **(n=599)**
Source of critical thresholds								
Literature				57%	48%		59%	
Consultation with clinicians	73%			21%	10%		41%	13%
When notification is not required?								
Result similar to previous	12%	36%					80%	<30%
Identification of critical results								
Retest sample to confirm result		all results - 56% some results - 31%				Private - 100% Govt - 100%		> 85%
Mode of notification								
Telephone	99%			89%	91%	Private - 89% Govt - 94%	inpatients - 96% outpatients - 92%	95%
Fax	30%			9%	17%	Private - 4% Govt - 1%	inpatients - 40%[a] outpatients - 60%[a]	0%
Computer	10%			18%	6%	Private - 30% Govt - 20%	EMR[b] alert - 4%	
Who should deliver critical results?								
Laboratory technician	inpatients - 91% outpatients - 77%	99%	91%	11%	scientist or pathologist - 87%		~ who performed test - 67%	> 90%
Section head	inpatients - 3% outpatients - 4%						67%	
Laboratory manager/director			8%	69%				
Doctor on call/duty				14%			29%	
Call centre		10%	18%	0%			2%	
Who should receive criticalresults?								
Requesting physician or physician caring for patient	inpatients - 9% outpatients - 17%	93%	75%	inpatients - 37% outpatients - 80%	87%		96%	95%
Physician on call	inpatients - 4% outpatients - 7%			inpatients - 18%				
Nurse	inpatients - 56% outpatients - 35%	91%	62%	inpatients - 29%	3%		75%	0%
Timeliness of reporting								
Delivery within set time limits		61%[c]			38%		54%	
Acknowledgement of receipt of result								
Read back of result			91%	62%		Private - 81% Govt - 72%	46%	
Recording result notification								
Requirement to record result notification		99%		58%		Private - 65% Govt - 74%		

n: number of laboratories participating in the survey; [a] mode of transmission - by fax or email; [b] EMR - electronic medical record system; [c] Timeframe approved by clinicians within last 12 months

published Chinese survey *(29).* Don-Wauchope *et al.* surveyed 115 physicians from two Canadian hospital corporations to assess the appropriateness of 11 alert thresholds in use by the laboratory. It was found that 7 thresholds did not meet the expected level of acceptance and thus required review *(31).* This again highlights the importance of consultation with clinician groups when laboratories assemble their alert list.

What should be defined in alert lists?

A key area of debate and confusion is which laboratory tests should be included in alert lists and what alert thresholds should trigger notification. National surveys point to significant disparities (Figure 1, Table 3-5). Figure 1 summarizes the frequency of tests for which published surveys collected alert threshold data, suggesting that these are the most likely tests that are expected to be included in most clinical biochemistry laboratories' lists. Table 3 shows the frequency of the most common biochemistry tests that laboratories reported in various surveys on adult alert thresholds. These data demonstrate the level of heterogeneity in judging which common biochemistry tests should be on the laboratory's alert list. Frequencies in Table 3 are not directly comparable due to differing designs of each survey and whether they addressed hospital inpatient or general practice patient settings. Data from Spain illustrate that laboratories have differing policies for phoning critical results for inpatient wards, where such results are more expected, than for outpatient settings where critical results are less common and might need to trigger urgent referral to hospital *(26)*. Findings of the Chinese survey, however, highlight somewhat differing practices of more frequent notifications of hospital wards than outpatient clinics *(29)*. This may be explained by the difficulties in the logistics of managing critical outpatient communications, rather than by real clinical needs. These variations may be attributed, in part, to differences in the patient populations and clinical settings that laboratories serve, as well as differences in the test methodologies they employ *(32).* However, the lack of published evidence-based clinical outcome data for all but a handful of laboratory medicine tests is probably the main contributor to the disparity in critical list composition between laboratories *(22,31,33).* Irrespectively, one would imagine that at least certain tests, such as sodium, potassium, glucose, and calcium would be on all laboratories' alert list since these are parameters where we have fairly firm understanding of pathophysiology and some evidence from guidelines and outcome studies showing the association of analyte concentrations with critical pathological responses *(17, 34-36).* For example, while blood glucose is included in all Australian laboratories' alert list, in other countries it is only on the list in 60-70% of survey participants. Similarly, except for Australia and the USA, only 60-75% of surveyed laboratories in other countries seem too provide alert thresholds and notification protocols for potassium.

Critical tests that are always reported regardless of the result are rarely defined and most national surveys have not addressed this question in sufficient detail to draw meaningful conclusions. In many institutions, alert lists are extended to include significantly abnormal or medically important results that are not particularly time sensitive *(33,37).* Some authors recommend more *customized approaches* whereby laboratory professionals review and assess the need for notifying alert results based on requester characteristics, patient location, medical history, previous results, laboratory result patterns, reflex testing algorithms, etc *(17, 38-40).* Alert lists that are too inclusive can greatly increase the number of telephone calls, which desensitises medical staff to truly critical results requiring immediate action as well as placing unnecessary burden on laboratory staff *(15,32,37).* On the other hand, lists that are too exclusive (or have thresholds that are too high or low) may lead to life threatening situations not being attended to *(32,37).*

Another area of contention is the selection of *alert thresholds*. The guiding principle for deciding alert thresholds should be that they represent clinical decision thresholds that trigger appropriate actions in order to prevent harm and improve patient outcomes *(28).* Table 4 and 5 show the adult median and range of the lower and upper alert thresholds for critical results of commonly used tests reported in surveys. While median values show fairly good agreement across the globe, the range of results in those surveys highlights sometimes substantial variations between laboratories. Alert lists can become quite complex and may include differing thresholds for critical and significantly

Table 3: Most common biochemistry tests on adult alert lists in published surveys

Laboratory test	US 2002*(22)* (n=623)	UK 2003 *(19)* (n=87)		US 2007 *(21)* (n=163)	Spain 2010 *(26)* (n=36)		Australia 2012 *(28)* (n=36)[a]	China 2013 *(29)* (n=246[b], n=599[c])		
		Phone to ward	Phone to doctor		Outpatients	Hospitalised		Emergency	Inpatients	Outpatients
Glucose (blood)	58%	62%	60%		72%	58%	100%	≈60%	≈90%	≈70%
Potassium	49%	63%	63%	99%	75%	58%	100%	≈65%	≈95%	≈70%
Sodium	43%	63%	63%	98%	75%	58%	97%	≈60%	≈90%	≈70%
Digoxin			44%				93%			
Lithium			40%	75%			92%			
Magnesium	9%	35%	30%	82%			88%			
Carbamazepine			26%				85%			
Phenytoin			35%				83%			
Amylase			39%		42%	22%	75%			
ALT					31%		73%			
Theophylline			24%				70%			
Bicarbonate	83%	17%	10%	84%			68%			
Creatinine	61%		28%	53%	61%	47%	67%	≈40%	≈60%	≈45%
Phenobarbitone			21%				67%			
Troponin T							67%	≈5%	≈10%	≈5%
Salicylate							65%			
Arterial pH	46%			56%			64%	≈70%	≈90%	≈65%
CK (total)							64%			
Phosphate	58%			64%	39%	25%	64%			
Calcium (corrected)		37%	37%				63%			
Calcium (total)	83%	33%	33%	98%	72%	58%	62%	≈60%	≈85%	≈65%
Paracetamol							62%			
Arterial pCO2	45%			56%			58%	≈65%	≈80%	≈60%
Lactate	86%						54%			
Urea	86%		41%		58%	39%	53%	≈40%	≈60%	≈45%
Troponin I				49%			53%	≈20%	≈25%	≈20%
Arterial pO2				56%			48%	≈65%	≈80%	≈60%
AST					33%		41%			
Ammonia	46%						41%			
Calcium (ionised)	17%						41%			
Glucose (CSF)	64%						30%			
CRP							29%			
Osmolality	86%						29%			
Triglyceride							29%			
Bilirubin				85%			25%			

Legends to Table 3:

Frequency (Australia 2012) = No. of laboratories that provided alert thresholds x 100% / No. of laboratories that perform that test
Frequency (all other surveys) = No. of laboratories that provided alert thresholds x 100% / No. of laboratories that participated in survey
n = number of laboratories participating in the survey
[a] Out of 58 survey participants, 36 laboratories provided alert lists. Responses from laboratories within a large public or private pathology network, if they used the same alert list, were included only once.
≈: approximately equal to (NB: the Chinese survey did not provide raw data; therefore percentages could only be approximated from Figures)
[b]: blood gas questionnaires
[c]: chemistry questionnaires

Figure 1: Laboratory tests considered important in published surveys to be included in alert lists

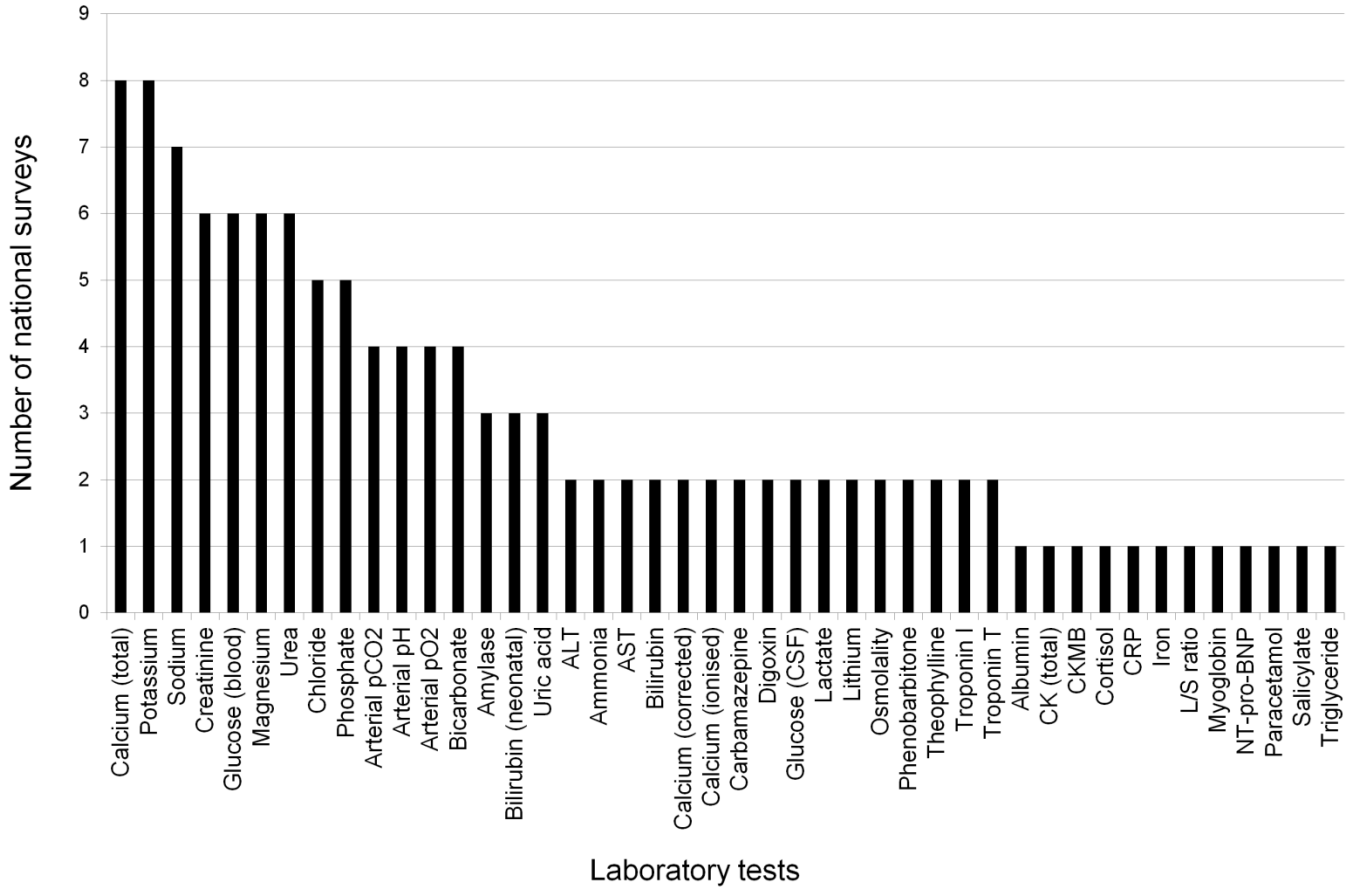

Table 4: Range of lower alert thresholds of common biochemistry tests in published surveys

Analyte	Units	US 2002 *(22)* Median (p10 – p90)	UK 2003 *(19)* Mean (Range)	US 2007 *(21)* Median (p5 – p95)	Italy 2010 *(25)* Median (p5 – p95)	Spain 2010 *(26)* Outpatients Median (p10 – p90)	Thailand 2010 *(27)* Mean (± SD)	Australia 2012 *(28)* Median (Range)	China 2013 *(29)* Median (p5 – p95)
Sodium	mmol/L	120 (110 - 125)	122 (110 - 130)	-	120 (110 - 130)	120 (115 - 129)	121 (± 7.3)	125 (120 - 130)	120 (110 - 125)
Potassium	mmol/L	2.8 (2.5 - 3.0)	2.7 (2.0 - 3.0)	2.9 (2.5 -3.1)	2.8 (2.0 - 3.0)	2.8 (2.5 - 3.0)	2.6 (± 0.4)	2.8 (2.2 - 3.0)	2.8 (2.5 - 3.0)
Bicarbonate	mmol/L	10 (10 - 15)	12 (5 - 18)	-	-	-	11 (± 3.0)	15 (10 - 18)	-
Urea	mmol/L	-	-	-	-	-	4 (± 5.7)	-	1.2 (0.2 - 2.0)
Creatinine	umol/L	-	-	-	-	-	16 (± 8.8)	-	27 (10 - 43)
Glucose	mmol/L	2.20 (2.20 - 2.75)	2.4 (1.5 - 3.4)	-	-	2.50 (1.74 - 2.78)	2.58 (± 0.48)	2.5 (1.5 - 3.0)	2.5 (2.1 - 3.0)
Calcium (total)	mmol/L	1.50 (1.50 - 1.75)	1.75 (1.5 - 2.0)	1.53 (1.50 - 1.78)	1.7 (1.4 - 2.1)	1.65 (1.50 - 1.86)	1.59 (± 0.13)	1.78 (1.50 - 2.10)	1.60 (1.50 - 1.75)
Magnesium	mmol/L	0.49 (0.39 - 0.57)	0.48 (0.30 - 0.70)	0.40 (0.35 - 0.55)	0.50 (0.41 - 0.80)	-	0.46 (± 0.22)	0.4 (0.2 - 0.6)	-
Phosphate	mmol/L	0.32 (0.32 - 0.65)	0.39 (0.30 - 0.60)	-	-	0.32 (0.32 - 0.57)	0.38 (± 0.13)	0.4 (0.3 - 0.6)	-

Table 5: Range of upper alert thresholds of common biochemistry tests in published surveys

Analyte	Units	US 2002 *(22)* Median (p10 – p90)	UK 2003 *(19)* Mean (Range)	US 2007 *(21)* Median (p5 – p95)	Italy 2010 *(25)* Median (p5 – p95)	Spain 2010 *(26)* Outpatients Median (p10 – p90)	Thailand 2010 *(27)* Mean (± SD)	Australia 2012 *(28)* Median (Range)	China 2013 *(29)* Median (p5 – p95)
Sodium	mmol/L	160 (150 - 170)	154 (147 - 170)	-	160 (150 - 160)	160 (150 - 162)	158 (± 11.3)	155 (150 - 160)	160 (150 – 170)
Potassium	mmol/L	6.2 (6.0 - 6.5)	6.1 (5.5 - 7.0)	6.0 (5.9 - 6.5)	6.2 (5.5 - 7.1)	6.3 (6.0 - 7.7)	6.4 (± 1.0)	6.0 (5.4 - 6.9)	6.2 (5.8 – 7.0)
Bicarbonate	mmol/L	40 (40 - 45)	39 (35 - 50)	-	-	-	39 (± 1.7)	40 (40 - 45)	-
Urea	mmol/L	29 (18 - 36)	26 (15 - 50)	-	-	61 (18 - 87)	31 (± 13.3)	30 (12 - 45)	35.7 (20.0 – 37.8)
Creatinine	umol/L	442 (265 - 884)	419 (200 - 1800)	-	-	442 (264 - 654)	670 (± 407)	300 (180 - 618)	650 (442 – 1000)
Glucose	mmol/L	24.8 (16.50 - 38.50)	21.8 (10 - 50)	-	-	22.2 (16.7 - 27.8)	23.9 (± 5.8)	20.0 (8.0 - 30.0)	22.2 (15.0 – 30.0)
Calcium (total)	mmol/L	3.25 (3.00 - 3.50)	3.1 (2.8 - 3.5)	3.25 (3.00 - 3.50)	3.2 (2.7 - 3.5)	3.25 (2.96 - 3.50)	3.29 (± 0.37)	3.00 (2.60 - 3.50)	3.50 (3.00 – 3.55)
Magnesium	mmol/L	1.91 (1.23 - 2.50)	1.83 (1.10 - 3.50)	2.05 (1.25 - 2.90)	2.00 (0.93 - 2.90)	-	2.11 (± 0.53)	2.0 (1.4 - 4.0)	-
Phosphate	mmol/L	2.58 (1.78 - 3.23)	-	-	-	2.87 (1.95 - 2.91)	2.81 (± 0.56)	3.0 (2.5 - 4.0)	-
Amylase	U/L	-	344 (70 - 1500)	-	-	375 (130 - 1000)	-	350 (90 - 1000)	-

p: percentile

abnormal results. Age, sex or other patient characteristics related to the condition or treatment, case mix and healthcare settings may also influence the selection of thresholds for notification.

Extensive data from various US national surveys reveals that adult and children's hospitals chose different alert threshold levels *(41).* A comparison of the thresholds used for urea, creatinine, platelets and prothrombin time suggests that children's hospitals are more conservative in their surveillance of renal and haemostasis problems. However, non-specialized hospital laboratories rarely use age related alert thresholds with the exception of newborns, where the first 28 days of life sees dramatic and rapid physiological changes in the respiratory, cardiovascular, hepatic, haematological and renal systems *(41,42).* A US survey revealed that 67% of laboratories used unique thresholds for populations distinguished by age, 16% for health care setting, and 10% for disease type. No laboratories reported unique thresholds for ethnicity *(21).* In the Australian survey, 97% and 81% of laboratories have thresholds for critical and significantly abnormal results, respectively. Some laboratories reported different policies for outpatients (21%), tests performed out-of-hours (27%), physicians external to their institution (8%), and tests performed on behalf of referral laboratories (4%) *(28).* The Royal College of Pathologists in the UK has issued a master list of alert thresholds for out of hours reporting to general practitioners in which it also used some age-dependent thresholds (Table 6) *(16).*

As highlighted in the definitions section, rapid changes in laboratory results might also indicate life threatening situations, which could go unattended if critical result reporting is performed solely on the basis of critical limits. For instance, overzealous correction of hyponatraemia can cause central pontine myelinolysis, an irreversible neurological condition with grave consequences for patients *(43).* Thus alert lists should contain rules to help laboratory staff identify significant changes in results that need clinical notification. Previous research based on patient's laboratory results at a hospital in Salt Lake City identified 60 potentially life-threatening conditions. Due to their medical implications and relative high frequency, a subset of these conditions was selected and evaluated by six experts in surgery, cardiology, internal medicine and critical care. Criteria for alerting to these situations, including dangerously rapid changes in test results (Table 6), were programmed into an electronic laboratory alert system *(44).*

Policies and practices are inconsistent about the needs for communicating *repeatedly critical results*. The Joint Commission (a health care organisation accrediting body in the USA) allows critical results to be defined differently for patients with a particular diagnosis and for repeat tests *(45).* There is disparity in various surveys in repeated communication of critical results, once the laboratory has notified the first occurrence of such results (Table 2). More laboratories in Australia seem to have policies of not reporting subsequent critical results than in any other country surveys *(28)*. As mentioned earlier, laboratories should try to limit the frequency of repeat calls to avoid alert fatigue and unnecessary distraction of clinical staff. The Massachusetts consensus group also recommended that laboratories reduce the number of notifications where the patient's condition is known by considering the amount, timeframe and direction in which the result has changed as well as the medical history of the patient *(15).* A recent retrospective study in a large tertiary hospital in China investigated the relationship between the frequency of repeat critical results for potassium and platelet count and clinical outcomes. This study found that increased frequencies of repeat critical results were associated with longer hospital stay and increased mortality rate *(46)*. Therefore, laboratories are advised to design repeat alert result policies and include not only critical and non-critical tests and their thresholds on their alert list but also instructions for the frequency of notification of repeat alert results. Policies on repeated communications should be developed only after careful risk analysis and in agreement with clinicians to ensure that they have appropriate procedures in place at their level for handover of information to shift staff and for careful monitoring and treatment of patients in persistently critical conditions *(32,46).*

Table 6: Conditional alert lists

Analyte	Units	Salt Lake City, USA *(44)*		Massachusetts, USA *(15)*			Royal College of Pathologists, UK *(16)*
		Low Limit	High Limit	Always phone within 1 hour	Phone within 1 hour first instance, and within 8 hours thereafter	Phone within 8 hours first instance only.	
Sodium	mmol/L	< 120 (or fallen by > 15 in previous 24hrs and < 130)	> 155	< 120 or > 160			< 120 or > 150
Potassium	mmol/L	< 2.7 (or fallen by > 1.0 in previous 24hrs and < 3.2; or patient on digoxin and < 3.3)	> 6.0	< 2.8 or > 6.0			< 2.5 or > 6.5
Bicarbonate	mmol/L	< 15: with urea > 50; < 18: with urea < 50 or no urea ordered; < 25: and bicarbonate fallen by ≥ 10 in 24hr		< 10	10 - 15	> 38	> 30 (> 10 if < 16yr)
Creatinine	umol/L					> 354	> 400 (> 200 if < 16yr)
Glucose	mmol/L	< 2.5	> 27.8	< 2.78 or > 22.20			< 2.5 or > 25.0
Calcium (total)	mmol/L				< 1.75 or > 3.25		
Magnesium	mmol/L				< 0.41 or > 2.06		< 0.4
Phosphate	mmol/L			< 0.32			< 0.3
Amylase	U/L					> 500	5 x Upper Limit of Normal

Table 7: National guidelines for managing critical laboratory results in Europe

Country	Authority/organisation	Nature of guidance document	Method/Source	Web address *(last accessed 30 August 2013)*
Croatia	Croatian Chamber of Medical Biochemists	Alert list of laboratory tests and thresholds for communicating critical results	Alert thresholds adapted from literature are provided as guidance to laboratory professionals	www.hkmb.hr/povjerenstva/strucna-pitanja.html
Italy	Intersocietary working group SIBioC-SIMeL-CISMEL	Best practice guideline with starter set for alert list and thresholds for communicating critical results which laboratories may adapt in consultation with their clinical users	Officially published consensus guideline for laboratory professionals *(30)*	http://www.sibioc.it/upload/bc/32/3/lippi.pdf http://www.simel.it/it/riviste/articolo.php/2349
Poland	Polish Society of Laboratory Diagnostics (PTDL)	Best practice guideline with starter set for alert list and thresholds for communicating critical results which laboratories may adapt in consultation with their clinical users	Expert opinion and literature-based document open to broad public commenting by laboratory specialists in form of a professional web-based blog	http://www.krytyczne.blogspot.com/ http://www.ptdl.pl/download/Wartosci_krytyczne.pdf
UK	Royal College of Pathologists	Guidelines for out of hours reporting of critical results to primary care physicians	Officially published consensus guideline *(16)*	http://www.rcpath.org/Resources/RCPath/Migrated%20Resources/Documents/G/g025_outofhoursreporting_nov10.pdf

How alert results are verified?

Re-testing to verify critical results before reporting is still quite common practice, although with lesser frequency in the USA (Table 2) *(23).* Most of these verification practices date back to times when laboratories used less sophisticated automated systems. Recent studies have shown that repeating measurements adds little to the safety of patients. Analytical error rates by repeat testing are only in the range of 2-3%, but repeat verifications have been shown to delay rapid release of critical results which calls for a reconsideration of such practices *(47,48)*.

What is the timeframe of communication?

A critical result communication consensus group in Massachusetts Hospitals recommended that alert lists are segmented into three levels of urgency: a red zone where the patient is in imminent danger of death unless treated immediately, with results to be notified within 1 hour; an orange zone where prompt clinical attention is required to avoid serious adverse outcomes, with results to be notified within 6 to 8 hours; and a yellow zone where serious adverse consequences may occur without treatment in a timely and reliable manner, with results to be notified within 3 days *(15)*. This segmentation allows laboratory staff to quickly and efficiently deliver urgent red zone results to the clinicians (as long as the red zone tests are kept to a small number), and later deal with delivery of the less urgent results (that may otherwise slip through the cracks). According to survey findings in Table 2, the timeframe within which alert results need to be communicated are defined in approximately half of the laboratories only which suggests that most laboratories do not have such prioritization of alert results and even when critical results are notified there might be significant delays. Delayed communication and the lack of appropriate monitoring of the effectiveness of critical result notification procedures were also highlighted in the previously mentioned WHO, National Quality Forum and the Clinical Excellence Commission reports *(1,3,4).*

What communication channels are used for delivering alert results?

In spite of the wide-spread use of electronic patient records and laboratory information systems, national surveys reveal that most countries still use traditional telephone communications for delivering critical results (Table 2). However, there is an increasing interest in automated alternatives. A 12-month study in an Italian teaching hospital revealed that the average time for acknowledged computerised critical result notification (SMS to referring physician plus video alert to ordering clinician) was 11 minutes compared to 30 minutes for verbal notification by telephone *(49).* A 1000 bed academic medical center in Nashville Tennessee introduced an electronic ALERTS system using alphanumeric pagers which eliminated approximately 9000 phone calls a year for laboratory technologists, with a small number of phone calls required for telephone operators where pagers were not acknowledged within 10 minutes *(50).* A recent meta-analysis has shown that call centers deliver critical results more efficiently than laboratory personnel *(51).* Survey summaries however indicate that such dedicated facilities are rarely accessible to laboratories in most countries (Table 2). The current state of information technology in most hospitals is still too rudimentary to allow the implementation of electronic notification systems with automated feed-back on receiving alert results. Using call centers in a carefully designed notification system is therefore still considered a more viable option than automated e-alerts, which in the longer run, however, are expected to gain more widespread use *(28)*.

Who should deliver and receive alert results?

In the majority of national surveys mostly laboratory technicians report critical results except in Italy where predominantly laboratory managers, or medically qualified laboratory staff are involved in such communications *(25)*. The Clinical Laboratory Improvement Amendments of 1988 (CLIA), of which all United States laboratories must adhere to in order to access Medicare payments, require laboratories to immediately alert the individual requesting the test (and if applicable the individual responsible for using the test) when the test result indicates an imminently life-threatening condition *(52).* In practice, attempting to contact a physician can be an arduous and time-consuming task. In a

US survey, 75% of respondent laboratories believed that outpatient physicians, not returning calls or pagers, was the greatest obstacle to critical result reporting success *(24)*. In an Italian survey, 56% of respondent laboratories considered that the major challenge in their critical result notification process was reporting the result to the actual physician assigned to the patient *(25)*. The ISO 15189 accreditation standard and the College of American Pathologists laboratory accreditation inspection checklist deem clinical personnel responsible for patient care (i.e. physicians or nurses) as suitable recipients of critical results *(8,10).* According to our survey summary, most laboratories deliver alert results to doctors and nurses and this practice seems fairly homogeneous across countries, except for Spain and China where nurses are much less or not at all involved in such communications (Table 2).

How is receipt of the results acknowledged?

Read-back of verbal communications of results is varied practice across countries (Table 2), even though inappropriate recording of results is a major potential patient safety hazard. Even when alert results are communicated electronically, some form of acknowledgement system must be put in place. However, receiving acknowledgement of receipt of a critical result from a clinician should not automatically lead to the assumption that timely follow up will occur. A study conducted at the Veterans Affairs Medical Centre in Texas found that for critical alerts not followed up clinically within 30 days, there was no significant difference between the number of alerts that were acknowledged (within the view alert window of the electronic medical record screen) and the number of alerts that went unacknowledged *(53).*

What communication details need to be recorded?

