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NZIMLS Fellowship treatise

Original article

Case study

Scientific letter

Regular features

In this issue

Rob Siebers, Editor

The implementation of ISO 15189:2012 management system and technical competence requirements remains the international standard of choice for the pathology services industry for demonstration of competence and quality achievements. In this issue, Dennis Mok and Eddie Ang, present an update of international standards and guidance documents, supplemented with recommendations and additional resources that can be used for ISO 15189:2012 implementation purposes.

Fellowship of the NZIMLS can be achieved, among other, by treatise. Emil Wasef, from Southern Community Laboratories, Dunedin, was recently awarded Fellowship for his treatise on von Willebrand factor activity assays, which is published in this issue. In his study 30 normal and healthy donor samples and 30 patients previously diagnosed with von Willebrand disease were assessed with the established von Willebrand ristocetin cofactor assay and the newer Siemens Innovance von Willebrand activity assay. He found a good correlation between the two assays, with the Innovance assay being superior in sensitivity and limit of detection over the ristocetin assay. He concluded that that the Innovance von Willebrand factor assay is a suitable activity assay that fulfils laboratory diagnosis of von Willebrand disease and, after assessment of all von Willebrand disease types and response to therapy, can replace the von Willebrand ristocetin cofactor assay in the screening panel for von Willebrand disease. Emil's fellowship treatise also gives an in-depth review on the diagnosis and laboratory evaluation of von Willebrand disease.

Metastasis to the breast from an extra-mammary site is uncommon. In this issue, Sharda Lallu and colleagues from Wellington Hospital describe the cytological findings of thyroid papillary carcinoma metastasizing to the breast, after 24 years following total thyroidectomy, along with histologic confirmation. They discuss the differential diagnosis and usefulness of immunohistochemical staining to distinguish a metastasis from a breast tumour.

It has become part of current clinical guidelines to endorse HbA1c as a diagnostic marker with concentrations above 50 mmol/mol consistent with diabetes mellitus. In this issue Shugo Kawamoto from Canterbury Health Laboratories, Christchurch presents a case where a patient was found to have an HbA1c of 26 mmol/mol measured on a HPLC analyser. An abnormal chromatogram was noted suggesting a possible analytical artefact, or a potential haemoglobin variant. HbA1c measured on the same sample using an alternative point-of-care instrument, that uses an immunoassay, returned a value of 50 mmol/mol. Upon further investigations the patient was found to have a haemoglobin D Punjab variant. Glycated haemoglobin D co-elutes with the haemoglobin Ao fraction resulting in abnormal peaks that causes interference in the HPLC method for HbA1c.

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The listed persons below reviewed submitted articles to the Journal between August 2015 and July 2016, some more than once. All submitted articles undergo peer review in order that the Journal maintains its high standard. Additionally, thoughtful comments and suggestions made by reviewers help authors in ensuring that their articles, if accepted, are put in front of the reader in the best possible light. The editors thank the reviewers for their valuable time and effort, and Dr. Nevil Pierse, Wellington for statistical review of many articles.

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NZIMLS FELLOWSHIP TREATISE

Is it time for Ristocetin to step down? Comparison study between a new automated von Willebrand factor activity assay and the von Willebrand factor ristocetin activity assay

Emil Wasef

Southern Community Laboratories, Dunedin

ABSTRACT

Background: von Willebrand disease (VWD) is one of the most frequent bleeding disorders; arising from absence or dysfunction of von Willebrand factor (VWF), a multimer plasma protein. Laboratory diagnosis of VWD requires an accurate detection and measurement of VWF in the patient's plasma. These measurements are required for classification and are a guide for best patient management. To date there is no one functional test available to detect VWD; rather a panel of testing is used to classify the disease, including VWF: RCo (ristocetin cofactor), VWF: CB (collagen binding) and VWF: Ag (antigen). Currently the test of choice for functional screening is VWF activity using ristocetin as a cofactor (VWF: RCo). Although this test is widely used, it lacks sensitivity and precision with a very high coefficient of variation. Moreover, no other available screening test has been established to replace VWF: RCo.
Aim: To evaluate the diagnostic efficiency and accuracy of the Innovance VWF Ac assay for measurement of VWF activity based on binding of VWF to platelet GPIb receptors using polystyrene particles coated with an antibody against GPIb.
Methods: 30 normal, healthy donor samples and 30 patients previously diagnosed with VWD were assessed for VWF: RCo, Innovance VWF Ac and collagen binding assays. Results were analysed for correlation between these three assays and sensitivity and specificity for Innovance VWF Ac.
Results: There was a good correlation between the VWF:Ac and VWF:RCo assays, with the VWF:Ac being superior in sensitivity and limit of detection over the VWF:RCo assay.
Conclusions: Our results showed that the Innovance VWF Ac assay is a suitable activity assay that fulfils laboratory diagnosis of VWD and, after assessment of all VWD types and response to therapy, can replace the VWF:RCo assay in the screening panel for VWD.
Key words: von Willebrand disease, von Willebrand factor, ristocetin.

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INTRODUCTION

von Willebrand disease (VWD) is the most common inherited haemorrhage disorder (1). The disease prevalence is not precisely known, however, it has been estimated to range from 0.01% to 1.0% in the general population (2). Furthermore, the prevalence estimation for VWD varies among haemostasis centres (3). VWD is a heterogeneous bleeding disorder that arises from either a quantitative or qualitative defect and/or a deficiency in von Willebrand factor (VWF). Like any other congenital disorders, mutations that occur in VWF gene include deletions, frameshift, splice-site, and nonsense. VWD is inherited as an autosomal disorder. The majority of type 1 and type 2A cases are inherited in a dominant fashion. However, few studies suggest recessive rather than dominant inheritance (4,5). Type 2B and 2M are autosomal dominant, while type 3 and type 2N are inherited as recessive disorders. Nevertheless, *de novo* mutation has been reported (6).

VWF is a large, complex, multimer plasma glycoprotein composed of repeated units that are polymerised from dimers by disulphide bonds (Figure 1) (7). VWF is manufactured in two cell types, endothelial cells and megakaryocytes (1). In endothelial cells, after being synthesised, VWF multimers are packaged into rod-shaped secretory vesicles called Weibel-Palade bodies, from which it is released upon stress or following drug exposure (5). The secreted VWF from endothelial cells represents approximately 85% of the circulating VWF level (9). The 15% remainder of VWF is formed by megakaryocytes and stored in α-granules of platelets and secreted upon platelet activation (8).

VWF has a half-life of approximately 12 hours, ranging from 9 – 15 hours (9), and is cleared from the circulation by macrophages in the spleen and liver in a process that is independent of its size (8). Upon secretion, the ultra-large VWF multimers have a high affinity to bind to platelets spontaneously without shear stress or any other stimulants (10). Subsequently, these large multimers undergo proteolytic degradation by metalloprotease ADAMST-13 (a disintegrin and metalloprotease with thrombospondin type 1 motifs), which cleaves the molecule in domain A2 to produce circulating VWF of various multimer sizes (10,11).

Several binding sites have been identified in the VWF subunit (Figure 1). Platelet GPIb interacts with domain A1 and integrin GPIIb/IIIa interacts with an Arg-Gly-Asp sequence in domain C1. Fibrillar collagens interact mainly with domain A3 and collagen VI binds to domain A1. Coagulation factor VIII (FVIII) binds to the N-terminal of D'D3 region (12).

The VWF gene is located on the short arm of chromosome 12, at position 12p13.3 and spans approximately 178 kb and contains 52 exons. (13,14). Moreover, there is an unprocessed VWF pseudo-gene located on chromosome 22q11.2 which

spans 25kb and corresponds to exons 23-34 of the VWF gene (15,16). Many genetic mutations and defects have been found to occur in the VWF gene which can affect different functional sites on the VWF molecules and explain the heterogeneous nature of the disorder (17).

VWF plays an essential role in primary and secondary haemostasis. At high shear stress and when vascular injury occurs, VWF multimer undergoes conformational changes that causes binding to different ligands in the sub-endothelial matrix and promotes platelet adhesion by interaction with the platelet glycoproteins Ib and IIb/IIIa (GPIb and GPIIb/IIIa) receptors (18). Subsequent to adhesion, platelets are activated, secrete the contents of their granules, and recruit additional platelets to the site of injury. Platelet aggregates then bind to fibrinogen through the GPIIb/IIIa receptor to form a platelet plug (19).

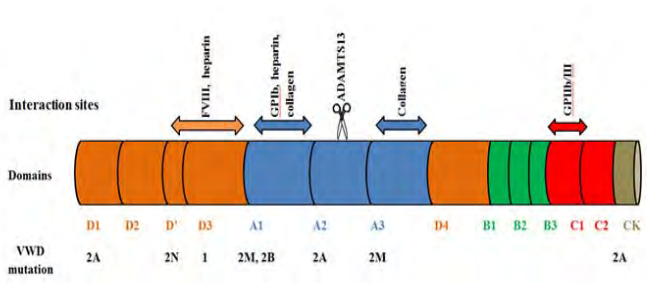

Figure 1. Schematic diagram of VWF. The pro-peptide and the mature subunit form pro-VWF consisting of 4 types of repeated domains. The main binding sites are shown together with the ADAMTS13 cleavage site. Major regions in which mutations have been found that are associated with VWD types 1 and 2 are also shown (adapted from ref. 20).

Furthermore, VWF functions as a carrier and stabiliser for coagulation factor VIII. VWF makes a non-covalent complex with factor VIII preventing it from proteolytic degradation and clearance from circulation (21), prolonging its half-life by five-fold (20) from approximately 2 hours to an average of 12 hours (range 9 – 18 hours).

Classification of VWD

In 2006, The VWF Scientific Standardisation Committee of the International Society on Thrombosis and Haemostasis revised the first classification, which was published in 1994 (12). This classification was based on available laboratory testing, however, the aim of the classification was to guide the diagnosis and treatment of patients with VWD. The committee disregarded genotypes of the disease due to limited access to genetic testing. The 2006 classification dropped the restriction of VWD due to mutations in the VWF gene, which was a criterion in the previous classification. VWD is classified into three main types (Table 1): type 1 and type 3 VWD are quantitative defects and type 2 VWD is a qualitative defect. Type 1 VWD is partial deficiency in VWF whereas type 3 VWD is virtual absence of plasma VWF. Furthermore, type 2 VWD has been divided into four subtypes according to their phenotype (2A, 2B, 2M, and 2N) (12).

Type 1 VWD represents partial quantitative deficiency in VWF that results in decreased normally functioning VWF (12), which is able to mediate platelet adhesion and binds to collagen and factor VIII under normal physiological conditions. The main laboratory findings show a reduction in both VWF antigen levels and function (9). The proportion of high molecular weight multimers patterns on protein electrophoresis are normal or show subtle decrease (23).

Table 1. Classification of VWD according to the VWF Scientific Standardisation Committee of the International Society on Thrombosis and Haemostasis (ref 22)

Type	Description	Comments	Inheritance
1	Partial quantitative deficiency of VWF	Includes mutations causing rapid VWF clearance	Mostly autosomal dominant inheritance when VWF <30 IU/dl. Mutations with levels >30 IU/dl show variable penetrance
2	Qualitative VWF defects		
2A	Decreased VWF-dependent platelet adhesion with selective deficiency of high molecular weight multimers	Some controversy exists regarding classification of VWF mutations associated with subtle reduction in high molecular weight multimers	Mostly autosomal dominant
2B	Increased affinity for platelet GPIb	Should be differentiated from platelet-type VWD; using ristocetin-induced platelet aggregation or genetic testing	Autosomal dominant
2M	Decreased VWF-dependent platelet adhesion without selective deficiency of high molecular weight multimers	Also includes defects of VWF collagen binding	Autosomal dominant
2N	Markedly decreased binding affinity for Factor VIII	Should be distinguished from haemophilia A	Commonly identified as a heterozygote with a VWF null allele rather than a homozygous form
3	Virtually complete deficiency of VWF	Results <3 IU/dl in most assays	Autosomal recessive

Type 1 is the most common form of VWD and accounts for approximately 80% of all cases (24). Patients with type 1 VWD are affected variably, may have only mild symptoms and mild decreased VWF levels, whereas others are affected more severely (1). Mostly the bleeding tendency in patients with type 1 VWD is attributed to a clearance of plasma VWF protein, not to specific abnormalities in ligand binding sites (12). Type 1 VWD is considered when laboratory assays show a reduction in VWF:Ag and VWF:RCo with a ratio close to 1 and normal multimer distribution (25). Several mutations have been identified which reduce plasma VWF levels by impairing synthesis through interfering with the intracellular transport of dimeric pro-VWF, or by enhancing rapid clearance of VWF from the circulation (9,23).

Type 1 VWD is characterised by low penetrance where people with same mutations show variable clinical signs and a variable bleeding tendency and others do not show any signs or symptoms for VWD, which makes the diagnosis of type 1 VWD a challenge (25). Patients with severe and moderate type 1 VWD can be diagnosed with ease, however, patients with mild or borderline VWF assays are difficult to diagnose. This is because these patients have no symptoms or signs and have normal lives. Also, their VWF levels are wide, ranging between 50 to 200 IU/ml. This makes 5% of population falling outside that range, in particular 2.5% of this population have VWF levels of less than 50 IU/ml. This reference range makes this group of people misdiagnosed as having VWD (26).

Furthermore, genetic variations have shown a substantial effect on VWF levels, such as the ABO blood group system. VWF levels are 25 – 35% lower for persons with blood group O compared with other blood groups. They have VWF levels ranging from 36 – 157 IU/ml (26). Also, bleeding is not uncommon in this population for many other pathological conditions.

Type 3 VWD is the most severe form of the disease and is inherited as an autosomal recessive condition (7). It refers to a virtually complete absence of the circulating plasma VWF (12). The absolute deficiency of VWF subsequently leads to a severe deficiency in coagulation Factor VIII with plasma levels ranging between 2 and 10 U/dl (27). Type 3 VWD is very rare and it has been estimated to occur in 0.1 to 5.3 per million people (27), although there is no accurate prevalence of the disease (1).

Type 2 VWD represents qualitative abnormalities of the structure and/or function of VWF (2) and it is further sub-classified into 4 categories according to the type of defect on the VWF. Current available laboratory assays allows distinguishment among different subtypes of type 2 VWD. Plasma VWF antigen usually shows a mild reduction in type 2 VWD, but may be normal. However, the assays that measures VWF activity, such as VWF:RCo and VWF:CB are reduced, except in type 2N VWD. Ideally, these assays are lower than antigen. The difference between antigen and activity assays is known as VWF functional discordance and expressed by a ratio (28).

Type 2A VWD is the most common form of type 2 VWD (1) and is characterised by the absence of large multimers that may be caused by increased susceptibility to proteolysis by ADAMTS 13 or by defective multimer assembly and retention in the endoplasmic reticulum (23,25). This results in production of small multimers that are not able to bind to platelets and connective tissue, which in turn leads to a significant decline in VWF activity (VWF:RCo and VWF: CB) (12). Levels of VWF antigen and factor VIII are normal or mildly reduced (28). To confirm the diagnosis multimer gel electrophoresis shows loss of high molecular weight multimers (25). Different mutations have been shown to reduce or interfere with multimerisation and occur in regions involved in the dimer and multimer (29). These mutations can be identified on high-resolution multimer gel electrophoresis (9). On the other side, mutations that increase VWF susceptibility to proteolysis occur within or near domain A2 (29).

Type 2B VWD is a variant that is associated with increased VWF affinity to platelet GPIb (1). Large multimers are assembled in a normal fashion but straight after secretion they bind spontaneously to platelets and are cleaved by ADAMTS 13, a disintegrin-like and metalloprotease domain with thrombosponding type 1 motifs (12). This results in the production of small multimers which are not able to mediate platelets adhesion effectively and consequently preventing their adherence to the site of injury (19,30). Often patients have associated thrombocytopenia due to increased platelet consumption. Primarily, mutations that cause type 2B VWD occur within or close to domain A1 in VWF which contains the GPIb-binding site. The mutations result in conformational changes in the A1 domain which increases the affinity of VWF for platelets and thus causing gain-of-function (31,32).

Laboratory diagnosis of type 2B VWD shows similar results to type 2A VWD with VWF:Ag, VWF:RCo, VWF:CB, and multimer gel electrophoresis. To discriminate between these two variants, ristocetin induced platelet aggregation (RIPA) is used with a low dose of ristocetin to enhance platelet agglutination in the presence of gain-of-function mutations (25).

Type 2M VWD includes a qualitative variant that is characterised by a functional defect in binding to platelet GPIb receptor (12). Patients usually have mutations within the VWF A1 domain that results in a reduced affinity to platelets and subendothelial cells (loss-of-function), while maintaining a normal assembly of the high molecular weight VWF multimers (1,31). Laboratory results are similar to type 2A VWD. However, discrimination between these two variants depends on the presence of high molecular weight multimers on gel electrophoresis (31,32).

Type 2N VWD is characterised by a reduced ability of VWF to bind coagulation factor VIII (33) that results in a marked reduction in factor VIII levels due to increased clearance from circulation (1). Patients with classical type 2N VWD show significant decreased plasma levels of factor VIII:C (< 10%) (9), despite normal VWF antigen and activity while maintaining the multimer pattern as shown by electrophoresis (33). The results from an international survey showed that factor VIII:C levels are positively correlated with the VWF capacity to bind factor VIII, with factor VIII:C plasma levels varying from approximately 10 – 30 % (34). The confirmation of type 2N VWD may require a VWF: factor VIII binding assay, usually in a solid-phase immunoassay (12). Mutations in type 2N VWD occur within the factor VIII binding site of VWF, which lies between amino acids Ser764 and Arg1035 and spans domain D' and the N terminal part of domain D3 (31,33).

DIAGNOSIS AND LABORATORY EVALUATION OF VWD

Clinical and laboratory evaluation of any patient suspicious for a haemorrhagic disorder, including VWD, requires an investigation of personal and family clinical history, physical examination and utilisation of several laboratory tests (Figure 2) (35). However, to confirm or exclude VWD it may require repeated laboratory testing as a significant proportion of false positives and false negatives are common. There are some factors that can affect the final outcome of the assays. For instance bleeding symptoms are frequent in normal populations without specific haemostatic defects and also the limitation of the available diagnostic assays (36). Also the wide range of VWF levels and cut-off limits for normal and low levels (mean ± 2SD) leaves 2.5% of the population as having low VWF levels. People with blood group O have VWF levels approximately 25% lower than any other blood group. This group of people can be misdiagnosed (false positive) as having type 1 VWD. Furthermore, VWF is an acute phase reactant that can increase in pregnancy, stress, infection and other inflammatory conditions. In addition, the current diagnostic assays have some issues with sensitivity, specificity, and the lower limit of detection that requires repeated testing (28). Finally, some pre-analytical issues can affect the final results, such as fear of needles, particularly in children.

Laboratory evaluation of VWD begins with screening tests followed by specific confirmatory assays. In the past, and for many years, the bleeding time was used as a gold standard screening test, but its clinical use has diminished due to difficulties with standardisation, reproducibility, and lack of sensitivity and specificity (25). Furthermore, initial haemostasis laboratory evaluation includes a complete blood count to assess the platelet count, a partial thromboplastin time (APTT) and a prothrombin time (PT). Nevertheless, this testing has limited value and does not exclude or confirm VWD (25).

In 1995, Dade-Behring introduced the platelet function analyser PFA-100 as a substitute for the bleeding time and to be used as a screening test for platelet function and bleeding disorders (37). The PFA-100 is a simple, rapid device that uses whole blood to measure platelet-based coagulation function through a

capillary device to mimic high shear stress conditions that occur *in vivo*. The instrument gives a single endpoint reading called the closure time. Two cartridges are available for use in the PFA-100, both utilise a membrane coated with collagen; moreover, one is also coated with epinephrine and the other with adenosine diphosphate (ADP). The PFA-100 has showed a good sensitivity to VWD, estimated between 70% and 90% (37,38). However, its effectiveness is reduced due to low specificity (24 – 41%) in individuals with VWF levels greater than 25 IU/dl (25). The PFA-100 also lacks specificity to VWD and shows abnormal results in a variety of other conditions (38-40).

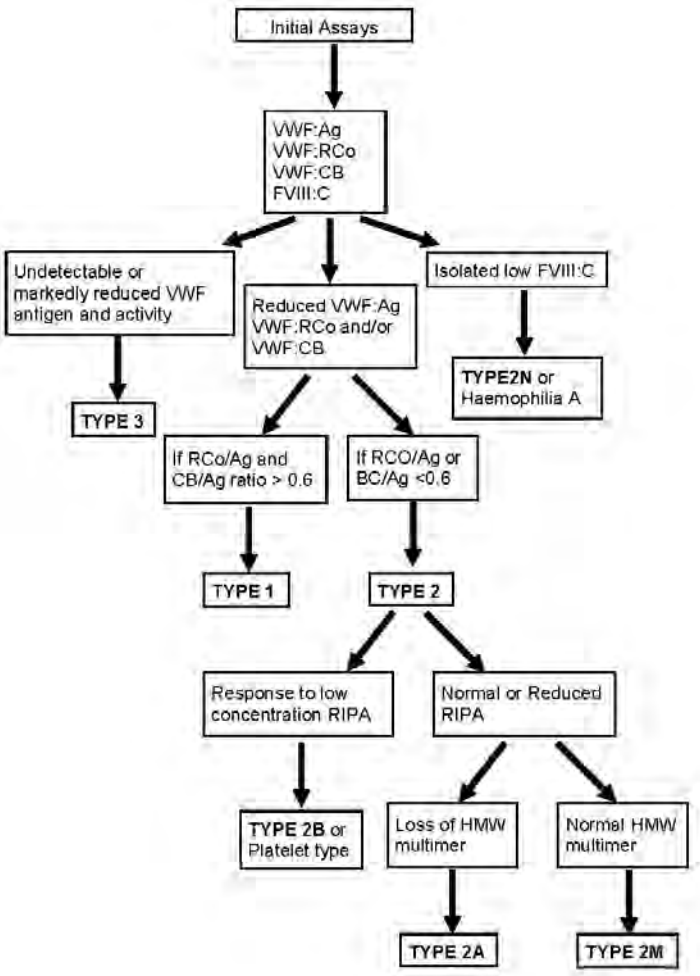

Figure 2. An algorithm for the investigation of VWD (adapted from ref. 22).

Recommended specific laboratory assays for VWD (Table 2) include VWF antigen, VWF activity and factor VIII coagulant plasma levels (22). When indicated, supplementary assays are used to confirm the diagnosis and assist in an accurate classification which is essential in patient management. These tests include multimer assay, ristocetin-induced platelet aggregation (RIPA), and the ability of VWF to bind factor VIII, and in some selected cases genetic testing may also be indicated.

VWF antigen assay (VWF:Ag)

This assay measures the concentration of the VWF protein in the patient's plasma. A variety of immunoassay methods are used by the majority of haemostasis laboratories to evaluate VWF:Ag levels. The most widely used are enzyme-linked immunosorbent assays (ELISA), and the automated latex immunoassay utilising a monoclonal antibody against VWF (1,36). This assay does not provide any information regarding the function or structure of the VWF protein.

Table 2. Summary of VWF assay methods in diagnostic laboratories (adapted from ref. 41)

Assay	Description
VWF:Ag	Measures plasma VWF protein level. Typically performed by ELISA or LIA based methods.
VWF:RCo	Assesses VWF activity utilising ristocetin and an agglutination assay. Is performed by platelet agglutination or LIA based methods. For platelet agglutination, the test can be performed using an aggregometer or a coagulation based instrument.
Factor VIII:C	Measures the activity of coagulation factor VIII. It utilises a one-stage coagulometric method.
VWF:CB	Measures VWF activity utilising collagen. Typically performed by ELISA.
Werfen-IL activity assay	Measures VWF activity using a monoclonal antibody binding assay, where the antibody is directed against the platelet GPIb binding site of VWF. Performed by an LIA based method.
Siemens Innovance activity assay (Inn VWF:Ac)	Measures VWF activity utilising a GPIb binding method. The system employs two gain-of-function GPIb mutations within a recombinant molecule that facilitates VWF binding. Performed by an LIA based method.

VWF ristocetin cofactor assay (VWF:RCo)

Historically, VWF activity was mostly measured using the antibiotic ristocetin as a cofactor, which enhances the binding of VWF to the platelet GPIb receptor (42). It is a functional assay of VWF that measures the ability to agglutinate platelets in the presence of the antibiotic ristocetin (43). Since its introduction in the early 1970s, ristocetin is considered the test of choice for measuring VWF activity (44). *In vivo*, the binding of platelets to VWF through interaction with platelet GPIb receptors under shear stress induces conformational changes in the VWF. However, this interaction is promoted by ristocetin under a static condition *in vitro* (44). Initially, the assay was performed using a platelet aggregometer, where ristocetin is added to a mixture of patient's plasma and formalin-fixed normal platelets. The slope of the agglutination curve is proportional to the amount of the VWF activity in plasma (42). Decreased VWF:RCo, in the presence of normal VWF:Ag, is indicative of dysfunctional VWF binding to GPIb (types 2A, 2B, and 2M VWD); whereas, proportional decreases in both assays are indicative of a quantitative decrease of a normal functioning VWF molecule (type1 VWD) (Table 3) (1).

The VWF:RCo assay is widely used to diagnose VWD and is accepted as the gold standard for VWF activity. Nevertheless, the VWF:RCo assay suffers various limitations and laboratory problems which include difficulty to perform, time consuming, poor reproducibility, sensitivity (43), difficult to interpret, and raises significant concerns in quality assurance surveys.

