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Symposium Monday 12 June - ADVANCES IN CANCER BIOMARKER DISCOVER

DETECTION, CHARACTERIZATION AND EX VIVO EXPANSION OF VIABLE CIRCULATING TUMOR CELLS

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Circulating tumor cells (CTCs) in blood are promising new biomarkers potentially useful for prognostic prediction and monitoring of therapies in patients with solid tumors including colon cancer. Moreover, CTC research opens a new avenue for understanding the biology of metastasis in cancer patients. However, an in-depth investigation of CTCs is hampered by the very low number of these cells, especially in the blood of colorectal cancer patients. Thus, the establishment of cell cultures and permanent cell lines from CTCs has become the most challenging task over the past year.

In 2015, we described for the first time the establishment of a permanent cell line from CTCs of one colon cancer patient. The cell line designated 'CTC-MCC-41' has been cultured for more than three years and cells have been characterized at the genome, transcriptome, proteome and secretome levels. This thorough analysis showed that CTC-MCC-41 cells resemble characteristics of the original tumor cells in the colon cancer patient and display a stable phenotype characterized by an intermediate epithelial/mesenchymal phenotype, stem-cell like properties and an osteomimetic signature indicating a bone marrow origin. Functional studies showed that CTC-MCC-41 cells induced rapidly in vitro endothelial cell tube formation and in vivo tumors after xenografting in immunodeficient mice.

More recent results highlighted that CTC-MCC-41 cells display a very specific transcription program. Interestingly, among the 1,624 transcripts exclusively upregulated in CTC-MCC-41 samples compared to other colon cancer cell lines obtained from primary tumors or from metastatic sites, key genes related to energy metabolism, DNA repair and stemness genes were observed.

Such data may supply insights for the discovery of new biomarkers to identify the most aggressive CTC sub-populations and for the development of new drugs to inhibit metastasis-initiator CTCs in colon cancer.

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Symposium Monday 12 June - ADVANCES IN CANCER BIOMARKER DISCOVER

MASS SPECTROMETRY FOR CANCER BIOMARKER DISCOVERY

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Mass spectrometry (MS) is a powerful technology that can provide insights into the composition, structure and function of various proteomes, including the human proteome. By harnessing this analytical tool, numerous researchers have explored the biomarker development pipeline for different disease states, including cancer. Proteomic methods based on MS have matured significantly over the past few years and hold promise to deliver candidate markers for diagnosis, prognosis or monitoring therapeutic response. However, a number of challenges to cancer biomarker discovery have been realized. This talk will cover the biomarker discovery pipeline and its associated difficulties with bringing a biomarker to the clinic.

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Symposium Monday 12 June - ADVANCES IN CANCER BIOMARKER DISCOVER

PROTEOGENOMICS OF CANCER: NEW OPPORTUNITIES IN CANCER BIOLOGY AND PRECISION MEDICINE

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Despite significant progress in understanding cancer through massively parallel sequencing genome programs, the complexity that comprises its diseases remains a daunting barrier. Optimism is because today we know that molecular drivers of cancer are derived not just from DNA alterations alone, but from protein expression and activity at the cellular pathway level - proteomics. To predict the downstream effects of gene alterations; however, orthogonal technologies such as next-generation proteomics are needed. This proteogenomics approach (interplay between the proteome and genome) is anticipated to transform oncology care from one that relies mainly on trial-and-error treatment strategies based on the anatomy of the tumor, to one that is more precisely based on the tumor's molecular profile. Understanding this molecular interplay and publicly releasing proteogenomic data sets and targeted assays to create community resources is anticipated to accelerate our understanding of cancer and its treatment. This seminar will discuss how genomics, transcriptomics, and proteomics must all be brought together in the quest to understand the etiology of cancer, in addition to highlighting efforts by the U.S. National Cancer Institute's Clinical Proteomic Tumor Analysis Consortium (CPTAC) program in this area of biomedical research. CPTAC began with the purpose of developing standardized (rigor & reproducibility) proteomic assays and workflows, in order to complement genomic and transcriptomic analyses. CPTAC's proteogenomics approach was recently successful in demonstrating the scientific benefits of integrating proteomics with genomics to produce a more unified understanding of cancer biology and possibly therapeutic interventions for patients, while creating open community resources that are widely used by the global cancer community. This seminar will also highlight the recently announced APOLLO (Applied Proteogenomics OrganizationaL Learning and Outcomes) program and the efforts of the International Proteogenomic Consortium. APOLLO brings together the U.S. National Cancer Institute, U.S. Department of Defense, and the U.S. Department of Veterans Affairs to create the nation's first healthcare system in which cancer patients will be routinely screened for genomic abnormalities and proteomic information with the goal of matching their tumor type to a specific targeted therapy.

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Symposium Monday 12 June - CHALLENGES IN THE DIAGNOSIS AND FOLLOW-UP OF MULTIPLE MYELOMA

DIAGNOSTIC PROBLEMS FOR THE DEFINITION OF RESPONSE IN MYELOMA PATIENTS WHO ARE TREATED WITH MONOCLONAL ANTIBODIES

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Multiple myeloma (MM) results from the proliferation of a malignant plasma cell and frequently leads to complications such as lytic bone disease, hypercalcemia, renal function decline and impaired immunity. Over the past 2 decades, progression-free survival (PFS) and overall survival for MM have more than doubled, largely due to improvements in therapy with the addition of novel agents such as immunomodulatory agents (IMiDs) and proteasome inhibitors (PIs). Today, plasma cell surface targets of monoclonal antibodies (mAbs) have already demonstrated significant clinical activity either alone or in combination with other approved MM drugs include signaling-lymphocytic-activation-molecule-F7 (SLAMF7) (elotuzumab [ELO]) and CD38 (daratumumab [DARA], isatuximab [ISA] [SAR659084], and MOR-202). The IMWG has established criteria for clinical response to treatment in MM, which include changes in serum/urine M-protein levels by serum-protein-electrophoresis (SPE) and immunofixation-electrophoresis (IFE), percentage of bone marrow plasma cells, and free-light-chain (FLC) ratios. For a patient to be classified as having a complete response (CR) by IMWG criteria, the serum and urine must be negative for M-protein and bone marrow plasma cells must be ″5%. For the more robust, deeper classification of stringent complete response (sCR), all of the criteria for CR must be met, along with a normal FLC ratio and absence of clonal plasma cells in the bone marrow, as measured by 2/4-color flow cytometry or immunohistochemistry. As SPE and IFE are used to quantify and characterize the clonal nature of immunoglobulins, respectively, these assays are subject to interference from therapeutic mAbs. Interference on serum IFE from treated patients has been reported with several mAbs, including daratumumab. Recently experimental and/or validated methods have been designed and developed to distinguish e.g. daratumumab from endogenous M-protein in serum IFE, the Daratumumab-Specific-Immunofixation-Electrophoresis-Reflex-Assay (DIRA) in order to confirm suspected daratumumab interference and to allow separation of daratumumab bands from residual endogenous M-protein.

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Symposium Monday 12 June - CHALLENGES IN THE DIAGNOSIS AND FOLLOW-UP OF MULTIPLE MYELOMA

MINIMAL RESIDUAL DISEASE FOR MULTIPLE MYELOMA: CAN WE DO BETTER?

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Recent advances in the treatment of Multiple Myeloma (MM) have achieved deep responses with favorable prognosis and higher survival rates. The presence of Minimal Residual Disease (MRD) has been correlated with response to treatment, clinical outcome and detection of early relapse, and thus, as "biomarker" for long-term MM monitoring. Next Generation Flow cytometry (NGF) is an advantageous method for monitoring MRD, combining high sensitivity with applicability to all patients and incorporating internal controls for quality assessment of bone marrow (BM) samples. The Euroflow consortium recently proposed an optimized, highly sensitive fully-standardized NGF approach for MRD detection in MM, which we established in our laboratory. We analysed BM samples from previously treated MM patients with minimum 24-months in complete remission, processed according to EuroFlow guidelines. Isolated cells were labeled using two 8-color panels for 10 different markers (CD38, CD138, CD45, CD19, CD27, CD56, CD81, CD117, CyIg$_\kappa$, CyIg$_\lambda$). At least $10x10^6$ events/sample were recorded on a BD FACSCantoII. Data analysis of merged events from both panels was conducted using the Infinicyt software (Cytognos, Salamanca, Spain) and a unified gating strategy allowing maximum information recovery. MRD was detected in ~45% of cases. In MRD+ cases, the same monoclonal population was detected in both panels, allowing quantification of aberrant/clonal plasma cells (aPC) to the level of 0,001% of total BM cells. Most informative markers were CD19, CD45 and CD27, since 100% of MRD+ aPC were CD19$^-$CD45$^{-/dim}$ and ~90% showed dimmer CD27 expression. Compared to conventional approaches, NGF provides a competent tool for MRD detection and aPC quantification among total BM nucleated cells. We propose NGF as a highly sensitive and reliable method for MRD assessment and, in the frame of clinical studies, the establishment of MRD as a primary endpoint for evaluating the depth and duration of the response of MM patients to administered therapies.

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Symposium Monday 12 June - CHALLENGES IN THE DIAGNOSIS AND FOLLOW-UP OF MULTIPLE MYELOMA

THE ROLE OF FREE LIGHT CHAIN IN THE DIAGNOSIS AND FOLLOW-UP OF MYELOMA PATIENTS

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Multiple myeloma is characterized by the production of clonal immunoglobulins which can be in the form a "complete" immunoglobulin molecule formed by a pair of heavy and a pair of light immunoglobulin chain, but, in many cases excess production of free, unbound, light chains occurs (circulating as free light chains - FLCs), while in a significant subset of myeloma patients only unbound FLCs are produced. FLCs are associated with specific clinical situations but also with challenges in the measurement of their amount. Measurement of the serum level of FLCs has became practical as a clinical blood test in recent decades and has facilitated the follow up of patients with monoclonal gammopathies, including multiple myeloma, AL amyloidosis and other clonal immunoglobulin-related disorders. Evaluation of circulating FLCs has diagnostic implications, is associated with prognosis, is critical for the evaluation of response to therapy and disease progression and is an everyday lab test for patients with monoclonal gammopathies. High levels of FLCs are associated with increased risk of myeloma cast nephropathy, a high risk of imminent progression of asymptomatic to symptomatic myeloma and a high risk of death in patients with light chain (AL) amyloidosis. Measurement of serum FLCs is critical for the assessment of response to therapy in patients with light chain only myeloma, identification of clonal escape to light chain only myeloma, evaluation of oligosecretory myeloma while, in patients with AL amyloidosis, treatment is tailored to the reduction of the FLCs. However, there are challenges in the measurement of the FLCs and the interpretation of the results, while in the meantime new assays have been developed but have not been extensively validated. Physicians should be aware of the challenge associated with FLCs measurements and interpretation of results as they guide clinical decisions in patients with monoclonal gammopathies.

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Symposium Monday 12 June - BIOMARKERS OF INFLAMMATION AND VASCULAR DAMAGE

DEL-1: A HOMEOSTATIC REGULATOR OF LEUKOCYTE FUNCTION

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Whereas multiple adhesion receptors promote the leukocyte adhesion cascade, little is known about endogenous inhibitors of leukocyte infiltration. Recently, we have identified Developmental endothelial locus-1 (Del-1) as an inhibitor of LFA-1 integrin-mediated neutrophil adhesion and recruitment (Choi et al., Science 2008) and of IL-17-dependent inflammation in the context of bone loss (Eskan et al., Nat Immunol 2012; Shin et al., Science Transl. Med 2015; Maekawa et al., Nature Comm 2015) and central nervous system autoimmunity (Choi, Lim et al., Molecular Psychiatry, 2015). More recently, we have identified a role of Del-1 as a homeostatic player in further aspects of inflammation. The presentation will focus on the role of this endogenous anti-inflammatory factor in the context of inflammatory disease.

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Symposium Monday 12 June - BIOMARKERS OF INFLAMMATION AND VASCULAR DAMAGE

SERUM MIRNAS AS BIOMARKERS OF INFLAMMATION: FROM BENCH TO BEDSIDE

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Evidence from animal models supports the contribution of cellular miRNAs in inflammatory processes. Using mouse models we have shown that multiple miRNAs including miR-155 and miR-146a differentially regulate inflammatory processes, with miR-155 being pro-inflammatory and miR-146a being anti-inflammatory. These miRNAs contribute in inflammatory disease development and have been studied in pre-clinical and clinical settings as therapeutic targets. A smaller number of miRNAs is also detected in the serum in the form of circulating miRNAs. These miRNAs can be found in exosomes, bound on lipoproteins or bound on proteins such as Ago2. Inflammation-related miRNAs are prominent in the serum and are upregulated in different inflammatory diseases including inflammatory bowel disease, sepsis, kidney disease as well as in metabolic syndrome, the latter characterized by low grade systemic inflammation (LGSI). Interestingly, expression levels of cellular miRNAs do not always correspond to their circulating levels. As example, our data showed that in LGSI serum miR-155 did not associate with inflammatory markers while serum miR-146a did. In contrast, we have shown that in chronic kidney disease multiple inflammatory miRNAs were associated with disease stage and inflammation. These miRNAs were reduced when patients underwent hemodialysis. MiRNA array analysis in serum samples before and after hemodialysis revealed that hemodialysis affected the pattern of circulating miRNAs. Serum levels of some miRNAs increased up to 30-fold, some remained unchanged and some were dialyzed out and their levels dropped significanlty after hemodialysis. The impact of such miRNA profile changes in inflammation and tissue homeostasis remains unknown. Overall, miRNAs are functionally contributing in inflammation both at the cellular and serum levels. Combination of pre-clinical and clinical studies allows deciphering the role of serum miRNAs in inflammatory processes and their potential as biomarkers of inflammatory diseases.

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Symposium Monday 12 June - BIOMARKERS OF INFLAMMATION AND VASCULAR DAMAGE

VASCULAR DAMAGE AND INFLAMMATION IN CHRONIC HEMODIALYSIS PATIENTS

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Background: Cardiovascular disease is the major cause of morbidity and mortality of patients with chronic kidney diseases, mainly patients with end-stage renal disease treated with hemodialysis. Pathogenesis of vascular damage is very complex with various mechanisms involved leading to subsequent complications. Inflammation goes hand in hand with oxidative stress, endothelial dysfunction and vascular calcifications.

Methods: The aim was to focus on selected biomarkers related to vascular damage in patients with chronic kidney disease treated with hemodialysis.

Results: Many biomarkers have been studied so far, starting with C-reactive protein, calcium and phosphate and continuing with vitamins, parathormone, fibroblast-growth factor-23 (FGF-23), oxidative stress markers, cytokines, metalloproteinases and pregnancy proteins. Several studies documented the significance of routine as well as novel biomarkers like pregnancy-associated plasma protein A (PAPP-A), retinol-binding protein 4 (RBP-4) and retinol or EN-RAGE (extracellular newly identified ligand of the receptor for advanced glycation end-products, protein S100A12) while the results of the significance of e.g. sclerostin differ. The reason can be given also by the different methodologies used for the determination of the biomarkers.

Conclusions: Many biomarkers can be measured now days. The results of various studies sometimes differ and the pathophysiological mechanisms of action sometimes also require further investigation, mainly in the special group of patients as hemodialysis patients are. In some cases standardization of methods is required. Sophisticated studies can disclose biomarkers that can represent a powerful instrument for modern treatment strategies and for monitoring of their effect.

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Symposium Monday 12 June - BIOMARKERS OF INFLAMMATION AND VASCULAR DAMAGE

VASCULAR DAMAGE FROM HEMOLYSIS: A ROLE FOR THERAPEUTIC NITRIC OXIDE

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Hemoglobin (Hb) release from red cells into plasma causes Nitric Oxide (NO) scavenging, vasoconstriction, inflammation and coagulation. We sought a method to prevent the noxious effects of hemoglobin release during cardiopulmonary bypass (CPB). Prolonged CPB (over 2 hours) injures red cells, due to pumping, oxygenation and cardiotomy suction. Red cells release large amounts of hemoglobin into plasma. Prolonged CPB is associated with acute renal failure in about 30% of patients. In a collaborative study in Xian, China we added either 80 parts per million (ppm) of NO or pure N2 to the oxygenator gas during CPB. Post-operative patients breathed either 80 ppm NO via a ventilator for up to 24 hours or pure N2 was added. We randomized 217 patients undergoing elective multiple valve replacements for rheumatic fever. One year follow-up visits were completed in May 2016.

We strategized that exposure to 80 ppm Nitric Oxide would oxidize circulating ferrous Hb to ferric Hb and thereby prevent NO scavenging. If the renal toxicity of CPB is partly due to NO scavenging by circulating free ferrous Hb, NO treatment should reduce the incidence of acute kidney injury (AKI). AKI was defined as a 50% increase of creatinine within 7 days of surgery or increase in serum creatinine by 0.3 mg/dl within 48 hours. Secondary endpoints included renal function and mortality at 30 and 90 days and 1 year.

AKI was significantly reduced with NO treatment (52 of 105 patients for NO vs control 71 of 112 patients). Plasma creatinine levels and eGFR were significantly improved in the NO group at 30 days. No adverse events were reported with the use of NO. Chinese patients undergoing cardiac surgery with prolonged CPB, administration of NO decreased the incidence of acute kidney injury and improved glomerular filtration rate at 1 year after surgery.

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Symposium Monday 12 June - THE ROLE OF LABORATORY IN STROKE DIAGNOSIS AND MONITORING OF PATIENTS

BIOMARKERS IN STROKE

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Stroke is a rapidly developing loss of brain function due to a disturbed cerebral blood supply. It encompasses a huge number of pathophysiological entities that include thrombosis, embolism, and hemorrhage. It is usually classified as ischemic or hemorrhagic, with ischemic stroke (IS) accounting for approximately 80-85% of the total number of cases. The remaining 15-20 % are caused by hemorrhages. IS is primarily caused by either intracranial thrombosis or extracranial embolism. Intracranial thrombosis is largely due to atherosclerosis, whereas extracranial embolisms commonly arise from the extracranial arteries or from the myocardium due to concurrent myocardial infarction, mitral stenosis, endocarditis, atrial fibrillation, dilated cardiomyopathy, or congestive heart failure. Hemorrhagic stroke (HS) can be classified as either intracerebral hemorrhage (ICH) or subarachnoid hemorrhage (SAH). ICH originates from weakened cerebral vessels, which rupture and form a localized hematoma within the parenchymal cerebral space. In SAH the hemorrhage occurs outside of the brain and is released into the cerebral spinal fluid (CSF). The common causes for both ICH and SAH are comparable and include hypertension, trauma, drug use, or vascular malformations.

The diagnosis of acute stroke (AS) is based on an experienced stroke specialist examination of the patient, supplemented by the results of brain imaging. However, in people who are admitted at Hospitals Emergency Departments with a suspected stroke, the clinical assessment within the first hours is not always straightforward. Many patients with AS are not assessed by a stroke specialist, the initial evaluation is often performed by a family practitioner, paramedic, or triage nurse. For those assessed in hospital, interpretation of brain imaging appearances can be difficult, as computerized tomography (CT) is often non-diagnostic and may remain normal in patients with mild ischemic strokes. MRI, though undoubtedly more sensitive than CT, especially in the diagnosis of mild stroke, is still not 100% sensitive or specific. MRI may not be feasible in acutely ill patients because they are restless, have a contraindication to MRI, or because is not available.

Achieving an accurate diagnosis quickly in patients with suspected AS is extremely important. Patients with IS, even with relatively mild symptoms, may be eligible for intravenous thrombolysis or other means of brain reperfusion if treatment can be started within a few hours of symptom onset. Patients who are not suitable for such acute treatments are at risk of early recurrent stroke. Approximately 8% of high risk patients have a recurrent stroke within the first 2 days. Prompt initiation of secondary preventative treatment can substantially reduce the risk of further stroke.

Despite of decades of intensive research and development that have tremendously improved our understanding of the vascular, cellular, and molecular mechanisms leading to brain tissue injury after an acute stroke, the current routine therapeutic arsenal for acute stroke is limited to intravenous administration of recombinant tissue plasminogen activator, which has proven to be safe and effective. However utilization rates of thrombolytics, remain low. As a result, there still is a need for improved diagnostics and therapeutics for acute stroke patients. To achieve these aims, a better insight in the basic disease mechanisms and the development of new diagnostic tools and prognostic markers are essential.