It is a requirement of the ISO 15189 accreditation standard (Subclause 5.8.10) that records are maintained of actions in response to critical results, with difficulties in meeting these requirements also recorded and reviewed during audits *(8).* Keeping records of alert result communications enables laboratories to monitor their performance in delivering such results and thus identify improvements for their management procedures. Ideally, records should be stored electronically within a database to allow for statistical analysis of the data. Information collected within the record should include:

- the identity of the individual who delivered the result,
- the date and time that the communication was made,
- the identity of the recipient of the result,
- the location of the recipient of the result (e.g. hospital ward, general practice, outpatient clinic)
- the identity of the patient tested,
- the type of sample tested,
- the date and time that the sample was collected,
- the test that was performed, and
- the test result with the unit of measure.

Recording other relevant factors, such as difficulties encountered in result delivery or whether acknowledgement of receipt was obtained, provides useful information for auditors of the communication process.

What escalation procedures are in place when communication is unsuccessful?

Locating an alternate caregiver who can take responsibility for following up an alert result can be a time consuming task. Laboratories should implement a step by step procedure to direct staff in identifying the most appropriate person to receive an alert result when the requesting doctor is unavailable. A flow chart published by Singh and Vij is a good example of an escalation procedure for notifying alert results *(13)*. In that procedure, laboratory staff attempts to contact the primary care

physician if the ordering doctor is not available. Failing that, staff should attempt to contact the primary care physician's supervisor, Chief of Service, then the Medical Center director. Designing similar escalation procedures depends on local circumstances and the levels of authority medical teams are willing to delegate to other health care staff that can responsibly action alert result notifications from the laboratory. While this is certainly not an area for harmonization, it is advised that laboratories develop escalation procedures in agreement with their clinical users.

How to assess performance and impact on patient outcome and safety?

Performance in the delivery and receipt of critical results should be monitored to check for compliance and to identify areas where procedures can be improved *(13,19,30).* Useful performance indicators for measuring laboratory staff compliance to alert result notification procedures include: i) the percentage of alert results requiring communication that were communicated, ii) the average time taken to communicate an alert result (from the time the result was first available), and iii) the percentage of communicated alert results for which acknowledgement was received (10,54). Alert result notification is a service the laboratory offers to clinicians to ensure that patients receive urgent medical treatment when they need it. The effectiveness of this service can and should be measured both from the process and clinical outcome point of view. Parameters of the process that could be improved by monitoring and review include the appropriateness of the chosen alert thresholds, setting timeframes in which various types of alert results should be communicated, determining who is best to receive the result, and identifying the most effective means of communication. The best way to assess the clinical outcome of the alert result management system is to monitor the actions taken and the health outcomes of the patients when such results are delivered.

Guidelines to Facilitate Harmonization of Practices

The above mentioned variations in procedures and what tests and thresholds are included in the alert lists of laboratories call for more clear guidance and at least some degree of harmonization of best practice for communicating critical and significantly abnormal results. The practice variations explored in a number of surveys and the lack of specific guidance available for laboratories to design their alert result management policies have led to the appearance of a number of safe practice recommendations in the literature *(13,15,16,30).* Information from 29 European countries who responded to our survey has revealed that 4 countries (Croatia, Italy, Poland and the UK) had some form of officially endorsed national guideline and/or alert list in 2012 (Table 7). Acknowledging the importance of harmonization for patient safety, in Australia the Royal College of Pathologists and the Australasian Association of Clinical Biochemists have formed a working party assigned to identify gaps in current laboratory practices and produce national guidance for managing alert results. This group is also working on the provision of a "starter" set of alert thresholds that individual laboratories can discuss with their local clinicians and tailor to meet their clinical needs. The Clinical and Laboratory Standards Institute is currently preparing an international guideline which is expected to provide comprehensive guidance and help harmonize critical result management procedures across various pathology disciplines worldwide. Global harmonization of management procedures in this field is expected to ensure that all laboratories will better contribute to patient safety, and to enable benchmarking of performance that is expected to improve service quality in the post-post-analytical phase of laboratory processes.

Whilst national and international guidelines aim at standardizing practice, it must be acknowledged that the "one size fits all" mentality in communicating alert results would most likely fail. Therefore guidelines should remain reasonably flexible to facilitate customized adoption and adherence where local specifics influence the feasibility and implementability of recommended procedures. Guidelines should aim at harmonization of practices where patient safety is at highest risk and in such areas recommendations should be more prescriptive. For example, some differences in practices, such as who notifies alert results to whom and by what mode of transmission, or how repeatedly critical

results are communicated are easily explainable with and much influenced by local, educational, organisational, legal and cultural circumstances. Other shortcomings, such as not involving clinicians in the design of the alert list and procedure, not defining the timeframes of reporting, not having agreed escalation processes when results cannot be delivered within predefined timescales, or lack of read-back and recording of verbally communicated results, are less easy to explain and accept for patient safety reasons.

Methods to Facilitate Harmonization of Alert Lists

Laboratories all around the world face difficulties when designing alert lists, as there is no agreement on what is deemed critical and a medical emergency. How should laboratories and clinicians decide what tests and what alert thresholds should be on their alert list? The answer to this question best starts with identifying an individual institution's and most importantly patients' needs and requirements.

How to decide which tests to include in alert list?

Laboratories should extensively consult with their clinical users to find out what tests they consider critical and what treatment protocols or referral pathways they have to manage alert results. As mentioned in the very beginning of this article, there is very little benefit in testing and designing systems for urgent notification of critical or significantly abnormal results, if such laboratory interventions do not fit into any clinical pathway or are not followed by appropriate medical action. Hospital incident records of unexpected fatalities and 'near miss' cases, root-cause analysis reports and findings from risk assessments and patient safety audits could inform such decisions. Review of the typical case mix and subspecialties of health care organisations to which the laboratory provides its services can also guide decisions. Review of well-described pathophysiological associations with certain biomarkers and test results as well as engaging clinical pharmacologists, toxicologists and infection control committees would grossly help in designing more relevant and up-to-date alert lists. The benefit of involving various stakeholders in the planning or updates of alert lists is that these consultations help implementing a shared policy for alert result notification. Our summary of multinational surveys presented in Table 3 and Figure 1 may also help in deciding which biochemistry tests should be on one's alert list. A larger multinational survey that has been recently conducted by the task force group of EFLM may shed even more light on the current state-of-the-art in Europe – so watch this space.

How to decide which thresholds to include in alert list?

There are currently no criteria for laboratories to refer to in setting alert thresholds. As discussed earlier, alert thresholds should grossly impact medical decisions and therefore we consider them as clinical decision limits. In this context they represent "the threshold above which there is significant morbidity and mortality and above which treatment has been shown to significantly improve these patient-centered outcomes – 'significant' meaning important to people's quality of life or lifespan, rather than statistical significance" (personal communication by Professor Les Irwig, University of Sydney).

Currently used alert thresholds, including the majority which has been published in the literature, are typically based on consensus and personal observations from clinicians and pathologists. Often laboratories do not even have information on the exact source of their alert thresholds as often these are inherited or had gone through a number of modifications over years. Before describing the conceptual framework and approaches for establishing alert thresholds, we would like to emphasize that the minimum requirement from laboratories is that they explicitly refer to the source of their alert thresholds and record any consultations and reasoning that justify the selection of those limits. These records are not only important for traceability but they may also be called upon in legal cases. It would be also desirable that apart from the source, the quality of the information behind the alert thresholds is explicitly stated so that laboratories and clinicians are aware of the strengths (or

weaknesses) of the evidence behind the data. This potentially has an influence on medical decisions, especially when recommended alert thresholds are locally modified and adapted.

A hierarchical model for setting analytical quality specifications was created by an international consensus in Stockholm in 1999 *(55)* Sikaris has proposed that a similar concept could be designed for ranking the quality of candidate reference intervals (i.e., healthy result ranges for laboratory tests) and clinical decision limits (i.e., test result thresholds beyond which clinical decisions are made for diagnosis or various treatment options) *(56).* Since alert thresholds are like clinical decision limits, we hypothesize that this modified version of the Stockholm hierarchy would be suitable for classifying the sources of alert thresholds and thus could assist in designing alert lists in a more evidence-based and transparent manner. According to Sikaris' concept, the quality of clinical decision limits can be ranked and based on different levels of evidence:

- Level 1: clinical outcomes in specific clinical settings
- Level 2: consultation with clinicians in local settings
- Level 3: published professional recommendations of national or international expert bodies
- Level 4: national or international surveys of current practice (i.e. the 'state-of-the-art')
- Level 5: individual publications, textbooks, expert opinion

Ideally, alert thresholds should be based on well-designed and conducted clinical outcome studies (Level 1). If high quality outcome studies were available for many tests, laboratory professionals could approach their clinician clients with a more objective and evidence-based "starter set" of proposed alert thresholds for further consultation and endorsement. In our view where reasonable quality outcome data exist for a specific patient population, alert thresholds could and should be harmonized. It is important to highlight the importance of appropriate translation of such evidence to local practice. Laboratory professionals therefore must scrutinize and critically appraise such evidence by asking the following questions:

- Is this outcome study relevant to my patient population and setting?

Consider prevalence of condition, heath care setting, patient demographics, comparability of clinical pathways, availability of adequate treatment and further diagnostic options, etc. If the answer to these questions is no, then the rest of the below questions should not even be addressed.

- Is this outcome study well designed and conducted?
- What patient-centered outcomes did this study investigate and are they relevant to my setting?
- Does this study use laboratory assays for measurement which has comparable analytical performance to my assay?
- Are the diagnostic or alert thresholds comparable to my assay?
- Are clinical performance characteristics (i.e. diagnostic or prognostic accuracy) of the published assay comparable to my assay? (e.g. the diagnostic accuracy of 4^{th} generation and 'high-sensitivity' Troponin assays are quite different)

In lack of suitable outcome data, the best practice that is also recommended in existing standards and guidelines is to form a consensus with clinicians on best course of action, as described earlier (Level 2). Published recommendations of professional organisations, such as those mentioned earlier (Table 7) and which are available in some countries represent Level 3 in this hierarchy *(13,15,16,30).* In this review, for selected tests, we have also collected all available alert threshold data from multinational surveys which illustrate current practice (Level 4). The problem is that such surveys represent very different health care settings and populations. Furthermore, surveys have revealed that most laboratories use thresholds or their modifications published by single experts or in textbooks many decades ago (i.e. Level 5 evidence) and summary data from global surveys simply reflect that practice and evidence level. Thus according to the current state of affairs Level 4 evidence is probably not any better than Level 5 on the above hierarchy. Therefore it is not

unreasonable to presume that the “state-of-the-art” is already distorted and it is neither transparent where the information came from nor is it based on any evidence or clinical observation which would link alert thresholds to pathophysiologic changes or adverse patient events.

Alert result notification must be a shared policy and responsibility of laboratory and clinical staff. Harmonization of some practices is necessary, but cannot be achieved for all aspects of alert result communications. Laboratory professionals should be engaged more proactively in clinical consultations about the needs of clinicians and patients and should be measuring quality indicators and perform clinical audits to monitor the clinical and cost-effectiveness of their alert communication system. The information gathered this way will help refine alert lists and communication policies and will contribute to safer and higher quality patient care.

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Chapter 3

Systematic review of critical result thresholds

3.1 New Terminology

From this chapter forward, the thesis adopts the critical result management terminology used in the Australian and international guidance documents released in 2015 (1, 2). The origin of some of these terms was a letter to the editor published in Clinical Chemistry (3) (i.e., critical risk-, significant risk- and high risk results), which made reference to the article in Chapter two of this thesis when justifying their need. Other terms (i.e., alert threshold and alert list) were proposed within the thesis article in Chapter two. The adopted terms (as defined within the Australian guidance document) are as follows:

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

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

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 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.

3.2 Chapter Background

Central to a high risk result management system is the alert list, which contains the alert thresholds that define critical risk (and significant risk) results. The creation of a universal alert list is desirable but generally regarded as unachievable, due to the differing clinical needs of the local populations served by laboratories as well as a lack of standardisation/harmonisation of test methodology. Therefore, laboratories are required to compile their own list, ideally in collaboration with clinicians who use their service. Professional bodies in some countries have produced "starter" alert lists for laboratories to adjust in consultation with their clinician clients to fit their local setting (4-6). National surveys reveal that laboratories commonly refer to the literature when compiling their alert lists (7-9). Thus a systematic review identifying the best available alert thresholds from the literature was considered to be a valuable resource for laboratories endeavouring to compile their list.

The article presented in this chapter directly addresses objective two of the thesis, by providing a systematic review of critical risk result alert thresholds reported in the literature for clinical chemistry, haematology, and endocrinology, with an explicit and ranked source of evidence for each of the values. Three databases (Medline, Embase and CINAHL) were used to perform the literature search for the review. Papers published between 1995 and 2014 containing adult or non-age specific alert thresholds based on clinical outcome studies, expert consensus-based guidelines issued by professional bodies, surveys of current practices or expert opinions, and laboratory or organizational thresholds were selected. The 30 analytes with the largest number of thresholds extracted from the literature were identified. An adaptation of the 1999 Stockholm Consensus hierarchy for setting analytical performance specifications in laboratory medicine (10) was used to rank the thresholds for these analytes according to the level of evidence that supported them. The quality of the supporting evidence for thresholds assigned to the top two ranks was appraised using the JAMA user's guide for an article about harm (11) (for alert thresholds derived from clinical outcome studies) and the AGREE II Instrument (12) (for alert thresholds recommended by professional bodies). The article was published in the journal *Clinical Chemistry*.

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3.4 Article II - What Alert Thresholds Should Be Used to Identify Critical Risk Results: A Systematic Review of the Evidence

The following journal article, *Campbell CA, Georgiou A, Westbrook J, Horvath AR. What Alert Thresholds Should Be Used to Identify Critical Risk Results: A Systematic Review of the Evidence. Clin Chem 2016;62(11):1445-57. DOI: 10.1373/clinchem.2016.260638,* is reproduced below with the permission of the American Association for Clinical Chemistry; permission conveyed through Copyright Clearance Center, Inc.

What Alert Thresholds Should Be Used to Identify Critical Risk Results: A Systematic Review of the Evidence

Craig A. Campbell,[1,2*] Andrew Georgiou,[1] Johanna I. Westbrook,[1] and Andrea R. Horvath[2]

BACKGROUND: Pathology laboratories are required to immediately report results which indicate a patient is at critical risk, but there is little consensus about what values are deemed critical. The aim of this review was to systematically review the literature on alert thresholds for common chemistry and hematology tests in adults and to provide an explicit and ranked source of this evidence.

METHODS: The literature search covered the period of 1995–2014. Evidence sources were critically appraised and ranked using the 1999 Stockholm hierarchy for analytical performance specifications in laboratory medicine modified for establishing decision limits.

RESULTS: The 30 most frequently reported laboratory tests with alert thresholds are presented with evidence rankings. Similar thresholds were reported in North America, Europe and Asia. Seventy percent of papers reported thresholds set by individual institutions, while 18% contained thresholds from surveys of laboratories or clinicians. Forty-six percent of the papers referred to 1 or both of the 2 American laboratory surveys from the early 1990s. "Starter sets" of alert thresholds were recommended by 6 professional bodies, 3 of which were collaborations between pathologists and clinicians. None of the 9 outcome studies identified dealt with confounding factors.

CONCLUSIONS: Recommendations by professional bodies based on outdated surveys of the former state of the art or consensus are currently the best sources of evidence for laboratories to build their alert list. Well-designed outcome studies and greater collaboration between clinicians and the laboratory are needed to identify the most appropriate alert thresholds that signify actionable, critical or significant risk to patient well-being.

When a pathology laboratory generates a test result that is indicative of a life threatening situation, it is standard practice for the laboratory to immediately notify the affected patient's physician so that appropriate action can be taken *(1–3)*. A variety of terms has been created to label these important laboratory results *(4)*. The term "critical risk result," also adopted by CLSI, focuses on the core attribute of such results; i.e., the risk to patient safety *(5, 6)*. To prevent critical risk results from being overlooked, most laboratories maintain an alert list; i.e., a list of pathology tests, each with upper and/or lower result thresholds that, when exceeded, represent a high risk of mortality (or serious morbidity) *(4, 7–9)*. Individual laboratories service unique populations with differing clinical needs (e.g., community based patients vs hospital inpatients; pediatric populations; frailer elderly vs fitter, younger patients; subpopulations where specific diseases are more prevalent), and test results are not consistent between laboratories owing to the lack of standardized methodologies. Laboratories and hospital administrators in countries where performance in critical result management is more closely scrutinized may prefer less conservative alert thresholds to avoid penalties associated with communication failures. As a consequence, the achievement of harmonization of alert thresholds is often questioned *(4, 9–13)*. On the other hand, there is clinical and patient demand, and also a legal imperative to provide universal and evidence-based alert thresholds that appropriately predict and signal potential harm to patient well-being. For instance, following coronial inquests into 2 deaths due to undiagnosed Addison disease, the New South Wales Coroner's Court recommended that the New South Wales Ministry of Health develop "a statewide guideline for notifiable thresholds for all critical results, including cortisol" *(14, 15)*. Without universal consensus or objective evidence, it is a major challenge for laboratories to create and maintain their own list(s) of actionable alert thresholds for tests. Various national surveys have been conducted in an attempt to explore the state of the art. These surveys have revealed that labora-

[1] The Centre for Health Systems and Safety Research (CHSSR), Australian Institute of Health Innovation, Macquarie University, NSW, Australia; [2] Department of Clinical Chemistry and Endocrinology, South Eastern Area Laboratory Services, NSW Health Pathology, NSW, Australia.
* Address correspondence to this author at: Department of Clinical Chemistry and Endocrinology, Prince of Wales Hospital, Sydney NSW 2031, Australia. Fax +612-93829099; e-mail craig.campbell@health.nsw.gov.au.
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tories typically refer to the literature and their peers when creating their alert list *(16–19)*. Ideally, before putting the list into use, laboratories should consult with their clinical users to decide the appropriateness of the list parameters to the local setting. Unfortunately, national surveys reveal that consultation with clinicians about the construction of alert lists is not common practice in laboratories outside of the United States *(16–20)*.

A systematic literature review of alert thresholds would be a useful resource for laboratories in preparing their alert list, which could then be refined in collaboration with users to fit their local setting. To our knowledge, such a review does not exist. Thus, our aim was to perform a systematic literature review of alert thresholds for laboratory tests, and to provide an explicit and ranked source of evidence behind the values.

Method

A systematic review of the literature was performed to identify papers that reported critical risk result alert thresholds for clinical chemistry, hematology, and endocrinology tests in adults.

LITERATURE SEARCH

Three databases were used to perform the literature search: Medline and Embase were searched using Ovid, and CINAHL was searched using EBSCOhost. A Web search was also undertaken using Google Scholar to locate unindexed papers.

Key terms that reflect the traditional terminology *(4)* were used in the search: i.e., "alert limits," "alert values," "critical alerts," "critical limits," "critical results," "critical values," and "panic values." The terms "alarm values" and "critical alarms" were omitted from the search algorithm, as they were found to refer to bedside medical monitoring devices rather than laboratory results. The recently proposed terminology to assist harmonization of laboratory management of life threatening results *(5, 6)* (i.e., "critical risk result," "significant risk result", "high risk result," "alert threshold") was not included in the search algorithm because it did not have sufficient time to permeate. Because the key terms are not particularly specific to the field of interest, the search was confined to a list of relevant medical subject headings. A full description of the search parameters can be viewed in Supplemental Table 1 that accompanies the online version of this review at http://www.clinchem.org/content/vol62/issue11.

The literature search was limited to papers published within the last 20 years (i.e., 1995–2014) to capture a sufficiently large amount of data while avoiding thresholds that reflect antiquated laboratory testing methods. There were no restrictions placed on the language of publication to obtain an international perspective. Medline and Embase were last searched on January 29, 2015. CINAHL and Google Scholar were last searched on February 1, 2015.

A survey conducted in 2012, by the Document Development Committee for the CLSI guideline *Management of Critical- and Significant-Risk Results (21)*, was used to identify countries with national guidelines for the management of critical risk results not published in journals. The survey was sent to 38 European and 16 Central and South American national societies of laboratory medicine. Professional recommendations for alert thresholds from countries that reported the availability of guidelines (or other relevant documents related to the management of critical risk results) were located by contacting the respondents or by internet searches of reported national resources.

SELECTION CRITERIA

The titles and abstracts of identified papers were assessed for relevance. Papers that reported alert threshold data, based on clinical outcome studies, consensus processes, surveys of current practices or expert opinions, and laboratory or organizational thresholds were retained. Because the bulk of the threshold data was obtained from adults or was not age specific, papers with only neonate- or child-specific alert thresholds were excluded. Published abstracts from Conference Proceedings were included in cases for which there was no follow-up journal paper presenting the same data. When multiple publications of the same data were encountered, only the original publication was included in the review.

DATA EXTRACTION AND ANALYSIS

When a paper offered a general and a conditional threshold (e.g., "for oncology" or "on heparin") for the same analyte, only the general threshold was used to simplify classification. For cases for which differing inpatient and outpatient thresholds were provided for an analyte, only the inpatient threshold was used; inpatient thresholds were chosen ahead of outpatient thresholds because care in an outpatient setting is more dependent on the actual healthcare system. For alert thresholds extracted from surveys, median values were used rather than mean values in cases for which both were provided. The top 30 analytes (i.e., analytes with the largest number of thresholds extracted from the literature) were identified, and all other analytes and associated thresholds were removed from the data set.

Analytes among the 30 reviewed that had harmonized reference intervals [in Nordic countries *(22, 23)*, the UK *(24)*, and Australia *(25)*] were identified to determine which alert thresholds are less likely to be affected by differences in analytical methods. Papers were grouped according to the year of publication to determine research trends. Alert thresholds were categorized

according to the authors' continent of residence, then the median and range for each analyte within each continent was compared to detect regional differences.

CRITICAL APPRAISAL AND RANKING OF THE EVIDENCE ON ALERT THRESHOLDS

The JAMA user's guide for an article about harm *(26)* was employed to appraise the strength of supporting evidence for alert thresholds derived from clinical outcome studies. The AGREE II Instrument *(27)* using a scoring scale of 1–7 (strongly disagree to strongly agree) was used by 2 independent assessors (CC and ARH) to critically appraise the methodological quality of professional body recommendations. Formal critical appraisal was not performed on surveys of laboratories or clinicians, and thresholds reported by individual institutions. Such studies would generally lack methodological detail and often it is not feasible to trace the quality of the sources of survey data.

The alert thresholds were ranked according to the level of evidence that supported them. To facilitate this, a 2-dimensional ranking system was created, using an adaptation of the 1999 Stockholm Consensus hierarchy for setting analytical performance specifications in laboratory medicine *(28)* and its application to medical decision limits *(29)*.

The first dimension of the ranking system addressed the source of alert thresholds. Alert thresholds reported by individual institutions were ranked the lowest, level 4, as they are most susceptible to biased personal opinions. Median thresholds from surveys of laboratories or clinicians represent the state of the art, and thus were ranked higher at level 3. Thresholds recommended by professional bodies were ranked at level 2, as professional bodies (*a*) have more authority to make recommendations, (*b*) are more likely to perform thorough expert analysis of the available evidence, and (*c*) are more likely to present thresholds based on a broader and more formal consensus process. The best evidence for alert thresholds is considered to derive from well-designed and conducted clinical outcome studies, where laboratory results are linked to morbidity indicators and mortality. Therefore, thresholds established from health outcome studies were assigned level 1 in the ranking system.

According to the CLSI guideline *Management of Critical- and Significant-Risk Results*, for critical risk result communication to be effective, the laboratory and its clinical users should agree that the alert thresholds used will reliably identify patients at risk for serious harm *(6)*. Therefore, for the second dimension of the ranking system, 3 subcategories were defined according to whether the threshold was derived by the laboratory (*c*; lowest), clinicians (*b*; intermediate), or both (*a*; highest). Thresholds derived by clinicians were given a higher subranking than those derived by the laboratory, because it is the clinicians who decide whether to take action on laboratory results. However, clinicians are often focused on their specialties; such focusing may result in a narrow view of the overall utilization and interpretation of laboratory results. Therefore, the highest subranking was assigned to thresholds that were derived by collaboration between clinicians and the laboratory. For each analyte within each subranking, the median and range of alert thresholds were calculated.

Results

The literature search generated 3500 documents across the 4 databases. After assessing relevance, only 108 papers contained adult alert thresholds for chemistry, hematology or endocrinology tests (see online Supplemental Fig. 1). Restriction of the data set to the most commonly reported 30 analyte thresholds reduced the number of papers for review to 92. The critical risk result management survey of European and South American countries uncovered 4 national recommendations for adult alert thresholds, which were included in the review. The 96 selected references together with the supporting evidence rankings for the alert thresholds extracted from them (according to the 2-dimensional ranking system) are listed in online Supplemental Table 2.

Fig. 1 shows the frequency at which adult alert thresholds for the top 30 analytes were reported in the literature. Twenty-one of these analytes were found to have harmonized reference intervals in at least 1 country. Analytes that narrowly missed the cutoff of 30 included phenobarbitone, osmolality, presence of blasts on blood smear, bilirubin (note that neonatal bilirubin had been excluded), gentamicin and creatine kinase.

The majority of the alert threshold data papers originated from North America (53%, n = 49), Europe (23%, n = 21) and Asia (16%, n = 15), while Africa, Australasia and South America only contributed 9% of the evidence, collectively. Fifty-two percent of the 92 papers reviewed were published between 2010 and 2014, 24% were published between 2005 and 2009, 10% between 2000 and 2005, and 14% between 1995 and 1999. Forty-two of the 92 papers reviewed (46%) referred to the US medical center survey of alert thresholds published by Kost in 1990 *(30)* and/or the College of American Pathologists (CAP) 1992 Q-Probes study *(16)*, with 10 of these papers acknowledging one or both of the surveys as sources for their alert thresholds *(9, 10, 31–38)*.

