

Quality Saves Your Life

# LMCE 2016 & KSLM

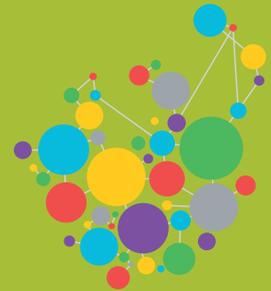
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57<sup>th</sup> ANNUAL  
MEETING

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October 26-28, 2016  
The-K Hotel, Seoul, Korea

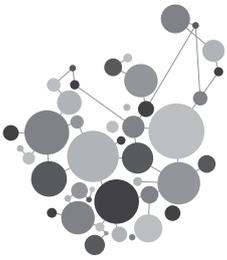
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## ABSTRACTS

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- Plenary Lectures
- Keynote Speeches
- Symposia



# PLENARY LECTURE

PL01

## Liver biomarkers and clinical implications

Hyon-Suk Kim

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### Liver diseases

The liver is a vital organ and supports almost every other organ in the body. The liver has a wide range of functions, including detoxification of various metabolites, protein synthesis, and the production of biochemicals necessary for digestion. Because of its multidimensional functions, the liver is also prone to many diseases.

Hepatitis is a common condition of inflammation of the liver. The most usual cause of this is viral, and the most common of these infections are hepatitis A, B, C, D, and E. Infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) is the main cause of liver cancer. Inflammation can also be caused by other viruses in the Herpesviridae family such as the *Herpes simplex virus*.

Other disorders caused by excessive alcohol consumption are grouped under alcoholic liver diseases and these include alcoholic hepatitis, fatty liver, and cirrhosis. Liver damage can also be caused by drugs, particularly paracetamol and drugs used to treat cancer.

Primary biliary cirrhosis is an autoimmune disease of the liver. It is marked by slow progressive destruction of the small bile ducts of the liver, with the intralobular ducts affected early in the disease. When these ducts are damaged, bile and other toxins build up in the liver (cholestasis) and damages the liver tissue in combination with ongoing immune related damage over time. This can lead to scarring (fibrosis) and cirrhosis.

Many diseases of the liver are accompanied by jaundice caused by increased levels of bilirubin in the system. The bilirubin results from the breakup of the hemoglobin of dead red blood cells; normally, the liver removes bilirubin from the blood and excretes it through bile.

There are also many other liver diseases, including biliary atresia, alpha-1 antitrypsin deficiency, etc. Diseases that interfere with liver function will lead to derangement of these processes. However, the liver has a great capacity to regenerate and has a large reserve capacity. In most cases, the liver only produces symptoms after extensive damage.

Liver diseases may be diagnosed by liver function tests, blood tests that can identify various markers. For example, acute-phase reactants are produced by the liver in response to injury or inflammation. If infection is suspected, then other serological tests will be carried out. Sometimes, an ultrasound or a CT scan is needed to produce an image of the liver.

A bio-artificial liver device intended for the treatment of liver failure using stem cells is developed. The artificial liver is designed to serve as a supportive device, either allowing the liver to regenerate upon failure, or to bridge the patient's liver functions until transplant is available. It is only made possible by the fact that it uses real liver cells (hepatocytes), and even then, it is not a permanent substitute.

Researchers from Japan found that a mixture of human liver precursor cells (differentiated from human induced pluripotent stem cells [iPSCs]) and two other cell types can spontaneously form three-dimensional structures dubbed "liver buds".

Liver transplantation is the only option for those with irreversible liver failure. Most transplants are done for chronic liver diseases leading to cirrhosis, such as chronic hepatitis C, alcoholism, autoimmune

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hepatitis, and many others. Less commonly, liver transplantation is done for fulminant hepatic failure, in which liver failure occurs over days to weeks.

Liver allografts for transplant usually come from donors who have died from fatal brain injury. Living donor liver transplantation is a technique in which a portion of a living person's liver is removed and used to replace the entire liver of the recipient. This was first performed in 1989 for pediatric liver transplantation. Only 20 percent of an adult's liver is needed to serve as a liver allograft for an infant or small child. With the recent advances of noninvasive imaging, living liver donors usually have to undergo imaging examinations for liver anatomy to decide if the anatomy is feasible for donation. The evaluation is usually performed by multidetector row computed tomography (MDCT) and magnetic resonance imaging (MRI). MDCT is good in vascular anatomy and volumetry. MRI is used for biliary tree anatomy.

The liver is the only human internal organ capable of natural regeneration of lost tissue; as little as 25% of a liver can regenerate into a whole liver. However, this is not true regeneration but rather compensatory growth in mammals. The lobes that are removed do not regrow and the growth of the liver is a restoration of function, not original form.

## Liver Biomarkers

### Liver Biomarkers for development of new therapeutics

Liver biomarkers are of increasing importance in the development of new therapeutics for treatment and prevention of a broad range of diseases to avoid hepatotoxicity. Just recently vitamin D-binding protein (Gc globulin) and liver fatty acid binding protein (L-FABP), have been identified as biomarkers of liver toxicity and injury. In the past limitations of existing biomarkers to detect liver injury in experimental animals highlight the need for new liver biomarkers to predict human liver toxicity.

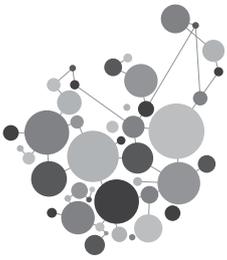
### New Biomarker for Predicting Liver Cancer Spread and Survival

New studies found that a unique pattern of microRNAs, small RNA molecules which regulate gene activity, might predict whether liver cancer will spread and whether liver cancer patients will have shorter or longer survival.

### Liver Biomarkers as noninvasive Tests for Liver Fibrosis and cancer

Non-invasive biomarkers of liver fibrosis are not only interesting in liver transplant patients to avoid liver biopsy or for haemophilia patients but for HCV-infected haemophilia patients. Recently a study has shown that a liver biomarker could correctly identified clinically advanced or minimal liver disease. Liver biopsy, due to its risks and limitations, is an imperfect gold standard for assessing the severity of the most frequent chronic liver diseases, chronic hepatitis C, chronic hepatitis B or non-alcoholic fatty liver diseases (NAFLD) and alcoholic fatty liver diseases (ALD).

The data from studies suggests that biomarkers might be used in some cases as an alternative to liver biopsy for the assessment of fibrosis stage in the four most common chronic liver diseases, namely chronic hepatitis C, chronic hepatitis B, non-alcoholic fatty liver diseases (NAFLD) and alcoholic fatty liver diseases (ALD). However neither biomarkers nor biopsy alone is sufficient for definitive liver diagnostic method; all the biological and clinical data should be taken into account. Other new approaches using the existing parameters, such as hyaluronic acid, alpha 2 macroglobulin and bile acids in serum or EDTA plasma, are tried and developed for diagnosis and monitoring of liver fibrosis and cirrhosis.



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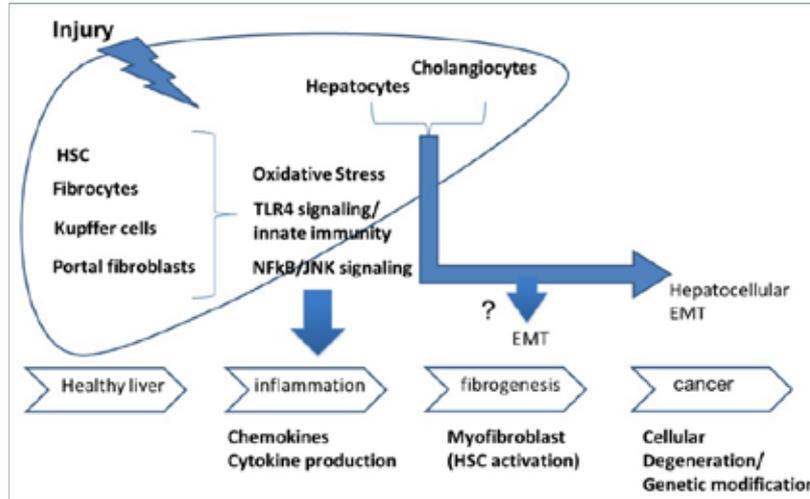


Figure 1. Fibrogenetic/hepatocarcinogenetic mechanisms in the liver. *From Translational Gastrointestinal Cancer 2012;1(1):88-94.*

Fibrotic injury distorts the normal liver architecture and can result in organ dysfunction and hypertension. Liver Fibrosis can progress silently and lead to cirrhosis and also hepatocellular carcinoma (HCC). Stage diagnosis is essential for optimal treatment decisions and serum hyaluronic acid (HA) measurement can assist in diagnosis and monitoring of liver fibrosis and cirrhosis. Serum levels of HA are typically low in healthy individuals as circulating HA is rapidly removed from the blood by sinusoidal endothelial cells (SECs) in the liver. Serum HA correlates with liver pathology, particularly in cirrhosis, where there is a reduction in HA receptors resulting in an increase in circulating HA.

Alpha 2 Macroglobulin is a glycoprotein used as a marker of membrane permeability and is a plasma proteinase inhibitor. Increases in alpha-2 macroglobulin may be observed in various pathological conditions. Decreased levels may be found during inflammatory processes. Alpha-2 Macroglobulin is one of the parameters included in the hepascore algorithm to assess liver fibrosis.

Bile acids are produced in the liver by cytochrome P450-mediated oxidation of cholesterol which are conjugate to form bile salts and stored in the gall bladder. Upon eating a meal the gall bladder secretes bile into the intestine where it serves to emulsify dietary fats. The bile acids form micelles with lipids and fat-soluble vitamins that can be absorbed via the villi of the small intestine. Bile acid production is a key route of cholesterol elimination, stimulates the flow of bile which eliminates catabolites from the liver and reduces the bacteria flora found in the small intestine and biliary tract. Bile Acids ready-to-use liquid reagents can be used to measure Bile Acids in serum or EDTA plasma. This colorimetric, kinetic assay is based on enzymatic recycling and has a measuring range of 1-180 µmol/L. 3-alpha-hydroxysteroid dehydrogenase (3-alpha-HSD) oxidizes bile acids to 3-keto steroids, whereby Thio-NAD is reduced to Thio-NADH. The reaction is reversible, and the same enzyme can convert 3-keto steroids and NADH to bile acids and NAD (recycling of bile acids). The rate of formation for Thio-NADH is determined by measuring the change of absorbance at 405nm.

## Clinical adoption of New Liver Biomarkers

Serologic markers, any marker alone or in combination of several markers are actively introduced in clinical laboratory. Actually various hepatitis markers and tumor markers are already adopted and used in clinical laboratories.

We will review and discuss several clinical cases in this lecture.



# PLENARY LECTURE

PL02

## Pediatric clinical chemistry: things that make it different

Patricia Jones

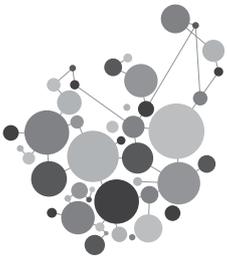
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The basic metabolic processes which occur during the course of normal growth and development of an individual are significantly more dynamic in infancy and childhood than in adulthood. Metabolism in general is more active and frequently more volatile in pediatric patients, and the basic processes themselves are often very different from those of adults. Because of these changing body chemistries in the pediatric population, concentrations of measurable biomarkers change as the individual progresses from birth through childhood and adolescence and into adulthood. Thus pediatric laboratory medicine involves the measurement of an array of biomarkers which often exceeds that measured in adults. The biomarkers include all those metabolites associated with normal growth and development, as well as the wide variety that are used to diagnose and monitor the range of disease states seen in pediatrics. Additionally disease states in pediatrics often are different from those seen in adults, requiring the pediatric lab to offer testing for sometimes esoteric disorders. Included in this group are the inborn errors of metabolism, as well as disorders related to abnormal development.

The broad spectrum of different testing which is essential in a pediatric laboratory thus often requires the utilization of technologies that may not be routinely found in laboratories serving predominately adult patients. Various types of mass spectrometry are often routine instruments in pediatric labs. Additionally some testing, such as sweat chloride testing for cystic fibrosis, is essentially never found in adult laboratories. Paradigms for testing and handling samples may be diverse in order to deal with the various issues related to pediatric patients, like specialized testing and/or dealing with small sample volumes. Another major difference between pediatric and adult laboratories is the necessary use of pediatric reference intervals when test results are reported. Because of the changing metabolite concentrations with normal growth, tests from a pediatric lab must use age-related, pediatric reference intervals. Test results may be incorrectly interpreted if adult reference intervals are used to interpret them. Even tests which are commonly performed in both pediatric and adult laboratories may require different test methods or interpretations. For example, drug testing in infants and young children is more likely to need screening for over-the counter medications which have been acutely ingested than for drugs of abuse, and thus may need mass spectrometry rather than immunoassay methods.

This talk will include some of the basic day to day mechanics of pediatric laboratory medicine, including handling small volume samples, and a discussion of ways to obtain and use pediatric reference intervals. Testing for some disorders which are specific to the pediatric population will also be discussed.



# PLENARY LECTURE

PL03

## Rapid evolution in diagnostic medical microbiology

Alex van Belkum

*Scientific Office, bioMérieux, La Balme Les Grottes, France*

Basic microbiology has been a very active field of research over the past couple of decades. New technologies came and several of these went again as well. However, the overall perception has been one of extreme dynamics with new biological concepts and innovative technologies being suggested on a near-daily basis. This has had a profound effect on clinical microbiology as well and has for instance resulted in the broad acceptance of molecular testing for infectious agents (1), the adoption of matrix-assisted laser desorption ionization time of flight mass spectrometry (MALDI TOF MS) for species identification (and beyond) of any cultivable organism (2) and the introduction of latest generation sequencing technologies for the detection, identification and minute characterization of disease invoking agent (3), either after culture, but more spectacularly also direct from clinical specimens (4). This has been interwoven with additional developments in the fields of data analysis, biomathematics, laboratory automation, identification of new pathogens, omics technologies in general (transcriptomics, metabolomics, proteomics, lipidomics, glycomics etc), epidemiology, infection control and quite some others. This sketches a picture of continuous development successes and optimized patient care. The main question is whether we have really significantly improved the level of care for our patients and whether this type of care is universally available to date (5).

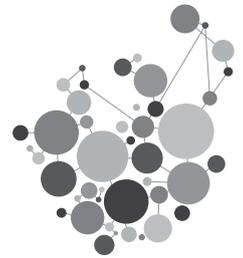
It is clear that we have witnessed rapid evolution in the clinical microbiology laboratory. It is also clear and important that increased awareness now exists on the most pressing issue in the field of bacterial infectious diseases: the continuous and pandemic increase in antimicrobial resistance leading to recent identification of pan-drug resistant organisms that would withstand all types of treatment with our current antibiotic portfolio. If not curbed this trend will continue and the number of deaths related to antimicrobial resistance (AMR) is going to be higher than the number of deaths in any other medical field within 30 to 40 years (6). So despite the diagnostic improvements mentioned above it seems as if adequate clinical care, based on characterization of both species nature and antibiotic resistance profile of infection causing agents, will be frustrated by microbial evolution culminating in high prevalence of microbes causing hard-to-treat infection.

Within the complex framework sketched superficially above, there still is clear room for extended improvement in the logistics of our diagnostic laboratories and in the sensitivity and specificity of the assays used. It has been stated regularly that optimized and rapid diagnostics is a key component in the battle against multi-drug resistance (7). The presentation will briefly summarize (a). the diagnostic needs (costs, reimbursement, regional differences, speed, automation, need for high throughput assays, biosafety requirements etc), (b). address the technologies that may allow for better and faster identification and more precise definition of antibiotic resistance levels and (c). reflect upon the lay-out of future laboratory facilities. Main question to be discussed is whether we can now definitively say good bye to some of the classical technologies that have been used for over a century in clinical microbiology and have them replaced by more modern-time technologies.

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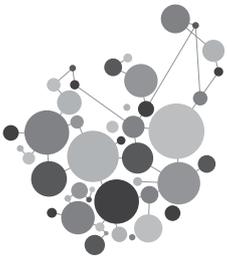
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# KEYNOTE SPEECH

KS01

## Quality issues and challenges of medical laboratory in the era of genomic medicine

Hayato Miyachi

*Department of Laboratory Medicine, Tokai University School of Medicine, Isehara, Japan*

Molecular-genetic testing has been widely expanding in use for clinical practice of patients, based on elucidation of molecular pathogenesis of diseases and clinical significance of biomarkers. Advance of molecular biology and analysis with emerging technologies has facilitated its utilization in personalized medicine. This has been promoted by companion diagnostics and molecular targeted therapy, tailoring the treatment to the individual characteristics of each patient. Such a series of paradigm shifts underscores a pivotal role of the medical laboratory on the best patient practice worldwide.

As clinical application of molecular-genetic testing is expanding and disseminating worldwide, its international standardization and quality assurance becomes increasingly important. Now a number of standards are proposed and developed for molecular-genetic testing on the basis of a product of regional and international efforts. OECD member countries have adopted the Guideline for Quality Assurance in Molecular Genetic Testing (OECD guideline) (Table 1). The Guideline addresses genetic testing for variations in germ line DNA sequences or products arising directly from changes in heritable genomic sequences that predict effects on the health, or influence the health management, of an individual. In responding to the OECD guideline, the Japanese Committee for Clinical Laboratory Standards (JCCLS) developed the Japan-version of Guideline for Quality Assurance in Molecular-Genetic Testing in 2012, and published its instruction manual in 2016. It addresses all the major categories of molecular-genetic testing for variations in pathogens and somatic cells in addition to germ line DNA sequences or products. In order to ensure the quality of genomic medicine, relevant ministries of Japan cooperated to hold a series of meeting by task force group for realization and promotion of genomic medicine (2015-2016). Based on considering urgent issues such as "how to ensure the quality of molecular-genetic testing", the Guideline for Quality Assurance in Molecular Genetic Testing was adopted for recommendation as a national standard.

In ISO/TC212 (Clinical laboratory testing and *in vitro* diagnostic test systems), ISO 15189 (Medical laboratories - requirements for quality and competence) was revised in 2012 (ISO 15189: 2012), expanding its scope to cover genetic testing. Currently ISO standards for molecular-genetic testing are under development for microbial pathogens, preanalytic process of various types of samples such as blood, frozen tissues and FFPE, and multiplex molecular analysis. Other international bodies such as CDC, CLSI and CAP are also engaged with development of the standards.

The OECD guideline requires a laboratory to get accredited or hold an equivalent recognition as a quality assurance system. In Japan, medical laboratory accreditation program has been implemented on the basis of the international standard ISO 15189, under the cooperation of JCCLS and the Japan Accreditation Board (JAB). There are major issues in ISO 15189 medical laboratory accreditation in Japan. As for the requirement in medical policy, conventionally the accreditation is not mandatory. Regarding the subject in the accreditation program, it is currently limited to common laboratory tests, which are covered by health insurance, with regulatory approval, and not applied to the molecular-genetic testing based on emerging technology. In 2015, clinical research core hospital was established to serve as the bases for conducting international-level clinical studies and playing a central role in implementing doctor initiated clinical trials, in order to create innovative drugs and medical devices. A medical laboratory in clinical research core hospital is required to get accredited under ISO 15189. In order to achieve the purpose of clinical research core hospital, there is a need for development of an accreditation program to cover a lack of insurance

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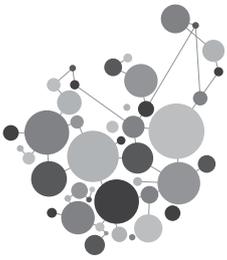
coverage, such as molecular-genetic testing. In its clinical implementation, medical laboratories are faced with challenges for a new and pivotal role concerning accurate measurement using stored samples, bioinformatics availability, practical decision-making algorithms, and ethical issues regarding incidental findings. To this end, the development of a guidance document intended for the molecular-genetic testing by which medical laboratories can implement a quality system to meet ISO 15189: 2012.

To meet the requirement of international standards in the era of genomic medicine, it is necessary to secure human resources who are familiar with implementation, operation and management of molecular-genetic testing. The medical laboratory has a new role in providing not only testing services but also an instructive approach to users to ensure the sample quality and privacy protection of personal genome information, supporting the quality of patient practice based on laboratory diagnosis. To this end, continuing education and training program for molecular-genetic testing is a cornerstone of its quality assurance, as underscored by the OECD guideline.

All of these activities for the global standardization of molecular-genetic testing should lead to ensure minimum international requirements for quality assurance of a total process of the laboratory systems and practices, allowing for the appropriate diagnosis and effective control of diseases. This presentation will focus on provision of information and thoughts on current efforts and expectations on medical laboratory to solve these quality issues on molecular-genetic testing in the era of genomic medicine with regards to the international standardization.

Table 1. General principles and best practices of the Guideline for Quality Assurance in Molecular-Genetic Testing (OECD).

Methods	Best Practice (selected)
1) Quality assurance systems	Accredited or hold an equivalent recognition. Internationally accepted standard terminology and nomenclature Policies and procedures to document the analytical validity of all tests performed
2) Proficiency testing	Acceptable performance levels Timely corrective actions Assess all phases Scheme for every disease or alternative methods
3) Quality of result reporting	Effectively communicable information with non-specialist health care professional
4) Education and training standards for laboratory personnel	Measures to assure professional competence, directors: MD or PhD or equivalent Continuing education and training program



# KEYNOTE SPEECH

KS02

## Individualising and personalising IVF using endocrine assays

Scott M Nelson

*University of Glasgow, UK*

In the era of personalized medicine, endocrine assays are now recognized as making a critical contribution to the individualization of IVF. Anti-müllerian hormone (AMH), is produced by the granulosa cells of pre-antral follicles and circulating concentrations reflect the functional ovarian reserve. The development of robust automated AMH assays have allowed its role to be extended from pre-treatment stratification and setting of expectations to one of being a full companion diagnostic and incorporation into novel drug design and dosing. The efficacy and safety of individualizing controlled ovarian stimulation based on pretreatment AMH, has recently been confirmed in an international multi-centre RCT (ESTHER-1). Oestradiol and progesterone monitoring, are being widely re-introduced with recognition that they facilitate selection of those who will benefit from an agonist trigger, elective cryopreservation of all embryos and tailoring of luteal phase support. These novel indications are however placing demands on existing assays with respect to precision. Moving forward IVF clinical decisions will require cautious interpretation based on laboratory- and method-specific data.

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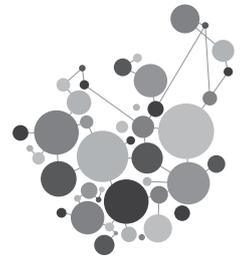
KS03

## Healthcare, laboratory medicine and patient care

Howard Morris

*School of Pharmacy and Medical Sciences, University of South Australia and Chemical Pathology, SA Pathology, Adelaide SA 5000 Australia*

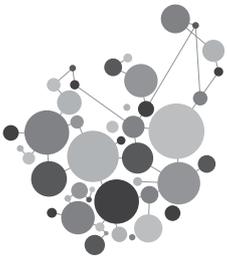
Demands on healthcare services continue to increase as the result of various drivers including community expectations and increased incidence of chronic diseases such as diabetes and cardiovascular disease arising in part from increased community wealth. A critical indicator of healthcare benefits is the marked increase in longevity recorded in developed countries over the last century, which is expected in all countries as economies transition from developing to developed status. Increases in longevity impact on improving the overall wealth of the community. Many factors have contributed to this increase but improvements in healthcare services and nutrition have been critical. Given that some 70% of clinical decisions are influenced by clinical laboratory investigations it is clearly evident that laboratory medicine continues to provide critical services to improve the well-being of the whole community through increased productivity and wealth generation. Such a role entails significant responsibilities. We need to ensure we provide an optimal service in an efficient and cost-effective manner to enhance access to clinical laboratory services for all members of our community. The large increases in productivity of clinical laboratories through technological innovation have entailed close collaboration between the in vitro diagnostic industry, laboratorians, health care providers and patient advocate groups. Such increased productivity has occurred at the same time as improving the quality of services. It has required the application of disciplines such as metrology to our clinical laboratory practices to improve standardization and harmonization of pathology test results. These developments continue to be driven by community demands for improved services and patient safety. Continuation of such progress heightens the requirements for highly trained clinical laboratory specialists to lead these changes within the laboratory. Within the community we need to effectively advocate through public education programs and demonstrate the real value of laboratory medicine to healthcare delivery. Investment in clinical laboratory services is central to the provision of cost-effective and optimal health care services to increase the overall wealth of the community.



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KS04

## The global spread of Dengue virus infection

Ida Parwati

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Dengue virus infection is major public health problem and a potentially fatal acute febrile illness caused by any of four dengue viruses; DENV-1, DENV-2, DENV-3, and DENV-4. DENVs are transmitted primarily through the bite of *Aedes aegypti* and *Aedes albopictus* mosquitoes. Because these mosquitoes are endemic throughout the tropics and sub-tropics, an estimated 40% of the world's population is at risk for DENV infection. Currently dengue fever is expanding into new geographic areas as a consequences of climate change, making the number of people at risk from the disease is growing faster than before.

The 2009 WHO criteria classify dengue according to levels of severity: dengue without warning signs; dengue with warning signs (abdominal pain, persistent vomiting, fluid accumulation, mucosal bleeding, lethargy, liver enlargement, increasing haematocrit with decreasing platelets); and severe dengue (dengue with severe plasma leakage, severe bleeding, or organ failure). Although up to 75% of individuals infected with a DENV will be asymptomatic, 5% of individuals that develop dengue will progress to severe dengue and potentially death. The case-fatality rate for individuals with severe dengue can be as high as 10% if untreated, or 0.1% with appropriate clinical management.

Because the clinical features of dengue are non-specific, early confirmatory laboratory diagnosis is essential for timely intervention. Diagnosis may involve virus isolation, detection of viral nucleic acid by real-time RT PCR, antigens or antibodies. In the early stage of the disease viral isolation, nucleic acid or antigen detection may be done. After the acute stage of infection antibody detection is used for diagnosis. Disease surveillance, vector surveillance and control with a mixture of environmental management, development of vaccine and health education are needed to prevent dengue outbreak.



# KEYNOTE SPEECH

KS05

## Tips of the latest WHO classifications

Gina Zini

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The WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues is a consensus-based classification which utilizes an integrated diagnostic approach including clinical data, morphology, immunophenotype and genetics, to be used both in daily practice and in basic/clinical investigations. A significant update of the 2008 edition is going to be published within the year 2016: we report herea summary of changes in the new document on myeloid neoplasms.

Morphology represents a fundamental stakeholder in the diagnostic process, but should be associated with genetics and molecular genetics that allow new diagnostic approaches, improved prognostic/predictive models, and hopefully innovative therapeutic approaches (Cazzola, 2016).

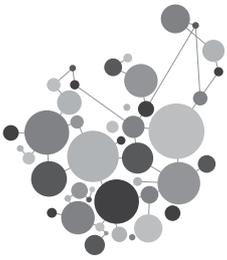
In the group of Myelodysplastic Syndromes (MDS) the first change is related to nomenclature to harmonize the denomination of the different subgroups: the proposal is to name MDS all the categories, maintaining the same diagnostic criteria as in the 2008 edition.

The WHO scheme now simply classifies MDS on the basis of dysplasia and blast count, not of the type of cytopenia. Type of dysplasia often does not fit with the cytopenic lineage in RCUD: subgroups of Refractory Anemia, Refractory Neutropenia and Refractory Thrombocytopenia are eliminated and merged in the subgroup of MDS with single lineage dysplasia.

The detection of *SF3B1* mutation, which is strongly associated with ringed sideroblasts (Malcovati, 2015) has become a novel diagnostic criterion: in the revised classification, although at least 15% of ring sideroblasts are still required in cases lacking a demonstrable *SF3B1* mutation, a diagnosis of MDS with ring sideroblasts with single lineage dysplasia (MDS-RSSLD) or MDS with ring sideroblasts with multilineage dysplasia (MDS-RDMLD), can be made if ring sideroblasts comprise as few as 5% of nucleated erythroid cells but an *SF3B1* mutation is detected. It is notable the re-introduction of the category of MDS-RSMLD, that was named as RCMD-RS in the 2001 WHO classification and was eliminated in the 2008 edition.

Acute erythroid leukemia (erythroid/myeloid type, previous FAB-M6) is proposed to become MDS with excess of blasts. The different AML and MDS subtypes with predominant erythropoiesis may be combined into one category and classified as MDS based on the ANC (All Nucleated Cells) blast count (Hasserjian, 2010). Pure erythroid leukemia remains a subtype of AML and diagnostic criteria are confirmed.

Focusing on Myeloproliferative neoplasms, the following changes are found in the 2016 update: i) mastocytosis is no longer listed in the group of MPNs and has been moved into a separate category; ii) the nomenclature of CGL *BCR-ABL1* positive (Chronic Granulocytic Leukemia *BCR-ABL1* positive in the 2008 edition) has changed in CML (Chronic Myeloid Leukemia), *BCR-ABL1* positive; iii) the resistance to TKI treatment is included in the definition of disease progression; iv) a new definition of lymphoid blast crisis is proposed, including presence of any lymphoblast(s) in the PB and/or detection of >5% lymphoblasts in the BM. Major changes are proposed in the diagnostic criteria for *BCR-ABL1* negative MPNs, due to the discovery of new findings with diagnostic/prognostic relevance. Diagnostic Criteria for Chronic Neutrophilic Leukemia (CNL) include the detection of *CSF3R T618I* or other activating *CSF3R* mutation (Elliott, 2014): in the absence of a *CSFR3R* mutation, WHO 2008 requirements are confirmed for the diagnosis. In WHO 2016, moreover, the diagnostic criteria for Polycythemia Vera (PV) have been revised (Siver, 2013), the presence of *JAK2V617F*, *MPL* or *CALR* gene mutation is included as one of the major criteria for the diagnosis of Essential Thrombocythemia (ET), and the presence of *JAK2V617F*, *MPL* or *CALR* gene mutation is required as one of the major diagnostic criteria in Primary myelofibrosis (PMF).



## KEYNOTE SPEECH

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Moving to the group of Myelodysplastic/Myeloproliferative neoplasms, WHO 2016 proposes refined criteria between MDS- vs. MPN-like subgroups and in the blast count for prognosis in Chronic myelomonocytic leukemia (CMML). The provisional entity in WHO 2006 Refractory Anemia with Ring Sideroblasts and Thrombocytosis (RARS-T) has promoted to a full entity and changed nomenclature in Myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis: *SF3B1* mutation is detected in 80-90% of cases.

A major change in the 2016 WHO revision (Arber, 2016) of the is the focus on Myeloid neoplasms with germ line predisposition, which includes cases of any type of myeloid tumors occurring on the background of a predisposing germ line mutation.

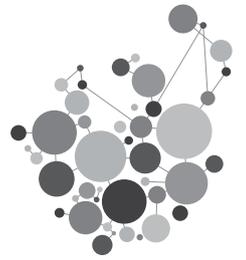
The criteria for the diagnosis of the eosinophilia-related proliferations associated with specific molecular genetic changes are retained in the classification, although it is noted that eosinophilia may be absent in a subset of cases. In the 2016 revision, the group of Myeloid/lymphoid neoplasms associated with eosinophilia and rearrangement of PDGFRA, PDGFRB, or FGFR1 is expanded with addition of the myeloid neoplasm with t(8;9)(p22;q24.1) and with the new provisional entity *PCM1-JAK2* positive.

Moving to the group of Acute Myeloid leukemia (AML) and related neoplasms, WHO 2016 revision highlights the relevance of the definition of specific AML entities by focusing on significant cytogenetic and molecular genetic subgroups, both in adult and in pediatric patients, in the group of AML with recurrent genetic abnormalities. The category of AML with myelodysplasia-related changes has been refined to better identify cases with poor prognosis, extending the list of those cytogenetic abnormalities sufficient to diagnose in presence of blast percentage in BM and/or PB  $\geq$  20% and in absence of a prior therapy. The group of Therapy-related myeloid neoplasms (t-MNs) may be further subdivided into therapy-related MDS (t-MDS) or AML (t-AML). A major change in the group of AML, not otherwise specified, refers to Acute erythroid leukemia, proposed to become MDS with excess of blasts, while there are no relevant changes in the two groups of Myeloid sarcoma and Myeloid proliferations of Down syndrome, neither new entities defined within the group of Acute leukemias of ambiguous lineage.

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# MEMO

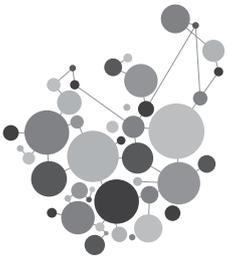


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SY01-01

## Protein electrophoresis in clinical diagnosis

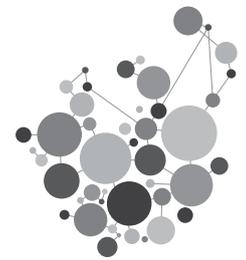
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### Guidelines for Clinical and Laboratory Evaluation of Monoclonal Gammopathies;

1. Guideline 1 recommends that electrophoretic techniques capable of providing high-quality resolution of major serum proteins be used to evaluate serum and urine on samples suspected of containing an M-protein. The practical suggestion is to use a method that provides crisp separation of the transferrin (β1) and C3 (β2) bands.
2. Guideline 2 recommends the use of IFE or immunosubtraction (ISUB) to define the M-protein type.
3. Guideline 3 recommends that after an M-protein is identified, it should be followed by measurement of the M-spike using densitometry or electropherogram. The International Myeloma Working Group (IMWG) guidelines for monitoring patients with MM require a measurable M-spike to be  $\geq 1$  g/dL in serum and  $\geq 200$  mg/24 hr in urine. The IMWG defines a minimal response to therapy as a reduction of the serum M-spike by  $\geq 25\%$  and a partial response as a reduction by  $\geq 50\%$ . For urine, a minimal response is the reduction in measurable M-spike as  $\geq 50\%$  and a partial response as  $\geq 90\%$ .
4. Guideline 4 recommends that clinicians order measurements of serum IgG, IgA, and IgM levels at the time of detection of the M-protein to determine the concentration of the uninvolved immunoglobulins. While densitometry and electropherograms provide good estimates of M-spikes, they fall off linearity when the M-spikes are present at high levels ( $> 5$  g/dL) where immunochemical measurements may provide useful information.
5. Guideline 5 recommends that all patients suspected of having plasma cell dyscrasias have a 24-hour urine sample studied as well as the serum. An early morning void may be adequate for the initial screening if a 24-hour urine sample is not obtained.
6. Guideline 6 recommends intervals that are useful to follow patients with previously identified M-proteins in serum or urine. Most patients in whom M-proteins are detected have MGUS. The laboratory can help to stratify the risk for progression by examining the isotype, quantity and rFLC on the initial serum. A follow-up measurement of the M-protein a few months after initial detection provides an estimate of the rate of growth of the neoplasm and helps to detect cases of early MM. Subsequent intervals of follow-up depend on the stability of the M-protein and the clinical picture. Low-risk MGUS patients may only need to be monitored by occasional laboratory assessments.
7. Guideline 7 speaks to the issue of hyperviscosity syndrome that is typically found in patients with Waldenström's macroglobulinemia (WM), but occasionally associated with other M-proteins, including MFLC. Hyperviscosity can require intervention by emergency plasma exchange. As a general guideline, hyperviscosity may occur when an IgM M-spike is  $> 3$  g/dL, for IgA M-proteins  $> 5$  g/dL and occasional IgG M-spike (often IgG3 subclass)  $> 6$  g/dL.
8. Guideline 8 recognizes that cryoglobulins are unique problems in evaluating patients with M-proteins, as well as some autoimmune and infectious conditions. For the evaluation, the initial collection and transportation of the specimen under temperature-controlled conditions are known to be critical.
9. Guideline 9 reaffirms the importance of the techniques used in evaluating M-proteins, and further

# SYMPOSIUM 01



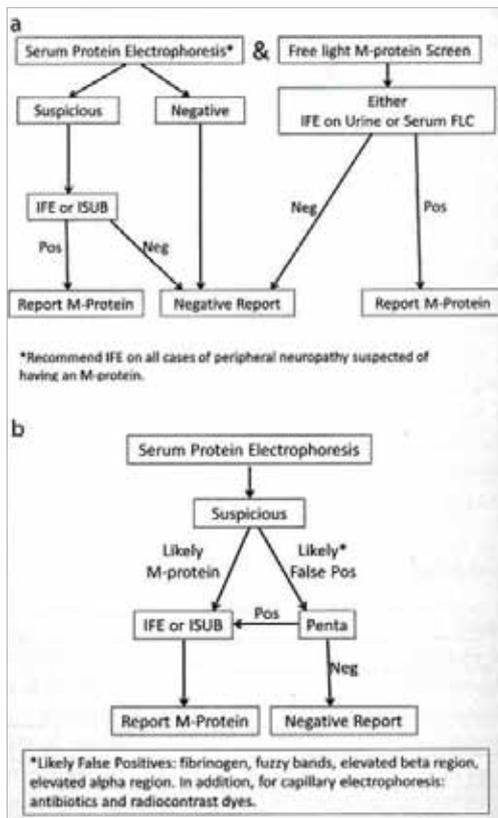
emphasizes the importance of using a method that provides crisp resolution of the 2 major bands in the  $\beta$  region.

## Algorithm for detecting M-proteins

### 1. Assumption about the Ordered Test

Tests for M-proteins are not to be used as general screens. The clinician has general clinical suspicion, based upon evidence from the history, or physical or laboratory information, and the patient may have a clinically significant M-protein-related process.