Recently many translational medical research programs are in progress and aimed to discover new diagnostic markers. Blood-based biomarkers could potentially provide a much-needed objective assessment tool. Biomarkers could improve stroke care by allowing early diagnosis even by clinical providers without extensive neurological training as well as by facilitating serial monitoring of patients and rapid assessment of the severity of brain injury.

A rapid blood test to confirm a clinical and imaging diagnosis of ischemic stroke (or to aid risk stratification in confirmed cases), based on a simple and low-cost near-patient technology, would be extremely useful. A single set or multiple sets of blood biomarkers that could be used in an acute setting to diagnose stroke, differentiate between stroke types, or even predict an initial/reoccurring stroke would be also extremely valuable. This is likely to increase the number of patients with IS receiving thrombolytic therapy, and improve the overall patient outcome and health care. In addition, using a panel of neuronal injury biomarkers would complement the present neuroimaging modalities for the diagnosis of stroke. These biomarkers would be

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particularly important in patients with non-localizing or transient neurological symptoms, those in whom neuroimaging cannot be obtained, or are non-diagnostic. The biomarker assessment could be performed during initial triage, avoiding delays in transporting stroke patients to appropriate care centers and allowing expedited treatment of patients at high risk for early stroke recurrence.

Certain biomarker could help the selection of appropriate treatment plans for patients with acute stroke. The information obtained from biomarker measures could be used in conjunction with acute neuroimaging patterns to determine if salvageable tissue is present and potentially to lead to more appropriate therapy. Early determination of certain biomarkers could potentially identify patients at risk of secondary complications of stroke, particularly hemorrhagic transformation leading to ICH and edema. In patients with high levels of such biomarkers, caution may be warranted while low levels of biomarkers may identify patients at lower risk of bleeding who would benefit from more aggressive revascularization measures or thrombolytic treatment. In addition, certain biomarkers of endothelial damage may identify patients at risk for developing malignant edema, for which presently no reliable clinical or imaging predictors exist.

Monitoring biomarker levels during the first few days of hospitalization may provide further insight into stroke progression and predict or evaluate the possible causes of worsening including infection, fever, metabolic derangement, edema, hemorrhagic transformation in ischemic stroke, or vasospasm in SAH. Serial monitoring of biomarker activity could potentially identify patients with continuing or delayed ischemia who may benefit from more aggressive stroke management.

The development of blood biomarkers for stroke faces many difficulties. The blood-brain barrier slows the release of brain tissue proteins into blood after stroke, delaying the release of glial and neuronal proteins. Many potential blood markers of cerebral ischemia and inflammation are found in other conditions that may mimic stroke. Also, the volume of damaged tissue may not correlate with disability. Small volumes of tissue damaged by ischemia in an “critical” area of the brain may lead to a more disabling deficit than a large volume of brain damaged by stroke in another part of the brain. Another problem is the assays themselves. Research immunoassays are not standardised and in many published studies in-house assays have been used. The results from clinical studies are difficult to compare if immunoassays from different manufacturers were used and meta-analyses and research studies often give “mixed” results. The analytical and biological variability in many of these biomarkers is not well studied or unknown making the estimation of “critical changes” difficult.

Although to date no clinically approved biomarker for stroke diagnostics is available, several blood biomarkers associated with different pathophysiological pathways of stroke have been identified as “potentially useful” in clinical management, possibly contributing additional information to current diagnostics, interventions, risk stratification, and monitoring of efficacy of therapy. Well-designed, large-scale clinical studies addressing relevant clinical questions are needed, as well as standardisation of the immunoassays of the most promising biomarkers in order to move forward.

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Symposium Monday 12 June - THE ROLE OF LABORATORY IN STROKE DIAGNOSIS AND MONITORING OF PATIENTS

STROKE IN THE 21ST CENTURY: A CRITICAL OVERVIEW

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The present lecture will outline the recent changes and developments in the field of stroke epidemiology, diagnosis and management. The improvements in the diagnosis if approach of Cryptogenic stroke will be highlighted while the new clinical construct termed ESUS (embolic stroke of undetermined source) will be discussed. This lecture will also provide a perspective regarding the 25-year development of acute systemic and endovascular reperfusion therapies. Given the latest positive trials, mechanical thrombectomy is the recent standard of care for patients with large vessel occlusion, while the indications of thrombolysis have been expanded to patients that were originally excluded from this therapy. The recent development of mobile stroke units (with available CT scan inside the ambulance) will be outlined. This lecture will also provide an update on the novel oral anticoagulation therapies and their antidotes that are available for secondary prevention of stroke associated with atrial fibrillation. Finally, the promising future stroke therapies both in the acute and the secondary prevention settings will be briefly presented.

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Symposium Monday 12 June - THE ROLE OF LABORATORY IN STROKE DIAGNOSIS AND MONITORING OF PATIENTS

ISCHEMIC STROKE NEUROPROTECTION – AN ONGOING STRUGGLE

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Ischemic stroke is one of the major health issues in the world, both in rich and developing countries. This has motivated enormous research efforts to map the disease's intricate pathophysiology and to find interventional strategies. Even though we now have extensive knowledge regarding the mechanisms that cause cellular damage, for example regarding the partially noxious involvement of the immune system, and even though a multitude of treatments have been demonstrated effective in animal experiments, development of clinically useful treatments have been very limited. In my talk, I will describe the pathophysiology of ischemic stroke, expand on the tested strategies for intervening in the disease process and finally comment on possible reasons for the lack of translational success.

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Symposium Monday 12 June - LABORATORY DIAGNOSIS OF PATHOLOGICAL CONDITIONS IN PREGNANCY

ADVANCES IN NON-INVASIVE PRENATAL TESTING FOR CHROMOSOMAL ABNORMALITIES

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Noninvasive prenatal testing (NIPT) of the fetal genotype in maternal plasma without the risk of miscarriage of invasive procedures was the "holy grail" of prenatal diagnosis for many years (Bianchi, 2004). Today, NIPT for aneuploidy using cell-free fetal DNA (cffDNA) in maternal plasma is a reality, and it is revolutionizing prenatal screening and diagnosis. The potential aim is to avoid invasive procedures such as chorionic villus (CV) and amniotic fluid (AF) sampling, which result in a pregnancy loss risk between 0.5% and 1%. The discovery of cffDNA circulating in the maternal blood (Lo et al., 1997) has provided scientists with a great opportunity for the development of NIPT methodologies.

Methodologies developed are mainly based on next-generation sequencing (NGS) technology and epigenetic genetic modifications, such as fetal maternal DNA differential methylation (Velissariou and Patsalis, 2017). Current NIPT methodologies, based on counting DNA sequences using NGS, involve whole-genome sequencing (WGS), targeted sequencing, and the assessment of single nucleotide polymorphism (SNP) differences between the mother and fetus. Such methods are used worldwide and are the most rapidly adopted genomic tests. Clinical trials have demonstrated the efficacy of NIPT for trisomy 21 (Down syndrome), trisomy 18 (Edwards syndrome), and possibly for trisomy 13 (Patau syndrome) and the sex chromosome abnormalities (Gil et al., 2015; Koumbaris et al., 2016). Investigators have also described the NIPT of subchromosomal imbalances, opening up further clinical possibilities (Neofytou et al., 2017) making NIPT one of the most exciting and fast-developing fields in both research and the clinical setting.

Since the implementation of NIPT for fetal aneuploidy as a clinical service in 2011 (Palomaki et al., 2011), the pace of NIPT is unprecedented in clinical laboratory medicine. The past years have seen rapid advances in fetal genomic analyses from maternal plasma and this will hopefully translate equally rapidly to advances in patient care. All studies to date indicate that NIPT produces lower false positive and higher positive predictive values than serum screening. Since a major objective in the field of prenatal testing is the reduction of the number of unnecessary invasive procedures, NIPT can significantly reduce procedure-related losses, while maintaining high detection rates. It provides clinicians and prospective parents with a powerful tool to help them make informed decisions regarding the need for an invasive procedure, without posing any risk for the pregnancy. The extent to which it can be applied as a universal screening tool for trisomy 21, 18, and 13 depends mainly on assay accuracy, a low number of nonreportable tests, and cost. With further advances in technology and reductions in costs, it is possible that noninvasive prenatal genome- wide analysis will play an increasingly important role in the future practice of prenatal medicine.

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Symposium Monday 12 June - LABORATORY DIAGNOSIS OF PATHOLOGICAL CONDITIONS IN PREGNANCY

FREE FETAL HEMOGLOBIN: A PREDICTIVE-DIAGNOSTIC BIOMARKER AND NOVEL TARGET FOR THERAPY OF PREECLAMPSIA.

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Preeclampsia (PE) is a serious pregnancy-related syndrome, affecting at least 8.5 million women worldwide. PE is a leading cause of maternal and perinatal morbidity and mortality and is responsible for about 18% of all maternal deaths and up to 40% of neonatal mortality, particularly in low and middle-income countries in sub-Saharan Africa. So far, PE lacks both a reliable, early means of diagnosis and a safe, effective therapy.

Results from our gene profiling and proteomic studies have independently shown that production and accumulation of free fetal hemoglobin (HbF) in the placenta may be an important mechanism in the pathophysiology of PE.

We have shown that elevated levels of HbF damage the placenta, and leaks into the maternal circulation. Free HbF is harmful to the vascular endothelium and maternal organs. Statistical analysis shows that free HbF has a higher sensitivity and specificity for PE than any other biomarker investigated. Elevated levels of free HbF are seen in the maternal circulation as early as 14 weeks of gestation in women that later developed PE, hence several months before the onset of the clinical symptoms. The Hb and heme scavenging proteins, alpha-1-microglobulin (A1M), haptoglobin and hemopexin, have recently been shown to be potential additional biomarkers for prediction of PE.

An effective diagnostic marker with high specificity and sensitivity could potentially be used to screen pregnant women in the first trimester, before the symptoms of PE begin to manifest. By identifying high-risk pregnancies, prophylactic treatment could be initiated. Elevated free HbF in combination with low amount of scavenger proteins probably represents an important ethiology in PE. By getting a deeper understanding of the underlying patho-physiological mechanisms, our research also explores the use of recombinant A1M as a new unique therapy for PE that is specific rather than symptomatic. Today the only curative intervention is to induce delivery.

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Symposium Monday 12 June - LABORATORY DIAGNOSIS OF PATHOLOGICAL CONDITIONS IN PREGNANCY

THE RELEVANCE OF HYPERGLYCEMIA IN PREGNANCY ON PERINATAL OUTCOMES AND FUTURE BURDEN OF NON-COMMUNICABLE DISEASES IN EUROPE AND THE FIGO GUIDELINE

Moshe Hod
President European Association of Perinatal Medicine, Chairman FIGO Working Group on Hyperglycemia in Pregnancy

The burden of pre-diabetes and diabetes fueled by urbanization, unhealthy eating, reduced physical activity and rising obesity continues to grow. The prevalence of diabetes in Europe among all age groups, including younger people in the reproductive age, is rising. About 60 million people are already affected and by 2040 this number is projected to reach 71 million people; there is an equally high burden of pre-diabetes - approximately 32 million, which is likely to rise to about 37 million in the same time period[3]. Approximately one in three pregnant women in Europe are obese or overweight[4]. The age at childbirth also continues to rise; in many countries, over 20% of births are to women aged 35 years or more[4]. It should therefore be no surprise that hyperglycemia in pregnancy (HIP) is one of the most common medical conditions affecting women during pregnancy. According to IDF, an estimated 14% of live births in Europe may be impacted by hyperglycemia during pregnancy[3]. Non-white immigrant mothers that account for a significant proportion of pregnancies[4] are even more vulnerable.

Inadequately managed (and by corollary undiagnosed) HIP significantly increases risk of pregnancy complications: hypertension, obstructed labor, postpartum hemorrhage, infections, still births, premature delivery, both large and small for gestational age babies, congenital anomalies, newborn deaths due to respiratory problems, hypoglycemia and birth injuries[5]. The risk and number of these complications are directly related to level of maternal hyperglycemia. This is why the St Vincent's declaration had laid special emphasis on pregnant women with diabetes with more marked hyperglycemia. Aside from striving to achieve the St Vincent's objective for pregnant women with known diabetes, Europe now has to deal with the challenge of increasing burden of previously undiagnosed type 2 diabetes in pregnancy (DIP) and gestational hyperglycemia (Gestational Diabetes Mellitus).

Although being overweight and obese along with increasing maternal age significantly increases the risk for HIP, in practice, only half of the women with HIP have these risk factors. The sensitivity to detect GDM is poor, thus supporting the contention that identification of HIP requires universal testing of all pregnant women[6]. There is lack of consensus on the optimal approach to testing for HIP in Europe[7] particularly, the utility of continued use of risk-based testing versus universal testing. There is evidence of both immediate and long term health and economic benefits of testing, diagnosis and management of HIP and providing post-partum preventive care. However some physicians have expressed concerns that universal testing and (consequently) increased diagnosis of GDM would place additional logistical and economic challenges to healthcare systems, as oral glucose tolerance tests (OGTT) are time-consuming and incur costs. On the other hand, the problem of complex protocols for testing based on risk factors, which places high demands on healthcare providers, with the consequent lower compliance and missed diagnosis has not been acknowledged.

While infant and maternal mortality in Europe is generally quite low and continues to decline, perinatal mortality and morbidity remains a major concern. The incidence of pre-term and very pre-term births, fetal growth restriction, and congenital anomalies has increased in many countries, reflecting limited achievements in preventing high risk situations[4]. About one-third of all fetal deaths and 40% of all neonatal deaths in Europe were among babies born before 28 weeks of gestation[4]. The proportions of live births with birth weight under 2500 g vary from under 4% to slightly over 9%. Stillbirths have also declined less rapidly, and in many cases their causes remain unknown[4]. Increased clinical and community awareness of the risks associated with common pre-gestational and gestational medical disorders (e.g., diabetes and hypertension) and implementation of best practice guidelines might improve management and lower associated stillbirth rates[8].

Most of the maternal deaths in Europe, as elsewhere in the world are directly due to hemorrhage, hypertension, thromboembolic disease, sepsis and obstructed labor, the risk for which is considerably increased with HIP. With the introduction of targeted interventions, there are declining rates of direct maternal deaths within Europe. Therefore efforts to further improve maternal health will have to be refocused on reduction of maternal morbidity and indirect causes of mortality. Addressing obesity and HIP may help lower maternal and newborn morbidity and mortality by lowering the risk of pregnancy complications such as pre-term births, still births, congenital anomalies, small and large babies which are critical problems for maternal and child health in

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Europe[4].

Without preventive care, almost half of women with gestational diabetes go on to develop type 2 diabetes and a significant proportion develops premature cardiovascular disease within 10 years of childbirth. Children born to women with HIP are also at very high risk of obesity, early onset type 2 diabetes and cardiovascular disease whereby, HIP perpetuates these conditions into the next generation.

Focusing on maternal obesity and HIP screening during pregnancy provides a unique opportunity to integrate services which would lower traditional maternal and perinatal morbidity and mortality indicators and address inter-generational prevention of NCDs such as obesity, diabetes, hypertension and CVD. But how can we achieve this when we bury our heads in the sand and continue to disregard the basic premise of testing all pregnant women for hyperglycemia? It is unbelievable, that health care funding has not been prioritized for this and for targeted, preventive post-partum care and health promotion for high-risk mother and child pairs.

An important reason for the lack of progress on the St. Vincent's goal related to pregnancy in women with diabetes perhaps was the lack of ownership and involvement of obstetricians. Most of the attention on gestational diabetes including setting diagnostic cut off values in the past has been based on the future risk of type 2 diabetes with scant attention paid to the perinatal outcomes particularly among women with the so called "mild gestational hyperglycemia". Studies in the last decade have shown significant associations between adverse pregnancy outcomes and levels of maternal glucose considered within the nondiabetic range[9, 10]. Meta-analysis of randomized control trials shows that treatment of gestational hyperglycemia improves pregnancy outcomes[11]. Therefore the recent focus of the International Federation of Gynecology and Obstetrics (FIGO) on hyperglycemia in pregnancy, resulting in the release of pragmatic guidelines[6] at the FIGO World Congress in Vancouver in 2015 and the subsequent setting up a working group on HIP is very welcome.

FIGO demands greater attention on the links between maternal health and non-communicable diseases in the sustainable developmental goals agenda; in particular, to gestational hyperglycemia and its propensity to fuel the global diabetes, obesity and cardiovascular disease pandemic. FIGO also asks for public health measures to increase awareness, access, affordability, and acceptance of preconception counseling, and prenatal and postnatal services for women of reproductive age to be prioritized. This stance is in line with the UN Declaration on non-communicable diseases[12] and the policy brief of the European Institute of Women's Health (EIWH) (http://eurohealth.ie/wp-content/uploads/2013/02/women_and_diabetes_policy_brief.pdf).

FIGO also recommends that ***all pregnant women*** should be tested for hyperglycemia during pregnancy using ***a one-step procedure as a minimum standard*** and encourages all countries and its member associations to adapt and promote strategies to ensure this.

Following a pregnancy complicated by GDM, the postpartum period provides an important platform to initiate beneficial health practices for both mother and child to reduce the future burden of several non-communicable diseases. FIGO recommends that obstetricians should establish links with family physicians, internists, pediatricians, and other healthcare providers to support postpartum follow-up of mothers with HIP and their children. A follow-up program linked to the child's vaccination and regular health check-up visits provides an opportunity for continued engagement with the high risk mother child pair.

FIGO seeks greater international research collaboration to address the knowledge gaps to better understand the links between maternal health and non-communicable diseases and create evidence-based best practice standards for testing, management, and care of women with GDM.

The FIGO guideline has received widespread support and recognition from many professional organizations from across the world particularly from Europe, Australia, Canada and the developing world including organizations in India, China and Africa. The European Association of Perinatal Medicine (EAPM), the European Board and College of Obstetrics and Gynecology (EBCOG) and the International Association of Diabetes in Pregnancy Study Groups (IADPSG) were amongst the first to endorse and support the document. It is about time that health planners and policy makers in Europe pay heed to these recommendations and take appropriate steps to implement the necessary actions.

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EFLM Symposium Monday 12 June - HARMONISATION IN LABORATORY MEDICINE

HARMONIZATION OF ACCREDITATION OF MEDICAL LABORATORIES:IMPORTANCE OF BEING INVOLVED IN ALL STEPS

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[1]*chair Committee Quality and Regulation of EFLM*

The harmonization of a quality management system for medical laboratories starts with using the same standard. Members of the WG Accreditation and ISO/CEN standards were involved from its start with ISO15189: medical laboratories: requirements for quality and competence. This standard has become the most prominent, as shown in publications which can be read on the EFLM website. t ISO/CEN standard22870 concern POCT , which usage should be combined with ISO15189. Other standards are directed on risk management, measurement uncertainty, reference methods and reference laboratories, pre-analytical requirements, and many other aspects. EFLM is a member organization in both ISOTC212 and CENTC140.

For good quality you need IVD products with sufficient information to support the verification of methods in your laboratory. For that reason we paid attention to the development of the new IVD Regulation. We succeeded in strengthening the paragraph on lot to lot variation.

To harmonize the use of the ISO standards we produce guidelines. Some examples are about retention time and reference values. We are planning more. In setting up guidelines it is important to be aware that situations in a country can be different.

In Europe only one institute in each country is allowed to perform accreditation. These national Accreditation Bodies cooperate in EA (European cooperation on Accreditation). They have an MLA (mutual recognition) for most of the standards we use. In the Heath Care committee, the EA members try to harmonize the way they perform their assessments in time, depth and interpretation of the different paragraphs of ISO15189. From its start around 2000 EFLM has been a member and most of the time the only representative of a medical laboratory society. We influenced the discussion about use of flexible scope.

Harmonization helps the medical laboratories to ascertain the quality of information the patie

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EFLM Symposium Monday 12 June - HARMONISATION IN LABORATORY MEDICINE

STEPS TOWARDS HARMONIZATION OF THE EVALUATION PROCESS IN THE CONTINUOUS PROFESSIONAL DEVELOPMENT OF LABORATORY MEDICINE SPECIALISTS ACROSS EUROPE

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Among other efforts to ensure uniform quality of laboratory medicine services in all EFLM countries, one of the EFLM missions includes harmonization of life-long education, thus ensuring CPD of specialists in clinical chemistry and laboratory medicine in all EFLM countries. The CPD programs introduced in the majority of EFLM countries lead to certification of different laboratory profiles but vary in contents, accessibility to non-medical laboratory scientists, and impact on relicensing. The CPD evaluation process considerably differs. To solve this problem, the EFLM has formed the Task and Finish group with the aim to standardize, harmonize and implement common rules for the CPD crediting system.