ALERT THRESHOLDS IN DIFFERENT CONTINENTS

Similar thresholds are used in North America, Europe, and Asia for most of the 30 analytes (see online Supplemental Table 3). Both upper and lower median thresholds were identical or very similar in all 3 continents for

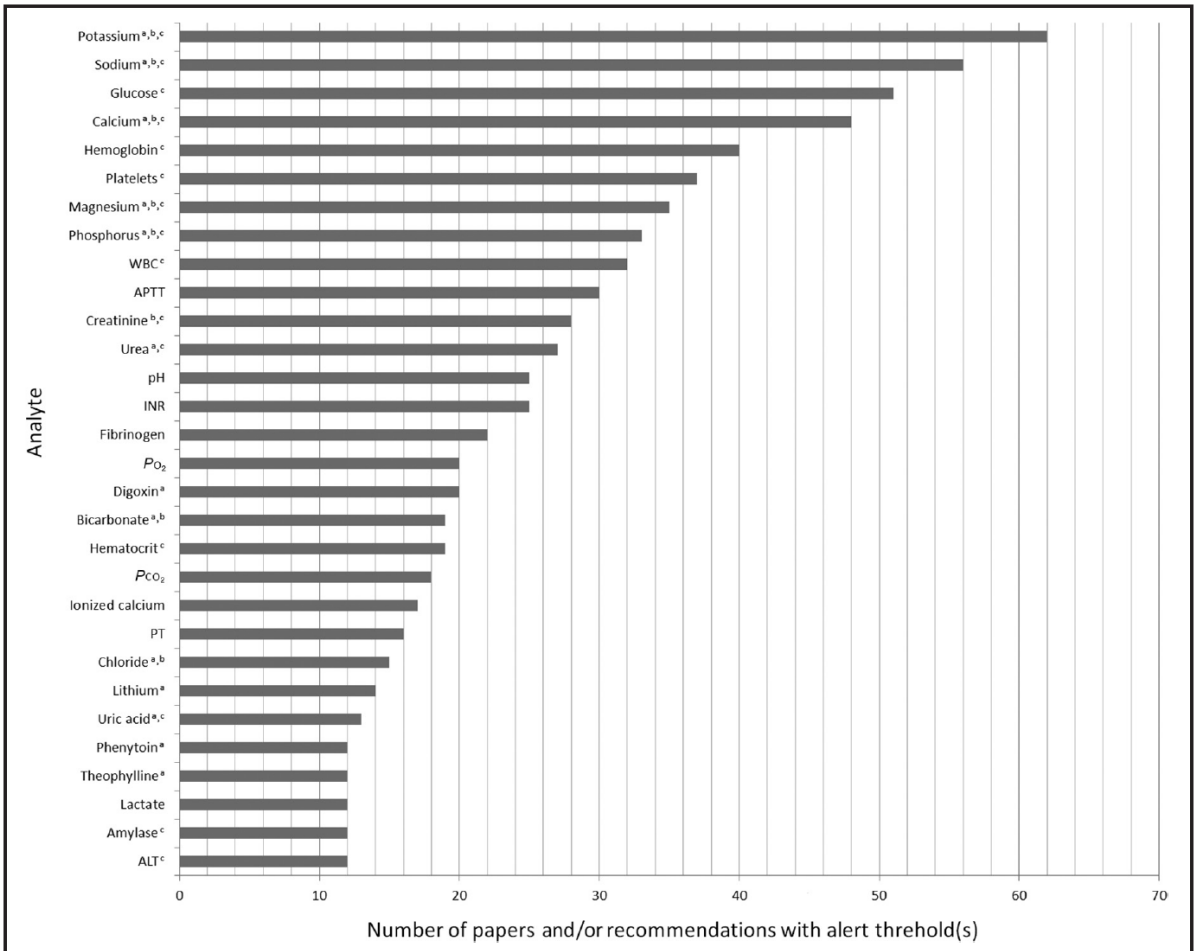

Fig. 1. Analytes with most frequently published adult- and non-age-specific alert thresholds. APTT, activated partial thromboplastin time; PT, prothrombin time; ALT, alanine aminotransferase.

[a] Analyte has a harmonized reference interval in the UK.

[b] Analyte has a harmonized reference interval in Australasia.

[c] Analyte has a harmonized reference interval in Nordic countries.

sodium, glucose, pH, bicarbonate, hematocrit, P_{CO_2} and ionized calcium. There was agreement between the 3 continents on median low thresholds for white blood cell count, phosphorus, and fibrinogen. Median high thresholds were almost equal for calcium (total), hemoglobin, platelets and uric acid. However, there was a distinct difference in the potassium high threshold used in North America (median = 6.0 mmol/L; range = 5.5–6.3 mmol/L) compared to Europe (median = 6.25 mmol/L; range = 6.0–7.0 mmol/L) and Asia (median = 6.5mmol/L; range = 6.0–7.0mmol/L). There was also a notable difference in the high threshold for creatinine between North America [median = 4.50 mg/dL (398 μmol/L); range = 1.70–7.40 mg/dL (150–654 μmol/L)] and Asia [median = 6.18 mg/dL (546 μmol/L); range = 5.00–7.58 mg/dL (442–670 μmol/L)].

THRESHOLDS REPORTED BY INDIVIDUAL INSTITUTIONS (LEVEL 4)

Sixty-four of the 92 papers (70%) contained alert thresholds reported by individual institutions and thus were ranked Level 4 in the evidence ranking system (Table 1; for SI units see online Supplemental Table 4). Thirteen papers provided thresholds that were allocated to rank 4a (i.e., laboratory and clinicians). These thresholds were generally from laboratory alert lists that were endorsed by the medical board of the institution. Twelve papers contained thresholds decided purely by clinicians from an

Table 1. Level 4 evidence–alert thresholds reported by individual institutions.[a]

Analytes, conventional units	4a. Laboratory and clinicians		4b. Clinicians		4c. Laboratory	
	Low threshold, median (range) [n]	High threshold, median (range) [n]	Low threshold, median (range) [n]	High threshold, median (range) [n]	Low threshold, median (range) [n]	High threshold, median (range) [n]
Potassium, mmol/L	2.75 (2.0–3.2) [12]	6.25 (6.0–7.0) [12]	2.5 (2.0–3.0) [7]	6 (5.5–7.0) [7]	2.8 (2.0–3.0) [21]	6.05 (5.9–7.0) [22]
Sodium, mmol/L	120 (115–125) [12]	160 (150–160) [12]	120 (105–125) [7]	157.5 (150–165) [6]	120 (110–125) [18]	160 (150–160) [17]
Glucose, mg/dL	45.1 (34.2–50.5) [11]	450 (301–799) [13]	43.4 (30.1–72.0) [6]	442 (324–800) [6]	45.1 (40.0–54.1) [17]	450 (360–991) [17]
Calcium, mg/dL	6.0 (6.0–6.6) [8]	13.0 (10.8–14.0) [10]	5.5 (5.0–6.0) [2]	14.0 (13.0–15.0) [2]	6.5 (6.0–7.2) [14]	13.0 (2.8–14.1) [15]
Hemoglobin, g/dL	6.25 (5.0–8.0) [8]	19.95 (19.9–20.0) [4]	6.6 (5.0–7.5) [3]	19.9 (19.9–19.9) [1]	6.6 (5.0–7.0) [15]	20.0 (19.9–20.0) [5]
Platelets, $\times 10^3/\mu L$	20 (10–40) [9]	1000 (999–1000) [5]	10 (5–50) [3]		40 (10–50) [13]	1000 (800–1000) [8]
Magnesium, mg/dL	1.0 (0.75–1.2) [5]	5.0 (4.7–7.0) [3]	1.2 (1.2–1.2) [1]		1.0 (0.56–1.3) [13]	6.0 (4.7–12.2) [10]
Phosphorus, mg/dL	0.99 (0.99–1.49) [6]	9.0 (5.5–9.0) [4]	1.6 (1.6–1.6) [1]		0.99 (0.93–1.7) [8]	9.4 (9.0–9.9) [2]
WBC,[b] count/μL	1,500 (500–3,000) [7]	50 000 (30 000–100 000) [6]			1,500 (500–2,000) [13]	50 000 (20 000–100 000) [11]
APTT, s	12 (12–12) [1]	82.5 (50–110) [6]		50 (50–50) [1]	19 (19–19) [1]	85 (75–200) [13]
Creatinine, mg/dL		3.6 (2.0–7.4) [4]		2.0 (1.7–7.4) [4]		5.7 (3.0–7.4) [6]
Urea, mg/dL		100 (35.0–216) [4]		34.6 (29.1–40.0) [2]	2.0 (2.0–2.0) [1]	92.0 (80.1–140) [6]
pH	7.20 (7.15–7.20) [5]	7.595 (7.58–7.60) [4]			7.20 (7.10–7.20) [10]	7.60 (7.59–7.70) [8]
INR		4.75 (3.5–7.0) [4]	1.5 (1.5–1.5) [1]	4.25 (3–5.0) [4]	1.5 (1.5–1.5) [2]	4.9 (3.5–7.0) [12]
Fibrinogen, mg/dL	100 (100–100) [2]	700 (700–700) [1]	100 (75–150) [3]		95 (50–100) [8]	750 (700–800) [2]
Po_2, mmHg	40 (40–40) [4]				40 (40–50) [7]	
Digoxin, ng/mL		3.0 (1.94–4.0) [5]				2.3 (2.0–2.5) [8]
Bicarbonate, mmol/L	12 (12–12) [3]	38 (36–40) [2]	14 (14–14) [1]	34 (34–34) [1]	10 (9–15) [7]	40.5 (40–50) [6]
Hematocrit, %	20 (15–24) [4]	60 (60–60) [2]	14.5 (14–15) [2]		20 (18–30) [7]	58 (54–60) [6]
Pco_2, mmHg	20 (20–25) [5]	70 (60–75) [5]			20 (10–20) [7]	67 (45–75) [7]
Ionized calcium, mg/dL	0.75 (0.75–0.75) [1]	6.46 (6.3–6.6) [2]			3.2 (3.0–3.2) [7]	6.2 (6.0–7.0) [7]
Prothrombin time, s	8 (8–8) [1]	30 (25–30) [3]				33 (30–60) [8]
Chloride, mmol/L	75 (75–75) [1]	125 (125–125) [1]	92 (92–92) [1]	120 (120–120) [1]	75 (75–80) [5]	122.5 (115–130) [4]
Lithium, mmol/L		1.75 (1.49–2.0) [4]				2.0 (1.5–2.0) [5]
Uric acid, mg/dL		13.0 (9.4–13.0) [4]				13.0 (13.0–13.0) [2]
Phenytoin, μg/mL		30 (30–30) [2]				28.5 (20–40) [6]
Theophylline, μg/mL		20 (20–20) [2]				20 (20–25) [4]
Lactate, mg/dL		31 (31–31) [1]				36 (31–45) [5]
Amylase, U/L		300 (110–400) [4]				200 (200–200) [2]
ALT, U/L		100 (75–1500) [3]		189 (189–189) [1]		1000 (1000–1000) [2]

[a] n = no. of papers used as source of data.
[b] APTT, activated partial thromboplastin time; ALT, alanine aminotransferase.

individual institution and thus were ranked 4b (i.e., clinicians). Thresholds assigned to rank 4c (i.e., laboratory) were drawn from 39 papers. Rank 4c thresholds were also mainly drawn from laboratory alert lists, with no statement about clinician endorsement.

Comparison of laboratory and clinician derived alert thresholds (from individual institutions) must be judged with caution considering the low volume of clinician data collected. There was agreement between laboratories and clinicians for both upper and lower thresholds for sodium, glucose and hemoglobin, as well as the upper potassium threshold and lower fibrinogen threshold. Laboratories were more conservative than clinicians in setting lower thresholds for potassium, calcium, platelets, and hematocrit. Clinicians were more conservative than laboratories in setting upper thresholds for creatinine, urea, and international normalized ratio (INR).

THRESHOLDS FROM SURVEYS REPRESENTING THE STATE OF THE ART (LEVEL 3)

Seventeen of the 92 papers (18%) contained alert thresholds based on surveys of laboratories (n = 15) or clinicians (n = 2) and thus were ranked Level 3 in the evidence ranking system (Table 2; for SI units see online Supplemental Table 5). Laboratory surveys (3c) included 12 national, 1 provincial, 1 municipal, and 1 medical center network survey. Clinician surveys (3b) comprised surveys of a wide range of specialist physicians from hospitals affiliated with a university, and a national survey of intensive care unit (ICU) physicians. In most cases, the university affiliated physicians selected thresholds of greater abnormality than those selected by laboratories. In contrast, the sole threshold provided by the national ICU physician survey (low hemoglobin threshold) was much closer to the reference limit than the corresponding median laboratory alert threshold.

THRESHOLDS RECOMMENDED BY PROFESSIONAL BODIES (LEVEL 2)

Two of the 92 papers (2%) contained threshold recommendations from professional bodies and thus were ranked Level 2 (Table 3; for SI units see online Supplemental Table 6). The American Society of Clinical Pathologists (ASCP)[3] published a paper in 1997 *(10)* with alert thresholds from the 1992 CAP Q-Probes survey. In 2005, the Massachusetts consensus group (MCG) representing the laboratory, cardiology, radiology professionals, and physicians and nurses developed a starter set of alert thresholds *(11)*.

Twenty-nine European and 5 Central and South American countries responded to the survey investigating the availability of national guidelines with alert thresholds [response rates of 76% (29/38) and 31% (5/16), respectively]. This survey identified 4 more sources of Level 2 evidence (Table 3; for SI units see online Supplemental Table 5). In 2006, the Croatian Chamber of Medical Biochemists (CCMB) endorsed alert thresholds *(39)* published by Lothar Thomas *(33)*, based on the 1990 Kost survey *(30)* and his own experience as a doctor of laboratory medicine. In the UK in 2010, the Royal College of Pathologists (RCPath) published advice for reporting laboratory results requiring urgent clinical action, with a suggested "starter set" of alert thresholds devised in consultation with specialty advisory committees on microbiology, virology and immunology, hematology, and the Royal College of General Practitioners *(40)*. In 2010, the Polish Society of Laboratory. Diagnostics (PSLB) published recommendations for critical result management including a "starter set" of alert thresholds, devised during a workshop of laboratory diagnosticians *(41)*. In 2013, the Norwegian Society for Medical Biochemistry (NSMB) in consultation with the Board of the Association of General Practitioners, developed a critical alert list for Norwegian laboratories to use as a guide for notification of doctors outside hospitals *(42)*.

Since the starter sets of the MCG, RCPath, and NSMB were devised in collaboration between pathologists and clinicians, they were allocated a higher ranking of 2a. Critical appraisal of Level 2 guidelines with the AGREE II Instrument resulted in the following overall quality ranking from highest to lowest: NSMB; MCG; RCPath; ASCP; PSLB; CCMB (detailed results of the appraisal can be obtained from the authors at request).

THRESHOLDS ESTABLISHED BY CLINICAL OUTCOME STUDIES (LEVEL 1)

Nine of the 92 papers (10%) contained thresholds evaluated in an outcome study (Table 4; for SI units see online Supplemental Table 7). These studies covered the following topics:

1. Determination of the upper alert threshold for total serum calcium that most reliably identifies patients in need of therapy *(43)*;
2. Influence of hyperkalemia on clinical decision making and the effect on recovery when critically high potassium concentrations are reported promptly *(44)*;
3. Consideration of whether the transfusion trigger and lower alert threshold for hemoglobin should be equal *(45)*;

[3] Nonstandard abbreviations: ASCP, American Society of Clinical Pathologists; CAP, College of American Pathologists; CCMB, Croatian Chamber of Medical Biochemists; INR, international normalized ratio; ICU, intensive care unit; MCG, Massachusetts consensus group; NSMB, Norwegian Society for Medical Biochemistry; PSLB, Polish Society of Laboratory Diagnostics; RCPath, Royal College of Pathologists (UK).

Table 2. Level 3 evidence–alert thresholds from surveys of laboratories or clinicians.[a]

Analytes, conventional units	3b. Clinicians		3c. Laboratory	
	Low threshold, median (range) [n]	High threshold, median (range) [n]	Low threshold, median (range) [n]	High threshold, median (range) [n]
Potassium, mmol/L	2.5 (2.5–2.5) [1]	6.0 (6.0–6.0) [1]	2.8 (2.6–2.9) [11]	6.2 (6.0–6.5) [11]
Sodium, mmol/L	120 (120–120) [1]	160 (160–160) [1]	120 (120–125) [10]	159 (155–160) [10]
Glucose, mg/dL	45.1 (45.1–45.1) [1]	541 (541–541) [1]	45.1 (39.6–50.1) [9]	418 (360–485) [9]
Calcium, mg/dL	5.2 (5.2–5.2) [1]	15.2 (15.2–15.2) [1]	6.4 (5.6–7.1) [11]	12.9 (12.0–14.0) [11]
Hemoglobin, g/dL	9.0 (9.0–9.0) [1]		6.75 (5.3–7.5) [8]	20.0 (18.4–20.0) [8]
Platelets, $\times 10^3/\mu L$			40 (30–50) [8]	999 (700–1000) [8]
Magnesium, mg/dL	0.97 (0.97–0.97) [1]		1.1 (0.80–1.2) [8]	4.9 (4.1–7.9) [8]
Phosphorus, mg/dL	0.77 (0.77–0.77) [1]		1.2 (0.99–1.2) [8]	8.7 (8.0–9.3) [7]
WBC,[b] count/μL			2,000 (2,000–2,000) [6]	33 500 (25 000–46 000) [6]
APTT, s			19 (18–20) [3]	87.5 (68–110) [8]
Creatinine, mg/dL			0.20 (0.18–0.31) [4]	5.2 (3.4–7.6) [9]
Urea, mg/dL			4.6 (3.1–11.2) [4]	87.7 (75.6–213) [9]
pH	6.90 (6.90–6.90) [1]	7.70 (7.70–7.70) [1]	7.205 (7.20–7.44) [4]	7.595 (7.55–7.60) [4]
INR				5.5 (5.0–6.0) [2]
Fibrinogen, mg/dL			100 (88–100) [3]	787.5 (775–800) [2]
Po_2, mmHg	35 (35–35) [1]		43.5 (40–60) [4]	102 (93–111) [2]
Digoxin, ng/mL				2.3 (2.0–3.0) [3]
Bicarbonate, mmol/L	10 (10–10) [1]		11 (10–15) [6]	40 (39–40) [6]
Hematocrit, %			20 (18–24) [3]	60 (60–61) [3]
Pco_2, mmHg			20 (19–20) [3]	68 (60–70) [4]
Ionized calcium, mg/dL	2.4 (2.4–2.4) [1]	6.8 (6.8–6.8) [1]	0.8 (0.75–0.82) [3]	6.2 (6.0–6.3) [3]
Prothrombin time, s			9 (9–9) [2]	28 (25–37) [5]
Chloride, mmol/L			80 (75–85) [6]	120.5 (115–126) [6]
Lithium, mmol/L				1.5 (1.4–2.0) [3]
Uric acid, mg/dL			1.0 (1.0–1.0) [1]	12.9 (11.8–13.0) [4]
Phenytoin, μg/mL				25 (25–30) [3]
Theophylline, μg/mL				23 (23–25) [3]
Lactate, mg/dL			0.5 (0.5–0.5) [1]	31 (4.0–45) [3]
Amylase, U/L				388 (350–470) [3]
ALT, U/L				750 (500–1000) [2]

[a] n = No. of papers used as source of data.
[b] APTT, activated partial thromboplastin time; ALT, alanine aminotransferase.

4. Appropriateness of upper and lower alert thresholds for calcium *(46)* and sodium *(47)*;
5. Effectiveness of rapid response team intervention in patients with severe hyperkalemia *(48)*;
6. Significance of increased lactate in the identification of critically ill patients *(49)*;
7. The relationship between alert thresholds for 8 common analytes and in-hospital mortality *(50)* (note that of the 8 analytes tested, only the upper threshold for potassium and lower threshold for sodium were deemed to be at suitable settings);
8. Relation of initial fibrinogen concentration to outcome in emergency trauma care *(51)*.

All of the above studies included mortality as an outcome indicator. Two also measured length of hospital stay *(46, 47)* and 1 used improvement in condition after treatment *(43)* as additional outcome measures. Seven of the outcome studies provided clinical characteristics of the study population (e.g., the incidence of certain conditions), *(43, 44, 46–49, 51)* but only 4 of these used those clinical characteristics in their analysis. Six of the

Table 3. Level 2 evidence–alert thresholds recommended by professional bodies.[a]

Analytes, conventional units	2a. Laboratory and clinicians		2c. Laboratory	
	Low threshold, median (range) [n]	High threshold, median (range) [n]	Low threshold, median (range) [n]	High threshold, median (range) [n]
Potassium, mmol/L	2.5 (2.5–2.8) [3]	6.2 (6.0–6.5) [3]	2.8 (2.8–2.8) [3]	6.2 (6.0–6.2) [3]
Sodium, mmol/L	120 (120–120) [3]	155 (150–160) [3]	120 (120–120) [3]	160 (160–160) [3]
Glucose, mg/dL	47.6 (45.1–50.1) [2]	414 (400–450) [3]	40.0 (39.6–45.1) [3]	446 (400–500.9) [3]
Calcium, mg/dL	7.2 (7.0–7.2) [3]	13.0 (12.8–14.0) [3]	6.6 (6.0–7.0) [3]	13.0 (12.0–14.0) [3]
Hemoglobin, g/dL	7.0 (7.0–7.0) [2]	19.0 (19.0–19.0) [1]	7.0 (6.6–7.0) [3]	20.0 (19.9–20.0) [3]
Platelets, $\times 10^3/\mu L$	25 (20–30) [2]	1250 (1000–1500) [2]	40 (20–40) [3]	1000 (999–1000) [3]
Magnesium, mg/dL	1.1 (0.97–1.2) [2]	5.0 (4.9–5.1) [2]	1.0 (1.0–1.0) [3]	8.4 (4.6–12.2) [2]
Phosphorus, mg/dL	0.96 (0.93–0.99) [2]		0.99 (0.93–0.99) [4]	9.0 (8.9–9.0) [4]
WBC,[b] count/μL	1,500 (1,500–1,500) [1]	100 000 (100 000–100 000) [1]	2,000 (2,000–2,000) [3]	40 000 (30 000–50 000) [3]
APTT, s				78 (75–120) [3]
Creatinine, mg/dL		4.5 (4.0–4.5) [3]		5.0 (4.0–7.4) [3]
Urea, mg/dL		100 (84.0–112) [3]		80.1 (46.8–99.7) [3]
pH	7.20 (7.20–7.20) [1]	70.60 (7.60–7.60) [1]	7.20 (7.20–7.20) [2]	7.60 (7.60–7.60) [2]
INR		6.25 (6.0–6.5) [2]		5.0 (5.0–5.0) [1]
Fibrinogen, mg/dL			80 (80–100) [3]	800 (800–800) [1]
P_{O_2}, mmHg	60 (60–60) [1]		41.5 (40–43) [2]	
Digoxin, ng/mL		2.5 (2.5–2.5) [1]		2.0 (2.0–2.0) [1]
Bicarbonate, mmol/L	15 (15–15) [1]		10 (10–10) [1]	40 (40–40) [1]
Hematocrit, %			20 (18–20) [3]	60 (60–61) [3]
P_{CO_2}, mmHg			19.5 (19–20) [2]	68.5 (67–70) [2]
Ionized calcium, mg/dL	3.4 (3.2–3.5) [2]	6.2 (6.0–6.4) [2]	3.1 (3.1–3.1) [1]	6.4 (6.4–6.4) [1]
Prothrombin time, s				35 (30–40) [2]
Chloride, mmol/L			77.5 (75–80) [2]	122.5 (120–125) [2]
Lithium, mmol/L		1.5 (1.5–1.5) [1]		
Uric acid, mg/dL				13.0 (13.0–13.0) [1]
Phenytoin, μg/mL		25 (25–25) [1]		
Theophylline, μg/mL		25 (25–25) [1]		
Lactate, mg/dL		45 (45–45) [1]		45 (45–45) [1]
Amylase, U/L		500 (500–500) [1]		1000 (1000–1000) [1]
ALT, U/L		587.5 (500–675) [2]		800 (600–1000) [2]

[a] n = No. of papers used as source of data.
[b] APTT, activated partial thromboplastin time; ALT, alanine aminotransferase.

outcome studies measured treatment in response to critical risk results *(43–48)*, but only 2 of these demonstrated the relationship between treatment and outcome.

Critical appraisal of the outcome studies revealed several limitations in study design. Less than half of the studies accounted for confounding factors; e.g., selecting appropriate comparison groups that have similar conditions and mortality risks without critical risk results, or documenting the clinical characteristics of each comparison group *(44, 48, 49, 51)*. Time elapsed between appearance of critical risk result and death was either not measured *(44, 45, 47, 48)*, inadequately measured *(46)* or of inappropriate duration *(43)* in most of the studies. Relative risk or odds ratio measurements were performed in only 2 of the studies *(50, 51)*. Some studies did not specify the analytical method used to obtain the critical risk results, although only 1 of these studies was for an analyte that does not have a harmonized reference interval *(49)*.

OUTCOME STUDIES THAT DID NOT QUALIFY TO BE RANKED LEVEL 1

There were several critical risk result studies that did not adequately test the appropriateness of alert threshold settings and were thus ranked 4a to 4c (i.e., thresholds used by individual institutions). Three studies provided a single mortality figure for a group of analytes thus the effectiveness of each individual threshold at predicting mor-

Table 4. Level 1 evidence–alert thresholds established by clinical outcome studies.[a]

Analytes, conventional units	1a. Laboratory and clinicians		1b. Clinicians		1c. Laboratory	
	Low threshold, median (range) [n]	High threshold, median (range) [n]	Low threshold, median (range) [n]	High threshold median, (range) [n]	Low threshold, median (range) [n]	High threshold, median (range) [n]
Potassium, mmol/L		6.2 (6.2–6.2) [1]		6.3 (6.3–6.3) [1]		7.0 (7.0–7.0) [1]
Sodium, mmol/L	120 (120–120) [2]	155 (155–155) [1]				
Calcium, mg/dL	7.0 (7.0–7.0) [1]	12.0 (12.0–12.0) [1]				12.0 (12.0–12.0) [1]
Hemoglobin, g/dL	7.0 (7.0–7.0) [1]					
Fibrinogen, mg/dL			229 (229–229) [1]			
Lactate, mg/dL		36 (36–36) [1]				

[a] n = no. of papers used as source of data.

tality could not be assessed *(52–54)*. Two further outcome studies focused on factors other than threshold suitability: 1 evaluated the impact of multiple occurrences of critical risk results for the same analyte *(55)*, and another assessed the automation of communication of critical risk results *(56)*. Three studies analyzed the impact of critical risk results on diagnostic and/or treatment decisions (as a kind of proxy outcome measure) without measuring health outcomes *(57–59)*.

CRITICAL CHANGES IN RESULTS

During the paper selection process, examples of the use of critical δ values (i.e., critical change in results over a predefined period of time) as alert thresholds were recorded when encountered. A list of the δ values collected is shown in Table 5.

Discussion

The alert thresholds identified in this review were rarely accompanied by supporting evidence to justify their selection. The majority of thresholds found in the literature were reported by individual institutions without elaboration of why or how they were established. Although median values from national surveys of laboratories are more reliable than those from individual institutions (as ex-

Table 5. Delta values for alert thresholds.

Test	Critical change in result	Reference
Creatinine	Previous sample >1.10 mg/dL (97 µmol/L) and current sample has risen by >20%	Mathew et al. *(60)*
	Initial result of >0.57 mg/dL (50 µmol/L) with a subsequent rise of >0.57 mg/dL (50 µmol/L) within 90 days	Flynn and Dawnay *(61)*
Hematocrit	<26% and has fallen 10% in 24 h; or <26% and has fallen 6% at rate faster than 0.4% per hour	Kuperman et al. *(53)*
Hemoglobin	Within 6 days: >30% drop for Hb 6.0–13.0 g/dL (60–130g/L); >4.0 g/dL drop for Hb 13.0–18.0 g/dL (130–180 g/L)	Piva and Plebani *(62)*
	Community patient annual screening: decrease of >3.29 g/dL (32.9 g/L) or increase of >2.99 g/dL (29.9g/L) compared to last year's result	Tran et al. *(63)*
Platelets	For detection of drug induced thrombocytopenia: >50% decrease compared to previous result; or a continual decrease over 3 consecutive blood collections with a total drop of >25%	Harinstein et al. *(64)*
Potassium	<3.2 mmol/L and has fallen 1 mmol/L in 24 h	Kuperman et al. *(53)*, Kuperman et al. *65)*
	<3.0 mmol/L and has fallen 1 mmol/L in 24 h	Iordache et al. *(66)*
Sodium	<130 mmol/L and has fallen 15 mmol/L in 24 h	Kuperman et al. *(53,* Kuperman et al. *65,* Iordache et al. *66)*
White blood cells	Previous sample >11 000/µL (11 × 10^9/L) and current sample has risen by >20%	Mathew et al. *(60)*

treme individual preferences have been filtered out), they are not traceable to definitive reasoning or proof that confirms their appropriateness. Some professional bodies have put little effort into researching alert thresholds, and instead have focused their efforts on developing safe procedures for critical result reporting. Alert threshold recommendations from the MCG *(11)*, RCPath *(40)*, and NSMB *(42)* have been developed in collaboration between pathologists and clinicians (rank 2a), and are probably the best official sources currently available for setting alert thresholds. The Norwegian recommendations *(42)* in particular provide clear and detailed methodology on how their alert thresholds were decided.

Clinical outcome studies for alert thresholds are rare, and generally fail to deal with confounding factors. For instance, Lum found that 9 out of 11 patients with calcium concentrations exceeding 12.0 mg/dL (3.0 mmol/L) died within 6 months *(43)*; however, all 9 patients had malignant tumors and addressing the hypercalcemia was unlikely to reverse those negative outcomes.