The most significant problem is its high inter- and intra-laboratory coefficient of variation (CV) which has been estimated between 20 – 30 %, particularly when VWF levels are lower than 12 – 15 IU/dl in some studies (25) and 20 – 30 IU/dl in others (45). In a large cross-laboratory study (41), VWF:RCo showed the highest intra-laboratory variability and the CV increases with a decrease in VWF levels. Furthermore, the VWF:RCo assay showed the highest lower limit of detection with approximately 20 IU/dl in samples with type 3 VWD where expected results should be extremely low or undetectable (41). Additionally, VWF:RCo is largely insensitive to acquired VWF abnormalities (46). Many factors are involved in imprecision, including variation of the donor platelets, suboptimal quality control, and standardisation of ristocetin reagents (24).

It has been reported that the VWF:RCo assay shows significant variations among races (47). African Americans have decreased ristocetin-induced platelet aggregation compared to

Caucasians. The explanation of these findings is that this population group have polymorphisms in exon 28 that affects ristocetin-based assays, which leads to underestimation of the VWF function. Furthermore, a mutation in the P14675, just outside the A1 loop and in a region previously indicated in VWF -ristocetin interactions, which has been described as a ristocetin binding site, results in an apparent decrease in binding to ristocetin. Subsequently, this results in a marked reduction in the VWF:RCo assay (44). Other studies have demonstrated that substitution of the VWF proline triplet with either arginine or aspartic acid at position 1465-1467 disrupts ristocetin-induced GPIb binding (44).

VWF collagen binding assay (VWF:CB)

The VWF:CB assay measures the functional ability of large VWF multimers to bind external collagen. It is an ELISA assay in which patient's plasma is added to a collagen-coated ELISA plate and the amount of bound VWF is evaluated using a horseradish peroxide conjugated anti-human VWF antibody (48).

Since the VWF:RCo assay suffers several limitations, recent global attention has focused on VWF:CB assay as a supplementary test of VWF function (49). Since the VWF:CB assay shows less variability, better sensitivity, better LOD, and better sensitivity to high molecular weight VWF, it should improve discrimination of VWD types. Indeed, incorporation of the VWF:CB assay into the core test panel was noted to reduce diagnosis error rates by about 50% (48). Furthermore, it is considered to be sensitive to the presence or absence of high molecular weight multimers. Yet, the VWF:CB assay does not provide an advantage over VWF:RCo as it suffers some limitations. It has not been well standardised and a wide range of animals and collagen types have been used and showed significant changes in results. In a study by Favaloro *et al.* (50) when assessing 21 different preparation of collagen used to bind VWF, results showed wide variation in binding ability and discrimination between VWD types. The best binding was observed for type III collagen.

Table 3. Expected values in VWD (ref. 9,53)

	VWF:Ag (IU/dl)	VWF:RCo (IU/dl)	VWF:CB (IU/dl)*	Factor VIII:C (IU/dl)	RIPA	LD-RIPA	VWF Multimer
Normal	50 – 200	50 – 200	50 - 250	50 - 200	N	absent	N
Type 1	↓ or ↓↓	↓ or ↓↓	↓ or ↓↓	N or ↓	N	absent	N
Type 2A	↓	↓↓ or ↓↓↓	↓ or ↓↓	N or ↓	↓	absent	abnormal
Type 2B	↓	↓↓	↓ or ↓↓	N or ↓	N	↑↑↑	abnormal
Type 2M	↓	↓↓	N	N or ↓	↓	absent	N
Type 2N	N	N	N	↓↓	N	absent	N
Type 3	absent	absent	absent	↓↓↓	absent	absent	absent

The VWF:Ag to VWF:CB ratio is believed to be useful in discriminating between type 1 and type 2 VWD, with ratios of < 0.7 being consistent with type 2 VWD (17,51). The most useful and advantageous collagen for this purpose was bovine type I/ III collagen and equine tendon type I/II and type III collagen. Moreover, concentration of these collagens showed a significant effect on the binding affinity (50). VWF:CB is considered to be sensitive to VWD variants with loss of large multimers. It has been suggested that a mixture of type 1 (95%) and type III (5%) collagen is best to use. However, this concept has been challenged by rare mutations located in the A3 domain characterised by a normal multimer pattern (17,52).

VWF: factor VIII binding assay

This assay allows accurate diagnosis of type 2N VWD in which VWF:Ag, VWF:RCo and VWF:CB levels are often normal but factor FIII:C is moderately to markedly reduced. The assay measures the ability of the patient's VWF to bind exogenous factor VIII. This assay is very complex and requires several steps. It starts with immobilisation of the patient's VWF on anti-VWF-coated plates followed by removal of endogenous factor VIII. Then, purified or recombinant factor VIII is added. The final step quantifies immobilised VWF and bound factor VIII (54). This complexity makes the assay limited to only a few reference laboratories which may lead to misdiagnosis of type 2N VWD in many haemostasis clinics.

Multimer analysis

Multimer analysis is carried out to demonstrate the distribution of the wide range of VWF multimers in a patient's plasma by electrophoresis, using agarose gel in the presence of sodium dodecyl sulphate. The multimers are stained with radiolabelled antibody to VWF and visualised by autoradiography or luminography.

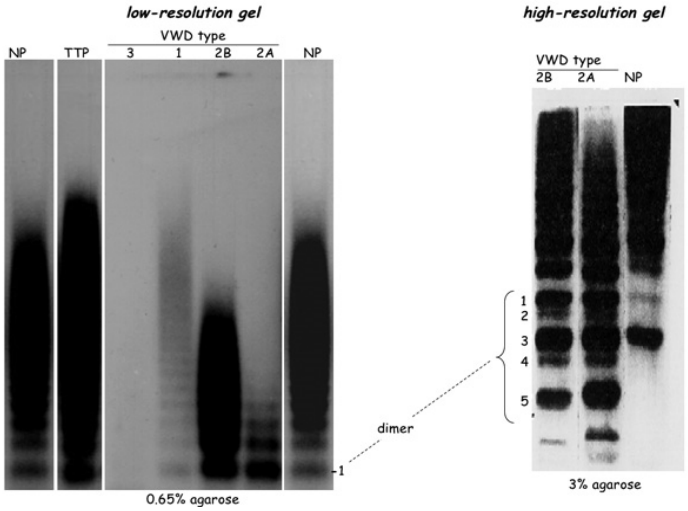

Figure 3. VWF multimer analysis. Low-resolution gels (0.65% agarose, left) shows the change in multimer distribution of the larger multimers, while high-resolution gels (3% agarose, right) separates each multimer into several bands that may be distinctive. For example, the lowest band in the 0.65% gel (1) can be resolved into 5 bands in the 3% agarose gel, but the 3% gel fails to demonstrate the loss of high molecular weight multimers seen at the top in the 0.65% gel (ref. 55. Reproduced with permission, courtesy of R. R. Montgomery, the Blood Centre of Wisconsin and Medical College of Wisconsin, Milwaukee, Wisconsin, USA).

Multimer analysis (Figure 3) is very important in the diagnosis of VWD, in particular type 2 VWD. Medium-resolution gels allow detection of the presence or absence of all multimer sizes. Low-resolution gels evaluate the presence of different sized multimers (56). Patients with types 2A and 2B VWD demonstrate the absence of high and intermediate molecular weight multimers. All multimers are detected in types 1, 2M and 2N VWD. No multimers can be seen in type 3 VWD (55).

Ristocetin-induced platelet aggregation (RIPA)

Generally, in normal people and at low concentrations (<0.7 mg/ml), ristocetin does not induce platelet agglutination (22). However, if the interaction occurs at this level, it reflects an abnormality in VWF-GPIb interaction. RIPA is carried out in platelet-rich plasma, using a low concentration of ristocetin (usually <0.7 mg/mL, although ristocetin lots vary, resulting in the use of slightly different ristocetin concentrations). This low concentration of ristocetin does not induce VWF binding and aggregation of platelets in samples from normal persons, however, it does cause VWF binding and aggregation of platelets in samples from patients who have either type 2B VWD or mutations in the platelet VWF receptor. The latter defects have been termed platelet—type VWD or pseudo VWD, and they can be differentiated from type 2B VWD by the VWF:PB assay. At higher concentrations of ristocetin (1.1-1.3 mg/ml), RIPA will be reduced in patients who have type 3 VWD. However, the test is not sufficiently sensitive to reliably diagnose other types of VWD (55).

The VWF:PB measures the ability of VWF to bind to formaldehyde-fixed platelets using ristocetin at low concentration (< 0.6 mg/ml) (57). The next step is to detect the amount of VWF bound to platelets using a labelled monoclonal antibody. At that level of ristocetin, normal individuals and all types of VWD, except type 2B VWD, show no binding to platelets. PLT-VWD has normal VWF:PB and can be discriminated from type 2B VWD, which has increased binding level at a low ristocetin concentration.

AIM OF STUDY

Recently, a commercial, automated, immunoturbidimetric VWF activity assay, Innovance® VWF Ac (VWF:Ac, Siemens Healthcare Diagnostics, Germany) became available. This assay measures VWF binding to GPIb without ristocetin. To measure VWF activity in plasma, the VWF:Ac assay uses a recombinant form of the VWF receptor with two gain-of-function mutations (G233V and M239V in the GPIb receptor protein) , captured on polystyrene particles that are coated with an antibody to GPIb. The aim of this study was to evaluate the performance of the VWF:Ac assay, comparing the results with the current platelet-based VWF:RCo assay and assessing the assay repeatability using a CS2100i coagulation analyser.

MATERIALS AND METHODS

Study population

This study was approved by Health Research South (University of Otago and Southern District Health Board) and informed consent was obtained from all participants (patients and healthy volunteers) and witnessed by the venepuncture staff member who bled the subject. The study population included 30 normal healthy volunteers and 30 individuals with type 1 and type 2 VWD. Patients (n= 30, 11 males/19 females, average age 43 years) had been recruited from the haemostasis clinic database at Dunedin Hospital.

Samples from 30 normal healthy volunteers (16 females/14 males, average age 44 year) were analysed. The selection criteria for healthy volunteers were no bleeding history and no current medication, regardless of sex and age.

LABORATORY METHODS

Sample collection

Blood was collected into 3.2% (0.109 M) sodium citrate vacutainer tubes (Becton Dickinson vacutainer®, UK), where the citrate to blood ratio is 1:9. Samples were centrifuged at 2000g for 10 minutes to obtain platelet poor plasma (PPP) within one hour then frozen in aliquots at -20°C if run within two weeks and -80°C for spare aliquots. Samples were thawed for 5 minutes in a water bath at 37°C directly before analysis.

VWF assays

VWF activity (VWF: Ac, Innovance VWF Ac®) and ristocetin cofactor activity VWF:RCo (BC von Willebrand Reagent®) both from Siemens Healthcare Diagnostics, Germany were measured according to the manufacturer protocol using the CS2100i coagulation analyser (Siemens Healthcare Diagnostics, Germany). Standard human plasma (Siemens Healthcare Diagnostics, Germany) was used for preparation of the calibration curves against the WHO standard for both assays. Two calibration curves for the VWF:Ac assay were obtained; a medium curve and a low curve for activity ranging from 15-160% and from 4-20%, respectively. Measurements were performed within routine laboratory analysis.

The Innovance® vWF:Ac kit contains three different reagents that are in ready to use liquid form. Reagent I is a suspension of polystyrene particles coated with anti-GPIb antibodies. Reagent II is a heterophilic blocking reagent and reagent III is the recombinant GPIb with activating mutations (68).

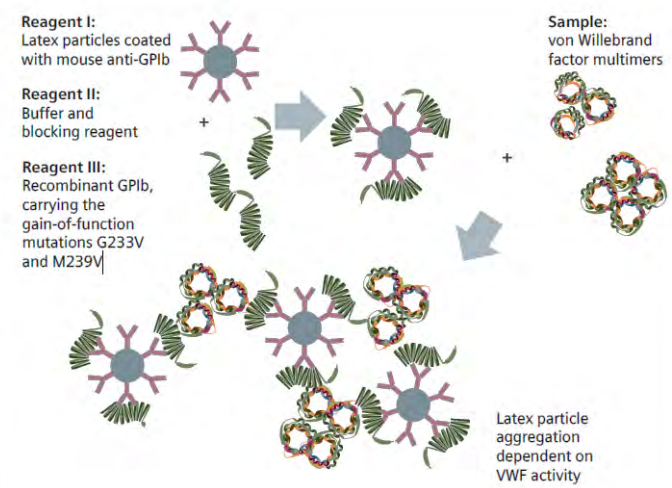

Figure 4. The Innovance VWF Ac assay principle (ref. 50).

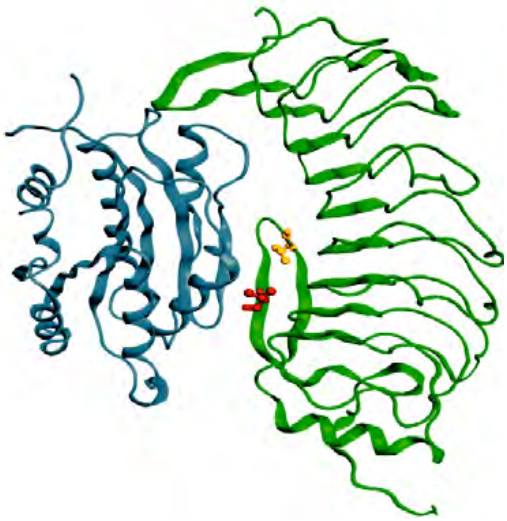

Figure 5. VWF interaction with platelet GPIb.
Blue: VWF A1 domain, green: mutant GPIb, mutations in red and yellow (ref. 50).

The VWF:Ac assay principle (Figures 4 & 5) mimics the reaction in which VWF binds to GPIb. Latex particles are coated with an antibody against GPIb, to which recombinant GPIb is added. The addition of patient plasma induces a VWF-dependent agglutination, which is detected turbidimetrically (59).

To compare results and as a supplementary functional assay, we have done the VWF:CB assay (performed at a reference laboratory). All results showed good correlation with VWF:RCo and vWF:Ac assays (Figures 10 & 11), but one normal healthy volunteer with no family history of VWD and no bleeding tendency showed normal VWF:RCo and VWF:Ac assays but a very low VWF:CB assay. These results were repeated with a new sample and we were able to confirm our results. However, no genetic analysis was performed to confirm mutation in the collagen binding site.

Statistical analysis

Agreement between VWF:RCo and VWF:Ac was assessed using Bland-Altman plots, i.e. the difference between the values of VWF:RCo (reference method) and VWF:Ac were plotted versus their means. Statistical analysis was performed using Analyse-it software. $p \leq 0.05$ defined statistical significance.

RESULTS

Table 4. Laboratory results for the study population.

Group	VWF:RCo Mean (SD) IU/dl	VWF:Ac Mean (SD) IU/dl	VWF:CB Mean (SD) IU/dl
Normal (n=30)	96 (35)	100 (40)	126 (61)
VWD (n=30)	21 (19)	23 (20)	31 (26)

Table 5. Laboratory results and VWD types of patient group.

Patient	VWD*	VWF:Rco IU/dl	VWF:Ac IU/dl	VWF:CB IU/dl
1	Type 1	48	48	89
2	Type 1	39	40	32
3	Type 1	23	26	33
4	Type 2	8	20	17
5	Type 1	9	5	20
6	Type 1	8	6	15
7	Type 1	57	61	77
8	Type 1	9	17	40
9	Type 1	8	11	9
10	Type 1	8	11	12
11	Type 1	8	5	20
12	Type 2	11	13	41
13	Type 1	10	2	14
14	Type 2	12	11	13
15	Type 2	8	15	85
16	Type 1	8	2	2
17	Type 2	54	76	70
18	Type 2	9	16	24
19	Type 2	8	5	5
20	Type 1	53	49	33
21	Type 2	9	18	27
22	Type 1	9	9	8
23	Type 2	9	2	2
24	Type 1	38	41	29
25	Type 1	69	61	90
26	Type 1	10	8	14
27	Type 2	8	2	7
28	Type 2	9	17	15
29	Type 1	34	36	39
30	Type 1	50	42	43

*Old hospital database classification and not enough information to confirm these subtypes.

The normal and patients samples exhibited good correlation between VWF:Ac and VWF:RCo (R^2 = 0.97, p < 0.0001) (Figures 6 &7), with a mean bias of 2.7 IU/dl (Figures 8 &9) as assessed by Altman-Bland plots.

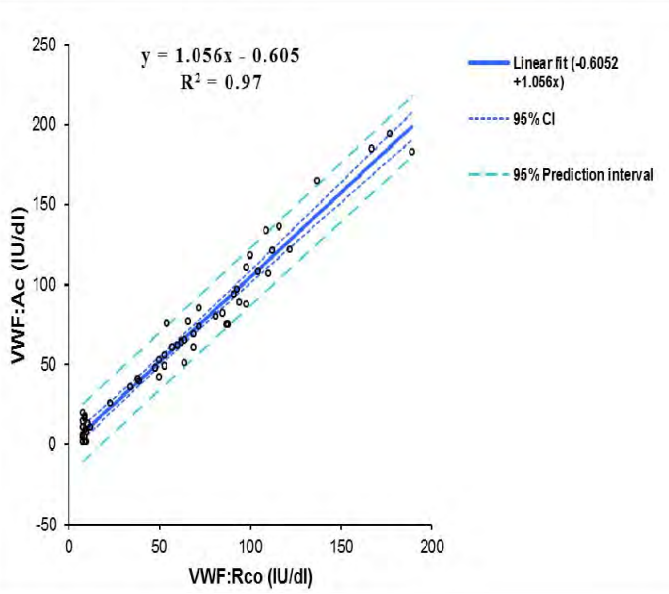

Figure 6. Comparison of Innovance VWF:Ac and VWF:RCo (R^2 = 0.97, p<0.0001).

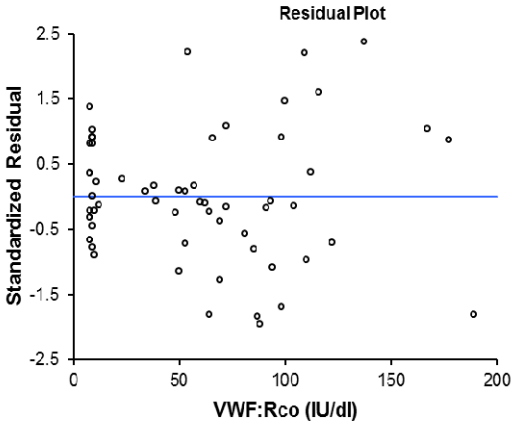

Figure 7. Residual plot (the difference between the observed value of the dependent variable VWF:Ac and the predicted value) showing that the points are randomly dispersed around the horizontal axis (VWF:Rco).

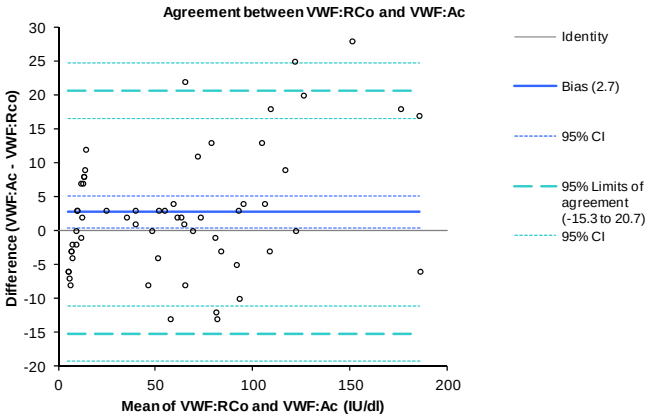

Figure 8. Bland-Altman plot showing the 95% limit of agreement (a prediction interval from -15.3 to 20.7) with the 95% confidence interval.

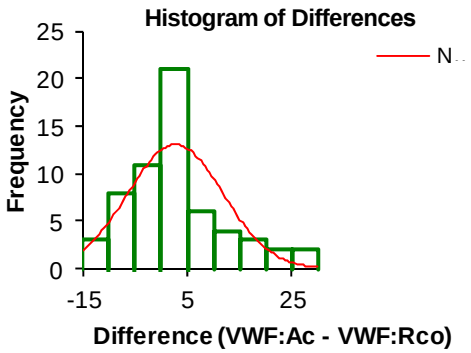

Figure 9. Histogram showing that the differences were normally distributed.

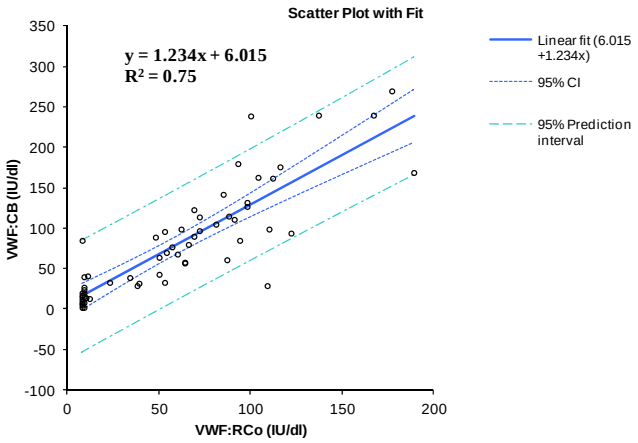

Figure 10. Comparison of VWF:RCo and VWF:CB (R^2= 0.75, p<0.0001).

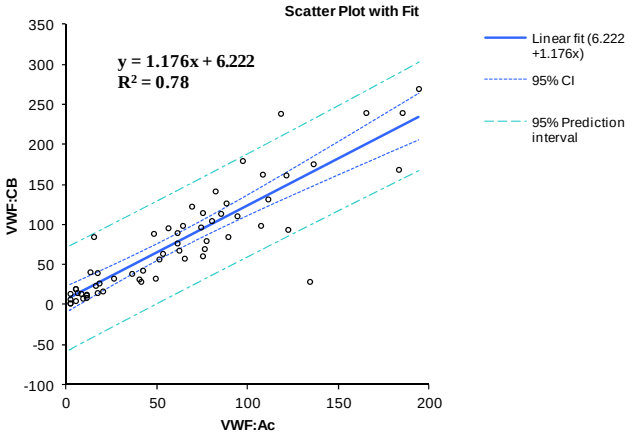

Figure 11. Comparison of Innovance VWF:Ac and VWF:CB (R^2 = 0.78, p<0.0001).

DISCUSSION

The VWF activity assay is critically important in the diagnosis and accurate classification and management of patients with VWD. Historically, the VWF:RCo assay, which measures the ability of VWF to agglutinate pre-washed and fixed platelets in the presence of cofactor ristocetin, is considered the reference method. Nevertheless, the VWF:RCo assay is still problematic for most haemostasis laboratories and suffers many diagnostic problems. For instance, it is imprecise with an average CV of 20 -30%, and is insensitive, particularly with VWF levels of <30 IU/dl, due to its lower detection limit (approximately 10-20 IU/dl) (46). In addition, the VWF:RCo assay shows a decrease in activity due to a mutation in the ristocetin binding site on the VWF domain A1 608). This mutation has no influence on normal VWF functions *in vivo*.

Some cross-laboratory studies (41,61,62) have confirmed these findings and showed a decrease in the number of laboratories using VWF:RCo activity and replacing it with new alternative methods. The assay precision refers to many factors, which include biological variation of the donor platelets. Furthermore, ristocetin is manufactured by only one manufacturer and suffers from significant lot-to-lot variability (63), which influences quality control, and standardisation of reagents. Moreover, it is insensitive to loss of high molecular weight multimer and acquired von Willebrand syndrome (46).

Consequently, various alternative VWF activity assays have been developed over the last few years in an attempt to overcome the limitations and improve the performance or even to replace the VWF: RCo assay; including the VWF collagen binding assay, an automated ristocetin cofactor activity assay using an automated coagulation analyser (64), a recombinant platelet GPIb-based ELISA assay (65,66), flow cytometric assays (67), the latex particle-enhanced immunoturbidimetric or chemiluminescence assay which utilises monoclonal antibody against VWF-GPIb binding site at domain A1 (2,46,68,69), and a gain-of-function GPIb ELISA assay (60). Despite these improvements in methodology and instrumentation over 25 years, with significant improvement in sensitivity and reliability, subsequent evaluation studies have shown no advantage in using these assays over the current VWF:RCo assay (43), and no other assay has been able to bring the VWF:RCo assay down from its throne.

Recently, a commercial automated immunoturbidimetric VWF activity assay, Innovance® VWF Ac (VWF:Ac, Siemens Healthcare Diagnostics, Germany) has become available. This assay measures VWF binding to GPIb without ristocetin. To measure VWF activity in plasma, the VWF:Ac assay uses a recombinant form of the VWF receptor with two gain-of-function mutations, captured on polystyrene particles that are coated with an antibody to GPIb. Since its introduction in 2011, the Innovance® VWF:Ac assay has improved the sensitivity and precision of the VWF:Rco assay (70).

The aim of this study was to evaluate the performance and agreement between the VWF:RCo and Innovance VWF:Ac. Despite different methodologies utilised by both assay, the VWF:RCo and VWF:Ac assays showed good agreement with minimal analytical bias. The comparison of the VWF:RCo and VWF:Ac assays with normal and clinical samples exhibited a good correlation, as shown in Figures 6 and 7 (R^2 = 0.97, *p* <0.0001). Although one sample showed a slight discrepancy between RCo and Ac with no clear clinical or sample issue, we assume it may be due to assay variability (random error). In similar study on 180 samples, Lawrie *et al.* (71) found similar results (r=0.99) and only one sample showed a discrepancy due to haemolysis.

The VWF:Ac assay showed a very good sensitivity with a LOD of <4 IU/dl, compared to 8-10 IU/dl for the VWF:RCo assay (all results <4 IU/dl, we have used the average of 2 IU/dl for statistical purposes). One study (71) showed a LOD of 3 IU/dl. Practically, we can achieve this level by using the low calibration curve; however, and after discussion with our haematologists, we consider this difference is not clinically significant.