### 2. Initial Testing & Evaluation of Suspicious Findings



## Maintain an Active File of all Monoclonal Proteins

To conserve time and laboratory resources, maintain a file on all patients with M-proteins. When a sample is received with a request for an SPE, UPE or IFE, the M-protein file is checked for previous findings.

## Screening and Follow-up of MFLC

If the patient has MFLC, 24-hour urine is still recommended. The total volume of urine is recorded, total protein determined, and densitometry used to establish the percentage of MFLC.

When the clinician sends urine to be evaluated for MFLC, we perform protein electrophoresis on urine usually concentrated at least 50-fold.

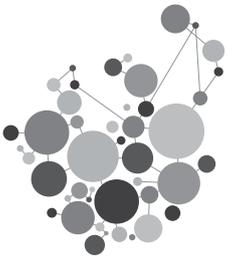
## Final Words

The guidelines and algorithm provide efficient processing of specimens, benefiting the patient, the clinician, and the laboratory. They help prevent inappropriate ordering and overutilization of the laboratory. One should achieve rapid turnaround time and efficiency.

When a small M-protein is identified, it is recommended repeating the evaluation in a few months. If it represents an early neoplastic monoclonal process, it will still be there or may have progressed to the point where it will be readily detectable. If it was merely part of an oligoclonal expansion due to a transient

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process such as an infection, it likely will have resolved by this time.

Finally, keeping channels of communication with clinicians is one of the critical points to success in dealing with difficult cases.

When uncertain about a result, repeat the procedure, speak to the clinician, perform further studies, occasionally send for a fresh sample, or send the sample off for reference work.

## **Bands Mistaken for M-proteins**

### **1. Fibrinogen**

The most common mimic of an M-protein is the presence of fibrinogen because it migrates in the  $\beta$ - $\gamma$  region of an SPE. It may be present if the patient is being treated with an anticoagulant or if the sample is collected in a tube containing an anticoagulant. When a band is present in the fibrinogen region, it is recommended performing an IFE to rule out its presence.

### **2. Genetic Variants**

Transferrin,  $\alpha$ 1-antitrypsin, and C3 have several possible alleles in the population and may give 2 bands or 1 band with an unusual migration. When twin bands are detected in the  $\alpha$ 1-antitrypsin area, it is recommended studies be performed to determine the individual's  $\alpha$ 1-antitrypsin phenotype for genetic counseling.

### **3. C-Reactive Protein (CRP)**

CRP normally is not seen on SPE. In cases with strong acute phase reaction pattern, a small CRP band may be found in the mid- to slow  $\gamma$  region on gel-based techniques. The laboratory can determine where CRP migrates on their gels by performing an IFE.

### **4. Hemolysis**

A hemoglobin-haptoglobin band usually migrates in the  $\alpha$ 2 to  $\beta$  region. It can resemble an M-protein. Usually, there is marked depletion of the normal haptoglobin band and the serum is red. If the serum is not red, or if the haptoglobin band is not depleted, it is recommended to perform an IFE to rule out an M-protein.

### **5. Radiocontrasts Dyes and Antibiotics**

On CE, radiocontrast dyes and some antibiotics create peaks anywhere from the prealbumin to the  $\gamma$ -globulin region. Because of this, any restriction suggestive on an M-protein that has not previously been characterized must be proven to be an M-protein by IFE or immunosubtraction before reporting it as such.

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## **Appendix: Example of Sign-Outs for Serum Protein Electrophoresis**

### **Normal pattern**

There is a decrease in all parameters suggesting hemodilution.

Normal albumin with decreased globulin fractions is most consistent with recent plasmapheresis and albumin replacement. Clinical correlation is recommended.

1 measured value is slightly outside the normal range. The pattern is otherwise within normal limits.

Decreased albumin.

Bisalbuminemia is present. A benign condition.

There is blurring of the anodal margin of the albumin band, which is seen with azotemia, jaundice, and/or complexing with a drug, esp. heparin or antibiotics.

A small restriction at the origin may indicate the presence of a cryoglobulin. Rec.: Evaluate serum for cryoglobulin on sample drawn in 37C tube and separated from erythrocytes at 37 C.

Haptoglobin is decreased, consistent with a hemolytic process or hereditary deficiency.

Increased  $\alpha$ 2 region likely reflects the presence of a radiocontrast dye. Clinical correlation is recommended (capillary electrophoresis only).

Increased  $\alpha$ 1- and  $\alpha$ 2-globulins, decreased albumin and transferrin, consistent with an acute phase response.

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The elevated  $\beta$  region is consistent with the presence of a radiocontrast dye (capillary electrophoresis only).  
The elevated  $\beta$  region reflects the presence of fibrinogen.

Polyclonal increased in IgG4 subclass. This may be seen in a variety of conditions, including IgG4 systemic disease, allergies, desensitization therapy, filarial infestations, and some autoimmune disease, including microscopic vasculitis.

A few tiny oligoclonal bands are seen in the  $\gamma$  region. These bands can be seen with infections and autoimmune diseases. Occasionally, they have been noted as part of lymphoproliferative processes.

An oligoclonal response is seen in the  $\gamma$  region. Such response may be seen following therapy such as stem

cell transplantation (use in patient with previous M-protein).

One of the oligoclonal bands is more prominent than the rest. Rec.: Urine protein EP now, and repeat serum

studies in 3-6 months.

Decreased albumin and haptoglobin with a polyclonal increased in  $\gamma$ -globulins and  $\beta$ - $\gamma$  bridging. This is consistent with liver disease.

Massive polyclonal increase in  $\gamma$ -globulins. This may be seen in chronic infections, esp., EBV, HCV, and HIV. It may also occur in autoimmune disease and rare lymphoproliferative disorders, such as angioimmunoblastic T-cell lymphoma (AILT).

Very low albumin, transferrin, and  $\gamma$ -globulin. Greatly increased  $\alpha$ 2-macroglobulin and/or haptoglobin. This protein loss pattern suggests renal disease (nephrotic syndrome) or protein-losing enteropathy.

Decreased total protein with low albumin and  $\gamma$ -globulin. This is a mild protein loss pattern. Rec.: Urine immunofixation for BJP, if light chain is part of the differential diagnosis.

Hypogammaglobulinemia is present. In adults, this may reflect the presence of common variable immunodeficiency disease (CVID), chemotherapy or B-cell neoplasm. Urine immunofixation for monoclonal free light chain, quantitative IgG, IgA, and IgM, and immunofixation of the serum are suggested, if they have not already been ordered.

A monoclonal gammopathy is present. Urine immunofixation for monoclonal free light chain and/or serum free light chain evaluation is suggested.

The M-protein is superimposed on a polyclonal and oligoclonal response. This suggests that the M-protein may be part of a reactive or lymphoproliferative process.

Serum free light chain measurement may be useful to follow patients with M-proteins. For patients with multiple myeloma, and in patients with monoclonal gammopathy of undetermined significance (MGUS), it

helps to identify those most likely to progress.

An abnormal free k/ $\lambda$  ratio, even in the presence of a normal protein electrophoresis, has been associated with the presence of some underlying lymphoproliferative conditions.

A tiny restriction is seen in the presence of a normal protein electrophoresis, has been associated with the presence of some underlying lymphoproliferative conditions.

The normal  $\gamma$ -globulins appear suppressed.

Markedly reduced  $\alpha$ 1-antitrypsin band. Rec.:  $\alpha$ 1-antitrypsin levels and phenotype studies to exclude congenital deficiency.

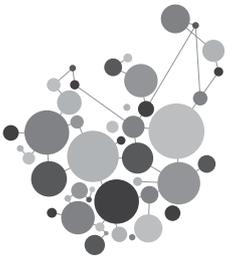
Abnormal  $\alpha$ 1-antitrypsin band. Rec.:  $\alpha$ 1-antitrypsin levels and phenotype studies.

The pattern differs from previous samples on this patient. This may reflect therapy, but a patient identity problem cannot be ruled out. Rec.: Repeat on a freshly drawn sample.

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SY01-02

## Laboratory tests for organ transplantation

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In patients with irreversible organ damage or failure such as end stage renal disease, the best way to treat the patients is organ transplantation. However, limited number of organ donors has restricted the opportunity for the patients to be histocompatible organ recipients. In this instance, various laboratory tests for organ transplantation play an important role not only in the judgement of histocompatibility between the recipient and donor but also in the evaluation of the patient's prognosis as well as the risk for the rejection of the allograft.

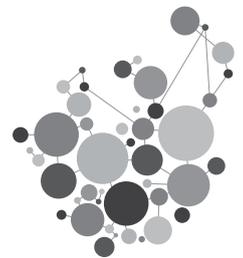
Meanwhile, recent advances in the technologies those are widely used in the field of clinical laboratory tests also have been applied to the tests performed before and after the organ transplantation. A notable example is the Luminex technology, the multiplex flow-bead microarray. Particularly, this technology has aided the human leukocyte antigen (*HLA*) typing and antibody screening. However, advances in the laboratory technology also led to the necessity for more experienced and specialized laboratory physicians and technicians to maintain the quality of the tests and to interpret complex results. In this lecture, various laboratory tests for organ transplantation and their method principles will be introduced.

HLA is the human major histocompatibility complex on the chromosome 6p21.1-21.3 with length of approximately 3.6 Mb. This legion contains about 128 genes those may be translated to proteins, and around 40% of those genes are considered as to be related with immune function and regulation. Many previous studies had revealed that matching of HLA antigens between the solid organ donor and recipient improves the outcomes of organ transplantation. To assess the concordance between the HLA antigens of the organ donor and recipient, several methods are used to determine HLA serotypes and allele types. For low resolution HLA typing (i.e. serotyping), sequence-specific priming PCR (SSP) and sequence-specific oligonucleotide hybridization (SSO) are commonly used. For high resolution HLA typing, i.e., allele-level typing for the donor and recipient of hematopoietic stem cell transplantation (HSCT), sequence-based typing (SBT) is the standard method, currently. Owing to the insufficient number of histocompatible organ donors, recent studies have tried to find out tolerable antigens after transplantation from a non-histocompatible donor. In addition, the advances in the immunosuppressant drugs and techniques for the management of immunocompromised patients would make HLA matching to be not crucial in the cases of solid organ transplantation, although HLA matching is still one of the most important factors for the prognosis of patients after HSCT.

During the pre-operative evaluation on the patients awaiting organ transplantation, detection of presensitized anti-HLA antibodies from the patients' sera are usually performed by using panel reactive antibody (PRA) tests. In these days, the PRA test is usually performed by using the flow-bead microarray method and includes three levels of tests such as 'screening', 'identification', and 'single antigen assay' according to the resolution on the antigen specificities of the test results and the bead groups used in the assay. The PRA test can also be used as a monitoring tool before and after the desensitization of anti-HLA antibodies in the patient by plasmapheresis.

When possible organ donor is available, lymphocyte crossmatch is widely used to detect donor-specific antibodies in the patient's serum. Few crossmatch methods have been developed till now, and the complement-dependent cytotoxicity principle and the flowcytometric method are utilized widely. When the result of T-cell crossmatch is positive, this implies the patient already has been sensitized to the donor HLA class I antigen(s), and the organ transplantation from the donor may not be successful owing to the acute or hyper acute rejection after surgery.

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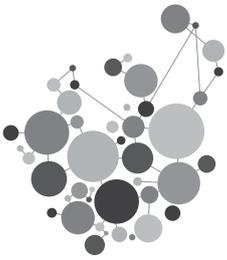
Before and after organ transplantation, some immunosuppressant drugs including tacrolimus, sirolimus, and cyclosporine are used to prevent rejection against transplanted organ. When excessive dose of the drug is used, the patient may suffer various infections, while the dose of immunosuppressant is insufficient, the probability of rejection against allograft would increase. Thus, monitoring of the drug level in the blood is one of the important ways to prevent rejection and infection after organ transplantation. However, the blood level of immunosuppressant may not always reflect the degree of immune suppression, and functional assays for measuring activities of lymphocytes would need and have been researched and are under development or restrictively used. In current laboratory practices, immunoassay including fluorescence polarization immunoassay (FPIA) method and enzyme-multiplied immunoassay technique (EMIT) are often used to quantify the levels of immunosuppressant in the blood, and mass-spectrometry is also one of the available methods for the monitoring of the drug levels.

In addition, various tests for detecting infectious agents such as cytomegalovirus (CMV), Epstein-barr virus (EBV), Parvovirus B19, and hepatitis viruses are utilized to monitoring pre- and post-transplantation patients, since some viral infections are known to be related with allograft failure or rejection. To detect these viruses, immunoassay method and molecular tests including real-time PCR are commonly performed as routine tests.

As other fields of laboratory medicine, assays for organ transplantation have been continuously developed and introduced. Some examples of these assays may include C1q assay, tests for various non-HLA antibodies, ImmuKnow cell function assay, and ELISPOT. The clinical usefulness of these assays are not fully researched and further studies on the newly introduced assays as well as efforts on developing novel assays to benefit the patients undergoing organ transplantation would need continuously.

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SY01-03

## Interpretation of bacterial growth on primary culture media in clinical microbiology

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The identification of bacteria is at a turning point with introduction of Matrix-assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry (MALDI-TOF) and wide use of 16s rRNA sequencing. It looks that we are in the front of the sample-to-result era of clinical microbiology. The change is larger than that of from manual identification technique based on biochemical reaction to automated devices, especially in the spectrum of identification. So these days we can identify more species faster and easily than before. Furthermore they impacts the classification of microbes and it happens sometimes re-classification or re-named as new species. But there are some limitations in clinical situations such as expensive devices, for example MALDI-TOF or sequencer, and trained technician is needed, and so on. Even though the MALDI-TOF or 16S rRNA from specimen showed to advantage, culture is still gold standard of diagnosis for infectious diseases. The information from primary culture is looked simple, but it is valuable and important because most of the technique and classification was based on that information. So in this session, the identification of bacterial growth on primary culture media in clinical microbiology will be reviewed, especially how to describe and report with case-based approach, mainly focused to bacteria isolated in culture from urine, sputum and blood.

# SYMPOSIUM 01



SY01-04

## Complications of blood transfusion

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Blood transfusion can provide clinical benefit to patients, but transfusion can be associated with some kinds of complications. Transfusion associated complications can be grouped by timing (acute or delayed), mechanism (immunologic or nonimmunologic, hemolytic or nonhemolytic), and etiology (infectious or non-infectious) [1-3]. Screening of blood donors using nucleotide testing and sensitive immunologic testing has reduced the incidence of transfusion transmitted viral disease including HIV, HBV, and HCV. However non-infectious complications of transfusion become relatively more important [3]. Thus, I will discuss noninfectious transfusion reactions. Hemolytic complications include acute hemolytic transfusion reaction (AHTR) or delayed hemolytic transfusion reaction (DHTR). Alternatively hemolytic transfusion reaction can occur, when red blood cells are exposed to heat or incompatible fluids. Nonhemolytic complications include febrile non-hemolytic transfusion reaction, allergic/anaphylactic reaction, transfusion related acute lung injury (TRALI), transfusion associated circulatory overload (TACO), hypotensive transfusion reaction, transfusion associated graft versus host disease, and bacterial contamination of blood component (Table 1).

Many transfusion associated complications can be prevented by following well-established guide lines including pretransfusion testing, pretransfusion identification of the recipient and the blood to be transfused, and inspection of blood to be transfused [4]. In order to detect transfusion reactions as early as possible, it is indispensable to observe the patient closely during the initial 15 minutes of a transfusion [4-5]. Before the start of the transfusion, the personnel involved in administering transfusion should encourage the patient to notify any personnel involved in the transfusion if he or she becomes aware of fever, chills, shivering, pain at infusion site, dyspnea, flushing, itching, urticarial, or nausea. Any symptoms, which may indicate transfusion reaction, should be considered seriously. Then the transfusion must be stopped and the possibility of transfusion reaction should be investigated thoroughly. When a transfusion reaction occurs, it is a challenge for physicians and health care providers to identify the cause of the reaction, make the differential diagnosis, using the clinical signs and symptoms because the signs and symptoms are not necessarily specific to the type of transfusion reaction. The personnel who administer blood transfusions must be able to recognize these complication so that appropriate treatment can be provided quickly [1,2].

Table 1. Classification of Transfusion Reactions

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### Hemolytic Transfusion Reactions

Acute hemolytic transfusion reaction  
Delayed hemolytic transfusion reaction  
Nonimmune hemolysis

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### Nonhemolytic Transfusion Reactions

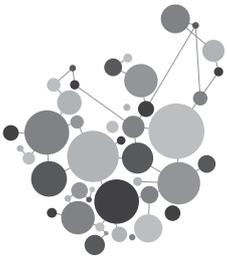
Febrile nonhemolytic transfusion reaction  
Allergic reaction  
Anaphylactic reaction  
Transfusion related acute lung injury (TRALI)  
Transfusion associated circulatory overload (TACO)  
Hypotensive transfusion reaction  
Transfusion associated graft versus host disease  
Bacterial contamination of blood component

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### Transfusion transmitted infections

Viruses/Bacteria/Rickettsia/Parasites

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## SYMPOSIUM 01

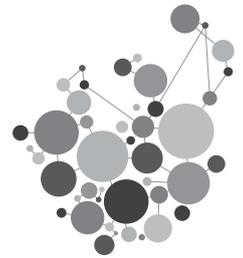
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5. World Health Organization ed. Clinical transfusion practice. Guidelines for medical interns [http://www.who.int/bloodsafety/transfusion\\_services/ClinicalTransfusionPracticeGuidelinesforMedicalInternsBangladesh.pdf](http://www.who.int/bloodsafety/transfusion_services/ClinicalTransfusionPracticeGuidelinesforMedicalInternsBangladesh.pdf)

# SYMPOSIUM 02



SY02-01

## The art of writing: Material, methods, and results

Ju-Won Roh

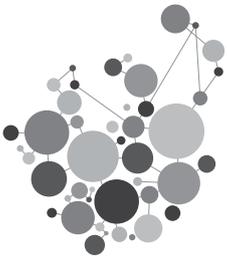
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Clear writing is essential for effective convenience of information in written form, but one of the major problems in scientific communication in English is the correct use of this language by authors for whom English is not a mother tongue. Most science writers start with the materials and methods section. For most people, the materials and methods section is also the easiest to write. However, keep in mind that experimental or clinical procedures are not only presented in the methods section. The most important aspect of the methods may be mentioned briefly in the abstract and the introduction. In addition, key procedures often introduce paragraphs in the results section.

The methods section has a simple pattern of organization. It tells the story of your research from beginning to end. Nevertheless, the methods section of clinical research reports requires a specific set of contents, as detailed by the Information of Authors. For basic science, the contents of the methods section may be quite different. The Information for Authors of the journals of basic science focus more on the reader's ability to understand the author's experimental procedures well enough to replicate them. This does not mean that all the details must be included in your own article. Common procedures should just be mentioned briefly with a citation to another article that describes them in detail. Use the present tense for known facts and hypotheses, and the past tense for describing experiments that have been conducted and the results of these experiments. Avoid shifting tenses within a unit of text.

The results section present your research findings and your analysis of those findings. It should an 'answer' for the question mentioned in the 'introduction' section. In clinical medicine, there are a number of organizations of scholars that have developed regulations for reporting on various types of studies. Before drafting your article, check the author's guidelines of a major journal for a list of these recommendations. Biomedical researchers doing basic science can follow a more flexible structure, depending on the nature of the study and the journal. Start with the most important finding, and continue through each result in a logical way. This may be according to time, if one result followed from the next, or it may be from most to least important. Keep in mind the logical flow through the article.



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### Ways to improve abstract, title, and cover page for a scientific paper

Sun-Young Lee, M.D., Ph.D.

*Department of Internal Medicine, Konkuk University School of Medicine, Seoul, Korea*

The abstract of an original article comprises Title, Background/Aims, Methods, Results, and Conclusions. The present tense is allowed for the Background, whereas past tense is allowed for the Aims, Methods and Results. Depending upon the journal style, either the present or past tense is used in the Conclusions.

**Title** – Make an attractive title related to the topic, study design, or the subjects. Other tips are to mention the study aims or to summarize the main findings of the study. Avoid starting the title with phrases such as “A study of” or “A novel finding on”.

**Background and Aims** – Depending upon the journal style, use two or three sentences to describe what is already known and explain why the study was conducted. Do not copy and paste from previous papers. Contractions such as “didn’t” should be avoided.

**Methods** - Use three or four sentences to let others know how the study was performed. Avoid copying sentences from previous publications.

**Results** - Use three or four sentences based on actual data and p-values to describe what you found. At the beginning of a sentence, all numbers should be written out in full. Otherwise, the numeral is allowed for numbers above ten.

**Conclusions** - Use one to three sentences to describe meaning of the study findings. References, tables, or figures should not be described in the Abstract for a scientific paper. Terms such as “might” or “could” are allowed only in the Conclusions, but there should be no discussion.

Writing an English scientific paper is difficult for medical doctors whose mother tongue is not English. Details on improving the skill in writing an abstract and title will be mentioned in the lecture.

# SYMPOSIUM 02



SY02-03

## Experience about submission to international journals

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Several points considered for the publication to the international journal are as below.

### 1. International journals & How to choose the right journal

Science Citation Index (SCI) is a data base for articles of science academic journals made by ISI (Institute for Scientific Information, USA). Science Citation Index Extended (SCIE) is an extended version of SCI. SCOPUS is a bibliographic database containing abstracts and citations for academic journal articles by Elsevier (Netherlands). Impact factor (IF) is a measure of an academic journal quality reflecting the yearly average number of citations. The journals with higher IFs are deemed to be more important than those with lower ones.

Choosing the right journal is one of the most important processes. Many different things are considered, including the best fit for my paper (scope, prestige/quality, IF, audience, editor, journal brand). The author should read "guide for authors" carefully, especially about the scope and format of the journal. The scope of the journal is decisive for the paper to be accepted. The manuscript should be described according to the format (layout, word limits, abbreviation, reference, figure, table) suggested by the journal.

### 2. Cover letter

The editor-in-chief reads all cover letters and abstracts submitted to the journal, and immediately decides to reject or proceed the manuscript to send a co-editor or associated editor. To avoid "desk-rejection" by the editor-in-chief, the cover letter should show the originality, novelty, impact of the work and contribution to the research field.

### 3. Electronic Submission

When the manuscript is submitted, the automatic message for complete submission is delivered to the author by e-mail. The manuscript is sent to the editor-in-chief. If no "desk-rejection" by the editor-in-chief, the co-editor or associated editor receives it and chooses 2 or 3 reviewers, and delivers it to each reviewer.

### 4. Peer Review & Author's Response

Each reviewer reads the manuscript and decides one among "rejection", "revision", and "accept". At this time English is very important. It should be clear, concise and accurate. And also it is as brief and specific as possible without omitting essential details. The repetition, redundancy, ambiguity and exaggeration should be avoided in English description. When the author receives the major and/or minor revision, he or she has to respond each remark of the major and/or minor revision line by line in a very humble way. Sometimes the major revision requires to perform a new experiment or reanalysis which takes several months. If the author responds really sincerely, usually he or she could get "Acceptance Notice".

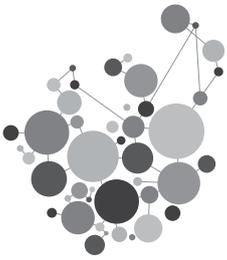
### 5. Proof Reading

After being accepted, the manuscript is delivered to the author in the form of the article. In the proof reading process, the author reads the paper several times, checks spelling, can add or delete the words or short sentences, and sends the complete article format of the manuscript to the publishing company.

### 6. Copyright etc

The journal or the publishing company requires to transfer the copyright of the article, and inquires about the color print, offprints and open access. Color prints are expensive, but sometimes inevitable for the good presentation. Usually offprints and open access are not necessary.

The most important things in the publication of the paper are the quality of the research contents (originality, novelty, innovativeness), and careful writing and processing of the manuscript.



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SY03-01

### Laboratory organization and personnel management (Large sized hospital)

Jeong-Nyeo Lee

*Department of Laboratory Medicine, Inje University Haeundae Paik Hospital, Korea*

Definition of management is an ongoing process that seeks to achieve the objectives of an organization in the most efficient ways possible. Based on the definitions, medical laboratory management could be defined. It is an ongoing process that seeks to achieve the objectives of a medical laboratory. Laboratory medicine is a medical specialty at the center of healthcare, and laboratory data informs a high percentage of clinical decisions in healthcare. The percentage is often estimated as being app. 70 %. When used optimally laboratory medicine generates knowledge that can facilitate patient safety, improve patient outcomes, shorten patient chaos and lead to cost-effective healthcare. Optimal use of laboratory medicine relies on dynamic and authoritative leadership outside as well as inside the laboratory. The medical laboratory director has three leading responsibility: medical, educational, and administrative. The medical responsibilities focus on the laboratory director's role in patient care as a physician health care provider. The educational responsibilities include establishing, and maintaining the scientific foundation of laboratory activities by education, research, investigation, and training. Finally, the administrative responsibilities focus on the activities of a business operation, including personnel, communications and interactions within the laboratory and between the laboratory and the outside.

#### Medical and clinical responsibilities

The laboratory director is a physician who is qualified to make judgments about the medical significance of clinical laboratory data. The laboratory director have to 1) communicate effectively in interpreting laboratory data 2) provide consultations to physicians regarding the medical significance and interpretation of disparate laboratory findings 3) functions as a peer member of the medical community 4) assist in the interpretation and correlation of laboratory data for patient management 5) manage from the on-site laboratory as well as any data from specimens sent to reference laboratories 6) manage the overall operation and administration of the laboratory, including fields of instrument, laboratory policies, quality assurance, safety, proficiency testing, personnel competency.

#### Educational responsibilities

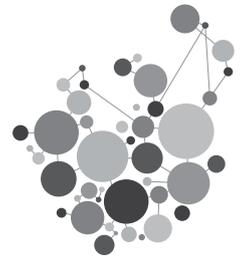
This education responsibilities include the initial training and orientation of laboratory staffs and must be continued education for science and technology advancements. The laboratory director must provide educational direction and opportunities for the medical and laboratory staff and participate in educational programs of the institution. All personnel including medical and laboratory staff and the other laboratory workers should have the opportunity to further their knowledge and skills through on the job training, in service education programs, workshops, and academic meetings. Education programs must be provided at defined intervals appropriate for the size and needs of the laboratory staff. Also, university hospital or training hospital have to manage residency training program according to Guideline for residency program and annual inspection by KSLM.

#### Administrative responsibilities

This responsibilities divide into two categories: internal and external.

A. Range of internal responsibilities : day-to-day operations, hours of operation, choice of methods, setting of new test items, purchase of instruments, scheduling of staff, quality assurance program, laboratory

# SYMPOSIUM 03



safety, strategic planning for short- and long-term goals, budget planning and control, communication within the laboratory operation as well as from the laboratory to other hospital services, medical staff personnel, and relevant outside agencies.

B. Range of external responsibilities : establishment, maintenance and communication of the laboratory relationship to the larger health care community, accreditation for laboratories- Korea Laboratory Accreditation Program, Korea Institute of Genetic Testing Evaluation, Korea Center for Disease Control, CAP et al, assist for hospital accreditation- Korea Institute for Healthcare Accreditation, .Korea Hospital Association Accreditation.

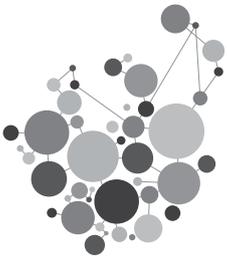
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SY03-02

### Laboratory organization and personnel management (Compact sized hospital)

Seonghee Lee

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I will introduce the experience of laboratory organization and personnel management of medical laboratory in a compact sized hospital, which was 17-year old with up to 250beds. Its laboratory technicians ten members including one laboratory supervisor and two managers.

The laboratory is sectionalized into phlebotomy, clinical chemistry, immunology, hematology, coagulation, urinalysis, parasitology, microbiology, blood bank and performs 1,000,000~1,500,000 tests a year. Its ten staff members work two shifts.

It participates in the Committee under the hospital for blood transfusion and infection control, running a service quality improving committee of its own.

The laboratory, approved by accreditation of Laboratory Medicine foundation since 2000, performs external quality control checks under the Korean Association of Quality Assurance for clinical laboratory.

Furthermore, the laboratory provides test guidelines for the purpose of giving information about examination. Laboratory Newsletter also provides information about susceptibility test for major microorganisms and recent test information six times a year.

The system of personnel management holds 2 monthly conferences to train personnel, and administrates yearly evaluation to check service availability and duty execution. It also requires the staff members complete two external educational programs and refresher training courses totaling more than 8 hours per year.

The staff is assigned to the position suitable for their aptitude to train them to become experts. The system optimizes small scale personnel. For this purpose, the administrator encourages their staff members to perform to the limits of their fullest potential, providing them with educational , and psychological assistance. This ensures their enthusiasm for their job.

Despite few medical technicians, external challenges, the laboratory strives to maximize the income of the hospital, providing prompt and exact results for medical treatment.



# SYMPOSIUM 03

SY03-03

## Effective management of hospital committee

Pil Whan Park

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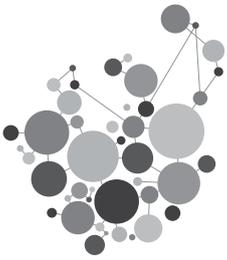
Committee system is useful system in terms of activating democratic decision-making, integration and coordination of opinion, and exchange of information and knowledge among departments. In the organization such as hospital which medical professionals and support staffs perform their own roles in various fields, the committee system may be useful for horizontal communication and coordination. Our country's hospital organization also manages various committees for clinic, education, and research area. Through hospital standardization audit, committee system is also evaluated as an internal organization which should improve quality of care and work.

Laboratory medicine doctor may play own roles by involving in numerous hospital committees. Laboratory medicine doctors are involved in quality improvement committee, blood transfusion committee, infection control committee, point of care testing committee, antibiotic committee, medical device advisory committee, and Therapeutic drug monitoring committee, which is a basic job of Laboratory medicine doctor as defined in study on the definition of 'practice of laboratory medicine'. Second, the committee which increases prestige or influence of laboratory medicine, are personnel committee, equipment advisory committee, computation and informatics committee, management committee et al.

In this symposium, I will share the author's experiences about committee characteristics, regulation, organization, management and assessment. Focusing on committee in which laboratory medicine doctor must play leading role such as blood transfusion committee, point of care testing committee, infection control committee, and Therapeutic drug monitoring committee. I will also discuss the issues that laboratory medicine doctor should consider for effective hospital committee management.

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SY04-01

### **'Outstanding Laboratory Accreditation' - Check points that laboratory directors and inspection team leaders must be aware of**

Woo In Lee

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Outstanding Laboratory Accreditation is conducted monthly, which grants accreditation which begins at the starting of the month through review by the committee. All areas which laboratory tests conducted are subject to accreditation, in which additional inspection is required when new tests of additional area has been installed within the accreditation period. Gram's stain for instance, or even stool occult blood test requires accreditation for area of Clinical Microbiology. In circumstances of HLA test overlapping between Histocompatibility and Molecular Genetics, both areas are subject to accreditation. An accreditation is granted when score ratio over 80% excluding 'Non-Applicable' items, with a period of one year. Accreditation is reserved when any area of score ratio less than 80% is received, and temporary accreditation of 3-months period is given. Any insufficiency adjusted during this temporary period and a re-inspection is conducted. Score ratio of 90% or more grants 2-year accreditation period through deliberation of the committee. However when single area has received score ratio more than 80% but less than 90%, and given that this area is one of flow cytometry, histocompatibility, cytogenetics, molecular genetics or POCT, 2-year accreditation can be granted through deliberation with the accreditation of corresponding area the next year.

Institutions that joins the outstanding laboratory accreditation program receives 1-year accreditation for the first two years in their program. Comprehensive verification must not include any disqualified (zero point) items and requires score ratio of more than 80%, although irrelevant to the accreditation period. Referral testing area are separately subjected to accreditation with a maximum period given for 1-year. Any change of Laboratory Medicine specialist status, title of institution, locale or registration are to be reported to the Laboratory Medicine Foundation within 30-day period, according to results of deliberation may require additional accreditation. The director of the laboratory is to attend the inspection and submit an opinion report to the foundation. At the end of an inspection, details of the inspection are reviewed to prevent complaints being filed after the inspection has finished. In institutions with residents, 1<sup>st</sup> years in 2016 must attend the outstanding accreditation program equally as a subject of the inspection, submitting their signed report at the end of the inspection. The team leader of inspection shall appoint the team members with their assigned area for inspection, notifying the foundation of the selection. Each member of the team should not be assigned for more than 2 major area of the accreditation program, and sufficient number of members should be recruited. Items not pertinent to 'Not-Applicable' must be reviewed and the documents (for non-electronic inspections) sent to the foundation as soon as possible.

# SYMPOSIUM 04



SY04-02

## Detailed methods of quality control in 'Transfusion Medicine'

Duck Cho

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Quality management/quality control in hospital-based transfusion services is not only a program for control of laboratory testings and training of laboratory personnels, it can also be a program/system in other areas of the blood bank, including specimen collection, transportation of blood product, patient identification, transfusion Committee, utilization review and so on. Some selected issues will be presented here.

### 1. Quality control of Reagents

- Reagent quality control must be performed and documented each day of use and whenever a new vial is opened during the day. Each day, a technologist must confirm that the reagents react as expected when used. If a reagent does not give the expected results, the control must be repeated. The QC is done to test the quality and specificity of reagents
- The following reagents must be tested each day of use:
  - a. blood grouping anti-serums (anti-A, anti-B, anti-D)
  - b. reverse grouping cells (A1 cells, B cells)
  - c. antibody screening cells
  - d. antiglobulin reagent (Coomb's)
  - e. others

### 2. Misidentification risk

- Mistransfusion occurs from misidentification of the intended recipient at the time of collection of the pretransfusion testing sample, during laboratory testing and preparation of units to be issued, and at the time of transfusion risk (checklist of CAP accreditation program).
- Suggestion of further Reading; Prevention of ABO Incompatible Blood Transfusion: '2-2-2 Safe Blood Transfusion Campaign'. *Korean J Blood Transfus.* 2013 ;24(1):79-81.

### 3. Automation in the blood bank

- Automation in the transfusion service allows laboratories to better utilize their personnel, while increasing quality of pre-analytical steps, reducing error rates and operator exposure to potentially hazardous biological materials. It is also expected that automation can achieve a "zero error" rate because of the use of barcoded samples, lack of performance error during the analytical phase, and absence of errors in interpreting or reporting results during post-analytical phase. However, caution is still required and a good quality control program is required.

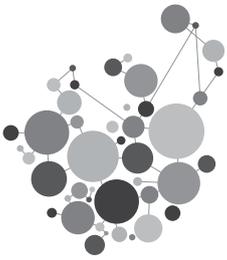
### 4. Selection of blood and components for transfusion

#### 4-1. Rh negative transfusion recipients

- The transfusion service has a written procedure for approving the transfusion of Rh-positive red cell-containing components to Rh-negative patients (checklist of CAP accreditation program).
- Suggestion of further reading; variants of RhD – current testing and clinical consequences. *British Journal of Haematology*, 2013, 161, 461-470

#### 4-2. Life-threatening situations

- Adequate policies and procedures have been established for the investigation and handling of life-threatening situations (such as the use of uncrossmatched blood or abbreviation of testing) that include the written authorization of a qualified physician (checklist of CAP accreditation program).
- Suggestion of further reading; Uncrossmatched blood transfusions for trauma patients in the emergency department: incidence, outcomes and recommendations. *Can J Surg.* 2011;54:111-5.



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SY04-03

## Quality management in flow cytometry laboratory

Dong Hee Whang

*Department of Laboratory Medicine, Inje University College of Medicine Seoul Paik Hospital, Seoul, Korea*

Immunophenotyping by flow cytometry is a robust and highly complex technology used in the enumeration and characterization of leukocytes. Samples consist of peripheral blood and many times irreplaceable samples, such as bone marrow. These samples are collected, transported, prepared, analyzed, and interpreted, resulting in diagnostic and prognostic information.

Results produced from flow cytometry laboratories needs to be as accurate and reliable as possible, since such information is critical to treatment decision for patient. How can we be confident in our results? The best solution would be the quality management of flow cytometry laboratory- establishment of optimized and standardized protocols and implementation of rigorous quality control programs encompassing preanalytic, analytic, and postanalytic processes.

The establishment of standardized protocols for each step of the process can reduce the potential margin for errors to occur. The flowcytometry laboratory should look at each step of the diagnostic process and validate that step to ensure that the results obtained are reliable.

### Standardization of protocols

The following list is the step where error may occur with potential variables.

#### Pre-analytical variable

- Specimen collection: patient information, labelling, clear indication of incorrect samples
- Anticoagulant: appropriate for target cells
- Sample transport and storage
- Viability
- Sample preparation
- Maximum allowed time gap between sampling and performance of the test

#### Analytical variable

- Morphology based panel selection in leukemia immunophenotyping
- Staining: appropriate clones of antibody, appropriate titer of antibody, fluorochrome, storage and expiration date of reagent, temperature and reaction time of cell-antibody mixture
- Lysing: method of lyse, incubation condition (how long and what temperature)
- Correct instrument setup, defined gating strategy
- Data acquisition and analysis: determination of appropriate number of events being acquired to ensure reliable results
- Staff with authority: appropriate training programs for new and experienced personnel

#### Post analytical variable

- Consolidated reports including clinical history, morphology findings and flowcytometry data
- Interpretation: age matched reference range
- Record retention: storage of raw data

This session focuses on quality control. Quality control in flow cytometry can be divided into two parts- internal quality control and external quality control.