Many papers (46% of the 92 reviewed) cited US national surveys from the early 1990s, either as a source for their own institution's thresholds or to highlight the heterogeneity of thresholds currently used by different institutions. The fact that the 1992 CAP Q-Probes survey of 623 institutions was not published in full until 2002 *(16, 31)* may mislead laboratories to believe that the data were more recent. The Medical Laboratory Observer journal publishes a table each year using the 1990 Kost survey for the adult thresholds *(30, 67)*, and some institutions may overlook the age of these data when referring to it. The high frequency at which this valuable but old data set is referred to simply reflects the lack of new research being performed in the area.

Ideally, alert thresholds should be based on well-designed clinical outcome studies. Studies should focus on specific clinical conditions where the concentration of the analyte of interest is already known to impact or be a primary indicator of the outcome. The main question to be answered by a study should be at what concentration is the analyte predictive of a poor outcome. Since the aim of setting alert thresholds is to prevent mortality, outcome studies should also measure the response to treatment to determine at what analyte concentration intervention is still helpful.

Our review assessed 2 evidence dimensions, i.e., the actual source of the data and the stakeholders involved in setting alert thresholds. For a number of analytes, the alert thresholds set by laboratories were notably different to those derived by clinicians. In cases where the laboratory and clinicians discussed and agreed on alert thresholds the level of consensus was reflected in the actual thresholds set, which were either in-between or leaned more towards the preference of laboratories. This suggests that more discussion is required between the laboratory and clinical professions for a better tailored critical risk result notification system.

Apart from more conservative thresholds used by North America for potassium and creatinine, alert thresholds were similar across different continents. It is reasonable to assume that these similarities are a result of all continents using the same literature sources for setting their thresholds. Specimen-type preferences of individual laboratories may have contributed to the variation in potassium thresholds between continents, since the mean estimated difference in the concentration of potassium in serum and plasma is 0.36 (0.18) mmol/L *(68)*. Unfortunately, it was not possible to explore the impact of specimen type on potassium thresholds, because this information was rarely specified in the reviewed documents.

In most papers retrieved, method-specific alert thresholds were not given, which makes the transferability of published data difficult. Therefore, the alert threshold data presented in this paper likely represent a mixture of non-standardized and non-harmonized assay methodologies. However, a global movement is currently underway to harmonize measurement and reporting of pathology results, so that results obtained from different laboratories are comparable *(69)*. Based on expert review of extensive analytical bias studies on multiple automated platforms, the UK *(24)*, the Nordic countries *(22, 23)* and Australasia *(25)* have developed nationally harmonized reference intervals for common biochemistry analytes. Thus, for the 21 analytes identified in this study as having harmonized reference intervals in at least 1 country, the methodology used to create the alert threshold evidence may not matter.

Looking forward, laboratories should first ensure that they are using traceable calibration material to minimize method bias. When building an alert list, laboratories should consider whether their methodology produces comparable results to the methodology used to create the alert threshold evidence. For tests that are commonly measured by analytical techniques that vary in specificity (e.g., cortisol by immunoassay or LCMS), laboratories should only use alert threshold evidence that is based on their analytical methodology.

Analytes with alert thresholds most frequently reported in the literature (i.e., potassium, sodium, glucose, calcium, hemoglobin and platelets) coincide with the clinically most important critical risk results. However, the majority of papers analyzed in this review presented alert thresholds that were only a portion of their institutions' alert list. Therefore, laboratories should not take failure of an analyte to be selected for review in this paper as evidence to remove such tests from their alert list.

To determine which analytes should be included on the alert list, the CLSI guideline *Management of Critical- and Significant-Risk Results* recommends that a risk assessment process is followed *(6)*. The risk assessment

should identify the likelihood and severity of harm associated with the proposed alert threshold, whether intervention can reduce the risk of harm, and the likelihood that routine reporting would not permit timely intervention. Whether or not routine reporting will lead to timely intervention may depend on organizational factors. For example, results reported routinely are more likely to be missed by clinicians than results delivered personally. Thus, institutions without other safeguards to prevent actionable results from being missed may need to include analytes that trigger less urgent intervention on their alert list.

Limitations of the Review

The terminology for describing critical risk results is not standardized. Consequently, it is possible that some evidence was missed owing to authors using less common terminology. Examples of less commonly used terminology include abnormal results, clinically significant results, significantly abnormal results, and markedly abnormal results. However, incorporating these terms into the search would have made the information unmanageably large for relatively little return. Relevant papers may also have been missed if they were not indexed by one of the subject headings used in the database searches.

It is not customary to publish best practice guidelines in peer reviewed journals. Guidelines are more typically disseminated via organizations that operate as national guideline repositories. In fact, two-thirds of the professional body recommendations described in this paper were identified by following up responses from a targeted survey of European and South American societies of laboratory medicine. Considering that several countries did not respond, and Asian and African countries were not invited to participate in the survey, it is likely that our search of the grey literature has missed some alert threshold recommendations by professional bodies.

Conclusion

There is a lack of evidence and explicit reasoning in the literature to support the selection of alert thresholds for communicating critical risk laboratory results. Most alert thresholds published in the literature come from individual institutions or national surveys which, at best, represent the state of the art. The majority of alert thresholds can be traced back to some relatively old surveys or publications. The best literature sources currently available to guide laboratories in setting their alert thresholds are recommendations based on consensus of clinicians and laboratory professionals from the Massachusetts group, Royal College of Pathologists (UK), and the Norwegian Society for Medical Biochemistry. Well-designed outcome studies and clinical audit are needed to test and validate proposed threshold settings.

Currently applied thresholds may have prognostic value but there is limited evidence that reversal of such critical risk results truly saves lives. Linking critical risk laboratory results to hard outcomes such as morbidity and mortality is important and informative, but future outcome studies should investigate thresholds that trigger medical action known to contribute to improved patient survival. Until higher level of evidence becomes available, we recommend the following:

1. Laboratories and researchers publishing in this field are encouraged to explicitly describe the methodology and the source of, and reasoning behind, their alert thresholds, as well as the patient population, the specimen type and the analytical methods of tests to which these thresholds apply;
2. Professional societies making recommendations for harmonized critical risk results should assess clinical needs by carrying out broader clinical surveys and consult widely with clinical stakeholders;
3. Laboratories should assess the quality and strength of evidence and seek local consensus from clinicians before adopting published alert thresholds.

We believe that the currently available evidence presented in this systematic review, even if weak, will support stakeholders in commencing greater collaboration and research that will ultimately support the contribution of medical laboratories to improved patient safety and outcomes.

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3.5 Article II - Corrections

The article "What Alert Thresholds Should Be Used to Identify Critical Risk Results: A Systematic Review of the Evidence" (Clin Chem 2016;62:1445–57), published in the November 2016 issue of *Clinical Chemistry*, contains transcription/conversion errors in 3 tables. In Table 1, the low threshold, median (range) [n] for ionized calcium under "4a. Laboratory and clinicians" should be 3.0 (3.0–3.0) *(1)*; the high threshold, median (range) [n] for uric acid under "4a. Laboratory and clinicians" should be 13.0 (10.0–13.0) *(4)*; the low threshold, median (range) [n] for magnesium under "4c. Laboratory" should be 1.0 (0.71–1.3) *(13)*; and the high threshold, median (range) [n] for calcium under "4c. Laboratory" should be 13.0 (11.2–14.1) *(15)*. In Table 2, the low threshold, median (range) [n] for ionized calcium under "3c. Laboratory" should be 3.2 (3.0–3.3) *(3)*. In Table 3, the high threshold, median (range) [n] for pH under "2a. Laboratory and clinicians" should be 7.60 (7.60–7.60) *(1)*. The corrected tables are included below. The authors and the Journal regret the errors.

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Table 1. Level 4 evidence–alert thresholds reported by individual institutions.[a]

	4a. Laboratory and clinicians		4b. Clinicians		4c. Laboratory	
Analytes, conventional units	Low threshold, median (range) [n]	High threshold, median (range) [n]	Low threshold, median (range) [n]	High threshold, median (range) [n]	Low threshold, median (range) [n]	High threshold, median (range) [n]
Potassium, mmol/L	2.75 (2.0-3.2) [12]	6.25 (6.0-7.0) [12]	2.5 (2.0-3.0) [7]	6 (5.5-7.0) [7]	2.8 (2.0-3.0) [21]	6.05 (5.9-7.0) [22]
Sodium, mmol/L	120 (115-125) [12]	160 (150-160) [12]	120 (105-125) [7]	157.5 (150-165) [6]	120 (110-125) [18]	160 (150-160) [17]
Glucose, mg/dL	45.1 (34.2-50.5) [11]	450 (301-799) [13]	43.4 (30.1-72.0) [6]	442 (324-800) [6]	45.1 (40.0-54.1) [17]	450 (360-991) [17]
Calcium, mg/dL	6.0 (6.0-6.6) [8]	13.0 (10.8-14.0) [10]	5.5 (5.0-6.0) [2]	14.0 (13.0-15.0) [2]	6.5 (6.0-7.2) [14]	13.0 (11.2-14.1) [15]
Hemoglobin, g/dL	6.25 (5.0-8.0) [8]	19.95 (19.9-20.0) [4]	6.6 (5.0-7.5) [3]	19.9 (19.9-19.9) [1]	6.6 (5.0-7.0) [15]	20.0 (19.9-20.0) [5]
Platelets, $\times 10^3/\mu L$	20 (10-40) [9]	1000 (999-1000) [5]	10 (5-50) [3]		40 (10-50) [13]	1000 (800-1000) [8]
Magnesium, mg/dL	1.0 (0.75-1.2) [5]	5.0 (4.7-7.0) [3]	1.2 (1.2-1.2) [1]		1.0 (0.71-1.3) [13]	6.0 (4.7-12.2) [10]
Phosphorus, mg/dL	0.99 (0.99-1.49) [6]	9.0 (5.5-9.0) [4]	1.6 (1.6-1.6) [1]		0.99 (0.93-1.7) [8]	9.4 (9.0-9.9) [2]
WBC,[b] count/μL	1,500 (500-3,000) [7]	50 000 (30 000-100 000) [6]			1,500 (500-2,000) [13]	50 000 (20 000-100 000) [11]
APTT, s	12 (12-12) [1]	82.5 (50-110) [6]		50 (50-50) [1]	19 (19-19) [1]	85 (75-200) [13]
Creatinine, mg/dL		3.6 (2.0-7.4) [4]		2.0 (1.7-7.4) [4]		5.7 (3.0-7.4) [6]
Urea, mg/dL		100 (35.0-216) [4]		34.6 (29.1-40.0) [2]	2.0 (2.0-2.0) [1]	92.0 (80.1-140) [6]
pH	7.20 (7.15-7.20) [5]	7.595 (7.58-7.60) [4]			7.20 (7.10-7.20) [10]	7.60 (7.59-7.70) [8]
INR		4.75 (3.5-7.0) [4]	1.5 (1.5-1.5) [1]	4.25 (3-5.0) [4]	1.5 (1.5-1.5) [2]	4.9 (3.5-7.0) [12]
Fibrinogen, mg/dL	100 (100-100) [2]	700 (700-700) [1]	100 (75-150) [3]		95 (50-100) [8]	750 (700-800) [2]
P_{O_2}, mmHg	40 (40-40) [4]				40 (40-50) [7]	
Digoxin, ng/mL		3.0 (1.94-4.0) [5]				2.3 (2.0-2.5) [8]
Bicarbonate, mmol/L	12 (12-12) [3]	38 (36-40) [2]	14 (14-14) [1]	34 (34-34) [1]	10 (9-15) [7]	40.5 (40-50) [6]
Hematocrit, %	20 (15-24) [4]	60 (60-60) [2]	14.5 (14-15) [2]		20 (18-30) [7]	58 (54-60) [6]
P_{CO_2}, mmHg	20 (20-25) [5]	70 (60-75) [5]			20 (10-20) [7]	67 (45-75) [7]
Ionized calcium, mg/dL	3.0 (3.0-3.0) [1]	6.46 (6.3-6.6) [2]			3.2 (3.0-3.2) [7]	6.2 (6.0-7.0) [7]
Prothrombin time, s	8 (8-8) [1]	30 (25-30) [3]				33 (30-60) [8]
Chloride, mmol/L	75 (75-75) [1]	125 (125-125) [1]	92 (92-92) [1]	120 (120-120) [1]	75 (75-80) [5]	122.5 (115-130) [4]
Lithium, mmol/L		1.75 (1.49-2.0) [4]				2.0 (1.5-2.0) [5]
Uric acid, mg/dL		13.0 (10.0-13.0) [4]				13.0 (13.0-13.0) [2]
Phenytoin, μg/mL		30 (30-30) [2]				28.5 (20-40) [6]
Theophylline, μg/mL		20 (20-20) [2]				20 (20-25) [4]
Lactate, mg/dL		31 (31-31) [1]				36 (31-45) [5]
Amylase, U/L		300 (110-400) [4]				200 (200-200) [2]
ALT, U/L		100 (75-1500) [3]		189 (189-189) [1]		1000 (1000-1000) [2]

[a] n = No. of papers used as source of data.
[b] APTT, activated partial thromboplastin time; ALT, alanine aminotransferase.

Table 2. Level 3 evidence–alert thresholds from surveys of laboratories or clinicians.[a]

Analytes, conventional units	3b. Clinicians		3c. Laboratory	
	Low threshold, median (range) [n]	High threshold, median (range) [n]	Low threshold, median (range) [n]	High threshold, median (range) [n]
Potassium, mmol/L	2.5 (2.5–2.5) [1]	6.0 (6.0–6.0) [1]	2.8 (2.6–2.9) [11]	6.2 (6.0–6.5) [11]
Sodium, mmol/L	120 (120–120) [1]	160 (160–160) [1]	120 (120–125) [10]	159 (155–160) [10]
Glucose, mg/dL	45.1 (45.1–45.1) [1]	541 (541–541) [1]	45.1 (39.6–50.1) [9]	418 (360–485) [9]
Calcium, mg/dL	5.2 (5.2–5.2) [1]	15.2 (15.2–15.2) [1]	6.4 (5.6–7.1) [11]	12.9 (12.0–14.0) [11]
Hemoglobin, g/dL	9.0 (9.0–9.0) [1]		6.75 (5.3–7.5) [8]	20.0 (18.4–20.0) [8]
Platelets, $\times 10^3/\mu L$			40 (30–50) [8]	999 (700–1000) [8]
Magnesium, mg/dL	0.97 (0.97–0.97) [1]		1.1 (0.80–1.2) [8]	4.9 (4.1–7.9) [8]
Phosphorus, mg/dL	0.77 (0.77–0.77) [1]		1.2 (0.99–1.2) [8]	8.7 (8.0–9.3) [7]
WBC,[b] count/μL			2,000 (2,000–2,000) [6]	33 500 (25 000–46 000) [6]
APTT, s			19 (18–20) [3]	87.5 (68–110) [8]
Creatinine, mg/dL			0.20 (0.18–0.31) [4]	5.2 (3.4–7.6) [9]
Urea, mg/dL			4.6 (3.1–11.2) [4]	87.7 (75.6–213) [9]
pH	6.90 (6.90–6.90) [1]	7.70 (7.70–7.70) [1]	7.205 (7.20–7.44) [4]	7.595 (7.55–7.60) [4]
INR				5.5 (5.0–6.0) [2]
Fibrinogen, mg/dL			100 (88–100) [3]	787.5 (775–800) [2]
Po_2, mmHg	35 (35–35) [1]		43.5 (40–60) [4]	102 (93–111) [2]
Digoxin, ng/mL				2.3 (2.0–3.0) [3]
Bicarbonate, mmol/L	10 (10–10) [1]		11 (10–15) [6]	40 (39–40) [6]
Hematocrit, %			20 (18–24) [3]	60 (60–61) [3]
Pco_2, mmHg			20 (19–20) [3]	68 (60–70) [4]
Ionized calcium, mg/dL	2.4 (2.4–2.4) [1]	6.8 (6.8–6.8) [1]	3.2 (3.0–3.3) [3]	6.2 (6.0–6.3) [3]
Prothrombin time, s			9 (9–9) [2]	28 (25–37) [5]
Chloride, mmol/L			80 (75–85) [6]	120.5 (115–126) [6]
Lithium, mmol/L				1.5 (1.4–2.0) [3]
Uric acid, mg/dL			1.0 (1.0–1.0) [1]	12.9 (11.8–13.0) [4]
Phenytoin, μg/mL				25 (25–30) [3]
Theophylline, μg/mL				23 (23–25) [3]
Lactate, mg/dL			0.5 (0.5–0.5) [1]	31 (4.0–45) [3]
Amylase, U/L				388 (350–470) [3]
ALT, U/L				750 (500–1000) [2]

[a] n = No. of papers used as source of data.
[b] APTT, activated partial thromboplastin time; ALT, alanine aminotransferase.

Table 3. Level 2 evidence–alert thresholds recommended by professional bodies.[a]

Analytes, conventional units	2a. Laboratory and clinicians		2c. Laboratory	
	Low threshold, median (range) [n]	High threshold, median (range) [n]	Low threshold, median (range) [n]	High threshold, median (range) [n]
Potassium, mmol/L	2.5 (2.5–2.8) [3]	6.2 (6.0–6.5) [3]	2.8 (2.8–2.8) [3]	6.2 (6.0–6.2) [3]
Sodium, mmol/L	120 (120–120) [3]	155 (150–160) [3]	120 (120–120) [3]	160 (160–160) [3]
Glucose, mg/dL	47.6 (45.1–50.1) [2]	414 (400–450) [3]	40.0 (39.6–45.1) [3]	446 (400–500.9) [3]
Calcium, mg/dL	7.2 (7.0–7.2) [3]	13.0 (12.8–14.0) [3]	6.6 (6.0–7.0) [3]	13.0 (12.0–14.0) [3]
Hemoglobin, g/dL	7.0 (7.0–7.0) [2]	19.0 (19.0–19.0) [1]	7.0 (6.6–7.0) [3]	20.0 (19.9–20.0) [3]
Platelets, $\times 10^3/\mu L$	25 (20–30) [2]	1250 (1000–1500) [2]	40 (20–40) [3]	1000 (999–1000) [3]
Magnesium, mg/dL	1.1 (0.97–1.2) [2]	5.0 (4.9–5.1) [2]	1.0 (1.0–1.0) [3]	8.4 (4.6–12.2) [2]
Phosphorus, mg/dL	0.96 (0.93–0.99) [2]		0.99 (0.93–0.99) [4]	9.0 (8.9–9.0) [4]
WBC,[b] count/μL	1,500 (1,500–1,500) [1]	100 000 (100 000–100 000) [1]	2,000 (2,000–2,000) [3]	40 000 (30 000–50 000) [3]
APTT, s				78 (75–120) [3]
Creatinine, mg/dL		4.5 (4.0–4.5) [3]		5.0 (4.0–7.4) [3]
Urea, mg/dL		100 (84.0–112) [3]		80.1 (46.8–99.7) [3]
pH	7.20 (7.20–7.20) [1]	7.60 (7.60–7.60) [1]	7.20 (7.20–7.20) [2]	7.60 (7.60–7.60) [2]
INR		6.25 (6.0–6.5) [2]		5.0 (5.0–5.0) [1]
Fibrinogen, mg/dL			80 (80–100) [3]	800 (800–800) [1]
Po_2, mmHg	60 (60–60) [1]		41.5 (40–43) [2]	
Digoxin, ng/mL		2.5 (2.5–2.5) [1]		2.0 (2.0–2.0) [1]
Bicarbonate, mmol/L	15 (15–15) [1]		10 (10–10) [1]	40 (40–40) [1]
Hematocrit, %			20 (18–20) [3]	60 (60–61) [3]
Pco_2, mmHg			19.5 (19–20) [2]	68.5 (67–70) [2]
Ionized calcium, mg/dL	3.4 (3.2–3.5) [2]	6.2 (6.0–6.4) [2]	3.1 (3.1–3.1) [1]	6.4 (6.4–6.4) [1]
Prothrombin time, s				35 (30–40) [2]
Chloride, mmol/L			77.5 (75–80) [2]	122.5 (120–125) [2]
Lithium, mmol/L		1.5 (1.5–1.5) [1]		
Uric acid, mg/dL				13.0 (13.0–13.0) [1]
Phenytoin, μg/mL		25 (25–25) [1]		
Theophylline, μg/mL		25 (25–25) [1]		
Lactate, mg/dL		45 (45–45) [1]		45 (45–45) [1]
Amylase, U/L		500 (500–500) [1]		1000 (1000–1000) [1]
ALT, U/L		587.5 (500–675) [2]		800 (600–1000) [2]

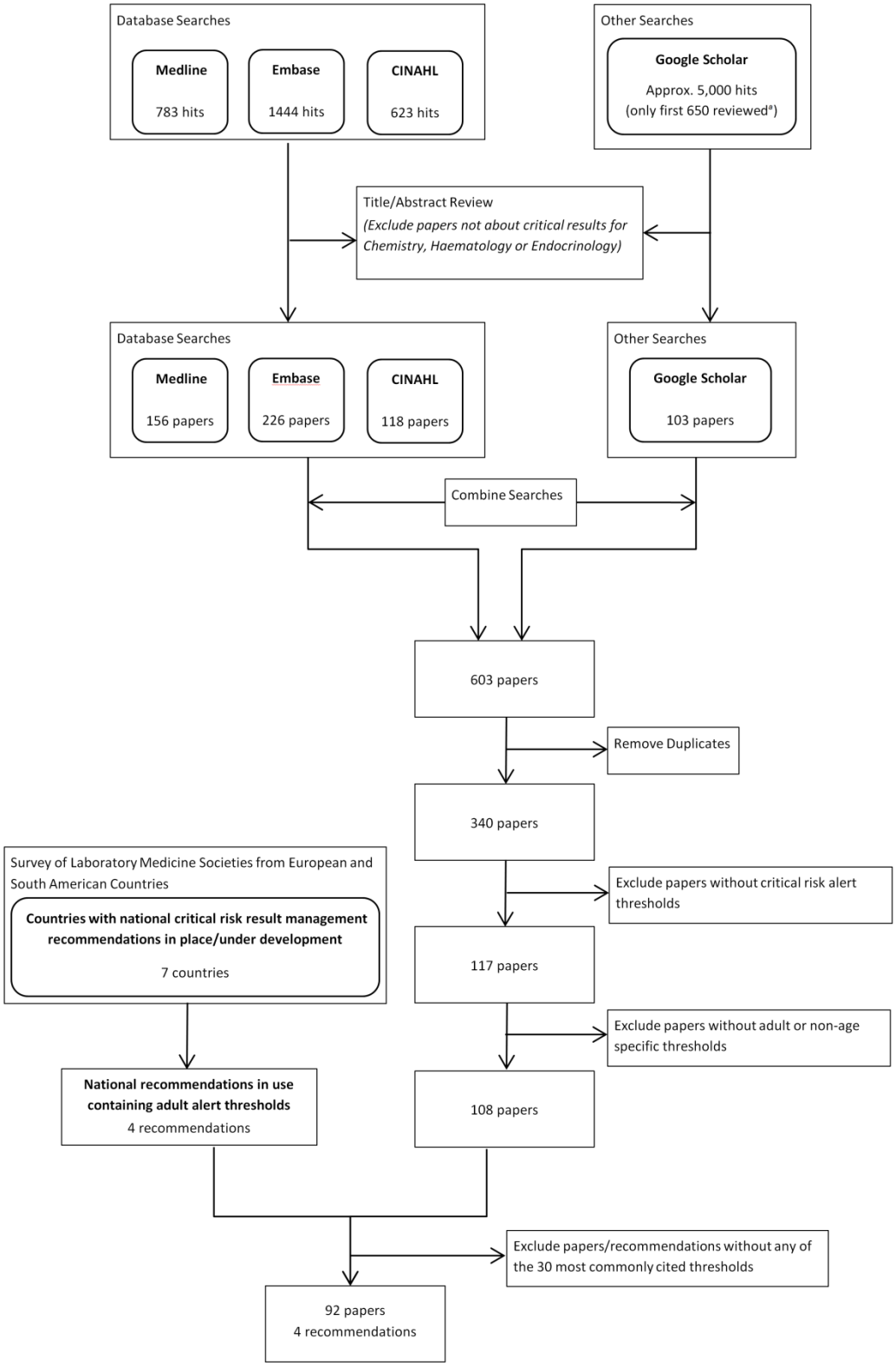
[a] n = No. of papers used as source of data.
[b] APTT, activated partial thromboplastin time; ALT, alanine aminotransferase.

3.6 Article II – Supplemental Data

Supplemental Table 1: Literature search parameters

DATABASE	Medline	Embase	CINAHL	Google Scholar
KEY TERMS (at least one of)	• alert adj3 limit(s) • alert adj3 value(s) • critical adj3 alert(s) • critical adj3 limit(s) • critical adj3 result(s) • critical adj3 value(s) • panic adj3 value(s)	• alert adj3 limit(s) • alert adj3 value(s) • critical adj3 alert(s) • critical adj3 limit(s) • critical adj3 result(s) • critical adj3 value(s) • panic adj3 value(s)	• alert N2 limit(s) • alert N2 value(s) • critical N2 alert(s) • critical N2 limit(s) • critical N2 result(s) • critical N2 value(s) • panic N2 value(s)	• critical values • critical laboratory values • critical results • critical laboratory results • critical limits • critical alerts • panic values • alert values
KEYWORDS (all of)				• pathology • laboratory • test
SUBJECT HEADINGS (at least one of)	• exp Laboratories/ • Pathology, Clinical/ • Clinical Laboratory Techniques/ • Diagnostic Tests, Routine/ • Chemistry, Clinical/ • exp Clinical Chemistry Tests/ • Endocrinology/ • exp Diagnostic Techniques, Endocrine/ • Hematology/ • exp Hematologic Tests/ • Reference Values/ • Communication/ • Clinical Laboratory Information Systems/ • Quality Assurance, Health Care/ • Practice Guidelines as Topic/ • Patient Safety/ • Societies, Medical/ • Questionnaires/ • Retrospective studies/	• exp clinical laboratory/ or exp hospital laboratory/ or exp core laboratory/ or exp laboratory/ • pathology/ • diagnostic procedure/ • diagnostic test/ or laboratory test/ • clinical chemistry/ • exp blood chemistry/ • endocrinology/ • exp endocrine system examination/ • hematology/ • exp blood examination/ • reference value/ • interpersonal communication/ • hospital information system/ • health care quality/ • practice guideline/ • patient safety/ • medical society/ • questionnaire/ • retrospective study/	• Laboratories+ • Pathology, Clinical • Diagnosis, Laboratory • Diagnostic Tests, Routine • Chemistry, Clinical • Blood Chemical Analysis+ • Endocrinology • Diagnosis, Endocrine+ • Hematology • Hematologic Tests+ Reference Values • Communication • Clinical Laboratory Information Systems • Quality Assurance • Practice Guidelines • Patient Safety • Medical Organizations • Questionnaires • Retrospective study	
DATE SEARCH LIMITS	Date: 1995 - 2014	Date: 1995 - 2014	Date: 1995 - 2014	Date: 1995 - 2014

Supplemental Figure 1: Paper selection process for literature review



[a] Only the first 650 of the 5,000 search results were reviewed. Note that the google scholar search results were sorted by relevance, and the review was halted after more than 100 consecutive non-relevant references were encountered.

Supplemental Table 2: References selected for the literature review, and rating of the thresholds within each reference (according to the 2 dimensional ranking system).