Traditionally, the RCo/Ag ratio is used to guide in the discrimination between type 1 and type 2 VWD and a ratio <0.7 indicates a qualitative defect. Unfortunately, we did not perform the VWF:Ag assay (due to funding limitations) and consequently we were not able to evaluate this ratio and review our patients classification . However, previous studies (58) have shown a good performance for the VWF:Ac assay in this aspect.

Like any other turbidimetric assays, the VWF:Ac assay could theoretically be compromised by several analytical factors, such as interference with icteric, lipaemia, rheumatoid factor, haemolysis, and some specific medications. Unfortunately, we were unable to assess any such interference. To date studies (71,72) have reported a discrepancy between WF:RCo and WF:Ac due to the haemoglobin content and the presence of heterophil antibodies. Recently, Patzke J *et al.* (73), who developed the Innovance WF:Ac assay, have confirmed an excellent correlation with the WF:RCo assay (r = 0.99).

Our study suffered from some limitations, such as that we have not evaluated the WF:Ac assay for acquired von Willebrand syndrome and its satisfactory use for monitoring of VWF post-treatment with DDAVP (desmopressin) and/or VWF concentrate. Also, we were not able to include all subtypes of VWD. One of the main drawbacks of our study is that we were not able to perform a full panel of assays to confirm our patients' classification or, if required, reclassify them.

In conclusion, the Innovance® VWF:Ac assay seems to be desirable for assessing VWF activity with low levels of imprecision and improved sensitivity at low concentrations, despite rare discrepant results. Further, the simplicity using reagents supplied in a liquid ready to use form would also make this new reagent suitable for the diagnosis of VWD, in particular where experienced personel are not available. More experience would be needed to further assess the ability to discriminate between various types of VWD before possible replacement of the VWF:RCo assay and use of the VWF:Ac assay as a part of screening panel for diagnosis of VWD.

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AUTHOR INFORMATION

Emil Wasef, BMLSc PGDipMLSc FNZIMLS, Medical Laboratory Scientist

Southern Community Laboratories, Dunedin

Correspondence: Emil.Wasef@sclabs.co.nz

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- Prevention
- Profiling
- Personalized Healthcare

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  Thanks to modern molecular technologies, many diseases can be detected quickly and reliably long before the first symptoms appear, allowing the right treatment to be started at an early stage.
- ***Profiling***
  QIAGEN is the global leader in Profiling. It offers more than 120 methods for detecting various pathogens, including the flu virus, the HI-virus that causes AIDS, as well as hepatitis B and C viruses, which cause life-threatening diseases. QIAGEN also sells multiplexing methods that can be used to detect several different pathogens in the course of a single test run.
- ***Personalized Healthcare***
  Patients often respond differently to drugs they are taking, independent of influencing factors such as age or weight. Tests in Personalized Healthcare, known as companion diagnostics, are carried out once a disease has been diagnosed in order to choose the best possible treatment for the patient according to his or her individual genetic makeup.

Sample to Insight

ORIGINAL ARTICLE

ISO 15189:2012 implementation: an update of related international standards and guidance documents for medical laboratory quality management

Dennis Mok[1] and Eddie Ang[2]
[1]Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates
[2]Health Sciences Authority, Singapore

ABSTRACT
The implementation of ISO 15189:2012 management system and technical competence requirements remains the international standard of choice for the pathology services industry for demonstration of competence and quality achievements. One major challenge is to keep current in the knowledge that applies to all areas of operations. To overcome this challenge, medical laboratories need to maintain an up-do-date quality management system in order to remain competitive and competent to carry out specific medical laboratory tasks. The intent of this update is to provide current information to medical laboratories that can be used for ISO 15189:2012 implementation purposes. The latest edition of related international standards and guidance documents are listed; and supplemented with recommended tools and additional resources for further reference.
Keywords: continuous quality management**,** quality control**,** quality improvement**,** total quality management.

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INTRODUCTION
The International Organization for Standardization (ISO) continues to contribute to the development of international standards and guidance documents to improve the provision of products and services internationally (1). For the pathology services industry, ISO 15189:2012 (2) maintains the direction established in ISO 9001:2008 (3), ISO 9001:2008/Cor.1:2009 (4), ISO/IEC 17025:2005 (5) and ISO/IEC 17025:2005/ Cor.1:2006 (6) whereby operational optimisation is achieved by meeting specific management system and technical competence requirements. However, the implementation of ISO 15189:2012 continues to pose relentless challenges for the industry.

The rapid advancement of the pathology services industry and changing nature of its related business practices have resulted in continuous updates of related international consensus standards and guidance documents. One of the main obstacles for a medical laboratory (ML) to negotiate is the on-going pressure to focus on quality management (QM) as well as the quality of the end product. Furthermore, the ML quality management system (QMS) must also remain relevant in all areas of operations. Most of the standards have been updated to reflect changes in business practices since the publication of 'ISO 15189:2012 implementation: an applied guide for medical laboratories' in the *Australian Journal of Medical Science* (7). In particular, one of the foundation documents has been updated recently to the fifth edition, ISO 9001:2015 (8), reflecting changes in current concepts and opinions relating to QM.

Laboratory management (LM) and MLs can use the definitions provided and the trends evident in the document to forecast future recommendations. When read together with ISO 9000:2015 (9), the clarification of terminology provides further clues to the future development of related international standards. Most importantly, ISO 15189:2012 has been specifically designed for MLs to implement all of the relevant requirements within their areas of operations in order to achieve accreditation by assessment bodies (10,11).

Overall, both LM and MLs need to formulate implementation strategies to fulfil all of the relevant requirements. It has been established that there are 1,515 conformance requirements (CRs) to be considered, if the areas of operations include all processes covered by ISO 15189:2012 (12). It is important to respond in accordance with the updated CRs because of the resulting changes to regulatory and statutory requirements; and appropriate change management needs to be applied based on the impact of such change (13). Nevertheless, it is necessary to understand that the intent of ISO 15189:2012 implementation or ISO 15189:2012 accreditation is not simply to meet all of the CRs competently as a 'one-shot' compliance exercise (14). It is a balancing act in the application of both hard (technical) and soft (human) QM skills with the ultimate aim of improving the quality of services to patients (15).

The aim of this paper is to provide an update on the information in 'ISO 15189:2012 implementation: an applied guide for medical laboratories' (7) at the application level by providing new information in the relevant areas and highlighting areas of concern that require determination of what may be reasonably practicable. Readers requiring further information may refer to 'ISO 15189:2012 implementation: an applied guide for medical laboratories' (7). This paper is divided into three main sections. First, selected organisations (n = 7) providing related guidance documents for the QMS are correlated (Tables 2-8). Second, all subclauses of Clause 4 of ISO 15189:2012 (2) and Clause 5 of ISO 15189:2012 (2) are discussed with provision of updated lists of related ISO guidance publications. Third, further strategic change management recommendations for meeting future implementation challenges are presented. Overall, this update provides the latest information critical to quality processes enhancement. This update should be used with the previously published 'ISO 15189:2012 implementation: an applied guide for medical laboratories' in the *Australian Journal of Medical Science* (7).

RELEVANT ORGANISATIONS PROVIDING RELATED INTERNATIONAL GUIDANCE DOCUMENTS

Introduction

The ISO collaborates with many international organisations in the preparation of ISO 15189:2012 (2). In addition to the organisations previously listed (7), this update includes guidance documents from further selected organisations (Table 1). These selected organisations offer highly relevant information to the implementation of ISO 15189:2012 (2) (Tables 2-8).

Table 1. Selected organisations providing related guidance documents in support of the implementation of ISO 15189:2012.

European Association for Professions in Biomedical Science*	International non-governmental organization
Institute of Electrical and Electronics Engineers†	Professional organization
International Atomic Energy Agency	International governmental organization
International Electrotechnical Commission	International non-governmental organization
International Federation of Biomedical Laboratory Science	International non-governmental organization
International Federation of Clinical Chemistry and Laboratory Medicine	International non-governmental organization
International Laboratory Accreditation Cooperation	International governmental organization
International Labour Organization	International governmental organization
International Organization of Legal Metrology‡	International governmental organization
World Health Organization	International governmental organization

* Contributor to *Policy statement on point of care testing (POCT)* (16).
† Contributor to ISO/IEC/IEEE 24765:2010 (17).
‡ Contributor to ILAC-G24:2007/OIML D 10:2007 (18).

Related international guidance documents for medical laboratory quality management system

Selected organisations (n = 7) are listed for correlation purposes (Tables 2-8). These organisations offer pertinent information to the implementation of Clause 4 of ISO 15189:2012 (2) and Clause 5 of ISO 15189:2012 (2). The selected organisations are listed in the following order: the International Atomic Energy Agency (IAEA) (Table 2), the International Electrotechnical Commission (IEC) (Table 3), the International Federation of Biomedical Laboratory Science (IFBLS) (Table 4), the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) (Table 5), International Laboratory Accreditation Cooperation (ILAC) (Table 6), the International Labour Organization (ILO) (Table 7) and the World Health Organization (WHO) (Table 8).

International Atomic Energy Agency

The IAEA provides specific guidance in relation to the application of radiation for both routine and research proposes. In particular, MLs that use radiation-associated diagnostic procedures, such as radioimmunoassay and immunoradiometric assay, must follow strict radiation safety precautions to operate. While Clause 18 of ISO 15190:2003 (19) provides general radiation safety requirements, further specific guidance can be sought from the selected IAEA guidance documents (Table 2).

Table 2. Selected International Atomic Energy Agency guidance documents associated with Clause 5 of ISO 15189:2012.

Classification of radioactive waste safety guide (20)	5.2.3
Disposal of radioactive waste (21).	5.2.3, 5.3.1.5 and 5.7.2
Fundamental safety principles: safety fundamentals (22)	5.1.4, 5.1.5, 5.1.6, 5.2.1, 5.2.2, 5.3.1.3 and 5.5.3
Governmental, legal and regulatory framework for safety (23)	5.2.2, 5.3.1.5, 5.3.2.6 and 5.3.2.7
IAEA safety glossary (24)	5
International basic safety standards for protection against ionizing radiation and for the safety of radiation sources (25)	5.2.2, 5.3.1.5, 5.3.2.4, 5.3.2.7 and 5.4.7
Predisposal management of radioactive waste (26)	5.2.3 and 5.3.1.5
Radiation protection and safety of radiation sources: international basic safety standards (27)	5.2.3, 5.3.1.5 and 5.4.7
Safety assessment for facilities and activities: general safety requirements (28)	5.2.2, 5.2.6 and 5.4.7
Schedules of provisions of the IAEA regulations for the safe transport of radioactive material (2012 edition) (29)	5.3.1.5 and 5.3.2.4
Schedules of provisions of the IAEA regulations for the safe transport of radioactive material (2012 edition) (29)	5.3.1.5 and 5.3.2.4
Security in the transport of radioactive material (30)	5.2.2 and 5.3.2.4
Storage of radioactive waste: safety guide (31)	5.2.3 and 5.3.1.5
The management system for the processing, handling and storage of radioactive waste: safety waste (32)	5.2.3, 5.2.6, 5.3.1.5, 5.3.2.4, 5.4.7 and 5.7.2

International Electrotechnical Commission

The IEC offers expertise in electrotechnical standardisation for all electrical, electronic and related technologies. Most of the IEC publications are jointly published, either with both the IEEE and the ISO (n =1), such as ISO/IEC/IEEE 24765:2010 (17) (Table 9) or with the ISO (n = 49) (Tables 9, 11, 19, 22, 24, 25 and 28). One guidance document offered by the IEC relating to Subclause 5.3.1.5 of ISO 15189:2012 (2) is IEC 62353:2014 (33) which offers electrical safety test specifications for medical electrical equipment (Table 3).

Table 3. Selected International Electrotechnical Commission guidance document associated with Clause 5 of ISO 15189:2012.

IEC 62353:2014	*Medical electrical equipment - Recurrent test and test after repair of medical electrical equipment* (33)	5.3.1.5

International Federation of Biomedical Laboratory Science

The IFBLS has released further specific guidance on learning and development in response to the requirements of ISO 15189:2012. The *Policy statement on establishment and assessment of staff competence* (34) provides guidance on training and competence assessment in relation to Subclause 5.1.6 of ISO 15189:2012 (2) and Subclause 5.1.9 of ISO 15189:2012 (2). Other areas of interest covered by the IFBLS that provide direct support to the implementation of ISO 15189:2012 include ethics (35), learning and development (36) and point-of-care testing (POCT) (16,37) (Table 4).

Table 4. Selected International Federation of Biomedical Laboratory Science guidance documents associated with Clauses 4 and 5 of ISO 15189:2012.

Code of ethics for biomedical laboratory scientists[§] (35)	4.1.1.3 and 5.1.5
IFBLS' guidelines regarding core competence and core curriculum[§] (36)	5.1.6
IFBLS' guidelines regarding point of care testing (POCT)[§] (37)	4.1.1.1, 4.1.1.2, 4.1.2.2, 4.2, 4.3, 4.4, 4.6, 4.7, 4.8, 4.9, 4.10, 4.11, 4.12, 4.13, 4.14, 4.15, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9.1 and 5.9.2
Policy statement on establishment and assessment of staff competence (34)	5.1.6 and 5.1.9
Policy statement on point of care testing (POCT) (16)	4.1.1.1, 4.1.1.2, 4.1.2.2, 4.2, 4.3, 4.4, 4.6, 4.7, 4.8, 4.9, 4.10, 4.11, 4.12, 4.13, 4.14, 4.15, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9.1 and 5.9.2

[§] These documents (n = 3) have been previously listed (7).

International Federation of Clinical Chemistry and Laboratory Medicine

The IFCC has released an additional guidance on POCT. *Thinking of introducing PoCT – Things to consider* (38) provides guidance on how to implement POCT services. However, the specific recommendations are derived from ISO 15189:2007 (39) and ISO 22870:2006 (40). The Committee of Clinical Laboratory Management of IFCC has released two guidance documents; and selected chapters from these documents provide useful support of the implementation of ISO 15189:2012 sub-clauses (Table 5).

Table 5. Selected International Federation of Clinical Chemistry and Laboratory Medicine guidance documents associated with Clauses 4 and 5 of ISO 15189:2012.

Basic quality control at low cost[**] (41)	5.6
Basic training in managerial skills[**] (42)	4.1
Environmental conditions[**] (43)	5.2.2, 5.2.6, 5.3, 5.4, 5.5.1.4 and 5.7
Managerial guidelines to set up a clinical laboratory under difficult circumstances[**] (44)	4.1
Managing the work process of laboratory work flow[††] (45)	4.2
Measuring and monitoring quality in analysis and reporting[††] (46)	4.14
Thinking of introducing PoCT - Things to consider (38)	4.1.1.1, 4.1.1.2, 4.1.2.2, 4.2, 4.3, 4.4, 4.6, 4.7, 4.8, 4.9, 4.10, 4.11, 4.12, 4.13, 4.14, 4.15, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9.1 and 5.9.2

[**] These chapters (n = 4) are in Essentials of clinical laboratory management in developing regions and this title has been previously listed (7).

[††] These chapters (n = 2) are in Quality of management & quality of analysis: a handbook for developing countries jointly developed by C-CLM and C-AQ of the EMD and this title has been previously listed (7).

International Laboratory Accreditation Cooperation

ILAC has released ILAC-P9:06/2014 (47) to clarify proficiency testing requirements that MLs need to consider during the implementation of Subclause 5.6.3 of ISO 15189:2012 (2) (Table 6).

Table 6. Selected International Laboratory Accreditation Cooperation guidance documents associated with Clauses 4 and 5 of ISO 15189:2012.

ILAC-G17:2002	*Introducing the concept of uncertainty of measurement in testing in association with the application of the standard ISO/ IEC 17025*[‡‡] (48)	5.5.1.3, 5.5.1.4 and 5.5.3
ILAC-G24:2007/ OIML D 10:2007	*Guidelines for the determination of calibration intervals of measuring instruments*[‡‡] (18)	4.13, 5.3.1.4, 5.3.1.7 and 5.5.3
ILAC-P9:06/2014	*ILAC policy for participation in proficiency testing activities* (47)	5.6.3
ILAC-P14:01/2013	*ILAC policy for uncertainty in calibration*[‡‡] (49)	5.3.1.4 and 5.5.3

International Labour Organization

The ILO has released guidance documents that have potentially significant implications for compliance in occupational health and safety (OH&S). These documents provide further information on the specific OH&S requirements that ISO 15190:2003 (19) demands (Table 7).

World Health Organization

The WHO provides practical guidance in the field of biosafety. One key publication is *Guidance on regulations for the transport of infectious substances 2015—2016* (61), which contains key information on the safe handling of infectious substances during transportation. Other areas of interest covered by the WHO and which provide direct support to the implementation of ISO 15189:2012 include biorisk management (62) and biosafety management (63,64) (Table 8).

Selected supporting international standards and guidance documents for terms and definitions

The ISO provides supporting guidance in relation to terms and definitions in association with other organisations, such as the IEC and the IEEE (Table 9). These guidance documents enable clarification of many terms present in Clause 4 of ISO 15189:2012 (2) and Clause 5 of ISO 15189:2012 (2). Although Clause 3 of ISO 15189:2012 (2) provides definitions of many terms (n = 27), there are still terms as yet undefined by the ISO and therefore open to subjective interpretation. It is important for readers to obtain clarification of commonly used terms as well as descriptive terms during the implementation. It has been suggested that descriptive terms could cause considerable alteration during the interpretation of requirements (65). Furthermore, ISO 9000:2015 (9) updates many definitions for terms that were previously provided by Clause 3 of ISO 15189:2012 (2).

Table 7. Selected International Labour Organization guidance documents associated with Clauses 4 and 5 of ISO 15189:2012.

Ambient factors in the workplace (50)	5.1.5 and 5.2.2
Code of practice on workplace violence in services sectors and measures to combat this phenomenon (51)	4.1.1.4(e), 4.14.6, 5.1.4, 5.1.5, 5.2.1 and 5.2.2
Fundamental principles of occupational health and safety (52)	4.1.1.4(e), 4.13, 4.14.6, 4.14.7, 4.14.8, 5.1.4, 5.1.5, 5.1.6(a), 5.2.1, 5.2.2, 5.3.1.3, 5.3.1.5, 5.4.4.3, 5.4.5(c), 5.5.3(h) and 5.7.2
ILO-OSH 2001. *Guidelines on occupational safety and health management systems* (53)	5.1.4, 5.1.5, 5.2.1, 5.2.2, 5.2.5, 5.3.1.3, 5.3.1.5, 5.3.1.6, 5.3.2.6, 5.4.5 and 5.5.3(h)
Investigation of occupational accidents and diseases: a practical guide for labour inspectors (54)	5.3.1.6 and 5.3.2.6
Radiation protection of workers (ionising radiations) (55)	5.3.2.6
Recording and notification of occupational accidents and diseases (56)	5.3.1.6 and 5.3.2.6
Safety and health in the use of machinery (57)	4.1.1.4(e), 4.14.7, 5.1.4, 5.1.5, 5.1.6(a), 5.2.2(e), 5.3.1.3 and 5.3.1.5
Safety in the use of chemicals at work (58)	5.2.3, 5.3.1.5 and 5.3.2.6
Technical and ethical guidelines for workers' health surveillance (59)	4.1.1.3
The prevention of occupational diseases (60)	4.1.14(e), 4.14.6, 4.14.8, 5.1.4, 5.1.5, 5.1.6, 5.2.1, 5.2.2(e), 5.3.1.3, 5.3.1.5, 5.4.4.3, 5.4.5(c), 5.5.3(h) and 5.7.2

Table 8. Selected World Health Organization guidance documents associated with Clauses 4 and 5 of ISO 15189:2012.

Biorisk management: laboratory biosecurity guidance[§§] (62)	4.1.1.4(e), 4.13, 4.14.6, 4.14.7, 4.14.8, 5.1.4, 5.1.5, 5.1.6(a), 5.2.1, 5.2.2, 5.3.1.3, 5.3.1.5, 5.4.4.3, 5.4.5(c), 5.5.3(h) and 5.7.2
Guidance on regulations for the transport of infectious substances 2015-2016 (61)	5.3.1.3, 5.4.2(h), 5.4.4.3(d) and 5.4.5
Laboratory biosafety manual[§§] (63)	4.1.1.4(e), 4.13, 4.14.6, 4.14.7, 4.14.8, 5.1.4, 5.1.5, 5.1.6(a), 5.2.1, 5.2.2, 5.3.1.3, 5.3.1.5, 5.4.4.3, 5.4.5(c), 5.5.3(h) and 5.7.2
Tuberculosis laboratory biosafety manual (64)	4.1.1.4(e), 4.13, 4.14.6, 4.14.7, 4.14.8, 5.1.4, 5.1.5, 5.1.6(a), 5.2.1, 5.2.2, 5.3.1.3, 5.3.1.5, 5.4.4.3, 5.4.5(c), 5.5.3(h) and 5.7.2

Table 9. Selected Institute of Electrical and Electronics Engineers, International Electrotechnical Commission and International Organization for Standardization guidance documents in relation to terms and definitions in Clauses 4 and 5 of ISO 15189:2012.

ISO/IEC Guide 2:2004	*Standardization and related activities - General vocabulary* (66)
ISO Guide 30:2015	*Reference materials - Selected terms and definitions* (67)
ISO Guide 73:2009	*Risk management - Vocabulary* (68)
ISO/IEC Guide 99:2007	*International vocabulary of metrology - Basic and general concepts and associated terms (VIM)* (69)
ISO/IEC 2382:2015	*Information technology - Vocabulary* (70)
ISO/IEC 2382-36:2013	*Information technology - Vocabulary - Part 36: learning, education and training* (71)
ISO 3534-1:2006	*Statistics - Vocabulary and symbols - Part 1: general statistical terms and terms used in probability* (72)
ISO 3534-2:2006	*Statistics - Vocabulary and symbols - Part 2: applied statistics* (73)
ISO 5127:2001	*Information and documentation - Vocabulary* (74)
ISO 9000:2015	*Quality management systems - Fundamentals and vocabulary* (9)
ISO 13943:2008	*Fire safety - Vocabulary* (75)
ISO 14050:2009	*Environmental management - Vocabulary* (76)
ISO/IEC 17000:2004	*Conformity assessment - Vocabulary and general principles* (77)
ISO/IEC TS 17027:2014	*Conformity assessment - Vocabulary related to competence of persons used for certification of persons* (78)
ISO 17724:2003	*Graphical symbols - Vocabulary* (79)
ISO/IEC 17788:2014	*Information technology - Cloud computing - Overview and vocabulary* (80)
ISO/IEC 19770-5:2015	*Information technology - IT asset management - Overview and vocabulary* (81)
ISO/IEC TR 20000-10:2015	*Information technology - Service management - Part 10: concepts and terminology* (82)
ISO 22300:2012	*Societal security - Terminology* (83)
ISO/IEC/IEEE 24765:2010	*Systems and software engineering - Vocabulary* (17)
ISO/IEC 27000:2016	*Information technology - Security techniques - Information security management systems - Overview and vocabulary* (84)
ISO 30300:2011	*Information and documentation - Management systems for records - Fundamentals and vocabulary* (85)
ISO 55000:2014	*Asset management - Overview, principles and terminology* (86)

UPDATE OF RELATED INTERNATIONAL STANDARDS AND GUIDANCE DOCUMENTS

In this section, the key implementation considerations of Clause 4 of ISO 15189:2012 (2) and Clause 5 of ISO 15189:2012 (2) are addressed, taking into account the emphasis on their future development and continuous monitoring. First, relevant information that influence the implementation of each sub-clause is provided and discussed. Second, terms used in the text of ISO 15189:2012 as well as highly relevant terms that aid interpretation are also selected for clarification. It should be noted that the definitions of terms for ISO 15189:2012 are principally provided by ISO/IEC Guide 2:2004 (66), ISO/IEC Guide 99:2007 (69), Clause 3 of ISO 15189:2012 (2) and ISO/IEC 17000:2004 (77); however, other resources also provide sound clarification for interpretation purposes. Third, selected guidance documents are provided for correlation. Guidance documents by the ISO and the IEC are listed for readers to explore. Fourth, additional resources for further readings are provided for future research purposes.

Subclause 4.1 - Organization and management responsibility

Subclause 4.1 - Organization and management responsibility

Subclause 4.1 of ISO 15189:2012 (2) contains 8 (7.3%) administrative requirements (ARs) (7) and 159 (10.5%) CRs (12). Selected ISO guidance documents essential to the implementation of Subclause 4.1 of ISO 15189:2012 are presented (Table 10).

Table 10. Selected International Organization for Standardization guidance documents associated with Subclause 4.1 of ISO 15189:2012

Subclause 4.1.1.3	*Ethical conduct*
ISO 19600:2014	*Compliance management systems - Guidelines* (100)
Subclause 4.1.1.4	*Laboratory director*
ISO 22301:2012	*Societal security - Business continuity management systems - Requirements* (120)
ISO 22313:2012	*Societal security - Business continuity management systems - Guidance* (121)
ISO 22320:2011	*Societal security - Emergency management - Requirements for incident response* (122)
ISO/TS 22317:2015	*Societal security - Business continuity management systems - Guidelines for business impact analysis (BIA)* (123)
ISO 22322:2015	*Societal security - Emergency management -Guidelines for public warning* (124)
ISO 22324:2015	*Societal security - Emergency management - Guidelines for colour-coded alerts* (125)
ISO 22397:2014	*Societal security - Guidelines for establishing partnering arrangements* (126)
Subclause 4.1.2.4	*Quality objectives and planning*
ISO 10005:2005	*Quality management systems - Guidelines for quality plans* (127)

Subclause 4.1.1.3 — Ethical conduct

Subclause 4.1.1.3 of ISO 15189:2012 (2) specifies that the LM must have appropriate arrangements in place to prevent ethical misconduct from occurring. The arrangements must provide coverage of competence (87), impartiality (88), judgement (89), integrity (90,91), undue pressures (92,93), undue influences (94), conflict of interest (95,96), examination ethics (97) and confidentiality (98,99). The ISO has published ISO 19600:2014 (100) in direct support of this implementation (Table 11). The LM should also consider the likely risks within its areas of responsibilities associated with authenticity (101,102), bribery (103), corruption (104), fraud (105,106), informational privacy (107), transparency (108-111), whistleblowing (112) and workplace privacy (113).