The group has gathered European professionals-experts in the field, whose steps towards harmonization include the following strategy: development of guidelines for CPD events accreditation, guidelines for certification of individuals, and its implementation in EFLM countries. The accreditation guidelines should contain rules and criteria for events that can be accredited as CPD events and credits to be allocated to them. At the same time, the questions who can be provider of events or who will evaluate the programs and many others will be elaborated. In developing the certification guidelines of individuals, it should be considered that currently there are more than 22 certification categories granted credits differently in EFLM countries. It is of utmost importance to harmonize this issue by joint activity of EFLM and national societies. Final step in the process of developing standardized and harmonized CPD crediting system is implementation of the above guidelines by EFLM societies.

Existence of harmonized CPD crediting system implemented in EFLM national societies will hopefully lead to harmonization of the CPD of specialists across Europe and the same high quality of laboratory medicine in all EFLM countries will be ensured despite free movement of laboratory specialists and patients throughout Europe.

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EFLM Symposium Monday 12 June - HARMONISATION IN LABORATORY MEDICINE

THE CONTRIBUTION OF THE EFLM WG-PRE TO THE HARMONISATION OF VENOUS BLOOD SAMPLING IN EUROPE

A. Simundic [1]
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European Federation for Clinical Chemistry and Laboratory Medicine (EFLM) has in 2012 established the Working group for Preanalytical phase (WG-PRE) whose aim to promote the importance of the quality of the preanalytical phase of laboratory medicine, to define the best practices and provide recommendations for some critical preanalytical activities, to assess the quality of current preanalytical practices and to organize preanalytical scientific and educational meetings. A lot of various projects have been initiated in the past years and the aim of this lecture is to present the most recent WG-PRE project on the harmonization of the venous blood sampling practices in Europe.

Venous blood sampling is the most common invasive procedure in the healthcare. It is available worldwide and done almost in every healthcare facility. Moreover, venous blood sampling is performed by different kind of personnel and sometimes even by non-healthcare personnel (like administrative staff, etc.) with different level of knowledge and understanding of the procedure, and varying degree of background education and life-long learning opportunities. Whereas only a very few EFLM National societies have national guidelines for venous blood sampling, most of them agree that harmonization of this important preanalytical step is of utmost importance. EFLM consensus European recommendation for venous blood sampling have been developed in close collaboration of more than 15 European countries, professional societies and representatives from nurses and phlebotomists. Document provides not only a recommendation of the procedure for venous blood sampling, but also gives guidance on how to implement this procedure into the everyday routine and monitor and maintain its quality. During the lecture, some useful tools accompanying EFLM consensus European recommendation for venous blood sampling shall also be presented. These tools are developed by EFLM WG-PRE and are freely available for all EFLM National societies and other interested parties. We hope that this project will contribute to the improvement of the quality of venous blood sampling and patient safety across Europe.

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EFLM Symposium Monday 12 June - HARMONISATION IN LABORATORY MEDICINE

THE RECOGNITION OF PROFESSIONAL QUALIFICATIONS

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EFLM's Profession Committee continues to press the EU Commission via our leads in Brussels for acceptance of a Common Training Framework that recognises the role of the 'Specialist in Laboratory Medicine' in making the most effective use of resources for better health and best care. The importance of a Common Training Framework is that it acts as a passport to allowing free professional migration across EU borders at 'specialist' level under EU Commission Directive 2013/55/EU as well as being a catalyst for raising awareness of laboratory medicine. Whilst the quality of the case for Recognition continues to be actively pursued in Brussels the priority within EFLM turns to adding quantity to the argument by growing EFLM's Register of specialists. Acknowledging the key work carried out in this regard by EC4's Register Commission a newly established 'Working Group: Register' was established when the work of EC4 was integrated into the EFLM infrastructure at the end of 2016. With strong support from its corresponding members across the Community the new group's responsibilities include adjudicating applications to hold the title European Specialist in Laboratory Medicine (EUSpLM and to grow the Register as a standard bearer of high quality practice

This talk will cover past, present and future strategy in pursuing Recognition, the growing role and opportunity that the Register represents for its registrants and our profession, and mechanisms by which individuals can become registered either individually or by automatic recognition mechanisms available to professional societies.

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Debate Monday 12 June - LESSONS FROM 30 YEARS OF CANCER SCREENING

SCREENING FOR BREAST CANCER: PRO

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Breast cancer is the most common cancer in women worldwide; an estimated 1.7 million new cases occurred in 2012 (the latest year for which information is available). While efforts to prevent breast cancer have recently been investigated, the backbone of breast cancer risk reduction has been in screening to prevent advanced disease and mortality. Ideally, a screening test would identify individuals with high-risk lesions that are not yet invasive, so that the precursors can be removed to prevent cancer occurrence. However, definitive precursor lesions cannot be reliably identified for many women who go on to develop breast cancer. Therefore, the aim of breast cancer screening is to reduce mortality and the morbidity associated with advanced disease, by providing early access to effective treatment. Recently, the International Agency for Research on Cancer (IARC) determined that the strength of evidence was sufficient that mammography screening reduces breast cancer mortality in women aged 50-74 years, and that screening has a net benefit for women aged 50-60 years if done with an organized screening program. A 2016 meta-analysis of trials for the U.S. Preventive Services Task Force found statistically significant 14% and 33% reductions in breast cancer mortality with screening mammography for women aged 50-59 years and 60-69 years, respectively. For women aged 40-49 years and 70-74 years, there were 8% and 20% reductions in breast cancer mortality, but the results were not statistically significant. This talk will present data from clinical trials and observational studies that support mammographic screening for reducing deaths from breast cancer in women at average risk for breast cancer. Open questions will be discussed, including screening effects on overall mortality, effectiveness based on risk factors, and different screening modalities.

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Debate Monday 12 June - LESSONS FROM 30 YEARS OF CANCER SCREENING

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While there is agreement that mammographic screening reduces breast cancer mortality, mammography has limitations, with reduced detection of cancers in women with dense breasts, over-diagnosis of benign breast lesions, and under-diagnosis of rapidly proliferative cancers. The performance of mammographic screening depends on various factors, including breast density and age. Both sensitivity and specificity decrease as breast density increases. Sensitivity and specificity are also lower in younger than older women, most likely because of the inverse association between age and breast density. Improvement of current screening strategies is thus most needed for younger women and women with dense breasts. In addition, for much of the world, systematic population screening by mammography is cost- and logistically-prohibitive. It has been suggested that circulating biomarkers could improve current screening strategies. These strategies include using circulating biomarkers as a complement to mammography in subsets of women for whom the sensitivity of mammography is the lowest, such as younger women and women with dense breasts, or between screening mammograms in women at high risk of breast cancer to improve the detection of interval cancers. Results of studies on the use of circulating biomarkers to detect breast cancer conducted to date, though, have been disappointing because of failure of biomarkers to be successfully validated and/or have low sensitivity. These results are not surprising given the heterogeneity of breast cancer which may limit the sensitivity of individual biomarkers. This talk will present data from multiple biomarker studies that support further evaluation of circulating biomarkers for screening for breast cancer, and emerging strategies for the design of biomarker validation studies.

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IFCC Symposium Monday 12 June - STANDARDIZATION IN ENDOCRINOLOGY

CLINICAL NEEDS FOR STANDARDIZATION IN ENDOCRINOLOGY

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Comparability of laboratory results is a major goal in the routine practice of laboratory medicine, being a key factor for an optimal patient care. Discrepancies between results obtained by different methods and in different laboratories may lead to inappropriate clinical decisions and eventually be deleterious to the patient. Besides, they generate difficulties in establishing global reference values and decision limits. Even though major advances have been made over the past decades, many fields of laboratory medicine still lack method standardization. In this regard, the IFCC Scientific Division, which has been promoter for many years in these activities, has progressively focussed on different specialized fields such as endocrinology. Indeed, the reliability of results in diabetes mellitus or other endocrine diseases is essential for the ensuring quality and efficiency in diagnosis, prognosis and monitoring. They generally allow to establish the diagnosis of chronic disease necessitating for life follow-up, with heavy consequences for the patient and the society. Standardization with traceability to reference measurement procedures is the preferred solution when possible. This has been achieved for HbA1c or free FT4 for example. When this goal cannot be achieved, harmonization of methods constitutes a valuable surrogate. This has been done for TSH. Another important challenge of this process lies beyond laboratory itself. Such initiatives must benefit from a close cooperation with clinical societies, since they can potentially lead to changes in reference values and decision limits, thus modifying clinical guidelines and routine practice. After achieving the analytical steps, a global campaign aimed to specialist clinicians, general practitioners and patients is sometimes necessary. Later steps include the retrospective evaluation of the benefits of these standardization processes in terms of patient care and public health. Some examples will be given during this lecture, mainly in the field of diabetes mellitus, as an introduction to the session.

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IFCC Symposium Monday 12 June - STANDARDIZATION IN ENDOCRINOLOGY

STANDARDIZATION OF GROWTH HORMONE: READY FOR PRIME TIME?

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Measurement of GH excretion is relevant in de diagnosis of both GH deficiency and GH overproduction. Standardization of the GH assays has been hampered by the unavailability of a commutable certified reference material and of an acknowledged reference method. The WHO standard IS 98/574, against which all current assays are calibrated, was found not to be commutable when tested together with patient samples in different methods. An alternative approach would be to use serum pools. In the Netherlands, a native serum pool obtained from healthy volunteers after exercise has been tested and was found to be suitable as a commutable harmonizer . Value assignment was done by determining the All Laboratory Trimmed Mean. The harmonizer is in use for more than ten years. Its use resulted in the external EQAS for GH in a reduction of interassay coefficient of variation from 24.3% to 14%.

We therefore aim to investigate the commutability of different potential calibrators based on native, or spiked, serum pools. More methods will be included as compared to those used in the Dutch pilot studies. If a commutable calibrator is identified, it will be tested on a larger scale. A LC-MSMS method for GH, calibrated against IS 98/574, will be used to target the potential GH calibrator, allowing for IS 98/574 traceable standardization of the different GH assays.

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IFCC Symposium Monday 12 June - STANDARDIZATION IN ENDOCRINOLOGY

STANDARDIZATION OF PARATHYROID HORMONE

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Chronic kidney disease (CKD) represents a major health issue worldwide, affecting >10% of the population in the United States. Appropriate identification and management of CKD and associated mineral and bone disorders (CKD-MBD) is critical to improving clinical outcome and reducing the risk of disease progression. Parathyroid hormone (PTH) measurement is widely used as a surrogate marker to assess CKD-MBD. However variability among test methods hampers clinical interpretation of PTH results and makes it difficult to develop evidence-based recommendations about consensus reference intervals and/or decision levels for treatment, and also complicates clinical audit. PTH results in some patients may differ by as much as four-fold depending on the assay method used.

Factors contributing to the observed variation in PTH results include lack of knowledge about which forms of PTH it is most clinically relevant to measure, poor calibration or lack of calibration against the same internationally recognised reference material and/or reference measurement procedure, and differences in antibody specificities and/or method design such that isoforms are measured to different extents in different methods.Consistent data from recovery experiments conducted by the UK National External Quality Assessment Service (UK NEQAS) suggest that if PTH methods were accurately calibrated in terms of the same commutable International Standard, between-method agreement would improve. In a UK NEQAS distribution of specimens in November 2016, relative recoveries of synthetic PTH(1-84) obtained from the Peptide Institute (Japan) ranged from 113 to 215%, depending on the PTH method used.

The IFCC Working Group for PTH is working to improve comparability of PTH results by developing a complete reference measurement system for PTH determinations. Current Working Group objectives include

(1) Achieving standardisation of commercially available PTH measurement methods in terms of the same International Standard (IS) and implementing this worldwide. [This requires demonstration of the commutability of the IS, work which is in progress.]

(2) Defining inclusion and exclusion requirements for an appropriate panel of plasma samples with which to establish reference intervals, and then establishing such a panel. [A systematic review has been undertaken by the Working Group to provide an evidence base underpinning these criteria.]

(3) Facilitating development of a candidate reference measurement procedure (RMP) for PTH(1-84) to a standard enabling its adoption by IFCC member national societies and ultimately its inclusion in the methods supported by the IFCC Reference Laboratory Network. [Mass spectrometry has been identified as the procedure of choice but further improvement of the analytical sensitivity of mass spectrometric methods for PTH so as to match that of existing immunoassay methods is essential.]

This IFCC project is actively supported by clinical and scientific communities as well as diagnostic companies providing PTH methods. Although ambitious, the Working Group's goal of enabling more effective clinical use of PTH measurements for the benefit of patients by improving the standardisation of PTH methods is clearly feasible and, with continued international support, is achievable.

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IFCC Symposium Monday 12 June - STANDARDIZATION IN ENDOCRINOLOGY

STANDARDIZATION OF THYROID FUNCTION TESTS

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It is well known that today the focus of the laboratory community is on comparability of measurements irrespective of time, location and test systems used. This is paramount for application of consistent standards of medical care and disease prevention, such as pooling of data from epidemiological studies in which different tests were utilized, developing/using evidence-based clinical practice guidelines with reference to common reference intervals (RIs) and/or decision limits, and incorporating laboratory data in electronic patient records.

To accomplish the above demand for thyroid hormone measurements, the IFCC established the Committee for Standardization of Thyroid Function Tests (C-STFT) (see http://www.ifcc.org/ifcc-scientific-division/sd-committees/c-stft/). Together with 14 globally operating diagnostic manufacturers, the committee identified the major steps in the process to establish traceability (= standardizing) in accordance with ISO 17511: i) define the measurand, ii) develop a reference measurement system (RMS), and iii) conceive a practical approach for implementation of the latter. Regarding item (iii) it was a crucial premise for C-STFT that traceability should be implemented by method comparison studies with panels of clinical samples. Meanwhile the process is put in place for establishing traceability of FT4 and TSH tests.

Up to now, C-STFT performed a sequence of studies to investigate/demonstrate the feasibility of standardizing thyroid function tests. Recently, the last but one phase was completed, i.e., the technical recalibration of the participating FT4 and TSH tests, followed by a proof-of- concept study. The latter gave evidence that recalibration may allow future RIs to be uniform. However, this is not the endpoint: both the laboratory and clinical communities now have to be prepared for the impact of recalibration on future numerical values and RIs. This means that to prevent the risk for interpretation errors, the next phase for C-STFT will be to reach out to an as broad spectrum of involved stakeholders as possible.

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Meet the expert Monday 12 June - ACCREDITATION AND LAB MANAGEMENT WHY AND HOW TO DO IT

ACCREDITATION

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ISO15189 is the standard directed on quality and competence in the medical Laboratories. It was written to summarize all the items required by patients and doctors to fulfill their wish of reliable and timely results. Because of this it encompasses pre-examination, examination and post –examination aspects, but as well stresses traceability, calibration and measurement uncertainty. It is important that results are comparable where patients travel between hospitals, cities and even countries.

Accreditation is done by an independent competent third party and helps to warrant trust in laboratory results. It is at least desirable and possibly it should become legally required. Luckily the way assessment for accreditation should be done is as well documented in ISO standards, and clarified in ILAC and EA guidelines. To get Mutual Lateral Agreement the accreditation bodies themselves are assessed.

Still the way assessment is performed is a critical step. It should stress the intention of the ISO15189 standard and not just look after fulfilling all “shall” items in paragraph 4 and 5 under 3.2 m. It requires attention for the calibration and judgment of the assessors, and a harmonized explanation of the standard. The contribution of the EFLM in the Health Care Committee of EA and of members of societies in their respective countries is important.

Specific items for discussion were:

Flexible scope

Calibration and Traceability

Measurement Uncertainty

POCT

Pre-examination aspect in cases where the laboratory was not directly responsible

Clarification of specific items of the standard: is the used “shall” intended as such.

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Meet the expert Monday 12 June - ACCREDITATION AND LAB MANAGEMENT WHY AND HOW TO DO IT

ACCREDITATION AND LAB MANAGEMENT. WHY AND HOW TO DO IT?

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French reform of Medical Biology led to an harmonization of private and public practices, choice of "medical" biology, reorganization of territorial multisite labs and proven quality by mandatory accreditation using ISO 15189 standard. This mandatory way has been chosen to increase the speed of labs restructuration. The labs were thus faced to the Bateson "double bind": improve quality towards accreditation and increase efficiency to compensate enhanced expenses. This is accompanied by a decrease in the number of labs, since the merge to multisite labs is an essential engine to simplify the accreditation process and to allow the respect of the regulation requirements (complete accreditation before 2020). The question is not for us: "WHY should we work for an ISO accreditation?" but "HOW to engage and maintain the lab in the accreditation process?"

The combination of a lab global quality management system with an achievement of the technical requirements leads to recognition of lab competency in laboratory medicine. A "partial" accreditation of the lab by COFRAC has now been achieved in 2016 for almost all 1000 French labs. Multisites and scope extensions, combined with intensive use of flexible scope, will allow us to obtain a complete accreditation before 2020.

Total mandatory accreditation was a big challenge since laboratory quality management was often heard as a constraint and an indirect restructuration tool. But, with the point of view of an accredited lab, it is also a very efficient lab management tool, a federative project for all the laboratory team and a necessary way for our "medical" specialty to assure an added value for patient care in the actual "industrial" context.

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Symposium Monday 12 June - TRACEABILITY IN LABORATORY MEDICINE: A MATTER OF PATIENT SAFETY

PRE-ANALYTICAL AND ANALYTICAL ASPECTS AFFECTING CLINICAL RELIABILITY OF PLASMA GLUCOSE RESULTS

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The measurement of plasma glucose (PG) plays a central role in recognizing disturbances in carbohydrate metabolism, with established decision limits that are globally accepted. This requires that PG results are reliable and unequivocally valid no matter where they are obtained. Nevertheless, PG results may vary due to pre-analytical, biological and analytical causes. To control the pre-analytical variability of PG and prevent in vitro glycolysis, the use of citrate as rapidly effective glycolysis inhibitor has been proposed. However, the commercial availability of several tubes showing different performance has created confusion among users. Moreover, and more importantly, studies have shown that tubes promptly inhibiting glycolysis give PG results that are significantly higher than tubes containing sodium fluoride only, used in studies generating the current PG cut-points, with a different clinical classification of subjects. From the analytical point of view, to be equivalent among different measuring systems PG results should be traceable to a recognized higher-order reference via the implementation of an unbroken metrological hierarchy. In doing this, it is important that manufacturers of measuring systems consider the uncertainty accumulated through the different steps of the selected traceability chain. In particular, PG results should be produced within an established degree of quality expressed in term of analytical performance specifications defined to fit the intended clinical application. Since PG has tight homeostatic control, its biological variability may be used to define these limits. Alternatively, given the central diagnostic role of the analyte, an indirect outcome model showing the impact of analytical performance of test on clinical classifications of subjects can also be used. Using these specifications, external quality assessment studies employing commutable control materials with values assigned with reference procedure have shown that the quality of PG measurements is often far from desirable and that this problem is exacerbated with point-of-care testing.

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PROGRESS AND IMPACT OF ENZYME MEASUREMENT STANDARDIZATION

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The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) has established reference measurement procedures (RMPs) for the most popular enzymes. Manufacturers should assign values to commercial calibrators traceable to these RMPs to achieve equivalent results in clinical samples, independent of reagent kits, instruments, and laboratory where the measurement is carried out. However, some manufacturers continue to market assays giving results that are not traceable to internationally accepted RMPs. Meanwhile, end-users often do not abandon assays with demonstrated insufficient quality. Of the enzyme measurements, creatine kinase (CK) is satisfactorily standardized and a substantial improvement in performance of marketed ©-glutamyltranspeptidase (GGT) assays has been demonstrated. Conversely, aminotransferase measurements often exceed the desirable analytical performance because of the lack of pyridoxal-5-phosphate addition in the commercial reagents. Measurements of lactate dehydrogenase (LDH), alkaline phosphatase (ALP), and ‹-amylase (AMY) still show major disagreement, suggesting the need for improvement in implementing traceability to higher-order references. The definition by laboratory professionals of the clinically acceptable measurement uncertainty for each enzyme together with the adoption by EQAS of commutable materials and use of an evaluation approach based on trueness represent the way forward for reaching standardization in clinical enzymology.