No.	Reference	Rank for Level of Evidence
1	Lum G. Should the transfusion trigger and hemoglobin low critical limit be identical? Ann Clin Lab Sci 1997;27:130-4.	1a
2	Howanitz JH, Howanitz PJ. Evaluation of total serum calcium critical values. Arch Pathol Lab Med 2006;130:828-30.	1a
3	Howanitz JH, Howanitz PJ. Evaluation of serum and whole blood sodium critical values. Am J Clin Pathol 2007;127:56-9.	1a
4	Sheldon SH, Saenger AK, Jaffe AS. Incidence and significance of elevated lactate in the identification of critically ill patients. Clin Chem Lab Med 2012;50:1819-23.	1a
5	Doering TA, Plapp F, Crawford JM. Establishing an evidence base for critical laboratory value thresholds. Am J Clin Pathol 2014;142:617-28.	1a
6	Rayan N, Baird R, Masica A. Rapid response team interventions for severe hyperkalemia: evaluation of a patient safety initiative. Hosp Pract (1995) 2011;39(1):161-9.	1b
7	Hagemo JS, Stanworth S, Juffermans NP, Brohi K, Cohen M, Johansson PI, et al. Prevalence, predictors and outcome of hypofibrinogenaemia in trauma: a multicentre observational study. Crit Care 2014;18(2):R52.	1b
8	Lum G. Evaluation of a laboratory critical limit (alert value) policy for hypercalcemia. Arch Pathol Lab Med 1996;120:633-6.	1c
9	Matsuo S, Yamamoto Y, Asano H, Takahashi H. Influence of hyperkalemia on clinical decision making [Japanese]. Rinsho Byori 1996;44:1087-92.	1c
10	Hanna D, Griswold P, Leape LL, Bates DW. Communicating critical test results: safe practice recommendations. Jt Comm J Qual Patient Saf 2005;31:68-80.	2a
11	The Royal College of Pathologists (UK). Out-of-hours reporting of laboratory results requiring urgent clinical action to primary care: Advice to pathologists and those that work in laboratory medicine. November 2010. https://www.rcpath.org/profession/publications/cross-specialty-publications.html (Withdrawn 2015, guideline under review).	2a
12	Aakre KM, Hov GG, Skadberg O, Piehler A, Distante S, Hager HB. Notification of highly abnormal laboratory results to doctors outside hospitals. Tidsskr Nor Laegeforen 2013;133(21):E1-6.	2a
13	Emancipator K. Critical values: ASCP practice parameter. American Society of Clinical Pathologists. Am J Clin Pathol 1997;108:247-53.	2c
14	Croatian Chamber of Medical Biochemists. Critical values. 15 Jan 2006. http://www.hkmb.hr/povjerenstva/strucna-pitanja.html#vrijednosti (Accessed January 2016).	2c
15	Polish Society of Laboratory Diagnostics. Principles of dealing with critical values. 14 Jan 2010. http://www.ptdl.pl/download/Wartosci_krytyczne.pdf (Accessed January 2016).	2c
16	Boldt J, Lenz M, Kumle B, Papsdorf M. Volume replacement strategies on intensive care units: results from a postal survey. Intensive Care Med 1998;24:147-51.	3b
17	Don-Wauchope AC, Chetty VT. Laboratory defined critical value limits: how do hospital physicians perceive laboratory based critical values? Clin Biochem 2009;42:766-70.	3b
18	Lum G. Critical limits (alert values) for physician notification: universal or medical center specific limits? Ann Clin Lab Sci 1998;28:261-71.	3c
19	Kost GJ. Table of critical limits. MLO Med Lab Obs 1999;31(7 Suppl):12-3.	3c
20	Howanitz PJ, Steindel SJ, Heard NV. Laboratory critical values policies and procedures: a college of American Pathologists Q-Probes Study in 623 institutions. Arch Pathol Lab Med 2002;126:663-9.	3c
21	Tillman J, Barth JH, Group ACBNA. A survey of laboratory 'critical (alert) limits' in the UK. Ann Clin Biochem 2003;40:181-4.	3c
22	Wagar EA, Friedberg RC, Souers R, Stankovic AK. Critical values comparison: a College of American Pathologists Q-Probes survey of 163 clinical laboratories. Arch Pathol Lab Med 2007;131:1769-75.	3c
23	Llopis Diaz MA, Gomez Rioja R, Alvarez Funes V, Martinez Bru C, Cortes Rius M, Barba Meseguer N, et al. Critical values reporting: Results of a Spanish laboratories survey [Spanish]. Rev Lab Clin 2010;3:177-82.	3c
24	Piva E, Sciacovelli L, Laposata M, Plebani M. Assessment of critical values policies in Italian institutions: comparison with the US situation. Clin Chem Lab Med 2010;48:461-8.	3c
25	Sirisali K, Manochiopinij S, Leelahakul P, Ruengrai V, Sattayakom A, Sirisali S. Critical value of the clinical laboratory test in Thailand. J Med Assoc Thai 2010;93(Suppl 6):S22-7.	3c
26	McClain CM, Owings R, Bornhorst JA. Heterogeneity of publicly accessible online critical values for therapeutic drugs. J Pathol Inform 2011;2:53.	3c
27	Pai M, Moffat KA, Plumhoff E, Hayward CP. Critical values in the coagulation laboratory: results of a survey of the North American Specialized Coagulation Laboratory Association. Am J Clin Pathol 2011;136:836-41.	3c
28	Campbell C, Horvath A. Towards harmonisation of critical laboratory result management-Review of the literature and survey of Australasian practices. Clin Biochem Rev 2012;33:149-60.	3c
29	Patra S, Mukherjee B, Sahoo S. An analysis of critical value system in tertiary care hospitals in Bhubaneswar, Odisha. Int J Bioassays 2013;2:430-2.	3c
30	Zeng R, Wang W, Wang Z. National survey on critical values notification of 599 institutions in China. Clin Chem Lab Med 2013;51:2099-107.	3c

31	Schapkaitz E, Mafika Z. Critical value reporting: a survey of 36 clinical laboratories in South Africa. S Afr Med J 2014;104:65-7.	3c
32	McFarlane A, Aslan B, Raby A, Bourner G, Padmore R. Critical values in Hematology. Int Jnl Lab Hem 2015;37:36-43.	3c
33	Tate KE, Gardner RM, Scherting K. Nurses, pagers, and patient-specific criteria: three keys to improved critical value reporting. Proc Annu Symp Comput Appl Med Care 1995:164-8.	4a
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Supplemental Table 3: Alert thresholds used in different regions of the world

Analytes	North America		Europe		Asia	
	Low Threshold Median (Range) [*n*]	**High Threshold Median (Range)** [*n*]	**Low Threshold Median (Range)** [*n*]	**High Threshold Median (Range)** [*n*]	**Low Threshold Median (Range)** [*n*]	**High Threshold Median (Range)** [*n*]
Potassium (mmol/L)	**2.8 (2.0 - 3.2)** [*24*]	**6.0 (5.5 - 6.3)** [*27*]	**2.65 (2.0 - 3.0)** [*18*]	**6.25 (6.0 - 7.0)** [*18*]	**2.6 (2.5 - 3.0)** [*11*]	**6.5 (6.0 - 7.0)** [*13*]
Sodium (mmol/L)	**120 (105 - 125)** [*23*]	**160 (150 - 165)** [*20*]	**120 (115 - 125)** [*18*]	**160 (150 - 165)** [*17*]	**120 (110 - 121)** [*10*]	**160 (155 - 160)** [*10*]
Glucose (mmol/L)	**2.5 (1.67 - 4.0)** [*20*]	**24.9 (18 - 44.4)** [*20*]	**2.5 (1.9 - 3.0)** [*15*]	**25 (16.7 - 55.0)** [*19*]	**2.5 (2.2 - 2.8)** [*10*]	**24.45 (22.0 - 44.3)** [*10*]
Calcium (mmol/L)	**1.50 (1.25 - 1.75)** [*15*]	**3.25 (2.99 - 3.80)** [*17*]	**1.65 (1.50 - 1.80)** [*15*]	**3.25 (2.70 - 3.53)** [*16*]	**1.545 (1.40 - 1.75)** [*8*]	**3.29 (3.00 - 3.50)** [*9*]
Hemoglobin (g/L)	**70 (50 - 75)** [*15*]	**200 (199 - 200)** [*8*]	**66 (50 - 80)** [*17*]	**199 (190 - 200)** [*9*]	**60 (50 - 70)** [*7*]	**200 (184 - 200)** [*3*]
Platelets (x 10^9/L)	**40 (5 - 50)** [*16*]	**999.5 (910 - 1000)** [*10*]	**20 (10 - 40)** [*13*]	**1000 (900 - 1500)** [*9*]	**40 (10 - 50)** [*7*]	**1000 (700 - 1000)** [*5*]
Magnesium (mmol/L)	**0.41 (0.29 - 0.50)** [*15*]	**2.02 (1.69 - 2.88)** [*13*]	**0.48 (0.40 - 0.50)** [*11*]	**2.225 (1.89 - 5.00)** [*8*]	**0.46 (0.41 - 0.51)** [*3*]	**2.11 (1.93 - 3.25)** [*3*]
Phosphorus (mmol/L)	**0.32 (0.25 - 0.52)** [*13*]	**2.725 (1.78 - 3.20)** [*6*]	**0.32 (0.30 - 0.39)** [*12*]	**2.90 (2.87 - 2.91)** [*5*]	**0.35 (0.32 - 0.40)** [*4*]	**2.81 (2.58 - 2.91)** [*3*]
WBC (x 10^9/L)	**2 (0.5 - 3)** [*12*]	**33.5 (20 - 100)** [*12*]	**1.75 (0.5 - 2)** [*8*]	**50 (40 - 50)** [*7*]	**1.5 (1 - 2)** [*7*]	**30 (20 - 50)** [*7*]
APTT (seconds)	**18 (12 - 19)** [*3*]	**90 (50 - 200)** [*15*]		**85 (75 - 120)** [*8*]	**20 (20 - 20)** [*1*]	**80 (70 - 180)** [*5*]
Creatinine (umol/L)	**18 (18 - 18)** [*1*]	**398 (150 - 654)** [*10*]		**481 (177 - 657)** [*14*]	**18 (16 - 27)** [*3*]	**546 (442 - 670)** [*4*]
Urea (mmol/L)	**1.1 (1.1 - 1.1)** [*1*]	**29.9 (10.4 - 42.8)** [*10*]		**35.6 (16.7 - 77.0)** [*11*]	**1.65 (0.7 - 4.0)** [*4*]	**31.3 (28.6 - 46.9)** [*5*]
pH	**7.20 (7.10 - 7.25)** [*10*]	**7.60 (7.55 - 7.70)** [*9*]	**7.20 (7.10 - 7.20)** [*6*]	**7.60 (7.60 - 7.70)** [*6*]	**7.20 (7.15 - 7.44)** [*4*]	**7.60 (7.58 - 7.60)** [*3*]
INR	**1.5 (1.5 - 1.5)** [*3*]	**5.0 (3.0 - 7.0)** [*12*]		**5.0 (4.5 - 7.0)** [*8*]		**4.0 (3.5 - 5.0)** [*3*]
Fibrinogen (g/L)	**1.0 (0.6 - 1.0)** [*10*]	**8.0 (7.75 - 8.0)** [*3*]	**1.0 (0.5 - 2.29)** [*9*]	**7.5 (7.0 - 8.0)** [*2*]	**1.0 (1.0 - 1.0)** [*2*]	**7.0 (7.0 - 7.0)** [*1*]
pO2 (mmHg)	**40 (35 - 60)** [*11*]	**111 (111 - 111)** [*1*]	**43 (40 - 50)** [*4*]		**40 (40 - 44)** [*3*]	**93 (93 - 93)** [*1*]
Digoxin (ng/mL)		**2.5 (2.0 - 4.0)** [*7*]		**2.25 (2.0 - 3.6)** [*8*]		**2.4 (2.4 - 2.4)** [*1*]
Bicarbonate (mmol/L)	**10 (10 - 14)** [*14*]	**40 (34 - 50)** [*10*]	**11 (9 - 15)** [*3*]	**41 (39 - 50)** [*3*]	**10.5 (10 - 11)** [*2*]	**39.5 (39 - 40)** [*2*]
Hematocrit (%)	**20 (14 - 30)** [*12*]	**60 (54 - 61)** [*8*]	**20 (18 - 20)** [*3*]	**60 (60 - 61)** [*3*]	**20 (20 - 20)** [*1*]	**60 (60 - 60)** [*1*]
pCO2 (mmHg)	**20 (10 - 25)** [*8*]	**68.5 (45 - 70)** [*8*]	**20 (19 - 20)** [*6*]	**67 (60 - 70)** [*5*]	**20 (20 - 20)** [*3*]	**70 (69 - 75)** [*3*]
Ionized Calcium (mmol/L)	**0.80 (0.60 - 0.88)** [*8*]	**1.58 (1.50 - 1.75)** [*9*]	**0.79 (0.75 - 0.80)** [*6*]	**1.60 (1.54 - 1.65)** [*5*]		
Prothrombin Time (seconds)	**8.5 (8 - 9)** [*2*]	**30 (25 - 37)** [*10*]		**35 (30 - 40)** [*2*]	**9 (9 - 9)** [*1*]	**30 (28 - 60)** [*5*]
Chloride (mmol/L)	**75 (75 - 92)** [*5*]	**125 (120 - 130)** [*5*]	**75 (75 - 85)** [*7*]	**125 (115 - 125)** [*7*]	**80 (80 - 80)** [*3*]	**120 (115 - 121)** [*3*]
Lithium (mmol/L)		**2.0 (2.0 - 2.0)** [*4*]		**1.5 (1.4 - 2.0)** [*5*]		**2.0 (2.0 - 2.0)** [*1*]
Uric Acid (umol/L)	**59 (59 - 59)** [*1*]	**773 (761 - 892)** [*4*]		**773 (595 - 774)** [*8*]		
Phenytoin (ug/mL)		**30 (20 - 40)** [*5*]		**27 (25 - 30)** [*5*]		**20 (20 - 20)** [*1*]
Theophylline (ug/mL)		**25 (20 - 25)** [*5*]		**21.5 (20 - 25)** [*4*]		**20 (20 - 20)** [*1*]
Lactate (mmol/L)	**0.06 (0.06 - 0.06)** [*1*]	**3.7 (0.44 - 5.0)** [*8*]		**5.0 (4.0 - 5.0)** [*3*]		
Amylase (U/L)		**305 (110 - 500)** [*2*]		**400 (200 - 1000)** [*8*]		**200 (200 - 200)** [*1*]
ALT (IU/L)		**189 (75 - 500)** [*3*]		**1000 (100 - 1500)** [*8*]		

n = No. of papers used as source of data

Supplemental Table 4: Level 4 evidence – alert thresholds reported by individual institutions (SI units)

Analytes (SI units)	4a. Laboratory and Clinicians		4b. Clinicians		4c. Laboratory	
	Low Threshold Median (Range) [*n*]	High Threshold Median (Range) [*n*]	Low Threshold Median (Range) [*n*]	High Threshold Median (Range) [*n*]	Low Threshold Median (Range) [*n*]	High Threshold Median (Range) [*n*]
Potassium (mmol/L)	**2.75 (2.0 - 3.2)** [*12*]	**6.25 (6.0 - 7.0)** [*12*]	**2.5 (2.0 - 3.0)** [*7*]	**6.0 (5.5 - 7.0)** [*7*]	**2.8 (2.0 - 3.0)** [*21*]	**6.05 (5.9 - 7.0)** [*22*]
Sodium (mmol/L)	**120 (115 - 125)** [*12*]	**160 (150 - 160)** [*12*]	**120 (105 - 125)** [*7*]	**157.5 (150 - 165)** [*6*]	**120 (110 - 125)** [*18*]	**160 (150 - 160)** [*17*]
Glucose (mmol/L)	**2.5 (1.9 - 2.8)** [*11*]	**25 (16.7 - 44.34)** [*13*]	**2.41 (1.67 - 4.0)** [*6*]	**24.55 (18.0 - 44.4)** [*6*]	**2.5 (2.2 - 3.0)** [*17*]	**25.0 (20.0 - 55.0)** [*17*]
Calcium (mmol/L)	**1.50 (1.50 - 1.65)** [*8*]	**3.25 (2.70 - 3.50)** [*10*]	**1.375 (1.25 - 1.50)** [*2*]	**3.50 (3.25 - 3.75)** [*2*]	**1.615 (1.50 - 1.80)** [*14*]	**3.25 (2.80 - 3.53)** [*15*]
Hemoglobin (g/L)	**62.5 (50 - 80)** [*8*]	**199.5 (199 - 200)** [*4*]	**66 (50 - 75)** [*3*]	**199 (199 - 199)** [*1*]	**66 (50 - 70)** [*15*]	**200 (199 - 200)** [*5*]
Platelets (x 10^9/L)	**20 (10 - 40)** [*9*]	**1000 (999 - 1000)** [*5*]	**10 (5 - 50)** [*3*]		**40 (10 - 50)** [*13*]	**1000 (800 - 1000)** [*8*]
Magnesium (mmol/L)	**0.41 (0.31 - 0.50)** [*5*]	**2.06 (1.93 - 2.88)** [*3*]	**0.49 (0.49 - 0.49)** [*1*]		**0.41 (0.29 - 0.55)** [*13*]	**2.46 (1.93 - 5.00)** [*10*]
Phosphorus (mmol/L)	**0.32 (0.32 - 0.48)** [*6*]	**2.89 (1.78 - 2.91)** [*4*]	**0.52 (0.52 - 0.52)** [*1*]		**0.32 (0.30 - 0.55)** [*8*]	**3.05 (2.90 - 3.20)** [*2*]
WBC (x 10^9/L)	**1.5 (0.5 - 3)** [*7*]	**50 (30 - 100)** [*6*]			**1.5 (0.5 - 2)** [*13*]	**50 (20 - 100)** [*11*]
APTT (seconds)	**12 (12 - 12)** [*1*]	**82.5 (50 - 110)** [*6*]		**50 (50 - 50)** [*1*]	**19 (19 - 19)** [*1*]	**85 (75 - 200)** [*13*]
Creatinine (umol/L)		**319.5 (177 - 653)** [*4*]		**178.5 (150 - 654)** [*4*]		**500 (265 - 657)** [*6*]
Urea (mmol/L)		**35.7 (12.5 - 77.0)** [*4*]		**12.35 (10.4 - 14.3)** [*2*]	**0.71 (0.71 - 0.71)** [*1*]	**32.85 (28.6 - 50.0)** [*6*]
pH	**7.20 (7.15 - 7.20)** [*5*]	**7.595 (7.58 - 7.60)** [*4*]			**7.20 (7.10 - 7.20)** [*10*]	**7.60 (7.59 - 7.70)** [*8*]
INR		**4.75 (3.5 - 7.0)** [*4*]	**1.5 (1.5 - 1.5)** [*1*]	**4.25 (3.0 - 5.0)** [*4*]	**1.5 (1.5 - 1.5)** [*2*]	**4.9 (3.5 - 7.0)** [*12*]
Fibrinogen (g/L)	**1.0 (1.0 - 1.0)** [*2*]	**7.0 (7.0 - 7.0)** [*1*]	**1.0 (0.75 - 1.5)** [*3*]		**0.95 (0.5 - 1.0)** [*8*]	**7.5 (7.0 - 8.0)** [*2*]
pO2 (kPa)	**5.3 (5.3 - 5.3)** [*4*]				**5.3 (5.3 - 6.7)** [*7*]	
Digoxin (nmol/L)		**3.8 (2.49 - 5.1)** [*5*]				**3.0 (2.6 - 3.2)** [*8*]
Bicarbonate (mmol/L)	**12 (12 - 12)** [*3*]	**38 (36 - 40)** [*2*]	**14 (14 - 14)** [*1*]	**34 (34 - 34)** [*1*]	**10 (9 - 15)** [*7*]	**40.5 (40 - 50)** [*6*]
Hematocrit (volume fraction)	**0.20 (0.15 - 0.24)** [*4*]	**0.60 (0.60 - 0.60)** [*2*]	**0.145 (0.14 - 0.15)** [*2*]		**0.20 (0.18 - 0.30)** [*7*]	**0.58 (0.54 - 0.60)** [*6*]
pCO2 (kPa)	**2.7 (2.7 - 3.3)** [*5*]	**9.3 (8.0 - 10.0)** [*5*]			**2.7 (1.3 - 2.7)** [*7*]	**8.9 (6.0 - 10.0)** [*7*]
Ionized Calcium (mmol/L)	**0.75 (0.75 - 0.75)** [*1*]	**1.615 (1.58 - 1.65)** [*2*]			**0.80 (0.75 - 0.80)** [*7*]	**1.54 (1.50 - 1.75)** [*7*]
Prothrombin Time (seconds)	**8 (8 - 8)** [*1*]	**30 (25 - 30)** [*3*]				**33 (30 - 60)** [*8*]
Chloride (mmol/L)	**75 (75 - 75)** [*1*]	**125 (125 - 125)** [*1*]	**92 (92 - 92)** [*1*]	**120 (120 - 120)** [*1*]	**75 (75 - 80)** [*5*]	**122.5 (115 - 130)** [*4*]
Lithium (mmol/L)		**1.75 (1.49 - 2.0)** [*4*]				**2.0 (1.5 - 2.0)** [*5*]
Uric Acid (umol/L)		**773 (595 - 774)** [*4*]				**773 (773 - 773)** [*2*]
Phenytoin (umol/L)		**120 (120 - 120)** [*2*]				**113 (80 - 160)** [*6*]
Theophylline (umol/L)		**110 (110 - 110)** [*2*]				**110 (110 - 140)** [*4*]
Lactate (mmol/L)		**3.4 (3.4 - 3.4)** [*1*]				**4.0 (3.4 - 5.0)** [*5*]
Amylase (U/L)		**300 (110 - 400)** [*4*]				**200 (200 - 200)** [*2*]
ALT (U/L)		**100 (75 - 1500)** [*3*]		**189 (189 - 189)** [*1*]		**1000 (1000 - 1000)** [*2*]

n = No. of papers used as source of data

Supplemental Table 5: Level 3 evidence – alert thresholds from surveys of laboratories or clinicians (SI units)

Analytes (SI units)	3b. Clinicians		3c. Laboratory	
	Low Threshold Median (Range) [*n*]	High Threshold Median (Range) [*n*]	Low Threshold Median (Range) [*n*]	High Threshold Median (Range) [*n*]
Potassium (mmol/L)	**2.5 (2.5 - 2.5)** *[1]*	**6 (6 - 6)** [*1*]	**2.8 (2.6 - 2.9)** [*11*]	**6.2 (6 - 6.5)** [*11*]
Sodium (mmol/L)	**120 (120 - 120)** [*1*]	**160 (160 - 160)** [*1*]	**120 (120 - 125)** [*10*]	**159 (155 - 160)** [*10*]
Glucose (mmol/L)	**2.5 (2.5 - 2.5)** [*1*]	**30 (30 - 30)** [*1*]	**2.5 (2.2 - 2.78)** [*9*]	**23.2 (20 - 26.9)** [*9*]
Calcium (mmol/L)	**1.3 (1.3 - 1.3)** [*1*]	**3.8 (3.8 - 3.8)** [*1*]	**1.6 (1.4 - 1.78)** [*11*]	**3.22 (3 - 3.5)** [*11*]
Hemoglobin (g/L)	**90 (90 - 90)** [*1*]		**67.5 (53 - 75)** [*8*]	**200 (184 - 200)** [*8*]
Platelets (x 10^9/L)			**40 (30 - 50)** [*8*]	**999 (700 - 1000)** [*8*]
Magnesium (mmol/L)	**0.4 (0.4 - 0.4)** [*1*]		**0.435 (0.33 - 0.51)** [*8*]	**2 (1.69 - 3.25)** [*8*]
Phosphorus (mmol/L)	**0.25 (0.25 - 0.25)** [*1*]		**0.385 (0.32 - 0.4)** [*8*]	**2.81 (2.58 - 3)** [*7*]
WBC (x 10^9/L)			**2 (2 - 2)** [*6*]	**33.5 (25 - 46)** [*6*]
APTT (seconds)			**19 (18 - 20)** [*3*]	**87.5 (68 - 110)** [*8*]
Creatinine (umol/L)			**18 (16 - 27)** [*4*]	**456 (300 - 670)** [*9*]
Urea (mmol/L)			**1.65 (1.1 - 4)** [*4*]	**31.3 (27 - 76)** [*9*]
pH	**6.9 (6.9 - 6.9)** [*1*]	**7.7 (7.7 - 7.7)** [*1*]	**7.205 (7.2 - 7.44)** [*4*]	**7.595 (7.55 - 7.6)** [*4*]
INR				**5.5 (5 - 6)** [*2*]
Fibrinogen (g/L)			**1 (0.88 - 1)** [*3*]	**7.875 (7.75 - 8)** [*2*]
pO2 (kPa)	**4.7 (4.7 - 4.7)** [*1*]		**5.8 (5.3 - 8.0)** [*4*]	**13.6 (12.4 - 14.8)** [*2*]
Digoxin (nmol/L)				**3.0 (2.6 - 3.8)** [*3*]
Bicarbonate (mmol/L)	**10 (10 - 10)** [*1*]		**11 (10 - 15)** [*6*]	**40 (39 - 40)** [*6*]
Hematocrit (volume fraction)			**0.20 (0.18 - 0.24)** [*3*]	**0.60 (0.60 - 0.61)** [*3*]
pCO2 (kPa)			**2.7 (2.5 - 2.7)** [*3*]	**9.0 (8.0 - 9.3)** [*4*]
Ionized Calcium (mmol/L)	**0.6 (0.6 - 0.6)** [*1*]	**1.7 (1.7 - 1.7)** [*1*]	**0.8 (0.75 - 0.82)** [*3*]	**1.55 (1.5 - 1.58)** [*3*]
Prothrombin Time (seconds)			**9 (9 - 9)** [*2*]	**28 (25 - 37)** [*5*]
Chloride (mmol/L)			**80 (75 - 85)** [*6*]	**120.5 (115 - 126)** [*6*]
Lithium (mmol/L)				**1.5 (1.4 - 2)** [*3*]
Uric Acid (umol/L)			**59 (59 - 59)** [*1*]	**767 (700 - 773)** [*4*]
Phenytoin (umol/L)				**100 (100 - 120)** [*3*]
Theophylline (umol/L)				**130 (130 - 140)** [*3*]
Lactate (mmol/L)			**0.06 (0.06 - 0.06)** [*1*]	**3.4 (0.44 - 5)** [*3*]
Amylase (U/L)				**388 (350 - 470)** [*3*]
ALT (U/L)				**750 (500 - 1000)** [*2*]

n = No. of papers used as source of data

Supplemental Table 6: Level 2 evidence – alert thresholds recommended by professional bodies (SI units)