Subclause 4.1.1.4 — Laboratory Director

Subclause 4.1.1.4(n) of ISO 15189:2012 (2) specifies that the laboratory director must design and implement a contingency plan. The ISO has published further guidance documents (n = 7) in support of contingency planning (Table 11). The laboratory director should conduct contingency planning at the strategic level in accordance with guidance from the ISO (114).

Subclause 4.1.2.7 — Quality Manager

Subclause 4.1.2.7 of ISO 15189:2012 (2) specifies that the LM must demonstrate commitment by appointing a quality manager. While the ISO provides limited information relating to this position, the Institute of Biomedical Science (IBMS) has published *Guidance on quality management in laboratories* (115) describing the role and responsibilities of the quality manager; and the American Society for Quality has published *The certified manager of quality/organizational excellence handbook* (116) describing the body of knowledge for the position. The LM should look for appointees who have extended skills in change management (117,118) as well as project management (119). Implementation of the next edition of ISO 15189 is highly unlikely to require a specific appointment for a quality manager. The position is no longer a requirement in the implementation of ISO 9001:2015 (8).

Additional resources

- Business Continuity Institute. BCM legislations, regulations, standards and good practice. Business Continuity Institute, Caversham, 2016.
- Dwyer J, Hopwood N. The business communication handbook. 10th edn. Cengage Learning Australia, South Melbourne, 2015.
- Kliem RL, Richie GD. Business continuity planning: a project management approach. CRC Press, Boca Raton, 2015.
- Ladkin D. Mastering the ethical dimension of organizations: a self-reflective guide to developing ethical astuteness. Edward Elgar Publishing, Cheltenham, 2015.
- Wieland J. Business ethics. In: Zeuch M, ed. Dos and don'ts in human resources management: a practical guide. Springer-Verlag, Berlin, 2015: 151-153.
- Linscott AJ, Medvescek P, Sewell DL. Emergency management. In: Garcia LS, Bachner P, Baselski VS, Lewis G, Linscott AJ, Schwab DA, Steele Jr JCH, Weissfeld AS, Wilkinson DS, Wolk DM, eds. Clinical Laboratory Management. 2nd edn. ASM Press, Washington, 2014: 545-563.
- Wong WNZ, Shi J. Business continuity management system: a complete guide for implementing ISO 22301. Kogan Page, London, 2015.
- Peterson C. Ethics: the price of admission in high-performing organizations. In: Ulrich D, Schiemann WA, eds. The rise of HR: wisdom from 73 thought leaders. HR Certification Institute, Alexandria, 2015: 55-60.
- Hollingworth D. Ethical decision-making in the operations function of organizations: managerial challenges and opportunities. In: Valentine S, ed. Organizational ethics and stakeholder well-being in the business environment. Information Age Publishing, Charlotte, 2014: 137-163.

- Wueste DE. Promoting integrity integritively: avoiding the Scylla and Charybdis of abdication and zealotry. In: Schwartz M, Harris H, Tapper A, eds. Achieving ethical excellence. Vol. 12. Research in Ethical Issues in Organizations. Emerald Group Publishing, Bingley, 2014: 5-27.
- Youngblood JR. A comprehensive look at fraud identification and prevention. CRC Press, Baca Raton, 2015.

Subclause 4.2 — Quality management system

Subclause 4.2 — Quality management system

Subclause 4.2 of ISO 15189:2012 (2) contains 4 (3.7%) ARs (7) and 66 (4.4%) CRs (12). Selected IEC and ISO guidance documents essential to the implementation of Subclause 4.2 of ISO 15189:2012 are presented (Table 11).

Table 11. Selected International Organization for Standardization guidance documents associated with Subclause 4.2 of ISO 15189:2012.

Subclause 4.2	*Quality management system*
ISO 9001:2015	*Quality management systems - Requirements* (8)
ISO 9004:2009	*Managing for the sustained success of an organization - A quality management approach* (128)
ISO/IEC 17025:2005	*General requirements for the competence of testing and calibration laboratories* (5)
ISO/IEC 17025:2005/ Cor.1:2006	*General requirements for the competence of testing and calibration laboratories - Technical corrigendum 1* (6)

Subclause 4.2.2.2 — Quality manual

Subclause 4.2.2.2 of ISO 15189:2012 (2) specifies that the ML must establish and maintain a quality manual. This document is highly unlikely to be required for the implementation of the next edition of ISO 15189. It is no longer a requirement in the implementation of ISO 9001:2015 (8). The quality manual could be incorporated into the documented information category.

Additional resources

- Klee GG, Westgard JO. Quality management. In: Burtis CA, Bruns DE, eds. Tietz textbook of clinical chemistry and molecular diagnostics. 7th edn. Saunders, Saint Louis, 2015: 90-106.
- Periañez-Cristobal R, Calvo-Mora A, Navarro-García A. Process approach, quality management and key business results. In: Peris-Ortiz M, Álvarez-García J, eds. Action-based quality management: strategy and tools for continuous improvement. Springer International Publishing, Cham, 2014: 83-96.
- Schifman RB, Cembrowski GS, Wolk DM, Brisbois JI. Quality management. In: Garcia LS, Bachner P, Baselski VS, Lewis MR, Linscott AJ, Schwab DA, Steele Jr JCH, Weissfeld AS, Wilkinson DS, Wolk DM, eds. Clinical laboratory management. 2nd edn. ASM Press, Washington, 2014: 421-446.
- Westgard JO, Westgard SA. Basic quality management systems: essentials for quality management in the medical laboratory. Westgard QC, Madison, 2014.

Subclause 4.3 - Document control

Subclause 4.3 - Document control

Subclause 4.3 of ISO 15189:2012 (2) contains 2 (1.8%) ARs (7) and 31 (2.0%) CRs (12). Selected ISO guidance document essential to the implementation of Subclause 4.3 of ISO 15189:2012 are presented (Table 12).

Subclause 4.3(j) of ISO 15189:2012 (2) specifies that an obsolete controlled document must be retained for a specified time period or in accordance with applicable specified requirements. The ML must check the regulatory and statutory requirements of the applicable jurisdictions relevant to the particular areas of operations. At the same time, the ML needs to meet relevant privacy obligations by securely destroying or permanently anonymising the personal information. The ML must meet these document control requirements by carefully checking that the applicable jurisdictions are adequately met to ensure compliance.

The continuation of this documented procedure requirement is highly unlikely for the implementation of the next edition of ISO 15189. It is no longer a requirement in the implementation of ISO 9001:2015 (8). However, the ML must determine which documents are the relevant ones to be under control. The concept of 'documented information' is likely to be used in the next edition of ISO 15189.

Additional resources

- Jones W. The future of personal information management, part 2: transforming technologies to manage our information. Synthesis Lectures on Information Concepts, Retrieval, and Services 28. Morgan & Claypool Publishers, San Rafael, 2014.
- Laudon KC, Laudon J. Essential of MIS. 11th edn. Prentice Hall, Upper Saddle River, 2014.
- Prokscha S. Writing and managing SOPs for GCP. CRC Press, Boca Raton, 2015.
- Wiwanitkit V. Overview of requirements and future perspectives on current laboratory information management systems. In: Moumtzoglou A, Kastania A, Archondakis S, eds. Laboratory management information systems: current requirements and future perspectives. Medical Information Science Reference, Hershey, 2014: 67-82.

Table 12. Selected International Organization for Standardization guidance document associated with Subclause 4.3 of ISO 15189:2012.

Subclause 4.3	*Document control*
ISO/TR 10013:2001	*Guidelines for quality management system documentation* (129)

Subclause 4.4 - Service agreements

Subclause 4.4 - Service agreements

Subclause 4.4 of ISO 15189:2012 (2) contains 3 (2.8%) ARs (7) and 35 (2.3%) CRs (12). Selected ISO guidance document essential to the implementation of Subclause 4.4 of ISO 15189:2012 are presented (Table 13).

Subclause 4.4.1 — Establishment of service agreements

Subclause 4.4.1 of ISO 15189:2012 (2) specifies that the ML must treat each authorised pathology request as a service agreement. It should also be noted that these service agreements are classified as documents, as described in Subclause 4.3 of ISO 15189:2012 (2). The ML must fulfil this document retention requirement in accordance with guidance from ISO 30301:2011 (130) as well as other relevant document retention guidance.

Additional resources

- Datta S. Understanding and managing IT outsourcing: a partnership approach. Palgrave Macmillian, Basingstoke, 2015.
- Fishman S. Consultant & independent contractor agreements. 8th edn. Nolo, Berkeley, 2014.
- Haapio H, Siedel GJ. A short guide to contract risk. Short Guides to Business Risk. Gower Publishing, Farnham, 2013.
- Parlour D. Successful outsourcing and multi-sourcing. Gower Publishing, Farnham, 2014.

Table 13. Selected International Organization for Standardization guidance document associated with Subclause 4.4 of ISO 15189:2012.

Subclause 4.4	*Service agreements*
ISO 37500:2014	*Guidance on outsourcing* (131)

Subclause 4.5 - Examination by referral laboratories

Subclause 4.5 - Examination by referral laboratories

Subclause 4.5 of ISO 15189:2012 (2) contains 5 (4.6%) ARs (7) and 32 (2.1%) CRs (12). Selected ISO guidance document essential to the implementation of Subclause 4.5 of ISO 15189:2012 are presented (Table 14).

Subclause 4.5.1 - Selecting and evaluating referral laboratories and consultants

Subclause 4.5.1 of ISO 15189:2012 (2) specifies that the ML must have a documented procedure for selecting and evaluating referral consultants and laboratories. The ML has no specific obligatory or regulatory requirements prescribing how to evaluate and select such external providers. However, the ML can extract relevant information from ISO 37500:2014 (131) in support of this implementation (Table 14). The ML should develop the documented procedure by incorporating suggestions from ISO 37500:2014 (131).

Subclause 4.5.1(a) of ISO 15189:2012 (2) specifies that the ML must ensure that the referral consultants or referral laboratories are competent to perform the requested examinations. The ML has no specific obligatory or regulatory requirements prescribing how to assess such competencies. The ML should establish an internal assessment process to ensure the referral consultants or referral laboratories or both are able to perform to the appropriate degree of professional competence. The ML must ensure that the external providers are qualified and selected according to their demonstrated effectiveness, along with applicable accreditation, certification and licensure.

Additional resources

- Cross R, Rebele R, Grant A. Collaborative overload. *Harv Bus Rev* 2016; 94: 74-79.
- International Association of Outsourcing Professionals®. Outsourcing professional body of knowledge – OPBOK version 10. 2nd edn. Van Haren Publishing, Zaltbommel, 2014.
- Nevin M. The strategic alliance handbook: a practitioners guide to business-to-business collaborations. Gower Publishing, Farnham, 2014.

Table 14. Selected International Organization for Standardization guidance document associated with Subclause 4.5 of ISO 15189:2012.

Subclause 4.5.1	*Selecting and evaluating referral laboratories and consultants*
ISO 37500:2014	*Guidance on outsourcing* (131)

Subclause 4.6 - External services and supplies

Subclause 4.6 - External services and supplies

Subclause 4.6 of ISO 15189:2012 (2) contains 3 (2.8%) ARs (7) and 26 (1.7%) CRs (12). Selected ISO guidance documents essential to the implementation of Subclause 4.6 of ISO 15189:2012 are presented (Table 15).

Subclause 4.6 of ISO 15189:2012 (2) specifies that the ML must establish a documented procedure for the purchasing and selection of external products and services that affect the quality of its service. The ML has no specific obligatory or regulatory requirements prescribing how to perform such selections. The ML should establish an internal selection process by formulating specific criteria in order to ensure the maintenance of quality expectations (132).

Additional resources

- Christopher M. Logistics & supply chain management. 5th edn. Pearson Education, Harlow, 2016.
- Monczka RM, Handfield RB, Giunipero LC, Patterson JL. Purchasing and supply chain management. 6th edn. Cengage Learning, Boston, 2015.
- O'Brien J. Supplier relationship management: unlocking the hidden value in your supply base. Kogan Page, London, 2014.
- The KPI Institute. The supply chain KPI dictionary: 360+ key performance indicator definitions. The KPI Institute, Docklands, 2015.
- Wisner JD, Tan K-C, Leong GK. Principles of supply chain management: a balanced approach. 4th edn. Cengage Learning, Boston, 2015.

Table 15. Selected International Organization for Standardization guidance document associated with Subclause 4.6 of ISO 15189:2012.

Subclause 4.6	*External services and supplies*
ISO/TS 22318:2015	*Societal security — Business continuity management systems — Guidelines for supply chain continuity* (133)
ISO 37500:2014	*Guidance on outsourcing* (131)

Subclause 4.7 - Advisory services

Subclause 4.7 - Advisory services

Subclause 4.7 of ISO 15189:2012 (2) contains 2 (1.8%) ARs (7) and 11 (0.7%) CRs (12). Subclause 4.7 of ISO 15189:2012 (2) specifies that the ML must establish arrangements for communicating with users for a range of advisory matters (n = 11) (12). However, Subclause 4.7(e) of ISO 15189:2012 (2) does not specify the extent of communication in resolution management. The ML should establish an internal process for discussion with users, including patients, in relation to the disclosure of diagnostic errors. Potential apology provision with an explanation may be required at the organisational level (134). Failure to provide appropriate resolution may hinder medical negligence investigation processes leading to further healthcare, injury compensation and insurance complications. The ML must manage these arrangements by using competent communication skills (135).

Subclause 4.7(e) of ISO 15189:2012 (2) specifies that the ML must have arrangements in place for communicating with users in relation to all logistic matters. The ML has no specific obligatory or regulatory provisions prescribing how far the arrangements should be invested in to ensure the provision of logistic support. However, the adoption of new diagnostic technology, especially in the environmental variability factors during the transportation of specimens during the preanalytical phase, can pose logistic challenges. It is important that the specimen integrity be ensured by internal environmental data logging and location tracking devices that are compliant with ISO/IEC 17025:2005 (5) and ISO/IEC 17025:2005/Cor.1:2006 (6). The ML must ensure the specimens are maintained within the quality specifications by implementing appropriate technology in the distribution process.

Additional resources

- Pannett A, Sequeira S, Dines A, Day A. Key skills for professionals: how to succeed in professional services. Kogan Page, London, 2013.
- Peppers D, Rogers M. Managing customer relationships: a strategic framework. 2nd edn. John Wiley & Sons, Hoboken, 2011.

Subclause 4.8 - Resolution of complaints

Subclause 4.8 - Resolution of complaints

Subclause 4.8 of ISO 15189:2012 (2) contains 1 (0.9%) ARs (7) and 4 (0.3%) CRs (12). Selected ISO guidance documents essential to the implementation of Subclause 4.8 of ISO 15189:2012 are presented (Table 16). Subclause 4.8 of ISO 15189:2012 (2) specifies that the ML must have a documented procedure for the management of complaints. The ML has no specific obligatory or regulatory provisions prescribing how to manage complaints. However, the ISO has published guidance documents in direct support of this implementation (Table 16). The ML needs to ensure all complaints and other feedback are correctly and effectively resolved on a timely manner.

Additional resources

- Eagan J. Conflict management. In: Garcia LS, Bachner P, Baselski VS, Lewis G, Linscott AJ, Schwab DA, Steele Jr JCH, Weissfeld AS, Wilkinson DS, Wolk DM, eds. Clinical laboratory management. 2nd edn. ASM Press, Washington, 2014: 272-280.
- Garding S, Bruns A. Complaint management and channel choice: an analysis of customer perceptions. Springer Briefs in Business. Springer International Publishing, Cham, 2015.

Table 16. Selected International Organization for Standardization guidance documents associated with Subclause 4.8 of ISO 15189:2012.

Subclause 4.8	*Resolution of complaints*
ISO 10001:2007	*Quality management - Customer satisfaction - Guidelines for codes of conduct for organizations* (136)
ISO 10002:2014	*Quality management - Customer satisfaction - Guidelines for complaints handling in organizations* (137)
ISO 10003:2007	*Quality management - Customer satisfaction - Guidelines for dispute resolution external to organizations* (138)
ISO 10004:2012	*Quality management - Customer satisfaction - Guidelines for monitoring and measuring* (139)

Subclause 4.9 - Identification and control of nonconformities

Subclause 4.9 - Identification and control of nonconformities

Subclause 4.9 of ISO 15189:2012 (2) contains 1 (0.9%) ARs (7) and 23 (1.5%) CRs (12). Subclause 4.9 of ISO 15189:2012 (2) specifies that the ML needs to identify all nonconformities and that appropriate corrective action must be implemented to eliminate the causes. However, nonconformity can be beneficial under certain circumstances (140). The ML must effectively manage both conformities and nonconformities at the same time.

Additional resources

- Stamatis DH. Introduction to risk and failures: tools and methodologies. CRC Press, Boca Raton, 2014.
- Stamatis DH. The ASQ pocket guide to failure mode and effect analysis (FMEA). Quality Press, Milwaukee, 2014.
- Taylor JR. Human error in process plant design and operations: a practitioner's guide. CRC Press, Boca Raton, 2015.

Subclause 4.10 - Corrective action

Subclause 4.10 - Corrective action

Subclause 4.10 of ISO 15189:2012 (2) contains 1 (0.8%) ARs (7) and 10 (0.7%) CRs (12). Subclause 4.10(b) of ISO 15189:2012 (2) specifies that the ML must determine the root causes of nonconformities, but it does not offer any specific guidance on the analytical method to determine such causes. The ML should extract relevant information from authoritative and established textbooks on root cause analysis. The ML must ensure corrective actions are effectively implemented to eliminate nonconformities.

Additional resources

- Andersen B, Fagerhaug T, Beltz M. Root cause analysis and improvement in the healthcare sector: a step-by-step guide. Quality Press, Milwaukee, 2009.
- Barsalou MA. Root cause analysis: a step-by-step guide to using the right tool at the right time. Productivity Press, Boca Raton, 2014.

Subclause 4.11 - Preventive action

Subclause 4.11 - Preventive action

Subclause 4.11 of ISO 15189:2012 (2) contains 1 (0.8%) ARs (7) and 10 (0.7%) CRs (12). Subclause 4.11(b) of ISO 15189:2012 (2) specifies that the ML must determine the root causes of potential nonconformities. Besides root cause analysis, the ML should also use predictive analytics, such as risk analysis and trend analysis for the determination. The ML must effectively eliminate the causes of potential nonconformities by implementing appropriate analytics. This documented procedure is highly unlikely to be included in the next edition of ISO 15189. It is no longer referred to in the implementation of ISO 9001:2015 (8).

Subclause 4.12 - Continual improvement

Subclause 4.12 - Continual improvement

Subclause 4.12 of ISO 15189:2012 (2) contains 2 (1.8%) ARs (7) and 34 (2.2%) CRs (12). Selected ISO guidance documents essential to the implementation of Subclause 4.12 of ISO 15189:2012 are presented (Table 17). The ML has no specific obligatory or regulatory requirements prescribing on the types of improvement activities in which the ML should participate. However, the ISO has published guidance documents in direct support of this implementation (Table 17). The LM must ensure the ML fulfils this continual improvement requirement by participating in appropriate continual improvement activities.

Additional resources

- Barsalou MA. The quality improvement field guide: achieving and maintaining value in your organization. Productivity Press, Boca Raton, 2015.
- Munro RA, Ramu G, Zrymiak DJ. The certified six sigma green belt handbook. 2nd edn. Quality Press, Milwaukee, 2015.
- Ramani S. Improving business performance: a project portfolio management approach. Best Practices and Advances in Program Management. Auerbach Publications, Boca Raton, 2016.
- Westcott RT, Duffy GL (Editors). The certified quality improvement associate handbook: basic quality principles and practices. 3rd edn. Quality Press, Milwaukee, 2014.

Table 17. Selected International Organization for Standardization guidance documents associated with Subclause 4.12 of ISO 15189:2012.

Subclause 4.12	*Continual improvement*
ISO 9004:2009	*Managing for the sustained success of an organization - A quality management approach* (128)
ISO 13053-1:2011	*Quantitative methods in process improvement - Six sigma - Part 1: DMAIC methodology* (141)
ISO 13053-2:2011	*Quantitative methods in process improvement - Six sigma - Part 2: tools and techniques* (142)
ISO/TS 22367:2008	*Medical laboratories - Reduction of error through risk management and continual improvement* (143)
ISO/TS 22367:2008/ Cor.1:2009	*Medical laboratories - Reduction of error through risk management and continual improvement - Technical corrigendum 1* (144)

Subclause 4.13 - Control of records

Subclause 4.13 - Control of records

Subclause 4.13 of ISO 15189:2012 (2) contains 1 (0.8%) AR (7) and 59 (3.9%) CRs (12). Selected ISO guidance documents essential to the implementation of Subclause 4.13 of ISO 15189:2012 are presented (Table 18). The ML must ensure that various records pertaining to the QMS are retained for a period of time. Applicable privacy legislative requirements must also be met by securely destroying or permanently anonymising personal information if it is no longer needed. The ML must meet the control of records requirements after carefully checking the applicable jurisdictions relevant to the particular activity. This documented procedure is highly unlikely to be included in the next edition of ISO 15189. It is no longer referred to ISO 9001:2015 (8). The term 'documented information' is likely to replace 'records' in the next edition of ISO 15189.

Additional resources

- Crockett M. The no-nonsense guide to archives and recordkeeping. Facet Publishing, London, 2015.
- Franks PC. Records and information management. Facet Publishing, London, 2013.
- Williams C. Records and archives: concepts, roles and definition. In: Brown C, ed. Archives and recordkeeping: theory into practice. Facet Publishing, London, 2013: 1-29.

Subclause 4.14 - Evaluation and audits

Subclause 4.14 - Evaluation and audits

Subclause 4.14 of ISO 15189:2012 (2) contains 10 (9.2%) ARs (7) and 133 (8.8%) CRs (12). Selected IEC and ISO guidance documents essential to the implementation of Subclause 4.14 of ISO 15189:2012 are presented (Table 19).

Subclause 4.14.7 - Quality indicators

Subclause 4.14.7 of ISO 15189:2012 (2) specifies that the ML must establish quality indicators to evaluate and monitor performance of critical aspects of all analytical processes. However, additional considerations need to be taken into account for the pre-analytical phase (159) and the post-analytical phase (160) because emerging opinions are available for the establishment of such quality indicators. The ML must fulfil the quality indicator requirements by incorporating contemporary factors into the development process.

Additional resources

- Bishoff L, Clareson TFR. Inventory and risk assessment for digital collections. In: Mallery M, ed. Technology disaster response and recovery planning: a LITA guide. American Library Association, Chicago, 2015: 11-22.
- Detert JR, Burris ER. Can your employees really speak freely? *Harv Bus Rev* 2016; 94: 80-87.
- Devey G. The manager's guide to employee feedback: master this essential management skill and boost your team's performance. Impackt Publishing, Birmingham, 2014.
- ISO 9001 Auditing Practices Group. Adding value. International Organization for Standardization, Geneva, 2016.
- Marr B. 25 need-to-know key performance indicators. Pearson Education, Harlow, 2014.
- Moeller R. Brink's modern internal auditing: a common body of knowledge. Wiley Corporate F&A. 8th edn. Wiley, Hoboken, 2015.
- Parmenter D. Key performance indicators: developing, implementing, and using winning KPIs. 3rd edn. John Wiley & Sons, Hoboken, 2015.
- Petersmann A, Schlüter K, Nauck M. Auditing of the preanalytical phase. In: Guder WG, Narayanan S, eds. Pre-examination procedures in laboratory diagnostics: preanalytical aspects and their impact on the quality of medical laboratory results. De Gruyter, Berlin, 2015: 337-344.
- Pitt S-A. Internal audit quality: developing a quality assurance and improvement program. John Wiley & Sons, Hoboken, 2014.
- Pritchard CL. Risk management: concepts and guidance. 5th edn. Auerbach Publications, Boca Raton, 2014.
- The KPI Institute. The production and quality management KPI dictionary: 180+ key performance indicator definitions. The KPI Institute, Docklands, 2015.

Table 18. Selected International Organization for Standardization guidance documents associated with Subclause 4.13 of ISO 15189:2012.

Subclause 4.13	*Control of records*
ISO 5963:1985	*Documentation - Methods for examining documents, determining their subjects, and selecting indexing terms* (145)
ISO 10196:2003	*Document imaging applications - Recommendations for the creation of original documents* (146)
ISO 15489-1:2001	*Information and documentation - Records management - Part 1: general* (147)
ISO/TR 15801:2009	*Document management - Information stored electronically - Recommendations for trustworthiness and reliability* (148)
ISO 16175-3:2010	*Information and documentation - Principles and functional requirements for records in electronic office environments - Part 3: guidelines and functional requirements for records in business systems* (149)
ISO 16175-1:2010	*Information and documentation - Principles and functional requirements for records in electronic office environments - Part 1: overview and statement of principles* (150)
ISO 16175-2:2011	*Information and documentation - Principles and functional requirements for records in electronic office environments - Part 2: guidelines and functional requirements for digital records management systems* (151)
ISO/TR 18492:2005	*Long-term preservation of electronic document based information* (152)
ISO/TS 21547:2010	*Health informatics - Security requirements for archiving of electronic health records - Principles* (153)
ISO/TR 21548:2010	*Health informatics - Security requirements for archiving of electronic health records - Guidelines* (154)
ISO/TR 22957:2009	*Document management - Analysis, selection and implementation of electronic document management systems (EDMS)* (155)
ISO 23081-1:2006	*Information and documentation - Records management processes - Metadata for records - Part 1: principles* (156)
ISO 23081-2:2009	*Information and documentation - Managing metadata for records - Part 2: conceptual and implementation issues* (157)
ISO 30301:2011	*Information and documentation - Management systems for records - Requirements* (130)
ISO 30302:2015	*Information and documentation - Management systems for records - Guidelines for implementation* (158)

Table 19. Selected International Electrotechnical Commission and International Organization for Standardization guidance documents associated with Subclause 4.14 of ISO 15189:2012.