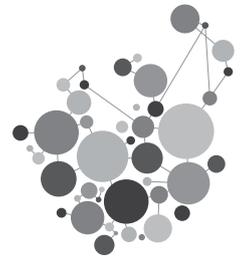
### Internal quality control

Internal quality control consists of a series of activities that are performed by the laboratories to ensure the instrument, reagent and staff are performing within the limits set by the laboratory.

Quality control of the instrument is divided into three procedures.

The first procedure is usually carried out once or twice a year by qualified service engineer who check the performance of components such as the lasers, photomultiplier tubes, optical filters, and log and linear

# SYMPOSIUM 04



amplifiers. The goal of optical alignment is to produce the brightest fluorescence and light scatter signal (measured as mean fluorescence channel) and the least variation (measured as percent coefficient of variation). Suboptimal alignment can lead to decreased fluorescence and light scatter signals, high signal variation, and increased noise.

The 2nd procedure is performed by the operator with each startup of the instrument (daily monitoring of performance). Using appropriate reference microbeads with dedicated plots and instrument settings, parameters such as CVs and mean median channel number can be recorded. Using Levey-Jennings plots, the data can be monitored for variation and trends. Tolerance limits can be assigned and protocols established to deal with values outside these limits.

The 3rd procedure consists of the calibration of the fluorescence channels. Calibration of flow cytometer's response to fluorescence signals is possible using microbeads, and there are many types of beads available. It is important to ensure that the instrument's response to fluorescence is both stable and reproducible over time, because the fluorescence signal intensity is used to discriminate between positive and negative populations.

In flow cytometry, when more than one fluorochrome are used concurrently that have overlapping emission spectrums; this spectral overlap needs to be eliminated or subtracted by a process called color compensation. This subtraction can be accomplished by using instrument setting or more recently, with software manipulation. Fluorescent compensation settings are linked to other instrument parameter, if change to PMT, voltage settings, laser power or optical filters are made, compensation settings must be revalidated. Appropriate compensation is essential for leukemia/lymphoma immunophenotyping.

Immunophenotyping is a very complex process and should be monitored by the use of appropriate control material like commercially available preparations. These preparations of either normal/ abnormal cells or cell lines fixed to preserve antigen staining characteristics. They can be either be suspensions of cells with no red blood cells present, known as part process controls, or with red blood cells present, known as full process controls.

There are many commercially prepared control cells available. Because of their stability, they can be used to monitor day to day reproducibility of the test being performed, and lot to lot reproducibility of reagents. They can also be used to establish scatter profiles of particular cell populations and demonstrate appropriate antibody binding. Some preparations have predefined percentages and/or absolute number of cell subsets present. Full process controls can also be used to check the lysing process. Documentation of internal control results is required as is noting the objective acceptability criteria for each population and each marker. Out of range values must be investigated and corrective action documented.

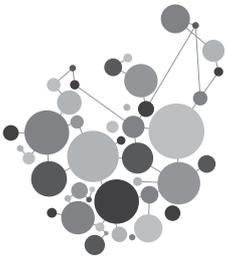
## External quality control

Control samples can be distributed on a regular basis and the laboratory is asked to process them as they would any other sample. Results are submitted back to a quality survey agency for analysis, and a report indicating the relative performance of each participating laboratory is issued. External quality control procedures check the complete process, from the technical side of sample preparation (staining, data analysis, interpretation) as well as the administrative part. (like error in reporting). Participation in any proficiency testing program is ideal and valuable. It facilitates direct inter-site comparisons, performance assessment and detailed method assessment, as well as emphasizing importance of methods, procedures or reagents used. Participation in external quality control schemes is also becoming increasingly required for regulation and accreditation. A great deal of data can be generated when we compare techniques, methods and reagents to those of a more experienced laboratory.

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SY04-04

## Questionnaires of 'Laboratory Information System (LIS)' and inspection

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### 1. Introduction

Laboratory Information System (hereinafter, LIS) is an important factor in the management of the laboratory, thereby it is possible to give various services from order entry to report. It is also essential for managing the flow of information among the laboratory, medical staff, and patients, and should be designed to optimize the clinical practice as well as laboratory management. Portion of the LIS of the laboratory management field of "good laboratory accreditation" is accounted for about 15% of requirements, and it is related with the whole of requirement distributed across all of the field. Examination for each module of the ideal LIS and important part of each requirement can help understanding the total laboratory process with the exact meaning of accreditation questions required for an objective assessment. And it is possible to examine the reality of the laboratory through each questionnaire result of requirements.

### 2. Analysis of requirements

According to the functional classification of the LIS, it can be divided into the information security, order entry, sample collection and processing, assay, results entry and verification, result reporting, notification management, data mining & cross sectional report, method validation, quality control, and administrative and financial issues, etc. (Fig. 1).

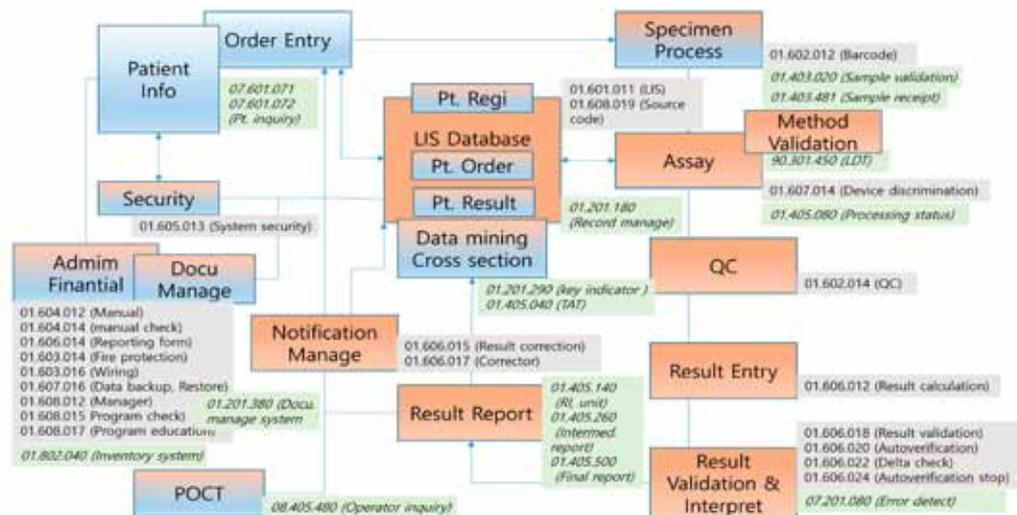


Fig. 1 Functional modules of LIS with each accreditation requirements

#### 1) Information security

The security features from unauthorized internal and external access to the user must be grouped according to different levels of security. The advanced login means (e.g. biosensor, RFID) are needed, and can be accessed by remote login tools into test entry and results (Web and mobile). It must also enable continuous real-time display of test results (e.g. operation room or emergency department pending stats). The electronic signature can also be worth a flexible and reliable.

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01.605.013 Are there the manual and the certificate of authority delegation to clearly identify the respective person who can use the computer system, have access to the patients' data, modify the results and change the program?

## 2) Test ordering

The system should receive inputs from the HIS or from the ordering provider (when the information is unavailable or inaccurate in the HIS) to include order provider, patient information, order information.

01.601.011 Is the laboratory utilizes regardless whether it is independent or partial to the hospital's information system?

01.608.019 Does the laboratory have the source codes of the LIS program?

## 3) Specimen collection and processing

Specimen collection lists as appropriate to institutional operation. Calculating a list of work to fit the sampling must inform the path and priority to access the patient in the most efficient. It can be entered information (sample number and sampling time, sampling site, whether fasting (last meal times), drug information, and difficulties in collecting) by sampling operator. The label must contain a minimum of two patient's recognizers and sampling date, sampling operator, emergency status, and test abbreviation may be included.

01.601.012 Is the laboratory use barcode to identify the specimen?

## 4) Analytic phase

Information on reagents, namely reagent name, manufacturer, should include the product number, lot number, laboratory arrival date, open date, capacity, expired date, and storage conditions and so on. Inspectors should be able to easily view and print work standard guidelines. Test equipment should be recorded respectively in the patient, and including equipment name, manufacturer, serial number, date of installation, the expected life, calibration history, and maintenance history. The worklist can be generated (a bundle, manual, automated tests), and must be able to show the incomplete list.

01.607.014 If same test items are performed by more than one piece of equipment, can the equipment be distinguished?

## 5) Result entry and validation

Results can be a variety of forms including numbers, letters, images, and should also be the same format as a table or graph from the outside through an electronic interface, including the referral laboratory. Also, the system should ensure that the results of the different stages and levels should have an expert system for automatic verification of results (delta check, cross-sectional check, specimen check, etc.)

01.606.012 Is the laboratory has manual and the evidence of performance which indicates that the accuracy of the computer calculations for the patient results (for example, an anion gap, etc.) should be annually checked?

01.606.018 Is there a confirmation process before reporting the final results of all the tests?

01.606.020 Are there the records that have verified the accuracy of automatic verification process?

01.606.022 Is the test items with delta check also excluded through the automatic verification process?

01.606.024 Does the laboratory has procedures to stop the automatic verification process immediately in case any problem such as an equipment malfunction occurs?

## 6) Result reporting

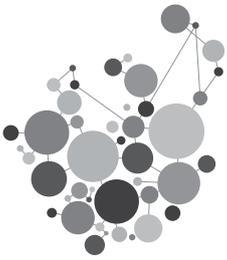
Standard reports and custom reports (test group, date, continuous or accumulated) should have a variety. For numeric unit results in addition to results, reference intervals, confidence interval analysis according to the variation, the flag, and an appropriate comment should be included.

## 7) Notification management

"Critical result" should have a reporting system for true positive results and increase the use of artificial intelligence and expert systems (dynamic vs fixed threshold). It should have the appropriate third party

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(infection control and public health departments) and rule-based notification system according to the test results. Any change or modification of the test results should also be notified immediately to the doctor.

- 01.606.015 If patient's results have been modified, is it possible to understand whether the new report, regardless of its type (report sheet, LIS screen, etc.), has been modified?  
01.606.017 Is there a proper system to identify all personnel who have edited the files?

### 8) Data mining and cross-sectional report

It can be used as a tool for the purposes of epidemiological research and clinical studies using the laboratory and clinical databases, for example, the report of turnaround time, the combination of the test results and clinical information, hospital infection reporting and survey of antibiotic resistance.

### 9) Method validation

Linearity, calibration verification, precision, correlation analysis, and interference test should be able to guide the statistical methods and graphs.

### 10) Quality management

The schedule of automatic quality control using criteria based on the total allowable error can be managed or should inform the examiner to be run. The results of the QC Levey-Jennings plot form should show a violation of the rules chosen by Westgard rules. This analysis should be performed and verified automatically stop when QC fails.

- 01.602.014 Is QC program being a part the one that composes the LIS?

### 11) Administrative and financial issues

Laboratory operating expense tracking, revenue analysis, workload analysis, productivity reporting, inventory management, document management, and personnel management, etc. are included.

- 01.604.012 Are the LIS manual and the computer instructions documented and accessible for an immediate use?  
01.604.014 Does the director of the Laboratory Medicine department or the Laboratory Medicine specialist review user manual and leave records at least once a year?  
01.606.014 Does the director of the Laboratory Medicine department periodically review and approve all the contents and formats of the reports that the computer has generated?  
01.607.016 Does laboratory has established preservation plans for data and equipment in case of fire, natural disaster or a failure of the software or hardware, etc.?  
01.608.012 Is the person who is responsible for receiving report of any critical system problems appointed in the laboratory?  
01.608.015 Does the laboratory has the manual and records for confirming if the system functions properly after an installation, change and a modification of a program; and of using the program?  
01.608.017 Does the laboratory has the records that all personnel have been fully trained for changes or new program of LIS?  
01.603.014 Is the fire-extinguishing facilities properly prepared in the computer room?  
01.603.016 Is the computer wiring (network and power cables) in the laboratory properly established and protected from the environment by being arranged in a conduit?

## 3. Result of Questionnaires

Organization answered to the questionnaire was 50 of 284 institutions (3<sup>rd</sup>;16, 2<sup>nd</sup>;28 1<sup>st</sup>;2, specialized referral laboratory;4). The result of answer is summarized to Table 1.

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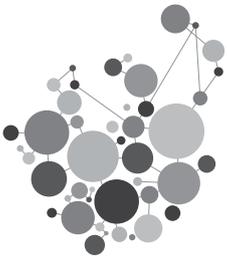


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Table 1. Summary of questionnaires about LIS and its result

Question	No. (%)	Others	
Labeling of common barcode	Pt. ID number	48(96%)	Container type; 13(26%) Sample volume; 6(12%) Infection information; 5(10%)
	Pt. name	49(98%)	
	Pt. age	20(40%)	
	Pt. sex	21(42%)	
	Working area	44(88%)	
	Sample type	47(94%)	
	Sample number	45(90%)	
	Order part	22(44%)	
	Test name	20(40%)	
Additional labeling on barcode for blood bank	Phlebotomist	29(58%)	Sampling time; 7(14%)
	ABO type	16(32%)	
	Blood component	6(12%)	
	Signature	9(18%)	
Barcode validation after reprinting	Dual check	37(74%)	
Use of stat barcode		42(84%)	
Labeling of stat barcode	Letter (e.g. E)	21(42%)	Number; 1 Comment; 1
	Color discrimination	17(34%)	
Data entry by interface		41(82%)	
LIS program	Self-development	29(58%)	
	3 <sup>rd</sup> party	20(40%)	
Westgard multi-rules	1 <sub>2s</sub>	38(76%)	
	1 <sub>3s</sub>	44(88%)	
	2 <sub>2s</sub>	44(88%)	
	R <sub>4s</sub>	40(80%)	
	4 <sub>1s</sub>	18(36%)	
	10x	20(40%)	
	2 of 3 <sub>2s</sub>	8(16%)	
Extinguisher	7 <sub>T</sub>	6(12%)	Clean extinguisher; 4(8%)
	CO <sub>2</sub>	8(16%)	
	Halon	33(66%)	
	Powder	16(32%)	
Access floor	Sprinkler	17(34%)	Protection cap; 12(24%)
		17(34%)	
Periodic cleaning of inner computer		21(42%)	
Support by hospital information team at site of accreditation audit		21(42%)	
Use of calculation formula in result	0-5	27(54%)	
	5-10	17(34%)	
	11-	6(12%)	
Recording after data correction	Result before correction	41(82%)	
	Result after correction	46(92%)	
	Corrector	42(84%)	
	Time of correction	43(86%)	
	Reason for correction	38(76%)	
	Supervisor	28(56%)	



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Result validation	Delta check	49(98%)	AMR check; 5(10%)
	Panic value check	49(98%)	
	CVR	45(90%)	
	Automatic verification	18(36%)	

#### 4. Q&A on bulletin board

1) Q: Should I verify all formula test including the calculated data from equipment such as A/G ratio? (01.606.012)

A: You can also check the results only excluded from the value provided by the testing equipment. You should list the kinds of calculations on a computer or LIS and have a document written for it.

2) Q: Following note is stated for 01.606.020 as 'The accuracy of the automatic validation process should be checked periodically'. Would you indicate a certain period specifically?

A: Usually, the period is judged by laboratory medicine specialist and documented on manual. In this case, it is expected to be determined in the conventional frequency of at least one a year, every quarter, or about 2 times per year.

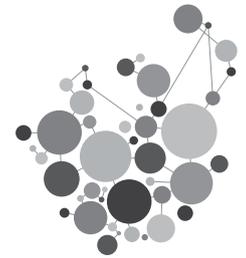
#### 5. Conclusion

The limit of ideal laboratory information system in laboratory management field depends on understanding what will be needed for laboratory and clinician and applying of the optimized tools. Its purpose is not for simply receiving certification audit or accreditation, but for upgrading it as a unique requirement development and training, and to find the circulation structure for correct audit. LIS should change in health care systems, new technologies or test equipment. Consequently, the professional knowledge to evaluate the LIS can be integrated into all aspect of laboratory with a focus on functional areas of total laboratory process.

#### 6. Reference

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# SYMPOSIUM 04



SY04-05

## Questionnaires of 'General Equipment and Instrument' and inspection

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### I. Overview

#### (1) As an element of a quality management

Proper management of equipment and instruments in a clinical laboratory is one of the essential elements of a quality management system. It is necessary to ensure accurate, reliable, and timely testing. The benefits of a good equipment management program are many as below:

- helps to maintain a high level of laboratory performance
- reduces variation in test results and improves the technologist's confidence in the accuracy of testing results
- lowers repair costs, as fewer repairs will be needed for a well-maintained instrument
- lengthens instrument life
- reduces interruption of services due to breakdowns and failures
- increases safety for workers
- produces greater customer satisfaction

Oversight of an equipment management program includes:

- assigning responsibilities for all activities
- assuring that all personnel are trained on operation and maintenance
- monitoring the equipment management activities
  - review all equipment records routinely
  - update maintenance procedures as necessary
  - ensure that all procedures are followed

#### (2) Oversight of equipment and instrument management

Day-to-day maintenance should be the responsibility of the technical operator. Everyone who uses the equipment should be trained in calibration and daily maintenance. However, it is the responsibility of the laboratory director to:

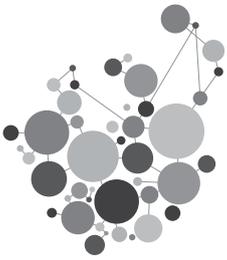
- oversee all the equipment management systems in the laboratory
- ensure that all persons who will be using the instruments have been appropriately trained and understand how to both properly operate the instrument and perform all necessary routine maintenance procedures. Equipment management responsibility may be specifically assigned to a technologist in the laboratory. In many laboratories there is a person who has good skills with equipment maintenance and troubleshooting. Giving this person the role of oversight of all equipment is recommended.

### II. Equipment and instrument management program

#### (1) Preventive maintenance

Preventive maintenance includes measures such as systematic and routine cleaning, adjustment, and replacement of equipment parts at scheduled intervals. Manufacturers generally recommend a set of equipment maintenance tasks that should be performed at regular intervals: daily, weekly, monthly, or yearly.

Following these recommendations will ensure that the equipment performs at maximum efficiency and will increase the lifespan of the equipment.



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## (2) Documentation

Each major piece of equipment will have its own equipment maintenance document. Smaller, commonly used equipment such as centrifuges and pipettes may be managed with an equipment maintenance document or manual that deals with all such equipment in the laboratory.

An equipment maintenance document should include:

- step-by-step instructions for routine maintenance, including frequency of performance, and how to keep records of performance
- instructions for carrying out function checks, frequency of performance, and how to record the results
- directions for calibrating the instrument
- guide for troubleshooting
- any required manufacturer's service and repair
- list of any specific items needed for use and maintenance, such as spare parts

## III. Management of commonly used laboratory equipment

### (1) Glassware

For new installations, the labwasher must be qualified first before the cleaning validation can be performed. For existing labs, the labwasher must be maintained and serviced in accordance with the manual. Then, an operational check plus a performance qualification of the labwasher should be done before proceeding with the cleaning. The best sources of help for validation/qualification requirements are the suppliers of the labwasher and detergent. They are the experts on the cleaning system, and working with them could save laboratories a lot of time and cost.

### (2) Pipettes

The major procedure for pipette maintenance is for verifying pipette performance using gravimetric tests of repeated aspirate and dispense cycles with distilled water (grade 3, ISO 3696), in controlled conditions. The procedure, which for small volumes includes a correction for evaporation loss, evaluates the total system of pipetting: pipette, tip, and operator. Therefore the procedure must be carried out by suitably qualified and trained technicians. In calculating the volumes from balance readings, corrections are made for the temperature and air pressure when the test was made (Z-factor).

ISO 8655 recommends that the gravimetric tests take place where the ambient and water temperature are stable ( $\pm 0.5$  °C) between 15 °C and 30 °C, the relative humidity is greater than 50%, and the barometric pressure is at  $1013 \pm 25$  hPa.

The Verification Procedure certifies both pipette accuracy and precision. Proper environmental conditions should be implemented to assure the validity of the test results. After pre-rinsing the tip, record ten individual weighings per selected volume. For variable volume pipettes, three volume settings are selected per pipette model based on the pipette's useful volume range (nominal, approximately 50% and minimum volume or 10% of the nominal volume). For fixed volume pipettes only the nominal volume is used.

- Set the pipette to its test volume.
- Estimate the evaporation loss (for small volumes).
- Perform the gravimetric test: record the weighings on the Verification Procedure Report.
- Perform the calculations: record the results on the Verification Procedure Report.
- Compare the results with the accuracy and precision specifications.

### (3) Analytical balances

Analytical balances are precision instruments that are important in clinical laboratories for accurate weighing. The most common uses include weighing for the preparation of reagents and for pipette calibration. Modern electronic analytical balances, used in the clinical laboratory, work on the principle of magnetic force restoration. When an object is weighed, the force that is registered is lifted by an electromagnet. The electrical current required to oppose the downward motion of the weight in the magnetic field is measured by a detector and converted to a weight that can be read on the balance's digital display panel.

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The required tests should be performed annually and under the following circumstances:

- Major maintenance is performed on the balance
- The balance is moved to a new location
- The performance of the balance is in question

Test Weights: Standard test weights should be treated as precision devices and handled with forceps. Direct hand contact should always be avoided. Care should also be taken to avoid sliding weight across any surface and especially stainless steel weighing pans. Weights should be stored in a covered protected box.

Temperature: The accuracy of an analytical balance is affected by room temperature. For the best stability there should be a variation of no more than one degree Celsius within any weighing period.

Air Drafts: Moving air will affect measurements of .001mg or less. An enclosure around the weighing pan to avoid fluctuations in moving air is recommended.

Static Electricity: Static electricity will affect the accuracy of an analytical balance. Sources of static electricity are carpets, plastic draft shields, and melamine or Formica table tops.

Vibration: Balances are very sensitive to any kind of vibration or movement. It may be necessary to obtain a very sturdy table for the analytical balance to minimize the affects of vibration or movement.

## (4) Thermometers

In the present computer age, thermometers may be grouped in electrical (i.e. which yield an electrical signal, like thermocouples and thermistors), and non-electrical (or mechanical, like mercury and bimetallic), which are seldom used in practice. The most used thermometer is the old liquid-in-glass familiar type. There are also chromophoric substances (in the shape of sticker labels, pellets, crayons, liquid crystals, etc).

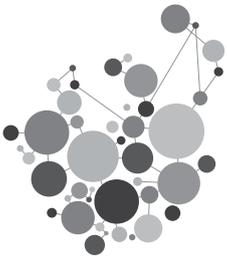
- Comparison with another calibrated thermometer at ambient temperature (NIST recommendation)  
For this measurement, we need to have another calibrated thermometer. We also will need a glass beaker or large cup, tap water at room temperature, a magnetic stir bar and a magnetic stirring plate, or a hot plate with a stirring option.

- ① Fill the beaker or cup so that the water is at least 20 cm (approximately 8 in.) deep.
- ② Let the water sit for 2 hours (or ideally, overnight) so that the water temperature is nearly the same as the room temperature.
- ③ Put the stir bar in the bottom of the beaker, place on the stir plate, and adjust to give a slow stir rate. The stir bar should revolve at about one revolution per second.
- ④ Insert the calibrated and test thermometers so that the tips of the probes are 10 cm to 15 cm (approximately 4 in. to 6 in.) below the surface of the water.
- ⑤ Wait 5 min.
- ⑥ Record the readings of the thermometer you are testing, and then the calibrated thermometer.
- ⑦ Repeat Step 5 and Step 6, but this time record the calibrated thermometer first, and then the test thermometer.
- ⑧ If the calibrated thermometer has a correction to apply, make this correction according to the calibration certificate for the results of both Step 5 and Step 6.
- ⑨ For both Step 5 and Step 6, subtract the corrected reading of the calibrated thermometer from the reading of the test thermometer. The result gives the error of the test thermometer.
- ⑩ The measured error from Steps 5 and 6 should agree to within the repeatability of the thermometer. If not, try repeating the series of measurements, beginning at Step 4.

## (5) Centrifuge

A new NIST or equivalent tachometer, timer or thermometer comes with a period of time for which it is certified. Centrifuge calibration/maintenance should include;

- Verification of rotation speed
- Verification of timer
- Verification of refrigeration temperature



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As a minimum, the manufacturers' guidelines should be followed. All three elements (rotation speed, timer, and refrigerator temperature) of centrifuge calibration verification that apply must be done when:

- the centrifuge is initially placed in service
- a malfunction is suspected
- after maintenance effecting function
- otherwise, at least once a year

### (6) Spectrophotometer

UV-Vis spectrophotometry is a frequently used technique in analytical laboratories for both quantitative and qualitative analysis. The quality of the results from the UV-Vis measurement depends on the performance of the spectrophotometer. It is necessary to verify the performance of the UV-Vis spectrophotometer according to a set of pre-determined criteria to ensure that the data generated by the system is reliable.

The performance tests includes :

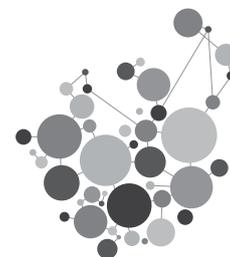
- wavelength accuracy
- wavelength reproducibility
- stray light
- resolution
- photometric accuracy
- photometric reproducibility
- noise
- baseline flatness
- system stability
- linearity of response

### IV. Summary

All laboratories should have a well-organized equipment management program. The program should address equipment selection, preventive maintenance, and procedures for troubleshooting and repair.

It is also essential that good documents and records be maintained. These will include a complete and accurate inventory of all laboratory equipment, documents provided by the manufacturer on operation, maintenance, and troubleshooting, and records of all preventive maintenance and repair activities including all of the commonly used smaller equipment in clinical laboratories.

# SYMPOSIUM 05



SY05-01

## Division of diagnostic hematology

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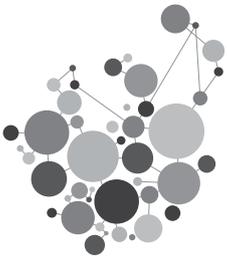
Residency program is an essential dimension of the transformation of the medical student to the independent practitioner along the continuum of medical education. The specialty education of physicians to practice independently is experiential, and necessarily occurs within the context of the health care delivery system. Developing the skills, knowledge, and attitudes leading to proficiency in all the domains of clinical competency requires the resident physician to assume personal responsibility for the care of individual patients. For the resident, the essential learning activity is interaction with patients under the guidance and supervision of faculty members who give value, context, and the meaning to those interactions. As residents gain experience and demonstrate growth in their ability to care for patients, they assume roles that permit them to exercise those skills with greater independence. This concept, graded and progressive responsibility, is one of the core tenets of American graduate medical education [1]. However, this is equally important in resident training and education programs for Laboratory Medicine of Korea.

The milestones were designed for use in evaluation of resident physicians in the context of their participation in the Accreditation Council for Graduate Medical Education (ACGME)-accredited residency programs. The milestones provide a framework for the assessment of the development of the resident physician in key dimensions of the elements of physician competency in a specialty or subspecialty. They are descriptors and targets for resident performance as a resident moves from entry into residency through graduation [2].

Diagnostic hematology is the practice of pathology concerned with the study and diagnosis of human diseases involving the hematopoietic tissues. Contrary to other fields in Laboratory Medicine, diagnostic hematology practitioners often feel pressure when interpreting hematology laboratory tests because their interpretation can be a critical factor to clinical management. For this reason, residents during diagnostic hematology training program must demonstrate competence interpersonal and communication skills that result in the effective exchange of information and collaboration with patients and their physicians. Medical knowledge and practice-based learning and improvement are of course the major components of the main items of residents' duty. In this session, I will suggest a proposal related to the professional core competency and milestones as well as evaluation methods which are appropriate to the particular circumstances of diagnostic hematology field.

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SY05-02

## Development of professional competency and competency assessment: Division of Clinical Chemistry

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### 1. Introduction

- The resident training committee in Korean Academy of Medical Sciences was to strengthen the capacity of common subjects and specific professional expertise throughout 2015-2016.
- Background of the study is to discharge the physician that fulfills the social responsibilities and competencies that meet specific criteria.
- Thus, the Korean Society of Laboratory Medicine organized task force team (TFT) to specify the training program improving the professional competencies and to develop appropriate evaluation program.
- TFT aimed to set a core competency for the domestic situation and to define the required behavior (milestone).

### 2. Resident training programs in foreign countries

- We investigated the resident training program in four countries: Accreditation Council for Graduate Medical Education (ACGME) of United States of America (USA), Royal College of Pathologist of United Kingdom, CanMEDS of Canada, and The Royal College of Pathologists of Australasia (RCPA) of Australia.
- Especially, here it will be dealt with the division of clinical chemistry

#### (1) USA

##### ① The Chemical Pathology Milestone Project

- The Milestones are designed only for use in evaluation of fellows in the context of their participation in ACGME-accredited residency or fellowship programs.
- The Milestones provide a framework for the assessment of the development of the fellow in key dimensions of the elements of physician competency in a specialty or subspecialty.

##### ② Milestone in Pathology

- Milestones are knowledge, skills, attitudes, and other attributes for each of the ACGME competencies.

##### ③ Milestone in Chemical Pathology

- For each period, review and reporting will involve selecting milestone levels that best describe each fellow's current performance and attributes.
- Milestones are arranged into numbered levels.
- Tracking from Level 1 to Level 5 is synonymous with moving from novice to expert in the subspecialty. These levels do not correspond with post-graduate year of education.
- Selection of a level implies that the fellow substantially demonstrates the milestones in that level, as well as those in lower levels.

Level 1: The fellow demonstrates milestones expected of an incoming fellow.

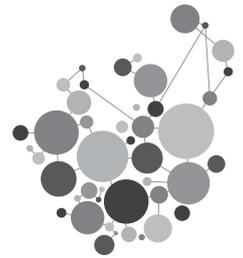
Level 2: The fellow is advancing and demonstrates additional milestones, but is not yet performing at a mid-fellowship level.

Level 3: The fellow continues to advance and demonstrate additional milestones, consistently including the majority of milestones targeted for fellowship.

Level 4: The fellow has advanced so that he or she now substantially demonstrates the milestones targeted for fellowship. This level is designed as the graduation target.

Level 5: The fellow has advanced beyond performance targets set for fellowship and is demonstrating

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“aspirational” goals which might describe the performance of someone who has been in practice for several years. It is expected that only a few exceptional fellows will reach this level.

#### ④ Core competency

- Practice-based Learning and Improvement (PBLI), Patient Care and Procedural Skills (PC), Systems-based Practice (SBP), Medical Knowledge (MK), Interpersonal and Communication Skills (ICS), and Professionalism (PROF)

- In Chemical Pathology, there are 15 ACGME Report Worksheet in Chemical Pathology Milestones: 2 PC, 3 MK, 3 SBP, 2 PBLI, 3 PROF, and 2 ICS (Table 1).

#### ⑤ Assessment tool for milestone [Table 2]

- Record review, Chart stim recall, Checklist, OSCE, Simulations & Models, 360° global rating, Portfolios, Exam oral, Procedure or case logs, Patient survey, and so on.

### (2) United Kingdom

- Royal College of Pathologist covers the resident training, and chemical pathology (ChP) is divided into medical fields relevant details laboratory medicine.

- There are core competencies, but specific milestone is not defined

- Assessment tool: Written exam, skills, on-site assessment,

- ChP training: 4 stages (A-D) and minimum 5 years are needed (12-24 months of training are needed in each stage): Table 3

- Residents can progress to the next step after learning the basic principles and technique for each stage and passing the test (workplace-based assessments, FRCP Path Part 1 or 2 etc.).

- Assessment tools: Workplace-based assessment, FRCPPath examination, and Annual Review of Competence Progression

- Workplace-based assessment

i. Case-based discussion (CbD) (minimum of 6 satisfactory outcomes required per year)

ii. Directly observed practical skills (DOPs) (minimum of 6 satisfactory outcomes required per year in ST1 and ST2)

iii. Evaluation of clinical events (ECE) (minimum of 6 satisfactory outcomes required per year)

iv. Mini-clinical evaluation exercise (Mini-CEX) (minimum of 6 satisfactory outcomes required per year)

v. Multi-source feedback (MSF) (minimum of 3 during training)

### (3) Canada

- Laboratory medicine discipline- General Pathology, Anatomical Pathology, Neuropathology, Hematological Pathology, Medical biochemistry, and Medical Microbiology

- Medical biochemistry : There must be adequate experience in test ordering and patient preparation, methodology, quality control, and interpretation of biochemical findings. In particular, there must be adequate experience in toxicology, newborn screening, immunoelectrophoresis, tumour markers, urine and other body fluid analysis, microscopy, and routine biochemical testing.

- Core competencies: Medical expert, Communicator, Collaborator, Manager, Health Advocate, Scholar, and Professional.

- Assessment tool for Medical Biochemistry: Written component (short answer question) and on-site assessment (Oral component)

- Feedback of assessment results should be carried out in accordance with regulations of ‘General Standards Applicable to All Residency Programs’.

### (4) Australia

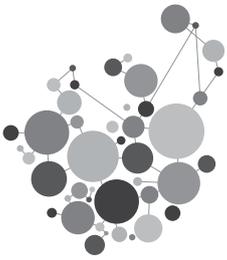
- In 2004, the RCPA established a program with the Royal Australasian College of Physicians (RACP) for trainees to train jointly in Endocrinology and Chemical Pathology.

#### ① Personal characteristics needed in chemical pathologist

- Strong aptitude for, and interest in, the scientific basis of medicine and laboratory work.

- The ability to lead, to work autonomously and to work well as part of a team of medical, nursing and laboratory staff, as well as the wider discipline of Pathology.

- The ability to make sound clinical judgments and to combine their laboratory and clinical roles seamlessly.



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- Familiarity with information systems and data analysis. The use of information systems is an integral part of practice in chemical pathology, where large amounts of numeric data are analysed.
- The ability to communicate well orally and in writing.
- The ability and willingness to guide and teach trainees.

### ② General aims of the training program

- Discipline specific functions as a medical specialist in the laboratory
- Functions as a manager in the laboratory
- Research and scholarship
- Professional attributes

### ③ Assessment (Table 4)

- Examinations: Basic Pathological Sciences examination (Usually taken before or during the first year of training), Chemical Pathology Part I examination (RCPA trainees may not take this examination until the third (3rd) year of training), and Chemical Pathology Part II examination (Trainees who pass Part I are eligible to sit for the Part II examination, which is ordinarily sat in the final year of chemical pathology training)
- Written assignments: In each of the first four (4) years of training, trainees must complete a 1500-2500 word assignment on topics designated by the chief examiner (a total of four assignments during training).
- Portfolio: The portfolio is a physical collection of workplace-based assessment forms and other documents that provide evidence that trainees have successfully completed a range of activities that form part of their daily work in the laboratory.
- Supervisor reports: Trainees must submit a supervisor report for each year of training, with additional reports for periods of rotation. Additionally a pre-exam report is required prior to oral component of the Part I and Part II exams.

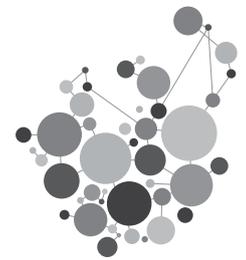
### 3. Training Guidelines for Resident in Laboratory Medicine (Korea)

- In Korea, Training Guidelines for Resident in Laboratory Medicine firstly established in 2002, and 3rd revised guidelines were published in 2014.
- In third edition of guidelines, molecular diagnostics and laboratory operating areas has expanded, and the infection control area was established.
- Mandatory training period was increased from 123 weeks to 130 weeks, and selected training courses (health medical examinations, specialized clinical laboratories, blood centers, bioethics, etc.) were established.
- In clinical chemistry, the contents to be addressed in 18 themes are divided into the essential learning goals and the necessary skills (Table 5)
- Essential learning goals: 113 basic levels (61%) and 73 advanced level (39%)
- Necessary skills: 79 basic levels (63%) and 46 advanced level (37%)

### 4. Improvement of training programs

- In current Training Guidelines for Residents in Laboratory Medicine, the items do not have specific difficulty settings, and the annual level is not broken.
- In addition, there is little proper evaluation of the training content, and no feedback is structured accordingly.
- The next goal is to develop the expertise and selection for the domestic status (Competency & milestones), to create a surface that can adequately evaluate the entries in the training guidelines for resident in Laboratory Medicine..
- By promoting the standardization of training for the specialty, we are going to minimize the difference in the degree of difference between training hospital residency training conditions.
- By developing an appropriate evaluation tool for the training program, it is expected to be an appropriate assessment of the individual's capabilities become available.