Analytes (SI units)	2a. Laboratory and Clinicians		2c. Laboratory	
	Low Threshold Median (Range) [*n*]	High Threshold Median (Range) [*n*]	Low Threshold Median (Range) [*n*]	High Threshold Median (Range) [*n*]
Potassium (mmol/L)	**2.5 (2.5 - 2.8)** [*3*]	**6.2 (6.0 - 6.5)** [*3*]	**2.8 (2.8 - 2.8)** [*3*]	**6.2 (6.0 - 6.2)** [*3*]
Sodium (mmol/L)	**120 (120 - 120)** [*3*]	**155 (150 - 160)** [*3*]	**120 (120 - 120)** [*3*]	**160 (160 - 160)** [*3*]
Glucose (mmol/L)	**2.64 (2.5 - 2.78)** [*2*]	**23 (22.2 - 25.0)** [*3*]	**2.22 (2.2 - 2.5)** [*3*]	**24.75 (22.2 - 27.8)** [*3*]
Calcium (mmol/L)	**1.80 (1.75 - 1.80)** [*3*]	**3.25 (3.20 - 3.50)** [*3*]	**1.65 (1.50 - 1.75)** [*3*]	**3.25 (3.00 - 3.50)** [*3*]
Hemoglobin (g/L)	**70 (70 - 70)** [*2*]	**190 (190 - 190)** [*1*]	**70 (66 - 70)** [*3*]	**200 (199 - 200)** [*3*]
Platelets (x 10^9/L)	**25 (20 - 30)** [*2*]	**1250 (1000 - 1500)** [*2*]	**40 (20 - 40)** [*3*]	**1000 (999 - 1000)** [*3*]
Magnesium (mmol/L)	**0.45 (0.40 - 0.50)** [*2*]	**2.05 (2.00 - 2.10)** [*2*]	**0.41 (0.4 - 0.41)** [*3*]	**3.455 (1.91 - 5)** [*2*]
Phosphorus (mmol/L)	**0.31 (0.30 - 0.32)** [*2*]		**0.32 (0.30 - 0.32)** [*4*]	**2.90 (2.87 - 2.90)** [*4*]
WBC (x 10^9/L)	**1.5 (1.5 - 1.5)** [*1*]	**100 (100 - 100)** [*1*]	**2 (2 - 2)** [*3*]	**40 (30 - 50)** [*3*]
APTT (seconds)				**78 (75 - 120)** [*3*]
Creatinine (umol/L)		**400 (354 - 400)** [*3*]		**442 (350 - 654)** [*3*]
Urea (mmol/L)		**35.7 (30.0 - 40.0)** [*3*]		**28.6 (16.7 - 35.6)** [*3*]
pH	**7.20 (7.20 - 7.20)** [*1*]	**7.60 (7.60 - 7.60)** [*1*]	**7.20 (7.20 - 7.20)** [*2*]	**7.60 (7.60 - 7.60)** [*2*]
INR		**6.25 (6.0 - 6.5)** [*2*]		**5.0 (5.0 - 5.0)** [*1*]
Fibrinogen (g/L)			**0.8 (0.8 - 1.0)** [*3*]	**8.0 (8.0 - 8.0)** [*1*]
pO2 (kPa)	**8.0 (8.0 - 8.0)** [*1*]		**5.5 (5.3 - 5.7)** [*2*]	
Digoxin (nmol/L)		**3.2 (3.2 - 3.2)** [*1*]		**2.6 (2.6 - 2.6)** [*1*]
Bicarbonate (mmol/L)	**15 (15 - 15)** [*1*]		**10 (10 - 10)** [*1*]	**40 (40 - 40)** [*1*]
Hematocrit (volume fraction)			**0.20 (0.18 - 0.20)** [*3*]	**0.60 (0.60 - 0.61)** [*3*]
pCO2 (kPa)			**2.6 (2.5 - 2.7)** [*2*]	**9.1 (8.9 - 9.3)** [*2*]
Ionized Calcium (mmol/L)	**0.84 (0.80 - 0.88)** [*2*]	**1.55 (1.50 - 1.60)** [*2*]	**0.78 (0.78 - 0.78)** [*1*]	**1.60 (1.60 - 1.60)** [*1*]
Prothrombin Time (seconds)				**35 (30 - 40)** [*2*]
Chloride (mmol/L)			**77.5 (75 - 80)** [*2*]	**122.5 (120 - 125)** [*2*]
Lithium (mmol/L)		**1.5 (1.5 - 1.5)** [*1*]		
Uric Acid (umol/L)				**773 (773 - 773)** [*1*]
Phenytoin (umol/L)		**100 (100 - 100)** [*1*]		
Theophylline (umol/L)		**140 (140 - 140)** [*1*]		
Lactate (mmol/L)		**5.0 (5.0 - 5.0)** [*1*]		**5.0 (5.0 - 5.0)** [*1*]
Amylase (U/L)		**500 (500 - 500)** [*1*]		**1000 (1000 - 1000)** [*1*]
ALT (U/L)		**587.5 (500 - 675)** [*2*]		**800 (600 - 1000)** [*2*]

n = No. of papers used as source of data

Supplemental Table 7: Level 1 evidence – alert thresholds established by clinical outcome studies (SI units)

Analytes (SI units)	1a. Laboratory and Clinicians		1b. Clinicians		1c. Laboratory	
	Low Threshold Median (Range) [*n*]	**High Threshold Median (Range)** [*n*]	**Low Threshold Median (Range)** [*n*]	**High Threshold Median (Range)** [*n*]	**Low Threshold Median (Range)** [*n*]	**High Threshold Median (Range)** [*n*]
Potassium (mmol/L)		**6.2 (6.2 - 6.2)** [*1*]		**6.3 (6.3 - 6.3)** [*1*]		**7.0 (7.0 - 7.0)** [*1*]
Sodium (mmol/L)	**120 (120 - 120)** [*2*]	**155 (155 - 155)** [*1*]				
Calcium (mmol/L)	**1.75 (1.75 - 1.75)** [*1*]	**3.00 (3.00 - 3.00)** [*1*]				**2.99 (2.99 - 2.99)** [*1*]
Hemoglobin (g/L)	**70 (70 - 70)** [*1*]					
Fibrinogen (g/L)			**2.29 (2.29 - 2.29)** [*1*]			
Lactate (mmol/L)		**4.0 (4.0 - 4.0)** [*1*]				

n = No. of papers used as source of data

Chapter 4

Evidence- and risk-based methodology for defining alert thresholds

4.1 Chapter Background

Pathology tests support the identification and management of a health problem by detecting changes in body fluids or tissues (1). Due to the complex interactions that occur within and between the body's cells and organ systems, detection of a particular change in a test sample usually does not definitively identify a specific illness or disease. Interpretation of test results is not a straightforward exercise, especially in patients with comorbidities, when a diagnostic hypothesis has not been established, or when results are not consistent with the suspected diagnosis. Thus decisions on which alert thresholds to include on the laboratory alert list can be complex. The risk of harm that a particular result poses is often dependent on the clinical context. For instance, high uric acid levels are of particular concern in patients receiving cancer treatment, as these patients are susceptible to tumour lysis syndrome; elevated troponin may not be due to acute myocardial injury in patients with chronic kidney disease. The Clinical Laboratory and Standards Institute (CLSI) guideline for the management of critical- and significant-risk results recommends a risk based approach to defining alert thresholds, which involves identifying the type of harm associated with the threshold under consideration, estimating the likelihood and severity of harm if the condition is not treated, and determining whether immediate intervention is necessary to reduce the risk of harm (2). The impact that a prospective alert threshold has on laboratory workflow should also be considered in a risk assessment, as selecting a more conservative threshold may only see a minimal reduction in the risk of patient harm while generating an unmanageably large volume of alerts. The burden of phoning this increased number of high risk results may cause undue risk by delaying the release of other important results. Interrupting clinicians with too many unnecessary alerts can cause alert fatigue and subsequent failure to act on genuine high risk alerts.

The article in this chapter describes an evidence- and risk-based approach for the identification and verification of alert thresholds. In recognition of my contribution to the harmonisation of high risk result management in Australia, this was an invited peer reviewed paper, published in a special issue of *Clinical Chemistry and Laboratory Medicine* on harmonization in laboratory medicine. The

approach described in the article was conceptualised by consensus in a meeting of the RCPA-AACB high risk results working party, drawing from both the evidence based methodology described in chapters two and three of this thesis and the risk based approach described in the CLSI guideline. The article fleshes out the working party's concept into a methodology, using the example of potassium alert thresholds to demonstrate how it works. The methodology considers the available evidence for the proposed threshold, the risk to the patient if no medical action is taken, analytical aspects that may impact result interpretation, and laboratory workload implications. This article directly addresses objective three of the thesis, to develop an evidence- and risk-based methodology for the identification and verification of critical result thresholds.

4.2 References

1. The Royal College of Pathologists of Australasia. Pathology - The Basis of Medicine. 2013. https://test.rcpa.edu.au/Library/Fact-Sheets/Fact-Files (last accessed on 10 November 2019).

2. CLSI. Management of critical- and significant-risk results. 1st ed. CLSI guideline GP47. Wayne, PA: Clinical and Laboratory Standards Institute; 2015.

4.3 Article III - An evidence- and risk-based approach to a harmonized laboratory alert list in Australia and New Zealand

The following journal article, *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(1): 89–94. https://doi.org/10.1515/cclm-2017-1114,* is reproduced below with the permission of Walter de Gruyter and Company; permission conveyed through Copyright Clearance Center, Inc.

Opinion Paper

Craig A. Campbell*, Que Lam and Andrea R. Horvath

An evidence- and risk-based approach to a harmonized laboratory alert list in Australia and New Zealand

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Abstract: Individual laboratories are required to compose an alert list for identifying critical and significant risk results. The high-risk result working party of the Royal College of Pathologists of Australasia (RCPA) and the Australasian Association of Clinical Biochemists (AACB) has developed a risk-based approach for a harmonized alert list for laboratories throughout Australia and New Zealand. The six-step process for alert threshold identification and assessment involves reviewing the literature, rating the available evidence, performing a risk analysis, assessing method transferability, considering workload implications and seeking endorsement from stakeholders. To demonstrate this approach, a worked example for deciding the upper alert threshold for potassium is described. The findings of the worked example are for infants aged 0–6 months, a recommended upper potassium alert threshold of >7.0 mmol/L in serum and >6.5 mmol/L in plasma, and for individuals older than 6 months, a threshold of >6.2 mmol/L in both serum and plasma. Limitations in defining alert thresholds include the lack of well-designed studies that measure the relationship between high-risk results and patient outcomes or the benefits of treatment to prevent harm, and the existence of a wide range of clinical practice guidelines with conflicting decision points at which treatment is required. The risk-based approach described presents a transparent, evidence- and consensus-based methodology that can be used by any laboratory when designing an alert list for local use. The RCPA-AACB harmonized alert list serves as a starter set for further local adaptation or adoption after consultation with clinical users.

Keywords: alert list; alert threshold; critical result; critical risk result; harmonization; hyperkalemia.

***Corresponding author: Craig A. Campbell,** NSW Health Pathology, Department of Clinical Chemistry and Endocrinology, Prince of Wales Hospital, Sydney, NSW 2031, Australia, Phone: +612 93829082, Fax: +612 93829099, E-mail: craig.campbell@health.nsw.gov.au; and Australian Institute of Health Innovation, Macquarie University, Sydney, NSW, Australia
Que Lam: Department of Pathology, Austin Health, Heidelberg, Victoria, Australia
Andrea R. Horvath: NSW Health Pathology, Department of Clinical Chemistry and Endocrinology, Prince of Wales Hospital, Sydney, NSW, Australia

Introduction

Inconsistencies and gaps in laboratory practices for managing critical and significant risk results (collectively known as high-risk results) may expose patients to unnecessary harm. In response to this, the Clinical Laboratory Standards Institute and a working party of the Royal College of Pathologists of Australasia (RCPA) and the Australasian Association of Clinical Biochemists (AACB) published best practice recommendations to guide laboratories in the design and maintenance of their high-risk result procedures [1, 2].

Central to these procedures is the alert list, a list of tests and alert thresholds outside which results require timely notification. According to guidelines, the composition of the alert list is the responsibility of individual laboratories in consultation with their clinical users [1, 2]. Despite ongoing efforts to harmonize and standardize analytical methods and reference intervals or clinical decision limits, there is considerable variation in the tests and thresholds that laboratories include on their alert list. Clinical and patient organizations, including patient safety advocates and medical indemnity organizations, have voiced the need for a more uniform and agreed procedure on when and how high-risk results should be communicated [3]. To enable laboratories to apply a uniform and risk-based approach for the safe delivery of care to patients, the working party has decided to compose a harmonized alert list, at least for the most common analytes, based on the best available evidence.

Approach to the development of a harmonized alert list

Minimum data set

Essential components of the harmonized alert list were determined by the RCPA-AACB working party to include the following:

- name of the tests as per national recommendation [4];
- measurement unit, as per national recommendation [4];
- sample type;
- alert (upper and lower, and/or delta change) threshold;
- source(s) and strength of evidence for the alert threshold;
- timeframe within which a result should be notified and acted upon; and
- clinical context such as patient age, gender, pregnancy status and patient setting (where relevant).

Selecting the tests

Thirty-eight tests were initially identified as possible candidates for the common alert list, based on the combined experience of working party members (Supplementary Data; Table 1). Consideration was given to whether the harmonized alert list should only contain tests that have demonstrated transferability of results across different methods, namely, analytes with reference intervals already harmonized at national level [5]. However, the consensus view of the working group was that this would eliminate a number of important tests. Instead, it was decided that analytes with alert thresholds transferable and non-transferable across different methods should be clearly distinguished, and that the suitability of method-specific decision limits for non-transferable analytes would be determined by reviewing their performance in external quality assurance program(s).

Process for deciding the alert thresholds

A six-step process for identifying and assessing the suitability of alert thresholds was devised and is summarized in Figure 1. This process is illustrated by an example of establishing the critical risk alert threshold in hyperkalemia.

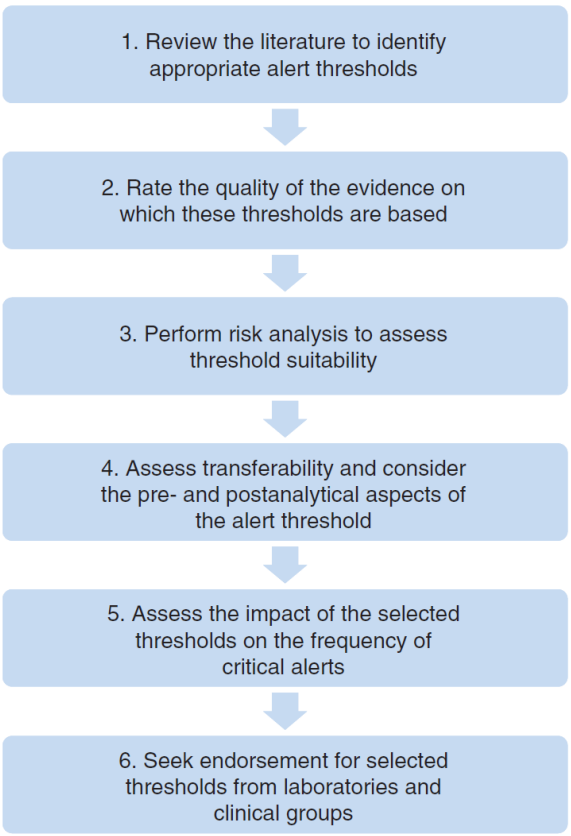

Figure 1: Process for identifying and assessing the suitability of alert thresholds.

Establishing the upper alert threshold for potassium

Hyperkalemia has a detrimental impact on muscle and nerve cell excitation causing weakness, fatigue, paraesthesia, depression of deep tendon reflexes, palpitations and potentially life threatening cardiac arrhythmias [6].

Step 1: Review the literature on alert thresholds

A published systematic review of the literature on alert thresholds revealed 62 papers that reported upper thresholds for potassium ranging from 5.5 to 7.0 mmol/L with a median of 6.2 mmol/L [7].

Step 2: Rating the evidence for alert thresholds

The quality of the evidence from the literature review was rated using an adaptation of a previously reported approach [8]. The highest level of evidence is derived from outcome studies (Level 1), followed by recommendations from professional bodies (Level 2), then thresholds sourced from laboratory or clinician surveys (Level 3), with

thresholds reported by individual laboratories ranking the lowest (Level 4). Thresholds derived by collaboration between the laboratory and clinicians are rated higher (subgroup a) than thresholds decided by one of these key stakeholders alone (subgroup b).

Out of the 62 papers identified for hyperkalemia, three were outcome studies (Evidence Level 1). Only one of the three involved collaboration between the laboratory and clinicians (Level 1a). In this 5-year retrospective hospital inpatient study, an upper potassium alert threshold of 6.2 mmol/L was deemed appropriate [9]. Among other findings, the study showed a time-dependent association between the degree of abnormality in the potassium results and increased rates of death. The 48-h in-hospital death rates of patients with potassium concentrations of 5.8–5.9, 6.0–6.1, 6.2–6.3 and >6.4 mmol/L were 2.5%, 2.7%, 3.2% and 3.9%, respectively; the overall in-hospital death rate was 2.0%. The second outcome study (performed by clinicians) evaluated the effectiveness of intervention by a rapid response team when potassium reached 6.3 mmol/L [10]. Over the 5-year study period, 890 patients with a discharge diagnosis code of "hyperkalemia" died, but only four of these deaths were found to be attributable to hyperkalemia (i.e. potassium >6.3 mmol/L within 8 h of death and no other likely cause of death). The third outcome study (performed by a laboratory) retrospectively investigated causes, outcomes and timeliness of clinical response for hyperkalemia [11]. In this 1-year study, the frequency of cardiac arrest/shock at various potassium levels was as follows: 10 of the 116 patient episodes (9%) with potassium between 6 and 7 mmol/L, 10 of the 38 patient episodes (26%) with potassium between 7 and 8 mmol/L and 11 of the 12 patient episodes (92%) with potassium >8 mmol/L. These researchers determined that an alert threshold of 7 mmol/L was optimal to prevent harm in a timely manner.

Six of the 62 papers identified for hyperkalemia were recommendations by professional bodies (Evidence Level 2). Three of these recommendations were developed in collaboration between the laboratory and clinicians (Evidence Level 2a; endorsing thresholds of 6.0, 6.2 and 6.5 mmol/L), whereas the other three were produced by laboratory professionals alone (Evidence Level 2b; with thresholds of 6.0, 6.2 and 6.2 mmol/L).

Step 3: Risk analysis to assess threshold suitability

Risk analysis, as described by the Clinical and Laboratory Standards Institute in the GP47 Guideline, has been performed to assess the suitability of the alert thresholds identified by the evidence review process [1]. This analysis involved the following:

- identification of the potential harm and clinical intervention associated with a critical risk result;
- estimation of the likelihood and severity of the potential harm (in absence of intervention) and the urgency of clinical intervention to reduce the risk of harm;
- evaluation of whether routine reporting of the result exposes the patient to an unacceptable risk of harm.

The most significant adverse outcome of hyperkalemia is immediate death due to cardiac arrest. Given this, even asymptomatic patients with mild hyperkalemia are treated. Procedures for potassium elimination (e.g. loop diuretics, ion-exchange resin delivered to the colon or dialysis) are generally slow to act. Therefore, patients with symptoms, electrocardiogram (ECG) changes or moderate to severe hyperkalemia require faster acting (albeit temporary) treatment to stabilize the myocardium (by calcium gluconate) and shift potassium into the cells (e.g. insulin or β-2 agonists) [12–16]. The laboratory should report moderate to severe hyperkalemia immediately to allow initiation of prompt and aggressive treatment, whereas routine reporting of mild hyperkalemia is adequate for less-urgent management. Unfortunately, there is little agreement on the threshold that distinguishes mild from moderate hyperkalemia, with various authors defining moderate hyperkalemia at as low as 6.0 mmol/L and mild hyperkalemia at as high as 7.5 mmol/L [17]. Common decision points for more aggressive treatment are either >6.0 mmol/L or >6.5 mmol/L [5, 12, 13, 15–18]. Some experts suggest a higher threshold (>7.0 mmol/L) for patients with chronic kidney disease and on potassium sparing medication assuming that cardiac mortality is associated with more acute rise in blood potassium concentration [19].

Aligning the laboratory's alert threshold with the decision limit used locally for aggressive treatment to prevent a dangerous clinical outcome rather than on limits linked to severe pathophysiological changes is a sensible and pragmatic approach as it harmonizes laboratory and clinical practice and guides timely medical intervention. In the absence of such local treatment protocols, the working party recommends the literature sourced threshold of 6.2 mmol/L (see Steps 1 and 2).

Step 4: Transferability and pre- and postanalytical aspects of the alert threshold

Determining whether different thresholds should be used for specific patient subsets or clinical settings is essential and offers an opportunity for customizing alert thresholds. In some cases, pre- or postanalytical factors may impact on the use of the alert threshold and its harmonization.

Population-specific alert thresholds

Patients receiving dialysis, if reliably identified by the laboratory, could reasonably have a higher hyperkalemia threshold. Acceptable identification could include a clear statement of "predialysis" on the pathology request form. Identifying predialysis patients purely based on ward location is inadequate, as this does not provide certainty that dialysis treatment is imminent.

Renal excretion of potassium is low during the first months of life, resulting in higher blood potassium levels in the neonatal period and early infancy [20]. The Australasian harmonized upper reference limit for serum potassium is 6.5 mmol/L from age 0 to 1 week and 6.7 mmol/L from the 2nd to the 26th week of age [4]. Babies often tolerate potassium of 7.5–8.0 mmol/L without ECG changes [21]. The UK National Health Service neonatal guidelines for management of hyperkalemia recommend administration of salbutamol (β-2 agonist) at serum potassium >7.0 mmol/L, and calcium gluconate when potassium exceeds 7.5 mmol/L and ECG changes are present [21]. On this background, the working party recommends an upper alert threshold of 7.0 mmol/L for infants aged between 0 and 6 months.

Preanalytical considerations – effect of sample type

Potassium is 0.3–0.4 mmol/L higher in serum compared to plasma, due to its release from platelets and white blood cells during clotting [4]. Clinicians are generally unaware of this issue, and it is rarely considered when treatment guidelines are formulated. Laboratories may have a preferred sample type, but they are unlikely to reject samples collected in alternate tubes. In the lack of specific information, it is reasonable to assume that retrospective outcome studies are commonly based on a mixture of sample types. A conservative approach is needed to set potassium alert thresholds when studies do not report the sample type for which their decision thresholds apply. The recommended adult upper potassium threshold of >6.2 mmol/L is conservative enough for use with serum or plasma, considering that 6.5 mmol/L is a commonly used treatment decision point. Due to the lack of preanalytical information in studies and guidelines, laboratories may consider lowering the infant threshold from >7 to >6.5 mmol/L if plasma is the preferred specimen.

Pseudohyperkalemia

The possibility of pseudohyperkalemia should be investigated and eliminated before a high-risk potassium result is communicated to clinicians. Some laboratories that receive samples collected from remote locations extend their upper reference limit for potassium to 5.5 mmol/L to allow for cellular leakage of potassium [4]. It is not advisable to apply a similar offset to the upper alert threshold because missed diagnosis of moderate hyperkalemia has more serious consequences than missed mild hyperkalemia.

Step 5: Impact of the selected threshold on the frequency of critical alerts

To assess the practical and organizational consequences of proposed alert thresholds, the frequency of alerts should be investigated. As the harmonized thresholds may flag differing number of cases in primary, secondary or tertiary care, this impact assessment is best performed on local databases. If the frequency of alerts presents an unmanageable workload both to the laboratory and the clinical recipients, the utility of the threshold and the preanalytical error rate for potassium measurements needs to be reevaluated and the risk-assessment revisited and refined (Step 3), in consultation with the clinicians involved (Step 6).

Potassium results were analyzed over a 3-month period within a network of seven laboratories servicing nine public hospitals in the Sydney metro and its catchment area. Of the 21 potassium results per day measured on infants (aged 0–6 months), one result per 1.4 days was >6.2 mmol/L, one result every 2.5 days was >6.5 mmol/L and one result every 10 days was >7.0 mmol/L. Therefore, lowering the infant alert threshold to match the adult threshold, if required, would not be a burden on workflow. There were 1789 potassium results per day across the nine hospitals on patients older than 6 months, of which 45 results per day were >5.5 mmol/L (i.e. the upper nationally harmonized reference limit), 13 results per day were >6.0 mmol/L, eight results per day were >6.2 mmol/L and four results per day were >6.5 mmol/L. Thus, for this laboratory network, adoption of the recommended upper alert threshold (i.e. >6.2 mmol/L) would produce an undemanding one hyperkalemia alert per laboratory per day. If local preferences dictated a lowering of the threshold to >6.0 mmol/L, the number of hyperkalemia alerts would still be manageable at two per laboratory per day.

Step 6: Endorsement for selected thresholds from laboratories and clinical groups

Alert lists developed in consultation with clinical users have a higher likelihood of successful implementation. Senior clinicians in various Australian hospitals in New South Wales are currently being surveyed through an

Table 1: Harmonized alert list for hyperkalemia.

Test name	Unit of measure	Sample type	Clinical context	Alert threshold	Notification timeframe	Level of evidence
Potassium	mmol/L	Serum	Age: 0–6 months	>7.0	Immediately	2b: NHS (UK) Neonatal guidelines 2015–2017
		Plasma	Age: 0–6 months	>6.5	Immediately	2b: NHS (UK) Neonatal Guidelines 2015–2017 ~ *Adjusted for sample type (Clin Biochem Rev 2014;35:213–35)*
		Serum/plasma	Age: >6 months	>6.2	Immediately	1a: Am J Clin Pathol 2014;142:617–28

online questionnaire regarding their acceptance of various alert thresholds. The survey has yet to be circulated to primary care physicians or their representative organizations, and endorsement of the list will be requested from a broad range of national colleges, patient and patient safety organizations such as the Clinical Excellence Commission.

For patients aged 0–1 month, 79% of survey respondents (53/67) agree with an upper alert threshold of >7.0 mmol/L. Among those that disagree, six have proposed a threshold of >6.2 mmol/L, whereas four suggested >6.5 mmol/L. For patients aged 28 days to 110 years, there was 71% agreement (57/79) for a threshold of >6.2 mmol/L. Alternative thresholds proposed by respondents for this age-group include >6.0 mmol/L (nine respondents) and >6.5 mmol/L (nine respondents). Fifty-five of 57 respondents (96%) thought that neonatal hyperkalemic critical risk results should be phoned immediately, whereas 58 of 69 respondents (84%) believed that hyperkalemic critical risk results on patients aged 28 days to 110 years require immediate phoning. However, overall clinician agreement for the proposed alert thresholds is strong.

Table 1 shows the harmonized alert list entry for the upper potassium threshold. It is important to emphasize that the Harmonized Alert List is only a recommendation that individual laboratories are advised to discuss with their clinical users. There remains the ability to modify and customize the alert list to align it with clinical practice guidelines used locally or when the local population has unique management requirements. Such deliberations and any deviations from the recommendations should be clearly documented.

Limitations and conclusions

In clinical research, randomized control trials are regarded as the strongest level of evidence. It is obviously unethical not to treat an individual's high potassium in order to measure the harm that it may cause. Consequently, outcome studies relevant to identification of alert thresholds are restricted to retrospective observations. This makes it difficult to control for factors external to the laboratory result that have contributed to the outcome. Furthermore, the temporal relationship between the result and the outcome may be difficult to assess due to inadequate documentation. A well-designed retrospective study that incorporates detailed clinical information into the analysis can reduce the impact of confounding factors and, thus, strengthen the measured relationship between the high-risk result and the outcome. Given the complexity of the task, it is not surprising that a systematic literature review of common chemistry and hematology alert thresholds identified only a few outcome studies that assess the appropriateness of alert thresholds [6]. In fact, the review revealed a lack of any kind of evidence or explicit reasoning for the selection of alert thresholds. For many tests, the best available literature evidence is state of the art, captured by laboratory surveys on alert lists currently in use.

Even if a study successfully identified a strong cause-and-effect relationship between a laboratory result threshold and mortality, this may not be enough to define an alert threshold. The communication of a high-risk result must trigger medical action in time to prevent harm. For some tests, action may need to be taken before the result reaches a life-threatening level, so intervention can occur before it is too late.

There is no sense in rapidly communicating results if they do not impact clinical decisions [22]. Therefore, it is important to seek clinical approval of alert thresholds. However, many clinicians have personal preferences for result thresholds at which action must be taken, and laboratories cannot be expected to cater for idiosyncrasies of individual clinicians. Having a systematic, clinical risk-based approach to determining alert thresholds should be seen as good clinical governance and overcome such individual preferences.

This harmonization initiative by the RCPA-AACB working party aims to provide laboratories and clinicians with a starter set of recommended alert thresholds for some common analytes. The thresholds can be adapted to local circumstances and clinical protocols and should

be brought in line with clinical pathways and treatment recommendations. Laboratorians have an important role in mediating these discussions and ensuring that a joint policy and procedures are developed and implemented. Furthermore, the impact of joint policies and procedures must be followed up to ensure safer care to patients [23].

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Supplementary Material: The online version of this article offers supplementary material (https://doi.org/10.1515/cclm-2017-1114).