Subclause 4.14.5	*Internal audit*
ISO 19011:2011	*Guidelines for auditing management systems* (161)
ISO/IEC 27007:2011	*Information technology — Security techniques — Guidelines for information security management systems auditing* (162)
Subclause 4.14.6	*Risk management*
ISO 31000:2009	*Risk management — Principles and guidelines* (163)
ISO/TR 31004:2013	*Risk management — Guidance for the implementation of ISO 31000* (164)
IEC/ISO 31010:2009	*Risk management — Risk assessment techniques* (165)

Subclause 4.15 - Management review

Subclause 4.15 - Management review

Subclause 4.15 of ISO 15189:2012 (2) contains 1 (0.9%) AR (7) and 49 (3.2%) CRs (12).

Subclause 4.15.2 - Review input

Subclause 4.15.2 of ISO 15189:2012 (2) specifies that the LM must include the information obtained from the evaluation process as review input. It is important to note that there are no specific provisions available that prescribe how evaluations should be conducted. The ML must ensure that the results derived from the evaluations contain representative and specific data as input.

Additional resources

- Theodorou D, Giannelos P. Medical laboratory quality systems – a management review. *Int J Health Care Qual Assur* 2015; 28: 267-273.
- Wilson ML, Procop GW, Reller LB. Test utilization and clinical relevance. In: Garcia LS, Bachner P, Baselski VS, Lewis MR, Linscott AJ, Schwab DA, Steele Jr JCH, Weissfeld AS, Wilkinson DS, Wolk DM, eds. Clinical laboratory management. 2nd edn. ASM Press, Washington, 2014: 876-889.

Subclause 5.1 - Personnel

Subclause 5.1 - Personnel

Subclause 5.1 of ISO 15189:2012 (2) contains 5 (4.6%) ARs (7) and 67 (4.4%) CRs (12). Selected ISO guidance documents essential to the implementation of Subclause 5.1 of ISO 15189:2012 are presented (Table 20).

Table 20. Selected International Organization for Standardization guidance documents associated with Subclause 5.1 of ISO 15189:2012.

Subclause 5.1.5	*Training*
ISO 10015:1999	*Quality management — Guidelines for training* (172)
ISO 19600:2014	*Compliance management systems — Guidelines* (100)
ISO 22398:2013	*Societal security — Guidelines for exercises* (173)
ISO 29990:2010	*Learning services for non-formal education and training — Basic requirements for service providers* (174)
ISO/TS 17975:2015	*Health informatics — Principles and data requirements for consent in the Collection, Use or Disclosure of personal health information* (175)

Subclause 5.1.5 - Training

Subclause 5.1.5(d) of ISO 15189:2012 (2) specifies that the ML must provide training in the fields of OH&S, including the prevention or containment of the effects of adverse incidents for all personnel. The term, 'adverse incidents', is not as yet defined by the ISO. It is also important to note that there are no general rules governing how detailed the training should be. However, the ML should consider adverse incident training topics based upon levels of business uncertainty and associated threat to operational continuity. The ML should meet the OH&S training requirements by incorporating emerging areas of concern into the training program; such as cyber attacks (166,167), industrial strikes (168), natural disasters (169), pandemics (170) and terrorism (171).

Additional resources

- Hughey K. Training management. In: Zeuch M, ed. Dos and don'ts in human resources management: a practical guide. Springer-Verlag, Berlin, 2015: 43-44.
- Kridelbaugh D. Onboarding: getting new hires up to speed. *Lab Manag* 2015; 10: 22-25.
- Passmore J, Velez MJ. Training evaluation. In: Kraiger K, Passmore J, Rebelo Dos Santos N, Malvezzi S, eds. The Wiley Blackwell handbook of the psychology of training, development, and performance improvement. John Wiley & Sons, Chichester, 2015: 136-153.
- Sarkanen A, Stoddard K. Training end-users in the workplace. In: Schopflin K, ed. A handbook for corporate information professionals. Facet Publishing, London, 2014: 159-178.
- The KPI Institute. The education and training KPI dictionary: 170+ key performance indicator definitions. The KPI Institute, Docklands, 2015.
- Tsimillis KC. Training needs to understand quality assurance. *Accred Qual Assur* 2015; 20: 53 59.

Subclause 5.2 - Accommodation and environmental conditions

Subclause 5.2 - Accommodation and environmental conditions

Subclause 5.2 of ISO 15189:2012 (2) contains 1 (0.9%) AR (7) and 88 (5.8%) CRs (12). Selected ISO guidance documents essential to the implementation of Subclause 5.2 of ISO 15189:2012 are presented (Table 21).

Table 21. Selected International Organization for Standardization guidance documents associated with Subclause 5.2 of ISO 15189:2012.

Subclause 5.1	*Accommodation and environmental conditions*
ISO 16813:2006	*Building environment design - Indoor environment — General principles* (177)
Subclause 5.2.3	*Storage facilities*
ISO 15190:2003	*Medical laboratories - Requirements for safety* (19)
Subclause 5.2.5	*Patient sample collection facilities*
ISO 7010:2011	*Graphical symbols - Safety colours and safety signs - Registered safety signs* (178)
ISO 15190:2003	*Medical laboratories - Requirements for safety* (19)
Subclause 5.2.6	*Facility maintenance and environmental conditions*
ISO 16813:2006	*Building environment design - Indoor environment - General principles* (177)

Subclause 5.2.2 - Laboratory and office facilities

Subclause 5.2.2(c) of ISO 15189:2012 (2) specifies that the ML must provide a suitable environment for examination purposes. One emerging challenge is the continuous generation of noise within the ML. Some common items include: centrifuges, compressors, freezers, telephones and automated equipment (176). The level of noise and duration of exposure, with noise exposure level normalised to a nominal 8 h working day (LEX,8h), needs to be monitored within the ML in order to implement appropriate noise control processes if required. The ML should minimise the potential risk associated with hearing disability from the occupational noise by controlling the personnel's LEX,8h.

Additional resources

- Doem CD, Holfelder M. Automation and design of the clinical microbiology laboratory. In: Jorgensen JH, Pfaller MA, Carroll KC, Funke G, Landry ML, Richter SS, Wamock DW, eds. Manual of clinical microbiology. 11th edn. Vol. 1. ASM Press, Washington, 2015: 44-53.
- Finch SA. Safety in the hematology laboratory. In: Keohane EM, Smith LJ, Walenga JM, eds. Rodak's hematology: clinical principles and applications. 5th edn. Saunders, Saint Louis, 2015: 8-18.
- Glendon I, Clarke S. Human safety and risk management: a psychological perspective. 3rd edn. CRC Press, Boca Raton, 2015.
- Lo SF. Principles of basic techniques and laboratory safety. In: Burtis CA, Bruns DE, eds. Tietz fundamentals of clinical chemistry and molecular diagnostics. 7th edn. Saunders, Saint Louis , 2015: 107-128.
- Sugarman SC. HVAC fundamentals. 3rd edn. The Fairmont Press, Lilburn, 2015.

Subclause 5.3 - Laboratory equipment, reagents, and consumables

Subclause 5.3 - Laboratory equipment, reagents, and consumables

Subclause 5.3 of ISO 15189:2012 (2) contains 10 (9.2%) ARs (7) and 154 (10.2%) CRs (12). Selected IEC and ISO guidance documents essential to the implementation of Subclause 5.3 of ISO 15189:2012 are presented (Table 22).

Subclause 5.3.1.2 - Equipment acceptance testing

Subclause 5.3.1.2 of ISO 15189:2012 (2) specifies that the ML must ensure that the equipment is in a serviceable condition when operated within specified levels of availability and performance. One key consideration is the electrical reticulation for major equipment (179). Two major electrical factors that must be carefully planned for are shortage and oversupply through measures such as sufficient availability of uninterrupted power supply units to counter the effects of power shortage and power surge protection units to counter the effects of oversupply. The ML should integrate these electrical requirements by incorporating these considerations into the equipment acceptance criteria.

Additional resources

- Atlas R, Snyder J. Reagents, stains, and media: bacteriology. In: Jorgensen JH, Pfaller MA, Carroll KC, Funke G, Landry ML, Richter SS, Wamock DW, eds. Manual of clinical microbiology. 11th edn. Vol. 1. ASM Press, Washington, 2015: 316- 349.
- Briggs C, Culp N, Davis B, D'Onofrio G, Zini G, Machin SJ. ICSH guidelines for the evaluation of blood cell analysers including those used for differential leucocyte and reticulocyte counting. *Int J Lab Hem* 2014; 36: 613-627.
- Ginocchio CC, Van Hom G, Harris P. Reagents, stains, and media: virology. In: Jorgensen JH, Pfaller MA, Carroll KC, Funke G, Landry ML, Richter SS, Wamock DW, eds. Manual of clinical microbiology. 11th edn. Vol. 2. ASM Press, Washington, 2015: 1422-1431.
- Lehman CM. Instrumentation for the coagulation laboratory. In: Bennett ST, Lehman CM, Rodgers GM, eds. Laboratory hemostasis: a practical guide for pathologists. Springer International Publishing, Cham, 2015: 33-43.
- Lindsley MD, Snyder JW, Atlas RM, Larocco MT. Reagents, stains, and media: mycology. In: Jorgensen JH, Pfaller MA, Carroll KC, Funke G, Landry ML, Richter SS, Wamock DW, eds. Manual of clinical microbiology. 11th edn. Vol. 2. ASM Press, Washington, 2015: 1955-1964.
- Linscott AJ, Sharp SE. Reagents, stains, and media: parasitology. In: Jorgensen JH, Pfaller MA, Carroll KC, Funke G, Landry ML, Richter SS, Wamock DW, eds. Manual of clinical microbiology. 11th edn. Vol. 2. ASM Press, Washington, 2015: 2310-2316.
- Stephens AD, Colah R, Fucharoen S, Hoyer J, Keren D, McFarlane A et al. ICSH recommendations for assessing automated high-performance liquid chromatography and capillary electrophoresis equipment for the quantitation of HbA2. *Int J Lab Hem* 2015; 37: 577-582.

Table 22. Selected International Electrotechnical Commission and International Organization for Standardization guidance documents associated with Subclause 5.3 of ISO 15189:2012.

Subclause 5.3.1.3	*Equipment instructions for use*
ISO 26800:2011	*Ergonomics - General approach, principles and concepts* (180)
Subclause 5.3.1.4	*Equipment calibration and metrological traceability*
ISO/IEC 17025:2005	*General requirements for the competence of testing and calibration laboratories* (5)
ISO/IEC 17025:2005/ Cor.1:2006	*General requirements for the competence of testing and calibration laboratories - Technical corrigendum 1* (6)
ISO 21748:2010	*Guidance for the use of repeatability, reproducibility and trueness estimates in measurement uncertainty estimation* (181)
Subclause 5.3.1.5	*Equipment maintenance and repair*
ISO 15190:2003	*Medical laboratories - Requirements for safety* (19)
Subclause 5.3.1.6	*Equipment adverse incident reporting*
ISO 15190:2003	*Medical laboratories - Requirements for safety* (19)
Subclause 5.3.1.7	*Equipment records*
ISO/IEC 19770-2:2015	*Information technology - Software asset management - Part 2: software identification tag* (182)
Subclause 5.3.2.6	*Reagents and consumables - adverse incident reporting*
ISO 15190:2003	*Medical laboratories - Requirements for safety* (19)

Subclause 5.4 - Pre-examination processes

Subclause 5.4 - Pre-examination processes

Subclause 5.4 of ISO 15189:2012 (2) contains 23 (21.1%) ARs (7) and 144 (9.5%) CRs (12). Selected ISO guidance documents essential to the implementation of Subclause 5.4 of ISO 15189:2012 are presented (Table 23).

Table 23. Selected International Organization for Standardization guidance documents associated with Subclause 4.2 of ISO 15189:2012.

Subclause 5.4.7	*Pre-examination handling, preparation and storage*
ISO 15190:2003	*Medical laboratories - Requirements for safety* (19)
ISO 16813:2006	*Building environment design - Indoor environment - General principles* (177)
ISO 28000:2007	*Specification for security management systems for the supply chain* (184)
ISO 28001:2007	*Security management systems for the supply chain - Best practices for implementing supply chain security, assessments and plans - Requirements and guidance* (185)
ISO 28002:2011	*Security management systems for the supply chain - Development of resilience in the supply chain - Requirements with guidance for use* (186)
ISO 28004-1:2007	*Security management systems for the supply chain - Guidelines for the implementation of ISO 28000* (187)
ISO 28004:2007/ Cor.1:2012	*Security management systems for the supply chain - Guidelines for the implementation of ISO 28000 - Technical corrigendum 1* (188)
ISO 28004-3:2014	*Security management systems for the supply chain - Guidelines for the implementation of ISO 28000 - Part 3: additional specific guidance for adopting ISO 28000 for use by medium and small businesses (other than marine ports)* (189)
ISO 28004-4:2014	*Security management systems for the supply chain - Guidelines for the implementation of ISO 28000 - Part 4: additional specific guidance for adopting ISO 28000 if compliance with ISO 28001 is a management objective* (190)

Subclause 5.4.7 - Pre-examination handling, preparation and storage

Subclause 5.4.7 of ISO 15189:2012 (2) specifies that the ML must maintain the stability of storage conditions during the preexamination related activities and during handling, preparation and storage. The ML has no specific guidance available for evaluating suitability of specimens for delayed analysis in relation to storage conditions. The ML may wish to establish internal guidelines in relation to the suitability for 'add-on' requests. The factors for consideration are complex due to the variability of analytical methodologies, manufacturer's recommendations, storage temperature and storage time (183). Overall, temperature-controlled logistics is the most demanding aspect for specimen integrity and must be controlled and monitored at each distribution point. Proactive efforts must be made to ensure temperature-controlled logistics for specimens that require frozen (≤ -20°C), refrigerated (2°C–8°C) and room temperature (15°C–25°C) conditions. For quality surveillance purposes, the environmental data logging and location tracking devices need to be compliant with ISO/IEC 17025:2005 (5) and ISO/IEC 17025:2005/Cor.1:2006 (6). The ML must ensure the specimens are maintained within the quality specifications by implementing appropriate technology in the distribution process.

Additional resources

- Baron EJ. Specimen collection, transport, and processing: bacteriology. In: Jorgensen JH, Pfaller MA, Carroll KC, Funke G, Landry ML, Richter SS, Wamock DW, eds. Manual of clinical microbiology. 11th edn. Vol. 1. ASM Press, Washington, 2015: 270-315.
- Bennett ST. Collection of coagulation specimens. In: Bennett ST, Lehman CM, Rodgers GM, eds. Laboratory hemostasis: a practical guide for pathologists. Springer International Publishing, Cham, 2015: 19-32.
- Birdsong GG, Davey DD. Specimen adequacy. In: Nayar R, Wilbur D, eds. The Bethesda system for reporting cervical cytology: definitions, criteria, and explanatory notes. 3rd edn. Springer International Publishing, Cham, 2015: 1-28.
- Dasgupta A, Wahed A. Clinical chemistry, immunology and laboratory quality control: a comprehensive review for board preparation, certification and clinical practice. Elsevier, San Diego, 2014.
- Guder WG, Narayanan S. Sample transport, treatment after arrival, storage and disposal. In: Guder WG, Narayanan S, eds. Preexamination procedures in laboratory diagnostics: preanalytical aspects and their impact on the quality of medical laboratory results. De Gruyter, Berlin, 2015: 251-263.
- Haverstick DM, Groszbach AR. Specimen collection, processing, and other preanalytical variables. In: Burtis CA, Bruns DE, eds. Tietz fundamentals of clinical chemistry and molecular diagnostics. 7th edn. Saunders, Saint Louis, 2015: 72-89.
- International Air Transport Association. Dangerous goods regulations. 54th edn. International Air Transport Association, Montreal, 2013.
- Keohane EM. Blood specimen collection. In: Keohane EM, Smith LJ, Walenga JM, eds. Rodak's hematology: clinical principles and applications. 5th edn. Saunders, Saint Louis, 2015: 19-33.
- Khalsa AK, Cruz MS, Saubolle MA. Principles of preanalytic and postanalytic test management. In: Garcia LS, Bachner P, Baselski VS, Lewis G, Linscott AJ, Schwab DA, Steele Jr JCH, Weissfeld AS, Wilkinson DS, Wolk DM, eds. Clinical laboratory management. 2nd edn. ASM Press, Washington, 2014: 488-505.
- McGowan K. Specimen collection, transport, and processing: mycology. In: Jorgensen JH, Pfaller MA, Carroll KC, Funke G, Landry ML, Richter SS, Wamock DW, eds. Manual of clinical microbiology. 11th edn. Vol. 2. ASM Press, Washington, 2015: 1944-1954.
- Plebani M, Sciacovelli L, Aita A, Pelloso M, Chiozza ML. Performance criteria and quality indicators for the pre-analytical phase. *Clin Chem Lab Med* 2015; 53: 943-948.
- Shimizu RY, Garcia LS. Specimen collection, transport, and processing: parasitology. In: Jorgensen JH, Pfaller MA, Carroll KC, Funke G, Landry ML, Richter SS, Wamock DW, eds. Manual of clinical microbiology. 11th edn. Vol. 2. ASM Press, Washington, 2015: 2293-2309.

Subclause 5.5 - Examination processes

Subclause 5.5 - Examination processes

Subclause 5.5 of ISO 15189:2012 (2) contains 9 (8.3%) ARs (7) and 71 (4.7%) CRs (12). Selected IEC and ISO guidance documents essential to the implementation of Subclause 5.5 of ISO 15189:2012 are presented (Table 24).

Table 24. Selected International Electrotechnical Commission and International Organization for Standardization guidance documents associated with Subclause 5.5 of ISO 15189:2012.

Subclause 5.5.1.4	*Measurement uncertainty of measured quantity values*
ISO/IEC Guide 98-1:2009	*Uncertainty of measurement - Part 1: introduction to the expression of uncertainty in measurement* (194)
ISO/IEC Guide 98-3:2008	*Uncertainty of measurement - Part 3: guide to the expression of uncertainty in measurement (GUM:1995)* (195)
ISO/IEC Guide 98-3:2008/Suppl.1:2008	*Uncertainty of measurement - Part 3: guide to the expression of uncertainty in measurement (GUM:1995) - Supplement 1: propagation of distributions using a Monte Carlo method* (196)
ISO/IEC Guide 98-3:2008/Suppl.1:2008/ Cor.1:2009	*Uncertainty of measurement - Part 3: guide to the expression of uncertainty in measurement (GUM:1995) - Supplement 1: propagation of distributions using a Monte Carlo method - Technical corrigendum 1* (197)
ISO/IEC Guide 98-3:2008/Suppl.2:2011	*Uncertainty of measurement - Part 3: guide to the expression of uncertainty in measurement (GUM:1995) - Supplement 2: extension to any number of output quantities* (198)
ISO/IEC Guide 98-4:2012	*Uncertainty of measurement - Part 4: role of measurement uncertainty in conformity assessment* (199)
ISO/TR 13587:2012	*Three statistical approaches for the assessment and interpretation of measurement uncertainty* (200)
ISO 21748:2010	*Guidance for the use of repeatability, reproducibility and trueness estimates in measurement uncertainty estimation* (181)

Subclause 5.5.2 - Biological reference intervals or clinical decision values

Subclause 5.5.2 of ISO 15189:2012 (2) specifies that the ML must define the biological reference intervals. The task of determining proper reference intervals for a specific cohort remains a continuous challenge, especially when there is no international guidance to prescribe the way to prepare such document. The ML must establish the intervals with widely variable factors for consideration (191).

Subclause 5.5.3 - Documentation of examination procedures

Subclause 5.5.3(o) of ISO 15189:2012 (2) specifies that the ML must document the reportable interval of examination results. The term 'reportable interval' remains undefined by the ISO, nor is there any specific guidance on how to determine it. The reportable interval has been adequately defined and discussed (192); however, it has also been suggested that the ML should select and justify its decision based upon a statistical approach and record the relevant interval as documented information (193).

Additional resources

- Bennett ST. Validation of hemostasis assays, analyzers, and reagents. In: Bennett ST, Lehman CM, Rodgers GM, eds. Laboratory hemostasis: a practical guide for pathologists. Springer International Publishing, Cham, 2015: 45-67.
- Boyd JC, Hawker CD. Automation. In: Burtis CA, Bruns DE, eds. Tietz fundamentals of clinical chemistry and molecular diagnostics. 7th edn. Saunders, Saint Louis, 2015: 154-271.
- Horowitz GL. Establishment and use of reference values. In: Burtis CA, Bruns DE, eds. Tietz fundamentals of clinical chemistry and molecular diagnostics. 7th edn. Saunders, Saint Louis, 2015: 60-71.
- King M-J, Garçon L, Hoyer JD, Iolascon A, Picard V, Stewart G et al. ICSH guidelines for the laboratory diagnosis of nonimmune hereditary red cell membrane disorders. *Int J Lab Hem* 2015; 37: 304-325.
- Oosterhuis WP, Theodorsson E. Total error vs. measurement uncertainty: revolution or evolution? *Clin Chem Lab Med* 2016; 54: 235-239.
- Torlakovic EE, Brynes RK, Hyjek E, Lee S-H, Kreipe H, Kremer M et al. ICSH guidelines for the standardization of bone marrow immunohistochemistry. *Int J Lab Hem* 2015; 37: 431-449.
- Westgard JO. Useful measures and models for analytical quality management in medical laboratories. *Clin Chem Lab Med* 2016; 54: 223-233.

Subclause 5.6 - Ensuring quality of examination results

Subclause 5.6 - Ensuring quality of examination results

Subclause 5.6 of ISO 15189:2012 (2) contains 7 (6.4%) ARs (7) and 54 (3.6%) CRs (12). Selected IEC and ISO guidance documents essential to the implementation of Subclause 5.6 of ISO 15189:2012 are presented (Table 25).

Table 25. Selected International Electrotechnical Commission and International Organization for Standardization guidance documents associated with Subclause 5.6 of ISO 15189:2012.

Subclause 5.6.2.2	*Quality control materials*
ISO Guide 33:2015	*Reference materials - Good practice in using reference materials* (201)
ISO Guide 80:2014	*Guidance for the in-house preparation of quality control materials (QCMs)* (202)
Subclause 5.6.3.1	*Participation*
ISO 13528:2015	*Statistical methods for use in proficiency testing by interlaboratory comparison* (203)
ISO/IEC 17043:2010	*Conformity assessment - General requirements for proficiency testing* (204)

Subclause 5.6.2.2 - Quality control materials

Subclause 5.6.2.2 of ISO 15189:2012 (2) specifies that the ML must use quality control materials (QCMs) that react to the examining system in a manner as close as possible to patient samples. The ML has no specific rules governing whether both negative (nonreactive) and positive (reactive) QCMs must be performed at the same time, nor is the possibility addressed that the manufacturer or third-party supplier may not provide negative (nonreactive) QCMs for a particular test. The ML should select QCMs based on the availability of analytical concentrations that include negative (nonreactive) and positive (reactive).

Additional resources

- Byrant RJ, Lewis MR. Benchmarking and performance monitoring: what is appropriate for your laboratory? In: Garcia LS, Bachner P, Baselski VS, Lewis G, Linscott AJ, Schwab DA, Steele Jr JCH, Weissfeld AS, Wilkinson DS, Wolk DM, eds. Clinical laboratory management. 2nd edn. ASM Press, Washington, 2014: 890-893.
- Cadamuro J. Internal quality assurance for preanalytical phase. In: Guder WG, Narayanan S, eds. Pre-examination procedures in laboratory diagnostics: preanalytical aspects and their impact on the quality of medical laboratory results. De Gruyter, Berlin, 2015: 345-351.
- Clymer M. Image is everything! Quality issues remain as digital pathology enters the clinical lab. *Med Lab Obs* 2015; 47: 34-38.
- Fritsma GA. Quality assurance in hematology and hemostasis. In: Keohane EM, Smith LJ, Walenga JM, eds. Rodak's hematology: clinical principles and applications. 5th edn. Saunders, Saint Louis, 2015: 42-64.
- Jones GRD. Average of delta: a new quality control tool for clinical laboratories. *Ann Clin Biochem* 2015; 53: 133-140.
- Kristensen GBB, Aakre KM, Kristoffersen AH, Sandberg S. External quality assurance for the preanalytical phase. In: Guder WG, Narayanan S, eds. Pre-examination procedures in laboratory diagnostics: preanalytical aspects and their impact on the quality of medical laboratory results. De Gruyter, Berlin, 2015: 352-364.
- Rao LV. FALTS: factors affecting laboratory tests. In: Williamson MA, Snyder LM, eds. Wallach's interpretation of diagnostic tests. 10th edn. Lippincott Williams & Wilkins, Philadelphia, 2014: 1-10.
- Wells LD, Winn Jr WC, Lewis MR. Benchmarking and performance monitoring for the clinical laboratory. In: Garcia LS, Bachner P, Baselski VS, Lewis G, Linscott AJ, Schwab DA, Steele Jr JCH, Weissfeld AS, Wilkinson DS, Wolk DM, eds. Clinical laboratory management. 2nd edn. ASM Press, Washington, 2014: 851-875.
- Westgard JO, Westgard SA. Quality control review: implementing a scientifically based quality control system. *Ann Clin Biochem* 2015; 53: 32-50.