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## 5. References

- <http://www.acgme.org>
- <http://www.gmc-uk.org>
- <http://www.royalcollege.ca/portal/page/portal/rc/public>
- <http://www.rcpa.edu.au>
- Training Guidelines for Resident in Laboratory Medicine, 3rd (2014), The Korean Society for Laboratory Medicine

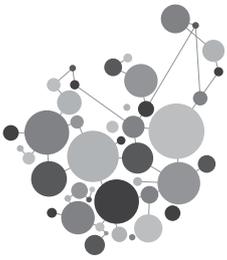
Table 1. An example of ACGME training program (Chemical Pathology)

PC2 — Interpretation, Reporting, and Diagnosis				
Level 1	Level 2	Level 3	Level 4	Level 5
Understands the indications for ordering specific tests	Understands principles of analysis and methodology of chemistry analytes	Understands more complex test platforms, methodology, and test indications	Understands the most complex test platforms, methodology, and test indications	Analyzes results of proficiency tests, identifies problems, and suggests corrective action
Observes and assists in the performance and interpretation of commonly used chemistry tests	Able to perform, interpret, and report commonly used chemistry tests	Able to perform and interpret all chemistry tests	Effectively teaches the salient features of chemistry testing, including the utility, and the strengths and limitations of the various methods of testing	Demonstrates expertise at the level expected of a subspecialist in chemical pathology
Becomes familiar with the test characteristics (e.g., sensitivity, specificity, and positive and negative predictive values (PPV and NPV)) for tests commonly used in chemical pathology, and understands how these affect the establishment of a definitive diagnosis	Observes and assists in the performance and interpretation of less commonly used (i.e., esoteric) chemistry tests	Understands the utility and methodology of currently outsourced chemistry tests	Interacts with other health care teams to discuss test results and make recommendations	
	Prepares a differential diagnosis for abnormal test results or findings	Observes and assists with interaction with other health care teams to discuss test results and make recommendations	Able to suggest an evidence-based diagnosis based on laboratory and clinical findings	
	Understands the strengths and limitations of tests commonly used in chemical pathology	Able to significantly narrow a differential diagnosis using laboratory and clinical findings		
	Becomes familiar with the test characteristics for less commonly used tests in chemical pathology, and understands how these affect the establishment of a definitive diagnosis	Understands justifications for additional testing		
		Understands the strengths and limitations of all tests used in chemical pathology, including those sent to a reference laboratory		
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Comments:				Not yet achieved Level 1 <input type="checkbox"/>

Table 2. An example of ACGME Competencies: Suggested Best Methods for Evaluation

Competency	Required Skill	Evaluation Methods												
		Record Review	Chart Stim. Recall	Check-list	Global Rating	SP	OSCE	Simulations & Models	360° Global Rating	Portfolios	Exam MCQ	Exam Oral	Procedure or Case Logs	Patient Survey
Patient Care	Caring and respectful behaviors			3		1			2					1
	Interviewing			1		2	1		3					
	Informed decision-making		1	2			2				2			
	Develop & carry out pt. Management plans	2	1	2	3			2	3					
	Counsel & educate pt's. & families			3		1	1		2					1
	Performance of procedures a) Routine physical exam			2		1	1							
	b) Medical procedures			1	3			1	2				3	
	Preventive health services	1				2	1			3			2	
Work within a team			3	3				1						

Ratings are 1 = the most desirable; 2 = the next best method; and, 3 = a potentially applicable method.  
 Director of Assessment Methods™ Accreditation Council for Graduate Medical Education (ACGME) and American Board of Medical Specialties (ABMS) Version 1.1.



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Table 3. Core Chemical Pathology Curriculum (STAGE A) - Laboratory Competencies in United Kingdom

Introduction to chemical pathology

Objective: to achieve sufficient knowledge of laboratory clinical biochemistry to offer basic advice on the interpretation of results.

Knowledge	Skills	Attitudes and behaviours
Principles of health and safety	Familiar with the principles of health and safety, particularly as they apply to laboratory working	Application to the working laboratory and avoiding risks.
IT and communication skills	Familiar with fundamental aspects of computing within the laboratory, databases, spreadsheets, internet. Use on a day-to-day basis.	Proactive attitude to new technology.
Principles of quality control and assurance	Discuss quality control and quality assurance. Explain External Quality Assurance (EQA) and National External Quality Assurance Service (NEQAS) Evaluate internal/external quality assurance data so as to identify the possible cause of aberrant data.	Applies principles to laboratory.
Presentation, diagnosis and management of common clinical biochemistry disorders	Recognise the biochemical/ metabolic features of diseases and their abnormal findings in the laboratory. Advise on the differential diagnosis and initial management of common clinical biochemistry disorders. Supervised participation in duty biochemist rota. Be aware of the need to consult about results that are not understandable.	Works as part of the clinical team. Relates laboratory results to patient care. Understanding the role of other specialties.

Table 4. Summary of assessment requirements for Part I of Chemical Pathology in the Royal College of Pathologists of Australia

Item	Completion	Assessed by	Comments
Written exams consisting of short answer, multiple choice and calculation questions	Before oral exam	Chief Examiner. Short answer questions are double marked by chemical pathology examiners.	Questions set by the Examinations Subcommittee.
Oral examination: multi-station set of structured interviews	After passing written exams.	Examiners with at least 5 years post-Fellowship experience	Questions set by the Examinations Subcommittee.

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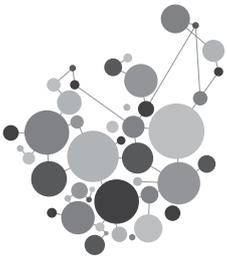


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Written assignments: One (1) per year, certified as candidate's own original work and signed off by supervisor or delegate before submitting for examination.	Two (2) to be completed before Part I written exams	Assessed by Chief Examiner or delegate prior to oral exam. Candidates may be required to revise and resubmit if not satisfactory.	Topics set by the Chief Examiner
Portfolio items to be signed off by supervisor or delegate.	All Part I requirements completed before Part I practical exams	Portfolio summary spreadsheet is checked for completeness by the BEA Registrar or Deputy Registrar. If incomplete, the candidate may be required to undertake further activities	Portfolio items are to be reviewed by the supervisor when preparing the supervisor report See Appendices 7, 8 The portfolio should not be sent to the College unless requested for audit
Supervisor reports for each year and/or rotation and an additional pre-oral exam report. A print copy of the portfolio summary spreadsheet must be appended to the annual report and the pre-oral exam report.	See RCPA web site for submission dates	Reviewed by BEA Registrar and Chief Examiner or delegate	Referral to Chief Examiner if necessary. See Appendix 4.

Table 5. Difficulty according to the training item in the division of clinical chemistry (Korea)

Training item	Essential learning goals		Necessary skills	
	Basic	Advanced	Basic	Advanced
1. Laboratory instruments and basic skills	12	0	9	0
2. Sampling and storage, the causes of physiological variation	7	0	4	0
3. Test device, method and principle	16	1	16	1
4. Chemistry analyzer and clinical laboratory automation	6	0	4	0
5. Comparison, selection and evaluation of the test method / setting reference values	11	0	4	0
6. Proteins and Enzymes	15	0	7	1
7. Tumor markers	4	1	11	0
8. Carbohydrates	9	1	4	1
9. Lipids profiles and tests of cardiovascular diseases	12	0	4	1
10. Electrolytes, minerals, bone metabolism tests, vitamins and trace elements	3	4	3	2
11. POCT and ABGA	4	3	4	2
12. Liver and biliary function tests	5	4	2	2
13. Renal function tests and urinalysis	5	3	4	3
14-1. Endocrine function tests - Hormones	4	4	3	3



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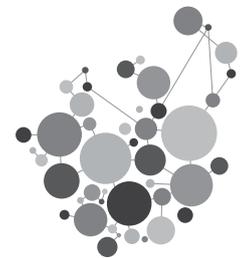
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14-2. Endocrine function tests - pregnancy tests and prenatal screening tests	0	6	0	7
15. Newborn screening tests and inherited metabolic disorders	0	13	0	13
16. Therapeutic drug monitoring and pharmacogenetics	0	23	0	5
17. Toxicology and heavy metals	0	10	0	5
Sum	113	73	79	46.
Proportion	61%	39%	63%	37%

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SY05-03

## Development of professional competency and competency assessment: division of diagnostic immunology

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### 1. Introduction

Korean Society of Laboratory Medicine organized task force team (TFT) was made to specify the training program improving the professional competencies and to develop appropriate evaluation program under the resident training committee in Korean Academy of Medical Sciences to strengthen the capacity of common subjects and specific professional expertise throughout 2015-2016.

### 2. Immunopathology training program in Australia

The TFT investigated the resident training program in four countries: Accreditation Council for Graduate Medical Education (ACGME) of United States of America (USA), Royal College of Pathologist of United Kingdom, CanMEDS of Canada, and The Royal College of Pathologists of Australasia (RCPA) of Australia. Especially, we can find the detailed forms for the immunopathology training in Australia.

The Royal College of Pathologists of Australasia (RCPA) has authority for the training program and quality assurance program for laboratories. RCPA has 9 disciplines; Anatomical Pathology, Chemical Pathology, Clinical Pathology, Forensic Pathology, General Pathology, Genetic Pathology, Haematology Pathology, Immunopathology, Microbiology. Each discipline has trainee handbook, portfolio-summary spreadsheet, and assignment topic.

The portfolio is a physical collection of workplace-based assessment forms and other documents that provide evidence that trainees have successfully completed a range of activities that form part of their daily work in the laboratory.

Trainee handbooks include the things to do, evidences of achievements and the evaluation parameters (Fig. 1). Assessment of the trainee includes several kinds of supervisor reports. The supervisor reports include assessment forms for case-based discussion (CbD) (Fig. 2), immunology teaching sessions, and the directly observed communication skill (DOCS). DOCS form should be completed for the 'phoning through results' (Fig. 3) and the 'oral presentations' (Fig. 4).

### 3. Training Guidelines for Resident in Laboratory Medicine (Korea)

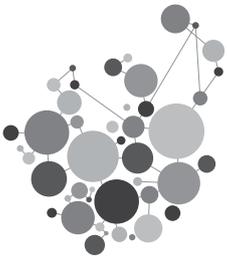
In Korea, third edition of training guidelines for resident in laboratory medicine was published in 2014. In diagnostic immunology, the contents to be addressed in 17 themes are divided into the essential learning goals and the necessary skills (Table 1). TFT classified the items into basic levels and advanced levels.

- Essential learning goals: 74 basic levels (54%) and 63 advanced level (46%)
- Necessary skills: 30 basic levels (58%) and 22 advanced level (42%)

### 4. Improvement of training programs

We need to focus what competencies are necessary for the board members of the Korean Society for Laboratory Medicine. The competencies might include the personal characteristics such as communication skills, ability to work autonomously, and ability to lead a team of staff. These essential competencies should be dealt in the training program and evaluation protocols.

TFT is going to classify the difficulty levels and the annual levels for training items. In addition, we need to develop the competency-assessment tools which should be performed and filled-up during the training program in each institution.



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<http://www.rcpa.edu.au>

Training Guidelines for Resident in Laboratory Medicine, 3rd (2014), The Korean Society for Laboratory Medicine

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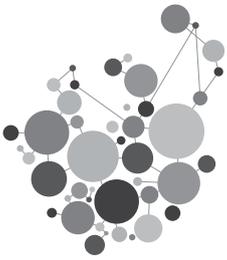


Figure 1. The trainee handbook for immunopathology trainee of RCPA

Item	Part I	Part II	Evidence
1 <b>Laboratory safety</b>	Checklist to be completed within 3 months of starting training.  Laboratory safety eLearning module to be completed during training		<b>Safety Checklist</b> - one only required during training.  <b>Certificate of completion</b> of eLearning safety module (see point 8 below)
2 <b>Supervisor report/s;</b> Portfolio summary spreadsheet to accompany annual and pre-exam reports	End-of-rotation and annual reports. An additional pre-exam report is required in the year of the Part II assessment  See RCPA website for submission dates.		<b>Supervisor Report Guidelines</b>  Appendix 4
3 <b>DOPS</b> A total of six (6) to be completed satisfactorily during training	Four (4) different instruments and/or techniques to be completed satisfactorily before Part I	An additional two (2) different instruments and/or techniques before Part II	<b>DOPS forms</b> Signed as satisfactory by supervisor or other appropriately qualified person.  Appendix 6
4 <b>DOCS</b>	One telephone DOCS every 3 months during full-time training.  One (1) oral presentation DOCS per year of full-time training.		<b>DOCS forms for</b> • <b>Telephone</b> • <b>Oral presentations</b> Signed as satisfactory by supervisor or other appropriately qualified person.  Appendix 6
Item	Part I	Part II	Evidence
5 <b>CbD</b> A minimum of 2 per year throughout training	Minimum two (2) per year for different types of cases before Part I exams	Minimum two (2) per year for different types of cases before Part II exams	<b>CbD forms</b> Signed as satisfactory by supervisor or other appropriately qualified person.  Appendix 6
6 <b>Laboratory investigations</b>	Investigations in all of these areas are to be carried out as opportunities arise during training: <ul style="list-style-type: none"> <li>• Autoimmune serology</li> <li>• Flow cytometry</li> <li>• Immunochemistry</li> <li>• Tissue typing</li> <li>• Lymphocyte function tests</li> <li>• Allergy tests</li> </ul> As trainees in some laboratories may not have access to the full range of these tests, no minimum number is required.		<b>Log book</b>  Trainees should record all investigations in a logbook.  Trainees should acquire a suitable logbook. It is <b>not</b> supplied by the College.  Signed as satisfactory by supervisor or other appropriately qualified person
7 <b>Teaching sessions</b> Minimum attendance of 12 per year and presentation at 3 per year during training.	Organise and attend small-group tutorials consisting of their peers, established immunopathologists, optimally including the supervisor(s).  Trainees should log sessions that they attend and record sessions that they present on the DOCS form (see above).		<b>Teaching sessions form</b> Teaching sessions that the trainee has attended and at which she/he has presented should be recorded in the form in Appendix 6  The supervisor should sight and sign off t logged sessions at supervisor's meetings and end-of-year formal review.
8 <b>Professional qualities eLearning modules</b>  Refer to Section 2 Learning outcomes and recommended training activities for weblinks	The following RCPA e-learning modules are required to be completed during training: Quality Management Laboratory Safety Ethics Cultural Competence		A <b>Certificate of completion</b> can be printed when the module has been completed (a workbook is required for the Ethics module).  Note: A cultural competence certificate issued by a recognised health service provider can substitute for the RCPA ethics module certificate.

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Figure 2. Immunopathology case-based discussion assessment form of RCPA

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		<b>Immunopathology          Case-based Discussion (CbD)          Assessment Form</b>				
<b>Trainee name</b>		<b>Trainee ID (RCPA)</b>	<b>Stage of training</b> Y1    Y2    Y3    Y4    Y5 if more than Yr5, please specify			
<b>Assessor name and position</b>						
<b>Focus of discussion</b>						
<input type="checkbox"/> An interesting or unusual autoantibody result (eg positive ANA with multiple ENAs, a positive anti-neuronal antibody); <input type="checkbox"/> An interesting or unusual fluorescence biopsy result; <input type="checkbox"/> An interesting or unusual immunophenotype; <input type="checkbox"/> A series of different positive results in the laboratory (eg cryoglobulinaemia, with a RF and paraprotein); <input type="checkbox"/> Other (please specify).....						
<b>Complexity of case (tick box)</b> <input type="checkbox"/> low <input type="checkbox"/> medium <input type="checkbox"/> high						
<b>Brief description of case presented, discussed and assessed</b>						
<b>Why was this case selected for discussion?</b>						
<b>Does this case broaden the trainee's experience by being different from previous cases that have been discussed?</b> <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> n/a						
<b>Please indicate whether these aspects of the trainee's performance are as expected or better than expected for the stage of training</b>				<b>Yes</b>	<b>No</b>	<b>n/a</b>
Ability to present case clearly and concisely						
Understanding of clinical issues relating to the case						
Understanding of laboratory issues relating to the case						
Understanding and awareness of current literature relevant to this case						
Ability to interpret results in a balanced and rational way						
Ability to provide and clearly communicate well reasoned professional advice						
Ability to correlate the laboratory test results with the patient's clinical presentation.						
Ability to suggest further relevant or more useful tests towards the management of the patient in relation to diagnosis and monitoring including prognostication.						
Understanding of management and financial aspects of the case						
Overall laboratory and clinical judgment						
<b>Please comment on other relevant aspects, especially on aspects for improvement (use the reverse side if insufficient room)</b>						
<b>Final outcome (please circle)</b>		<b>Date of assessment</b>	<b>Time taken for presentation</b>	<b>Time taken for feedback</b>		
As expected for the stage of training						
Below expected for the stage of training						
Name (print) and signature of assessor			Signature of trainee			
Laboratory						

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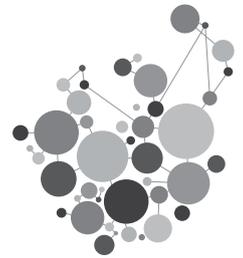
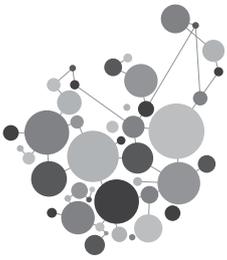


Figure 3. Directly observed communication skill report form for phoning through results of RCPA

		<b>Immunopathology</b> <b>DOCS form: phoning through results</b> (DOCS = Directly Observed Communication Skill) This form is to be completed by the observer	
<b>How to use this form</b> The supervisor should be present when the trainee rings through an important laboratory result (eg on speaker phone) and assess the trainee's ability to communicate the result and provide interpretative discussion. At the beginning of the call the trainee should disclose to the clinician that the supervisor is listening on speaker phone.  One form should be completed every three months of full-time training in Immunopathology (this will be a two-year period for joint trainees and a five-year period for RCPA-only trainees).  <b>Completed forms for are to be retained in the portfolio</b> and should be sighted by the supervisor and signed off on the annual supervisor report.			
<b>Trainee name</b>		<b>Trainee ID</b>	<b>Stage of training</b> (laboratory year for Joint trainees) Y1   Y2   Y3   Y4   Y5 if >Y5 please specify
<b>Observer/Assessor name</b>		<b>Observer/Assessor position</b> <input type="checkbox"/> consultant Immunopathologist <input type="checkbox"/> other (please specify):	
<b>Case description and number</b>			
<b>Please indicate whether these aspects of the trainee's performance are as expected (or better than expected) for the stage of training</b>			<b>Yes</b>
			<b>No</b>
			<b>n/a</b>
<b>Opening</b> State name, laboratory, verify identity of clinician, state reason for calling, allow time for clinician to find patient records.			
<b>Information sharing - quality of communication</b> Speak clearly at an appropriate pace for comprehension. Invite additional clinical information. Invite questions. Invite opinions. Confirms (directly or indirectly) that the clinician has understood the information shared			
<b>Information sharing - quality of information</b> Accurate synthesis of clinicopathological findings Suggest appropriate further investigations Discuss appropriate management plan			
<b>Closing</b> Explain what can be done if problem is not resolved. Give contact details for follow-up, including offering clinical consultation if needed.			
<b>Please comment on areas of strength and on areas for improvement.</b>			
<b>Final outcome (please circle)</b> As expected for the stage of training		<b>Date of assessment</b>	<b>Time taken for assessment</b>
Below expected for the stage of training			<b>Time taken for feedback</b>
Name (print) and signature of assessor		Signature of trainee	
Laboratory			



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Figure 4. Directly observed communication skill report form for oral presentation skills of RCPA

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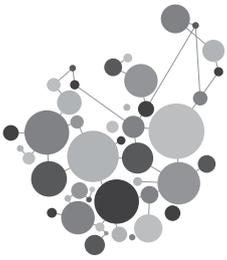
		<b>Immunopathology</b> <b>DOCS form for oral presentations</b> (DOCS = Directly Observed Communication Skill) This form is to be completed by the observer			
<b>How to use this form</b> <p>The trainee should present the pathology results for particular cases to a predominantly clinical audience. The supervisor or delegate should assess the trainee's ability to discuss the pathology and the diagnostic implications. Trainees should have a DOCS form completed for one presentation each year of training.</p> <p><b>Completed forms for are to be retained in the portfolio</b> and should be sighted by the supervisor and signed off on the annual supervisor report.</p>					
<b>Trainee name</b>		<b>Trainee ID</b>	<b>Stage of training</b> <i>(laboratory year for joint trainees)</i> Y1    Y2    Y3    Y4    Y5 if >Y5 please specify		
<b>Observer/Assessor name</b>		<b>Observer/Assessor position</b> <input type="checkbox"/> consultant pathologist <input type="checkbox"/> senior registrar <input type="checkbox"/> other (please specify)			
<b>Case description and number</b>					
<b>Please indicate whether these aspects of the trainee's performance are as expected (or better than expected) for the stage of training</b>			<b>Yes</b>	<b>No</b>	<b>n/a</b>
<b>Planning and organisation</b> Ideas organized into clear, concise, logical order Uses transitions and repetition to keep audience on track Content indicates effective prior planning					
<b>Content</b> Clearly defined and explained subject and main messages Stayed focused on main messages throughout Supplied appropriate amount of detail, examples, evidence Effective visual aids – visible to audience					
<b>Delivery</b> Language is clear, appropriate to purpose and audience Enunciates clearly, audibly, at appropriate pace Responsive to audience reaction – adapts delivery to meet their needs Responsive to audience questions, comments Uses the chosen technology competently					
<b>Please comment on areas of strength and on areas for improvement.</b>					
<b>Final outcome (please circle)</b> As expected for the stage of training Below expected for the stage of training		<b>Date of assessment</b>	<b>Time taken for assessment</b>	<b>Time taken for feedback</b>	
<b>Name (print) and signature of assessor</b>			<b>Signature of trainee</b>		
<b>Laboratory</b>					

# SYMPOSIUM 05



Table 1. Difficulty levels of the contents of training guidelines in the division of diagnostic immunology (Korea)

Training item	Essential learning goals		Necessary skills	
	Basic	Advanced	Basic	Advanced
1. Principles of immunoassays	14		6	
2. Serologic tests for syphilis	9		4	
3. Diagnosis and monitoring of HBV infection	7	2	5	1
4. Diagnosis and monitoring of HCV infection	6	3	2	1
5. Laboratory evaluation of immunodeficiency diseases and AIDS	4	4	2	
6. Diagnosis of viral infections associated with tumor, pregnancy, and immunosuppression	2	3	1	2
7. Immunoserologic diagnosis of infectious diseases	2	4	1	1
8. Clinical and laboratory evaluation of systemic rheumatic diseases	6	2	2	2
9. Vasculitis		6		2
10. Organ-specific autoimmune diseases		7		3
11. Tests for allergic diseases	6		3	
12. Tests for humoral immunity and immunoglobulins	9		3	
13. Complements and immune mediators		8		2
14. Laboratory evaluation of the cellular immune system	5	3	1	
15. Flowcytometry	4	5		3
16. Transplantation immunology and HLA		9		4
17. Tumor immunology and tumor markers		7		1
Totals	74	63	30	22



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SY05-04

## Development of professional competency and competency assessment: division of clinical microbiology

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### 1. Introduction

- The resident training committee of Korean Academy of Medical Sciences was to strengthen the capacity of common subjects and specific professional expertise throughout 2015-2016.
- Background of the study is to discharge the physician that fulfills the social responsibilities and competencies that meet specific criteria.
- Thus, the Korean Society of Laboratory Medicine organized task force team (TFT) to specify the training program improving the professional competencies and to develop appropriate evaluation program.
- TFT aimed to set a core competency for the domestic situation and to define the required behavior (milestone).

### 2. Resident training programs in foreign countries

- We investigated the resident training program in four countries: Accreditation Council for Graduate Medical Education (ACGME) of United States of America (USA), Royal College of Pathologist of United Kingdom, CanMEDS of Canada, and The Royal College of Pathologists of Australasia (RCPA) of Australia.
- Especially, here it will be dealt with the division of clinical microbiology.

#### [1] USA

##### ① Position of Clinical Laboratory Medicine

- As a part of pathology with anatomical pathology

##### ② Milestone Project

- The Milestones are designed only for use in evaluation of fellows in the context of their participation in ACGME-accredited residency or fellowship programs.
- The Milestones provide a framework for the assessment of the development of the fellow in key dimensions of the elements of physician competency in a specialty or subspecialty.
- Milestone in Pathology
  - : Milestones are knowledge, skills, attitudes, and other attributes for each of the ACGME competencies.
- Milestone in Clinical Microbiology
  - : Selection of a level implies that the fellow substantially demonstrates the milestones in that level, as well as those in lower levels

■ Level 1: The fellow demonstrates milestones expected of an incoming fellow.

■ Level 2: The fellow is advancing and demonstrates additional milestones, but is not yet performing at a mid-fellowship level.

■ Level 3: The fellow continues to advance and demonstrate additional milestones, consistently including the majority of milestones targeted for fellowship.

■ Level 4: The fellow has advanced so that he or she now substantially demonstrates the milestones targeted for fellowship. This level is designed as the graduation target.

■ Level 5: The fellow has advanced beyond performance targets set for fellowship and is demonstrating "aspirational" goals which might describe the performance of someone who has been in practice for several years. It is expected that only a few exceptional fellows will reach this level.



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## ③ Core competency

- Practice-based Learning and Improvement (PBLI), Patient Care and Procedural Skills (PC), Systems-based Practice (SBP), Medical Knowledge (MK), Interpersonal and Communication Skills (ICS), and Professionalism (PROF)
- In Chemical Pathology, there are 15 ACGME Report Worksheet in Chemical Pathology Milestones: 2 PC, 3 MK, 3 SBP, 2 PBLI, 3 PROF, and 2 ICS (Table 1).

## ④ Assessment tool for milestone

- Record review, Chart stim recall, Checklist, OSCE, Simulations & Models, 360° global rating, Portfolios, Exam oral, Procedure or case logs, Patient survey, and so on.

## (2) United Kingdom (Figure 1)

- Royal College of Pathologist covers the resident training, and medical microbiology is divided into general part and higher specialty training part.
- There are core competencies, but specific milestone is not defined
- Assessment tool: Written exam, skills, on-site assessment,
- Residents can progress to the next step after learning the basic principles and technique for each stage and passing the test (workplace-based assessments, FRCP Path Part 1 or 2 etc.).
- Assessment tools: Workplace-based assessment, FRCPPath examination, and Annual Review of Competence Progression
- Workplace-based assessment
  - Case-based discussion (CbD) (minimum of 6 satisfactory outcomes required per year)
  - Directly observed practical skills (DOPs) (minimum of 6 satisfactory outcomes required per year in ST1 and ST2)
  - Evaluation of clinical events (ECE) (minimum of 6 satisfactory outcomes required per year)
  - Mini-clinical evaluation exercise (Mini-CEX) (minimum of 6 satisfactory outcomes required per year)
  - Multi-source feedback (MSF) (minimum of 3 during training)

## (3) Canada

### ① Position of Clinical Laboratory Medicine

- As a part of general pathology with anatomical pathology
- There are primary specialties such as general pathology, hematological pathology, medical biochemistry, medical genetics, medical microbiology.

### ② Core competencies

#### Medical expert

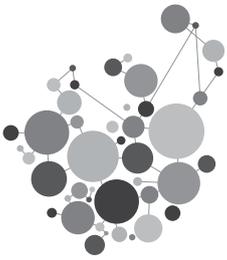
- Function effectively as consultants, integrating all of the CanMEDS Roles to provide optimal, ethical and patient-centered medical care
- Establish and maintain clinical knowledge, skills and attitudes appropriate to General Pathology
- Perform a complete and appropriate clinicopathological assessment of a case
- Use preventive and therapeutic interventions effectively
- Demonstrate proficient and appropriate use of procedural skills, both diagnostic and therapeutic
- Seek appropriate consultation from other health professionals, recognizing the limits of their own expertise

#### Communicator

- Develop rapport, trust, and ethical therapeutic relationships with patients and families
- Accurately elicit and synthesize relevant information and perspectives of patients and families, colleagues, and other professionals as appropriate
- Convey relevant information and explanations accurately to patients and families, colleagues and other professionals
- Develop a common understanding on issues, problems and plans with patients, families, and other professionals
- Convey effective oral and written information about a medical case

#### Collaborator

- Participate effectively and appropriately in an interprofessional health care team
- Work with other health professionals to prevent, negotiate, and resolve conflict



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### Manager

- Participate in activities that contribute to the effectiveness of their health care organizations and systems
- Manage their practice and career effectively
- Allocate finite health care resources appropriately
- Serve in administration and leadership roles, as appropriate

### Health Advocate

- Respond to individual patient health needs and issues as part of patient care
- Respond to the health needs of the communities that they serve
- Identify the determinants of health for the populations that they serve
- Promote the health of individual patients, communities, and populations

### Scholar

- Maintain and enhance professional activities through ongoing learning
- Critically evaluate medical information and its sources, and apply this appropriately to practice decisions
- Facilitate the learning of other health professionals, patients, families, students, residents, the public and others, as appropriate
- Contribute to the development, dissemination, and translation of new knowledge and practices

### Professional

- Demonstrate a commitment to their patients, profession, and society through ethical practice
- Demonstrate a commitment to their patients, profession and society through participation in profession-led regulation
- Demonstrate a commitment to physician health and sustainable practice

### ③ Milestones

- Objectives of Training in the Specialty of General Pathology, Final In-Training Evaluation Report (FITER)

### ④ Assessment and Feedback

- Written component, Practical component, Oral component
- Every rotation, feedback is provided according to the "GENERAL STANDARDS APPLICABLE TO ALL RESIDENCY PROGRAMS".
- Feedback form: "Final In-Training Evaluation Report (FITER)"

## (4) Australia

### ① Position of Clinical Laboratory Medicine

- As a part of general pathology
- Among the 9 parts of general pathology, 6 parts are related with laboratory medicine

### ② Core competencies

#### PERSONAL CHARACTERISTICS NEEDED

- the ability to make sound clinical judgments;
- good computing skills and organisational ability;
- the ability to lead, to work autonomously and to work well as part of a team of medical, nursing and laboratory staff as well as the wider discipline of Pathology;
- ability to be patient, inquiring, accurate, listen attentively, be persistent and self-motivated;
- good observation, interpretation and report-writing skills;
- an enjoyment of the scientific basis of medicine and research;
- the ability to communicate well orally and in writing;
- the ability and willingness to offer guidance and teaching to trainees in microbiology, medical, nursing and science undergraduate and postgraduate students

#### GENERAL AIMS OF THE TRAINING PROGRAM

- Competently use a microscope to examine specimens, troubleshoot problems, identify artifacts and staining problems and to ensure accurate and high quality material is available for the formulation of diagnostic opinions, as well as to be able to talk to scientific staff about the laboratory and its problems, and write a relevant report;
- Competently examine cultures, recognise contaminants, interpret antimicrobial susceptibility results and write a relevant report;



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- Competently interpret serological and molecular microbiology techniques and write a relevant report;
- Apply and interpret laboratory information relevant to clinical care;
- Apply clinical information to cost effective laboratory practice;
- Participate in and advise as part of the infection control team;
- Function effectively as a team member;
- Demonstrate sufficient knowledge and personal communication skills to regularly participate in microbiology review meetings and clinical rounds;
- have a working knowledge of laboratory management procedures including budgeting and financial probity, safety and human resources;
- Understand the need for, and principles of, continuing education and participation in the continuing professional development program (CPDP);
- Be prepared and able to offer guidance and teaching to trainees in microbiology; junior medical staff and undergraduate students;
- Be open to research opportunities and applications;
- Demonstrate commitment to professional and ethical values in the workplace and in clinical practice

### ③ Milestones

-Practical performance, topic review, oral presentation, phoning through results, case base discussion, student education

### ④ Assessment and Feedback

-In every part, there are tests including written component, practical component, oral component.  
-Feedback should be performed based on reports.

### 3. Training Guidelines for Resident in Laboratory Medicine (Korea)

-In Korea, Training Guidelines for Resident in Laboratory Medicine firstly established in 2002, and 3rd revised guidelines were published in 2014.

-In third edition of guidelines, molecular diagnostics and laboratory operating areas has expanded, and the infection control area was established.

-Mandatory training period was increased from 123 weeks to 130 weeks, and selected training courses (health medical examinations, specialized clinical laboratories, blood centers, bioethics, etc.) were established.

-In clinical microbiology, the contents to be addressed in 15 themes are divided into the essential learning goals and the necessary skills (Table 2)

-Essential learning goals: 115 basic levels (80%) and 28 advanced level (20%)

-Necessary skills: 79 basic levels (74%) and 28 advanced level (26%)

### 4. Improvement of training programs

- In current Training Guidelines for Residents in Laboratory Medicine, the items do not have specific difficulty settings, and the annual level is not broken.

- In addition, there is little proper evaluation of the training content, and no feedback is structured accordingly.

- The next goal is to develop the expertise and selection for the domestic status (Competency & milestones), to create a surface that can adequately evaluate the entries in the training guidelines for resident in Laboratory Medicine.

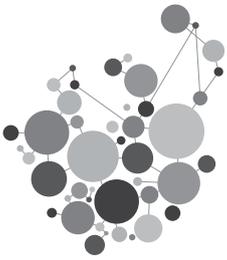
- By promoting the standardization of training for the specialty, we are going to minimize the difference in the degree of difference between training hospital residency training conditions.

- By developing an appropriate evaluation tool for the training program, it is expected to be an appropriate assessment of the individual's capabilities become available.

### 5. References

<http://www.acgme.org>

<http://www.gmc-uk.org>



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<http://www.royalcollege.ca/portal/page/portal/rc/public>

<http://www.rcpa.edu.au>

Training Guidelines for Resident in Laboratory Medicine, 3rd (2014), The Korean Society for Laboratory Medicine

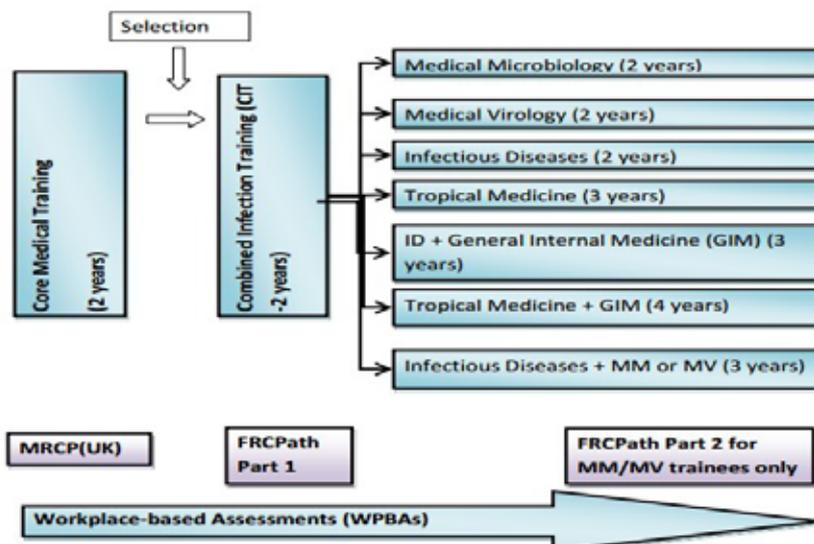
Table 1. An example of ACGME training program (Medical Microbiology)

Version 5/2014 Medical Microbiology Milestones: ACGME Report Worksheet

PC1 — Consultation				
Level 1	Level 2	Level 3	Level 4	Level 5
Understands the role of the medical microbiologist as a consultant to all health care providers  Observes and assists in the consultation	Performs clinically useful consultations in a timely manner with faculty member guidance (e.g., guiding appropriate test ordering, optimal specimen collection, results interpretation)	Independently performs clinically useful consultations in a timely manner (e.g., guiding appropriate test ordering, optimal specimen collection, results interpretation)  Effectively communicates consultative action plans and recommendations to other health care providers	Effectively teaches consultation skills to rotating residents and supervises resident consultations	Proficient in medical microbiology consultations, including those involving complex clinical scenarios
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Comments:				Not yet achieved Level 1 <input type="checkbox"/>

Suggested Evaluation Methods: Direct Observation, Portfolio, 360 Evaluations, EMR Review

Fig 1. Curriculum of specialty training in medical microbiology in United Kingdom



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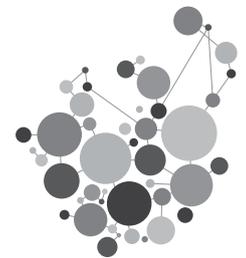


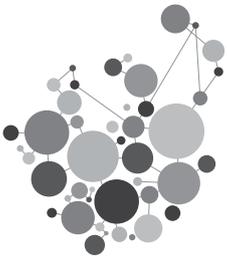
Table 2. Difficulty according to the training item in the division of clinical microbiology (Korea)

Training item	Essential learning goals		Necessary skills	
	Basic	Advanced	Basic	Advanced
1. General issues	5	2	6	4
2. Methods of infection diagnosis	7	2	5	3
3. Bacterial infection diagnosis: organ based	9	0	7	1
4. Pathogen detection and identification	5	2	4	2
5. Antimicrobials and Antimicrobial susceptibility testing	12	7	5	1
6. Gram positive cocci	5	2	7	4
7. Gram positive rod	5	0	10	0
8. Gram negative rod	10	2	2	6
9. Gram negative cocci	3	0	1	0
10. Mycobacteria	6	4	8	5
11. Anaerobes	10	3	3	0
12. Mycoplasma	6	0	6	0
13. Virus	8	0	5	0
14. Fungus	8	3	6	2
15. Parasites	16	1	4	0
Total	115(80%)	28(20%)	79(74%)	28(26%)

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## Development of professional competency and competency assessment: division of transfusion medicine

Chunhwa Ihm<sup>1\*</sup> and Kyung hee Kim<sup>2</sup>

<sup>1</sup>Department of Laboratory Medicine, Eulji University Hospital, Daejeon, Korea, <sup>2</sup>Department of Laboratory Medicine, Gil University Hospital, Incheon, Korea

### 1. Introduction

The Korean Society of Laboratory Medicine organized TFT to specify the training program improving the professional competencies and to develop appropriate evaluation program, which is supported by residency training committee in Korean Academy of Medical Sciences. TFT has been working to set a core competency and to define the required behavior (milestone) for the domestic situation.