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ROLES AND RESPONSIBILITIES IN VERIFICATION OF TRACEABILITY OF IN VITRO MEDICAL DIAGNOSTICS (IVD)

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To be accurate and equivalent, laboratory results should be traceable to higher-order references. Furthermore, their analytical quality should fulfil acceptable measurement uncertainty defined to fit the intended clinical use. With this aim, IVD manufacturers should define a calibration hierarchy to assign traceable values to calibrators of their measuring systems and to fulfil during this process uncertainty limits for calibrators, which should represent a proportion of the uncertainty budget allowed for clinical laboratory results. It is therefore important that laboratory profession clearly defines the clinically acceptable uncertainty for relevant tests and end-users may know and verify how manufacturers have implemented the traceability of their calibrators and estimated the corresponding uncertainty, including, if any, the employed goal. However, full information about traceability and combined uncertainty of calibrators is usually not available as manufacturers only provide the name of higher-order reference material or procedure to which the assay calibration is traceable without any description of steps and their corresponding uncertainty of the implemented traceability chain. In general, it should be possible to establish if the status of the measurement uncertainty budget associated with the proposed traceability chain is suitable or not for clinical application of the test. Important tools for IVD traceability surveillance are the verification by clinical laboratories of the consistency of declared performance during daily operations performed in accordance with the manufacturer's instructions [Internal Quality Control (IQC) component I] and the organization of appropriately structured External Quality Assessment (EQA) programs. The former activity should be accomplished by analyzing system control materials and confirming that current measurements are in the manufacturer's established control range. With regard to EQA, it is mandatory that target values for control materials (including their uncertainty) be assigned with reference procedures by accredited reference laboratories, that materials are commutable and that a clinically allowable inaccuracy for participant's results is defined in order to prove the suitability of laboratory measurements in the clinical setting. In a separate way, clinical laboratories should also monitor the reliability of employed commercial measuring systems through the IQC component II devoted to estimate the measurement uncertainty due to the random effects, which includes the analytical system imprecision together with the individual laboratory performance in terms of variability.

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Symposium Monday 12 June - TRACEABILITY IN LABORATORY MEDICINE: A MATTER OF PATIENT SAFETY

TRACEABILITY OF HBA1C MEASUREMENTS: WEAK AND STRONG POINTS

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The metrological chain for the measurement of HbA1c has been established since several years, and it is essential in order to guarantee long-term stability of the various assay methods for this important laboratory test. The top of the chain is represented by the primary reference materials produced by the IRMM (IRMM 466 and 467), consisting of highly purified non glycated and glycated human hemoglobins. The primary reference measurement procedure developed by the IFCC in 2002, and calibrated with mixtures of the materials, permits the assignment of HbA1c title to panels of whole blood samples delivered to the manufacturers. Such activities are held by the IFCC laboratory network under network's coordinator responsibility. The middle of the chain is under the responsibility of the manufacturers and the bottom of the chain (i.e. the handling of routine methods) is under the responsibility of laboratory professionals. The IFCC Network operates regular exercises twice a year since many years, and the long term stability of the reference measurement procedures as well of the calibrators and controls have been documented. It is difficult to obtain from most of the manufacturers evidences of their alignment to the top part of the chain, mostly when the uncertainty of their calibrators is asked. On the contrary, evidences from EQAS exercises allover the word, prove that the weak part is at the bottom part of the chain, and improvements are still need in order to globally achieve the required analytical goals (5 mmol/mol total error).

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Symposium Monday 12 June – NEW PERSPECTIVES IN CLINICAL FLOW CYTOMETRY

DEVELOPMENTS IN CLINICAL FLOW CYTOMETRY

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Flow cytometry (FCM) is increasingly used in clinical laboratories for diagnosis of various hematological disease, follow up of treatment and immunological screening. The rapid and sensitive multi-parameter detection, even at a single cell level, renders FCM to a powerful tool to distinguish malignant cells from normal. However, this identification demands a special configuration of the instrument, e.g. stable and powerful lasers, excellent optics and sufficient PMT's. Multi-color immunophenotyping (up to 15 parameters) can be performed due to recent developments of flow cytometers with high sensitivity, resolution, and dynamic range with high-speed data collection combined with fast and easy-to-use software. Furthermore, the use of highly specific MoAbs conjugated with new fluorescent dyes, enables optimal characterization of cell populations. In particular, determination of minimal residual disease or detailed characterization of rare lymphocyte subsets needs high-level polychromatic analyses.

Although this multi-color FCM offers many advantages, the technical problems and pitfalls are increasing with the number of applied parameters. The balancing and titration of the combination of MoAbs and fluorochromes are crucial. Due to complexity of multi-color combinations less optimal PMT settings and compensation are difficult to detect, even resulting in a wrong interpretation. Besides, combination of conjugates on the single cell level can influence each other tremendously resulting in quenching or FRET effects.

As a consequence the question raises "how to guarantee the quality of immunophenotyping". Standardization of all facets of clinical FCM might be essential but is expensive and hampers innovation. Harmonization appears to be more applicable and affordable while giving same results and can be assisted by new developments in techniques, such as specially dried reagents, improved viability staining and instruments that offer a complete pre-analytical treatment and analysis of samples (like the Aquios flow cytometer). All these developments render clinical FCM anno 2017 to a sophisticated multi-color analysis.

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Symposium Monday 12 June – NEW PERSPECTIVES IN CLINICAL FLOW CYTOMETRY

FLOW CYTOMETRY IN CANCER IMMUNE MONITORING AND IMMUNOTHERAPY: AN OVERVIEW

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Cancer immunotherapy is a promising therapeutic approach aimed at stimulating sustained antitumor immune responses. A variety of treating approaches for eliciting and enhancing antitumor immunity have been developed and are in the clinic, including various types of vaccines, monoclonal antibodies targeting molecules crucial to the control of immune responses, and adoptive T cell therapies.

Although overall survival (OS) and progression-free survival (PFS) are the primary endpoints in clinical immunotherapy trials, immunomonitoring assays are needed for elucidating immunological mechanisms of antitumor responses, assessing therapeutic effects, monitoring disease progression, identifying candidates for immunotherapy and defining biomarkers predictive of clinical outcomes and response to treatment.

Flow cytometry is an effective and reproducible technology that is largely used in immune monitoring. Depending on the type of cancer and the mechanism of action of the immunotherapeutic intervention, it is used for the characterization of many different immunological parameters, including detailed description of the tumor immune infiltrate, assessment of antigen-specific T cell induction and function, monitoring of tumor-induced changes of circulating innate immune cells.

The strengths and limits of flow cytometry-based assays in immune monitoring of cancer patients will be illustrated and discussed.

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Symposium Monday 12 June – NEW PERSPECTIVES IN CLINICAL FLOW CYTOMETRY

GLOBAL QUALITY AND CERTIFICATION IN CLINICAL FLOW CYTOMETRY

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Attempts to establish an European network of scientists devoted to Flow Cytometric (FCM) diagnostic applications date back to 1988, at the dawn of the validation of HIV diagnosis and monitoring, and of leukaemia/lymphoma management. A pioneer European Quality Control of Cellular Phenotyping by Flow Cytometry took place in 1988 involving 230 centers. In 1996 the EWGCCA cooperative group made major achievements on the standardisation of absolute cell counting techniques for clinical purposes and on the technical requisites of the CD34+ stem cell enumeration for autologous and allogeneic transplantation. EWGCCA took part in the successful EC-funded multicentre Eurostandards Project, that generated a number of technical guidelines on all the major diagnostic FCM procedures.

ESCCA (European Society for Clinical Cell Analysis) continued the activities of EWGCCA and since 2005 it organizes the largest educational events for diagnostic clinical cell analysis, involving both technicians and academics, with specific training pathways.

CCA has developed as an autonomous discipline within Laboratory Medicine with applications in a wide range of clinical conditions and therefore involving different medical specialities, such as Immunology, Haematology, Transplantation, Rheumatology, Allergology, Pneumology, Transfusion Medicine, Pathology and Laboratory Medicine practice, with a full spectrum of validation and process controls covering all the analytical steps.

Clinically validated FCM applications are performed with CE-marked instrumentation and reagents, and most analytical procedures are under ISO 17043-compliant international external quality assessment schemes provided by UKNEQAS.

Instruments, reagents and procedures can be now fully aligned on a multicenter basis, to achieve a high degree of analytical standardization, which is now the indispensable technical prerequisite for complex international studies, like the ones promoted by the EuroFlow consortium and the ONE Study on transplantation. The full clinical validation of minimal residual disease evaluations in haematologic malignancies by FCM represents one of the most significant recent achievements of clinical cell analysis.

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Symposium Tuesday 13 June - KIDNEY DISEASES - HOT QUESTIONS ON ESTABLISHED AND NOVEL BIOMARKERS

CLINICAL CHEMISTRY AND NEPHROLOGY: AN ESSENTIAL LINK

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There is an essential link between Nephrology and Clinical Chemistry. One of the highest leveled recommendation of the KDIGO calls for a continuous dialogue between nephrologists and laboratory specialists. Until recently, creatinine determination was the only way to estimate kidney function. In the late nineties, a first revolution came with the publication of the MDRD formula. This opened a new era since laboratories started then to report an estimation of the GFR together with creatinine results. Since then, many formulas have been made available to estimate GFR. This probably helped non-nephrologists to detect more rapidly a decrease in kidney function but also, unfortunately, this led to an overestimation of the burden of CKD, especially in the older subjects. From the laboratory point of view, this has forced specialists in laboratory medicine and diagnostic companies to focus again on « good old » creatinine determination and standardization which was (wrongly) considered as a « basic » clinical chemistry test. Nowadays, enzymatic assays and IDMS standardization are strongly recommended, but this was not so obvious 10 years ago.

Finally, we face now an important cornerstone in pharmacology. Indeed, drug dosage has been for years based on creatinine clearance. However, creatinine clearance and estimation of the GFR are two different concepts and cannot be used interchangeably. Since most of clinical laboratories systematically provide an estimation of the GFR, it is tempting to use it to adapt the posology of the treatments. This has led to important over and under dosage with is potentially harmful for the patient. The recent recommendations of the European Medicine Agency request now that pharma companies measure precisely the renal function (like with the iohexol clearance) in their pre-market study to avoid these errors.

Another milestone in the relation between nephrology and laboratory medicine was the discovery that new biomarkers could detect more rapidly an acute kidney injury than creatinine. This was particularly the case with NGAL and a major IVD company (namely Abbott Diagnostics) has invested a lot to spread the knowledge on AKI and promote the use of NGAL as an early marker. At the beginning, NGAL was even considered as the « nephrologist's troponin ». This definitely opened a new field of investigation and since then?, new biomarkers of AKI have been discovered and the « troponin's nephrologist » has turned on to a more multi-pararameters approach. However, real evidence of the interest of biomarkers of AKI still needs to be proven.

A disease is rarely linked to a single organ without impact on the others. The bone-heart-vessel-kidney axis has been extensively explored these last years. Very recent findings have found that predictor of GFR could also be predictors of cardiovascular mortality.

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CREATININE AND CYSTATIN C: TO EVALUATE GFR AND/OR TO PREDICT RISK?

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The glomerular filtration rate (GFR) is one of the most important parameters in human physiology. Because precise measurement of this parameter is difficult and costly, methods for estimating GFR from endogenous filtration markers have been developed. Traditionally, creatinine has been the most important marker used for this purpose, but cystatin C and other substances are increasingly being used in both research and clinical work. In addition to being the best overall indicator of the functional state of the kidney, the GFR is also a predictor of morbidity, in particular of cardiovascular disease. GFR estimated from creatinine and cystatin C substitutes for measured GFR both in the functional assessment of the kidney and as a risk predictor. Epidemiological studies have found that the performance of estimated GFR in these two roles is not necessarily concordant. Superior performance in risk prediction does not necessarily indicate accurate estimation of GFR and vice versa. Estimated GFR is also a better risk predictor than measured GFR for some outcomes. This is most likely caused by non-GFR determinants of the serum levels of creatinine and cystatin C, which may correlate with other risk factors. These non-GFR determinants are also the most probable explanation for the different performance of estimated GFR based on creatinine and cystatin C as risk predictors. Consequently, there are still important questions about GFR as a risk factor that remain unresolved by research based on estimated GFR.

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Symposium Tuesday 13 June - KIDNEY DISEASES - HOT QUESTIONS ON ESTABLISHED AND NOVEL BIOMARKERS

GFR AND DRUG DOSAGE ADAPTATION: ARE WE STILL IN THE MIST?

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Excretory renal function plays a fundamental role in the pharmacokinetics. This is particularly the case for water-soluble compounds. For this reason, it is recommended that pharmacokinetics of new drug be studied in the context of chronic kidney disease. Dosage adjustment according to glomerular filtration rate (GFR) is required for many medications. However, there is a debate regarding the best way to estimate GFR for the purpose of pharmacotherapy. Ideally, GFR should be measured by a reference method such as plasma clearance of iohexol. These methods are, however, difficult to implement in daily practice. GFR is thus estimated by creatinine based equations. Several publications have illustrated potential discrepancies in estimated GFR (eGFR) results and thus in dosage prescription if different equations are used. For drug dosage adjustment, the sharpest debate consists in choosing between the Cockcroft–Gault (CG) equation, promoted by clinical pharmacologists, and the Chronic Kidney Disease Epidemiology (CKD-EPI) equation, promoted by nephrologists. From the nephrological point of view, the superiority of the CKD-EPI equation over the CG equation to estimate GFR is easy to demonstrate in the general population. Moreover, CKD-EPI truly estimates GFR, whereas CG estimates creatinine clearance. Finally, the CG equation cannot be used with modern and calibrated serum creatinine values whereas the CKD-EPI equation can be used with all creatinine assays traceable to isotope dilution mass spectrometry (IDMS). Conversely, there are arguments to support the CG equation. Indeed, the CG equation is the equation that has been used to elaborate drug dosage adjustments for majority of drugs. Furthermore, the CG equation better predicts the risk of adverse events. This may reflect the presence of the variable ‘body weight’ in the CG equation, not in the CKD-EPI equation. Other strength and limitations of each equation will be discussed, even if a definitive conclusion cannot be reached.

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Symposium Tuesday 13 June - KIDNEY DISEASES - HOT QUESTIONS ON ESTABLISHED AND NOVEL BIOMARKERS

NEW AND OLDER BIOMARKERS IN AKI. ARE THEY FIT FOR PURPOSE?

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So far, therapeutic interventions aiming at limiting risk of AKI or at mitigating consequences of renal insult have failed to demonstrate any benefit. Most of the trial performed to date suffers from the unavoidable delay between renal injury and interventions which may have affected impact of tested interventions. Hence, oliguria is poorly specific of renal injury and small creatinine increase can only be detected several hours following a profound and prolonged decrease in glomerular filtration rate. In addition to this unavoidable delay, the bulk of critically-ill patients are admitted to the ICU long after the renal injury, up to 83% of critically-ill patients with AKI being admitted to the ICU admission with overt AKI. Thus, opportunities to prevent or mitigate renal injury are limited except in specific situation such planed surgery or use of nephrotoxic agents. Although both functional biomarkers and markers of tubular injury have been developed, initially promising preliminary studies have translated into poor to modest performance of these biomarkers to diagnose AKI early, predict course of renal injury or renal outcome. These disappointing results might reflect several limits of studies performed to date, limits of the tested biomarkers or both. First, gold standard of these studies is systematically debatable and most of them used the imperfect oliguria or serum creatinine changes which may have led to misleading results. In addition, studied population is imperfect and by including non-selected patients, with various pre-test probabilities, results may be non-representative of diagnostic test performance in selected patients. Last, potential uses in modifying clinical practice have been poorly studied leading to uncertainties regarding clinical relevancy of these biomarkers. Thus, we have been, so far, unable to demonstrate whether we do have at hand a biomarker that may fit or if biomarker developed so far are too imperfect to be clinically relevant.

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Symposium Tuesday 13 June - ADVANCES IN NEURODEGENERATION DISORDERS

ADVANCES IN MULTIPLE SCLEROSIS

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Introduction - Multiple sclerosis (MS) has been classically regarded as a disorder of the white matter of the central nervous system (CNS). However, early alterations of the neuronal compartment occurring in this disorder are partially independent of demyelination. Soluble inflammatory cytokines and glutamate have been proposed as major determinants of neurodegeneration in MS as well as in its experimental animal model, experimental autoimmune encephalomyelitis (EAE). The relationship between these two major determinants has been largely elusive. In recent years, unexpected connections have emerged between immune cells and soluble cytokines on one hand, and synaptic transmission and neurodegeneration, on the other.

Method & Results - Neurophysiological recordings have recently demonstrated that glutamate-mediated excitatory transmission is enhanced during the early phase of EAE, due to altered expression and phosphorylation of AMPA and NMDA receptors and the concomitant down-regulation of GABA synapses. The synaptic alterations occurring during neuroinflammatory diseases are largely mediated by inflammatory cytokines released from infiltrating T cells and from activated microglia, and are responsible, at least in part, of irreversible dendritic pathology. On the other hand, synaptic plasticity plays an essential role in the compensation of neurological deficits in MS, and clinical progression has been associated in recent studies to the exhaustion of plasticity reserve at central synapses.

Discussion - Collectively, these data suggest that CNS-confined inflammation in MS is associated with the release of soluble molecules, which are capable of altering excitatory and inhibitory synaptic transmission.

Conclusion - Synaptic transmission and plasticity plays a role both in the compensation of neuronal damage but also in secondary neurodegenerative grey matter pathology in MS.

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Symposium Tuesday 13 June - ADVANCES IN NEURODEGENERATION DISORDERS

PRE-ANALYTICAL AND ANALYTICAL ASPECTS OF CSF BIOMARKERS ASSAY

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Tau, pTau181 proteins, A®1-42 peptide or A®1-42/ A®1-40 ratio and 14.3.3-protein in CSF are currently used as an aid in the diagnosis of Alzheimer Disease (AD) and Creutzfeldt-Jakob Disease (CJD) respectively. Alpha-synuclein (a-syn), neurofilament, prion protein (PrP) are proposed as candidate biomarkers in the field of neurodegenerative disorders… There is important between-centre variability and consequently, a lack of consensus cut-off values for a CSF AD signature. Variability is explained both by analytical and pre-analytical factors.

CSF sampling is a major critical issue: as it could affect the levels of a-syn, the presence of blood in CSF must be avoided using atraumatic needles. Moreover, haemolyis is a main confounder for 14.3.3 protein positivity. The diversity of Polypropylene tubes is able to explain significant variations in Ab42, Ab40 and PrP levels. Using the A®1-42/ A®1-40 ratio instead of raw peptide values could minimize this heterogeneity. The modalities of storage must be controlled. For new biomarkers, we need to have a global knowledge about the impact of possible confounders.

The between-centres variability is well detected by the Alzheimer's Association external quality control programme. Some factors are impacting variability: lot to lot variability, temperature incubation management….

For AD biomarkers, collaborative efforts were done concerning different pre-analytical and analytical steps as harmonization of sampling tubes, ready to use calibrators… Introducing semi-automatization permitted to decrease significantly repeatability, whereas next full automatized assays will decrease both intermediate fidelity and inter-centre reproducibility by introducing a Certified Reference Material for Ab42. For 14.3.3, we will present some results of the automatization of size separation of proteins. Differences in AD biomarker outcomes before and after harmonization CSF collection tubes in AD diagnosis resulted in a modification of the predictive value of Ab42, highlighting the need to revalidate cut-offs after harmonization.

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Symposium Tuesday 13 June - ADVANCES IN NEURODEGENERATION DISORDERS

THE ROLE OF LABORATORY BIOMARKERS IN THE DIAGNOSIS OF ALZHEIMER'S DISEASE

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Research advances in Alzheimer's disease (AD) molecular pathogenesis have given several promising drug candidates targeting ®-amyloid (A®) metabolism and aggregation, or tau pathology, that are currently tested in clinical trials. However, since AD is notoriously difficult to diagnose clinically, especially in the earlier stages of the disease, when neurodegeneration is not too advanced and such drugs have the chance to show clinical benefits, biomarkers are essential to enrich for patients that do have AD pathology. Diagnostic biomarkers will also be critical if such drugs are approved and reach the clinic.