Subclause 5.7 - Post-examination processes

Subclause 5.7 - Post-examination processes

Subclause 5.7 of ISO 15189:2012 (2) contains 4 (3.7%) ARs (7) and 21 (1.4%) CRs (12). Selected ISO guidance documents essential to the implementation of Subclause 5.7 of ISO 15189:2012 are presented (Table 26).

Subclause 5.7.1 - Review of results

Subclause 5.7.1 of ISO 15189:2012 (2) specifies that the ML must review results of examinations by authorised personnel prior to release. The ML must ensure the authorised personnel who perform the reviewing have competent diagnostic capability. However, the ML has no specific rules governing the process to maintain such capabilities and competencies. The reviewing process can be demanding because it requires the personnel to interpret various representations of indicator, indices and scales (205). This requires the personnel to have both the skills essential for diagnosis as well as analytical judgment (206). The ML should authorise personnel who maintain and update skills in both scientific and technical areas; and select personnel who have demonstrated effectiveness through applicable accreditation, certification or licensure.

Additional resources

- Bakerman S. Bakerman's ABC's of interpretive laboratory data. 5th edn. Interpretive Laboratory Data, Scottsdale, 2014.
- Khalsa AK, Cruz MS, Saubolle MA. Principles of preanalytic and postanalytic test management. In: Garcia LS, Bachner P, Baselski VS, Lewis G, Linscott AJ, Schwab DA, Steele Jr JCH, Weissfeld AS, Wilkinson DS, Wolk DM, eds. Clinical laboratory management. 2nd edn. ASM Press, Washington, 2014: 488-505.

Table 26. Selected International Electrotechnical Commission and International Organization for Standardization guidance documents associated with Subclause 5.7 of ISO 15189:2012.

Subclause 5.7.2	*Storage, retention and disposal of clinical samples*
ISO 15190:2003	*Medical laboratories - Requirements for safety* (19)
ISO 16813:2006.	*Building environment design - Indoor environment - General principles* (177)
ISO 28000:2007	*Specification for security management systems for the supply chain* (184)
ISO 28001:2007	*Security management systems for the supply chain - Best practices for implementing supply chain security, assessments and plans - Requirements and guidance* (185)
ISO 28002:2011	*Security management systems for the supply chain - Development of resilience in the supply chain - Requirements with guidance for use* (186)
ISO 28004-1:2007	*Security management systems for the supply chain - Guidelines for the implementation of ISO 28000* (187)
ISO 28004:2007/ Cor.1:2012	*Security management systems for the supply chain - Guidelines for the implementation of ISO 28000 - Technical corrigendum 1* (188)
ISO 28004-3:2014	*Security management systems for the supply chain - Guidelines for the implementation of ISO 28000 - Part 3: additional specific guidance for adopting ISO 28000 for use by medium and small businesses (other than marine ports)* (189)
ISO 28004-4:2014	*Security management systems for the supply chain - Guidelines for the implementation of ISO 28000 - Part 4: additional specific guidance for adopting ISO 28000 if compliance with ISO 28001 is a management objective* (190)

Subclause 5.8 - Reporting of results

Subclause 5.8 - Reporting of results

Subclause 5.8 of ISO 15189:2012 (2) contains 4 (3.7%) ARs (7) and 47 (3.1%) CRs (12). Selected ISO guidance documents essential to the implementation of Subclause 5.8 of ISO 15189:2012 are presented (Table 27).

Subclause 5.8.2 - Report attributes

Subclause 5.8.2 of ISO 15189:2012 (2) specifies that the ML must ensure the report attributes are meeting users' needs. One of the key functions is to provide interpretive comments on critical results in order to support effective clinical decision-making for patients. Reporting that incorporates appropriate graphic representation of relevant indices and scales remains the preferred format (205). Furthermore, the ML has no specific guidance documents prescribing a method for interpretative commenting besides referring to peer-reviewed literature (160,207). The ML should consider meeting the user's needs by developing innovative methods to present results, drawing on infographics and interpretative comments where available and suitable.

Additional resources

- Bain BJ. Blood cells: a practical guide. 5th edn. Wiley-Blackwell, Chichester, 2015.
- Nayar R, O'Connor DM, Darragh TM. Education notes and comments appended to cytology reports. In: Nayar R, Wilbur D, eds. The Bethesda system for reporting cervical cytology: definitions, criteria, and explanatory notes. 3rd edn. Springer International Publishing, Cham, 2015: 301-304.
- Palmer L, Briggs C, Mcfadden S, Zini G, Burthem J, Rozenberg G, et al. ICSH recommendations for the standardization of nomenclature and grading of peripheral blood cell morphological features. *Int J Lab Hem* 2015; 37: 287-303.
- Tripodi A, Lippi G, Plebani M. How to report results of prothrombin and activated partial thromboplastin times. *Clin Chem Lab Med* 2016; 54: 215-222.

Table 27. Selected International Organization for Standardization guidance documents associated with Subclause 5.8 of ISO 15189:2012.

Subclause 5.8.3(i)	*Report content*
ISO 80000-1:2009	*Quantities and units - Part 1: general* (208)
ISO 80000-1:2009/ Cor.1:2011	*Quantities and units - Part 1: general - Technical corrigendum 1* (209)
ISO 80000-2:2009	*Quantities and units - Part 2: mathematical signs and symbols to be used in the natural sciences and technology* (210)
ISO 80000-3:2006	*Quantities and units - Part 3: space and time* (211)
ISO 80000-9:2009	*Quantities and units - Part 9: physical chemistry and molecular physics* (212)

Subclause 5.9 - Release of results

Subclause 5.9 - Release of results

Subclause 5.9 of ISO 15189:2012 (2) contains 8 (7.3%) ARs (7) and 45 (3.0%) CRs (12).

Subclause 5.9.1 - General

Subclause 5.9.1 of ISO 15189:2012 (2) specifies that the ML must establish documented procedures for the release of examination results. This requirement poses continual challenges to the ML because the patient confidentiality requirements are becoming increasingly onerous. First, the ML must ensure the identification process is in place to conduct identity checks. Ideally, the identifier needs to match pre-recorded information organised by reference to that same identifier. However, this can pose difficulties to an intermediary identifier who requires specific information for urgent medical decision-making purposes. Second, the ML must ensure the access of information is available on authorised request and is accurate, complete and up-to-date, while maintaining patient confidentiality. Third, the ML must be prepared to release information to a foreign country that has a comparable information privacy scheme or legal framework. For instance, countries that have ratified the *Convention on the Taking of Evidence Abroad in Civil or Commercial Matters* (213) are required to present information to each other upon request, as long as the requested information is relevant to the issues. Overall, the ML should consider the controllability of the release of information so that it does not cause an unreasonable impact on patient's privacy.

Additional resources

- Stapleton JJ. Security without obscurity: a guide to confidentiality, authentication, and integrity. Auerbach Publications, 2014.
- Van Buren III HJ. Confidentiality agreements. In: Kolb RW, ed. Encyclopedia of business ethics and society. Vol. 1. SAGE Publications, Thousand Oaks, 2008: 398-401.

Subclause 5.10 - Laboratory information management

Subclause 5.10 - Laboratory information management

Subclause 5.10 of ISO 15189:2012 (2) contains 2 (1.8%) ARs (7) and 142 (9.4%) CRs (12). Selected IEC and ISO guidance documents essential to the implementation of Subclause 5.10 of ISO 15189:2012 are presented (Table 28).

Subclause 5.10.2 - Authorities and responsibilities

Subclause 5.10.2 of ISO 15189:2012 (2) specifies that the ML must define the authorities and responsibilities of all personnel who have access to the laboratory information management system (LIMS). The ML must ensure that the internal process is reasonably practicable, so that the handling of information does not cause an unreasonable impact on patient's privacy.

Subclause 5.10.3 - Information system management

Subclause 5.10.3(a) of ISO 15189:2012 (2) specifies that the ML must use appropriately validated software for the LIMS. The software performance of the LIMS is crucial for the ML to provide consistent service to users (214). A common area of concern is the ability of the software to perform as per specifications. One way to ensure this is to purchase software that has been independently certified and evaluated by the supplier. The defined quality characteristics and requirements for the intended use of the products can be evaluated and specified using validated measures. This enables a very low level of verification prior to implementation (215-217). The ML should consider using certified software to ensure there is an acceptably low level of residual design defects (216,218).

Subclause 5.10.3(c) of ISO 15189:2012 (2) specifies that the ML must protect the LIMS from unauthorised access. Increasing reliance on the internet is posing continuous defensibility challenges to the LIMS. The emerging trends, such as 'the internet of things', cloud computing and cybercriminal activities, are widening the vulnerability window for the LIMS. Responses to susceptibility and vulnerability issues continue to be defensive and reactive (166,219), particularly when confronted by a new generation of offensive software (220,221). The turnaround time for a security vendor to release a patch in response to a threat could take up to 204 days (222). Not surprisingly, cybercriminals continue to steal private information by direct attack on institutions both externally and internally (223). The ML must ensure cyber incident response procedures are in place are to protect personal information from unauthorised access, disclosure and modification.

Additional resources

- Bailey T, Kaplan JM, Rezek C. Repelling the cyberattackers. *McKinsey Q* 2015; 54-63.
- Campos JM. The laboratory information system: making the most of it in the clinical microbiology laboratory. In: Garcia LS, Bachner P, Baselski VS, Lewis G, Linscott AJ, Schwab DA, Steele Jr JCH, Weissfeld AS, Wilkinson DS, Wolk DM, eds. Clinical laboratory management. 2nd edn. ASM Press, Washington, 2014: 458-470.
- Joyce J. Considering the cloud. *Lab Manag* 2015; 10: 32-35.
- Kroenke DM, R.J. B. Using MIS. 8th edn. Prentice Hall, Upper Saddle River, 2015.
- National Academies of Sciences, Engineering, and Medicine,. Privacy research and best practices: summary of a workshop for the intelligence community. The National Academies Press, Washington, 2016.
- Sennewald CA, Baillie C. Effective security management. 6th edn. Butterworth-Heinemann, Oxford, 2016.
- Snedaker S, Rima C. Business continuity and disaster recovery planning for IT professionals. 2nd edn. Syngress, Waltham, 2014.
- Thejendra BS. Disaster recovery and business continuity: a quick guide for organisations and business managers. 3rd edn. IT Governance Publishing, Ely, 2014.

Table 28. Selected International Electrotechnical Commission and International Organization for Standardization guidance documents associated with Subclause 5.10 of ISO 15189:2012.

Subclause 5.10	*Laboratory information management*
ISO/TS 17975:2015	*Health informatics - Principles and data requirements for consent in the Collection, Use or Disclosure of personal health information* (175)
ISO/IEC 18028-4:2005	*Information technology - Security techniques - IT network security - Part 4: securing remote access* (224)
ISO/IEC 27001:2013	*Information technology - Security techniques - information security management systems - Requirements* (225)
ISO/IEC 27001:2013/ Cor.1:2014	*Information technology - Security techniques - Information security management systems - requirements - Technical corrigendum 1* (226)
ISO/IEC 27002:2013	*Information technology - Security techniques - Code of practice for information security controls* (227)
ISO/IEC 27002:2013/ Cor.1:2014	*Information technology - Security techniques - Code of practice for information security controls - Technical corrigendum 1* (228)
ISO/IEC 27003:2010	*Information technology - Security techniques - Information security management system implementation guidance* (229)
ISO/IEC 27004:2009	*Information technology - Security techniques - Information security management - Measurement* (230)
ISO/IEC 27005:2011	*Information technology - Security techniques - Information security risk management* (231)
ISO/IEC 27006:2015	*Information technology - Security techniques - Requirements for bodies providing audit and certification of information security management systems* (232)
ISO/IEC 27007:2011	*Information technology - Security techniques - for information security management systems auditing* (162)
ISO/IEC 27010:2015	*Information technology - Security techniques - Information security management for inter-sector and interorganizational communications* (233)
ISO/IEC 27013:2015	*Information technology - Security techniques - Guidance on the integrated implementation of ISO/IEC 27001 and ISO/IEC 20000-1* (234)
ISO/IEC 27017:2015	*Information technology - Security techniques - Code of practice for information security controls based on ISO/IEC 27002 for cloud services* (235)
ISO/IEC TR 27023:2015	*Information technology - Security techniques - Mapping the revised editions of ISO/IEC 27001 and ISO/IEC 27002* (236)
ISO/IEC 27031:2011	*Information technology - Security techniques - Guidelines for information and communication technology readiness for business continuity* (237)
ISO/IEC 27033-1:2015	*Information technology - Security techniques - Network security - Part 1: overview and concepts* (238)
ISO/IEC 27033-2:2012	*Information technology - Security techniques - Network security - Part 2: guidelines for the design and implementation of network security* (239)
ISO/IEC 27033-3:2010	*Information technology - Security techniques - Network security - Part 3: reference networking scenarios - Threats, design techniques and control issues* (240)
ISO/IEC 27033-4:2014	*Information technology - Security techniques - Network security - Part 4: securing communications between networks using security gateways* (241)
ISO/IEC 27033-5:2013	*Information technology - Security techniques - Network security - Part 5: securing communications across networks using Virtual Private Networks (VPNs)* (242)
ISO/IEC 27036-1:2014	*Information technology - Security techniques - Information security for supplier relationships - Part 1: overview and concepts* (243)
ISO/IEC 27036-2:2014	*Information technology - Security techniques - Information security for supplier relationships - Part 2: requirements* (244)
ISO/IEC 27036-3:2013	*Information technology - Security techniques - Information security for supplier relationships - Part 3: guidelines for information and communication technology supply chain security* (245)
ISO/IEC 27039:2015	*Information technology - Security techniques - Selection, deployment and operations of intrusion detection systems (IDPS)* (246)
ISO/IEC 27040:2015	*Information technology - Security techniques - Storage security* (247)
ISO 27789:2013	*Health informatics - Audit trails for electronic health records* (248)
ISO 27799:2008	*Health informatics - Information security management in health using ISO/IEC 27002* (249)

Strategic change management recommendations for implementation

Strategic business direction and organisational maturity play important roles in determining the availability of resources to the ML. Considerations for resource allocation must allow for improvement as well as the implementation of ISO 15189:2012 requirements. The effort must be sufficient for stakeholder satisfaction (for customers, external providers and laboratory personnel). There are three potential implications that the ML should consider while implementing improvements and updates to the QMS. The first potential implication relates to the consideration of comfort, engagement and ergonomics for laboratory personnel. It is important to remember that the productivity of employees is inextricably linked to the physical work environment (250,251); therefore focusing solely on the implementation of requirements in Subclause 5.2 of ISO 15189:2012 (2) is likely to suppress this consideration. The level of effectivity and productivity can be reflected from the facilities' management style. Ideally, facilities management should incorporate the buildings, personnel, services and technology for implementation purposes (252). One recommendation is to apply the concepts of change readiness and flexibility for facilities to both human and physical aspects. The human aspects can include change capabilities development (253), change readiness capabilities (254,255) and change resistance management (256,257). At the same time, the physical aspects can include change readiness (258) and flexibility of physical assets, such as circulation, expansion and volume (258). The competent application of flexibility has the potential to transform the ML's capacity into a competitive advantage (259-261).

The second potential implication concerns the level and type of quality training provided by the ML. Although Subclause 5.1.5 of ISO 15189:2012 (2) requires the ML to provide training in the QMS, the extent of soft (human)-related dimensions of QM practices are not given sufficient recognition. It is apparent that technical QM skills are essential for interpreting data for a range of scientific analysis, and instruction in the use of these technical tools is usually provided at various training establishments (15); but the application of human skills is also paramount (262-264). This subject matter is mainly confined to courses for human resource management staff; and this limitation in training opportunity for scientific staff may hamper the progress of senior personnel who wish to obtain both human and technical skills. The lack of training provided in human skills to medical scientists is a significant issue. Medical scientists are recommended to obtain these skills by completing training that contains human-related QM competencies.

The third potential implication concerns the ability for the ML to be open to emerging technologies and trends within areas of operations. Subclause 4.12 of ISO 15189:2012 (2) requires the ML to improve the QMS effectiveness on a continual basis, but it is possible to miss out on innovative developments if the continual improvement programme does not scout for potential advantages of emerging technologies. There is a range of disruptive technologies that can potentially have major impacts on service delivery; particularly health-related technologies that are likely to change the existing processes, mainly due to the improved connectivity and changing consumer preferences (222,265). Representative technologies that are likely to cause major disruptions include: automation (266,267), 'the internet of things' (268,269), advanced robotics (270), next generation sequencing (271) and additive manufacturing (272,273). Overall, the ML needs to gain a comprehensive situational awareness of its rapidly changing social and technological context in order to be competitive in the pathology services industry.

AUTHOR INFORMATION

Dennis Mok[1], MAIMS CSci MIBMS MNZIMLS CAHRI FCMI FAIM FNZIM, Medical Laboratory Scientist
Eddie Ang[2], PhD, Advisor

[1]Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates
[2]Chemical Metrology Laboratory, Health Sciences Authority, Singapore

Author for correspondence: Dr Eddie Ang.
Email: hsa_cmleqa@hsa.gov.sg

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NZIMLS Annual Scientific Meeting—Hugh Bloore Poster Award

In recognition of their late father's passion for science, learning and capacity building for young people to live on through the NZIMLS, the family of Hugh Bloore have given a grant to the NZIMLS to go to the Hugh Bloore Memorial Poster Prize.

This prize is to the value of $1,000 for the best poster submitted to the NZIMLS Annual Scientific Meeting by a current financial NZIMLS member. To be eligible to collect this award, the person submitting the poster must be present at the Hugh Bloore Poster Session at the NZIMLS annual scientific meeting.

The posters will be judged by two NZIMLS Council appointed judges and the judge's decision will be final. The recipient will be announced at the Hugh Bloore Poster Session and awarded a certificate and cheque at this time.

The winner of the award must use the money to go towards attendance at a scientific meeting or research. The recipient is to report back to Council on how the award money was spent.

Hugh Grovenor Bloore
3 March 1918 -10 September 2005

Hugh Bloore was a foundation member of the New Zealand Association of Bacteriologists (as the NZIMLS was then known as).

His involvement with the NZIMLS was:

- Council member: 1954 – 1958
- Vice President: 1958 – 1963
- President: 1963 – 1966
- Elected a Fellow in 1968
- Life member in 1982

All Hugh's working life was as the Charge Technologist at the Wairau Hospital Laboratory in Blenheim.

CASE STUDY

Fine needle aspiration cytology of an unusual case of papillary thyroid carcinoma metastatic to the breast

Sharda Lallu, Sarla Naran and Catherine Koleda

Anatomic Pathology, Wellington SCL, Wellington

ABSTRACT

We report the fine needle aspiration cytology of a case of thyroid papillary carcinoma metastatic to the breast in a 63 year female who presented with a mobile lump in the right breast. She had past history of thyroid papillary carcinoma in 1991 with metastasis to the lung in 2005. Also, she had a right middle lobectomy for a bronchial carcinoid 30 years previously. Fine needle aspiration of the breast lump revealed a cellular sample composed of cell groups with a tubulopapillary architecture, with the cells showing mild atypia. A cell block preparation showed numerous papillary groups of cells exhibiting nuclear overlapping, occasional nuclear grooves, rare intranuclear inclusions and psammomatous calcifications. On immunohistochemical staining the tumour cells were positive for TTF-1, weakly positive for thyroglobulin and negative for ER, PR, GATA3, GCDFP-15, CD56, synaptophysin and chromogranin. The breast is an unusual site of metastasis for thyroid papillary carcinoma.

Key words: Fine needle aspiration, breast cancer, thyroid papillary carcinoma, metastasis.

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INTRODUCTION

Papillary carcinoma of the thyroid is the most common form of thyroid malignancy, generally carries a good prognosis and tends to metastasize locally to regional lymph nodes. Distant metastases are uncommon and are usually to the lung and bone (1-3). Less common sites of metastases are the brain, liver, kidneys, skin and breast (1,3-5). Carcinoma of the thyroid metastasising to the breast is particularly uncommon.

In general, metastasis to the breast from an extra-mammary site is uncommon, constituting approximately 2 to 4% of all breast malignancies (5). Malignant melanoma is the most common tumour metastasize to the breast followed by lymphoma, lung cancer, ovarian carcinoma, soft tissue sarcoma, gastrointestinal and genitourinary tumours (4-6). In males, the most frequent site is from the prostate.

In this case report we describe the cytologic findings of thyroid papillary carcinoma metastasizing to the breast, after 24 years following total thyroidectomy along with histologic confirmation. We also discuss the differential diagnosis and usefulness of immunohistochemical staining to distinguish a metastasis from a breast tumour.

CASE REPORT

A 63 year old female with past history of a well differentiated papillary thyroid carcinoma of the left thyroid lobe, diagnosed in 1991, presented with a new breast lump. The thyroid tumour was treated with total thyroidectomy plus radioiodine ablation. She was diagnosed with lung metastases in 2005 with further radioiodine treatment. Also, she had a previous right middle lobectomy for a bronchial carcinoid some 30 years ago. On examination she had a small mobile mass in the inner upper aspect of her right breast, 24 years following total thyroidectomy. There was no obvious axillary lymphadenopathy. Serum thyroglobulin was increased at 1060 µg/L (normal: <58 µg/L). Fine needle aspiration (FNA) and simultaneous core biopsy of the right breast mass were performed.

MATERIALS AND METHODS

FNA material was collected in Thin Prep cytolyt (TP, Hologic cytyc, Malborough, Massachusetts, USA) fixative for liquid-based, thin-layer preparations. The aspirate sample was spun at 3700 rpm for 2 minutes and from the sediment, 1-2 drops were added to a Thin Prep Preserv-cyt vial. A Thin Prep slide was prepared using a TP 2000 processor, fixed in 95% ethanol and stained by the Papanicolaou method. The remainder of the sediment was used to make a cell block, fixed in 10% formalin, embedded in paraffin, routinely processed, and stained with hematoxylin-eosin (H & E).

Immunohistochemical studies were carried out on the cell block and core biopsy sections using antibodies TTF-1 (1:200; Leica), thyroglobulin (1:1000; Dako), ER (1:50; Dako), PR (premade; Leica), GATA3 (1:200; Cell Marque), GCDFP-15 (1:500; Leica), CD56 (Premade; Leica), synaptophysin (1:200; Dako), chromogranin (1:200; Cell Marque), PAX8 (1:100; Cell Marque), villin (1:100; Leica), CK 7 (1:400; Dako) and CK20 (1:200; Novocastra).

RESULTS

The Thin Prep sample was highly cellular showing blood, scattered macrophages, and numerous groups of cells with a tubulopapillary architecture and mild cytologic atypia (Figure 1a). Also seen were some cells with nuclear grooves (Figure 1b). The cell block showed numerous papillary structures (Figure 2) lined by cells which exhibited overlapping of nuclei, occasional nuclear grooves and rare intranuclear inclusions (Figure 6). Scattered psammomatous calcifications were seen.

Histologic findings

A H & E stained section of the breast core biopsy showed multiple fragments of low grade papillary tumour comprising fibrovascular cores lined by cells with overlapping nuclei, occasional nuclear grooves and rare intranuclear inclusions (Figure 3).

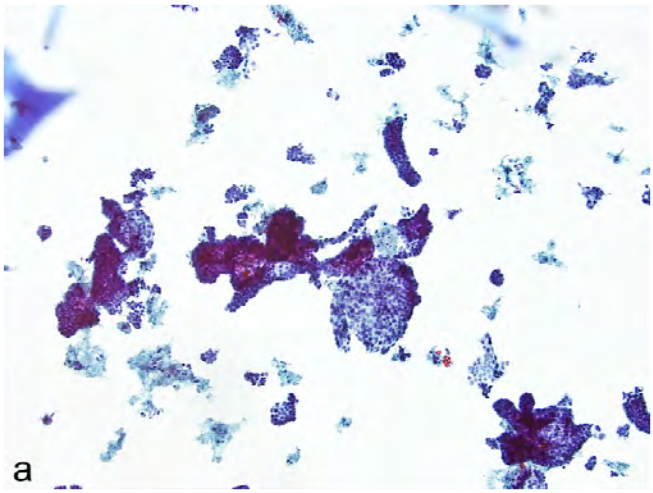

Figure 1a. Thin prep from FNA showing numerous groups of cells with a tubulopapillary architecture (Papanicolaou stain X 100).

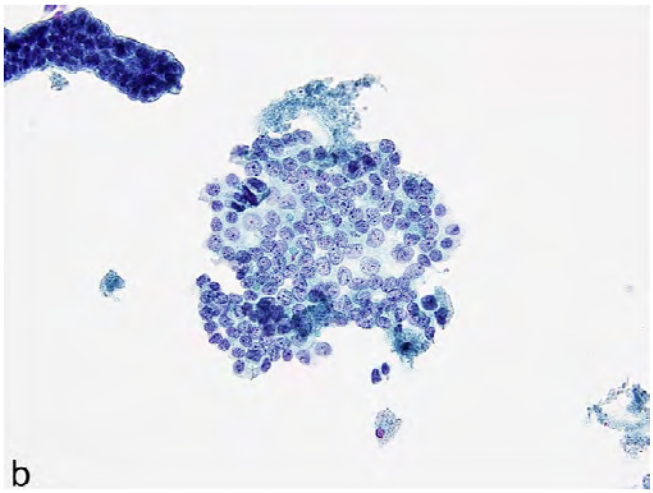

Figure 1b. Thin prep from FNA showing numerous groups of cells with nuclear grooves (Papanicolaou stain X 400).