Here, it will be dealt with the residency (occasionally fellow) training program of foreign countries as well as the Korean system, especially about the division of transfusion medicine.

### 2. Training programs of transfusion medicine in foreign countries

- Training program in four countries

: Accreditation Council for Graduate Medical Education (ACGME) of United States of America (USA), Royal College of Pathologist of United Kingdom, CanMEDS of Canada, and The Royal College of Pathologists of Australasia (RCPA) of Australia.

#### 1) USA (Table 1)

(1) The Blood Banking and Transfusion Medicine Milestone Project

- The Milestones are designed only for use in evaluation of fellows in the context of their participation in ACGME-accredited residency or fellowship programs.

- The Milestones provide a framework for the assessment of the development of the fellow in key dimensions of the elements of physician competency in a specialty or subspecialty.

(2) Milestone in Pathology

- Milestones are knowledge, skills, attitudes, and other attributes for each of the ACGME competencies.

(3) Milestone in Blood Banking and Transfusion Medicine

- For each period, review and reporting will involve selecting milestone levels that best describe each fellow's current performance and attributes.

- Milestones are arranged into numbered levels.

- Tracking from Level 1 to Level 5 is synonymous with moving from novice to expert in the subspecialty. These levels do not correspond with post-graduate year of education.

- Selection of a level implies that the fellow substantially demonstrates the milestones in that level, as well as those in lower levels.

Level 1: The fellow demonstrates milestones expected of an incoming fellow.

Level 2: The fellow is advancing and demonstrates additional milestones, but is not yet performing at a mid-fellowship level.

Level 3: The fellow continues to advance and demonstrate additional milestones, consistently including the majority of milestones targeted for fellowship.

Level 4: The fellow has advanced so that he or she now substantially demonstrates the milestones targeted for fellowship. This level is designed as the graduation target.

Level 5: The fellow has advanced beyond performance targets set for fellowship and is demonstrating "aspirational" goals which might describe the performance of someone who has been in practice for several years. It is expected that only a few exceptional fellows will reach this level.

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## (4) Core competency

- Practice-based Learning and Improvement (PBLI), Patient Care and Procedural Skills (PC), Systems-based Practice (SBP), Medical Knowledge (MK), Interpersonal and Communication Skills (ICS), and Professionalism (PROF)
  - In Blood Banking and Transfusion Medicine, there are 16 ACGME Report Worksheet in Blood Banking and Transfusion Medicine Milestones: 3 PC, 2 MK, 3 SBP, 3 PBLI, 3 PROF, and 2 ICS (Table 1).
- (5) Assessment tool for milestone
- Record review, Chart stim recall, Checklist, OSCE, Simulations & Models, 360° global rating, Portfolios, Exam oral, Procedure or case logs, Patient survey, and so on.

## 2) United Kingdom (Table 2)

### (1) In general

Clinical haematology in the UK encompasses both clinical and laboratory aspects of the specialty. This curriculum describes specialist training in clinical haematology. In the UK specialists in haematology are both clinicians involved in direct patient care and haematology pathology laboratory practitioners, therefore specialist training covers both components, including training in transfusion medicine.

### (2) Training will be undertaken in haematology training posts which:

- include core and special interest haematology, including haematological oncology, transplantation, paediatric haematology, haemostasis and thrombosis and blood transfusion practice
- allow the trainee exposure to the broad range of diseases of the blood and bone marrow, both primary and secondary to other systemic disease
- permit haematology training in a range of different settings including an academic environment, a District

### (2) Blood Transfusion

The trainee will need to acquire a basic knowledge of blood transfusion practice to be able to provide advice in transfusion related matters to clinical colleagues and provide laboratory staff with clinical advice. The trainee wishing to pursue a career in blood transfusion may spend a significant period of training in the special interest area after acquiring basic haematology training.

## 3) Canada

### (1) Laboratory medicine discipline

- General Pathology, Anatomical Pathology, Neuropathology, Hematological Pathology & transfusion medicine, Medical biochemistry, and Medical Microbiology

### (2) Transfusion medicine

- There must be adequate experience in transfusion medicine, hemostasis and coagulation, morphology, immunohistochemistry, flow cytometry, applied molecular diagnostics, cytogenetics, and interpretation of these results.

### (3) Core competencies

- Medical expert, Communicator, Collaborator, Manager, Health Advocate, Scholar, and Professional.

### (4) Assessment tool

- Written component, Practical component, Oral component
- Feedback of assessment results should be carried out in accordance with regulations of 'General Standards Applicable to All Residency Programs' using Final In-Training Evaluation Report (FITER).

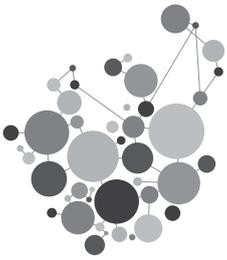
## 4) Australia

### (1) In general

Haematology encompasses both clinical and laboratory aspects of primary disorders of the blood as well as how other diseases affect the blood.

To gain the FRCPA (Fellow of the) Royal College of Pathologists of Australasia)

In haematology requires five (5) years of accredited training and satisfactory completion of the assessment program detailed below. There are two pathways. Training may be undertaken fully according to the RCPA



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Fellowship program (FRCPA) or under a joint training program with the Royal Australasian College of Physicians (RACP, (Fellow of the) Royal Australasian College of Physicians). Trainees in both pathways undertake the same examinations. No more than four (4) years in the one institution will be allowed for RCPA trainees and three (3) years for joint RCPA-RACP trainees.

(2) General aims of the training program

- Discipline specific functions as a medical specialist in the laboratory
- Functions as a manager in the haematology laboratory
- Research and scholarship
- Professional qualities

(3) Assessment

- Trainees in both the single and dual discipline pathways undertake the same examinations, which are solely under the control of the RCPA Board of Education and Assessment.
- Assessment is by formal examination and by submission of a portfolio, which is a record of workplace-based assessment and other achievements during training. The periodic and annual supervisor reports are also kept in the portfolio. The requirements are summarised below.

- Examinations

Basic Pathological Sciences examination, usually taken before or during the first year of training. All trainees are required to undertake (or apply for exemption from) the Basic Pathological Sciences examination. Whilst Joint trainees who have completed the requirements of Basic Physician Training are exempt, they must formally apply for exemption.

-The Haematology Part I examination, with written, practical and oral components. This examination may be taken by RCPA single discipline trainees during or after their third year of training, or by Joint RACP/RCPA trainees who have completed a minimum aggregate of 18 months of accredited laboratory training at the time of the examination.

-The Haematology Part II examination consists of an oral component and a review of training, original work and publications. This examination may not be attempted until the final year of approved training.

-All durations refer to full-time training or part-time equivalent training in an accredited laboratory.

### 3. Training Guidelines for Resident in Laboratory Medicine (Korea) (Table 3)

- In Korea, the 1st Training Guidelines for Residency in Laboratory Medicine established in 2002, and 3rd revised guidelines were published in 2014.
- In transfusion medicine, the contents to be addressed in 12 themes are divided into the essential learning goals and the necessary skills.
- Essential learning goals: 33 basic levels (47%) and 37 advanced level (53%)
- Necessary skills: 20 basic levels (54%) and 17 advanced level (46%)

### 4. References

<http://www.acgme.org>

<http://www.gmc-uk.org>

<http://www.royalcollege.ca/portal/page/portal/rc/public>

<http://www.rcpa.edu.au>

Training Guidelines for Resident in Laboratory Medicine, 3rd (2014), The Korean Society for Laboratory Medicine

# SYMPOSIUM 05

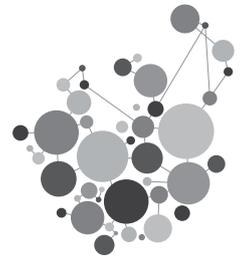
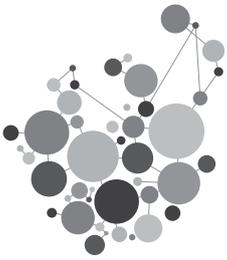


Table 1. An example of ACGME training program (Blood Banking and Transfusion Medicine)

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PC1 – Consultation				
Level 1	Level 2	Level 3	Level 4	Level 5
Understands the role of the consultant in blood banking/transfusion medicine (BB/TM) (including therapeutic apheresis)  Observes and assists in the consultation  Able to use the electronic medical record (EMR) and other electronic resources to obtain clinical and disease information	Performs timely, clinically useful consultation for requests for blood products, apheresis, transfusion reactions, and other immunohematology work-ups and evaluations  Independently prepares full and complete consultative reports	Effectively communicates consultative recommendations and action plans  Develops a portfolio of consultations	Competently and independently performs consultation during night and weekend emergent situations, as well as during normal hours  Effectively teaches rotating residents and fellows in performing consultations	Demonstrates proficiency at BB/TM consultation
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Comments:				Not yet achieved Level 1 <input type="checkbox"/>

PC2 – Interpretation, Reporting, and Diagnosis				
Level 1	Level 2	Level 3	Level 4	Level 5
Observes and assists in the interpretation of immunohematology tests  Understands basic indications for tests	Accurately interprets and reports results  Understands basic test platforms and methodology	Prepares a differential diagnosis for abnormal test results or findings  Demonstrates knowledge of the current literature related to test results and testing algorithms  Critically evaluates and applies the current literature	Interacts with other health care teams to discuss test results and make recommendations  Understands justifications for additional testing  Effectively teaches rotating residents and fellows in performing consultations	Demonstrates proficiency in interpretation, reporting, and diagnosis in BB/TM
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Comments:				Not yet achieved Level 1 <input type="checkbox"/>



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Table 2. Transfusion medicine Curriculum (STAGE A) – Hematology Competencies in United Kingdom

Objective – To acquire sufficient knowledge of blood transfusion practice to provide safe advice to clinical colleagues in a general hospital

Knowledge	Skills	Attitudes
Outline the principles of blood transfusion laboratory practice including : -Blood grouping -Identification of allo and auto antibodies -Crossmatching techniques -Automation in blood transfusion -Use of computers in blood transfusion	Interprets blood transfusion laboratory results to an adequate standard	Liases between laboratory and clinical staff
Describe the basic principles of donor selection and the preparation of blood components including: -Donor safety -Preparation of blood components, including for paediatric/neonatal use -Donation testing -Role of Quality System		Recognises the hazards of transfusion of blood products
Describe the principles of clinical blood transfusion practice including : -Hazards of blood transfusion -Appropriate use of blood products -Special requirements -Alternatives to blood and blood products -Exchange transfusion and plasma exchange therapy -SHOT and SABRE reporting -The role of the Hospital Transfusion committee -Organisation of the laboratory and relevant transfusion legislation	Practices the appropriate use of blood and blood products Manages complications of blood transfusion appropriately Gives appropriate advice in patients with allo or auto antibodies, including in pregnancy Advises appropriately on the indications for exchange transfusion and plasma exchange	

Table 3. Difficulty according to the training item in the division of transfusion medicine (Korea)

Training item	Essential learning goals		Necessary skills	
	Basic	Advanced	Basic	Advanced
1. Blood donation and blood components	3	4	3	2
2. Blood donor test & transfusion transmitted infections	6	3	1	1
3. RBC antigen-antibody reactions	4	2	3	4
4. Blood grouping	7	2	4	2
5. Pretransfusion testing	4	3	5	2
6. Blood bank management	1	3	2	1
7. Blood transfusion practice	5	2	2	1



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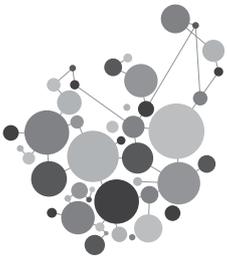
8. Transfusion in special condition	0	6	0	1
9. Complications of blood transfusion	2	2	0	1
10. Therapeutic apheresis & cell therapy	1	10	0	2
Sum	33	37	20	17

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SY05-06

## Development of professional competency and competency assessment: division of molecular diagnostics

Moon-Woo Seong

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### 1. Residency programs in overseas countries

#### (1) USA

- ① Medical Genetics and Genomics Specialty
  - Three subspecialties: Clinical informatics, Medical biochemical genetics, Molecular genetic pathology
- ② Medical Genetics and Genomics Milestone
  - The milestones provide a framework for assessment of the development of the resident physician in key dimensions of the elements of physician competency in a specialty or subspecialty (Table 1 & 2)
  - Milestone level: level 1 (milestones expected of an incoming resident) ~ 5 (advanced beyond performance targets set for residency and is demonstrating "aspirational" goals)

Table 1. Example of Medical Genetics and Genomics Milestone Project

Obtain and interpret medical, social, and family histories, as well as physical exam findings necessary for the evaluation of patients with or at-risk for genetic disorders — Patient Care				
Level 1	Level 2	Level 3	Level 4	Level 5
<input type="checkbox"/> Obtains general medical and social history	<input type="checkbox"/> Obtains and interprets a genetics-focused family, medical, and social history with substantial guidance	<input type="checkbox"/> Obtains and interprets a genetics-focused family, medical, and social history with minimal guidance	<input type="checkbox"/> Independently obtains and interprets a genetics-focused family, medical, and social history	<input type="checkbox"/> Makes a nationally recognized contribution by discovering a new genetic or congenital entity or mechanism
<input type="checkbox"/> Constructs pedigrees and recognizes simple patterns of inheritance	<input type="checkbox"/> Performs a genetics-focused physical examination with substantial guidance	<input type="checkbox"/> Performs a genetics-focused physical examination with minimal guidance	<input type="checkbox"/> Independently performs a genetics-focused physical examination	<input type="checkbox"/> Makes a nationally recognized contribution by developing educational materials for patients and/or providers
<input type="checkbox"/> Performs general medical examination for children and adults	<input type="checkbox"/> Synthesizes findings from history and physical exam to make a diagnosis with substantial guidance	<input type="checkbox"/> Synthesizes findings from history and physical exam to make a diagnosis with minimal guidance	<input type="checkbox"/> Independently synthesizes findings from history and physical exam to make a diagnosis	<input type="checkbox"/> Makes a nationally recognized contribution by participating in the development of clinical practice guidelines
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Comments:				Not yet rotated <input type="checkbox"/>

Table 2 Subcompetency in Milestone Project

Patient Care	Obtain and interpret medical, social, and family histories, as well as physical exam findings necessary for the evaluation of patients with or at-risk for genetic disorders
	Incorporate genetic tests into patient management
	Incorporate whole genome or exome tests into patient management
	Diagnose and manage patients with inborn errors of metabolism
	Evaluates infants with abnormal newborn screens in a cost-effective and sensitive manner and educates community providers
	Develop proficiency in cancer genetics

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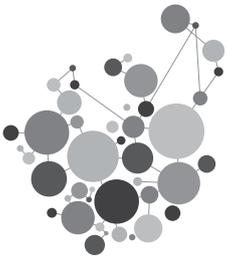
	Evaluate and manage patients with single malformations, multiple congenital anomalies, developmental disabilities, and growth abnormalities by utilizing knowledge of embryology, teratology, developmental pathways, pathophysiology, and etiologic mechanisms
	Develop proficiency in prenatal risk assessment, screening, diagnosis, and counseling
	Provide longitudinal management and reproductive counseling in pregnancies with known or suspected genetic conditions in the mother or fetus
Medical Knowledge	Apply knowledge of anatomy, development, pathophysiology, natural history, clinical history, and inheritance to provide counseling, anticipatory guidance, and longitudinal management to patients with multisystem genetic disorders
	Assess and participate in a clinical or translational research study or clinical trial involving patients with or at-risk for a genetic disorder
Systems-based Practice	Function effectively within the larger context of health care systems, and practice cost-effective medicine
	Use technology to accomplish safe health care delivery
Practice-based Learning and Improvement	Implement a quality improvement project
Professionalism	Is sensitive and responsive to diverse patient populations with respect to gender, age, culture, race, religion, disabilities, and sexual orientation
	Adhere to the ethical principles relevant to the practice of medicine
	Demonstrate personal responsibility to maintain emotional, physical, and mental health and accountability to patients, society, and the profession
Interpersonal and Communication Skills	Relationship building, teamwork, and conflict management
	Information gathering and sharing

## (2) United Kingdom

- Royal College of Pathologist covers Chemical pathology, Medical microbiology and virology
- Joint Royal Colleges of Physicians Training Board covers Clinical Genetics specialty
- There are core competencies, but specific milestone is not defined
- Assessment tool: Written exam, skills, on-site assessment,

## 2. Training Guidelines for Resident in Laboratory Medicine (Korea)

- In Korea, Training Guidelines for Resident in Laboratory Medicine firstly established in 2002, and 3rd revised guidelines were published in 2014.
- In third edition of guidelines, molecular diagnostics and laboratory operating areas has expanded, and the infection control area was established.
- Mandatory training period was increased from 123 weeks to 130 weeks, and selected training courses (health medical examinations, specialized clinical laboratories, blood centers, bioethics, etc.) were established.
- In molecular diagnostics, the contents to be addressed in 8 themes are divided into the essential learning goals and the necessary skills (Table 3)
- Essential learning goals: 56 basic levels (59%) and 39 advanced level (41%)
- Necessary skills: 22 basic levels (32%) and 46 advanced level (68%)



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Table 3. Difficulty according to the training item in the division of clinical chemistry (Korea)

Training item	Essential learning goals		Necessary skills	
	Basic	Advanced	Basic	Advanced
1. Cytogenetic diagnosis for constitutional disorders	7	5	1	1
2. Cytogenetic diagnosis for hematologic malignancies	5	2		2
3. Cytogenetics for prenatal diagnosis	6	4		2
4. Molecular cytogenetics	7	4	1	2
5. Principles and technologies in molecular diagnosis	8	7	1	2
6. Molecular diagnosis for genetic diseases	4	6	1	1
7. Molecular diagnosis for malignant disorders	4	3	1	3
8. Molecular diagnosis for infectious diseases	8	3	1	1
Sum	56	39	7	4615
Proportion	59%	41%	32%	68%

### 3. Improvement of training programs

- In current Training Guidelines for Residents in Laboratory Medicine, the items do not have specific difficulty settings, and the annual level is not broken.
- In addition, there is little proper evaluation of the training content, and no feedback is structured accordingly.
- The next goal is to develop the expertise and selection for the domestic status (Competency & milestones), to create a surface that can adequately evaluate the entries in the training guidelines for resident in Laboratory Medicine..
- By promoting the standardization of training for the specialty, we are going to minimize the difference in the degree of difference between training hospital residency training conditions.
- By developing an appropriate evaluation tool for the training program, it is expected to be an appropriate assessment of the individual's capabilities become available.

### 4. References

- <http://www.acgme.org>
- <http://www.gmc-uk.org>
- <http://www.royalcollege.ca/portal/page/portal/rc/public>
- <http://www.rcpa.edu.au>
- Training Guidelines for Resident in Laboratory Medicine, 3rd (2014), The Korean Society for Laboratory Medicine



# SYMPOSIUM 06

SY06-01

## The role of the laboratory medicine in nutritional support

Ian S.Young

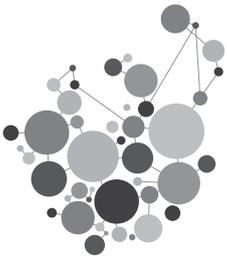
*Professor of Medicine, Queen's University Belfast, Northern Ireland.*

Nutritional status has an important impact on clinical outcomes across a wide range of medical and surgical conditions. Assessment of nutritional status should form a part of any patient's assessment, and is based on clinical and dietary history, examination and laboratory assessment where appropriate. Laboratory assessment has a particular role in the identification of vitamin and trace element deficiency, and monitoring of parenteral nutrition.

Assessment of vitamin and trace element status may be done by direct measurement of levels in serum, plasma or red blood cells, or by functional assays which frequently rely on measuring an enzyme activity dependent on a specific micronutrient. Each of these approaches has advantages and drawbacks.

Assessment of vitamin status is made more challenging by the absence of assay standardization in many cases, the complex range of metabolites which may be present, and the marked effect of the acute phase response on relevant biomarkers.

It is important for any laboratory providing nutritional support to fully understand the pre-analytical and analytical factors which influence their results, and to use appropriate assay-specific reference intervals and decision limits. It is also important to provide support in the post-analytical phase to ensure the appropriate interpretation of results, particularly in the context of the acutely ill patient.



## SYMPOSIUM 06

SY06-02

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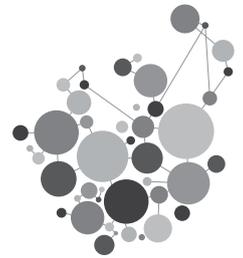
### **Is Vitamin D Critical for improved health outcomes? when to assess Vitamin D status**

Howard Morris

*School of Pharmacy and Medical Sciences, University of South Australia, and Chemical Pathology, SA Pathology, Adelaide, South Australia*

The well characterised endocrine pathway of vitamin D metabolism and its activities are solely responsible for vitamin D regulation of plasma calcium and phosphate homeostasis under control of serum 1,25-dihydroxyvitamin D, the biologically active metabolite of vitamin D. This pathway protects against the metabolic bone disease of rickets in children or osteomalacia in adults. The critical level for serum 25-hydroxyvitamin D to maintain adequate serum 1,25-dihydroxyvitamin D is 20 nmol/L (8 ng/ml) and is synthesised by the kidney. In contrast adequate serum 25-hydroxyvitamin D protects against osteoporosis and reduces risk of fracture at a higher level because this activity depends on 1,25-dihydroxyvitamin D being synthesized by bone cells. This protective effect against fracture is only observed in combination with adequate dietary calcium intake. Similar metabolism of vitamin D protects against cancer death and infectious disease. Metabolism of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D by macrophages has been well described to enhance killing of microorganisms. The critical level for serum 25-hydroxyvitamin D for metabolism by non-renal cells is 50 to 75 nmol/L (20 to 30 ng/ml). Such autocrine actions of 1,25-dihydroxyvitamin D have now been demonstrated in skin, prostate, breast and colonic tissues, in these latter tissues to protect against cancer. In these tissues activities of vitamin D include reduction of cell proliferation and stimulation of cell maturation, activities which reduce the risk of cancer. The critical level of serum 25-hydroxyvitamin D for optimal health of these tissues is dependent on the level of the enzyme which converts 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D (CYP27B1) and therefore may vary for different tissues. There is general international consensus that screening for vitamin D status is of limited value but a number of high risk groups warrant evaluation of serum 25-hydroxyvitamin D levels. These include patients with chronic kidney disease, osteoporosis or fragility fractures and elderly individuals who are institutionalized.

# SYMPOSIUM 06



SY06-03

## Measurement of Vitamin D in clinical laboratories

Sung Eun Cho

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### 1. The Roles and Metabolism of Vitamin D

#### 1) Roles of Vitamin D

- Plays an important role in maintaining calcium homeostasis in the body
- Deficiency is closely related with the occurrence of metabolic bone disease such as rickets in children
- Regulates numerous cellular functions; metabolic syndrome, diabetes, autoimmune diseases, and some types of cancer
- Vitamin D deficiency in infants due to an increase of breast-feeding
- Vitamin D insufficiency is expected to be prevalent among school-aged children
- The analysis of 25-hydroxyvitamin D (25(OH)D) levels is used to diagnose hypovitaminosis D

#### 2) Metabolism of Vitamin D

- 25(OH)D is the precursor to active 1, 25-dihydroxyvitamin D (1, 25(OH)D) and has a longer half-life of 3 weeks compared to 24 hours
- 2 types of 25(OH)D that can be found in the circulation
  - \* 25-Hydroxyvitamin D<sub>3</sub> (cholecalciferol, 25(OH)D<sub>3</sub>); endogenously derived
  - \* 25-Hydroxyvitamin D<sub>2</sub> (ergocalciferol, 25(OH)D<sub>2</sub>); derived from plant sources and fish
- 25(OH)D<sub>3</sub> is more potent and is normally present in higher concentrations in the body compared to 25(OH)D<sub>2</sub>

### 2. Measurement of Vitamin D Concentrations

#### 1) Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS)

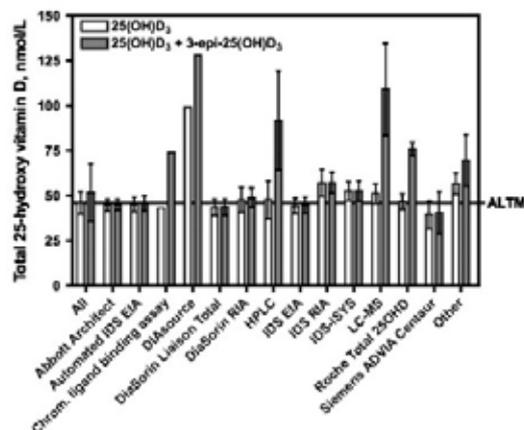
- Candidate reference method for 25OHD assay

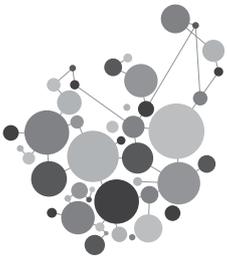
#### 2) Radioimmunoassay (RIA)

- Diasorin 25OHD assay

#### 3) Automated Chemiluminescence Immunoassays

- Roche Elecsys Total 25OHD assay
- Abbott Architect 25OHD Vitamin D assay
- Advia Centaur Vitamin D Total assay
- DiaSorin Liaison
- IDS iSYS



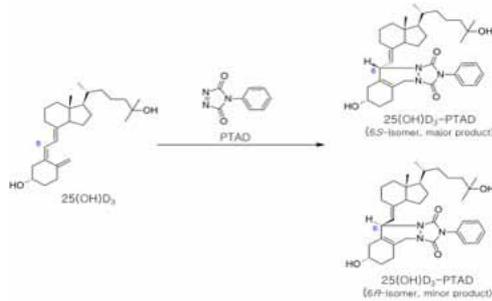


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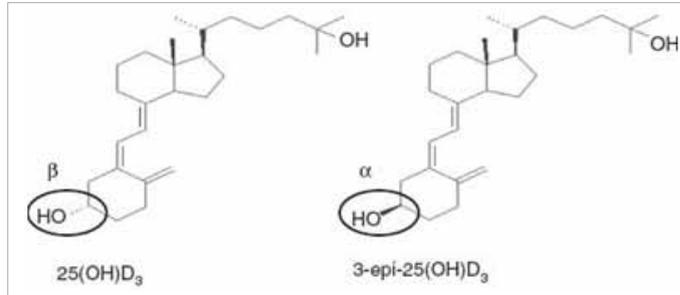
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### 3. LC-MS/MS and Measurement of 3-epi-25-Hydroxyvitamin D<sub>3</sub> (3-epi-25(OH)D<sub>3</sub>)

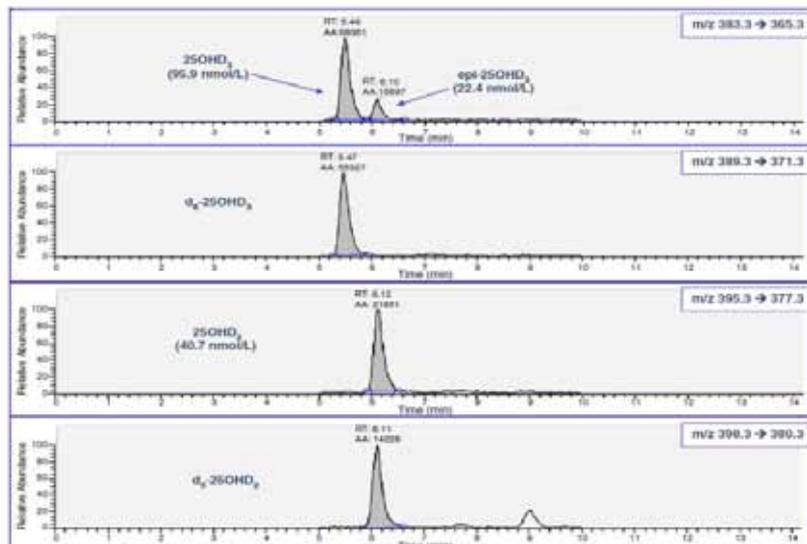
- Isotope dilution-LC-MS/MS : reference measurement procedure for 25(OH)D assessment
- LC-MS/MS requires technical expertise, specialized equipment, and expensive deuterated internal standards [IS]
- LC-MS/MS measures both 25(OH)D<sub>3</sub> and D<sub>2</sub>
- LC-MS/MS is increasingly popular for measuring 25(OH)D metabolites because of its high degree of accuracy and selectivity
- LC-MS/MS method can use PTAD derivatization to increase the sensitivity

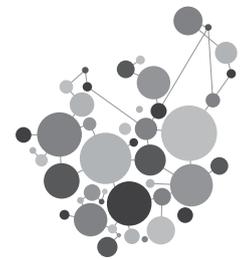


- LC-MS/MS methods have identified an epimeric form of 25(OH)D<sub>3</sub> that has been shown to contribute significantly to the total 25(OH)D<sub>3</sub> concentration, particularly in infant populations
- The C-3 epimerization pathway leads to the conversion of the configuration of the hydroxyl group at C-3 of the A-ring and produces 3-epi-25(OH)D<sub>3</sub> from 25(OH)D<sub>3</sub>



- Typical chromatograms from a quality control serum containing 3-epi-25(OH)D<sub>3</sub>, 25OHD<sub>3</sub> and 25OHD<sub>2</sub>





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- In 2006, Singh et al. separated 3-epi-25(OH)D<sub>3</sub> from 25(OH)D<sub>3</sub> for the first time, and reported that 3-epi-25(OH)D<sub>3</sub> is found in 23% of infants and contributes 8.7–61.1% of the total 25(OH)D<sub>3</sub>
- Several studies have quantified 3-epi-25(OH)D<sub>3</sub> in various populations

**Table 1**  
Quantification of 25(OH)D<sub>3</sub> and 3-epi-25(OH)D<sub>3</sub> in pediatric, infant, and adult populations.

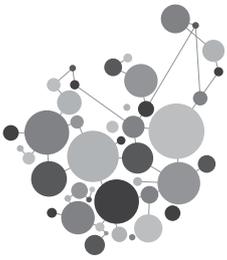
Reference	Age group <sup>a</sup>	N	% with detectable 3-epi-25(OH)D <sub>3</sub>	Epi-25(OH)D <sub>3</sub> mean (median; range) nmol/L <sup>b</sup>	% 3-epi-25(OH)D <sub>3</sub> of total 25(OH)D <sub>3</sub> mean (median; range) <sup>b</sup>
Singh et al. [2]	Infant	172	22.7%	40.2 (22.5; 12.5–230)	27.8 (24; 8.7–61.1)
	Pediatric	47	None		
	Adult <sup>c</sup>	53	None		
Stephan et al. [3]	Adult <sup>d</sup>	147	None		(15.0–41.0) (2.5–17.0)
	Infant	6	100%		
	Adult	32	100%		
Schleicher et al. [9]	Adult	98	43%	1.90 (1.5; 0–18.9)	
	Adult <sup>e</sup>	35	80%	3.7 (3.7; 1.3–100)	
van den Ouweland et al. [5]	Infant	51	100%		11.1 (9.3; 2.3–49.2) 6.2 (5.7; 2.5–20.0) 3.5 (3.1; <2–10.6)
	Pediatric	74	100%		
	Adult	104	75%		
Shah et al. [10]	Adult	5	80%	(0–6.3)	(0–16.7)
	Infant	31	93%	4 (3.5; 0–12.25)	10.0 (8.8; 0–26.5)
Keevil [7]	Pediatric	27	93%	2.5 (2; 0–7.5)	4.9 (5.0; 0–7.1)
	Adult	156	90%	1.3 (1.3; 0–8.5)	4.3 (4.2; 0–16.2)
	Infant	125	100%	14.7 (15.0; 0.3–117.5)	26.2 (26.0; 2.0–60.0)
Strathmann et al. [4] <sup>f</sup>	Adult	501	90.2%	5.5 (5.0; 0–27.5)	7.0 (6.0; 1.0–47.0)
	Infant	2	99%	3.75 (0.3–59.3)	4.75 (0–25.5)
Baecher et al. [6]	Adult	212	78%	<2.0–22.5)	7 (4–20)
	Adult	50	78%	<2.0–22.5)	7 (4–20)
Weighted mean (range across studies)	Infant			18.2 (0–230)	21.4 (0–61.1)
	Pediatric			2.5 (0–7.5)	5.9 (0–20.0)
	Adult			4.3 (0–22.5)	6.1 (0–47.0)

<sup>a</sup> Infant (<1 year of age); pediatric (>1 year–18 years of age); adult (>18 years of age).  
<sup>b</sup> Range provided according to primary publication in either minimum–maximum value or 2.5th–97.5th percentile.  
<sup>c</sup> Adults with compromised liver function.  
<sup>d</sup> Adults without known liver disease.  
<sup>e</sup> Pregnant female adults.  
<sup>f</sup> Data communicated by A. Hoofnagle.

- Relative C3-epimer concentrations, as compared to total 25(OH)D<sub>3</sub>, appear to decrease across infancy and to remain stable in the adult population
- Little is definitively known regarding the in vivo importance of 3-epi-25(OH)D<sub>3</sub>
- Clinical laboratories face the decision of whether or not to include 3-epi-25(OH)D<sub>3</sub> in the measurement of total 25(OH)D

## 4. Immunoassays and Analytical Problems with Vitamin D Binding Protein (VDBP)

- Vitamin D metabolites circulate bound to VDBP and, to a lesser extent, albumin
- 25(OH)D binds to VDBP with high affinity and is thus strongly influenced by VDBP
- It remains unclear whether the automated methods are sufficiently effective in liberating 25(OH)D from VDBP
- Incomplete extraction from VDBP leads to falsely low 25(OH)D concentration results
- Variations in VDBP concentrations between various patient groups (healthy individuals, pregnant women, dialysis patients, ICU patients, etc) may be the cause of the differences in 25(OH)D concentrations
- Problems in 25(OH)D immunoassays
  - Hydrophobic nature of the analyte
  - High concentration and affinity of VDBP in serum
  - Different methods to release vitamin D from its VDBP
  - Cross-reactivity requirements due to the broad spectrum of metabolites of vitamin D
  - Matrix interferences
  - Antibody specificity (polyclonal or monoclonal)
  - Competition between the 25(OH)D capture antibody and VDBP in patient samples
  - Quality and source of calibrator materials
  - Lack of standardization
- Essential quality requirements for 25(OH)D immunoassays ; detectability, precision, traceability, comparability to the reference method of LC-MS/MS
- Clinical laboratories can apply performance goals based on biological variation to decide if a 25(OH)D as say is analytically acceptable; mean bias ≤ 15.8%, imprecision ≤ 9.1%
- Automated immunoassays demonstrated variable performance and not all tests met the minimum performance goals



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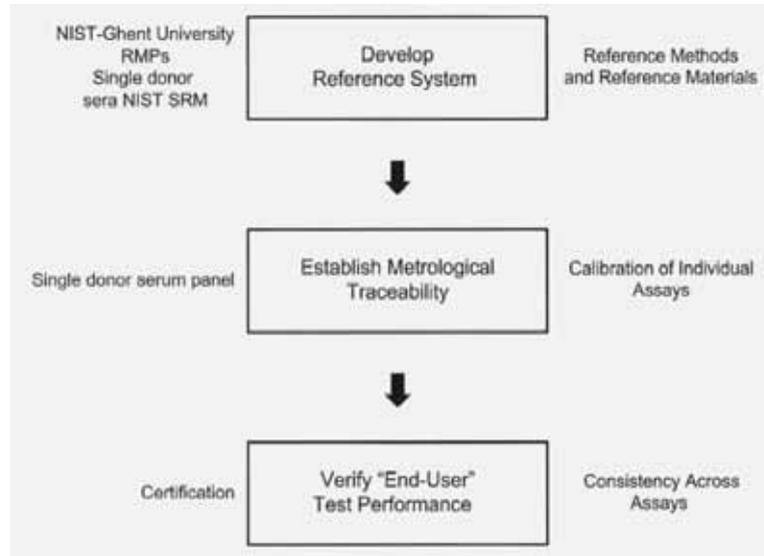
## 5. Standardization of measurements of Vitamin D

- Vitamin D Standardization Program (VDSP) is a collaboration; NIH Office of Dietary Supplements, NIST, CDC, and Ghent University

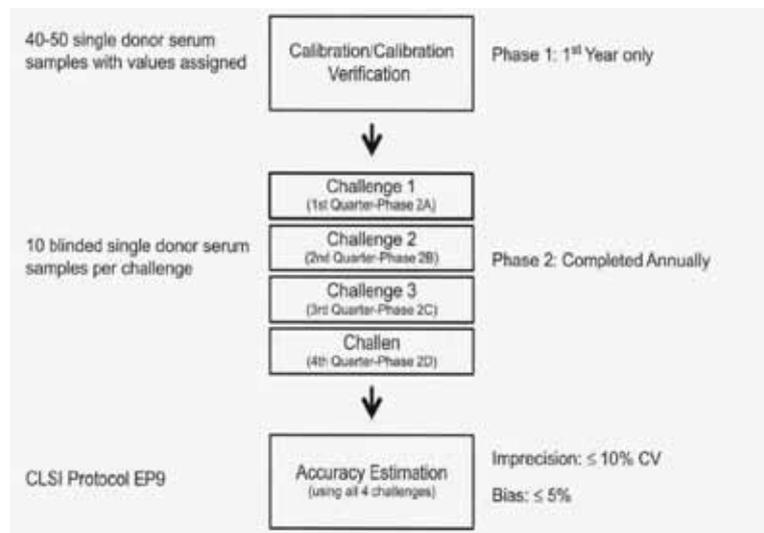
- Objectives of VDSP

- Standardize measured 25(OH)D concentrations in national health surveys to the recently developed NIST-Ghent University reference measurement procedures (RMP)
- Evaluate differences in measured 25(OH)D concentrations among standardized national health surveys
- Expand standardization services from national surveys to include assay manufacturers and clinical and research laboratories
- Promote the standardization of emerging metabolites of vitamin D status
- Enable the use of standardized data in patient care and public health activities

- Vitamin D Standardization Program: Steps in the Standardization Process



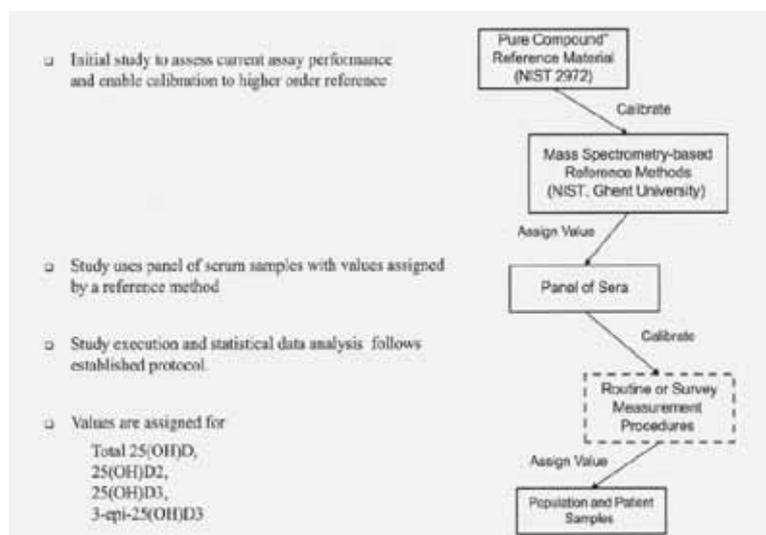
- VDSP Metrological Traceability Plan. Baseline or Interlaboratory Comparison Study Design



# SYMPOSIUM 06



- Centers for Disease Control and Prevention (CDC) Certification Program. Vitamin D Standardization Scheme



- Accuracy-based PT programs
  - Vitamin D External Quality Assessment Scheme (DEQAS)
  - The College of American Pathologists (CAP)
  - NIST-NIH Vitamin D Metabolites Quality Assurance Program (VitDQAP)
- National Institute of Standards & Technology (NIST) Standard Reference Material (SRM) 972a from Vitamin D Metabolites in Frozen Human Serum have 4 levels; 3 for 25(OH)D<sub>2</sub> & D<sub>3</sub>, 1 for 3-epi-25(OH)D<sub>3</sub>

## 6. Conclusion

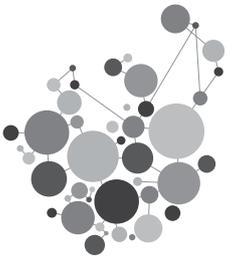
Laboratories should be cognizant of the limitations of their method and indicate to clinicians which assay they are using and the limitations of that assay, for example, in terms of 25(OH)D and epimer detection in LC-MS/MS method, VDBP problem in immunoassays. Even though there are problems in standardization of measurement of vitamin D now, the standardization activities are still ongoing.