CSF collection by lumbar puncture is a routine procedure in clinical medicine. The CSF biomarkers total tau (T-tau), phosphor-tau (P-tau) and □-amyloid (A□42 or A□42/40 ratio) have very consistently been found to have high diagnostic accuracy to identify AD, also in the early (prodromal) stage of the disease. While CSF A□42 and amyloid PET have almost complete (≈95%) concordance to identify brain amyloid deposition (and thus to diagnose AD), they differ substantially in cost, with for CSF biomarker analyses is very limited as compared to an amyloid PET scan. In addition, CSF collection can be performed in any clinic, and the sample sent to a lab performing the assays, while availability in clinical PET scanners for AD diagnostics is limited.

However, current assays for the AD CSF biomarkers are based on ELISA methodology, and have been shown to have high between-lab and between-batch variability. Thus, to enable a general implementation of CSF biomarkers in clinical routine, several standardization efforts have been initiated.

Work within the IFCC-WG for CSF proteins has resulted in a mass spectrometry-based Reference Measurement Procedure (RMP) for CSF A□42, and a Reference Material (RM) with three (high, medium and low) certified A□42 levels will be released within short, to enable harmonization between assay readouts. RMPs for both CSF A□42 and tau are under development. Biotech companies have developed new high-quality assays on fully automated lab analysers, that show excellent between-laboratory CVs in the Alzheimer's Association QC program. Taken together, these efforts will ascertain a high quality of the AD CSF biomarkers, and will pave the way for their large-scale introduction in clinical diagnostic routine.

Last recent research has given tools to monitor synaptic dysfunction by CSF biomarkers. Recent studies show a marked increase in CSF levels of the post-synaptic (dendritic) protein neurogranin both in AD dementia and in prodromal AD, with higher levels predicting a more rapid cognitive decline and more severe neurodegeneration. Synaptic biomarkers will be valuable to understand disease pathogenesis and to monitor drug effects on synaptic function in clinical trials.

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Symposium Tuesday 13 June - STATE OF THE ART IN CARDIAC MARKERS

CARDIAC AND KIDNEY MARKERS FOR CARDIOVASCULAR PREDICTION IN CHRONIC KIDNEY DISEASE

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The incidence of cardiovascular disease (CVD) is seven- to tenfold greater in patients with chronic kidney disease (CKD) compared to people without CKD. By the time patients develop the need for renal replacement therapy, there is an approximately 17 times greater risk of cardiovascular death/nonfatal myocardial infarction compared to individuals without kidney disease. Among patients treated by dialysis, the prevalence of coronary artery disease and left ventricular hypertrophy (LVH) are approximately 40% and 75% respectively. Cardiovascular mortality has been estimated to be approximately 9% per year in dialysis patients, accounting for 50% of deaths of all patients with kidney failure and being 10 to 20 times higher than in the general population. Patients with kidney failure should be considered in the highest risk group for subsequent cardiovascular events. The spectrum of CVD predominant among patients with CKD (hypertensive cardiomyopathy, arrhythmias, heart failure, valvular disease, and peripheral vascular disease) differs from that in the general population (atheromatous coronary artery disease).

Risk factors for CVD in CKD consist of a mixture of traditional (e.g. diabetes, hypertension, obesity, smoking, dyslipidemia) and CKD-specific factors (e.g. low glomerular filtration rate [GFR], albuminuria, calcium/phosphate/parathyroid hormone abnormalities, sodium overload, anaemia). Some traditional risk factors are more prevalent in CKD patients but recent studies have highlighted that they have lower predictive power compared to CKD-specific risk factors such as GFR and, particularly, albuminuria, which offer powerful additive information and should be included in risk prediction models. Other emerging markers may further improve the power of CVD risk prediction in CKD, including cystatin C, cardiac troponin, natriuretic peptides, asymmetric dimethylarginine, copeptin and others. However, the strength of risk prediction may outstrip current knowledge regarding management and prevention of CVD in CKD, for example using statin or aspirin treatment. This lecture will review the evidence for current and novel biomarkers as CVD risk predictors in CKD.

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Symposium Tuesday 13 June - STATE OF THE ART IN CARDIAC MARKERS

HOW CAN THE LABORATORY HELP CLINICIANS? THE "HIGH-SENSITIVITY" TROPONIN PARADIGM

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The availability of so-called "high-sensitivity" troponin assays (hsTns) has scored a compelling goal for Laboratory Medicine, allowing the safe clinical application of international recommendations for the definition of acute myocardial infarction (AMI). However, clinicians, claiming an increase in "false-positive" results, have often not welcomed the introduction of hsTns. In fact, the availability of hsTns has reinforced the need of changes to diagnostic rules and only serial testing incorporated in running algorithms may allow an accurate diagnosis of AMI. To guide interpretation of results, typical release patterns suggestive for AMI should be identified by evaluating the significance of hsTns concentration changes. Fast track protocols for ruling out/in non-ST elevation AMI have been optimized to recommend sampling at presentation and after 3 h only. Accordingly, hsTns have markedly shortened the time to rule out or rule in AMI. However, rapid diagnostic protocols should be performed only using well-validated hsTns and the use of assays before their robust analytical and clinical validation should be discouraged. Finally, a cost-effective use of hsTns should account for all clinical variables increasing the pre-test probability in order to ensure that tests are ordered only for patients at medium to high risk for acute coronary syndrome.

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IFCC Symposium Tuesday 13 June - INCREASING CLINICAL EFFECTIVENESS IN LABORATORY MEDICINE

A PROPOSED STRUCTURE FOR DEFINING, UNDERTAKING AND REPORTING STUDIES TO ASSESS THE CLINICAL EFFECTIVENESS OF LABORATORY MEDICINE

G. Beastall [1]
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Laboratory medicine specialists and their partners in the diagnostics industry have been successful in enabling high quality, low cost diagnostics. Whilst this achievement is commendable and generally good for patients there is a downside. Unthinking clinicians can use a 'scattergun' approach to investigation, which can result in:

• A high percentage of unnecessary tests (over-diagnosis)

• A perception that the laboratory is a 'factory' not a clinical specialty

• Rising costs for the clinical laboratory

• Challenges in introducing new, specialist, 'high cost' investigations

Today laboratory medicine specialists recognize the need for a more discriminatory and evidence-based approach, including:

• Workload management (laboratory utilization in some countries)

• Education of clinicians on appropriate use of the laboratory

• Initiatives to demonstrate the clinical effectiveness of appropriate laboratory investigations

IFCC has committed to two clinical effectiveness projects:

• Partners in the ICE Award (winners will present in the symposium)

• A 'standard approach' to demonstrating clinical effectiveness, which will lead to a growing library of case studies published in a standard format.

The standard approach starts by identifying a specific clinical outcome. The impact of laboratory medicine on that outcome is assessed both in terms of current impact and potential future impact. A simple study is then performed (literature review or new study) to provide additional information on the specific contribution that optimal use of laboratory medicine makes to the clinical outcome. Examples will be provided.

The clinical effectiveness of laboratory medicine needs to be demonstrated at international, national and local levels. Practical tools and examples are required, which may have to be based on less than perfect evidence.

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IFCC Symposium Tuesday 13 June - INCREASING CLINICAL EFFECTIVENESS IN LABORATORY MEDICINE

CLINICAL EFFECTIVENESS: WHAT IS IT? HOW IS IT MEASURED?

P. Epner [1]
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The role that laboratory physicians and scientists play in patient care and health care systems has often been reduced to the task of producing timely, accurate, low cost test results. This focus on operational efficiency has led to increases in centralization and automation driven by health system financial needs, not patient needs. The inability of laboratory professionals to effectively articulate an alternative role has led to further commoditization and cost reductions. The emphasis on the clinical laboratory solely as a cost center is ironic given that the service typically accounts for only 3-5% of national health expenditures globally, so even substantial cuts in laboratory-related expenditures would have little impact on the cost of health care nationally. However, the inappropriate ordering of tests and misapplication of test results can have significant and costly "downstream" impact on patient outcomes and the overall cost of health care. Yet these costs are often not recognized nor discussed.

An alternative to the almost singular focus on operational efficiency is to balance it with a comparable effort to improve health outcomes, i.e. clinical effectiveness. To justify the necessary change in resource allocation, measurement of the value of laboratory medicine in patient care and outcomes is needed. In 2014, a coalition of more than a dozen US-based laboratory organizations began work on the development of such measures. A framework has emerged, the result of a comprehensive literature search, a field survey of laboratory professionals, deliberation by an expert panel, and ongoing efforts from a taskforce. Five domains of clinical effectiveness have been described. Five levels reflecting increasing value delivery are in development for each domain along with an assessment tool. A standardized approach to measuring and articulating clinical effectiveness will provide a roadmap that clinical laboratories can use to increase both their value and their resources.

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IFCC Symposium Tuesday 13 June - INCREASING CLINICAL EFFECTIVENESS IN LABORATORY MEDICINE

DEMONSTRATING CLINICAL EFFECTIVENESS IN PRACTICE

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1. The Royal College of Pathologists is undertaking a review of its key performance indicators (KPI) with the intent of developing indicators suited to serve as key assurance indicators (KAI). This will assess the quality rather than the quantity of what is achieved for patient management.

Discussion on the modification of existing KPIs to KAIs will be discussed and will include KAIs that measure quality of pathology input into patient pathways beyond the laboratory.

2. Choosing Wisely (CW) started as a clinician-led initiative in North America with the aim "to promote conversations between doctors and patients by helping patients choose care that is supported by evidence, not duplicative of other tests or procedures already received, free from harm and truly necessary". CW has been adopted in many countries, and was initiated in 2014 in the UK by the Academy of Medical Royal Colleges.

CW embeds a culture in which patients and clinicians discuss the clinical value and effectiveness of proposed treatments or interventions, explicitly aiming to reducing the amount of inappropriate clinical activity. Although it is about waste, it is not about saving money and there will be scenarios where patients may want the option of an investigation or treatment not currently offered as routine in every organisation.

3. The Review of Pathology Quality Assurance (published January 2014) recommended that a 'Pathology Quality Assurance Dashboard (PQAD)' be developed, that would draw 'transparent and meaningful information from existing data sources to provide a national picture of quality improvement across England'.

Dashboards are in common use as access to summary evidence in the assessment of performance and quality improvement in hospitals, including laboratories. Against this background the PQAD was issued in late 2016 and progress in the achievement of its aims will be explored.

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IFCC Symposium Tuesday 13 June - INCREASING CLINICAL EFFECTIVENESS IN LABORATORY MEDICINE

HIGH SENSITIVITY CARDIAC TROPONIN I AT ADMISSION ENABLES EARLY SAFE DISCHARGE, REDUCES HOSPITAL STAY AND PREVENTS UNNECESSARY HOSPITAL ADMISSIONS

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In 2012, patients attending our Trust with suspected acute coronary syndrome (ACS) were admitted for a cardiac troponin T test 12 hours after onset of pain for confirmation or exclusion of acute myocardial infarction (AMI).

Introduction of the Abbott ARCHITECT STAT high-sensitivity cardiac troponin I (hs-cTnI) assay, in April 2013, allowed implementation of a novel pathway using an admission hs-cTnI of ≤1·9ng/L to discharge patients with suspected ACS. Discharge does not occur for patients at high ACS risk nor if the admission hs-cTnI sample is within one hour of chest pain. High risk patients are admitted and low risk patients with an hs-cTnI >1.9ng/L transferred to a Decision Unit to await a second hs-cTnI three hours post admission.

The novel pathway including 2573 patients was audited over 6 months, between July 2013 and January 2014. Patients with an admission hs-cTnI of ≤1·9ng/L were followed up for Major Adverse Cardiac Events (MACE).

The pathway reduced patient admissions (60.9% to 38.4%) and mean length of stay (23 hours to 9.5 hours). 849 patients (32%) had an admission hs-cTnI ≤1·9ng/L and 688 (27%) were immediately discharged. Thirty day review of all 849 patients identified three MACE; two deaths (one unrelated malignancy, one peri-arrest sample) and one percutaneous coronary intervention (PCI). Nine month follow-up showed a further 11 MACE; 9 deaths (8 unrelated malignancy, one pulmonary fibrosis) and two PCIs. There were no AMI or ACS re-presentations. Only one discharged patient had a MACE; elective PCI following ED referral to cardiology. The negative predictive value of hs-cTnI ≤1.9ng/L on admission for MACE at 30 days and 9 months was 99.6% (95% CI 98.9-99.9) and 98.4% (95% CI 97.2-99.1) respectively.

We have used hs-cTnI ≤1.9ng/L on admission to safely discharge over 25% of low risk patients with suspected ACS and thereby reduce hospital admissions by 22.5%.

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IFCC Symposium Tuesday 13 June - INCREASING CLINICAL EFFECTIVENESS IN LABORATORY MEDICINE

THE LABORATORY'S ROLE IN REDUCING TIME TO ANTIBIOTIC IN FEBRILE NEUTROPENIC PATIENTS

G. Pearl [1]
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Fever in patients with neutropenia may quickly become a medical emergency. National Best Practice standards assert that patients who present with febrile neutropenia should receive intravenous antibiotics within 1-hour of triage. In 2012 an interdisciplinary group was developed to review our Time to Antibiotic (TTA) statistics for our large tertiary pediatric hospital. A limiting factor identified was turnaround time (TAT) for the absolute neutrophil count (ANC) reported in the complete blood count (CBC.) The TAT goal for a CBC with differential is 45 minutes, with an average TAT of 35 minutes from specimen receipt in the laboratory. We sought to decrease the ANC turnaround time to < 18 minutes, thereby potentially improving TTA in febrile neutropenic patients.

The interdisciplinary group included Oncologists/BMT and Emergency Department physicians, Oncology nurses, Clinical Informaticists, Process Improvement and Laboratory Specialists. The improvement process focused on children with cancer that presented to the clinic or the ED. To decrease TAT, the hematology section of the laboratory developed a modified CBC test (CBC Sepsis) which allowed the automated ANC to be released before slide review. A small precision study was performed and the agreement between the analyzer ANC and differential ANC were assessed, focusing on the antibiotic decision point of 500 cells/mcL. Differences in TTA before and after use of the modified CBC were assessed by report review.

The precision study showed excellent results with CVs of 0.04% and 0.06%. Manual review of 122 CBC results demonstrated that 15.6% of ANC results would have been discrepant. However, at the antibiotic decision point, only 1 of 8 results would have demonstrated discrepant ANC results. Based on these data, we implemented a practice change allowing release of the automated ANC before slide review. Initial data (phase 1 before development of CBC Sepsis test) surveyed the time of patient presentation to clinic to time to TTA included review of charts from 1/2012 to 6/2012. Of the 72 cases; the median TTA was 111.3 minutes. Of these cases, 44 CBCs were ordered and had an average TAT of 43.0 minutes from receipt in the laboratory to result. Follow up data (phase 2 after development of CBC Sepsis test) included review of charts from 12/2012 to 5/2014. Of the 179 cases; the median TTA was 42.2 minutes. Of these cases, 96 CBCs were ordered and had an average TAT of 12.0 minutes from receipt in the laboratory to result.

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IFCC Symposium Tuesday 13 June - ROLE OF COMMUNICATION IN P4 LABORATORY MEDICINE

E-LEARNING AND ONLINE EDUCATIONAL TOOLS IN LABORATORY MEDICINE

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Since the advent of the Internet use of the Internet and Social Media has developed into a major strategy for businesses and organizations for the purpose of education. We have seen a massive increase in web based traffic as a major education resource allowing networking between organizations and individuals on the web for the purpose of education. Web 2.0 is a two way process which can facilitate learning by allowing for prolonged interaction between the provider and recipient of the education which has the effect of reinforcing the information provided before the recipient progresses. Thus, e-learning can encourage "consultation patterns" within a network so as to reinforce and cement ideas within the learning group whether that is students, public or members of a vocational or professional group. The internet and social media networking can raise awareness of health issues and help educate patients and health care consumers with accurate and trustworthy information. It also allows health care professionals and organizations to connect and engage with the community and their colleagues to further their education.

CME is an ongoing requirement of our 'profession' and one of the roles of professional associations is to design and promote education and training activities for their members. One of the advantages of the internet in education is that it has allowed us to provide education in a usable format, where and when members want or need it and because of this we have seen online education increase exponentially primarily due to the rapid expansion in the use of tablets and smart phones. Amongst the tools available in laboratory medicine are the IFCC eAcademy, AACC Certificate Programs, AACB and EFLM Webinar Programs, Medscape, UpToDate, Clinical Learning, Open Learning Platforms (e.g. Open University), MOOCS and Universities (e.g. Imperial College London) to name a few.

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IFCC Symposium Tuesday 13 June - ROLE OF COMMUNICATION IN P4 LABORATORY MEDICINE

ELECTRONIC APPS AND MEDICAL DIAGNOSTICS DATA MANAGEMENT

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Laboratory medicine is a domain which offers a unique opportunity to analyze objective patient laboratory data and enable ready communication to both healthcare workers as well as patients. In recent years, an increasing number of web-based and mobile applications has been developed to improve access to laboratory test information and test result interpretation. They range from simple apps that provide reference lab value information to complex medical diagnostics data management. As examples, the "eLab" developed by Tru-Solutions Inc. is a comprehensive medical diagnostic center and lab management software that provides a user friendly interface and access control. It is linked iMedDx.com to allow flexible patient search and selection and includes an eLab Dashboard on mobile/tablet, allowing patients and labs/hospitals access to lab reports online. The Davis's Laboratory & Diagnostic Tests medical app provides another useful app with a wide-breadth of tests, as well as guidance on how to counsel and collect tests. The app is available on multiple platforms including the iPhone/iPad, Android and Blackberry. The "LabGear" is a medical lab reference app providing a pocket tool for medical laboratory test and is integrated with MedCalc with normal lab value reference information for over 200+ lab tests. There are several other medical apps that provide reference lab values including CALIPER, MedRef, Normal Lab Values, and Lab Tests. The CALIPER App has been developed for paediatricians, family physicians, other healthcare workers, as well as parents worldwide. It is a user friendly and easy tool to assess a child's laboratory test results using the latest reference value database developed based on values in healthy children and adolescents. In this presentation, I will review some of the key web based tools and mobile resources in laboratory medicine and will discuss the critical importance of electronic apps in management of medical diagnostics data.

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IFCC Symposium Tuesday 13 June - ROLE OF COMMUNICATION IN P4 LABORATORY MEDICINE

ONLINE RESOURCES FOR PATIENTS AND HEALTHCARE PROFESSIONALS

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The internet provides a vast portal for patients and healthcare professionals to access healthcare information. For patients, websites offering disease-specific information are increasing and are contributing immensely to the "participatory" aspect of P4 medicine. Moreover, patients can also access professional information, especially from open-access publications. Online resources also offer the opportunity for communication between patients and between patients and health care providers. Such resources can also be useful for disease management and this is especially noteworthy in diabetes and asthma where frequent monitoring can lead to early detection of impending crises. Online resources are also valuable for patients with extremely rare conditions eg. inborn errors of metabolism where experiences can be shared with other patients or healthcare providers across the world.

In laboratory medicine, Lab tests online, Labs Are Vital and Know Pathology, Know Healthcare are three prominent resources that patients can access to gain specific information about clinical laboratory tests. Lab Tests Online was designed to help patients and caregivers understand the many lab tests that are a vital part of medical care and to understand the meaning and implications of results. Labs Are Vital began as an online community to support pathologists and laboratory professionals worldwide to elevate the role and reputation of pathology and laboratory medicine in health care. Know Pathology, Know Healthcare is an initiative of Pathology Awareness Australia.

Social media platforms are also important in the scope of portals accessible to both patients and health-care professions alike. Patients and healthcare professionals can obtain realtime updates on the major microblogging platforms such as Twitter and Facebook. Healthcare professionals can engage in case discussions, research collaborations, medical education and crowdsourcing/crowdfunding and likewise with patient groups. It is clear that the use of online resources will increase and grow in sophistication, especially with the advent of Web 2.0.

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Meet the expert Tuesday 13 June - HOW TO SUCCEED IN SCIENCE MEDICINE AS A WOMAN

HOW TO SUCCEED IN SCIENCE AND MEDICINE AS A WOMAN

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Success can be defined as the "accomplishment of an aim or purpose". To succeed in science requires hard work, talent, and perhaps a little luck. In many ways, the path to success is the same for men and women. However, historically, women have faced social, political, and institutional barriers to their entrance and success in the sciences.

This presentation will review best practices for a successful every scientist, provide specific advice for women, and will discuss changes that are required to improve the chances for women to succeed in science.