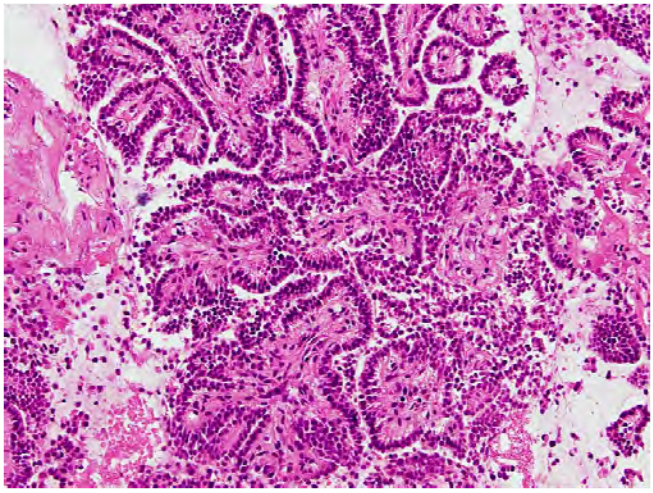

Figure 2. Cell block preparation from FNA showing papillary groups of cells with fibrovascular cores (Papanicolaou stain X 200).

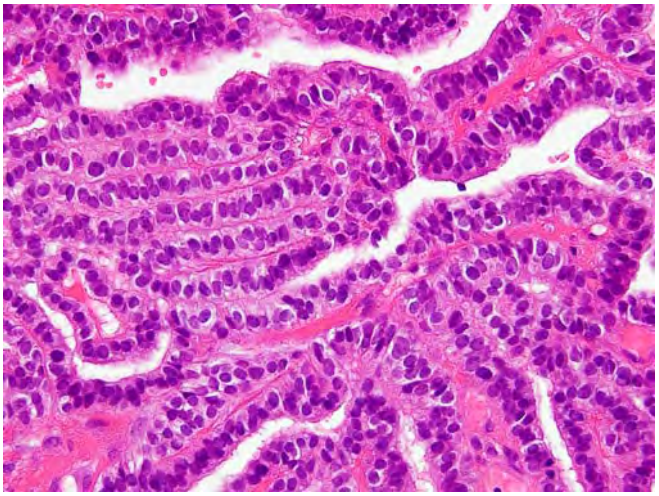

Figure 3. Breast core biopsy section showing papillary fragments of cells with overlapping nuclei, occasional nuclear grooves and rare intranuclear inclusions (Haematoxylin-eosin X 400).

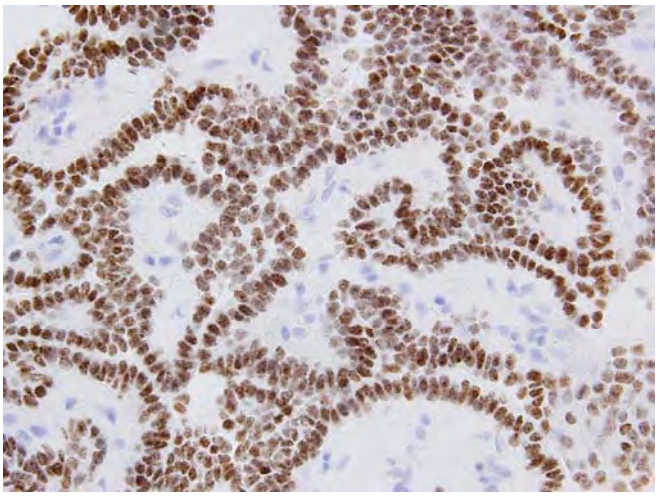

Figure 4. Immunohistochemical stain on cell block showing nuclear positive staining for TTF-1 (TTF-1 stain X 400).

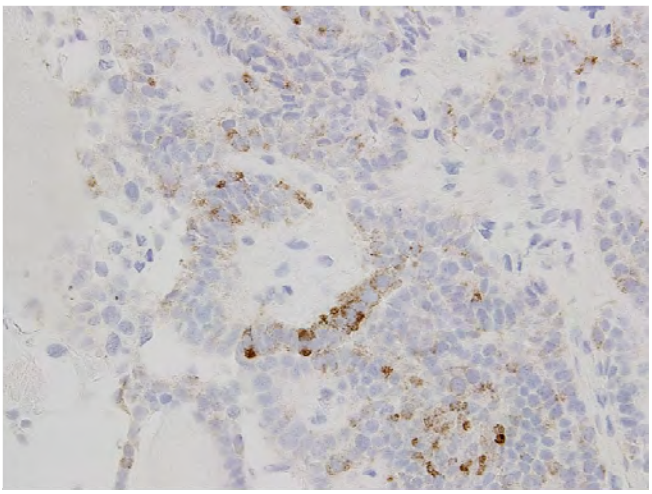

Figure 5. Immunohistochemical stain on cell block showing focal cytoplasmic positive staining for thyroglobulin (thyroglobulin stain X 400).

Immunohistochemical findings

Immunohistochemical stains on the cell block showed the tumour cells were positive for TTF-1 (Figure 4) and they showed focal weak positivity for thyroglobulin (Figure 5). The tumour cells were negative for ER, PR, GATA3, GCDFP-15, CD56, synaptophysin and chromogranin.

Immunohistochemical stains on the core biopsy showed the tumour cells were positive for TTF-1, PAX8, CK7 and occasional cells were positive for thyroglobulin. The tumour cells were negative for ER, PR, CK20, villin, and GCDFP-15 .

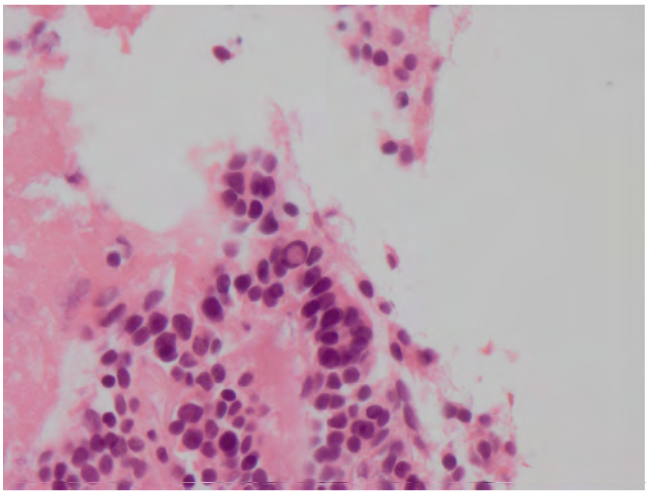

Figure 6. Cell block preparation from FNA showing cell with intranuclear inclusion (Papanicolaou stain X 400).

DISCUSSION

Papillary and follicular carcinomas of the thyroid gland are often referred to together as differentiated thyroid cancer (DTC). They are typically low-grade and slowly progressive. The prognosis is usually favourable and the 10 year survival rate is as high as 80 -95%. Papillary carcinoma of the thyroid is the most common form of thyroid malignancy and generally carries a good prognosis since it usually remains confined to the thyroid gland and tends to metastasize locally to regional lymph nodes alone. However, distant metastasis mainly to lung and bone occurs uncommonly (1-3, 5, 7-9). Metastasis to other sites is distinctly rare and includes brain, breast, liver, kidney, muscle and skin (1,3-5,8,9). The presence of distant metastasis is a poor prognostic factor for survival, with only 50 % of patients surviving after 10 years. Recognizing distant metastasis from DTC has a significant impact on clinical decision making. Metastasis to the breast from DTC is extremely rare. To date, only 11 cases have been described in the literature. All of the patients were female.

Metastasis to the breast from extra-mammary primary cancer in general is rare. The first reported case of metastasis to the breast was in 1903 by Trevithick who reported a reticulum cell sarcoma metastasis to the breast (4). The incidence of breast metastases from extra-mammary tumours in an autopsy series was reported between 1.4 and 6.6% (5). Malignant melanoma, lymphoma, lung cancers, neuroendocrine-like tumours, ovarian carcinoma, soft tissue sarcoma, gastrointestinal and genitourinary tumours are the most common cancers metastasize to the breast. Differentiating primary mammary disease from extra-mammary sources may be difficult on the clinical examination alone. The suspicion of metastasis to breast is generally straightforward when a known primary tumour is present. It is important to differentiate metastatic malignancies from primary breast tumours to avoid surgery such as mastectomy. Immunohistochemical staining is helpful for accurate diagnosis. Anti-thyroglobulin antibody, as in this case, is a good marker in confirmation of the pathological diagnosis of differentiated thyroid cancer metastasis.

The majority of breast metastases present as palpable, rapidly growing, well-circumscribed and painless breast masses with predilection to the upper outer quadrant. Unlike primary tumours, the vast majority of metastases do not demonstrate retraction of the skin or nipple, despite their superficial location (6). Distinguishing a breast metastasis from a primary mammary adenocarcinoma, based on mammographic findings, may be extremely difficult due to the wide range of imaging manifestations of the metastatic lesions. Thus, metastasis may mimic a primary malignancy or even a benign breast tumour. Occasionally, metastases to the breast demonstrate features that lead the pathologist to a correct diagnosis, such as cells with nuclear grooves, intranuclear inclusions, powdery chromatin and psammoma bodies as seen in our case. However, carcinomas with micropapillary components have been described in many organs including the breast, urinary bladder, ovary, salivary gland, thyroid and lung. Multiple psammoma bodies may be seen in metastatic ovarian carcinoma, papillary carcinoma of the thyroid, primary breast and lung carcinoma (6).

The distinction between metastasis from lung adenocarcinoma particularly that with an extensive papillary pattern, thyroid papillary carcinoma, ovarian papillary carcinoma and primary breast papillary carcinoma may cause a diagnostic dilemma. Immunohistochemistry may assist to the correct diagnosis. TTF -1 is most commonly expressed in lung adenocarcinoma and thyroid carcinoma. Although in much lower percentage, TTF-1 nuclear expression has been recently reported in tumours arising from other sites such as female genital tract, gastro intestinal tract, prostate, salivary gland and breast (less than 1%) (10).

Thyroglobulin positivity excludes a breast primary, metastatic ovarian carcinoma and metastatic lung adenocarcinoma. The positive staining for TTF- 1, thyroglobulin, and negative staining for ER, PR, GCDFP-15, GATA3 ruled out primary breast papillary carcinoma, papilloma and tubular carcinoma. CD56, chromogranin and synaptophysin were negative which ruled out a neuroendocrine tumour as our patient had a remote history of carcinoid of the lung. A panel of markers must be used as no single antibody is 100% sensitive and false negative results do occur. In our case TTF-1 and thyroglobulin positivity directed towards metastatic papillary carcinoma from thyroid. Metastatic disease to the breast, although rare, should be considered in differential diagnosis of malignant breast lesions as the treatment and prognosis differ significantly.

Life-long follow up is recommended for all patients with papillary carcinoma of the thyroid since the tumour may metastasize even decades after thyroid surgery. Metastatic thyroid papillary carcinoma to the breast, although rare, should be considered in the differential diagnosis of mammary tumours particularly those with a papillary pattern. The contribution of immunohistochemistry to the correct diagnosis is important. Thyroidectomy, postoperative iodine ablation, thyroxine replacement and careful follow up with serum thyroglobulin levels are associated with fewer cancer recurrences and tumour related deaths (9).

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AUTHOR INFORMATION

Sharda Lallu, BSc CFIAC, Cytotechnologist
Sarla Naran, BSc CFIAC, Cytotechnologist
Catherine Koleda, FRCPA MBBS BMedSc(Hons), Histo and Cytopathologist

Department of Cytology, Anatomic Pathology, Wellington SCL, Wellington Hospital

Addess for correspondence and reprint requests:
Dr Catherine Koleda, Cytology Unit, Anatomic Pathology, Wellington SCL, Wellington Hospital, Wellington, New Zealand.
E-Mail: Catherine.Koleda@wellingtonscl.co.nz.

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NZIMLS Annual Scientific Meeting 2016 - International Speakers

Dr Sasha Jaksic

Dr Sasha Jaksic trained as a pathologist in former Yugoslavia and after working in Europe and USA, she relocated to Australia where she got her specialist degree (FRCPA) in 2000.

Sasha has worked both in public hospital laboratories and in private pathology in Australia (Darwin, Perth, Brisbane and now Melbourne) and New Zealand (Pathology Associates in Tauranga, Hamilton and Rotorua). She has been a College Examiner for Microbiology since 2002 and a Chief Examiner for two years. She is also a NATA assessor (NATA is the equivalent of IANZ).

Sasha is a member of RCPA Microbiology Advisory Committee, Infectious Diseases Society of America, American Soc. Microbiology, European Soc. Clinical Microbiology & Infectious Diseases, British Society of Antimicrobial Chemotherapy, Australian Society of Antimicrobials and JSAC (Joint Special Advisory Committee for joint training program in Infectious diseases and Microbiology).

Special interests for Sasha are antimicrobial resistance and prudent use of antibiotics.

Mike Murphy MD, FRCP, FRCPath, FFPath

Mike Murphy is Professor of Transfusion Medicine at the University of Oxford and is Consultant Haematologist for NHS Blood & Transplant (NHSBT) and the Oxford University Hospitals.

The work done by Mike and his Oxford colleagues using technology to improve the safety and effectiveness of transfusion practice has won numerous national awards and serves as an exemplar for the National Health Service Quality, Innovation and Productivity initiative.

Mike is a recipient of the British Blood Transfusion Society's Kenneth Goldsmith Award, and co-founded the NHSBT Clinical Studies Unit, its Systematic Reviews Initiative for transfusion medicine and the Transfusion Evidence Library (www.transfusionevidencelibrary.com).

Currently, Mike is chairing a guideline on blood transfusion for the National Institute for Health and Clinical Excellence (NICE). He is a Board Member of the American Association of Blood Banks. He has received numerous research grants and is the author of more than 250 articles. He has co-edited all four editions of the textbook Practical Transfusion Medicine.

SCIENTIFIC LETTER

Discordant results from different HbA1c methods: implications of a haemoglobin variant

Shugo Kawamoto

Canterbury Health Laboratories, Christchurch

A 52 year old male patient was found to have an HbA1c of 26 mmol/mol (4.5% NGSP) on the primary method of analysis. Our laboratory uses a High Pressure Liquid Chromatography (HPLC) analyser (Bio Rad Variant), and an abnormal chromatogram was noted suggesting a possible analytical artefact, or a potential haemoglobin variant. HbA1c measured on the same sample using an alternative point-of-care instrument (DCA2000), that uses immunoassay, was measured to be 50 mmol/mol (6.7% NGSP) (Table 1) (1).

This raises key questions regarding the nature of HbA1c measurements:

1. Which HbA1c (if either) is the correct result?
2. What is a haemoglobin variant and how can we investigate this further?
3. If HbA1c was being used for diagnosis what implications does this have?

Table 1. Glucose and HbA1c results by different methods in a patient with HbD (ref. 1).

Glucose (random) (mmol/L)	HbA1c by HPLC [Bio Rad Variant] (mmol/mol)	HbA1c by Immunoassay [DCA 2000] (mmol/mol)
15.0	26	50

Reference range HbA1c = 20-40 mmol/mol.

DISCUSSION

Clearly, there is discordance in results between the two analytical methods and either, or both, could be misleading. As an abnormal chromatogram was detected, it suggests there may be problems with the measurement on the primary analyser (Bio Rad Variant). To determine the true result, HbA1c could be measured using alternative analytical methods; including boronate affinity chromatography, capillary electrophoresis (2), or mass spectrometry (3). However, the first question is which HbA1c most closely matches with the clinical picture? In this patient, the plasma glucose was 15.0 mmol/L, suggesting that the higher HbA1c result (from the point-of-care instrument) was more likely to be the true result. Notwithstanding, the laboratory must find out more about the haemoglobin variant with the involvement of clinicians before we may be certain this is the case.

In 2010, 950 haemoglobin variants were known and novel variants continue to be found (4). An important role of the diagnostic laboratory is to recognise the relatively small number of variant haemoglobins of clinical significance and to distinguish them from the large number of variants that are not clinically significant. Nonetheless, for individual patients the recognition of an unstable or high affinity haemoglobin is an important part of HbA1c analysis as it can lead to misinterpretation of results and inappropriate management that can result in misdiagnosis. HPLC is used as the primary method for HbA1c analysis in many laboratories in New Zealand and an abnormal chromatogram trace does not give specific result of the precise variant, but can elucidate different haemoglobins by means of their physicochemical characteristics, in the context of clinical and family history, ethnic origin, blood count and blood film (4). For this reason it is desirable to always use at least two different laboratory techniques to provide a reasonably reliable identification. Further investigation may include haemoglobin electrophoresis, mass spectrometry studies and DNA analysis (5). This particular patient was found to have a haemoglobin D Punjab (HbD), the replacement of glutamate by glutamine at position β- 121 that increases the molecular charge by one so that any glycated HbD co-elutes with HbAo fraction resulting in abnormal peaks that cause interference in the HPLC method (Bio Rad Variant), falsely reducing the HbA1c result. In contrast, the immunoassay (DCA 2000) for HbA1c uses a monoclonal antibody which recognises the glycated N-terminal valine of the β chain and is unaffected by the substitution at position β-121. HbD is a benign variant ubiquitous in the population of India, especially the Punjab region. Variants alter charges on the haemoglobin molecule and give misleading HbA1c results, both higher and lower than the true level of HbA1c (6).

Traditionally, HbA1c measurements were used to monitor long term glycaemic control in patients with diabetes. However, since 2011, according to the New Zealand Ministry of Health, it has become part of current clinical guidelines to endorse HbA1c as a diagnostic marker with concentrations above 50 mmol/mol consistent with diabetes mellitus (7). If patients have a result at or above this level, and hyperglycaemic symptoms are apparent, it confirms the diagnosis. In the absence of symptoms, a repeat HbA1c of >50 mmol/mol confirms the diagnosis as this maximises the specificity of the criteria. In this patient, the HPLC (Bio Rad Variant) result was within the reference interval, however the true result was actually much higher and closer to the diagnostic threshold. In this case, the diagnosis may have been delayed if the laboratory test was being used for that purpose. As such, inspection of the HPLC chromatogram for abnormal peaks is crucial to identify erroneous HbA1c results due to the potential presence of haemoglobin variants.

It is unknown how common haemoglobin variants are in New Zealand, but it is particularly important to have a heightened awareness for their presence when HbA1c is increasingly becoming used as a diagnostic test. Therefore, it is more important than ever to encourage a greater interaction between clinicians and laboratories to identify clinically, but not biochemically, undetectable variants to achieve a valid estimation of glycaemic control in affected patients.

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AUTHOR INFORMATION

Shugo Kawamoto, BMLSc, Medical Laboratory Scientist

Canterbury Health Laboratories, Christchurch

Correspondence: Shugo.Kawamoto@cdhb.health.nz

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NZIMLS Annual Scientific Meeting 2016 - More International Speakers

Michelle Brererton

Michelle Brereton trained in the UK as a Biomedical Scientist and has more than 10 years experience as a Chief Biomedical Scientist in Laboratory Haematology at Central Manchester (CMFT). The laboratory provides pathology services for several hospitals in the city including one of the largest children's hospitals in Europe. Michelle is responsible for the routine haematology and Morphology reporting for all areas including the specialist haemato-oncology, transplant and haemoglobinopathy units.

With a keen interest in leukaemia and morphology Michelle completed her MSc on haemopoiesis and cell culture in chronic myeloid leukaemia in 1995. She is a member of the haematology scientific advisory panel for the Institute of Biomedical Science (IBMS) in the UK and responsible for presenting the morphology session at the national bi-annual IBMS meeting for the laboratory professionals. Michelle is a specialist advisor for the UK National External Quality Assurance Scheme for blood cell morphology and had a key role in the development and implementation, in 2008, of the UK national scheme for Digital Morphology for continuing professional development (CPD). This scheme has more than 1000 participants for each morphology case. Michelle has also worked with both the National Pathology Harmony group and the International Council for Standards in Haematology (ICSH) on units of measurement and standards in reporting for the blood count.

Assoc Professor Erica Wood

A/Prof Erica Wood is vice-president of the International Society of Blood Transfusion (ISBT), and a member of the ISBT working parties on haemovigilance, clinical practice and transfusion-transmitted infectious diseases. Erica is president of the International Haemovigilance Network, past-president of the Australian and New Zealand Society of Blood Transfusion, and a member of the WHO Expert Advisory Panel in Transfusion Medicine.

Erica is head of the Transfusion Research Unit in the Department of Epidemiology and Preventive Medicine at Monash University in Melbourne, Australia. She is a consultant haematologist at Monash Health and holds an honorary appointment at the Peter MacCallum Cancer Centre.

Erica has served as Chief Examiner (Haematology) for the Royal College of Pathologists of Australasia and chair of the Joint Specialist Advisory Committee in Haematology.

Erica is a founding member of the Victorian Blood Matters program advisory committee and member of the expert group of its Serious Transfusion Incident Reporting (STIR) regional haemovigilance programme.

THE Pacific WAY

GREETINGS TO YOU ALL

Health and safety and infectious disease 2016

A Health and Safety course was provided by the PPTC in April of this year at its centre in Wellington, and the following students attended: Rhomson Nuake from the Solomons and Tagi Sapini from Samoa. The course was divided into two sections, the content of which is described below:

a) Health and Safety Component

Implementation of a laboratory health and safety programme, hazard Identification, risk assessment, laboratory premises and design, biohazard waste and disposal of contaminated material; personal protection; code of conduct; staff health and medical surveillance; administrative procedures; chemical and dangerous goods storage; material data safety sheets; major incident response; laboratory emergency planning; and laboratory biosecurity concepts.

b) Infectious diseases component

Notifiable diseases; role of Public Health; Surveillance and monitoring disease outbreak; workforce occupational exposure; communicable diseases; what makes an epidemic; vaccines now available; bacterial causes of infectious diseases: isolation procedures to identify and confirm major bacterial pathogens associated with gastrointestinal infections; seafood poisoning and marine environments; food and water contaminating organisms; bacterial agents of pneumonia, septicaemia and meningitis; agents of sexually transmitted infections. Viral causes of infectious diseases: a selective summary of disease specific viruses such as gastrointestinal viruses; respiratory viruses; parasites of infectious disease and mycology review.

PPTC staff and students
Health and Safety and Infectious Disease

Laboratory quality management 2016

Two students attended this course: Rhomson Nuake from the Solomons and Sandra Semi - Time from Samoa.

Over the duration of four weeks, a comprehensive theoretical component and a series of practical workshops were provided to students attending the course. The content of the course included such topics as: overview of LQMS and associated guidelines; laboratory manager and quality manager roles; setting policies, aims and objectives; developing a quality statement; devising a quality plan; quality performance indicators; the organisational responsibility. A workshop practical based on organisation charts, role documents, title page, document formats, and set up numbers etc. was provided. Quality manual, structure and contents; contents of personnel, health & safety manuals; standard operating procedures (SOP); documentation control and preparation; out takes, copies, draft SOP's, obsolete documents, worksheet versions; record keeping; report presentation; archives. worksheet practical in SOP creation, policy creation, and staff training logs; Specimen management manual contents; Personnel (staff records); CPD training logs; induction records; monitoring and evaluation; job descriptions; orientation; skill listing; structure of departmental manuals; health & safety SOP's; incident and accident reporting complaints; compliments and surveys; quality improvement projects; IATA transport requirements; procurement management; inventory; specimen management and collection. Group discussions in all of the above processes were carried out in terms of the document required. Auditing and review processes for LQMS and agenda for management review meetings were also discussed.

PPTC staff and students
Laboratory Quality Management

Centre based courses for the remainder of 2016:

- Biochemistry
  18 July – 12 August 2016
- Haematology and Blood Cell Morphology
  15 August – 3 September 2016
- Microbiology
  5 September – 30 September 2016
- Becoming an Effective Laboratory Manager:
  3 October – 28 October 2016
- Blood Transfusion Science
  31 October – 25 November 2016

For Further information on any of the above courses contact:
Navin Karan:
Telephone (64) (4) 389 6294
E-mail: pptc@pptc.org.nz or navink@pptc.org.nz

Welcome to the PPTC's biochemistry technical specialist

Filipo Faiga, *BSc, Dip MLSc, MNZIMLS, RNZMLS*

It is with great pleasure that we welcome Filipo Faiga as a permanent staff member and biochemistry technical specialist to the PPTC.

Filipo began his professional career in 1987 as a senior laboratory technician in biochemistry at the Samoan National Hospital in Apia. Between 1989 and 1991 Filipo was employed by Wellington Hospital as a medical laboratory intern and in 1992 registered as a NZ medical laboratory scientist. He has accumulated more than 20 years of experience in biochemistry and has a comprehensive understanding of all processes involved, including laboratory quality management systems, IANZ standards ISO15189, and quality assessment and evaluation.

He has also held supervisory and management positions in biochemistry for many years, and has been extensively involved in teaching, coaching coordinating and managing staff and students. Over the years Filipo has been involved with the PPTC through the teaching of clinical biochemistry to Pacific students attending courses at its Centre in Wellington, through the biochemistry PPTC REQA programme, through in-country training during consultancy visits, and more recently through the PPTC's distance learning Diploma programme.

Filipo has a passion to contribute towards the development and improvement of laboratory quality standards within the Pacific region and the PPTC is most fortunate to have him as its biochemistry technical specialist.

Overseas travel

March 2016

Russell Cole, the PPTC's laboratory quality manager travelled to Vanuatu to deliver a two week training workshop in microbiology and Navin Karan, the PPTC's programme manager visited the Solomons for two weeks to also teach and train the laboratory staff in microbiology.