4.4 Article III – Supplemental Data

Supplemental Table 1: Tests identified as candidates for the harmonised alert list

Test	Lower threshold	Upper threshold
Sodium	yes	yes
Potassium	yes	yes
Bicarbonate	yes	yes
Urea		yes
Creatinine		yes
Glucose	yes	yes
Calcium (total)	yes	yes
Calcium (ionised)	yes	yes
Magnesium	yes	yes
Phosphate	yes	yes
Neonatal Bilirubin (total)		yes
Neonatal Bilirubin (direct)		yes
ALT		yes
Albumin	yes	
Ammonia		yes
Lipase		yes
CK		yes
Troponin		yes
Triglycerides		yes
Iron		yes
Vitamin B12	yes	
Uric Acid (pregnancy)		yes
Urine Protein (pregnancy)		yes
pH	yes	yes
pO_2	yes	
pCO_2		yes
Lactate		yes
Cortisol	yes	
Free T4	yes	yes
TSH	yes	yes
Paracetamol		yes
Digoxin		yes
Lithium		yes
Carbamazepine		yes
Phenytoin		yes
Valproate		yes
Gentamicin		yes
Vancomycin		yes

Chapter 5

Application of high risk delta thresholds to serum creatinine

5.1 Chapter Background

The progression of disease can be tracked by monitoring for changes in a patient's pathology test results compared to previous measurements. For instance, serum carbohydrate antigen 19-9 (CA 19-9) is not specific or sensitive enough to screen for pancreatic cancer as it is elevated in many other gastrointestinal intestinal tumours and in many benign conditions (1). Also, patients with the Lewis blood group phenotype a-b- (5% of the population) cannot make CA 19-9 antigen. However, serial measurements of CA 19-9 can be used to monitor the clinical response to chemotherapy, radiotherapy or surgery (1). Falling CA 19-9 levels are expected if treatment is successful. For some pathology tests, such as calcium (2), sodium (3) and potassium (4), detection of a rapid change in the result is as important as the magnitude of the result for predicting the development of symptoms. Sudden changes in test results can also help distinguish between acute and chronic disease. For example, a patient is considered to have myocardial injury if their serum or plasma cardiac troponin level exceeds the 99th percentile upper reference limit (5). To confirm acute myocardial injury, a rise and/or fall in troponin levels must be observed (5). Thus alert thresholds for detecting magnitude of change within a defined timeframe, when appropriate, are valuable additions to a laboratory's alert list.

AKI is an abrupt decrease in renal function, which is associated with a high risk of the development of chronic kidney disease, cardiovascular disease, and mortality (6). The 'Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury' defines AKI as a rise in serum creatinine from baseline by at least 50% within a week, or by 26.5µmol/L or more within 48 hours. The article in this chapter presents a study in which serum creatinine magnitude of change thresholds for AKI detection, as defined in the KDIGO guideline, were used to retrospectively determine the incidence of AKI across four New South Wales public hospitals. Baselines for creatinine were calculated using a formula standardised by the UK National Health Service (7). Laboratory identified AKI cases were compared to AKI diagnoses recorded in hospital discharge data to estimate the frequency at which AKI was unreported and potentially unrecognised. This article directly

addresses objective four of this thesis, to assess the value of using serum creatinine high risk delta thresholds to identify patients with acute kidney injury across four public hospitals in the in the South-Eastern Sydney/Illawarra regions of New South Wales, Australia. The study is part of a larger (ongoing) project to measure the effectiveness of AKI alerting at the study hospitals, including the burden on hospital personnel and resources, and the impact on health outcomes. This evidence-based approach for verification of creatinine (magnitude of change) alert thresholds is compliant with the methodology described in Chapter four of this thesis, and thus meets objective three. It was accepted for publication in the *Internal Medicine Journal on the 21st of February 2019*.

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5.3 Article IV - Under-detection of Acute Kidney Injury in Hospitalised Patients – A Retrospective, multi-site, longitudinal study

The following article: *Craig A. Campbell, Ling Li, Sradha Kotwal, Andrew Georgiou, Andrea R. Horvath, Johanna Westbrook and Zoltan Endre. Under-detection of acute kidney injury in hospitalised patients: a retrospective, multi-site, longitudinal study. Intern Med J 2019; https://doi.org/10.1111/imj.14264 (forthcoming),* has been accepted for publication, and the Author Accepted Manuscript version is reproduced below with the permission of John Wiley & Sons, Inc.

Under-detection of Acute Kidney Injury in Hospitalised Patients – A Retrospective, multi-site, longitudinal study

Craig A. Campbell[1,2], Ling Li[1], Sradha Kotwal[3,4], Andrew Georgiou[1], Andrea R. Horvath[2], Johanna Westbrook[1] and Zoltan Endre[3]

[1]Australian Institute of Health Innovation, Macquarie University; [2]NSW Health Pathology, Department of Clinical Chemistry and Endocrinology, Prince of Wales Hospital; [3]Department of Nephrology, Prince of Wales Clinical School, University of New South Wales; and [4]The George Institute for Global Health, University of New South Wales, Sydney, New South Wales, Australia.

Abstract

Background: Acute kidney injury (AKI) is a rapid deterioration of renal function, often caused by a variety of co-existing morbidities complicating its recognition and treatment, leading to short- and long-term adverse clinical outcomes. There are limited data on the incidence of AKI in Australia using the Kidney Disease Improving Global Outcomes (KDIGO) creatinine-based consensus definition.

Aim: To determine the incidence and estimate the extent of under-reporting of AKI in four hospitals in the South-Eastern Sydney/Illawarra regions of New South Wales, Australia.

Method: A laboratory algorithm based on the KDIGO creatinine-based definition for AKI was applied retrospectively to laboratory data for adult patients admitted to the study hospitals between 2009 and 2013 to identify those with AKI. The results were compared to the incidence of AKI based on diagnostic codes for AKI reported for the same period.

Results: AKI was detected in 12.4% of all hospitalisations (46,101/370,969) and 16.4% of patients (31,448/192,133) across the 5 year study period using the laboratory algorithm. Of these, 72.1% were AKI Stage 1 (33,246/46,101). AKI was coded in only 15.9% of hospitalisations with AKI Stage 1 (5,294/33,246), 38.5% of hospitalisations with Stage 2 (2,381/6,185), and 46.8% with Stage 3 (3,120/6,670). Yearly incidence of laboratory-identified AKI trended downward between 2009 and 2013, while annual incidence determined by coding trended upward.

Conclusion: Although coding trends suggested a continuous increase in clinician awareness of AKI across the study period, AKI in hospitalised patients remained significantly under-reported.

Keywords

Acute kidney injury, laboratory alert values, ICD-10, diagnostic errors, azotemia.

Abbreviations/Acronyms

ADQI	Acute Dialysis Quality Initiative
AKI	Acute kidney injury
AKIN	Acute Kidney Injury Network
AIHW	Australian Institute of Health and Welfare
CKD	Chronic kidney disease
GFR	Glomerular filtration rate
ICD-10-AM	International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification
ICU	Intensive care unit
KDIGO	Kidney Disease: Improving Global Outcomes
LIS	Laboratory Information Systems
MDRD	Modification of Diet in Renal Disease
NHS	National Health Service (United Kingdom).
PAS	Patient Admission Systems
RIFLE	Risk, Injury, Failure, Loss of function, and End-stage disease
SAS	Statistical Analysis Software
UK	United Kingdom

Introduction

Approximately 13.3 million people globally are estimated to experience acute kidney injury (AKI) each year, with approximately 1.7 million deaths per annum and mortality expected in 10 to 15% of affected individuals (1). Annual healthcare expenditure attributable to hospital acquired AKI is estimated to exceed $10 billion in the United States alone (2). Based on national data for the year 2012 to 2013 (i.e., 131,780 AKI hospitalisations (3); 5.8 days longer length of stay for AKI hospitalisations (3); and $1,764 average cost for admitted acute care per day (4)), we estimate that the increased length of stay associated with AKI hospitalisations costs the Australian healthcare system approximately $1.3 billion per year. Despite the accepted negative impact of AKI, little effort has been made in most countries to educate healthcare professionals in the management of this potentially preventable and treatable disease (5).

Historically, the lack of consensus around the definition of AKI has limited comparable estimates of prevalence. The first standardised international consensus classification system for AKI was published by the Acute Dialysis Quality Initiative (ADQI) in 2004. Dubbed the RIFLE criteria (Risk, Injury, Failure, Loss of function, and End-stage disease), it graded AKI into 5 levels of severity based on percentage rise in serum creatinine, percentage drop in glomerular filtration rate (GFR), urine output, and use of renal replacement therapy (6). Modifications to the RIFLE criteria were made by the Acute Kidney Injury Network (AKIN) with removal of the GFR criteria and inclusion of an absolute increase in serum creatinine (of 26.4umol/L) within 48 hours (7). The AKIN and RIFLE criteria were combined in international consensus guidelines published by the Kidney Disease: Improving Global Outcomes Work Group (KDIGO) (8, 9), which have been ratified in Australian and New Zealand guidelines (10). The addition of damage biomarkers to these definitions has been advocated by the ADQI group when appropriate cut-offs are agreed (11).

In the United Kingdom (UK), it was recognised that the uncoordinated development of electronic AKI alerting systems in individual hospitals led to variation in the application of internationally accepted

definitions (12). Also, despite evidence that late identification and poor management of AKI lead to high mortality (National Confidential Enquiry into Patient Outcome and Death report (13)), many hospitals were not providing AKI alerts (12). To address this variability, a standardised algorithm based on the increases in serum creatinine described in the KDIGO guidelines was developed, with standardised methodology for calculating the serum baseline creatinine value (12). In 2014, the National Health Service (NHS) issued a patient safety alert requiring all English healthcare provider trusts to implement the AKI algorithm and forward all prospective data from AKI cases to the UK Renal Registry (12).

In 2015, the Australian Institute of Health and Welfare (AIHW) reported the first national snapshot of AKI in Australia (3). For this report the AIHW used the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM) codes to capture AKI diagnoses from their national mortality and hospital morbidity databases. The report revealed 131,780 hospitalisations for AKI between 2012 and 2013, with an average length of stay twice that of overall hospitalisations. In the same period, hospitalisation and death rates for AKI increased rapidly with age and were higher for socioeconomically disadvantaged people and indigenous Australians. The report suggested that AKI is on the rise in Australia, with AKI hospitalisations increasing on average by 6% per year between 2000 and 2013.

Studies relying solely on coded hospital discharge data to measure changes in AKI incidence should be interpreted with caution despite the increased sensitivity of coding over time. However, studies in the United States and Western Europe applying consistent creatinine-based definitions over time have revealed 'true' rises in the incidence of AKI over the past two decades (14). These rises may be attributed to increases in known precipitants of AKI such as sepsis, major surgery, congestive heart failure, higher age, comorbidities that increase the risk of AKI, and use of a widening range of nephrotoxic medications (14).

AKI is commonly first encountered in the community or hospital setting by non-nephrologist healthcare providers who may be unfamiliar with the risk factors and mild or absent symptoms in the early stages of the disease (1). Based on the UK experience, it is likely that some patients are discharged with unrecognised AKI while others are managed sub-optimally (13). There are very limited data on the incidence of AKI in Australia using the KDIGO creatinine-based definition. Although AKI is believed to be under-reported in Australian coded data, a direct comparison of incidence determined by creatinine measurement and coded data has not been conducted on a large study population so far.

The aim of this study was to: i) determine the incidence of AKI using a laboratory-based algorithm on data from four New South Wales hospitals, and ii) identify unreported cases of AKI by comparing the incidence of AKI identified using the laboratory algorithm to AKI diagnoses recorded using ICD-10-AM codes.

Methods

Study Population and Setting

The study population included all patients aged 18 and over, who were admitted to any of three metropolitan principal referral hospitals (hospitals A,B and C) and one inner regional public acute group A hospital (hospital D) in the South-Eastern Sydney/Illawarra regions of New South Wales, Australia between January 2009 and December 2013. Patients who did not have a serum/plasma creatinine test at any time during the study period were excluded. For patients identified as receiving maintenance dialysis, only data produced prior to their first dialysis session were included in the study. Maintenance dialysis was identified when a patient's length of stay was less than 12 hours, and an ICD-10-AM code for dialysis was recorded within the hospital stay (Table 1).

Laboratory Methods

Two methods were used for creatinine measurement throughout the study period: i) a kinetic modification of the Jaffe method performed on the Beckmann Coulter DxC 800 (Reagent Catalogue No: OSR6178) was used between January 2008 and January 2011; and ii) a compensated, rate-blanked kinetic Jaffe method performed on the Roche Cobas 6000 and 8000 Modular Analyzer Series (Reagent Catalogue No: 0640713790) was used between January 2011 and December 2013. Since both methods were traceable to the reference method (isotope dilution mass spectrometry), creatinine results produced from the two methods were comparable.

Condition	**ICD-10-AM code**
Dialysis	Z49.0, Z49.1, Z49.2, Z99.2
Acute myocardial infarction	I21, I22, I252
Congestive heart failure	I50
Peripheral vascular disease	I71, I790, I739, R02, Z958, Z959
Cerebral vascular accident	I60, I61, I62, I63, I65, I66, G450, G451, G452, G458, G459, G46, I64, G454, I670, I671, I672, I674, I675, I676, I677 I678, I679, I681, I682, I688, I69
Diabetes	E109, E119, E139, E149, E101, E111, E131, E141, E105, E115, E135, E145
Diabetes complications	E102, E112, E132, E142 E103, E113, E133, E143 E104, E114, E134, E144
HIV	B20, B21, B22, B23, B24
Chronic kidney disease	E10.2, E11.2, E13.2, E14.2, I12, I13, I15.0, I15.1, N00 – N08, N11, N12, N14, N15, N16, N18, N19, N25 – N28, N39.1, N39.2, Q60 – Q63, T82.4, T86.1, Z49.0, Z94.0, Z99.2
Acute kidney injury	N00, N10, N17, E10.29, E11.29, E13.29, E14.29, O90.4, O08.4, N99.0

Table 1: ICD-10-AM codes used in the study

Data Linkage and Analysis

De-identified data were extracted from the Patient Admission Systems (PAS) and Laboratory Information Systems (LIS) of the study hospitals. Data from the two information systems were linked using de-identified patient medical record number, gender and date of birth. In order to provide the required lookback period for baseline creatinine calculations on patients during the first year of the study, LIS data were also obtained for the year preceding the study start date (i.e., January 2008 to December 2008).

The NHS-endorsed laboratory-based AKI algorithm (Figure 1) was programmed in the statistical software package R (15), where it was applied to the de-identified laboratory data to determine

laboratory-identified AKI. The highest AKI stage reached per hospital stay was used in all analyses. The incidence of laboratory-identified AKI was calculated for each AKI stage based on total hospitalisations.

Comorbidities that increase the risk of developing AKI were selected from the conditions used to calculate the Charlson Comorbidity Score (16). The ICD-10-AM codes to identify these comorbidities are listed in Table 1. Patients diagnosed with chronic kidney disease (CKD) were identified using the ICD-10-AM codes applied in the AIHW national AKI study (Table 1) (3). Every ICD-10-AM code recorded in the PAS (for primary and secondary diagnoses) was included to determine comorbidities. Incidences for each AKI stage were obtained for these comorbidities.

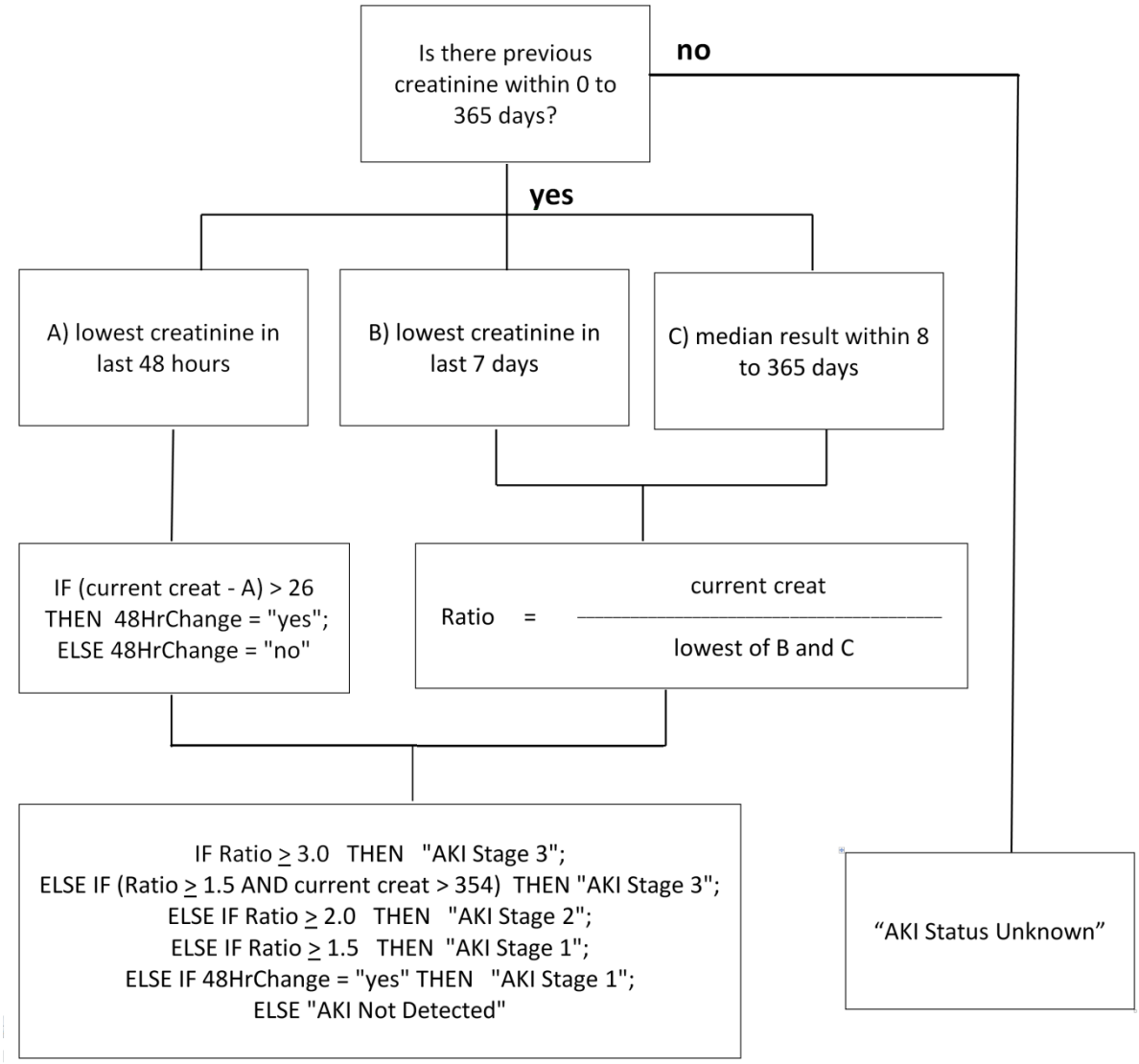

Figure 1: Laboratory-based AKI algorithm (Adapted from the NHS England standardised algorithm: Nephron 2015;131(2):113-7.)

Patient hospitalisations coded with a diagnosis of AKI (ICD-10-AM codes from the AIHW study (Table 1) (3)) were compared with AKI status identified using the laboratory algorithm for each admission. Every recorded diagnostic code was reviewed to determine 'coded AKI'. The percentage of hospitalisations coded with an AKI diagnosis was calculated for each AKI stage identified using the laboratory algorithm. Analyses were carried out using R version 3.4.0 and SAS version 9.4.

Ethics Approval

Ethics approval was obtained from the South Eastern Sydney Health District human research ethics committee and ratified by Macquarie University.

Results

Cohort Characteristics

A total of 192,133 patients and 370,969 hospitalisations were included across the 5-year study period. Most patients (121,583/192,133, 63.2%) were hospitalised only once within the study period. Demographics were captured using the first hospitalisation of each patient (Table 2). Within the first hospitalisation, laboratory-identified AKI was slightly more common in males than females; and the median age of patients with AKI was 8 years higher than those without AKI.

Gender	Number of Patients N (row%)				Median Age Years (25th - 75th Pctl)			
	AKI Status Unknown	AKI Not Detected	AKI Positive	Total	AKI Status Unknown	AKI Not Detected	AKI Positive	Total
Male	33,466 (35.4%)	52,436 (55.5%)	8,644 (9.1%)	94,546	50 (34 – 66)	64 (48 – 76)	71 (59 – 81)	61 (43-75)
Female	37,181 (38.1%)	52,711 (54.0%)	7,695 (7.9%)	97,587	49 (32 – 69)	65 (44 – 80)	75 (60 – 84)	61 (38 -78)
All Patients	70,647 (36.8%)	105,147 (54.7%)	16,399 (8.5%)	192,133	49 (33 - 68)	65 (46 – 78)	73 (60 – 82)	61 (40 - 76)

Table 2: Patient demographics and laboratory-identified AKI status at first hospitalisation within the study period 2009-2013

Incidence of Laboratory-Identified AKI

Throughout the study period, 16.4% of patients (31,448/192,133) had at least one hospitalisation during which laboratory-identified AKI occurred. Most patients (107,616/192,133, 56.0%) did not test positive for AKI at any time, and had at least one hospitalisation in which they were AKI negative (not detected). The remaining 27.6% of patients (53,069/192,133) did not have consecutive creatinine measurements within a year at any time during the study, rendering their AKI status unknown.

Laboratory-identified AKI was detected in 12.4% of hospitalisations over the 5-year study period (i.e., 9.0% with AKI Stage 1 (33,246/370,969), 1.7% with Stage 2 (6,185/370,969) and 1.8% with Stage 3 (6,670/370,969)). AKI was negative in 65.4% of hospitalisations (242,789/370,969), while 22.1% of hospitalisations (82,079/370,969) were of unknown AKI status. The incidence of AKI was substantially higher in hospitalisations with the selected comorbidities (16.2% to 47.4% of hospitalisations, Figure 2) compared to AKI incidence for all hospitalisations. AKI Stage 3 was disproportionately high in hospitalisations with CKD and diabetes complications (compared to other comorbidities and hospitalisations overall).

There was little difference in laboratory-identified AKI incidence between hospitals A, B or C (12.4%, 13.7% and 12.7% of hospitalisations respectively). Hospital D had a lower incidence of AKI (8.5% of hospitalisations) than the other hospitals, but also had the highest proportion of hospitalisations with unknown AKI status (Supplemental Table 2).

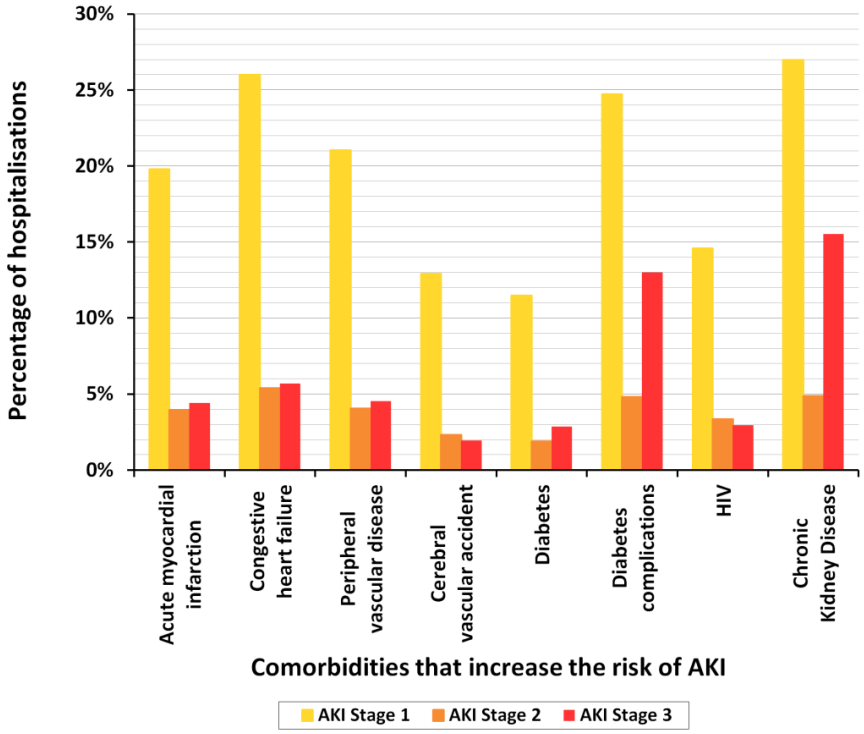

Figure 2: Incidence of the laboratory-identified AKI stages in hospitalisations with comorbidities known to increase the risk of AKI

Footnote: See Supplemental Table 1 for detail.

The proportion of hospitalisations that were AKI negative (not detected) and AKI Stage 3 remained steady for each of the 5 years analysed (Figure 3). There was a downward trend in the percentage of hospitalisations with AKI Stages 1 (9.8% in 2009 down to 8.1% in 2013) and 2 (1.9% in 2009 down to 1.5% in 2013), while hospitalisations of unknown AKI status showed an upward trend (20.9% in 2009 up to 22.9% in 2013).

Comparison of Laboratory-Identified and ICD-10-AM Coded AKI

Figure 4 shows a downward trend in the incidence of laboratory-identified AKI across the study period (13.6% of hospitalisations in 2009 down to 11.3% in 2013). In contrast, coded AKI trended upward over the same period (4.0% in 2009 up to 6.4% in 2013). The increase in coded AKI was most apparent in AKI Stage 2, where 50.5% of laboratory-identified Stage 2 hospitalisations were coded in 2013 compared to 29.3% in 2009 (Figure 5). The overall (5-year) rates at which the laboratory-identified AKI stages were coded were: 15.9% for Stage 1 (5,294/33,246; 95%CI: 15.5% - 16.3%); 38.5% for Stage 2 (2,381/6,185; 95%CI: 37.3% - 39.7%); and 46.8% for Stage 3 (3,120/6,670; 95%CI: 45.6% - 48.0%).

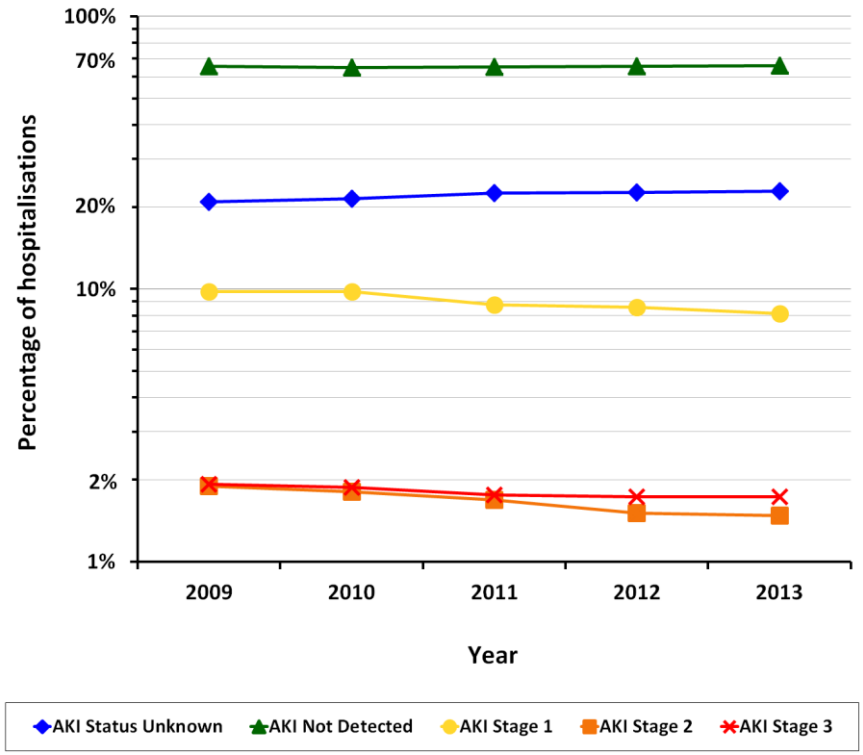

Figure 3: 5-year trends in the incidence of the laboratory-identified AKI stages

Footnote: See Supplemental Table 3 for detail.