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Meet the expert Tuesday 13 June - ASSESSING VITAMIN D STATUS IN THE CLINICAL LABORATORY

ASSESSING VITAMIN D STATUS IN THE CLINICAL LABORATORY: ASSAYS AND INTERPRETATION ARE THE KEY ISSUES

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The provision of a service to assess vitamin D status in the clinical laboratory is a demanding task both with regard to analytical and post-analytical aspects of the assay process. Vitamin D metabolites bound to vitamin D binding protein (DBP) are stable from the effects of light and moderate temperatures. The development of a reference measurement system for serum/plasma 25-hydroxyvitamin D (25D) and its adoption for the standardization of clinical immunoassays has largely resolved the major difficulties with the accuracy of these assays. However the reliability of individual results is a far more difficult problem and can undermine the confidence in 25D results. Such variation suggests that these assays are subject to interference from other components of the sample matrix such as the level of DBP or vitamin D metabolites, particularly 24,25-dihydroxyvitamin D. At the post-analytical phase, interpretation of serum/plasma 25D levels is also challenging. Limited understanding of the physiology of vitamin D is likely to significantly contribute to this difficulty. 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/plasma 1,25-dihydroxyvitamin D (1,25D). This pathway protects against the metabolic bone disease of rickets in children or osteomalacia in adults. The critical level for serum 25D is 8 ng/ml (20 nmol/L), which is sufficient for adequate synthesis of 1,25D by the kidney. In contrast adequate serum 25-hydroxyvitamin D to protect against bone loss and reduce the risk of osteoporotic fractures is of the order of 20 to 30 ng/ml (50 to 75 nmol/L). This higher level is required for synthesis of 1,25D by bone cells which is necessary for anabolic biological activity on bone tissue. Such autocrine activities of vitamin D are likely to be widespread throughout numerous organs.

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Symposium Tuesday 13 June – NEW PERSPECTIVE ON PHARMACOGENETICS AND PHARMACOGENOMICS

PHARMACOGENOMICS, A PARADIGM FOR DIGITAL MEDICINE

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The development of omics-based approaches to predict an individual's drug response is one of the visions of pharmacogenomics (PGx), personalized medicine and precision medicine (1). New generation sequencing and microarrays enable accurate and inexpensive measurement of all presently known genetic components of interindividual variability in drug response. However, clinical implementation of pharmacogenomic testing has not been widely adopted to improve routine patient care. One reason is that in order to guide prescribing decisions, preemptive pharmacogenomic test results should be available to physicians at the point of care.

For an increasing number of actionable gene-drug interactions, practice guidelines based on genetic and clinical information have been established (2). The incorporation of pharmacogenetic test results combined with clinical decision support (CDS) into machine-readable electronic medical records (EMRs) allows clinical implementation of this information. Results of preemptive testing in several institutions with multiple pharmacogenes and "high risk" drugs indicates that 95 % of patients carry at least one actionable "high risk" genotype. The lecture presents an overview of present studies of clinical implementation of digital signatures of the drug response profiles (3,4). In the future, the question may not be whether to order a pharmacogenomic test but how to best apply the already existing digital genomic and other omics information to optimize drug response.

1) Meyer UA, Zanger UM, Schwab M. Annu Rev Pharmacol Toxicol 2013; 53: 475-502.

2) Clinical Pharmacogenetics Implementation Consortium:
http://www.pharmgkb.org/page/cpicGeneDrugPairs

3) Van der Wouden CH et al, 2017; Clin Pharmacol Ther ; doi:10.1002/cpt.602 (Epub ahead of print)

4) Luzum JA et al. 2017; Clin Pharmacol Ther ; doi:10.1002/cpt.630 (Epub ahead of print)

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Symposium Tuesday 13 June – NEW PERSPECTIVE ON PHARMACOGENETICS AND PHARMACOGENOMICS

REGULATION OF ADME-GENES BY MIRNAS

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There is increasing evidence that individual phenotypic differences may result not only from genetics, but also from epigenetic alterations such as histone-acetylation or DNA-methylation. Moreover, interactions with non-coding RNAs contribute to protein expression and may modulate drug action. Of significant importance are the consequences of miRNA interaction for drug resistance in cancer by regulating target genes and efflux transporters. miRNA is increasingly used as biomarker particularly in malignant diseases cancer or as marker of drug response. The understanding of the rapidly emerging field of epigenetics will contribute to the better understanding of a variety of diseases, but also to the explanation of mechanisms of drug resistance. Most challenging is the development of non-coding RNA approaches to target specifically gene expression as future treatment options.

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Symposium Tuesday 13 June – NEW PERSPECTIVE ON PHARMACOGENETICS AND PHARMACOGENOMICS

VEGF-A, A POTENTIAL BIOMARKER FOR SYSTEMS MEDICINE

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Vascular endothelial growth factor–A (VEGF–A) is implicated in angiogenesis, lymphangiogenesis, vascular permeability, and haematopoiesis. It is associated with numerous pathologies including cardio-vascular diseases and several types of cancer.

We specifically developed an integrative systems biology strategy for clinical improvement of this biomarker.

A high heritability of this trait, 60%, was estimated in the STANISLAS cohort giving us the needed arguments to continue for a deep characterization of the genetic component of VEGF–A levels.

Therefore, we searched, by a Genome Wide Association Study (GWAS), the VEGF–A genetic variants and the inter-connexions of these biomarkers with other disease-associated molecules in healthy populations.

The GWAS was performed in 3,527 healthy participants (Framingham Heart Study) and the most significant results (P <5x10-8) were replicated in 1,727 individuals (STANISLAS Family Study, PIVUS study). Functional transcriptomic analyses were performed in peripheral blood mononuclear cells (PBMCs). Furthermore, in 403 healthy adults the associations between VEGF–A and adhesion/inflammation molecules were tested. Also, associations between VEGF–A and blood lipids were assessed in a discovery (n=1,006) and in a replication population (n=1,145) of healthy individuals.

Four polymorphisms (rs6921438, rs4416670, rs6993770, rs10738760) explaining ~50% of VEGF–A heritability were identified. These variants, directly or via gene x gene x environment interactions had significant effects on HDL, LDL, TNF-a, IL-6, E selectin and ICAM-1 plasma levels. SNP rs6993770 was shown to increase VEGF121 mRNA levels and rs4416670 was associated with L-selectin expression. Recently, thanks to a meta-GWAS we identified 6 additional rs further explaining VEGF–A levels variability and ongoing investigations focus on clinical implementation of the '–omics' determinants of this biomarker.

Our integrative strategy resulted to significant results indicating molecular links between VEGF–A and cardio-vascular disease biology and the importance of epistatic and gene x environment interactions. This example illustrates an improved strategy to be applied for every biomarker with high heritability levels, consequently with potential interest in Personalised Medicine, using familial design and the existing biobanks.

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Symposium Tuesday 13 June – IMPLEMENTING AND MAINTAINING STANDARDIZATION IN LABORATORY MEDICINE

QUANTITATION OF SERUM APOLIPOPROTEINS USING A BOTTOM-UP PROTEOMICS APPROACH: REQUIREMENTS FOR STANDARDIZATION

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BACKGROUND: Direct and calculated measures of lipoprotein fractions are the cornerstone for cardiovascular risk assessment in clinical guidelines. In this era of personalized medicine, measurement of the apolipoprotein counterparts might contribute to better insight into pre-, pro- and antiatherosclerotic processes. As LC-MS/MS has proven to be suitable for multiplexed quantification and phenotyping of serum apolipoproteins (1), we decided to develop a semi-automated LC-MS/MS assay for quantification of multiple clinically relevant serum apolipoproteins (apo) and for simultaneous qualitative assessment of apoE phenotypes (2).

METHODS: During method development, the concepts of commutability and metrological traceability were anchored right from the start. To that end, native, human serum calibrators were produced and value assigned to higher order reference materials, if available. Stable isotopic-labeled (SIL) peptide-based internal standards were added before sample preparation. Serum proteins were denatured, reduced, and alkylated according to standard mass spectrometry-based proteomics procedures. Trypsin digestion was optimized to guarantee equimolar conversion between the serum apolipoproteins intended to measure and the quantifying peptides generated after trypsin digestion. Peptides were analyzed by LC-MS/MS and for each peptide, two transitions were measured. Bias and imprecision of the multiplex LC-MS/MS apo test were evaluated and compared to test characteristics of CE-approved, uniplex immunoassay-based apo tests.

RESULTS: Intraassay CVs were 2.3%–5.5%, and total CVs were 2.5%–5.9%. The LC-MS/MS assay correlated (R = 0.975 - 0.995) with immunoturbidimetric assays for serum apoA-I, apoB, apoC-II, apoC-III, and apoE in normotriglyceridemic (n=54) and hypertriglyceridemic (n=46) sera. Results were interchangeable for apoA-I $\leq$ 3.0 g/L (Deming slope 1.014) and for apoB-100 $\leq$ 1.8 g/L (Deming slope 1.016) and were traceable to higher-order standards.

CONCLUSIONS: Fully optimized trypsin digestion and the use of commutable, value-assigned serum calibrators in combination with internal standards going through the entire workflow, are essential prerequisites for adequate standardization of serum apolipoproteins by mass spectrometry.

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Symposium Tuesday 13 June – IMPLEMENTING AND MAINTAINING STANDARDIZATION IN LABORATORY MEDICINE

STANDARDIZATION OF CHOLESTEROL AND STEROID HORMONES USING ACCURACY-BASED QUALITY CONTROL SAMPLES AND EQA PROGRAMS

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The goal of clinical laboratory standardization is to improve the detection, diagnosis and treatment of diseases through accurate and reliable laboratory measurements. This is achieved by establishing a structured process in which reference laboratories, assay manufacturers and providers of laboratory surveys work together to ensure testing performed in patient care, public health and research is accurate, comparable and reliable.

The CDC programs for standardizing cholesterol, other blood lipids, steroid hormones and vitamin D maintain reference laboratories with eight reference methods. They operate a network of reference laboratories that supports assay manufacturers with assay calibration and verification of measurement accuracy and precision. These programs use well-established analytical performance criteria to evaluate participants. CDC's clinical standardization programs evaluated and certified over 400 laboratories and manufacturers in 2016. They provided accuracy-based quality control materials to research laboratories to monitor measurement accuracy and reliability over time, and issued over 900 analytical performance evaluations to participants. Furthermore, they collaborated with three External Quality Assurance (EQA) providers on accuracy-based surveys.

Data obtained from accuracy-based EQA surveys show a high level of accuracy for total cholesterol measurements. Data from a survey on testosterone suggest that those assays certified by the CDC Hormone Standardization Program have a higher level of accuracy than those not certified. Among participants of the CDC Vitamin D Standardization Certification Program, the variability in measurement accuracy improved notably. These observations demonstrate that standardization programs can improve and maintain measurement accuracy and reliability in patient care. Despite these improvements, inaccurate measurements in individual patient samples can occur for example because of lack of specificity. CDC's clinical standardization programs support participants in overcoming these challenges by providing reference measurements on individual patient samples. CDC's clinical standardization programs provided over decades consistent and transparent evaluations of analytical assay performance and at the same time were flexible to address specific participant needs.

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Symposium Tuesday 13 June – IMPLEMENTING AND MAINTAINING STANDARDIZATION IN LABORATORY MEDICINE

STANDARDIZATION OF HBA1C AND MONITORING ITS IMPACT BY EUROPEAN EQA ORGANIZERS SHARING THE SAME SAMPLES

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Diabetes is the most prevalent chronic disease and treatment depends nearly fully on the results of laboratory tests, especially HbA1c. For this reason the quality of HbA1c is vital for optimum clinical practice.

The starting point for good quality in the medical laboratory is a reference measurement procedure (RMP). This was well recognized by the IFCC and a working group developed a RMP and in place: the method is officially approved, implemented in a worldwide network of reference laboratories, used by the manufacturers to target their kit calibrators, and by organisers of external quality assessment programmes to assign values to the samples of their EQA/PT programme.

This analytical effort had a beneficial impact: from 1993 to 2014 the between laboratory CV of the assay dropped from 22 to 3.5%. This improvement caused a change in paradigma: quality is that good now that, rather than fasting plasma glucose, HbA1c is considered more and more as the gold standard for diagnosis and screening of diabetes.

This new application raised to the question how good an HbA1c assay should be. To address this question the IFCC developed a model (published in the May 2015 issue of Clin Chem). The model can be applied at the level of a) the individual laboratory (within one lab, within one method), b) the manufacturer (between laboratories, within one method), and c) a country (between laboratories, between methods).

In the lecture examples will be shown of the application of this model, especially of the results of the EurA1c initiative: EQA organisers in 15 European countries used the same samples in their respective programs. Results demonstrate the present general status of the assays of HbA1c and if they meet the quality targets set by the IFCC. The general picture will be differentiated to performances per country and per manufacturer.

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Symposium Tuesday 13 June – IMPLEMENTING AND MAINTAINING STANDARDIZATION IN LABORATORY MEDICINE

THE IMPORTANCE OF REFERENCE METHODS AND COMMUTABILITY IN ACCURACY-BASED PROFICIENCY, EXAMPLES FROM THE FRENCH EQA PROGRAM

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Along with reference method target values, commutability of External Quality Assessment (EQA) materials is a key requirement for their use in accuracy-based EQA surveys. For the first time in France, the French Agency for the Safety of Health Products (ANSM) organized an accuracy-based EQA program relying on commutable Certified Reference Materials from LNE, the French Metrology Institute. These materials were distributed end 2016 to all 1100 French Medical Laboratories as part of the mandatory national quality control. Target values were determined using higher order reference measurement procedures listed in JCTLM database for the following 6 parameters: glucose, creatinine, total cholesterol, total glycerides, LDL-C, HDL-C. Commutability of these materials was evaluated for the 7 most popular systems in France based on market share (Roche Cobas, Siemens Vista, Abbott Architect, Beckman AU, Beckman DxC, Ortho CD Vitros, Siemens Advia and Siemens EXL). We took advantage of this study to characterize commutability of 28 other EQA materials, including 6 CRMs prepared according to CLSI C37A guidelines, 6 frozen serum pools and 16 lyophilized serum pools for 14 parameters (glucose, creatinine, total cholesterol, total glycerides, LDL-C, HDL-C, urea, uric acid, calcium, chloride, sodium, potassium, total iron and albumin). Results show that commutability of materials prepared according to CLSI C37A guidelines is generally better than for lyophilized materials, especially for HDL-C and LDL-C. However, some lyophilized materials exhibit very good commutability so it's not possible to anticipate commutability of a material a priori. Results also show that some materials are more appropriate than others for certain groups of biomarkers (eg. electrolytes, lipids, metabolites). Since materials were rarely found commutable for all methods, it is therefore quite difficult to accurately estimate between-methods agreement. In the future, it is expected that this type of study will be extended to other parameters.

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Symposium Tuesday 13 June – BIG DATA IN THE ERA OF PERSONALIZED MEDICINE

LOCAL REGULATORY NETWORKS ACROSS TWO TISSUES AND APPLICATIONS TO ANALYZE RARE NON-CODING VARIANTS

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Population measurements of gene expression and genetic variation enable the discovery of thousands of expression Quantitative Trait Loci (eQTL), a great resource to determine the function of non-coding variants. To describe the effects of eQTL on regulatory elements such as enhancers and promoters, we quantified gene expression (mRNA) and three key histone modifications (H3K4me1, H3K4me3 and H3K27ac) across two cell types (Lymphoblastoid Cell Lines and Fibroblast) in 320 and a subgroup of 80, respectively, densely genotyped European samples.

We find that nearby regulatory elements forms local chromatin modules often comprising multiple sub-compartments and overlapping topologically associating domains. These modules bring multiple distal regulatory elements in close proximity, vary substantially across cell types and drive co-expression at multiple genes. This regulation is under strong genetic control as ~34k chromatin QTLs (cQTLs) affect ~30% of the histone marks and as ~70% of module are associated with QTLs.

Chromatin modules empower association studies of rare variants when whole genome sequencing is available. For example, using the Geuvadis transcriptomic data we unravel that expression of ~10% of genes is associated with rare non-coding variants in modules.

Coordination between regulatory elements located on distinct chromosomes (i.e. in *trans*) is well supported by Hi-C sequencing data and seem to drive in some cases *trans* eQTL effects. We replicated up to 80% of the strongest inter-chromosomal Hi-C contacts.

Overall, this large-scale study integrating gene expression, chromatin activity and genetic variation across two cell types and hundreds of samples provides key insights into the biology underlying gene regulation and eQTLs.

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Symposium Tuesday 13 June - THE MICROBIOME: PRESENT AND FUTURE CHALLENGES IN LABORATORY MEDICINE

HUMAN MICROBIOME IN HEALTH AND DISEASE

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The human microbiota consists of the 10-100 trillion symbiotic microbial cells harbored by each person, primarily bacteria in the gut; the human microbiome consists of the genes these cells harbor. Microbiome projects worldwide have been launched with the goal of understanding the roles that these symbionts play and their impacts on human health. Emerging technologies such as 16S rRNA and whole-genome sequencing techniques gave us the opportunity to study and analyze the microbiome and its synthesis in different part of the human body and especially in the gut. The four most abundant phyla are Actinobacteria, Bacteroidetes, Firmicutes and Proteobacteria, which presence and rate depend on the anatomic area of the human body tested. Although microbiome's composition continues to be influenced by environment; antibiotics, diet, genetics, inflammation, hygiene, lifestyle, its microbial stability is established after 1 year of life. According to literature, human microbiome seems to play an important role in the pathogenesis of many diseases such as cancer, autism, obesity, metabolic disorders, allergies, but also in their development and prognosis. Human microbiome plays also an important role in the maturation and development of the immune system, primarily through the production of pathogen-associated molecular patterns (PAMPs) and metabolic by-products. Once we have the opportunity to establish whole genome sequencing techniques in many more laboratories, the study and the analysis of microbiome's composition will be crucial in the prognosis of many diseases and in the deeper understanding of their pathogenesis. Moreover, we will have the power to interfere and manipulate interactions between humans and the bacteria that live in or on the body, in order to treat many diseases, such as inflammatory bowel disease or liver diseases. Expert scientists predict that new microbiome-derived drugs and therapies will come to market within a few years, through the understanding of the mechanisms by which specific bacteria affect the body. In conclusion, human microbiome is definitely a challenge in laboratory medicine and it is going to positively affect many aspects of it.

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Symposium Tuesday 13 June - THE MICROBIOME: PRESENT AND FUTURE CHALLENGES IN LABORATORY MEDICINE

IS DYSBIOSIS OF THE INTESTINAL MICROBIOTA A PATHOGENIC MEDIATOR IN COMMON CHRONIC DISORDERS? THE CASE OF TYPE 2 DIABETES

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Is dysbiosis of the intestinal microbiota a pathogenic mediator in common chronic disorders? The case of type 2 diabetes

Human-associated microbes have until recently primarily been viewed through the lens of a single species and its environment. Advances in next-generation culture-independent technologies and bioinformatics have, however, shown an enormous diversity and functional capacity of the human microbiota. A large number of microbes reside in the distal gut, and dysbiosis of intestinal microbiota associates with a multiplicity of common chronic diseases. Major efforts are currently concentrated on exploring potential causality and related microbial-mediated disease mechanisms with the hope that an improved understanding will fuel the conception and realization of novel and maybe stratified therapeutic and preventative means. In my lecture I will discuss recent progress in studying the possible role of imbalances in the intestinal microbiota in the pathogenesis of insulin resistance, pre-diabetes and overt type 2 diabetes.

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Symposium Tuesday 13 June - THE MICROBIOME: PRESENT AND FUTURE CHALLENGES IN LABORATORY MEDICINE

MOVING BEYOND THE HYPE: EXPLOITING THE MICROBIOME FOR RATIONAL BACTERIOTHERAPY OF SKIN DISEASE

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A revolution in understanding of human immunity has taken place with recognition that bacterial and other microbial cell types, not only human-derived epithelial and bone marrow derived cells, play critical roles in immune defense. Twenty-years ago we discovered that mammalian skin produces antimicrobial peptides (AMPs), and have since learned that various cell types such as keratinocytes, leukocytes and dermal adipocytes produce these AMPs to provide an essential elements of host defense. Dysregulation of some AMPs drives the pathogenesis of human diseases such atopic dermatitis (too little AMP production) and Rosacea and Psoriasis (too much AMP production). Furthermore, it became obvious that AMPs are not indiscriminate antibiotics but rather have evolved to permit a defined community of microbes to exist within us. High-throughput functional analysis of the action of the human skin microbiome has revealed surprising functions and previously unknown molecules from commensal skin bacteria that are critical components of health. Animal data demonstrated how AMPs made by the microbiome limit the growth of pathogens and influence epithelial growth. Furthermore, discovery of the strain-specific production of these genes by the microbiome permitted design of a clinical trial of a rational biotherapeutic approach to transplant commensal microbes onto patients colonized by S. aureus that lack these appropriate defensive bacteria. Early clinical trial results have been highly successful, suggesting a clear cause and effect relationship between these specific members of the skin microbiome and human health. Therefore, we now conclude that some members of the skin microbiome provide the first layer of skin immunity. We propose that the skin immune system is the product of coordinated interactions of cells in a superorganism. Recognizing this dictates that we respect both human and microbial elements of immunity when treating infections, cancers and inflammatory diseases.