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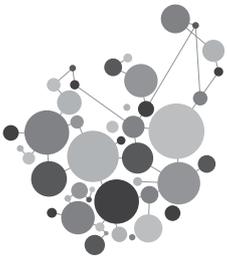
## SYMPOSIUM 06

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SY07-01

### Current technology platforms to detect antimicrobial resistance

Dongun Yong

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The role of clinical microbiology laboratory has become more important in the differential diagnosis of infection and other diseases. To guide the antimicrobial therapy, species identification of pathogenic bacteria is an important information. Selecting appropriate antibiotics directly affect the patient's prognosis. Antimicrobial susceptibility testing is to provide the basic essential information on which the antimicrobials selection and dose adjustment are based. Hence, it provide one of the most valuable information in the clinical microbiology laboratory.

In the management of MRSA infection which causes the most clinically serious infection, rapid detection of the pathogen was reported to reduce the burden for quarantine upto 90% in the low endemic setting or upto 20% in the high endemic setting.

Traditional antimicrobial methods which are currently performed in clinical micorbiology laboratory include agar dilution, broth dilution, Etest, disk diffusion method and automated biochemical kit. But recently, as well as MALDI TOF MS which has revolutionized microorganisms identification process, image analysis by using the digital microscope has been presented as new alternative technologies for rapid antimicrobial susceptibility testing.

In the near future, the next-generation sequencing analysis, Raman spectroscope might be introduced in the clinical microbiology laboratory. Given the most important factors in antimicrobial susceptibility testing are speed and reliability, these new technologies are likely to bring many changes in this field.

Since the ultimate goal of antimicrobial susceptibility testing is to improve the clinical outcome of infection treatment, laboratory physicians need to make efforts continuously to choose the most appropriate and sensitive methods for antimicrobial susceptibility testing based on each hospital situation. Also, an endeavor to rapidly reflect the susceptibility results on patient care will be required.



# SYMPOSIUM 07

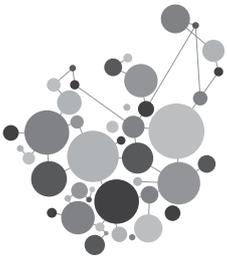
SY07-02

## Multi-resistance among fungal isolates

Maurizio Sanguinetti

*Catholic University of Rome, Italy*

In the last years, the incidence of life-threatening fungal diseases has increased significantly, because of the rising number of human individuals susceptible to fungal infections, which are in part complicated by the emergence of antifungal drug-resistant pathogens. Among yeasts, *Candida albicans* and *Candida glabrata* are the most common organisms responsible for invasive fungal diseases, whereas *Aspergillus fumigatus* is one of the most prevalent moulds to cause invasive fungal disease. Particularly, the raising of multi-resistant isolates of these species is becoming an important concern in treating this type of infection. This topic will be treated with particular attention to the epidemiology of these resistant isolates, to the mechanisms of resistance, and to the possible strategies to overcome this problem.



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SY07-03

### Dengue situation in Vietnam and quasispecies of Dengue viruses

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*Center of International Collaborative Research, Nagasaki University, Nagasaki, Japan  
Vietnam Research Station of Nagasaki University, in National Institute of Hygiene and Epidemiology (NIHE), Hanoi, Vietnam*

Vietnam is a dengue hyperendemic country where all the four serotypes of causative agents (DENV-1, -2, -3, and -4) are present. The prevalence of dengue serotypes has been shifting in neat chronological order from the southern part to the northern part in Vietnam because of the difference in climatic environment and human movement. Genotype shift from Asian 1 to Asian/American type occurred around 2003, however it did not lead to dengue epidemic. Huge outbreak of DENV-1 and DENV-4 were observed in the north in 2009 and in the central provinces in 2013, respectively. We performed molecular analyses on genetic diversity of DENV-1 and DENV-4 isolated in both outbreaks. According to the envelope gene sequencing results, the DENV-1 and -4 isolates did not show dramatic changes. All DENV-1 and -4 strains have been present in Vietnam for long time and evolved within the country. There are several possible considerations for the sudden dominance of DENV-4: 1) viral genome adaptation in mosquito vectors or humans, 2) decreasing human immune level to each dengue virus serotype, and 3) some environmental changes that increased the mosquito population and/or activities.

Attempts have been done to determine dengue viral gene variations through next-generation sequencing. Subjected to next-generation sequencing analysis were (1) DENV-1 and DENV-2 viral genome amplicons produced by direct RT-PCR using serum samples from infected patient and (2) the cDNA of all DENV-1, -2, -3, -4 synthesized from viral RNA extracted from infected culture fluid collected after a second passage of the virus (originally from serum) in C6/36 and Vero cells. Quasispecies variants with different cellular tropism in mosquito cell line and mammalian cell line were confirmed.

Two phenotypes of DENV-2 strains with and without strong binding ability and infectivity to the plasmacytic B-lymphocytes were isolated from the serum of a single patient. In the cerebrospinal fluid (CSF) of another patient (a dengue encephalitis patient) DENV-3 genotype III strain was isolated. This is the first time for this genotype of DENV-3 to be noted in Vietnam. Our data indicate that the CSF-derived DENV3 has unique virulence features which might play a crucial role in the neuropathogenesis of DENV infection.

# SYMPOSIUM 08



SY08-01

## Defining immunodominance in antibody responses to influenza A Virus

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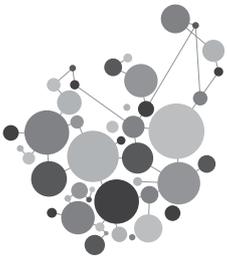
Influenza A virus (IAV) imposes a significant socio-economic burden on humanity, killing hundreds of thousands, and costing tens of billions of dollars worldwide each year. Vaccination, the best hope for reducing the impact of influenza, is effective in only 60% of individuals even under optimal circumstances. The difficulty stems from the remarkable ability of influenza A virus (IAV) to evade existing immunity.

IAV has an error prone polymerase that enables the rapid antigenic evolution of the two virion surface glycoproteins, neuraminidase and hemagglutinin (HA). Since the most potent antibodies (Abs) at neutralizing viral infectivity are directed the head of the HA, amino acid substitutions in this region enable IAV to evade Ab-based immunity.

Although Ab responses have been studied since the discovery of IAV in the 1930's, many questions remain.

- What proportion of Abs are directed against the various viral gene products?
- What is the balance of antibody responses to the major antigenic sites in the HA head and newly discovered protective antigenic sites in the conserved stem region?
- How does this vary with genetic background?
- How does prior exposure to related IAVs skew the response?
- How do vaccines compare to infectious virus in generating Ab responses?
- How do CD4+ T cells and other immune cells subsets influence the anti-HA repertoire?
- How do responses differ among B cells in different anatomic locations (lymph node, spleen, local tissue) and differentiation states (naive, plasma cells, plasmablast, memory cells)?

To address these questions, my laboratory has developed a unique panel of viruses that allows us to quantify mouse anti-HA Ab and germinal center B cell responses at the level of individual antigenic sites. Our findings show that B cell responses demonstrate a characteristic immunodominance hierarchy that changes dynamically among the sites as the response progresses, and is influenced in a complex manner by many of the variables listed above.



## SYMPOSIUM 08

SY08-02

### Vaccine development for the emerging virus diseases

Lin-Fa Wang

*Program in Emerging Infectious Diseases, Duke-NUS Medical School, Singapore*

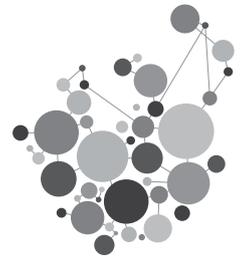
Vaccines remain the most successful and cost-effective public health investments. However, the current model of vaccine development, production and marketing is very costly and takes a long time. This is not suitable for vaccines against emerging viruses, which usually have non-predictable course of onset and progress, sometime with an explosive nature in terms of outbreak impact on public health. In this presentation, I will review the current challenging issues facing the development of vaccine for emerging viruses and the international effort aiming to improve the current situation. I will end the presentation with one successful story of developing and marketing the first commercial vaccine for a biosafety level 4 (BSL4) agent, using an One Health approach.

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# SYMPOSIUM 08



SY08-03

## Antibody reactions in patients with MERS-CoV infections

Kyong Ran Peck

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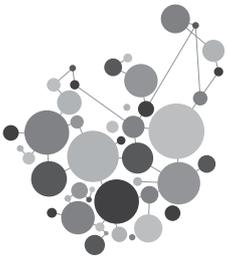
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Middle East respiratory syndrome (MERS) is an emerging lethal respiratory disease caused by a novel betacoronavirus (MERS-CoV), which has unceasingly causing small and large outbreaks since its first report in 2012. During a hospital-associated MERS outbreak in the Republic of Korea in 2015, it was even more difficult to control the outbreak because of insufficient scientific knowledge about MERS. Many clinical and laboratory researches have been reported thereafter.

As an emerging viral disease with zoonotic reservoir, serologic investigation has played an important role in epidemiologic survey both in human and animals. Serologic studies suggested association between human MERS and camels. Subclinical infections among household contacts were documented by a serologic survey, while studies in health care workers did not demonstrate subclinical infections.

Several studies about antibody response in patients with MERS-CoV infection have been reported very recently. IgG antibody seroconversions usually occurred during the first 2 weeks after diagnosis or by week 3 of illness, and levels of IgG and neutralizing antibodies were inversely correlated with viral loads. Case fatality was associated with weak antibody response. IgM detection provided no advantage in sensitivity over IgG detection in a study.

These findings of serologic studies suggest several points in clinical application: Serologic evaluation is not helpful for diagnosis of MERS in acute phase like any other infectious diseases. Antibody detection is useful for serologic surveillance of exposed individuals. Serum sampled at least 3 weeks after exposure should be used for the serologic surveillance. Likewise, convalescent plasma infusion therapy for MERS patients should use plasma collected at least 3 weeks of illness, although the treatment efficacy of convalescent plasma infusion therapy has to be studied further.



## SYMPOSIUM 09

SY09-01

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### Antiplatelet agents: physiology and pharmacology

Neil Harris<sup>1</sup>, John Mitsios<sup>2</sup> and Michael Laposata<sup>3</sup>

<sup>1</sup> Department of Pathology, Immunology & Laboratory Medicine, University of Florida College of Medicine, Gainesville, FL, <sup>2</sup> Special Coagulation Laboratory, BioReference Laboratories, Elmwood Park, NJ, <sup>3</sup> Department of Pathology, University of Texas Medical Branch, Galveston, TX, USA

**Background:** While anticoagulants such as heparin and warfarin are used to prevent venous thrombosis, antiplatelet agents are important in preventing arterial thromboses in the coronary and cerebral system.

**Methods:** The mechanism of action of aspirin, clopidogrel and dipyridamole will be reviewed.

**Results:** Aspirin (acetylsalicylic acid) irreversibly inactivates the cyclooxygenase function of the enzyme prostaglandin H synthase (PGHS) or prostaglandin endoperoxide synthase.

It acetylates the serine 530 of the active site. Clopidogrel belongs to the group of ADP receptor blockers, specifically the P2Y<sub>12</sub> receptor. Clopidogrel is a prodrug.

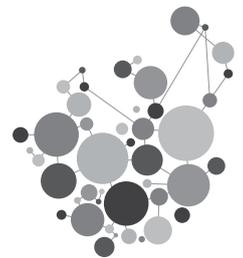
The active metabolite links covalently to the receptor. Clopidogrel metabolism involves many enzymes including Cytochrome p450. Polymorphisms have been identified in CYP2C19 with the CYP2C19\*1 allele being the wild type with full activity, while CYP2C19\*2 has reduced activity. Prasugrel is broadly similar to clopidogrel but is less dependent on CYP2C19 polymorphisms and metabolism to the active form is much more rapid compared with clopidogrel.

A new group are the direct, reversible P2Y<sub>12</sub> inhibitors: Ticagrelor and Cangrelor. Ticagrelor binds to the receptor at a site distinct from ADP while Cangrelor is an intravenous ATP analog. Dipyridamole elevates plasma adenosine via blockade of adenosine transport. The adenosine acts on platelets via the A<sub>2A</sub> and A<sub>2B</sub> receptors and elevates cyclic nucleotides. Dipyridamole is also an inhibitor of platelet phosphodiesterase thereby raising cAMP and cGMP. Finally, dipyridamole enhances endothelial PGI<sub>2</sub> release and initiates vasodilatation

**Conclusions:** Testing for the action of these drugs in the clinical laboratory requires a knowledge of their mechanisms of action and their metabolism

*Keywords: Aspirin, Cyclooxygenase, P2Y<sub>12</sub>, Dipyridamole*

# SYMPOSIUM 09



SY09-02

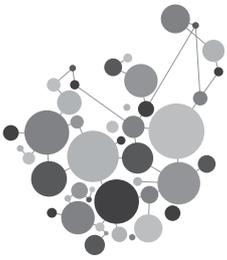
## Clinical implications of monitoring direct oral anticoagulants

Chad M. Botz, MD<sup>1</sup> and Michael Laposata, MD, PhD\*

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This presentation involves a description of the mechanisms, indications for treatment, and laboratory monitoring for the direct oral anticoagulants that have been introduced as alternative anticoagulants to warfarin. For each one, the impact on the coagulation cascade and how new reversal agents act to restore a pro coagulant effect will be presented. Each anticoagulant has a growing number of clinical indications. The complexities associated with consideration of renal function and half-lives, among other issues, will be highlighted. Despite the lack of standardization for routine monitoring in clinical practice regarding these agents, there is a need to monitor patients receiving these medications who present with a bleeding episode or a recurrent thrombotic event. The testing which is available for each of the direct oral anticoagulants will be presented, as well as the specific clinical circumstances and the turnaround times required to address selected patient focused issues.



## SYMPOSIUM 09

SY09-03

### Platelet function testing

John V. Mitsios<sup>1</sup>, Neil Selwyn Harris<sup>2</sup>, Michael Laposata<sup>3</sup>

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Platelet function testing is used to help diagnose and monitor platelet function, to screen at-risk patients, to monitor anti-platelet therapy and to detect aspirin resistance. The interpretation of results of the various types of platelet function tests depends on why the tests are performed. In the investigation of excessive bleeding or the potential for bleeding during surgery, abnormal results may indicate the presence of a platelet disorder. Further testing, such as specific bleeding disorder tests or clinical evaluation, is often necessary to identify an inherited disorder or acquired condition as the cause of the dysfunction. Examples of inherited platelet function disorders include: Von Willebrand disease, Glanzmann's thrombasthenia (GT, GPIIb/IIIa deficiency), Bernard-Soulier syndrome (BSS, deficiency in GPIb) and storage pool disease. A number of acquired platelet dysfunctions are also present and may be due to chronic conditions such as: Kidney failure (uremia) or Myelodysplastic Syndrome (MDS). In addition, some acquired platelet disorders are temporary/transient and include but are not limited to, decreased function due to medications (aspirin and non-steroidal anti-inflammatory drugs) and abnormal function after prolonged cardiac bypass surgery.

In this presentation basic platelet physiology will be covered as well as the basic principles of platelet function testing. Pre-analytical variables, such as venipuncture, anticoagulants, and specimen processing, play an important role in platelet function analysis. The importance of proper blood collection is critical in maintaining the platelet structure intact and allowing proper platelet function analysis. The most common method used to assess platelet functionality is platelet aggregation and is often considered the "gold standard" method. Platelet aggregation measures the ability of various soluble agonists to induce in-vitro platelet activation/aggregation. There are two types of platelet aggregation studies that can be performed. The first type of platelet aggregation study is classically referred to as Born aggregometry or light transmission aggregometry and uses platelet rich plasma (PRP). The second type of platelet aggregation study is known as impedance aggregometry and uses whole blood. Moreover, this presentation will emphasize point of care instrumentation with a particular focus on the platelet function analyzer-100 (PFA-100) and the VerifyNOW (aspirin resistance), and will examine their usefulness as screening tools for the assessment of global hemostatic function. Flow cytometry will also be discussed as an additional means to assess platelet functionality and responsiveness to drug therapy, specifically to clopidogrel (Plavix). The most commonly used flow cytometry tests relevant to platelet function are the quantification of glycoprotein receptor density in the diagnosis of defects such as GT and BSS, detecting their heterozygous states, and Vasodilator-stimulated Phosphoprotein (VASP). The presentation will conclude by stressing the necessity and importance on the part of the clinical laboratory to understand basic platelet physiology, the principles of testing and the most common factors that could potentially influence patients' results when performing platelet function testing.

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# SYMPOSIUM 10

SY10-01

## The cases of redemption occurred in the national health screening

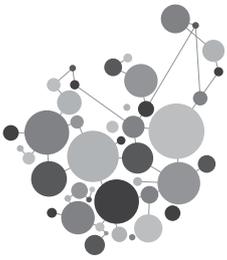
Se-Myeong Jang

*Department of Health Promotion, National Health Insurance Service, Korea*

**Purpose:** The purpose of this study is to provide some cases of redemption that violate some rules related to Act on the National Health Screening. The National Health Screening is classified 5 types according to ages and gender.

**Methods:** About 21 thousand of medical institutions are registered for The National Health Chekup. They must follow some rules that Act on the National Health Chekup and medical law etc. The NHIS has managed medical institutions through inspecting them by visiting. We inspected all medical institutions biennially to keep management rules of facilities, equipment and employment.

**Result:** According to the result of inspecting medical institutions, there are variety cases of redemption related to the violation of employment etc.



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SY10-02

### **Stability of laboratory samples for NIS (National Health Insurance) health checkup**

Eun-Hee Nah

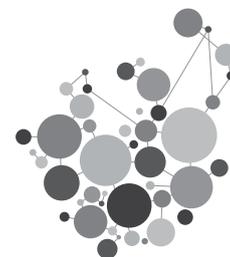
*Department of Laboratory medicine/Health Promotion Research Institute, Korea Association of Health Promotion, Seoul, Korea*

**Introduction:** Though it is highly recommended to analyze tests from freshly drawn serum or plasma, delay in the testing process, reuse of the samples for missing results or deliver to other laboratory for test are sometimes inevitable. Thus, the extra-analytical factors affecting the analysis process such as different transportation conditions, prolonged storage at high or low temperature, improper handling should be interested. The aim of the study was to determine the handling and storage condition of samples for the stability of analytes in National Health Insurance (NHI) health checkups.

**Materials and Methods:** I searched the electronic bibliographic database (Pubmed and KoreaMed) and used the following keywords in the MeSH database search: "enzyme stability", "serum", and "storage". And Performance evaluation-Analytical addendum for instruments and reagents were also searched.

**Results:** Samples for the complete blood count (CBC) was stable for 2 hours in room temperature (RT) and 24 hrs in 4°C. Analytes including creatinine, cholesterol, triglycerides, gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT) were stable in samples kept at RT or at 4°C for at least three days after centrifugation, regardless of tube types. Glucose concentration decreased markedly beginning from the first hour of storage in plain serum. The stability maximized for the analytes including glucose, total bilirubin, BUN, uric acid stored at 4°C in gel tubes. High density lipoprotein (HDL) concentration was stable in gel tubes at 24°C, in plain tubes at 4°C stored up to 36 hrs. Samples for HBsAg, anti-HBs, anti-HCV qualitative tests, and AFP were stable at RT for 1 day and at 2-8°C for up to 7 days, and at -20°C for 120 days.

**Conclusion:** The findings of this study suggests that protocols for sample handling and storage are needed for the stability of analytes. Those protocols would be considered in turnaround time (TAT) in the laboratory.



# SYMPOSIUM 10

SY10-03

## Brief of assessment guideline for health checkup hospitals

Yeongchun Park

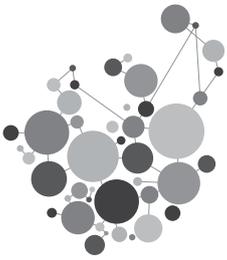
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The national health screening program of Korea was launched in 1980. The nationwide screening program changed its target diseases to chronic diseases such as hypertension and diabetes in 1988, and the national cancer screening program was expanded to cover a larger target population in 2004. Many hospitals attended to the health screening program, that the National Health Insurance Services begun to Assess-ment the hospitals for the quality improvement in national health examination. Here I want to introduce the brief of assessment guideline for health checkup hospitals in laboratory medicine. The assessment in-cluded 4 part. First part was structure area, which included personnel, facilities, equipment, reagent. Sec-ond part was pre-analysis process, such as collection and storage of specimen, and handling of medical waste. Third part was analysis process, such as examination manual, external and internal quality control, individual test item. The last part was post-analysis process, such as method for the result reporting, stor- age of test result. If your laboratory already received the accreditation of the Laboratory Medicine Founda- tion, then all above process will not difficult for you, because many of the test items are overlapped. Before receiving the assessment, the clinical pathologist working in health screening center, need to receive the education about assessment guideline for health checkup. The lecture will be of help to the hospitals who preparing to receive assessment from the National Health Insurance Service.



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SY10-04

## Algorithm in assessment of health examination results

Yungzoon Jung

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Among the various health checkups, discuss the algorithm in the assessment of the comprehensive health checkup results.

In many cases, the physicians get the support of commercial software or in-house programming for decision makings. There are many medical algorithms in these programs.

The medical algorithms can reduce errors, and decrease time demands on physicians.

However, due to the shortage of programming personnel in small or middle sized hospitals, the physicians must do the job without an aid of computerized system.

I am using Microsoft Excel program to solve the assessment of health checkup results, especially apply the VBA(Visual Basic for Applications).

There are several advantages to using Excel spreadsheets: 1. Due to the dominance of Microsoft Office, Excel is ubiquitous. 2. The spreadsheet interface is familiar to many physicians. 3. The rich set of formulas built in to Excel means programming is not needed to encode medical algorithms, 4. Excel spreadsheets are relatively simple to create, modify and maintain.

Viewing the medical tests in comprehensive health checkups from a different perspective, these tests are Direct-to-consumer (DTC) test, also known as direct access testing, permits consumers ( a person or companies) to order medical tests directly from a hospital without the involvement of a physician.

These test results may be used to monitor an existing health condition, identify a unknown medical disorder, or provide data regarding legal purposes. DTC testing is an important element of the ongoing efforts to enhance individuals' engagement in managing their healthcare, and it is important that DTC test results are accurate and well understood.

Due to the competition between health checkup clinics, the consumer-driven testing has expanded to non-traditional medical tests those results were "of little or no practical use".

Medical reports have been developed to provide information to the healthcare providers highly trained. Therefore, the reports generally provide the numeric value and the reference interval, and also include a brief description of the result.

This minimal information, when considered with all other factors such as any symptoms of disease, is sufficient for physicians to make medical decisions.

Individual consumers will need a much larger context to fully understand the meaning of the test and to determine next steps.

For example, an abnormal test result may or may not indicate underlying health problems.

On the contrary, an individual may be falsely reassured by the result of the test in the normal range even when signs and symptoms warrant medical attention.

Consumers, because there is a possibility that do not understand the limitations of the test, it is possible to interpret their test results in the wrong way.

Laboratory physicians can play an important role in all aspects of this consumer-driven tests, including educating individuals about the benefits and limitations related to the tests and supporting the choice of the most appropriate test on a particular person.

In addition, laboratory physicians with experience who received advanced training can help the interpretation of test results and can provide consumers guidance on whether additional testing is required to confirm or clarify results, directing them to physicians for any necessary follow-up medical care.

Consumers can also access reliable information through resources such as Lab Tests Online (<http://www.labtestsonline.kr/>), which was developed by laboratory professionals to help patients and caregivers understand the many laboratory tests that are a critical part of medical care.



# SYMPOSIUM 11

SY11-01

## Individualized Quality Control Plan (IQCP): Overview and examples of implementation

Earle S. Collum, MD, FCAP

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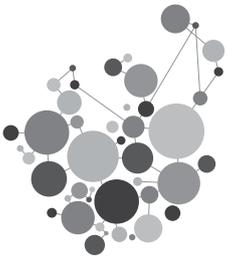
An Individualized Quality Control Plan (IQCP) is a voluntary, flexible, alternative QC protocol with added value that, if followed, grants compliance with United States (US) Clinical Laboratory Improvement Act (CLIA) QC regulations and provides equivalent quality. IQCP was developed due to changes in the healthcare environment and delivery of services as well as advances in technology. It addresses the entire testing process and gives the laboratory flexibility in how the quality of testing is assured.

There are three components of an IQCP:

1. Risk assessment - Sources of the potential failures/errors are identified and evaluated. All elements of the testing process are reviewed. These include the specimen, environment, reagent, test system, and testing personnel. The pre-analytic, analytic and post-analytic phases are all included.
2. Quality Control Plan (QCP) - practices and procedures to control test quality
3. Quality Assessment (QA) - ongoing monitoring of the effectiveness of IQCP

The College of American Pathologists (CAP) has added a new section in the All Common checklist with five new IQCP requirements. The discipline-specific checklists (e.g. Chemistry, Microbiology, etc.) have been changed to address the use of IQCPs. The design and construction of an IQCP is discussed.

Implementation of IQCPs is a challenge. Two examples of implementation of an IQCP are discussed. Step-by-step examples of how to implement an IQCP in chemistry (iSTAT) and microbiology (Phoenix) are presented in detail.



# SYMPOSIUM 11

SY11-02

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## Reducing laboratory errors through Individualized Quality Control Plan (IQCP): How do we begin?

Eun Hee Lee

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Individualized Quality Control Plan (IQCP) is a recently developed, risk management-based quality control plan. Each IQCP is unique because the combination of device, setting, medical requirements, operators and patient population may differ between laboratories. Therefore, it will allow you to develop customized QC for your laboratory specific to specimens you test, your test system, reagents, environment, and testing personnel. In near future IQCP will replace the current Equivalent Quality Control (EQC) procedure, which was designed as a standardized approach and intended to minimize the amount of external QC required and laboratory costs. While classical QC plan is a general standardized plan ("one size fits all"), IQCP is a laboratory-specific tailored plan. The IQCP is composed of three parts (1) Risk Assessment, (2) Quality Control Plan, and (3) Quality Assessments (surveillance). Once implemented, the IQCP is monitored for effectiveness and modified as needed to maintain risk at a clinically acceptable level.

### (1) Risk Assessment

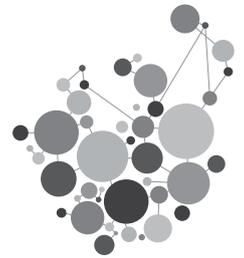
A Risk Assessment identifies and evaluates potential failures and sources of errors in testing process. It must include, at a minimum, an evaluation of the following five components: specimen, test system, reagent, environment, and testing personnel covering the pre-analytic, analytic, and post-analytic phases. And a risk assessment process include ranking those identified risks by their severity and frequency. That process requires information gathering that includes regulatory/accreditation requirements, measuring system information (i.e., manufacturer's information), factors impacting the methodology, and patient care factors (i.e., effect on results). Testing load, frequency of testing, and complexity of testing methodologies are also considerations. The risk assessment should be primarily assessed using in-house obtained data (verification, validation data; QC data), although other relevant data may be considered (published data or manufacturer's data).

### (2) Quality Control Plan

A Quality Control Plan (QCP) is a written document describing the practices and procedures performed by each laboratory to reduce the chance of possible failures and errors in test processes. That plan is based on the identified risks, is a comprehensive strategy that includes all control procedures to reduce residual risk and methods to immediately detect errors, using both prevention and monitoring strategies. The QCP is intended to proactively address potential risks before they occur and result in failures, compared to the practice of addressing failures after they occur. The QCP will also describe how to monitor performance through the use of quality assessment after implementation and over time.

### (3) Quality Assessment

Quality Assessment (QA) is a method of surveying QCP effectiveness/performance through ongoing laboratory monitoring and review of documentation generated as part of the QCP. Monitoring is not limited to one-time data review, but includes trending over time. Documentation examples include quality control review, results of proficiency testing and competency assessments, patient test result review, specimen rejection rates, test turnaround times, complaints reports and corrective/preventive action and follow-up records. The assessment may identify a lack of effectiveness, unanticipated failures, or underestimated risks requiring identification of root cause, corrective action and preventive action, and follow-up. Conversely, it may identify reliable performance that qualifies for less stringent quality control. Either finding may result in modification of the QCP, making it a "living" document.



# SYMPOSIUM 11

The IQCP may allow each laboratory to reduce external QC frequency if it is determined that a test system's internal controls are sufficient to monitor proper test function, in conjunction with your pre-analytic and post-analytic QC processes.

Laboratory can achieve following things through developing IQCP

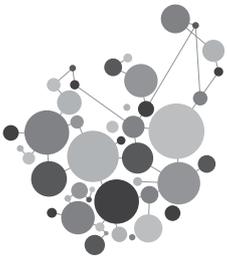
- 1) Balancing internal control processes with external controls
- 2) Reducing frequency of liquid QC to minimum recommended by manufacturer
- 3) Maximizing clinical outcome, available staff resources and cost effectiveness in the lab

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SY12-01

## Introduction of WHO IB-VPD surveillance network: the activities of WPRO regional reference laboratory of NIH

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Meningitis and pneumonia are the leading causes of morbidity and mortality in children infected with *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*, especially in populations in developing countries with limited access to quality medical care. In 2008, WHO established invasive bacterial vaccine preventable diseases (IB-VPD) sentinel surveillance network monitors the disease etiologies and circulating strains/serotypes under 5 years of age admitted to sentinel hospitals with suspected meningitis for evidence-based decision making for vaccine (Hib and/or PCV) introduction and evaluation of vaccine impact on disease epidemiology.

As of January 2016, the IB-VPD surveillance global network includes 117 Sentinel Hospital Laboratories (SHL), 20 National Laboratories (NL), 9 Regional Reference Laboratories (RRL), and 1 Global Reference Laboratory (GRL). SHLs conduct the initial laboratory tests such as gram stain and bacterial culture for diagnosis and then, send the CSF specimens and isolates to NLs for the PCR detection testing and/or strain characterization. RRLs are a critical component of this surveillance system which they provide direct support to the SHLs and NLs for all laboratory practices and conduct the confirmatory testing and the molecular typing of isolates. A GRL develop standardized laboratory procedures and guidelines for data collection and quality assurance/quality control system in this surveillance.

As part of the strengthening of the Quality Assurance (QA) and Quality Control (QC) system for the IB-VPD network, the WHO implemented two external quality assessment programs in coordination with the National EQA unit at Public Health England (PHE) and GRL at CDC, USA to strengthening the capabilities of all laboratories for identification and characterization of three pathogens by culture, microscopy, serotyping/grouping, antimicrobial susceptibility testing, and molecular test.

Since 2011, Korea NIH has been conducted a role of RRL of the western pacific region in IB-VPD global surveillance network. We performs confirmatory testing of PCR detection and serotyping/grouping of three pathogens on CSF and blood culture broth referred from the NL of Mongolia and report laboratory data on cases of suspected meningitis to a WPRO office. Discrepant results have occasionally arisen and tried to be resolved by on-site technical training to improve the bacteriology and molecular testing capacities of the NL of Mongolia.

There are many challenges that need additional resources and capacity building activities in WPRO region. A strong laboratory component must complement the clinical syndrome surveillance to allow for the etiological diagnosis of the specific disease. But, still, consistent case reporting and accurate laboratory diagnostics in resource-limited areas, especially culture, isolation of organisms and PCR test, remain difficult. The WPRO region has vision to build capacities at NLs and improve the qualities of lab data to support the objectives of the IB-VPD global surveillance network. There should be continued efforts to improve the infrastructure for PCR testing in the laboratories and overcome the discrepant lab results for generating the highest integrity of data.

*Keywords: IB-VPD Surveillance Network, EQA Program, Meningitis, Vaccine*



# SYMPOSIUM 12

SY12-02

## Initiation and development of laboratory standardization: The Korean Laboratory Accreditation Program (KLAP)

Woo In Lee

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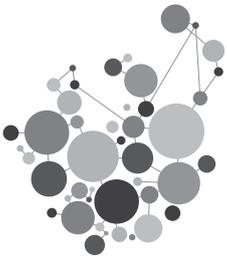
The laboratory accreditation program began in 1961 by the College of American Pathologists (CAP) with the purpose of quality improvement of laboratory service [1]. The Korean Laboratory Accreditation Program (KLAP) was prepared from June 1998 to May 1999 through Ministry of Health and Welfare project under the lead of Korean Society of Laboratory Medicine, which was introduced in 1999 with its goals of quality improvement and accurate assessment of the quality of laboratory service [2].

The checklist of KLAP was developed based on the CAP accreditation program's checklist to fit the domestic needs. The composition of checklist includes 11 areas of laboratory management, diagnostic hematology, clinical chemistry, clinical microbiology, blood bank, diagnostic immunology, flow cytometry, histocompatibility, cytogenetics, and molecular genetics. After workshop regarding comprehensive verification convened December 1999 which included education for accreditation program participants [3]. At the time the general accreditation program applied to small-scale laboratories not conducting special laboratory tests or clinics, however is now excluded for equity of the program between institutions and operational issues. Currently the accreditation program includes total 13 areas with the addition of POCT and referral testing.

The period of accreditation depending on the result of the accreditation, are 1-year, 2-year and non-certification. Until 2003, scoring over 90% upon introduction of KLAP grants 2-year certification, 60-90% 1-year certification. During 2004 and 2005, 80% over has granted 2-years for institutions under 400 hospital beds. Since of July 2005, less than 80% scoring denies accreditation but a chance for re-evaluation is given. According to Shin et al. from data analysis of 8 years, 2-year accreditation was awarded for 32.4% of institutions in 2000, 45.6% in 2001, 53.3% in 2002, 47.3% in 2003, 68.5% in 2004, 37.7% in 2005 and 47.7% in 2006 [4]. The result of this analysis shows growing participation of the accreditation program and also stabilization of the program.

Annual workshop after the first in 1999, participants of the accreditation program were updated of the program through following educative sessions and workshops. Since of February 2000, revision process of the accreditation checklist was started with the experienced reviewers and cumulated accreditation results. The revision included changing of clauses and questions which their meanings were possibly conveyed ambiguously, removing redundant phrases, addition of description to each and all items, allotting different points based on the significance of the item and also the organizing system [2, 3]. Minimization of influence on the score by individual subjectivity and sustainable quality control was available through this revision process.