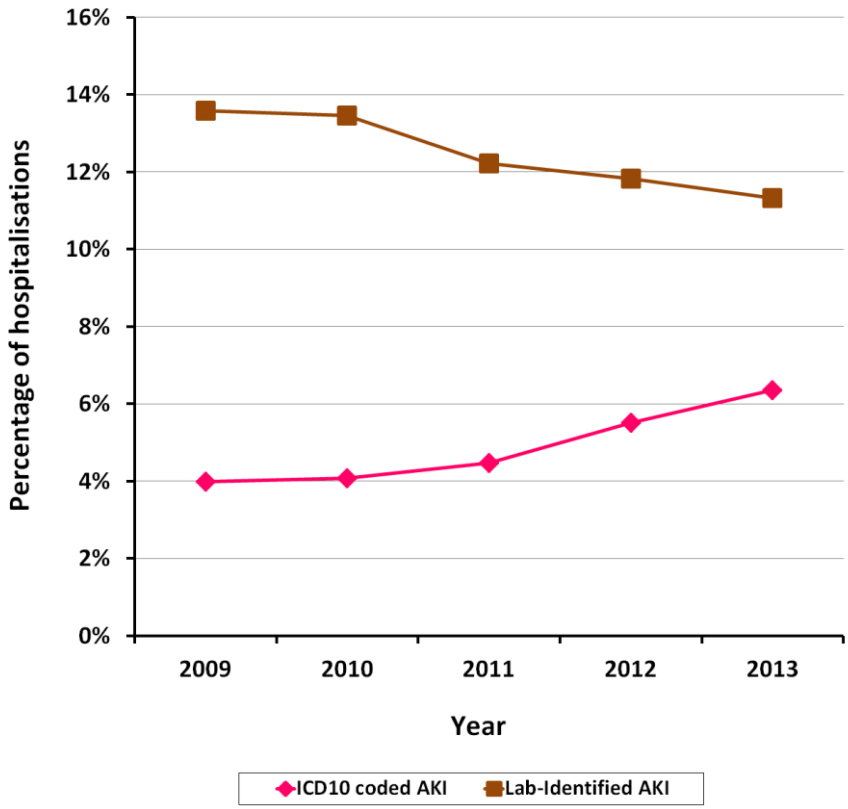

Figure 4: Comparison of the 5-year trend for AKI identified by ICD-10-AM diagnosis coding and the laboratory algorithm

Footnote: See Supplemental Table 4 for detail.

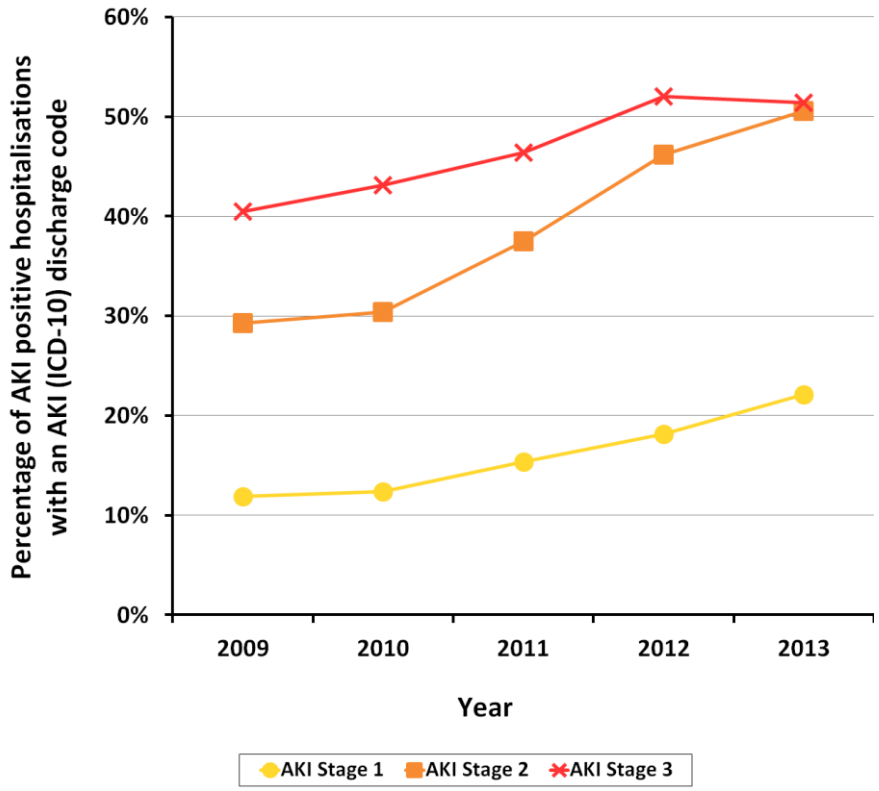

Figure 5: 5-year trends for the rates at which the laboratory-identified AKI stages were coded

Footnote: See Supplemental Table 5 for detail.

Discussion

In this large study, AKI was a common disorder that was significantly under-reported. The laboratory-based algorithm detected AKI in 16.4% of patients and 12.4% of hospitalisations across the 5-year study period. Patients suffering from cardiac, vascular, or kidney disease, or from diabetic complications, had a higher incidence of AKI than the general hospitalised population. Stage 1 was typically the highest AKI stage reached. AKI Stages 2 and 3 occurred at approximately equal rates in the overall hospital population and in most comorbidity subgroups. However, Stage 3 occurred at twice the rate of Stage 2 in patients with CKD, possibly due to the fact that a lower percentage rise is then required to trigger Stage 3 (i.e., in patients whose creatinine is greater than 354umol/L, Figure 1). Diabetes is a major cause of CKD, which could explain the disproportionately high rate of AKI Stage 3 also observed in patients with diabetic complications.

There was a lower incidence of AKI in hospital D, compared to the metropolitan principal referral hospitals. Hospital D has smaller scale intensive care, cardiology, surgical and renal units compared to the metropolitan hospitals, so it likely serves a lower proportion of high AKI risk patients.

There was a downward trend in the AKI incidence per year over the 5 years of the study, especially for AKI Stage 1. This may be due more to a rise in total hospitalisations (by an average of more than 3,000 each year) than to a decline in the number of AKI cases, with the number of Stage 1 hospitalisations in 2012 (6,702) exceeding the 2011 and 2009 levels (6,559 and 6580 respectively).

Given that the incidence of laboratory-identified AKI declined during the study period, the upward trend in coded AKI suggests an increasing awareness of AKI among clinicians. The largest rise in AKI coding occurred in 2012, the year that the KDIGO Clinical Practice Guideline for AKI was released. There remains much room for improvement in the recognition of AKI, especially for AKI Stage 1 which was coded less than a quarter of the time at its highest annual rate (i.e., 2013, Figure 5). Some

of the discrepancy between laboratory detection and coded diagnosis may reflect a failure by coders to transcribe AKI from the clinicians' notes. Spurious laboratory readings for creatinine may also increase false positive AKI detection rates. However, these factors can only account for a small portion of unreported AKI cases.

Comparison to other studies

Our results are similar to the incidence of AKI in patients at the Austin Hospital in Victoria, evaluated over 3 years using the RIFLE criteria, where approximately 20% of patients 16 years and older had an episode of AKI, and hospital mortality increased almost linearly with AKI and AKI stage (17). The incidence of AKI in the ICU is usually higher than in general hospital patients. For example, between 2000 and 2005, in patients treated in any of 57 ICUs in Australia and New Zealand, 36.1% patients were reported to have AKI (as defined by the RIFLE criteria) within 24 hours of their first admission to ICU (18). This is similar to other reports in the ICU setting where the incidence ranges between 20 and 50% (19). Although AKI incidence is likely higher in ICU patients, the use of the Modification of Diet in Renal Disease (MDRD) equation to back-calculate creatinine baselines may have overestimated AKI in some studies (20). Reliance on previous measurements to calculate baseline creatinine still left 36.8% of patients with an unknown AKI status during their first hospitalisation in our study. As some must have had AKI, our estimation of AKI incidence is likely to be an under-estimate. An underestimate of AKI incidence may also result from the increasing use of day-only admissions for procedures which will lead to more admissions without repeated creatinine measurements precluding awareness of AKI.

The AIHW national report on AKI related hospitalisations and deaths in Australia found that 1.6% of all hospitalisations between 2012 and 2013 were coded for AKI with ICD-10-AM (3). Using the same codes as the AIHW to identify AKI diagnosis, the proportion of hospitalisations coded for AKI in our study was much higher (4.9%). Contributing factors to this discrepancy include: i) the AIHW study population included patients between 0 and 18 years of age; and ii) the hospitals in our study had a relatively high capacity to perform major surgery, and treat critically ill and kidney disease patients compared to Australian hospitals overall. In the national report, hospitalisations with a principal diagnosis of AKI tended to have diabetes or other kidney diseases as an additional diagnosis. When AKI was an additional diagnosis, the principal diagnosis tended to be cardiovascular- or respiratory system-related disease. These findings are consistent with trends for comorbidities with AKI identified in our study.

Implications

There is increasing evidence to suggest that even mild acute impairment of kidney function may lead to serious clinical consequences, with various studies reporting odds ratios of 2.2, 2.5 and 4.4 for in-hospital mortality in patients with AKI Stage 1 (2, 9). It is therefore imperative that every episode of AKI is identified and managed appropriately. Automatic reporting of estimated glomerular filtration rate has provided a sensitive, readily available measure of loss of kidney function, but is not valid under non steady-state conditions such as AKI. Studies show that implementation of laboratory-based AKI detection systems coupled with clinical decision support ensure that patients with AKI are recognised, and that they receive treatment to mitigate the increased CKD and mortality risk (21).

Limitations

Identification of AKI using serum creatinine measurements relies on an accurate estimation of baseline creatinine. Since patients do not attend hospital when they are well, creatinine histories may be dominated by previous AKI episodes, which would lead to baseline overestimations and failure to detect current AKI episodes. Conversely, previous creatinine measurements that were uncharacteristically low, e.g., from dilution by intravenous fluids may lead to baseline underestimations and false positive AKI diagnosis.

It is possible that our methodology failed to identify the first maintenance dialysis treatment in some patients, due to such patients being admitted for a reason other than a scheduled dialysis. Thus AKI may have been incorrectly detected in a small number of patients post maintenance dialysis, due to false low estimations of baseline creatinine.

Although a 26 umol/L rise in creatinine is significant in patients with normal kidney function, the biological variation of creatinine in CKD patients is unknown (22). Thus we may have falsely identified AKI in some CKD patients based on the algorithm's 26 umol/L change rule and this definition remains suspect when the baseline creatinine is high (23). We also acknowledge that creatinine is not a perfect gold standard for AKI and that small rises in creatinine may occur without kidney injury in certain settings, such as drug-induced changes in tubular secretion of creatinine (24).

Limited recording of comorbidity could change the AKI incidence within specific subgroups. Since AKI is often secondary, it is probable that some patients known to have AKI were not recorded in the ICD-10-AM coding system. Given the continuous attention AKI has received in recent years, it is likely and also suggested by our data, that the coded incidence and clinical awareness of AKI may have further increased since our cohort was collected. Finally, as mortality data were not available, we could not assess the impact of AKI within the study population.

Conclusions

This is the largest Australian study to calculate a baseline from previous serum creatinine results to detect AKI in a hospital setting. Therefore the AKI incidence is likely to be the most accurate estimate in the Australian hospital population. The results suggest that AKI is frequently unreported and thus untreated. Objective laboratory-based classification of AKI in Australian hospitals should be reported routinely to prompt clinical review and management.

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5.4 Article IV – Supplemental Data

Supplemental Table 1: Incidence of the laboratory-identified AKI stages in hospitalisations with comorbidities known to increase the risk of AKI

Comorbidity	Number of hospitalisations	Highest Lab-Identified AKI stage reached per hospitalisation N (row %)				
		Unknown	Not Detected	AKI Stage 1	AKI Stage 2	AKI Stage 3
Acute myocardial infarction	13,718	837 (6.1%)	9,017 (65.7%)	2,716 (19.8%)	544 (4.0%)	604 (4.4%)
Congestive heart failure	18,557	570 (3.1%)	11,113 (59.9%)	4,823 (26.0%)	1,001 (5.4%)	1,050 (5.7%)
Peripheral vascular disease	2,421	191 (7.9%)	1,514 (62.5%)	509 (21.0%)	98 (4.1%)	109 (4.5%)
Cerebral vascular accident	15,125	1,771 (11.7%)	10,765 (71.2%)	1,950 (12.9%)	347 (2.3%)	292 (1.9%)
Diabetes	16,832	2,203 (13.1%)	11,901 (70.7%)	1,932 (11.5%)	318 (1.9%)	478 (2.8%)
Diabetes complications	13,707	439 (3.2%)	7,442 (54.3%)	3,390 (24.7%)	657 (4.8%)	1,779 (13.0%)
HIV	240	17 (7.1%)	173 (72.1%)	35 (14.6%)	8 (3.3%)	7 (2.9%)
Chronic kidney disease	29,134	908 (3.1%)	14,428 (49.5%)	7,860 (27.0%)	1,420 (4.9%)	4,518 (15.5%)

Supplemental Table 2: Comparison of laboratory-identified AKI stage incidence between the four study hospitals

Hospital	Number of hospitalisations	Highest Lab-Identified AKI stage reached per hospitalisation N (row %)				
		Unknown	Not Detected	AKI Stage 1	AKI Stage 2	AKI Stage 3
Hospital A	100,267	24,029 (24.0%)	63,848 (63.7%)	9,143 (9.1%)	1,670 (1.7%)	1,577 (1.6%)
Hospital B	120,006	23,096 (19.2%)	80,475 (67.1%)	11,938 (9.9%)	2,212 (1.8%)	2,285 (1.9%)
Hospital C	105,393	21,419 (20.3%)	70,565 (67.0%)	9,330 (8.9%)	1,696 (1.6%)	2,383 (2.3%)
Hospital D	45,303	13,535 (29.9%)	27,901 (61.6%)	2,835 (6.3%)	607 (1.3%)	425 (0.9%)

Supplemental Table 3: 5-year trends in the incidence of the laboratory-identified AKI stages

Year	Number of hospitalisations	Highest Lab-Identified AKI stage reached per hospitalisation N (row %)				
		Unknown	Not Detected	AKI Stage 1	AKI Stage 2	AKI Stage 3
2009	67,300	14,058 (20.9%)	44,094 (65.5%)	6,580 (9.8%)	1,274 (1.9%)	1,294 (1.9%)
2010	70,561	15,148 (21.5%)	45,916 (65.1%)	6,899 (9.8%)	1,279 (1.8%)	1,319 (1.9%)
2011	74,856	16,845 (22.5%)	48,867 (65.3%)	6,559 (8.8%)	1,264 (1.7%)	1,321 (1.8%)
2012	78,163	17,701 (22.6%)	51,225 (65.5%)	6,702 (8.6%)	1,183 (1.5%)	1,352 (1.7%)
2013	80,089	18,327 (22.9%)	52,687 (65.8%)	6,506 (8.1%)	1,185 (1.5%)	1,384 (1.7%)

Supplemental Table 4: Comparison of the 5-year trend for AKI identified by ICD-10-AM diagnosis coding and the laboratory algorithm

Year	Number of hospitalisations	Number of hospitalisations coded for AKI	Number of hospitalisations with lab-identified AKI
2009	67,300	2,680 (4.0%)	9,148 (13.6%)
2010	70,561	2,876 (4.1%)	9,497 (13.5%)
2011	74,856	3,340 (4.5%)	9,144 (12.2%)
2012	78,163	4,305 (5.5%)	9,237 (11.8%)
2013	80,089	5,087 (6.4%)	9,075 (11.3%)
Total	370.969	18,288 (4.6%)	46,101 (12.4%)

Supplemental Table 5: 5-year trends for the rates at which the laboratory-identified AKI stages were coded

Year	AKI Stage 1 hospitalisations			AKI Stage 2 hospitalisations			AKI Stage 3 hospitalisations		
	Total	**Coded**	**Percent**	**Total**	**Coded**	**Percent**	**Total**	**Coded**	**Percent**
2009	6,580	783	11.9%	1,274	373	29.3%	1,294	524	40.5%
2010	6,899	852	12.3%	1,279	389	30.4%)	1,319	569	43.1%
2011	6,559	1,006	15.3%	1,264	474	37.5%	1,321	613	46.4%
2012	6,702	1,215	18.1%	1,183	546	46.2%	1,352	703	52.0%
2013	6,506	1,438	22.1%	1,185	599	50.5%	1,384	711	51.4%

Chapter 6

Discussion

The aim of this thesis is to improve the quality of high risk laboratory result identification, reporting and follow up by establishing evidence- and risk-based systems for the safe and effective management of results that may lead to rapid deterioration of patients. To achieve this goal, the following investigations, analyses and development of methodologies were performed: a review of the current status of international high risk result management practices; development of an evidence-based framework and methodology to assist laboratories with the design of their high risk result management procedures; a systematic literature review of critical risk result thresholds with an explicit and ranked source of evidence for each of the values; development of an evidence- and risk-based methodology for identifying and verifying the alert thresholds to include on a laboratory alert list; and retrospective measurement of the impact of introducing creatinine rate of change alert thresholds on patient management workload in public hospitals located in South-Eastern Sydney/Illawarra. In this Chapter, the achievements of this thesis are discussed, including the impact of the work on pathology laboratories and the implications for health care in Australia.

6.1 Laboratory Management of High Risk Results

The review of current international practices for high risk result management presented in Chapter two revealed large variations and gaps in laboratory procedures. The literature contained a variety of alternative terms and definitions for high risk results and alert thresholds. This lack of consistency in terminology complicates literature searches, analysis and comparison of research in high risk result management, and confuses stakeholders seeking to apply published evidence within their institution. The review provided a summary of the key components of a laboratory high risk result management system, extracted from general laboratory standards, published recommendations for high risk result management, and laboratory surveys of management practices. Analysis of the laboratory surveys revealed procedural variations in: the design and composition of alert lists; the appropriate individuals to deliver and receive high risk results; the timeframe for result delivery; acknowledgement of receipt of results; and record keeping of the communication. The need for harmonization of best practice in high risk result management was stressed throughout the review, especially in areas where the risk of patient harm is highest, such as: which results require timely

delivery; timeframes for result delivery; escalation of unsuccessful communication (through locally designed protocols); and acknowledgement of receipt of results. The review also introduced a framework for an evidence- and risk-based approach for compiling an alert list, which was subsequently expanded upon in Chapters three and four of the thesis.

The review of current practices has had an international impact on the design of subsequent guidelines and recommendations for high risk result management. The international guideline for the management of critical- and significant-risk results (1) published by the CLSI, refers to my review a number of times; i.e., when discussing inconsistences in the alert thresholds used by laboratories, the need for harmonisation of key management processes, and the evidence-based approach described in the review for defining alert lists. Some of the descriptive terminology proposed in the review (i.e., alert threshold and alert list) was adopted by the guideline. The impact of the review within Australia has been even more pronounced. Given the knowledge of best practice that I acquired while writing the review, I was concurrently assigned the task of drafting best practice recommendations for the high risk results working party of the RCPA and AACB. The draft was reviewed and adjusted by the working party into an official guidance document (2) for Australian chemical pathology laboratories to use in the design of safe and effective procedures for the management of high risk results. Although the review is not cited within the guidance document (due to the timing of the production of each of the pieces of work), the guidance document incorporates many of the ideas and concepts from my review. The guidance document is currently being promoted and field tested across all specialties in pathology through the RCPA Key Incident Management and Monitoring System (KIMMS) program, with the aim of informing the National Pathology Accreditation Advisory Council (NPAAC) who have initiated drafting a national laboratory standard for the communication of high risk pathology results. On October 21st 2019, I presented my thesis research at an NPAAC members meeting in Sydney, and the slides from my presentation were later forwarded to NPAAC members and to the technical drafting committee for the new standard.

If achieved, standardisation of high risk result management in laboratories throughout Australia would have implications beyond pathology. Australian specialist medical colleges other than the RCPA (e.g., Royal Australasian College of Physicians, Royal Australian College of General Practitioners, and Australasian College of Emergency Medicine) would likely be approached by the standardisation committee to formalise clinician involvement in the process, such as in the design and composition of alert lists and the obligations of recipients in result delivery. Formal clinician involvement in the design of the laboratory procedures would foster a more co-operative relationship between pathology and clinicians which would improve the communication process. Also, if standardisation of the identification and delivery of high risk results can be achieved, expectations would rise for the development of accompanying procedures to ensure safe and reliable follow up of test results.

6.2 Available Evidence for Alert Thresholds

The systematic review presented in Chapter three identified the best available adult alert thresholds from the literature for 30 common clinical chemistry and haematology tests. A ranking system, based on an adaptation of the 1999 Stockholm Consensus hierarchy for setting analytical performance specifications in laboratory medicine (3) and its application to medical decision limits (4), was created so that each threshold extracted from the literature could be ranked according to the level of evidence that supported its selection. Most of the published alert thresholds came from individual institutions or national surveys, low level evidence which, at best, represent the state of the art. A few clinical outcome studies evaluating alert thresholds were uncovered in the literature search. However, flaws in study design such as failure to deal with confounding factors and inadequate consideration of the temporal relationship between the critical risk result and outcome weakened the value of much of this evidence. Thus, the best available thresholds for most tests were recommendations based on consensus of clinicians and laboratory professionals. The review verified a lack of evidence and explicit reasoning in the literature to support the selection of alert thresholds, and identified the need for well-designed outcome studies and clinical audit to test and validate proposed threshold settings.

The systematic review of alert thresholds offers laboratories throughout the world a useful resource to support the compilation or adjustment of their institution's alert list. The explicit and ranked source of evidence provided for each alert threshold empowers laboratories to challenge unfounded requests from their clinician clients to modify existing thresholds, and aids decision making for threshold adjustment when a new source of evidence becomes available. The review has had an impact at the state and national level within Australia. My knowledge of the evidence for alert thresholds, acquired while performing the review, led to my involvement in three independent New South Wales Health Pathology harmonisation projects. These projects generated the following consensus documents that have been adopted by many laboratories in the state: a source document for therapeutic drug monitoring containing therapeutic intervals, alert thresholds and interpretive text; a "Between the Flags" limits document for point of care blood gas testing with reference intervals, abnormal intervals and critical risk thresholds; and a general chemistry critical risk alert list. The systematic review provided many of the alert thresholds contained in these documents. A limitation of the review was that it may have missed literature evidence where the common laboratory terminology for high risk results was not used. For instance, clinicians typically use test specific terminology to describe abnormal results, such as "severe hypoglycaemia" for a critically low glucose result. With this in mind, the RCPA-AACB high risk results working party in conjunction with the Australian Institute of Health Innovation at Macquarie University have decided to conduct test specific literature reviews to capture relevant outcome studies that may have been missed by the

alert threshold systematic review. Evidence from these test specific outcome study reviews will be combined with the alert threshold review evidence to create a national harmonised “starter” alert list.

The systematic review of alert thresholds highlighted the need for more research in this area. In particular, the need for well-designed clinical outcome studies which identify the analyte concentration where the risk of potential harm becomes unacceptably high in the absence of timely medical intervention. This review may facilitate more work by researchers with an interest in high risk result management to fill the gap in high quality evidence by conducting outcome studies that define alert thresholds. The scope for research is wide when one considers the range of tests that may have high risk results and the variety of clinical specialties and patient subgroups which may influence alert threshold settings. The review also provides the inspiration and foundation for professional bodies in pathology (outside of Australia) to produce their own provincial/national harmonised alert list.

6.3 Methodology for Defining Alert Thresholds

Clinical outcome studies can provide valuable evidence for determining alert thresholds by measuring the relationship between laboratory results and the likelihood of harm within a specific population and setting. However, laboratory results need to be interpreted within the clinical context of a patient’s circumstances, which casts doubt on the accuracy of harm estimates from outcome studies and their transferability to other populations and settings. There are also practical issues around the measurement and delivery of high risk results that affect the suitability of alert thresholds. Thus defining alert thresholds is not a straightforward task. The methodology presented in Chapter four describes an evidence- and risk-based approach for the identification and verification of alert thresholds. The approach was conceptualised by consensus in a meeting of the RCPA-AACB high risk results working party, drawing from both the evidence-based methodology described in chapters two and three of this thesis and the risk-based approach described in the CLSI guideline (1). Chapter four fleshes out this concept into a methodology and uses the determination of upper alert thresholds for potassium to demonstrate how it works. The method involves a six step process where: i) evidence for the alert threshold is extracted from the literature; ii) the quality of the evidence is rated to determine the best available threshold; iii) a risk assessment is performed to assess whether rapid communication of results at the proposed threshold will reduce the risk of harm; iv) pre-analytical and analytical factors that may affect the reliability of the proposed threshold are assessed; v) the volume of alerts generated at the proposed threshold is quantified, to assess whether the risk reduction benefits of result communication are not outweighed by undue patient

risk caused by frequent disruption of laboratory and clinical services; and vi) consultation with shareholders is undertaken to ensure that the proposed threshold is appropriate for the setting in which it is applied.

Laboratories that follow the methodology for identifying and verifying alert thresholds will produce robust alert lists that will withstand challenge from clinicians with non-evidence based alternative views. It will sometimes be the case that clinicians provide new or previously unconsidered alert threshold evidence, which laboratories can run through the systematic verification process to determine whether alert threshold adjustment is warranted. Systematic verification is far superior to simply accepting the clinician's evidence only to find out later that the change was inappropriate. Sharing the methodology with clinical users could foster support for the laboratory alert list and strengthen co-operation between the laboratory and clinicians in the management of high risk results. In Australia, the methodology is currently being used by the RCPA-AACB high risk results working party to build a national harmonised starter alert list.

A widely adopted Australian national harmonised starter alert list, constructed through a systematic evidence- and risk-based process, could conceivably evolve with performance monitoring and benchmarking into a robust starter list that could be standardised. Other countries may follow suit and utilise or adapt the methodology to produce a starter list that is suitable for their nation. Alternatively, since the evidence for alert thresholds is sourced internationally, it is possible that an Australian standardised starter alert list could gain international acceptance.

6.4 Application of Delta Alert Thresholds to Serum Creatinine

The study presented in Chapter five retrospectively determined the incidence of Acute Kidney Injury (AKI) across four New South Wales hospitals by applying the serum creatinine delta alert thresholds defined in the "KDIGO Clinical Practice Guideline for Acute Kidney Injury" (5) to laboratory results of adult inpatients over a 5 year period. The creatinine alerts identified AKI in 12.4% of hospitalisations across the study period. Comparison of AKI incidence determined by the creatinine alerts to reported AKI based on diagnostic codes in the hospital discharge data revealed that AKI is frequently unreported and thus untreated; especially when loss of kidney function is less severe (i.e., only 15.9% of AKI Stage 1 hospitalisations were coded). There is emerging evidence to suggest that patients with AKI Stage 1 are at an increased risk of in-hospital mortality (5, 6). Although yearly trends (for AKI coding) in the study suggested that clinician awareness of AKI is rising, laboratory alerts are needed to ensure that every episode of AKI is identified and managed appropriately.

The AKI study justified the establishment of laboratory alerts at the study hospitals. It predicted the proportion of (suspected) AKI patients that currently do not receive treatment thus providing an estimate of the burden introduction of AKI alerting will place on hospital resources. A pilot study is currently underway at one of the study hospitals, where live automated laboratory AKI alerts are being generated together with a compulsory checklist that guides the clinical team looking after the patient through safe management of AKI. I am also involved in this study. Laboratory AKI alerts are widely implemented in the UK and US. Australia is behind in this respect, with very few laboratories providing AKI alerts. I expect that the above mentioned research will inspire other Australian laboratories to come on board and help combat this silent killer by introducing AKI alerting.

6.5 Conclusion

The research undertaken in this thesis provides pathology laboratories with guidance for the development of safe and effective procedures for managing high risk results. Harmonisation of laboratory practice is encouraged to raise the overall standard of high risk result delivery and to drive further improvement by enabling benchmarking. Beneficiaries of this research include patients, who will receive earlier diagnosis and timely medical treatment when needed, and should less likely be sent home with undiagnosed serious illness. Hospitals should benefit with reduced hospital stays due to a reduction in complications from delayed or missed treatment. Governments will appreciate the savings in health funding provided by this improvement in quality of care. Last, but not least, pathology and clinicians benefit by having safe and reliable procedures in place for high risk result management.

More research is needed in the area of alert threshold definitions, and hopefully this thesis will inspire researchers to help fill this gap. Collaboration between pathology and clinicians is encouraged to ensure that high risk result management procedures are fit for purpose, and to foster improved co-operation between these two key stakeholder groups. Establishing formal co-operation could lead to future expansion of high risk result management to include result interpretation and medical action, thus closing the loop in diagnostic testing.

6.6 References

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