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EFLM Symposium Wednesday 14 June - PERFORMANCE SPECIFICATIONS IN LABORATORY MEDICINE

ARE TOTAL ERROR AND UNCERTAINTY OF MEASUREMENT TWO SIDES OF THE SAME COIN?

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Uncertainty methods offer simpler and more practical procedures than error methods for calculating uncertainty as well as application in quality control procedures in clinical chemistry. For that reason the total error concept currently represents the method of choice. Uncertainty methods, however, are endorsed by other fields of metrology as reflected by GUM. Amongst the simplifications in error methods is the way bias is combined with imprecision to add uncertainties. Total error methods have advantages when evaluating results from single measurements of control samples in quality assessment and defining performance specification in the case of single measurement results. Total error methods have also been used for summarizing results of the measurement of reference materials. However, when using laboratory results for supporting medical diagnoses, the total uncertainty consists only partially of analytical uncertainty, while biological variation and pre-analytical variation also need to be considered. Total error methods have been proposed as general solutions for interpreting patient results, for performance evaluations using “allowable total analytical error” and for internal quality control. However, like GUM measurement uncertainty methods, total error methods need substantial developments in order to include all relevant sources of variation in the diagnostic process. Performance specifications for measurement systems and laboratory organizations with several measurement systems should express the total diagnostic uncertainty. In order to minimize this uncertainty, separate estimates of bias and imprecision are needed. In general, combination of bias and imprecision is only preferable when single measurements of control samples are employed.

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EFLM Symposium Wednesday 14 June - PERFORMANCE SPECIFICATIONS IN LABORATORY MEDICINE

CRITERIA FOR ALLOCATION OF LABORATORY TESTS TO THE THREE MILAN MODELS FOR PERFORMANCE SPECIFICATIONS

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During the EFLM Strategic Conference held in Milan in 2014 the following three models to derive analytical performance specifications were defined: Model 1, based on the effect of analytical performance on clinical outcome; Model 2 based on components of biological variation of the measurand and Model 3, based on state-of-the-art of the measurement. Model 1 is the model of choice for measurands that have a central role in the decision-making of a specific disease or clinical situation and where cutoff / decision limits are established for either diagnosing, screening or monitoring. Total cholesterol, glucose, HbA1c, serum albumin and cardiac troponins represent practical examples. Model 2 should be applied to measurands that do not have a central role in a specific disease or clinical situation, but where the concentration of the measurand is in a steady state. This is best achieved for measurands under strict homeostatic control in order to preserve their concentrations in the body fluid of interest, but it can also be applied to other measurands that are in a steady state in biological fluids. In this case, it is expected that the "noise" produced by the measurement procedure will not significantly alter the signal provided by the concentration of the measurand. This model especially applies to electrolytes and minerals in blood plasma (sodium, potassium, chloride, bicarbonate, calcium, magnesium, inorganic phosphate) and to creatinine, cystatin C, uric acid and total protein in plasma. Model 3 is the least preferred method because there may be no relationship between what is technically achievable and what is clinically needed. It should be used for all the measurands that cannot be included in models 1 or 2.

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EFLM Symposium Wednesday 14 June - PERFORMANCE SPECIFICATIONS IN LABORATORY MEDICINE

DEFINING PERFORMANCE SPECIFICATIONS IN LABORATORY TESTING

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Measurements in clinical laboratories produce results needed in the diagnosis and monitoring of patients. These results are always characterized by some uncertainty. What quality is needed and what measurement errors can be tolerated without jeopardising patient safety should therefore be defined and specified for each analyte having clinical use. When these specifications are defined, the total examination process will "fit for purpose" and the laboratory professionals should then set up rules to control the measuring systems to ensure they perform within specifications. The laboratory community has used different models to set performance specifications. Recently, it was felt that there is a need to revisit different models to try to simplify them and, at the same time, to emphasize the presuppositions for using the different models. To this aim, in 2014 the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) organized a Strategic Conference in Milan. It was felt that there was a need for more detailed discussions on, for instance, performance specifications for EQAS, which measurands should use which models to set performance specifications and how to set performance specifications for the extra-analytical phases. There was also a need for more quality data on biological variation and further discussing the use of total error concept. Consequently, EFLM established five Task Finish Groups (TFGs) to address each of these topics. The TFGs are finishing their activity on June 2017 and the program of this symposium includes deliverables from these groups.

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EFLM Symposium Wednesday 14 June - PERFORMANCE SPECIFICATIONS IN LABORATORY MEDICINE

PERFORMANCE SPECIFICATIONS IN EQAS

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Satisfactory participation in external quality assurance schemes (EQAS) is both a regulatory requirement and a vital tool for ensuring analytical quality in pathology laboratories. For both of these purposes there is an implied recognition that there is a way of identifying performance which demonstrates that an assay is fit for purpose. The tool provided by most EQAS providers are the Analytical Performance Specifications (APS). These may also be known as quality specifications, performance criteria, limits of performance or other names. They are applied to results submitted by participants to assess whether the difference of the submitted result from the program target indicates satisfactory performance. However when a laboratory is assessing performance against a provided APS, it is necessary to understand the nature of the APS, how they are derived and possible limitations to make a satisfactory interpretation.

The European Federation of Laboratory Medicine (EFLM) in 2015 commissioned a task group to address the issue of APS. The initial work has been to describe the key pieces of information needed to fully understand an APS. The key factors that must be described are as follows:

1. The nature of the EQA material, specifically whether it is commutable for the intended use.

2. The manner of target value assignment.

3. The data set for the application of the APS. Are they applied to single results, averages, medians or other calculated outputs.

4. The quality being assessed. This may be total error, bias or imprecision.

5. The rationale for selecting the APS, i.e. is it a minimum standard that all labs should pass, or an aspirational standard set with the aim of driving improvement.

6. The model used to derive the APS. This should be selected from the Milan criteria of clinical outcome, biological variation or state of the art.

In addition to ensuring the correct interpretation of performance when an APS is applied, the use of this list of factors allows valid comparison of APS from different providers. The future goal is harmonisation of APS, an outcome only possible if the factors involved in establishing them are clearly defined.

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EFLM Symposium Wednesday 14 June - PERFORMANCE SPECIFICATIONS IN LABORATORY MEDICINE

PERFORMANCE SPECIFICATIONS IN EXTRA-ANALYTICAL PHASES

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The main priority in the current healthcare scenario should be to address errors in laboratory testing, which account for a significant proportion of diagnostic errors. Efforts made in laboratory medicine to enhance the diagnostic process have been directed toward improving technology, greater volumes and more accurate laboratory tests being achieved, but data collected in the last few years highlight the need to re-evaluate the total testing process (TTP) as the unique framework for improving quality and patient safety. Valuable quality indicators (QIs) and extra-analytical performance specifications are required for guidance in improving all TTP steps. Yet in literature no data are available on extra-analytical performance specifications based on outcomes, and nor is it possible to set any specification using calculations involving biological variability. The collection of data representing the state-of-the-art based on quality indicators is, therefore, underway. The adoption of a harmonized set of QIs, a common data collection and standardised reporting method is mandatory as it will not only allow the accreditation of clinical laboratories according to the International Standard, but also assure guidance for promoting improvement processes and guaranteeing quality care to patients.

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EFLM Symposium Wednesday 14 June - PERFORMANCE SPECIFICATIONS IN LABORATORY MEDICINE

THE NEW EFLM BIOLOGICAL VARIATION DATABASE BASED ON A CRITICAL APPRAISAL CHECK-LIST

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Data from biological variation are used for many purposes, the two most common are to set performance specifications and to generate reference intervals as well as reference change values.

One of the Task and Finish Groups (TFGS) after the 1th EFLM Strategic conference was the TFG of the biological variation database. This TFG should a) use a critical appraisal check list to evaluate literature on biological variation, to evaluate the literature on biological variation and extract essential information from the papers as well as summarise the information.

It should generate a database on the EFLM website with essential information about the biological variation and derived performance specifications for different measurands as well as the evidence behind. The TFG consisted of people interested in the work and was a cooperation between the TFG, the Analytical Quality Commission of the Spanish Society of Clinical Chemistry, the WG of biological variation in EFLM and interested individuals, altogether more than 30 persons.

Different groups are established for different measurands. The groups have categorised papers as A, B, C and D depending on their methodological quality, with category A papers indicating high-quality and D poor quality using a checklist that contains 14 items. From each paper 22 items are extracted and presented in the database. The lecture will give a status of the present work.

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Symposium Wednesday 14 June - THE ROLE OF LABORATORY IN THE MANAGEMENT OF ICU / CRITICALLY ILL PATIENTS

ABGS (ARTERIAL BLOOD GASES) IN A CRITICAL CARE SETTING

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Arterial blood gases are the most commonly performed laboratory test in ICU patients. They reflect adequacy of gas exchange in the lungs, which is determined by the balance between pulmonary ventilation and capillary blood flow. Critically ill patients commonly develop complicated disorders of Po2, Pco2, and blood H+ concentration that usually demand an advanced understanding of both chemistry and physiology.

A significant reduction in arterial Po2 is due to either alveolar hypoventilation, pulmonary disorders associated with a high shunt fraction or an imbalance between oxygen delivery and uptake in the systemic circulation. In such cases, high flow oxygen administration, mechanical ventilatory support with the addition of positive end-expiratory pressure (PEEP) and cardiovascular optimization constitute the major therapeutic strategies in order to maintain tissue oxygenation, preventing at the same time iatrogenic injury due to lung damage.

Increased arterial Pco2 (Pco2 > 45 mm Hg) is due to either increased rate of CO2 production, or decreased rate of CO2 elimination by alveolar ventilation. In general, hypercapnia is related to an underlying lung disease that increases dead space ventilation (eg, COPD exacerbation). Respiratory muscle weakness is the most common cause of alveolar hypoventilation during chronic critical illness, prolonging length of ventilation, pulmonary infections and ICU stay.

Changes in blood pH occur as the result of changes in volatile acids (Pco2) that are considered as respiratory and in nonvolatile acids that are considered as metabolic. Three distinct approaches for the assessment of acid-base disorders have been identified: the physiological approach, the base excess approach and the physical-chemical approach and each differs only in the description of the metabolic component. The last method is more suitable in the ICU, describing better disorders of chloride homeostasis, water and albumin effects, as well as other unmeasured ions as common sources of metabolic acidosis.

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Symposium Wednesday 14 June - THE ROLE OF LABORATORY IN THE MANAGEMENT OF ICU / CRITICALLY ILL PATIENTS

THE CASE FOR POC TESTING IN CRITICAL ILLNESS: DOES IT IMPROVE WORKFLOW EFFICIENCY IN ED AND ICU.

V. Van Hoof [1]
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Point-of-Care Testing (POCT) for critical analyses has been introduced in emergency departments (ED) and intensive care units (ICU) in order to reduce turn-around-time (TAT) between sample taking and result availability. Following the universal and increasing demand to demonstrate that implementation of a new product within a healthcare environment results in better patient outcomes and economic benefits, the use of POCT in the ED should reduce overcrowding, improve patient flow, improve patient satisfaction and reduce morbidity and mortality, while in the ICU, rapid identification of alterations in levels of parameters that exhibit rapid changes in critically ill patients, should lead to improved outcomes.

Reducing TAT is one factor, but whether the implementation of POCT will result in an optimized workflow efficiency and/or better patient outcomes in the ED and in the ICU depends on more than the sole shortening of TAT. Important additional issues are the availability of clinicians to interpret results, rapid delivery of an appropriate intervention following diagnosis and quick therapeutic adjustment based on follow-up values. In short, process redesign is often needed. Additional requirements to take full advantage of a reduced therapeutic TAT are the evidence-based choice of analytes, user-friendliness of the POCT systems, critical value reporting, and laboratory oversight to support users and to monitor POCT quality. POCT regulations and guidelines, issued by FDA/CLIA, CLSI, JCI, CAP, EU, and implementation of ISO22870 standards, should guarantee a qualitative and safe diagnostic care. Nevertheless, as a consequence of loopholes in current POCT regulations, serious adverse events have occurred following the use of POCT.

To conclude, implementation of POCT in critical illness will only improve workflow efficiency and patient safety in the ED and ICU when (1) overall procedures within these departments are critically assessed and reengineered if needed, and (2) loopholes in the current POCT regulations are closed.

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Symposium Wednesday 14 June - THE ROLE OF LABORATORY IN THE MANAGEMENT OF ICU / CRITICALLY ILL PATIENTS

MONOCYTE-DERIVED ALVEOLAR MACROPHAGES DRIVE LUNG FIBROSIS AND PERSIST IN THE LUNG OVER THE LIFESPAN

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Alveolar macrophages are increasingly recognized as important effector cells in the development of lung fibrosis. Strategies to therapeutically target alveolar macrophages during lung fibrosis have traditionally considered that they are a single population of monocyte-derived cells. This paradigm has been challenged by developmental studies that identified tissue-resident alveolar macrophages as highly specialized cells that populate the lung shortly after birth and persist over the lifespan. During fibrosis, a new population of monocyte-derived alveolar macrophages is recruited to the lung, which cannot be readily distinguished from the population of tissue-resident alveolar macrophages. It is not known whether these two populations act in concert or play distinct roles in disease pathogenesis. To address this, we developed systems to genetically track the fate and measure the function of these populations over the lifespan. During lung fibrosis, monocyte-derived alveolar macrophages expressed higher levels of fibrotic genes compared with tissue-resident alveolar macrophages. Specific genetic deletion of monocyte-derived alveolar macrophages ameliorated lung fibrosis. Lung fibrosis in young mice permanently altered the composition of the alveolar macrophage pool during aging, as monocyte-derived alveolar macrophages persisted one year after the resolution of injury, when they closely resembled tissue-resident alveolar macrophages. These findings suggest that consideration of the ontologic and functional heterogeneity of alveolar macrophages is important to therapeutically target them during disease and to understand their contributions to aging phenotypes.

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Symposium Wednesday 14 June - THE INTERFACE OF LABORATORY MEDICINE AND CLINICAL DIAGNOSIS

HARMONISING STEPS OF THE TOTAL TESTING PROCESS AT THE CLINICAL INTERFACE WHERE LABORATORY PROFESSIONALS SHOULD TAKE THE LEAD

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High quality laboratory testing is essential for delivering adequate patient care, service and safety. Harmonisation of laboratory testing can be instrumental in providing this, but must encompass all parts of the total testing process, from the pre-(pre)-analytical steps of requesting to post-(post)-analytical steps such as interpretation and communication of laboratory test results to both the physician and patient. Traditionally laboratories have had their focus on the analytical phase, but it is essential that laboratory professionals also take the lead for the steps at the clinical interface. The last years increasing emphasis has been put on harmonising the steps of the pre-analytical and post-analytical phases, and there are several national and international harmonisation initiatives led by laboratory professionals ongoing. Harmonisation of the different steps of the total testing process can be achieved locally, nationally and internationally, but depends on the availability of evidence-based knowledge as well as systems that can initiate, monitor and maintain the harmonisation results. Successful harmonisation of the total testing process including the steps at the clinical interface as well as those primarily under the control of clinicians requires input from a range of national and international stakeholders such as laboratory associations, regulatory bodies, accreditation systems and external quality assessment organisations.

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Symposium Wednesday 14 June - THE INTERFACE OF LABORATORY MEDICINE AND CLINICAL DIAGNOSIS

HOW DO LABORATORIES IN EUROPE DEAL WITH THE POSTANALYTICAL PHASE? ARE WE READY TO TRANSLATE LABORATORY TESTS TO CLINICAL MEANING?

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Laboratories are getting now more focused on extraanalytical (EA) phases in order to achieve the greatest impact of laboratory results on their patients' outcome. EA tasks that can potentially lead to better clinical utilization of laboratory test results involve assisted test ordering in the pre-pre-analytical phase, reflex- and reflective-testing in the postanalytical (PA) phase, as well as individualized interpretive commenting and reporting results with clinical urgency in the PA phase. Implementation of the above EA activities can only be performed successfully in shared responsibility of laboratories and clinicians, which represent a new challenge for laboratory profession.

So far, only sporadic data is available on EA activities that can lead to better clinical utilization of laboratory test results of laboratories. Existing methods in assisted test requesting as well as the applied PA practices of European laboratories will be presented through the findings of recent surveys of the joint Working Group on Postanalytical Phase (WG-POST) of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) and European Organisation for External Quality Assurance Providers in Laboratory Medicine (EQALM). Practice of laboratories in interpretive commenting will get special emphasis. In addition to the applied EA practices the content of the laboratory report forms and critical result lists used in European laboratories will be also discussed.

Understanding common features and limitations of the investigated EA practices leading potentially to better clinical utilization of laboratory test results in European laboratories may assist the development of best practice recommendations in these fields. This also can help laboratories in reviewing and redesigning their own actual practice and improving the clinical utility of their services to patients.

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Symposium Wednesday 14 June - THE INTERFACE OF LABORATORY MEDICINE AND CLINICAL DIAGNOSIS

HOW GOOD ARE LABORATORY SPECIALISTS TO ADVISE CLINICIANS?: RESULTS FROM UK NEQAS SURVEYS

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UK NEQAS offers a range of EQA programmes which address different areas of the patient pathway with respect to laboratory testing. The UK NEQAS for Interpretative Comments in Chemistry has been in operation in its present web-based form since 2001 but, under the direction of Gordon Challand, had been running on a 'bulletin board' prior to this.

The Scheme operates by posing a clinical question with a small amount of history and test results. Participants are asked to record the comments that they would append in response. They only have 250 characters in which to do this. In taking part in such an EQA program one has to suspend belief and the default "I would phone the clinician to discuss" option, while true, doesn't attract good marks.

Each comment is marked by a number of independent peer Assessors and a simple average Participant Case Mark is awarded. The marking Scheme is based on 'adding value' and ranges from -1 to 3. Participants are scored over a time-window in the same way as they are with their UK NEQAS analytical schemes. Participants are therefore familiar with the data presentation style and ethos. Assessors themselves are also marked, so that we can identify strict or lenient marking, and are given their own report.

Encouragingly, participants are generally good at adding value. The Scheme design recognises that there is often not a single correct answer and so the report commentary is a useful teaching aid. Average Case Marks do differ reflecting both the difficulty of the case or the knowledge of the participant. Assessment is over a rolling six month time window and participants see their general 'trend' as well as any specific area of weakness highlighted by a 'blip' that they may wish to improve on.

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Symposium Wednesday 14 June - PERSONALISED MEDICINE

P4 MEDICINE: PREDICTIVE, PREVENTIVE, PERSONALIZED AND PARTICIPATORY. A NEW TREND IN LABORATORY MEDICINE

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Personalized medicine, which simply means selection of treatment best suited for an individual, involves integration and translation of several new technologies in clinical care of patients. The scope is much broader than indicated by the term genomic medicine because many non-genomic factors are taken into consideration in developing personalized medicine.

The wide and public availability of the human genome sequence and the other tools spawned by the Human Genome Project have helped to create an unparalleled era of biomedical discovery.

Researchers have discovered hundreds of genes that harbour variations contributing to human illness, identified genetic variability in patients' responses to dozens of treatments, and begun to target the molecular causes of some diseases. In addition, scientists are developing and using diagnostic tests based on genetics or other molecular mechanisms to better predict patients' responses to targeted therapy. Since the completion of the mapping of the human genome, we have seen whole new areas of research evolve such as genomics, proteomics, and metabolomics.

Advances in DNA analysis to develop methods, which are increasingly specific, sensitive, fast, simple, automatable, and cost-effective, are considered paramount. These demands are currently driving the rapid evolution of a diverse range of newer technologies.

Although the potential diagnostic applications are unlimited, most important current applications are foreseen in the areas of biomarker research, cancer diagnosis and detection of infectious microorganisms.