Improvement of the quality of laboratory service can only be achieved through accurate assessment of the current, and as standardization of the overall laboratory service was more emphasized, a dedicated full-time organization for accreditation program. For this very purpose the Laboratory Medicine Foundation in affiliation to the Ministry of Health and Welfare was established. Through this establishment of the Laboratory Medicine Foundation, efficient improvement of domestic laboratory service was made to meet the global standards, and acquisition of International Society for Quality in Health Care (ISQua) is in process which will benefit for the persistent improvement of laboratory service quality. KLAP has been a success through the lead of Korean Society of Laboratory Medicine establishing the Laboratory Medicine Foundation, and will continue to contribute to the future improvement of the program.



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# SYMPOSIUM 12

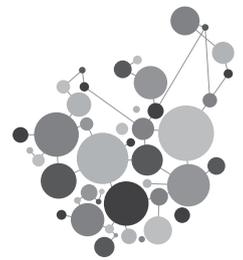
SY12-03

## National HIV External Quality Assurance Schemes (EQAS)

Byeong-Sun Choi

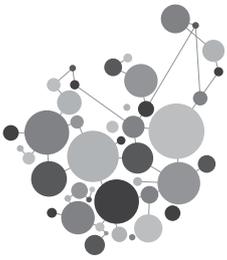
*Deputy Scientific Director, Division of AIDS, Korean NIH, Korea*

We have conducted HIV External Quality Assessment Schemes (EQAS) as one of the quality management programmes in KCDC, specialized for public and private HIV test laboratories in Korea since 2005. KCDC manages HIV EQAS using the online information system(<http://is.cdc.go.kr>) and all participants in KCDC HIV EQAS are provided with a unique identified code. About 600 HIV test laboratories participate in this programme two times every year as follows: Provincial HIV confirmatory institutes(Institute of Health and Environment), public health centers in public sector and general hospitals/clinics, blood centers, commercial testing centers in private sector. The HIV EQAS panel consists of > four plasma samples including positive samples, negative samples, and diluted samples. HIV EQAS samples are manufactured according to ISO Guidelines and then are qualified by testing the homogeneity and the stability for the duration of HIV EQAS period. Finally, we make the summary report for the performance of this HIV EQAS panel every year.



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## Quality control (QC) and quality assurance for the best result in hospital laboratory

Jae-Seok Kim, M.D., Ph.D.

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Continual and consistence considerations to the quality of clinical microbiology laboratory are a hallmark of good clinical practice in hospital laboratories. Quality assurance is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. Quality assurance can be accomplished entirely internally or may be done as part of an external program[1]. It should involve all steps of the procedures in the microbiology laboratory, while quality control is kind of systematic evaluation to make sure that the final test results might be consistent with the previously established acceptance limits of precision and accuracy[2].

The documentation of the performance of microbiology tests, evaluation of the technical personnel and the skill of personnel who perform tests are required internally. In Korea, clinical laboratory accreditation programs are provided by the Laboratory Medicine Foundation. And, the external proficiency testing are provided by the Korean Association of Quality Assurance for Clinical Laboratory (KAQACL) with Korean Association of External Quality Assessment Service (KAEQAS).

In a broad sense, quality control in microbiology is more an art than a science. It involves intangible items such as common sense, good judgement, and constant attention to detail [2]. Considering the types of testing, clinical microbiology tests have quite different characteristics compared to other qualitative tests requiring various validation of analytical procedures. Identification of bacterial colony may require the validation of specificity, while the validation of antimicrobial susceptibility may require more validation procedures.

Monitoring laboratory equipment is also important for the clinical microbiology laboratory irrespective of various steps with manual procedures. All media and reagents must be checked against appropriate controls for the proper reactivity [2]. Quality control at the each hospital are necessary for some of commercially available media and reagents. Consensus on the quality control might be needed on the routine procedures, while many other tests might be not necessary for routine quality control. Recently, individualized quality control plan process seems to have a more intense effect on clinical microbiology laboratory. With more discussions and gathering consensus, less daily quality control may be sufficient for the microbiology laboratory which can suggest its accumulated results of quality control procedures in the past.

Table. Characteristics to consider during validation of analytical procedures (WHO technical report. modified)

Type of analytical procedures	Identification	Testing for impurities	
		Quantitative tests	Limit tests
Accuracy	-	+	-
Precision	-	+	-
Specificity	+	+	+
Detection limit	-	- (may be needed)	+
Quantitation limit	-	+	-



# SYMPOSIUM 12

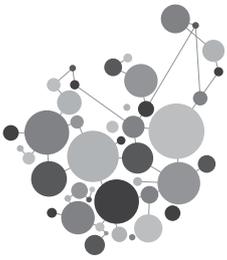
Linearity	-	+	-
Range	-	-	-

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SY13-01

## Mutation detection by next-generation sequencing in acute leukemia

Seung-Tae Lee

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Recent advance of genomic technologies have enabled expanding our understanding on the pathobiology of acute leukemias. Next-generation sequencing (NGS) has uncovered several recurrent somatic mutations that better define the landscape of leukemia genomics. Unlike most solid tumors, acute myeloid leukemia (AML) genomes appear to have a limited number of mutations, with an average of 13 mutated genes per case. In addition to the pre-established *FLT3* and *NPM1* genes, other genes including *DNMT3A* [20-25%], *IDH1/IDH2* [15-30%], *TET2* [10%], *ASXL1* [5-16%], *CEBPA* [10-18%], *WT1* [10-13%], *RUNX1* [5-13%], *RAS* [20-30%], *TP53* [~2%] have been shown to be mutated in AML. Based on functional analysis and known pathways, the genetic abnormalities can be grouped into categories based on biological function: (1) myeloid transcription-factor fusions or mutations, (2) *NPM1* mutations, (3) tumor-suppressor gene mutations, (4) epigenome-modifying gene mutations, (5) activated signaling-pathway gene mutations, (6) cohesin-complex gene mutations, and (7) spliceosome-complex gene mutations. From analysis of mutual exclusivity and cooccurrence between these genetic abnormalities, patterns of interplay between pathways were identified that may help delineate further subsets of AML and provide more insight into disease biology.

Somatic mutations in several genes are present in B-cell precursor acute lymphoblastic leukemia (BCP-ALL). These mutations have identified in genes which are involved in RAS signaling (48%), B-cell differentiation and development (18%), JAK/STAT signaling (11%), TP53/RB1 tumor suppressor (6%) and noncanonical pathways and in other/unknown genes (17%). Moreover, copy number changes involving *IKZF1*, *CRLF2*, *PAX5* and *EBF1* have been implicated in BCP-ALL with clinical significance. T-cell acute lymphoblastic leukemia (T-ALL) has been associated with four different classes of mutations: (i) Affecting the cell cycle (*CDKN2A/CDKN2B*); (ii) Impairing differentiation (*HOX genes*, *MLL*, *LYL1*, *TAL1/2* and *LMO1/2*); (iii) Providing a proliferative and survival advantage (*LCK* and *ABL1*); (iv) Providing self-renewal capacity (*NOTCH1*).

Introduction of NGS methods into clinical diagnostic laboratories has created an opportunity to profile the multiple actionable driver genes in patients with known and/or suspected myeloid malignancies. It can provide "actionable" information in four broad clinical utility categories: 1) diagnosis, 2) prognostic risk stratification, 3) eligibility for targeted therapy, 4) and minimal residual disease (MRD) detection and monitoring.

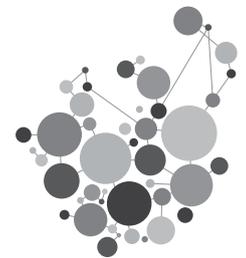
### Diagnostic Utility

The presence of a pathologic leukemia-associated driver mutation can establish the existence of clonal hematopoiesis and thus support a leukemia diagnosis.

### Prognostic Utility

In cytogenetically normal AML, consensus risk stratification recommendations include the routine assessment of mutations in the *FLT3* (poor risk), *NPM1*, and *CEBPA* (favorable risk) genes to inform treatment decisions, including the use of hematopoietic stem cell transplantation. In patients with a normally favorable risk core binding factor AML, the presence of a *KIT* mutation conveys a relatively poorer prognosis, such that these patients should be considered intermediate risk. Some studies suggest other molecular markers for AML risk stratification, including *TP53*, *IDH1/2*, *DNMT3A*, *TET2*, and *RUNX1* (all conferring poor risk). Multigene sequencing panels are also often used to stratify risk in ALLs, with several

# SYMPOSIUM 13



common gene mutations and copy number changes conferring a poor prognosis.

## Therapeutic Utility

Detection of specific mutations can define a likely response (or nonresponse) to a targeted therapy. Proven or promising examples include second-generation *FLT3* kinase inhibitors in *FLT3*-ITD-positive AML, inhibitors to the mutant IDH1/2-generated oncometabolite in AML, hypomethylating agents in *TET2*/*DNMT3A*/*ASXL1*-mutant cases.

## MRD Utility

NGS-based profiling can be used for monitoring the persistence of leukemia-associated mutations ("minimal residual disease") after therapy. The persistent detection of these mutations is predictive of future relapse, and may indicate the need for more aggressive therapy.

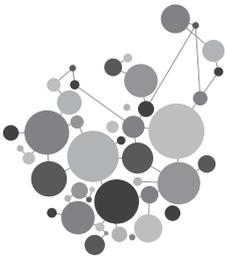
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SY13-02

## Mendelian exome in Japan

Naomichi Matsumoto

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Genome analysis in patients with genetic diseases has been developed and sophisticated together with technology advances. The advent and frequent update of next generation sequencers (NGSs) can attain the appropriate accuracy for mutation analysis and push genome analysis of human diseases into the new stages. We started NGS analysis in early 2009 and have been working as one of NGS centers for rare diseases in Japan. To focus on whole exome regions, we utilized exon capture methods such as SureSelect (Agilent). The current NGS protocol uses 100-108-bp pair-end reads and usually produces 6-7 Gb sequences (per one sample) could be enough for analysis of the whole exome: 90 % of whole exome regions are covered by 20 reads or more. Sequences are aligned by Novoalign, and nucleotide changes are detected and annotated using GATK and ANNOVAR, respectively. Copy number variations are also analyzed byXHMM or Nord method. More than 9000 exomes have been sequenced. We have been successful in addressing culprit mutations in various Mendelian diseases as well as acquired diseases arising from somatic mutations. During these researches, we witnessed high genetic complexity of human genetic diseases due to genetic and allelic heterogeneities. I will present some of our interesting data showing how NGS technologies brought us a new stage of researches dissecting human genetic diseases.



# SYMPOSIUM 13

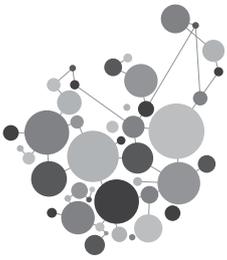
SY13-03

## Clinical exome sequencing for genetic disorders in Korea

Chang-Seok Ki

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Recent advances in next-generation sequencing (NGS) technologies have made disease-targeted gene panels, whole exome (WES), or genome sequencing (WGS) a realistic option for molecular diagnosis of genetic disorders. In addition, the novel sequencing technologies have boosted the discovery pace of novel disease genes. Before the WES/WGS is available, a priori information on the causative genes that might underlie a genetic condition is a prerequisite for molecular diagnostics but, theoretically, WES/WGS does not require any information on candidate genes. Although disease-targeted gene panel testing or WES/WGS is still expensive, it may be a cost-effective approach for molecular diagnosis of some genetic disorders with extensive genetic heterogeneity such as hearing impairments, muscular disorders, Charcot-Marie-Tooth disease, etc. In addition, WES/WGS may find unexpected mutations in genes known to cause different conditions from the initial diagnosis. However, there are still many hurdles that should be overcome before implementing gene panel testing or WES/WGS in clinical practice for molecular diagnostics. In this talk, I'll present recent advances in molecular diagnosis and personal experience of clinical exome sequencing.



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SY14-01

## Laboratory quality assurance in Indonesia

Yusra Yusra

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Chairman of External Quality Assurance of Indonesian Association of Clinical Pathologist and Laboratory Medicine*

External quality assurance (EQA) is quality assurance activities organized periodically by other parties outside of the laboratory for monitoring and assessing the performance of a particular laboratory in the field of examination. Organizing of EQA implemented by government, private or international and followed by all laboratories, both public and private, and is associated with health laboratory accreditation, and licensing of private health laboratories.

In the legislation, the Indonesian Ministry of Health assign periodically the implementation of accreditation in a period of at least 3 years in improving the quality of care. Internal and external quality assurance is one of the requirements for accreditation. Data from their survey showed approximately 60.8% hospital laboratories have participated the external quality assurance in the field of hematology, 59.4% clinical chemistry, 25.9% imunoserologi, 29.2% microbiology, and 29.8% urinalysis.

The National Program on External Quality Assessment Scheme (NEQAS) in Indonesia was first started in 1979, organized by the Indonesian Ministry of Health collaborating with professional bodies. The other EQAS (External Quality Assessment Scheme) programs conducted by professional organization, such as Indonesian Association of Clinical Pathologist and Laboratory Medicine for hemostasis, clinical chemistry and hematology programs, since 2006. In a year, the EQA was conducted two cycles.

Performance of participant was assessed by the index deviation for hematology, the variance index score (VIS) for clinical chemistry, and the deviation ratio for coagulation program. Participants with poor performance should attend workshop, which is held every year.



# SYMPOSIUM 14

SY14-02

## Quality issues of clinical laboratory in Thailand

Nisarat Opartkiattikul MD, PhD

*President of Royal College of Pathologists of Thailand*

In Thailand, there are 1,264 clinical laboratories, most of which are part of a hospital. There are three Acts that are related to clinical laboratory service. The purposes of these Acts are to ensure high standards of health care and to provide for the control and licensing of health care institutions including clinical laboratories. However, the quality of clinical laboratories in the country varies greatly ranging from total laboratory automation with ISO 15189 accreditation to manual laboratories staffed by personnel trained in-house.

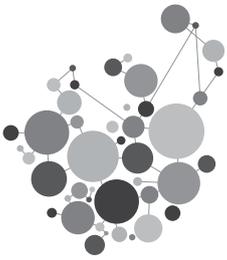
Several attempts have been made to improve the quality of clinical laboratories in our country. There are three parties that are involved in this issue.

The first party is the institutes that produce qualified laboratory personnel. In the branch of pathology, nine medical institutes have established a 3-year residency training program for clinical pathology, anatomical pathology and forensic medicine which can produce 13 clinical pathologists per year. Among 573 members of Royal College of Pathologists of Thailand (RCPT), there are only 70 clinical pathologists. In the branch of medical technology, there are ten universities which can produce a total of 900 medical technologists per year and there are approximately 14,000 medical technologists in our country.

The second party is the institutes that are taking care of the quality of clinical laboratory services by providing an external quality assessment scheme (EQAS). Though there is no legal requirement for enrolling in EQAS in our country, over 90% (1173/1264 labs) of clinical laboratories are voluntarily participating. The two main institutes providing EQAS are 1) Ministry of Public Health and 2) Mahidol University, which started their schemes under support from the World Health Organization (WHO) in 1978 and 1987 respectively. The Bureau of Laboratory Quality Standard (BLQS), Ministry of Public Health has been accredited by National Association of Testing Authorities, Australia (NATA) since 2002 for EQAS of hematology, clinical chemistry, microbiology and blood bank. It provides EQAS for clinical chemistry, hematology, clinical microscopy, clinical microbiology and blood banking. National Institute of Health (NIH), Ministry of Public Health also provides EQAS for HIV testing which has been accredited by ISO 17043 since 2010. Mahidol University provides EQAS for clinical chemistry, clinical microscopy, clinical microbiology, parasitology and coagulation. In 2008, there is one private company which provides EQAS for clinical chemistry and Point of Care glucose testing. In addition, RCPT also provides EQAS for cytology and anatomical pathology.

The third party is the institutes that provide laboratory accreditation. At the national level, there are 2 authorized bodies i.e. The Royal College of Pathologists of Thailand (RCPT) and The Medical Technology Council (MTC). Both started to give laboratory accreditation in 2001. There are 24 laboratories of medical schools have been accredited by RCPT and 993 laboratories by MTC. At the international level, BLQS which is a mutual recognition arrangement (MRA) of the International Laboratory Accreditation Committee (ILAC) and the Asia Pacific Laboratory Accreditation Committee (APLAC), is responsible for clinical laboratory accreditation using the ISO 15189 and ISO 22870 standards. There are 153 clinical laboratories that have been accredited by ISO 15189 and 4 hospitals that have been accredited by ISO 22870.

These three parties work together to promote and improve the quality of clinical laboratories in Thailand toward international standards.



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SY14-03

## Survey the influence of EQAs and biosafety to clinical laboratories at southern provinces in Vietnam

Tran Huu Tam

*Center for Standardization and QC in Medical Laboratory of HCMC, Vietnam*

Introduction: External quality assessment scheme (EQAs) and biosafety were two of the activities of Ministry of Health for improvement of quality in medical diagnosis in Vietnam, they were set up as the regulation from 2013. However, there are many arguments from the clinical laboratories, because of the cost to do. So, the aim of this study is to evaluate the effective of EQAs and biosafety to the quality assurance in clinical laboratories.

### The results:

- The EQAs: the participants increase from 1 province to 32 provinces (with 50 labs in 2007 to 1,235 labs in 2016). The scheme increase year by year (from 1 scheme in 2007 to 13 schemes in 2016). The rate of unacceptable EQA result decrease, example: biochemistry total error from 18.6% (2007) to 11.7% (2015), hematology total error from 18.4% (2008) to 9.8% (2015), immunology total error from 13.3% (2009) to 4.5% (2015), microbiology total error from 58% (2008) to 15.5% (2015).
- Biosafety: after complying with biosafety requirements, there are 137 clinical labs with many good changes when practicing the criteria of biosafety such as infrastructure, personnel, process, equipment,... that contributed much to the improvement of quality.

Conclusion: By the results of the survey, the influences of EQAs and biosafety to the quality of clinical laboratories are very effectively, so we should do the EQAs and biosafety by their effect to quality ourselves not by the regulation of MOH.

*Keywords: EQAs, Biosafety, Clinical Laboratory.*



# SYMPOSIUM 14

SY14-04

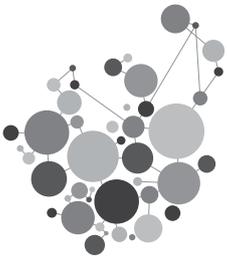
## Quality issues of clinical laboratories in Myanmar

Khin Saw Aye<sup>1</sup>, Moh Moh Htun<sup>1</sup>, Htay Htay Tin<sup>2</sup>, Cho Cho Nyunt<sup>3</sup>, Myo Nyunt<sup>4</sup> and Kyaw Zin Thant<sup>1</sup>

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Quality control (QC) in the medical laboratory is a statistical process used to monitor and evaluate the analytical process that produces patient results. When a diagnostic test is performed in the medical laboratory, the outcome of the test is a result. The result may be a patient result or it may be a quality control result. The result may be quantitative (a number) or qualitative (positive or negative) or semi-quantitative (limited to a few different values). QC results are used to validate whether the instrument is operating within pre-defined specifications, inferring that patient test results are reliable. Once the test system is validated, patient results can then be used for diagnosis, prognosis, or treatment planning. This result is then used by the physician to determine whether the patient has a low, normal or high level. But how does the person performing the test know that this result is truly reliable? It could be possible that the instrument is out of control and the patient's result may not be accurate. The question of reliability for most testing can be resolved by regular use of quality control materials and statistical process control. A quality control product is a patient-like material ideally made from human serum, urine or spinal fluid. A control product can be in liquid form or freeze-dried (lyophilized) material and is composed of one or more constituents (analytes) of known concentration. Control products should be tested in the same manner as patient samples. A quality control product usually contains many different analytes. A normal control product contains within normal range level of the tested analytes. An abnormal control product contains the analyte at a concentration above or below the normal range. Good laboratory practice requires testing normal and abnormal controls for each test at least daily to monitor the analytical process. If the test is stable for less than 24 hours or some change has occurred which could potentially affect the test stability, the controls should be assayed more frequently. Regular testing of quality control products creates a QC database that the laboratory uses to validate the test system. Validation occurs by comparing daily QC results to a laboratory-defined range of QC values. The lab-defined range is calculated from QC data collected from testing of normal and abnormal controls.

Quality Assurance in Health Laboratory Services in Myanmar - Administratively, the country is divided into 14 states and regions with 74 districts, 330 townships (rural and urban). The population of the country is 50 million with more than 75 % population residing in the rural areas. The laboratory services provide the essential backbone support for the prevention, control and treatment of diseases and other related health care programs being carried out in Myanmar in the context of the National Health Plan. In general, laboratory facilities in Myanmar are graded into three types A, B and C with the National Health Laboratory as the Central Reference Laboratory. Type A laboratories serve the states and regional level, Type B at the district level and type C at the township level. There are 38 type A laboratories attached to teaching hospitals, general hospitals, and specialist hospitals, 74 type B laboratories attached to district hospitals and 330 township hospitals that are served by type C laboratories. Type A and type B laboratories are generally headed by consultant pathologists. They take care of histopathology, hematology, microbiology, clinical chemistry and blood banking. Type C laboratories are headed by medical technologists whom take care of microbiology, clinical chemistry and hematology. Type A laboratories serve the 200 and above bedded hospitals. The 100-150 bedded hospitals are served by type B laboratories. Type C laboratories serve the 16 to 50 bedded hospitals and carry out the essential tests in clinical chemistry, hematology, public health microbiology and blood banking. In general, 200-500 tests in type A laboratories, 50 to 200 tests in type B laboratories, and 10-50 tests in type C laboratories can be carried out each day.



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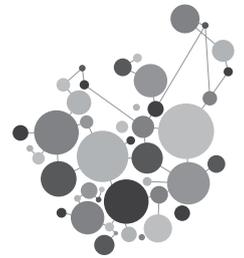
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Level	Type of Labs
Central level	NHL Yangon
State level	38 (Type A)
District level labs	74 (Type B)
Peripheral – Township	330 (Type C)

International and National training on quality assurance has been carried out from time to time in Myanmar. They are WHO National Training Course on Quality Control in Clinical Microbiology, National Workshop on introduction of Quality Standards and Appropriate Technology for Primary Health Care Laboratory Services, National Workshop on the Introduction and Establishment of External Quality Assurance Network, Workshop on Development of Laboratory Efficiency and Quality Assurance Scheme, training course for Key Trainers in Quality Assurance and NEQAS in microbiology which is conducted by NHL.

All laboratories are not equipped with facilities for carrying out complex investigations. The structure and function of a clinical laboratory varies according to the level of health care facility. Peripheral laboratories carry out simple tests whereas higher centers are equipped with sophisticated technology and trained manpower to carry out complex investigations. Establishing a network between peripheral and higher laboratories allows collection of specimen at periphery and their storage and transport for testing at higher centers and communicating report to the peripheral center efficiently without transferring the patient actually. In the event of patient transfer, the higher centers do not need to repeat investigations carried out at the peripheral health center, thereby saving crucial time as well as cost and providing continuity in patient care. Networking between laboratories is also essential in disease surveillance programme and outbreak investigations in order to obtain quick and reliable results. The expert committee on National Health Laboratory identified the surveillance and control of diseases as an important function of public health system. This formed the conceptual framework of Integrated Disease Surveillance Programme (IDSP). The key components of IDSP are coordination and decentralization of disease surveillance activities, improvement of laboratory support and strengthening data quality. Inclusion of private laboratories to act as sentinel sites and improve community participation is also important for wider coverage. The outlines need for accreditation of service quality including protocols for quality assurance and certification. In biomedical research too, achieving a set standard of quality produces credible results and allows comparison between studies carried out at different institutes Nationally and Internationally. This saves enormous time, money and resources and duplication of research work. The International Conference on Harmonization (ICH) provided Good Clinical Practices (GCP) Guidelines which describe standards to be followed by researchers while designing, conducting and reporting trials involving human participants. Realizing the rapid pace, wide spectrum and potential for clinical research in our country, the Department of Medical Research (DMR) launched the Ethical Guidelines for Biomedical Research on Human Subjects in 2005. To harmonize practices and generate mutually acceptable data for non-clinical health and environmental safety studies evolved Good Laboratory Practice (GLP) guidelines. To ensure reliability of data quality, WHO/TDR (Research and Training in Tropical Diseases) has developed good practice guidelines for laboratories involved in clinical trials. The proposed DMR guidelines for Good Clinical Laboratory Practices (GCLP) aim to elucidate step wise procedures which should be followed by laboratories to strengthen the quality of test results. These guidelines should be adopted by all laboratories engaged in research as well as patient care. DMR carries out research activities through its own institutes as well as through approved research centers in the public and private health systems. It also provides financial support to projects submitted by individual researchers and institutes. Adopting these guidelines lead to generation of uniformly acceptable and good quality laboratory data. Subsequently, a checklist is prepared to monitor these laboratories for compliance with these guidelines.

# SYMPOSIUM 14



SY14-05

## Quality assurance of clinical laboratories in UAE

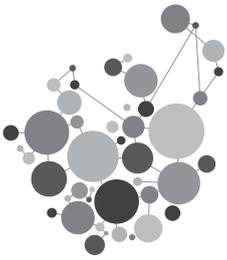
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United Arab Emirates (UAE) is a federal system composed of seven Emirates, such as Abu Dhabi and Dubai. Each Emirate has its own government and health care system. There are no nation-wide accreditation system or external quality assurance programs for clinical laboratories. However, Abu Dhabi government has own health authority, Health Authority Abu Dhabi (HAAD), and operates own CAP-style laboratory accreditation system inside Abu Dhabi Emirate. Dubai Emirate also has Dubai Health Authority (DHA) and own laboratory accreditation system. For the rest five Emirates, federal government has authority and Ministry of Health (MOH) operates health care system, but no accreditation system for clinical laboratories. To be a reference laboratory, internationally accepted accreditation is required to get insurance payment, so CAP accreditation has been an essential part to get lab tests from outside. In 2016, almost 40 laboratories are CAP accredited around UAE so far including governmental and private sectors, hospitals and reference laboratories. But, recently there are trends initiated from the governmental insurance systems that laboratory accreditation would be shifted to ISO 15189.



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SY14-06

## Accreditation of clinical laboratories in India

Praveen Sharma

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Accreditation is the formal acknowledgment, approval and registration of a clinical laboratory that has demonstrated its competence and capability to carry out its specified scope. It is a third party attestation procedure that provides feedback to applicant laboratories regarding their performance relative to International standards for technical competence. Though accreditation of clinical laboratories is a mandatory criteria in many countries, it is only voluntary and not essential in India. The sole authorized laboratory accreditation body in India is National Accreditation Board for Testing and Calibration Laboratories (NABL).

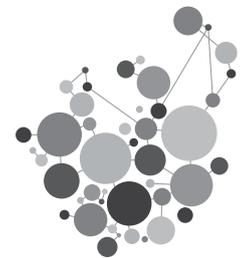
NABL is an autonomous body under the aegis of the Dept. of Science & Technology, Govt. of India, and is registered under the Societies Act. It was initially established with the objective to provide accreditation to testing & calibration laboratories. Gradually it extended its services to the clinical laboratories of this country. It offers accreditation to testing, calibration, and clinical laboratories and its activities include surveillance and re-assessment visits, proficiency testing programmes, and the withdrawal, suspension, or reduction in scope of accreditation.

With time NABL established links with international bodies - Asia Pacific Laboratory Accreditation Cooperation (APLAC) and International Laboratory Accreditation Cooperation (ILAC). This has imparted international recognition to NABL accredited laboratories. The international standard currently followed by NABL is ISO 15189, specific for medical laboratories.

Besides getting international recognition and acceptance, accreditation gives confidence to both the testing laboratory and referring physician regarding the reliability of the test report to diagnose an individual patient and also manage patient empirically by generating reliable epidemiological data. With periodical assessment, accreditation will provide a sustainable and good Quality Management System for laboratories. However, accreditation of clinical laboratories in India is in its infancy with the surge of getting accredited increasing only in private laboratories mainly to meet commercial requirements and to increase their brand value and customer base.

Lack of proper knowledge and training is also contributing towards the hindrance from getting accredited. NABL has started training laboratory personnel's in various areas to increase their competency and help them to set up a clinical laboratory maintaining the quality standards as per requirements. Accreditation should be taken as a positive tool for laboratory improvement. Author is an assessor of NABL and has regularly participated in assessment of a number of clinical laboratories for accreditation since last four years. The pathway for accreditation of clinical laboratories in India with future directions will be discussed.

# SYMPOSIUM 15



SY15-01

## Patients benefit from complementary quality solutions: CAP and ISO15189

Richard C. Friedberg, MD, PhD, FCAP

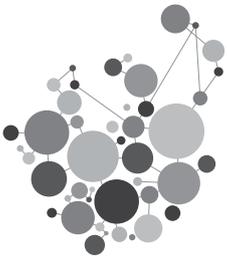
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The ISO15189 Standard, published by the International Organization for Standardization (ISO) and entitled “Medical Laboratories-Particular Requirements for Quality and Competence” was formally established in 2003. With significant input from the College of American Pathologists (CAP) liaison members, ISO15189 applies the quality management system developed in the ISO9000 series of documents to the medical laboratory. Like ISO9001:2000, ISO15189 provides a structured quality management system that allows for both preventive (before) and corrective (after) action to potential and actual problems, as well as a client-centric emphasis to laboratory operation.

First introduced in 1961, the CAP Laboratory Accreditation Program leverages the deep scientific and practice expertise of the College’s pathologist membership in the design and continuous update of its standards. It is the gold standard in the United States for the state of the art in pathology and laboratory medicine, and is also recognized internationally for its depth, focus, and consistent, standardized application no matter where a laboratory is located around the globe. The CAP Accreditation Program serves to ensure laboratory quality compliance at levels that exceed US regulatory requirements and it addresses in detail the full spectrum of elements that go into ensuring a quality patient test result—from preanalytical to post analytical measures.

Both the CAP and ISO15189 accreditation standards are recognized global standards. While there are differences between the standards, both serve to improve the quality of patient testing. In his presentation, Dr. Richard Friedberg will provide an overview of the substantive differences between these standards. From attendance in this session, participants will learn how many laboratories have benefitted from the rigorous integration of compliance to both ISO and CAP requirements. Dr. Friedberg will also discuss how these benefits result in better outcomes for patients.



# SYMPOSIUM 15

SY15-02

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## Implementation and future perspectives of laboratory accreditation program in Korea

Hwan Sub Lim, MD, PhD

*Seoul Clinical Laboratories, Seoul Medical Science Institute, Yongin, Korea*

Laboratory accreditation became an essential part for laboratories. Through laboratory accreditation activities, laboratories recognize the importance of accreditation program and number of participating laboratories steadily increased.

In 1998, laboratory accreditation program launched as a research project titled as "inspection and quality certification program for improving and managing the quality of clinical laboratory tests" to increase the quality of laboratories given by Ministry of Health and Welfare (MHW), Korean Government. Pilot project launched in 1999. Korean laboratory accreditation program (KLAP) was organized by Korean Society for Clinical Pathology (KSCP; currently KSLM, Korean Society for Laboratory Medicine).

KLAP started with participation of 93 laboratories in 1999 and increased up to 283 laboratories in 2016. Checklists revised to reflect the current status and to upgrade standards for laboratories since the KLAP started. KLAP has its own unique system that are different from CAP and ISO 15189 (Table 1).

Table 1. Comparison of KLAP with CAP and ISO 15189

	CAP	ISO 15189	KLAP
Participation	Mandatory (in US) Voluntary (outside US)	Voluntary	Voluntary
Accreditation	Peer-review	3 <sup>rd</sup> Party	Peer-review
Assessment	Competence Technical Procedure	Conformity Risk assessment	Competence Conformity
Assessment Method	Pass/Fail Phase 1 Phase 2	Pass/Fail	Unique scoring system
Accreditation	2-year Accepted/Deficiency/ Recommendations Corrections needed before accreditation	3-4year Deficiency Report	1-year :80-89% 2-year : ≥90% Fail : < 80%

In 2010, Laboratory Medicine Foundation (LMF) founded by KSLM to make every effort to contribute this system to improve quality of laboratory medicine in Korea. In 2016, KLAP prepare for acquisition of international accreditation from International Society for Quality in Health Care (ISQua) to spread this program to achieve quality improvements in overseas laboratories.



# SYMPOSIUM 15

SY15-03

## International laboratory quality systems: CAP, ISO, and etc.

Noel M. Adachi, MBA

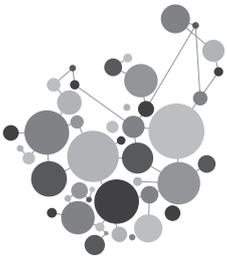
*International Market Development, College of American Pathologists, Northfield, Illinois, USA*

The term “quality” is subjective especially in healthcare. According to the ISO definition quality is defined as “The totality of features and characteristics of a product or service that bear on its ability to satisfy stated or implied needs”. Essentially, good quality is based on client requirements. So what are the client’s requirements?

There have been numerous studies conducted that try to measure what people want from their healthcare. For most people, the doctor-patient relationship remains at the heart of people’s perceptions of health care. So, where does the clinical laboratory fit into this quality definition? With the growing complexity of diagnostics, so much could go wrong that would directly impact the quality of care and patient outcomes. Selection of the right tests, proper sample collection, accurate results, appropriate interpretation, and proper and timely recording requires an integrated network of people, processes, procedures and technology that all has to work together seamlessly. Many laboratories go through heroic efforts to ensure compliance to best practices as defined by a variety of standards that serve as the proxy measurement stick for achieving these quality outcomes. But which standards are right for your laboratory? Is there a ‘silver bullet’ standard that pulls it all together. The simple answer is “not yet”.

The good news is that the principles of high quality laboratory testing are the same anywhere in the world—it is one area of health care that can be and should be highly standardized. The ISO 15189 standard and the College of American Pathologists (CAP) requirements have emerged as the most comprehensive guidance to achieving high quality laboratory testing and effective quality management system design. While they have very different beginnings and both integrate Clinical and Laboratory Standards Institute (CLSI) guidelines, both standards reflect agreement that most medical laboratory errors are caused by systems and process issues, not people. If we can get the systems, processes and procedures standardized, people are less likely to make errors.

In her presentation, Ms. Noel Adachi will provide a brief overview of the histories of these standards, how and where they are used today, and strengths that together both bring to improving laboratory quality.



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SY16-01

## Definitions in Myelodysplastic syndromes and the clinical utilization of molecular markers of disease and disease progression

Annette S Kim, MD, PhD

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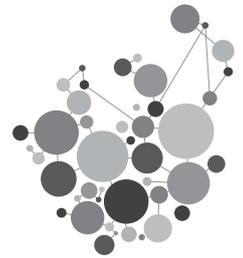
Myelodysplastic syndromes (MDS) are a group of clonal hematopoietic stem cell disorders with defects in hematopoiesis, resulting in cytopenias clinically and dysplasia pathologically. MDS occurs most commonly in the elderly with a median age of 71-76.<sup>1</sup> The clinical presentation and prognosis of MDS is quite varied, depending upon the morphologic subtype and prognostic score. Survival in patients with only unilineage dysplasia and a good prognostic score may not differ significantly from the background normal population, while those with excess blasts have a median survival of as little as nine months, similar to acute myeloid leukemia (AML). In patients who succumb to the disease, the most common cause of death is related to cytopenias, such as infection and bleeding;<sup>2</sup> however, a subset of MDS patients will transform to AML, the rate of transformation ranging from less than 2% to up to 33% in MDS with excess blasts-2 (MDS-EB2).<sup>3</sup> Those patients who transform to AML have extremely poor prognosis. Despite a relatively low overall incidence of up to 75/100,000,<sup>4</sup> MDS is in fact a diagnostic consideration for a large proportion of the elderly population with low blood counts. As 8-44% of all elderly have anemia and additional individuals may have low platelet or neutrophil counts,<sup>5</sup> MDS is a major health concern for this population

However, MDS is difficult to diagnose and therefore likely underdiagnosed. The most recent World Health Organization (WHO) 2016 revisions still rely upon the morphologic findings of dysplasia and increased blasts as the only diagnostic criteria for nearly all subtypes of MDS.<sup>6</sup> Yet, the elderly have numerous other comorbidities that may also lead to dysplasia unrelated to MDS. Immunophenotypic aberrancies are common, but not specific and are not recognized yet as diagnostic criteria.<sup>7,8</sup> While some karyotypic changes are sufficient for a presumptive diagnosis of MDS, in approximately 50% of cases the karyotype is normal.<sup>9</sup> Moreover, the karyotype is often not available at the time of issuance of the bone marrow report. Thus, pathologists have tended to render conservative descriptive diagnoses, delaying diagnosis until the MDS declares itself. Mature individuals with cytopenias and insufficient morphologic support for a diagnosis of MDS are considered to have idiopathic cytopenias of uncertain significance (ICUS).<sup>10</sup>

The advent of next generation sequencing (NGS) ushered in an era of exponential discovery in all areas of medicine. In MDS, several large studies emerged between 2011 and 2014, characterizing the mutational landscape of MDS.<sup>11-14</sup> Numerous exciting new categories of mutations were discovered to be drivers in MDS. Even so, the 2016 revisions to the WHO do not include ANY mutations in their diagnostic criteria for MDS, with the exception of *SF3B1*.<sup>6</sup> This is due to the discovery in late 2014 of the prevalence of many of these same mutations in the normal aging population, termed clonal hematopoiesis of indeterminate potential (CHIP).<sup>15-17</sup> Therefore, the diagnosis of MDS still relies upon the, often challenging, identification of dysplasia. Patients with cytopenias, mutational evidence of clonality, but insufficient dysplasia to make a diagnosis of MDS are considered to have clonal cytopenias of uncertain significance (CCUS).<sup>18</sup>

Delays in diagnosis consequently delay the institution of therapy. Presently therapy for MDS utilizes DNA methyltransferase inhibitors (DNMTIs) or definitive intervention by stem cell transplantation, the only available potential cure.<sup>19,20</sup> Studies have shown that early institution of DNMTI therapy not only improves survival (19.3 months on DNMTIs versus 12.9 months with supportive care), but also can delay and decrease transformation to AML by 2.5 fold.<sup>19,20</sup> In fact, due to the challenges inherent in diagnosing MDS, many patients are actually diagnosed when they progress to AML (secondary AML, sAML), although antecedent MDS may be presumed due to the patient's history of cytopenias or due to the presence of mutations in

# SYMPOSIUM 16



one of 8 key genes shown to have >95% specificity for sAML, *SF3B1*, *SRSF2*, *ZRSR2*, *U2AF1*, *ASXL1*, *EZH2*, *BCO2*, and *STAG2*.<sup>21</sup> At the Brigham and Women's Hospital, we routinely test many of our cytopenic patients with a 95 gene MiSeq-based Rapid Heme Panel (RHP). Several examples of the impact of this panel on our clinical understanding of CHIP, CCUS, MDS, and sAML are provided.