April 2016

Navin visited Port Vila, Vanuatu to assess the laboratory's progress in quality management and Filipo Faiga the PPTC's biochemistry specialist later in the month visited Samoa to provide biochemistry training to the laboratory staff in Apia.

May 2016

Russell visited the Solomons to implement further training in quality management and Filipo later in the month re-visited Vanuatu to continue quality management implementation. Navin also visited Vanuatu to assess TB diagnostic processes within the region and to provide technical support to Vanuatu in its establishment of a service in Santo for the testing of tuberculosis. He is currently involved in the purchase of equipment, staff training and the evaluation of the entire service in association with the Immigration NZ Health Team.

June 2016

Yvonne Bird, one of the PPTC's newer consultants, visited Tonga to assess progress in quality management implementation, and Navin visited the Solomons providing technical support in the commissioning of a new dengue fever laboratory as well as facilitating its ongoing function. Filipo has returned to Samoa for two weeks in order to provide training for the newly installed Cobas e411 analyser provided by the PPTC as its contribution towards service development.

Welcome to Marion Clarke, the PPTC's newly appointed Board Member

Marion has extensive governance, management, and public policy experience, in New Zealand and Australia and has worked effectively with a range of stakeholders to achieve effective and workable solutions to identified issues. She has worked in senior public policy roles in Department/Ministry of Health, Ministry of Foreign Affairs and Trade, New Zealand; Australian Health Ministers Council and Queensland Health in Australia and with health officials in the Pacific and South East Asia. She is an experienced leader with excellent relationship management and communication skills. The PPTC is most fortunate to have Marion as a member of its Board of Governance.

To contact the PPTC:
Phone: +64 4 389 6294
Email: pptc@pptc.org.nz
Post: PO Box 7013
Wellington 6242
New Zealand

Fellowship of the NZIMLS

The NZIMLS encourages members to consider Fellowship as an option for advancing their knowledge and career prospects. Fellowship provides an attractive option to academic postgraduate qualifications at a fraction of the cost.

Recently, changes to the regulations have been made, the main one doing away with the examination route to Fellowship.

Fellowship of the NZIMLS may be gained by thesis, by peer reviewed publications; or by treatise in case of a member holding an appropriate postgraduate or professional qualification.

Fellows may use the nominals FNZIMLS if a current financial member of the Institute.

Thesis
The thesis must be based on the style of Master of Science by thesis requirement of New Zealand universities.

Publications
A minimum of ten peer reviewed publications in international or discipline acknowledged biomedical journals. The candidate must be the 1st or senior author of at least six of these publications. A comprehensive review of the submitted publications is also required.

Treatise
By submission of a treatise in the form of a dissertation of 3000 - 5000 words on a medical laboratory science subject. The dissertation may take the form of a review, a scientific study, development of a hypothesis, or any other presentation that meets with the approval of the Fellowship Committee.

Candidates going for Fellowship by this route must be holders of at least a Master's degree in medical laboratory science or a closely related subject; or have a professional qualification such as Fellowship of the following professional bodies: the Australian Institute of Medical Science (FAIMS); the Institute of Biomedical Science (FIBMS); the Faculty of Science of the RCPA, the Australian Association of Clinical Biochemists (FAACB), or the Royal Institute of Biology, London (FRSB).

For full Fellowship regulations and the application process visit the NZIMLS website at www.nzimls.org.nz

Congratulations to Emil Wasef from Southern Community Laboratories, Dunedin for being awarded Fellowship for his Treatise "*Is it time for ristocetin to step down? Comparison study between the new automated von Willebrand factor activity and the von Willebrand factor ristocetin activity assays*", published in this issue of the Journal.

Current Financial Fellows

Jenny Bennett
Jillian Broadbent
Jennifer Castle
Marilyn Eales (also Life Member)
Christine Hickton
Michael Legge (also Life Member)
Ron Mackenzie (also Life Member)
Maxine Reed
Robert Siebers (also Life Member)
Vanessa Thomson
Emil Wasef
Rubee Yee
Mark Bevan
Ailsa Bunker
Jan Deroles-Main
Susan Evans
Sheryl Khull
Christine Leaver
Howard Potter
Mohammad Shahid
Andrew Stewart
Vasanthan Thuraisamy
Jacqueline Wright
Sheryl Young

Barrie Edwards & Rod Kennedy Scholarship


Barrie Edwards


Rod Kennedy

The Barrie Edwards & Rod Kennedy scholarship is one of the most significant awards offered by the NZIMLS. The scholarship provides the winner with support to attend an international or national scientific meeting up to a maximum value of $7,500.

Application for this prestigious scholarship is invited from Fellows, Members and Associate Members of the NZIMLS. Applicants must be a current financial member of the NZIMLS and have been a financial member for at least two concurrent years prior to application. To be eligible applicants must make an oral presentation or present a poster as 1st author at their nominated scientific meeting.

All applications will be considered by a panel consisting of the President and Vice -President of the NZIMLS and the Editor of the New Zealand Journal of Medical Laboratory Science (who are ineligible to apply for the scholarships). The applications will be judged on your professional and academic abilities together with your participation in the profession. The panel's decision is final and no correspondence will be entered into.

Application is by letter. Please address all correspondence to:
NZIMLS Executive Officer
PO Box 505
Rangiora 7440

There is one scholarship awarded in each calendar year. Closing date is December 20th in any given year.

In your application letter please provide the following details:

- Full name, position, work address, email address and contact phone number
- The length of time you have been a financial member of the NZIMLS
- The conference you wish to attend – please provide dates
- A budget comprising airfares, conference registration and accommodation costs
- The abstract of your intended oral or poster presentation and whether it has been accepted for presentation (proof required)
- Your intentions to publish your results
- State briefly your history of participation in the profession over the last 5 years
- State the reasons why you wish to attend your nominated scientific meeting

Successful applicants will be required to provide a full written report on return which will be published in the Journal. If not intended to publish elsewhere, successful applicants will be required to submit their study results for consideration by the New Zealand Journal of Medical Laboratory Science .

2016 NICE Weekend

The 27th National Immunohaematology Continuing Education (NICE) weekend was held over the 14th and 15th of May at the Bayview Wairakei Resort in Taupo. Over the weekend we were treated to 49 distinctive and stimulating presentations. This year the presentations varied in topics, ranging from clinical, blood banking right through to tissue typing. Also on show over the weekend were 10 conversation motivating poster presentations, four more than last year. All presenters and poster writers put extraordinary effort into preparation and displaying of their posters and presentations.

Congratulations to all those attendees who took away awards for their presentations/posters.

The Abbot Award for best overall presenter went to Liz Thrift (NZBS Palmerston North) – *Transfusion Information for Patients with Intellectual Disabilities*.

The Ortho Clinical Diagnostics Award for most promising transfusion scientist went to Sunny Jumati (NZBS Waikato) - *Platelets made HLA deficient by acid treatment aggregate normally and escape destruction by complement and phagocytes in the presence of HLA antibodies.*

The Pharmaco Award for best poster went to Maria Alyssa Alega (NZBS Auckland) - *A Case of Allo anti-Jka in an AIHA Patient*.

The CSL Biotherapies award for a New Zealand attendee to attend NICE Australia was this year won by Liz Thrift (NZBS Palmerston North) – *Transfusion Information for Patients with Intellectual Disabilities.*

The award sponsored by BioRad for the best first time speaker is for a presenter who has never attended NICE weekend before, giving them the title of NICEst Virgin. This went to the joint speakers Rebecca Lopes and Ayesha Iqbal (NZBS Auckland) – *Deceased Donor Testing and Crossmatching Overview.*

The statistics: NICE 2016 was attended by 81 people in total including 21 trade representatives, one sponsored convenor, one sponsored student, 61 delegates including one participating TMS and one Australian visitor. Of these, 57 were NZIMLS members and 25 were non-NZIMLS members.

The theme for this year's NICE weekend was Under the Sea – all attendees dressed in astounding and imaginative costumes. This year provided an evening of fun for all which again included the annual parade.

A big thank you to the judges who had a difficult role as this year was even more challenging than the last to pick the winners.

A huge thank you on behalf of all must be extended to our astonishing and delightful NICE Convenors – Raewyn Cameron and Natalie Fletcher. They yet again delivered another outstanding educational weekend, so on behalf of the TSSIG and the wider NICE group I would like to extend a huge Thank You. We look forward to NICE 2017, where the theme is Fame/ Infamy.

Aous Al-Ibousi. TSSIG Committee member.

Left to right. Ayesha Iqbal, Rebecca Lopes, Liz Thrift, Alyssa Alegra, Sunny Jumati and Rahul Pala.

NZIMLS ASM 2016
"Working Together"
Plenary Sessions Programme

Wednesday 17 August	
0900 – 1230	**Opening Plenaries**
	Welcome **NZIMLS Award Presentations** *Ross Hewett, President, NZIMLS* **TH Pullar Address** *Russell Cole, PPTC, Wellington* **Opening Scientific Presentation** **RA – Changes, Progress and the Role of the Laboratory** *Dr John Petrie, Rheumatologist, Rotorua* **ESR Surveillance** *Dr Virginia Hope, Health Programme Leader, ESR, Wellington* **Synthetic Anatomy** *Hamish McIntosh, Industrial Designer* and *Victoria University of Wellington*
Thursday 18 August 2016	
0900 – 1030	**Plenary Session**
	Error Prevention in Airline Operations *Arthur Gatland, Air New Zealand, Airline Instructor & Flight Examiner, B787 / B777* **Taking the Lab for Granted** *Dr Johan Morreau, Paediatrician, Lakes DHB, Rotorua*
Friday 19 August 2016	
1100	**Final Plenary and closing**
	Working Together for the Future **Clinical registries: expanding opportunities in transfusion and haematology research** *Associate Professor Erica Wood, Monash University, Melbourne, Australia* **Building a better blood service for New Zealand** *Dr Peter Flanagan, National Medical Director, New Zealand Blood Service, Auckland* **Title to be advised** *Dr Richard Massey, Anatomical Pathologist, Pathlab Bay of Plenty, Tauranga*

Immunology SIG Seminar

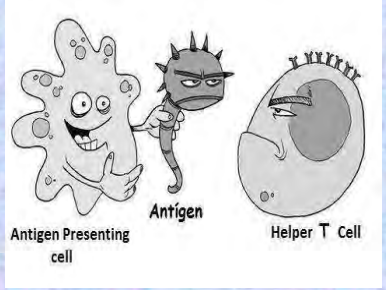
24 September 2016

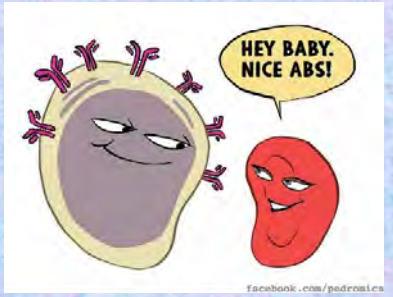
Waipuna Conference Suites, Highbrook

Contact Lisa Aspin: lisa.aspin@labtests.co.nz

Presentations welcome!

Register at www.nzimls.org.nz





NZIMLS

PRE-ANALYTICAL

Special Interest Group

including

Phlebotomy
Donor Services
Specimen Services

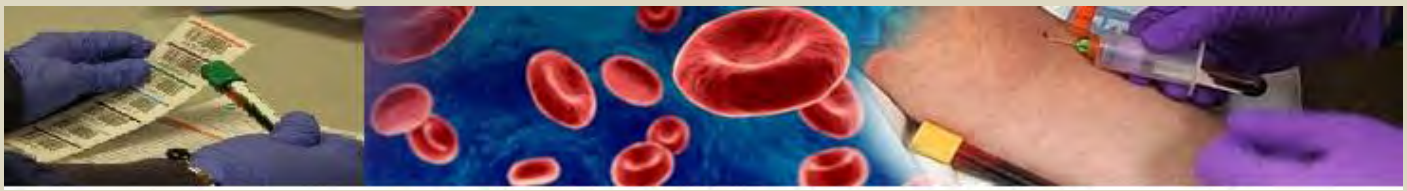
Annual Seminar

SATURDAY 1st OCTOBER

WAIPUNA Hotel & Conference Centre

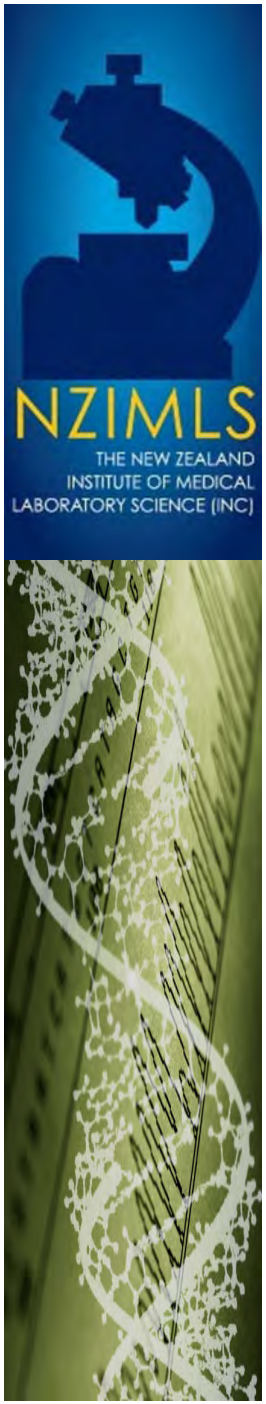
Mt Wellington, Auckland. www.waipunahotel.co.nz

- **REGISTRATION, MEET & GREET, COFFEE 9:00am**
- **SESSIONS START AT 09:50am**
- **FINISH AT 16:3Opm**



CONTACT: NZIMLS PA SIG CONVENORS:
Phlebotomy: Annette Bissett: annette.bissett@waitematadhb.govt.nz
Specimen Services: Lisa Bloore: lisa.bloore@waitematadhb.govt.nz

Online registrations available http://www.nzimls.org.nz/



Molecular Diagnostics SIG Meeting 2016

The NZIMLS Special Interest Group in Molecular Diagnostics
Returns to Auckland on

Friday 7th October, 2016,

At the Ernest & Marion Davis Lecture Theatre,
Auckland City Hospital, Grafton, Auckland.

For the first time the SIG will be held on a Friday, leaving Saturday free for shopping in Auckland!

This could be an opportunity to tie in a visit to the LabPLUS laboratories, and see Molecular Diagnostics in action!

Presentations (oral and poster) are invited for the following disciplines:
Molecular Genetics, Biochemical Genetics,
Molecular Virology, Microbiology, Molecular Haematology and Cytogenetics

Closing Date for Abstracts: Friday 19th August 2016

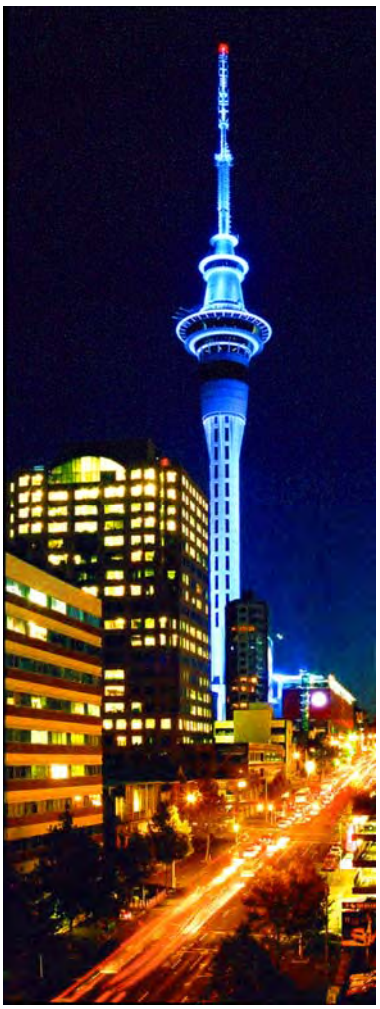
For further information, please contact either:
Roberto Mazzaschi (Genetics) RobertoM@adhb.govt.nz
Indira Basu (Microbiology) IndiraB@adhb.govt.nz
or Fahimeh Rahnama (Virology) FahimehM@adhb.govt.nz

Registration is only available online at www.nzimls.org.nz

Haematology SIG

Waipuna Hotel and Conference Centre

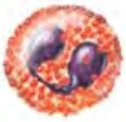
18th October 2016



Presentations welcome

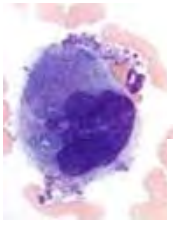
Come and learn something

Meet some old friends



Make some new friends

Check out **www.nzimls.org.nz** for details



Email Christine Algie
calgie@adhb.govt.nz

NZIMLS
THE NEW ZEALAND INSTITUTE OF MEDICAL LABORATORY SCIENCE (INC)

Biochemistry SIG

Ibis Tainui Hotel, Hamilton

Saturday 29th October 2016

Presentations welcome!

We look forward to seeing you in the mighty Waikato!

For further information and to register interest for presentations, please contact:

kate.mclaughlin@pathlab.co.nz

Registration available at www.nzimls.org.nz (From August 2016)

NZIMLS
THE NEW ZEALAND INSTITUTE OF MEDICAL LABORATORY SCIENCE (INC)

HISTOLOGY SIG SEMINAR

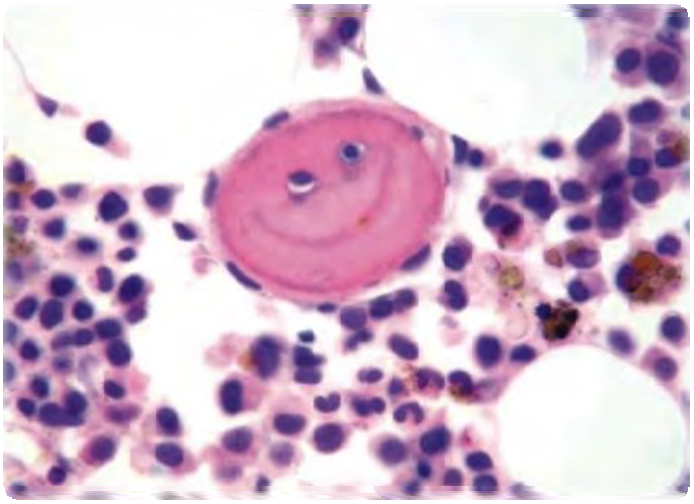
HOSTED BY ANATOMIC PATHOLOGY SERVICE (ADHB)

WHEN: Saturday, 29 October 2016

WHERE: Waipuna Conference Centre Auckland

TIME: 9:00am

Please send all presentations to
pcoles@adhb.govt.nz or gpereira@govt.nz



MORTUARY SIG PRESENTS

2016 SEMINAR

WHANGAREI

WHERE THE SURF MEETS THE TURF

Saturday 12 November

Whangarei Hospital
NDHB 2nd Floor Conference Room

This year featuring a number of interesting and informative presentations by our own Technicians

Supported by local Specialists

Visit the latest refurbished Mortuary in New Zealand

Enjoy beautiful and very friendly Northland

Other SIG members are welcome to register and attend

Book accommodation early!

Any further information you require please contact

Clive Matthews clive.matthews@northlanddhb.org.nz

Registration only available at www.nzimls.org.nz

Journal Questionnaire

Below are 10 questions based on articles from the August 2016 issue. Read the articles carefully as most questions require more than one answer.

Answers are to be submitted through the NZIMLS web site. Make sure you supply your correct email address and membership number. It is recommended that you write your answers in a word document and then cut and paste your answers on the web site.

The site has been developed for use with Microsoft's Internet Explorer web browser. If you are having problems submitting your questionnaire and you are using the Firefox web browser, try resubmitting using Microsoft's Internet Explorer.

You are reminded that to claim valid CPD points for successfully completing the journal questionnaire you must submit an individual entry. It must not be part of a consultative or group process. In addition, members who have successfully completed the journal questionnaire cannot then claim additional CPD points for reading the articles from which the questions were derived.

The site will remain open until Friday 14 October 2016. You must get a minimum of eight questions right to obtain five CPD points.

The Editor set the questions but the CPD Coordinator, Jillian Broadbent, marks the answers. Please direct any queries to her at cpd@nzimls.org.nz.

AUGUST 2016 JOURNAL QUESTIONNARE

1. Name two (out of three) potential implications the medical laboratory should consider while implementing improvements and updates to the laboratory's quality management system.
2. To determine a true HbA1c result which alternative analytical methods can be used?
3. Name the less common sites of metastases of thyroid carcinoma.
4. What is a good marker in the confirmation of the pathological diagnosis of differentiated thyroid cancer metastasis?
5. What is associated with fewer cancer recurrences and tumour related deaths from metastatic thyroid papillary carcinoma to the breast?
6. von Willebrand disease is a heterogeneous bleeding disorder arising from what?
7. How is von Willebrand disease inherited and what type of mutations can occur in the von Willebrand factor gene?
8. Name the limitations and laboratory problems for the von Willebrand factor ristocetin cofactor assay.
9. What type of assay is the von Willebrand factor collagen binding assay and what does it measure?
10. The Innovance von Willebrand factor activity (vWF:Ac) assay can theoretically be compromised by which analytical factors?

APRIL 2016 JOURNAL QUESTIONNAIRE ANSWERS

1. Oxidative damage to sperm is handled by which reactive oxygen species?

   Hydroxyl radical, superoxide ion, and hydrogen peroxide.

2. Which antioxidant enzymes surround the human sperm?

   Superoxide dismutase, glutathione peroxidase, and catalase.

3. Name three antioxidants that have been shown to be reduced by cryopreservation of human semen.

   L-cartinine, glutathione, and superoxide dismutase.

4. Sperm cryopreservation-thawing leads to alterations in which two mechanisms that enhance the generation of reactive oxygen species?

   NADPH oxidase in the plasma membrane, and the electron transport chain of the mitochondria.

5. What is the main conclusion of the semen cryopreservation study?

   Cryopreservation of human semen reduces the effectiveness of the antioxidant defense mechanism surrounding the sperm.

6. Multiple myeloma is a malignant disorder characterized by what, what do they produce, and where are they derived from?

   Proliferation of a single clone of plasma cells. Monoclonal protein. B cells in the bone marrow.

7. Multiple myeloma of the IgD isotype is often accompanied by which clinical features?

   Hepatomegaly, lymphadenopathy, extraosseous lesions, renal failure, and amyloidosis.

8. What is the most common neurological complication of multiple myeloma, and what is its reported incidence?

   Spinal cord compression. 11-24% of patients.

9. IgD multiple myeloma is characterized by what biochemical features?

   Small or absent M-protein band in electrophoresis, a Lambda light chain bias, and Bence-Jones proteinuria.

10. Laboratory analysis of IgD multiple myeloma cases by serum protein electrophoresis typically demonstrate which features?

    Minimally detectable M-protien spike, often in the beta, gamma, or beta-gamma region.

2016 NZIMLS CALENDAR *Dates may be subject to change*		
DATE	***SEMINARS***	***CONTACT***
24 September 2016	Immunology SIG Seminar	Lisa.aspin@labtests.co.nz
01 October 2016	PreAnalytical SIG Seminar, Auckland	Annette.bissett@waitematadhb.govt.nz
07 October 2016	Molecular Diagnostics SIG Seminar	robertom@adhb.govt.nz
15 October 2016	Haematology SIG Seminar	calgie@adhb.govt.nz
29 October 2016	Histology SIG Seminar	pcoles@adhb.govt.nz
12 November 2016	Mortuary SIG Seminar	Bill.little@southerndhb.govt.nz Clive.matthews@northlanddhb.org.nz
DATE	***NZIMLS EXAMINATIONS***	***CONTACT***
07 November	QMLT Examinations	fran@nzimls.org.nz
DATE	***COUNCIL***	***CONTACT***
14&15 August	Council Meeting, Rotorua	fran@nzimls.org.nz
18 August	Annual General Meeting, Rotorua	fran@nzimls.org.nz
November 2016	Council Meeting	fran@nzimls.org.nz
DATE	***EVENTS***	***CONTACT***
16-19 August	Annual Scientific Meeting, Rotorua	raewyn.cameron@lsr.net.nz joanne.hartigan@lsr.net.nz fran@nzimls.org.nz
DATE	***MEMBERSHIP INFORMATION***	***CONTACT***
January	Membership and CPD enrolment due for renewal by 28 February 2017	sharon@nzimls.org.nz
January	CPD points for 2016 to be entered before 31 January 2017	cpd@nzimls.org.nz
15 February	Material for the April issue of the Journal must be with the Editor	rob.siebers@otago.ac.nz
17 June	Nomination forms for election of Officers and Remits to be with the Membership (60 days prior to AGM)	fran@nzimls.org.nz
15 June	Material for the August Journal must be with the Editor	rob.siebers@otago.ac.nz
7 July	Nominations close for election of officers (40 days prior to AGM)	fran@nzimls.org.nz
27 July	Ballot papers to be with the membership (21 days prior to AGM)	fran@nzimls.org.nz
3 August	Annual Reports and Balance Sheet to be with the membership (14 days prior to AGM)	sharon@nzimls.org.nz
10 August	Ballot papers and proxies to be with the Executive Officer (7 days prior to AGM)	fran@nzimls.org.nz
15 September	Material for the November Journal must be with the Editor	rob.siebers@otago.ac.nz

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Presenting the 11th Biennial

Sysmex User Group Conference

Millennium Hotel
Queenstown, New Zealand
6th - 7th October 2016

Join us in Queenstown as we cover future development and innovations in health IT: laboratory, pathology and clinical

- Registration is free of charge and includes the conference dinner
- Earn NZIMLS CPD points
- Accommodation has been reserved for conference delegates at the Millennium Hotel, Queenstown

PROGRAMME CONTENT

Guest speakers, customer case studies and product experts

Delphic LIS Workshop

Delphic AP Workshop

Eclair Workshop

To register or for more information, including programme details, go to www.sysmex.co.nz/services/2016UserGroup