However, only 40-47% of patients see any hematologic improvement with DNMTIs, and many respond only after several cycles of therapy.<sup>19,20</sup> Moreover, critical time is lost both in making the diagnosis of MDS, deciding to initiate therapy, and finally in waiting the 3-6 months before acknowledging the failure of therapy in the majority of cases. These delays narrow the window of opportunity to transplant these elderly patients.<sup>4,22</sup> Therefore, we need better ways to predict patients and genetic profiles likely not to respond to existing therapies. There is also prognostic need for methods to predict patients likely to progress to AML, before they accumulate excess blasts.<sup>23,24</sup> Even using the recently revised International Prognostic Scoring System (IPSS-R) there are patients with long survival in poor prognostic categories and patients who succumb early despite better prognosis disease. Although several studies have suggested markers to predict either response to therapy or progression to AML, most have seen little clinical utility, making prognostication in MDS a continued clinical need.

Some groups, including our own, have turned to small non-coding RNAs (sncRNAs) to identify novel diagnostic and prognostic biomarkers for MDS.<sup>25-30</sup> The decision to study sncRNAs was driven by the importance of various small RNA species in regulating cellular differentiation, in particular microRNAs (miRNAs), their isomers (isomiRs) and transfer RNA (tRNA)-derived fragments (tDFs). There is a wealth of literature supporting the critical regulatory role of microRNAs (miRNAs) in cell differentiation.<sup>31,32</sup> However, more recently tRNA-derived fragments (tDRs) and miRNA isomers (isomiRs) have also been found to regulate translation through miRNA-like mechanisms.<sup>33,34</sup> Small RNA-seq is a platform that simultaneously can interrogate all these species with the goal of identifying novel prognostic markers in MDS.

We have hypothesized that sncRNAs regulating differentiation should be aberrant in MDS. In a series of studies, we have shown that aberrant miRNA expression does characterize MDS, and that corresponding manipulation of miRNA expression can recapitulate many of the aberrant clinical features of MDS.<sup>25,26,35</sup> In addition, we have identified sncRNA prognostic biomarkers in MDS. By studying paired samples from patients before and after therapy with DNMTIs, we have identified patterns of sncRNAs in the pre-therapy specimen that can predict future response to DNMTIs.<sup>30</sup> In a separate study, we compared MDS patients who never progressed to AML to MDS patients who later progressed to an AML. We successfully identified key sncRNAs that predict which patients are likely to progress to an AML before they begin to accumulate excess blasts.

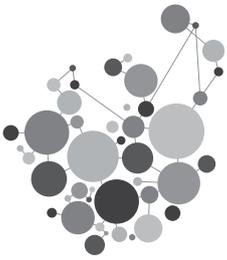
This presentation should provide an introduction to MDS, define several key terms in clinical diagnostic practice, demonstrate the routine clinical utilization of panel-based sequencing for mutations in diagnosing and monitoring MDS patients, and finally describe investigational studies on the potential role of sncRNAs in the diagnosis and prognosis of MDS.

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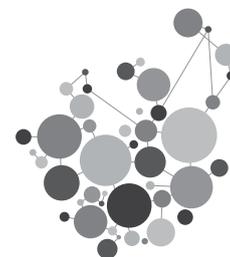


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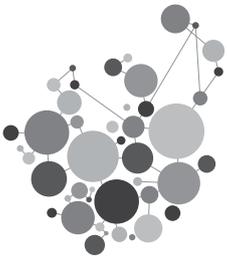
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## Molecular markers of MDS and aplastic anemia in Korean

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Hee-Sue Park<sup>1</sup>, Si Nae Park<sup>5</sup>, Kyongok Im<sup>5</sup>, Kwantae Kim<sup>5</sup> and Sung-Min Kim<sup>5</sup>

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### An association of U2AF1 S34Y mutation and isolated trisomy 8 in Korean myelodysplastic syndrome

We performed target sequencing for 87 genes in 153 Korean myelodysplastic syndrome (MDS) patients. Epidemiologically, the median age of MDS diagnosis in Asian patients was approximately 60 years, which is approximately 10 years younger than that reported in Western patients, whose median age is approximately 70 years. Most frequently mutated genes were *ASXL1* (23%) and *U2AF1* (25/153, 16%: 6 *S34Y*, 11 *S34F*, and 8 *Q157P* mutations). The profile of frequently mutated genes were similar to those of Caucasians, but frequency of *U2AF1* mutations (25/153, 16%: 6 *S34Y*, 11 *S34F*, and 8 *Q157P* mutations) was much higher than other reports. Of note, we found a significant association between *U2AF1 S34Y* mutations and trisomy 8 in MDS patients, which have not been reported and patients with *U2AF1 S34Y* mutations were characterized by younger age of onset (median 39 years), compared to those without *U2AF1 S34Y* mutations. We compared the frequency of *U2AF1* mutations in Korean MDS patients with that of other countries. The frequency of *U2AF1* mutations reported in China was 8.6%, and that of Korean AML patients with myelodysplastic feature was 8.6%. In Caucasian MDS, it was reported as ranging from 8.7% to \*\*%. These frequencies are significantly lower than the *U2AF1* mutation frequency in Korea. The distribution *U2AF1* mutation in Korean MDS clearly differs from that of other countries. *S34Y* is significantly more common than *S34F* in Asians, contrary to Caucasians. Wu reported that *S34* mutation is associated with del (20q) or trisomy 8. (Cho mentioned that *U2AF1* mutation and trisomy 8 are associated in AML patients, but did not report an exact number.) These studies, however, did not report an association between *U2AF1 S34Y* mutation region and trisomy 8. When we screened *U2AF1* germline mutation in the peripheral blood of 200 healthy by allele specific PCR, and *S34Y* mutation was not found.

*U2AF1* mutation causes mis-splicing, exon skipping, increased frequency of splicing, etc. and it possibly leads to ER stress within cell. *S34F* is a mutation in which amino acid with a relatively small residue changes to one with a bulky aromatic ring. Such mutation causes the coil structure, which is the core structure of zinc finger motif, to collapse, and therefore leads to a problem in the perception region of RNA. *S34Y*, too, is a mutation in which amino acid changes to one with a bulky aromatic ring, and is thus expected to demonstrate similar aspects. One expected difference, however, has to do with the degree of hydrophile property, due to OH at the end of the aromatic ring. Tyrosine is strongly hydrophilic, while Phenylalanine is a non-polar aromatic amino acid, and is therefore more similar to the pre-mutation amino acid Serine. Considering that a difference in the amino acid property indicates a greater impact of the mutation, we can predict that Phenylalanine may cause a greater difference in theory, although they are both expected to collapse the coil structure of *U2AF1* due to a similar-shaped aromatic ring.

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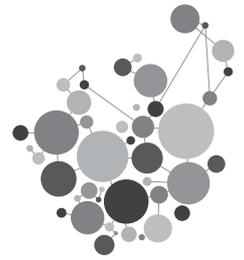
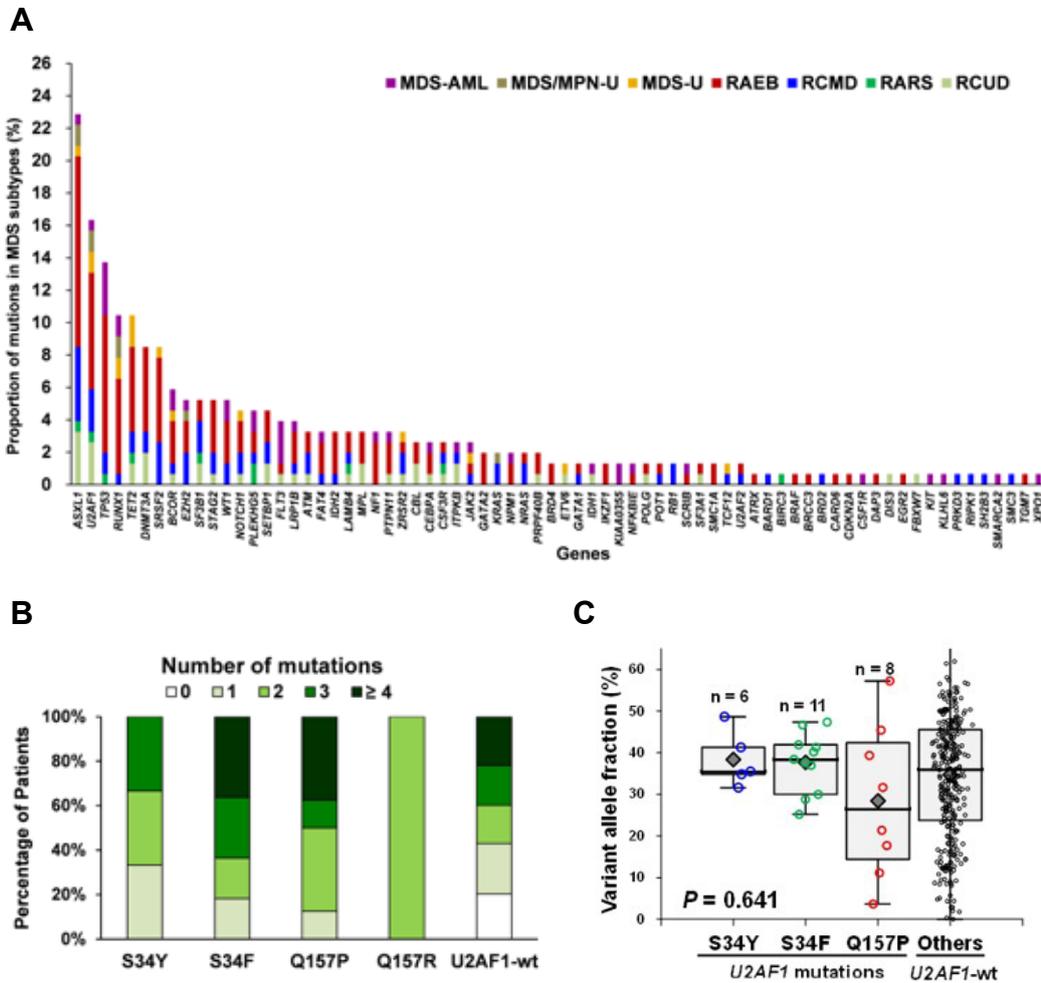


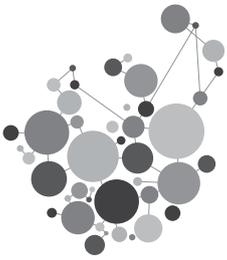
Figure 1. (A) Frequency of the mutations identified in the multi-gene target sequencing in 153 myelodysplastic syndrome (MDS) patients. (B) number of mutations according to *U2AF1* mutation types. (C) Distribution of variant allele fractions of *U2AF1* mutations and other mutations.



## Short Telomere Length and its Correlation with Gene Mutations in Myelodysplastic Syndrome

Telomere length of cell reflects the cellular age and short TL suggest the potential susceptibility to DNA damage. It is well known that persistently long TL in cancer cells confers an immortality and telomere attrition is the signature of aplastic anemia or bone marrow failure syndrome. We investigated whether 1) the treatment response is associated with TL of hematopoietic cells (HPC) and 2) whether somatic mutations are associated with TL in patients with aplastic anemia. We adopted a method, quantitative fluorescence in situ hybridization, that can evaluate the telomere length at a single cell level, so that not only average length, but the distribution pattern of TL among BM cells, assessment of population with short telomere below lower 10th percentile of normal control can be made.

MDS patients showed eroded telomeres and narrow distribution compared to the NC ( $P < 0.001$ ). Patients with any gene mutation, showed significantly higher TL and lesser cells under the 10 percentile of NC ( $P = 0.017$ ). Those patients with *CSF3R* mutation and anemic patients showed significantly lower percentage of cells under 10 percentile of NC ( $P = 0.037, 0.020$ , respectively). However, no other differences were found according to specific somatic mutations or to cytogenetic abnormalities. Those patients with a high percentage ( $> 80\%$ ) of cells with TL below the lowest 10 percentile of NC's TL showed poorer overall survival ( $P = 0.017$ ). In the multivariate Cox analysis, the revised IPSS and TP53 mutation were found as independent prognostic factors ( $P = 0.003, 0.027$ , respectively). The shortest TL in each patient, which determines the fate of the cell, was evaluated in MDS patients and it was significantly shorter than that



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of the NC ( $P < 0.001$ ). The present study revealed that TL was shorter in patients with MDS and a higher burden of cells with short TL correlated with poor survival, suggesting the need to measure TL in single cells using Q-FISH.

Table 1. Telomere length parameters of MDS patients and normal control

Parameters	Average $\pm$ SD		P-value
	MDS (n = 58)	NC (n = 23)	
Age	63.7 $\pm$ 14.6	60.9 $\pm$ 9.5	0.175
Gender (M:F)	37:21	16:7	0.796
No. of cells assessed for telomere lengths	77.6 $\pm$ 38.9	98.1 $\pm$ 26.3	0.004
Telomere lengths (T/C ratio)			
Minimum	1.97 $\pm$ 1.47	4.41 $\pm$ 1.36	<0.001
25 percentile (Q1)	5.49 $\pm$ 3.04	11.79 $\pm$ 3.06	<0.001
Median	8.56 $\pm$ 4.45	15.92 $\pm$ 3.93	<0.001
Average	10.08 $\pm$ 4.73	17.29 $\pm$ 4.42	<0.001
Average of 0-10 percentile	2.95 $\pm$ 1.76	6.64 $\pm$ 1.74	<0.001
Standard Deviation	6.67 $\pm$ 3.01	8.07 $\pm$ 2.73	0.018
Cells under 10 percentile of NC (%)	52.1 $\pm$ 24.9		

MDS: myelodysplastic syndrome, NC: normal control

## Somatic Mutations and Telomere Length in Correlation with Response to Immunosuppressive Treatment in Aplastic Anemia

We investigated whether 1) the treatment response is associated with TL of hematopoietic cells and 2) whether somatic mutations are associated with TL in patients with aplastic anemia (AA). We measured the mean TL and heterogeneity of bone marrow nucleated cells at the single cell level by quantitative fluorescence in situ hybridization. A total of 148 AA patients were enrolled; AA (n=148) and normal peripheral blood control (n=147). TL was expressed as telomere/centromere ratio. We analyzed the average and the distribution of TL belonging to the lowest 10<sup>th</sup> percentile of cell population. Along with measurement of TL, target sequencing for 87 hematopoiesis-related genes was performed to detect somatic mutations. Mean TL of AA (T/C ratio 6.08) was significantly shorter than normal control (T/C ratio 10.06). Of note, AA patients with short TL (<4.38 T/C ratio) showed significantly adverse treatment response to immunosuppressive therapy (specificity 98.3%). Patients with cytogenetic aberrations (CA) and/or somatic mutation (SM) showed significantly shorter TL compared to AA with normal karyotypes. When the patients were divided by clonal (CA and/or SM, 13.5%), and non-clonal (86.5%), IST in clonal group showed adverse response compared to non-clonal group ( $p < 0.05$ ), while BMT treatment showed similar response between 2 groups. In contrast to that 5.0% of AA patients showed disease progression, 7.6% of patients with SM showed disease progression. The number of mutated genes was 21 and frequently mutated genes was *NOTCH1* (3/26, 11.5%), *MED12* (3/26, 11.5%), *NF1* (3/26, 11.5%), *SCRIB* (2/26, 7.6%), *BCOR* (2/26, 7.6%), and *DIS2* (2/26, 7.6%). In conclusion, patients with TL attrition showed poor response to IST. Short TL can be used not only as a biomarker for AA, but also as a predictive marker for treatment response to IST. In addition, CA and/or SM was strongly associated with adverse prognosis or treatment response, so we strongly suggest to adopt more sensitive test for the detection of minor clonal cell population in AA.

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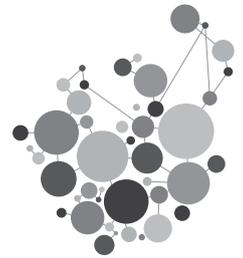
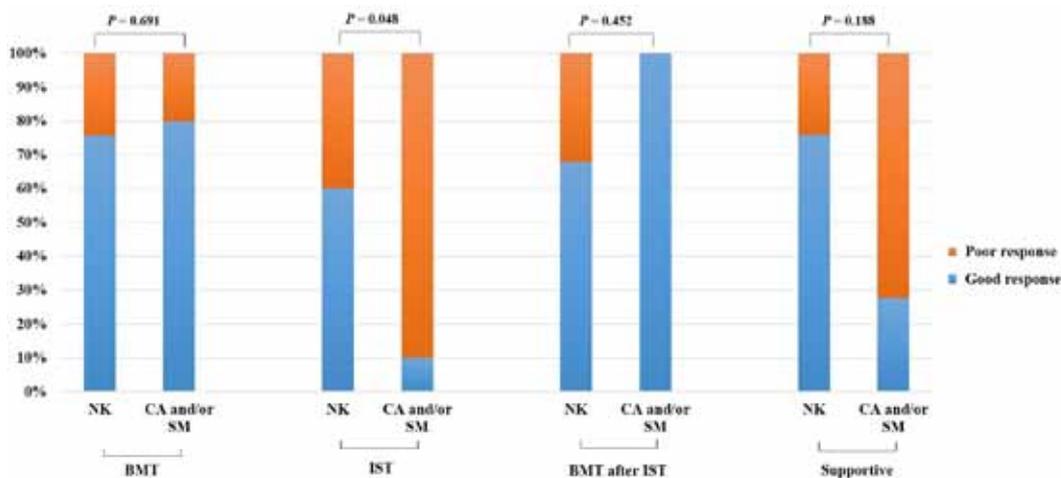


Fig.2 Effect on cytogenetic aberration and/or somatic mutation on treatment response therapy



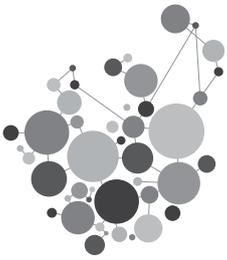
We divided AA patients into 4 groups according to treatment. In IST group, patients with cytogenetic aberration and/or somatic mutation had adverse response but not BMT group.

## Increased Expression of Interferon Related Genes in the Bone Marrow Microenvironment of Myelodysplastic Syndromes

For a long time, MDS is thought to be a kind of immune dysregulated disease and changes of cytokines have been steadily reported. From that perspective, role of bone marrow stromal cells consisting bone marrow microenvironment deserves attention. There are several studies focused on the disturbance of cytokine production or supporting ability of MDS BM microenvironment, while there is only one published study at global gene expression profiling for pediatric MDS BM microenvironment. However, pathogenesis of pediatric MDS is thought to be "inherited bone marrow failure syndrome, while adult MDS is acquired disease. So we investigated gene expression profile of adult MDS. We questioned 1) whether microenvironment of bone marrow (BMME) in MDS differ from BMME of normal person. In that case, which genes are involved? 2) what kind of pathways are involved in differential expressed genes (DEG)? Are the gene expression profiles of BMME different among MDS subtypes? 3) Changes of gene expression between BM hematopoietic cells and BMME are involved in similar pathways?

The genes involved in immunity pathway, especially interferon pathway, were up-regulated in MDS BM microenvironment. Though there was rare overlap between DEG of RCMD vs. normal and RAEB vs. normal, similarity analysis revealed those DEG are very similar each other in function ( $p=0$ ). In other words, DEG of RCMD vs. normal and RAEB vs. normal was different each other, but their DEG resulted in same phenotypic changes. What is more, pathway analysis of DEG revealed upregulation of interferon alpha/beta signaling, interferon gamma signaling, ISG15 antiviral mechanism and immune system related genes. This finding fall into a long continued hypothesis that MDS is a chronic inflammation or immune disease. We infer that upregulation of immune related genes in BM stromal cells results in clinical symptoms like immune disease and increased cytokines levels in patients with MDS.

The gene expression profile of RCMD BM microenvironment is clearly different from that of RAEB BM microenvironment: Suggestion for the role of BM stromal cells in disease progression. Though DEG in RCMD and RAEB showed upregulation of interferon related genes, their expression pattern was clearly separated each other. Pathway analysis between RCMD and RAEB revealed downregulation of RNA polymerase I, RNA polymerase III, and mitochondrial transcription. Of note, mitochondrial transcription is mentioned as spotlighted genetic changes in RARS. Our results also showed downregulated mitochondrial transcription in RAEB, compared to RCMD. We infer that phenotypic changes of BM stromal cells might contribute to the disease progression of MDS. Microenvironmental changes according to disease progression can be a potential target for drug discovery, which is realized in solid tumor. Finally,

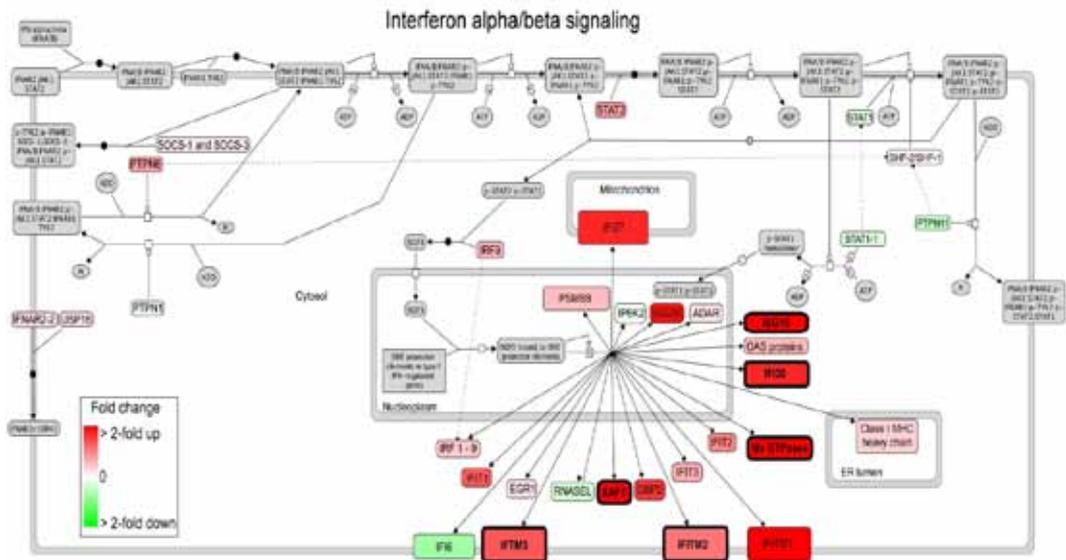
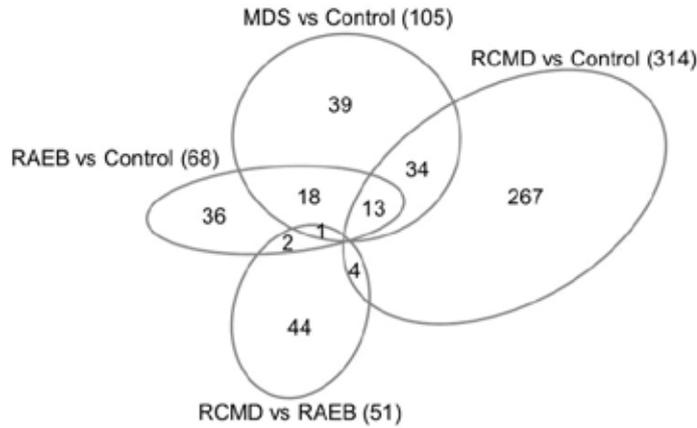


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the gene expression profile of MDS BM microenvironment is distinguished from that of normal BM microenvironment.

Figure 3. Up-regulation of interferon alpha / beta signaling. Fold change values in MDS vs. control comparison were used for coloring. Nodes with thick black border represent differentially expressed genes.





# SYMPOSIUM 17

SY17-01

## **Problem solving for difficult erythrocyte antibodies in unexpected antibody screening and identification tests**

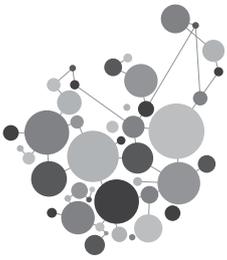
Hein Hustinx

*Swiss National Immunohematology Reference Laboratory, Switzerland*

Due to pregnancy or blood transfusions patients can form antibodies against blood group antigens (alloimmunization). To prevent hemolytic or delayed transfusion reactions, an antibody screen and / or compatibility testing is performed. In most cases, these tests will show a negative result, however in rare cases a positive result is obtained. Antibody identification will mostly result in a clear antibody specificity, but in some special cases this result can not be obtained by routine immunhematological laboratory work-ups. This lecture will show several aspects (different methods) of the process of identifying "rare antibodies" and their clinical relevance.

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SY17-02

## Blood regulation affairs in Japan

Masahiro Satake

*Japanese Red Cross Central Blood Institute, Tokyo, Japan*

### 1. Blood law and blood authorities in Japan

A new Japanese blood law, the Law for the Stable Supply of Safe Blood Products, was enacted in 2003. This law governs the entirety of regulatory blood affairs in Japan from donation to transfusion. In this new law, the national government is clearly designated as the body responsible for the following: 1) establishing basic and comprehensive policies for the stable supply of safe blood products; 2) educating nationals for an accurate understanding of blood donation practices and procedures; and 3) establishing measures to promote the proper use of blood products. According to the law, all blood-related affairs are to be handled directly by the Blood and Blood Products Division of the Pharmaceutical and Food Safety Bureau, which is a part of the Ministry of Health, Labour and Welfare (MHLW). However, the Blood Services Division of the Japanese Red Cross (JRC) is the actual institute that carries out all blood-related procedures from procurement to delivery. The JRC is the only facility in Japan currently authorized to handle blood-related procedures. The JRC carefully considers future plans for blood collection, the development of testing strategies, blood processing and supply, and then presents the points of them to the government. The current conditions of and any existing problems related to blood affairs are reported to the government in a timely fashion. A blood affairs committee, which is composed of several subcommittees, such as a steering committee, a commission on safety and technology, a commission on the proper use of blood products, a commission on blood supply and demand, and a commission on the promotion of blood donation, is included in a council convened by the MHLW to discuss pharmaceutical affairs and food sanitation. After plans presented by the JRC are discussed and approved, they are implemented at the JRC headquarters and local blood centers.

### 2. The manufacturer/distributor of drugs

In Japan, the Blood Services Division of the JRC is regarded as a typical pharmaceutical company. Because it is defined as a "manufacturer/distributor" of blood components, the organization of its facilities, the quality of its products, and its production processes are under the strict control of the Pharmaceuticals and Medical Devices Law, which sets the standards of drugs and items for good manufacturing practices. Each blood center must undergo regular inspections by the government that is nearly identical in precision to those applied to pharmaceutical companies. This law also establishes the rules for reporting adverse events that occur in transfused patients.

### 3. Patient and donor relief system

Blood products in Japan are subject to the Product Liability Law. However, it is widely considered inevitable that blood will be contaminated or transfusion-related adverse events will occur. Therefore, the JRC is not held legally liable for adverse events such as transfusion-transmitted infections (TTIs) if an obvious failure in the production process goes undetected, or contamination by pathogens, even when the most advanced technologies are employed. To provide relief to victims of transfusion-related adverse events, the Japanese government established a system in which companies such as the JRC that produce labile biological products contribute money to a fund that can be used to compensate victims. A similar system was also established for blood donors who become ill during or after blood donations. The basic idea for this fund is to ensure that blood donations are carried out on a national level, which is necessary in modern medicine and thus promoted heavily by the government. Therefore, victims of blood donation-related illnesses are compensated by the national government unless any apparent failure in the JRC process is found.



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## 4. Cost of blood products

The price of all medicines in Japan, including blood components and plasma derivatives, are determined centrally by the government. The financial basis of the Blood Services Division of the JRC, which is treated as a pharmaceutical institution, is the payment for blood components by medical facilities. Under Japan's health insurance system, all Japanese residents are insured and therefore only responsible for paying 30% of their total medical expenses.

## 5. Look-back guidelines

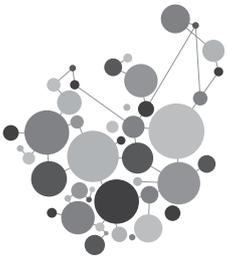
Special guideline that determines the purpose and methods of a look-back study was established to avoid the spread of TTIs that could be preventable by withdrawing blood components that may harbor harmful pathogens. This guideline establishes the risk-harboring period of blood donation depending on the type of pathogens identified in donors or transfused patients. It is essential to identify TTIs as early as possible in order to prevent further infection from suspected blood components. To promote the early identification of TTIs, the look-back guideline strongly recommends that physicians test both pre- and post-transfusion blood samples for TTIs at an appropriate time. Unfortunately, the current rate of compliance to this guideline among physicians seems to be less than 50%. On the other hand, JRC blood centers can contact blood donors implicated in TTIs and conduct retesting for the suspected pathogen. This is necessary because a small window of possibility for detection remains, even when the donor's implicated repository sample is found to be negative for the pathogen suspected in the TTI. This look-back guideline has also helped estimate the residual risk of TTIs and introduce new testing strategies.

## 6. Hemovigilance system

A system of hemovigilance is extremely important in establishing safe blood transfusion procedures. Hemovigilance systems survey the entire process of blood use, from donation, processing, testing, and delivery to medical facilities to transfusion or discarding. Any adverse event occurring during any step of this process has to be traced and evaluated to identify its cause and extent. The JRC started hemovigilance activity in 1993 through the establishment of the Department of Adverse Event Analysis within the JRC Central Blood Center. One of the characteristics of the JRC hemovigilance system is that it possesses the function of analyzing the pathogenesis of transfusion-related adverse events using both donor and patient blood samples. To operate this system effectively, in 1999, the JRC started preserving and storing samples from all donated blood for 11 years. This enabled the JRC to determine the causal relationship between transfused blood and adverse events, especially TTIs, much more efficiently. Another characteristic of the hemovigilance system is that it regularly refers to articles on TTI. All Japanese manufacturers of labile biological products are obligated to report articles that describe newly identified TTI agents, routes of infection, and increasing epidemics of such agents to the government on a monthly basis. Therefore, the JRC thoroughly surveys articles on infectious diseases, looking at approximately 70 journals every month. It is essential for blood centers to have a good relationship with medical facilities in order to conduct efficient hemovigilance activities. Because the JRC is considered a pharmaceutical company, medical facilities are not obligated to report adverse events to the JRC. However, presently, almost all of the medical facilities in Japan willingly report severe transfusion-related adverse events to the JRC. Even if such events are not reported to the JRC, medical facilities are obligated to report them to the government, who in turn shares this information with the JRC. Eventually, the JRC is able to collect information on all severe transfusion-related adverse events that have occurred nationwide. However, as the JRC only collects information on severe adverse events, no detailed statistics are available for minor or moderately severe adverse events. Therefore, the National Institute of Infectious Diseases plans to establish a national hemovigilance system for minor or moderately severe transfusion-related adverse events. Good coordination is expected between these systems, leading to the establishment of a more efficient national hemovigilance system.

## 7. Transfusion guidelines for medical facilities

The new blood law also discusses the responsibility of physicians in saying that those who conduct blood transfusions shall endeavor to use blood products properly and to gather information on blood safety that can be provided to patients. After explaining the processes and risks involved in blood transfusions,



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physicians must obtain informed consent from patients. Without informed consent, a portion of cost associated with transfusion cannot be reimbursed by the health insurance system. The blood transfusion policy is described in two guidelines: the guidelines for blood transfusion medicine and the guidelines for the use of blood products. The former describes the basic transfusion policy with a particular emphasis on the optimal use of blood products or good blood management. This resulted from a reflection on HIV infection among hemophiliacs caused by contaminated blood products, the underlying cause of which was the abuse of plasma products by physicians. Accordingly, Japanese physicians have been striving to use blood products properly in terms of indications for transfusion and transfused blood volume. Although this more careful blood management trend is contributing to a decrease in the worldwide use of blood components, blood usage in Japan has not drastically changed, probably because the indications for transfusion and transfused blood volume have been followed relatively closely by physicians. The guidelines for the use of blood products describe the proper indications for the use of each blood component. These guidelines are currently being revised on the basis of evidence-based medical policy.



# SYMPOSIUM 17

SY17-03

## Blood management system using RFID

Quehn Park

*Armed Forced Medical Research Institute, Korea*

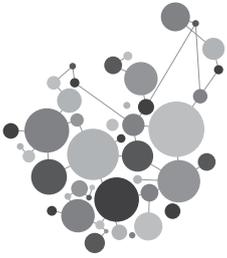
Radio-frequency identification (RFID) uses electromagnetic fields to automatically identify and track tags attached to objects. RFID system is a wireless system consisting tags and readers. The readers have more than one antenna that receive the signals from tags. The tags are IC chips embedded into thin film media. The information stored in the memory chips are transferred to the readers in the form of radiowaves. The tags can be classified as read-only and read/write tags or passive and active tags. The passive tags do not need battery because power is provided from the readers. The factors that affect the capabilities of the tags include type of IC chip, the ability to read and write, power settings, and environment. If high-tech tags are used, some advanced functions such as locking, encryption, or disabling can be applied.

Since the first patent for RFID was registered in 1973, the industry have to wait until mid-2000's to actively apply the technology to facilitate the inventory management. Now the RFID market have increased to more than 2 billion dollars worldwide. In the field of medical practice, the scopes of the application of RFID technology is as follows: inventory management, equipment tracking, out-of-bed detection and fall detection, personnel tracking, ensuring that patients receive the correct medications and medical devices, providing data for electronic medical records systems, etc. The implementation of RFID in medical field is relatively slow, because the initial cost is burdensome. The RFID technology can be used in the field of transfusion medicine especially for preventing clerical errors and facilitating inventory management. Because it is the ultimate methodology to prevent errors associated with transfusion, the transfusion medicine is regarded as the high priority area implementing the RFID technology in the medical field.

Since the introduction of ISBT 128 in 1994, many people thought something more advanced technology than optical barcode system would be developed some day because the scanning procedure is a somewhat laborious process. Now they have been recognizing that the RFID is the one they have been waiting for. The RFID-applied transfusion system has been developed during 2010's and It is repeatedly reported that both work-time and errors have been reduced through the implementation of RFID system in transfusion chain. So the International Society of Blood Transfusion (ISBT) issued a guideline in 2010 that covers the information around RFID technology application for transfusion area.

The type of information that can be stored in RFID tags are contents, location, date manufactured, order number, batch number, dosage information, and shipping data. Many kinds of clerical errors can be ultimately prevented and the entire chain from blood donation to transfusion can be monitored on a real-time basis.

In this lecture, several examples of the successful adaptation of RFID system in transfusion field will be presented and the topics and barriers around the application of RFID as well as the potential risks of RFID system will be discussed.



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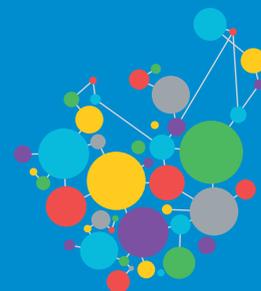
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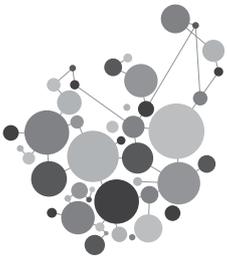
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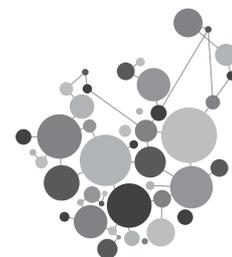


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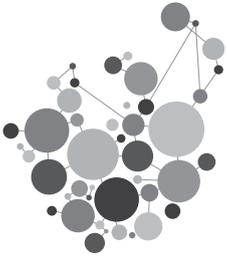
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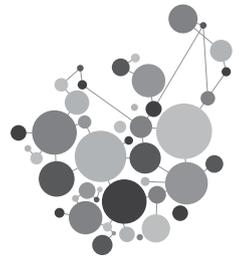
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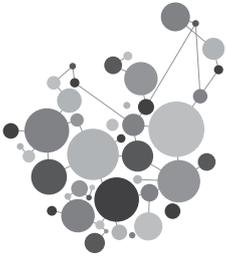
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