There has been an explosion in the number of validated markers but relatively little independent analysis of the validity of the tests used to identify them in biologic specimens. The success of personalized medicine depends on having accurate diagnostic tests that identify patients who can benefit from targeted therapies.

Another important step will be expanding efforts to develop tissue banks containing specimens along with information linking them to clinical outcomes.

In this arena Laboratory Medicine should play a major role.

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Symposium Wednesday 14 June - PERSONALISED MEDICINE

PERSONALIZED GENOMIC MEDICINE APPROACHES IN THE STUDY OF CANCER

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Prevention and treatment strategies that take individual variability into account or personalized medicine are not new. Applying this concept broadly has been improved by development of large-scale genomic-based databases, powerful genomics, metabolomics, cellular assays and computational methods for characterizing patients. Oncology is the clear choice to benefit from precision medicine. Cancers are common diseases which are among the leading causes of death worldwide, and their incidence is increasing as the population ages. Individual cancers harbor a set of genetic aberrations that can be informative for identifying rational therapies. However, cancer genetic assessment to guide use of therapies has been limited to single biomarkers. Improvements in sequencing technologies and implementation of genome analysis tools have enabled clinicians to identify functional and/or disease-associated genomic variants. These approaches have provided clues potential therapeutic targets or genomic markers for novel clinical applications when standard therapy has failed. Whole-genome, exome, transcriptome and targeted sequencing can detect somatic cancer genome alterations including nucleotide substitutions, insertions, deletions, copy number variations and chromosomal rearrangements. However, challenges remain like the ability to generate enough coverage throughout the genome in a cost-effective and timely manner, the high heterogeneity of many tumors, the identification of low frequency mutations and the vast amounts of computational resources needed to process and store the data. The objective of this talk is to review existing technologies including reversible terminator SBS, semiconductor-based SBS, single molecule RT sequencing, single-strand DNA/RNA nanopore-based sequencing as well as to note emerging technologies. Examples of whole transcriptome analysis including non-coding RNA and whole genome amplification from isolated circulating tumor cells (CTC) in metastatic breast cancer (MBC) patients will illustrate applications of these technologies to deciphering the molecular basis of disease providing rationale for targeted, personalized drug treatment.

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Symposium Wednesday 14 June - PERSONALISED MEDICINE

PHARMACOGENETICS & PERSONALIZED THERAPY

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Adverse drug reactions are responsible for 5-7% of hospitalizations each year. Interindividual variation in drug metabolism is a factor affecting successful drug therapy. Predicting the capacity of patients to metabolize drugs based on their DNA profile, targeting genetic polymorphisms in drug metabolizing enzymes will allow prior adjustment of drug therapy to fit their personal genomic profile. With over 5,000 articles per year currently being published on genomic markers to guide drug therapy, there is a huge potential. A number of these candidates seems fit to be tried into clinical practice. Laboratory Medicine can play a an important role in providing this personalized therapy for health care professionals and patients.

Our 10 year experience in implementing pharmacogenetics in the Netherlands will be illustrated in this talk, covering the value of clinical evidence, education, availability of testing, laboratory and clinical guidelines, quality, feedback from clinicians and patients, reporting options as well as financial and ethical aspects. Successes as well as unexpected challenges will be addressed. Also European initiatives such as the European Pharmacogenetics Implementation Consortium (www.eu-pic.net), the IFCC Task Force Pharmacogenetics and the European Society for Pharmacogenomics and Personalized Therapy (ESPT) (www.esptnet.org) will be highlighted.

At Erasmus MC Rotterdam, the IFCC Expertcenter Pharmacogenetics at the Department of Clinical Chemistry provides since 2015 DNA passports, with information on drug metabolizing potential, which fits in the trend of a pre-emptive genotyping approach. With this passport, one can visit any pharmacy in the Netherlands to obtain medication adjusted on genomic profile for over 80 drugs. The question is, therefore: “Do YOU have your DNA passport?”

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Symposium Wednesday 14 June - FUTURE OUTLOOK ON POCT AND CLINICAL EFFECTIVENESS

EMERGING TECHNOLOGIES AND REGULATORY CHANGES FOR POCT

J. Nichols [1]
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Point-of-care testing (POCT) is laboratory testing conducted outside of a formal laboratory, closer to the patient. A variety of tests are available on portable devices and kits that can deliver fast results while the clinician is still seeing the patient. This provides the opportunity for expediting patient care, enhancing medical efficiency and improving clinical outcomes. However, POCT also presents risk. POCT is conducted by clinical staff with little laboratory experience and minimal training, so the reliability of results is often questionable. The possibility of implementing changes in medical management based solely on POCT results has led to increased scrutiny of POCT by laboratory regulators. Historically, laboratory regulations for quality control, operator training/competency, reagent management, and equipment validation/maintenance has been enforced for POCT the same as if the test was conducted in a core laboratory. However, the methodologies are different and many POCT devices have built-in control processes and manufacturer engineered features that detect and prevent errors with each test, unlike central laboratory equipment. Laboratory regulations developed for high volume, automated instrumentation don't necessarily fit the unitized kits and testing processes for POCT. Quality control mandating 2 levels of liquid control each day of testing is redundant with many of the built-in control processes on POCT devices. Newer molecular diagnostics integrating hundreds of tests on a single chip make performing 2 levels of daily control for every test cost prohibitive. Minimally invasive/non-invasive devices, like bilirubinometers and continuous glucose meters, cannot even sample liquid controls in the traditional fashion. So, laboratory regulations are changing to accommodate the new technologies and operational processes. This presentation will highlight the adoption of risk management principles into the U.S. CLIA interpretive guidelines and what laboratories have learned from implementing risk management and individualized quality control plans. The hazards of using capillary blood from critically ill patients with poor peripheral circulation for glucose meters, coagulation and other POCT devices will also be discussed as well as enforcement of off-label use of POCT devices by laboratory inspectors. Home self-testing and direct-to-consumer marketing of laboratory tests will also be highlighted along with the risks that these developments pose through internet purchase of laboratory diagnostics without physician interaction. The presentation will allow time for discussion of the changing regulatory climate in light of the rapid technological advancement of laboratory diagnostics and new devices available for POCT.

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Symposium Wednesday 14 June - FUTURE OUTLOOK ON POCT AND CLINICAL EFFECTIVENESS

IMPLEMENTATION ON POCT QUALITY STANDARDS TO OPTIMIZE THE CLINICAL RELIABILITY

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The French legislation constrains a mandatory accreditation for all medical laboratories under ISO 15189 standard and legalizes POCT for medical labs under the condition of a complementary EN ISO 22870 accreditation. Medical labs must achieve accreditation before 2020. France is one of the first countries to take such drastic measures. Regulations differentiate between the medical biology examinations with analytical phase realized outside the laboratory, placed under the responsibility of a specialist in laboratory medicine on one hand, and diagnostics guidance tests, which can be done by patients or by specified health professionals in defined contexts and medical indications, on the other hand. In the first case, we find usual POCT and/or critical care testing examinations: biochemistry (blood gases/CO-oximetry/electrolytes/glucose/lactate, cardiac markers, HbA1c, CRP…), hemostasis (ACT, viscoelastic and aggregometric tests), hematology (hemoglobin). A restriction of use is however the strict context of "urgent therapeutic decision", to limit the POCT to critical care testing. In the second case, no accreditation is needed and the laboratory is not involved. We find in that category patient self-tests, health professionals tests. There are slight requirements for quality management for these tests (minimum operator training and traceability).

I will present the POCT processes and quality indicators involved in ISO 22870 accreditation, both for operational, supporting and management processes, together with a 20-years' experience in Saint-Antoine hospital. Our experience of POCT accreditation in Saint-Antoine hospital was beneficial for the entire staff, laboratory and clinical units, and particularly improved communication. At the national level, the objective of a complete POCT accreditation, in public and private sectors, is now possible and useful for a better management by quality and for an improvement of patient care.

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Symposium Wednesday 14 June - FUTURE OUTLOOK ON POCT AND CLINICAL EFFECTIVENESS

POCT INTEGRATED INTO CLINICAL CARE TO ENSURE BETTER OUTCOMES

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Pathology tests play a significant role in contributing to best practice care for patient diagnosis and management. Point of Care Testing can successfully substitute for laboratory tests when performed within a quality framework, enhancing clinical management by providing diagnostic results at the time of consultation. This is particularly important to bridge geographical barriers to accessing pathology services.

For PoCT to be a success and provide improved patient outcomes implementation must occur in collaboration with the clinical team and PoCT must integrated into the clinical framework of the health service. Integrating PoCT into the clinical service helps to establish a patient centered clinical service, rather than the silo approach health services tend to adopt. It is important that clinicians using PoCT have an understanding of the differences between laboratory and PoCT pathology testing and accept that they are not interchangeable. When clinicians are included in the implementation of PoCT, they will have more confidence in the results produced and will be more likely to use PoCT for their patients.

Successful integration of PoCT into the clinical service requires extensive consultations with all key stakeholders to develop systems of care that include the whole clinical picture. Results from PoCT devices should be electronically transferred to a clinical database which is accessible by all health professionals involved in patient care. Electronic decision support algorithms can also be developed to assist with patient management, such as for warfarin management and basal bolus insulin administration.

A gold standard PoCT service producing optimal patient outcomes is involved in a quality management program, gathers and stores results electronically, utilises electronic decision support when appropriate and is fully integrated into the clinical service.

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Symposium Wednesday 14 June - FUTURE OUTLOOK ON POCT AND CLINICAL EFFECTIVENESS

POINT OF CARE TESTING, CONNECTIVITY, AND INFORMATICS

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Background: Point of Care Testing (POCT) is a rapidly growing and maturing area of laboratory testing, both in volume and in testing complexity. As clinical demand for mobile, fast testing increases, POC testing menus are expanding throughout hospitals and within physician offices as vendors pack more testing targets into small, portable platforms. Combined with increasing patient expectations for mobile health products, spurred on by the current smartwatch, health, and fitness tracker trend, there is a clear need for POCT to come of age within the laboratory community.

Discussion: Historically, informatics tools and connectivity solutions to manage point of care testing has been lacking, which has lead to disparate solutions regarding the technical, regulatory, reporting, and quality aspects of POCT. This session will review the current and future states of point of care testing, exploring the challenges facing the field in relation to test/device selection, clinical workflow considerations, and information management, all with the goal of maintaining proper regulatory compliance.

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Symposium Wednesday 14 June - TRACEABILITY IN LAB MEDICINE: WHAT IS IT AND WHY IS IT IMPORTANT?

TRACEABILITY AND HARMONIZATION - POWERFUL TOOLS FOR TRUENESS OF LABORATORY RESULTS

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Samples for measuring the same analyte from a certain patient are likely to encounter several measurement systems over time in the process of diagnosis and treatment. Bias between measurement systems represents a major source of uncertainty in laboratory medicine while imprecision has been successfully managed.

Standardization, e.g. using traceable reference materials includes mechanisms for maintaining trueness of measurement results geographically and over several years of time. During its more than a centenary long history, classical metrology has established and maintained traceability mechanisms in physical metrology. The same principles are improving chemical measurements – a relative newcomer in the field.

Laboratory medicine has much to gain by embracing the principles and practice of classical metrology. However, it is currently only possible to standardize about ten percent of measurement methods in laboratory medicine due to lack of pure substance reference materials, lack of appropriate reference measurement procedures and due to matrix effects in laboratory medicine samples. International, national and local procedures for harmonization of measurement results using natural patient samples for secondary adjustment of properly calibrated measurement systems and methods are therefore crucial complementary measures for trueness of laboratory results.

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Symposium Wednesday 14 June - TRACEABILITY IN LAB MEDICINE: WHAT IS IT AND WHY IS IT IMPORTANT?

TRACEABILITY IN LABORATORY MEDICINE: WHAT EVERY LABORATORY SPECIALIST SHOULD KNOW.

G. Myers [2], R. Wielgosz [1]
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Laboratory medicine specialists have a professional responsibility to provide high quality service that is optimized to the needs of the patient. An increasingly important quality objective is to ensure that patient test results are traceable (equivalent) between different methods, laboratories and healthcare systems over time. Metrological traceability (or more commonly referred to as "traceability" in the appropriate context) is the process which links laboratory test results through a "traceability chain" to reference systems consisting of reference measurement procedures and/or reference materials of a higher order. Understanding the traceability chain for the specific methods used in their laboratory, the laboratory medicine specialist can ensure the comparability and quantitative equivalence of laboratory test results. In support of global traceability, the Joint Committee for Traceability in Laboratory Medicine (JCTLM) was formed to promote traceability by bringing together the sciences of metrology, laboratory medicine and laboratory quality management. JCTLM's key role in the field of traceability has been the formation of a searchable database of certified reference materials, reference measurement procedures and reference measurement services. Materials and measurement procedures submitted to JCTLM for consideration are thoroughly reviewed by subject experts for compliance with respective ISO standards. The status of the database as of December 2016 includes: 293 certified reference materials (CRMs), 180 reference measurement procedures covering 80 analytes and 146 reference measurement services covering 39 analytes. These refence measurement procedures, reference materials and reference measurement laboratories provide the necessary tools for the manufacturers of diagnostic testing systems and the end user laboratory medicine specialists to work together to reduce between method variability and provide improved patient care.

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Symposium Wednesday 14 June - TRACEABILITY IN LAB MEDICINE: WHAT IS IT AND WHY IS IT IMPORTANT?

TRACEABILITY, EDUCATION AND PROMOTION: GETTING THE MESSAGE OUT

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Laboratory medicine is an essential clinical specialty providing users with pivotal information for the prevention, diagnosis, treatment and management of health and disease. Therefore, laboratory medicine specialists have a professional responsibility to provide a high quality service that is optimized to the needs of the patient. One increasingly important quality objective is to ensure that patient test results are traceable (equivalent) between different methods, laboratories and healthcare systems over time. At a global level traceability in laboratory medicine (TLM) centres on reducing between method variability, which is an important area of science that is often poorly understood by laboratory medicine specialists.

Achieving traceability is a global multi-stakeholder cooperative activity involving metrologists; international standards organizations; scientific and clinical experts from international professional bodies; healthcare regulators; and the in-vitro diagnostics (IVD) industry that is responsible for the manufacture and sale of diagnostic testing systems. These stakeholders work together in the Joint Committee for Traceability in Laboratory Medicine (JCTLM).

In order to improve the knowledge and understanding of TLM the JCTLM established a working group for traceability, education and promotion (WG-TEP). The WG-TEP has embarked on several work streams, including:

• Definition of terms associated with TLM

• Mini-presentations to explain the scientific concepts associated with TLM

• Clarification of the importance of TLM to the diagnostics industry and to patients

• Preparation of a review stressing the global impact of TLM

• Preparation of material for trainees in laboratory medicine

• Increasing the visibility of TLM in international conferences

These work streams have been brought together in a new website, which contains freely available educational and promotional resources (www.jctlm.org). Participants are invited to visit this website and use the available material to promote TLM in their community.

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Symposium Wednesday 14 June - TRACEABILITY IN LAB MEDICINE: WHAT IS IT AND WHY IS IT IMPORTANT?

WHY TRACEABILITY IN LABORATORY MEDICINE IS IMPORTANT FOR PATIENTS

G. Jones [1]
[1]*SydPath, St Vincent's Hospital, Sydney*

Our final goal in medicine is to serve patients by improving their health. In laboratory medicine we perform this task by providing results and derived information and advice which assist with medical decision making. In order to optimise this purpose we need to consider how laboratory results are used.

A major use for laboratory results is the monitoring of a patient over time. A patient may reasonably expect that the results from different laboratories are comparable so that they may monitor their health wherever they travel within their city, country or the world. Indeed many patients (rightly) envisage a database of their results that can be accessed by their doctor, or themselves, from anywhere at any time.

Another use is to compare results with reference intervals. If a doctor (or a patient) receives reports from more than one laboratory, as well as the results, the reference intervals will be compared. If they are different the interpretation may differ. To avoid this, the methods used to set reference intervals and those used in routine laboratories must produce comparable results.

Patients also expect that results can be interpreted using the best evidence. This is done by comparing results with clinical guidelines and decision points derived from research papers. Again this is not valid unless the results are comparable.

The information we use in our laboratories, and also the movements of our patients, are global in nature. Our patients want the same result, no matter where or when. The tool to meet this need for comparability is the correct traceability of results. This implies globally agreed reference materials and methods and accurate transfer of values to routine laboratories to provide the comparability that patients need and want.

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Debate Wednesday 14 June - DIRECT TO CONSUMER TESTING

DIRECT TO CONSUMER LABORATORY TESTING: PROTECTING PATIENTS FROM DATA THAT HARMS

D. Holmes1
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The world has entered an era where data is generated and stored at a rate unimaginable in the early 1990s. This has led to a widespread perception that more data – irrespective of the source – is valuable, interpretable and actionable. In application to healthcare, consumers have become enthusiastic participants in the so-called "Quantified Self" movement wherein they employ technology to monitor their activity, caloric expenditure, sleep and other quantifiable parameters. The consumer may perceive laboratory testing as a natural extension of this trend without realizing the complexity of lab testing, the hazards of its indiscriminate use and their own vulnerability to financial predation from unscrupulous or unskilled laboratory entrepreneurs. Based on the medical principle of primum non nocere, in this debate I will present the position that lab testing is a medical service to which patients should not have unfettered direct access – both for their own benefit and that of society.

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Meet the expert Wednesday 14 June - EXISTING AND EMERGING TECHNOLOGIES IN POCT

EXISTING AND EMERGING TECHNOLOGIES IN POCT: THE LABORATORY TESTS FROM THE CENTRAL LABORATORY TO CLINIC TO FAMILY PRACTITIONER TO PATIENT

R. Tirimacco[1]
[1]*iCCnet, Country Health South Australia*

The history of laboratory medicine can be said to have come full circle. Originally pathology samples such as microscopy of freshly voided urine were tested by the treating physician adjacent to the patient. In the latter half of the 20th century, pathology moved to large highly automated centralised pathology laboratories. Today with advanced technologies in Point of Care Testing (PoCT) it is possible to perform sophisticated sample analysis for a wide array of analytes while consulting with the patient.

While PoCT in emergency rooms and critical care areas accounts for the majority of tests performed, PoCT in physician's office is increasing to encourage more patients to be assessed in primary care rather than the more expensive secondary and tertiary hospitals. In this era of ageing populations and increasing chronic disease burden, healthcare delivery changes are focusing on delivering less costly care closer to the patient's home and wherever possible keeping patients out of hospital. PoCT has been shown to improve patient care, particularly in rural and remote areas where pathology laboratories are limited.

Provided the PoCT is part of a quality framework, it can safely transition management of some patients from hospital environment to an out-of-hospital strategy which may include the patient's home. PoCT complements Telehealth initiatives with results downloaded to an electronic health record accessible to all involved in patient care. Home monitoring of clinical parameters for chronic disease such as diabetes, heart failure and chronic obstructive pulmonary disease have been shown to improve patient outcomes.

PoCT has the potential to help reform healthcare bringing pathology testing closer to the patient but it is important that implementation is within a quality framework to ensure positive patient outcomes.

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Symposium Wednesday 14 June – REFERENCE INTERVALS IN CLINICAL CHEMISTRY

GLOBAL INITIATIVES IN PEDIATRIC REFERENCE INTERVALS: THE CALIPER AND CHMS INITIATIVES

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Clinical laboratory reference intervals provide valuable information to medical practitioners in their interpretation of quantitative laboratory test results, and therefore are critical in the assessment of patient health and in clinical decision-making. The reference interval serves as a health-associated benchmark with which to compare an individual test result. Unfortunately, critical gaps currently exist in accurate and up-to-date pediatric reference intervals for accurate interpretation of laboratory tests performed in children and adolescents. These critical gaps in the available laboratory reference intervals have the clear potential of contributing to erroneous diagnosis or misdiagnosis of many diseases. To address these important gaps, several initiatives have begun internationally by a number of bodies including the KiGGS initiative in Germany, the Aussie Normals in Australia, the AACC-National Children Study in USA, the NORICHILD Initiative in Scandinavia, and the CALIPER study in Canada.

The CALIPER project has begun to substantially close critical gaps that exist in pediatric reference values. A comprehensive database of age and gender specific pediatric reference intervals for a larger number of assays has been developed based on a large and diverse healthy children cohort. Substudies conducted using CALIPER samples have helped to elucidate the methods required to transfer reference intervals between different laboratory testing systems. Data from all phases of the project are currently available through the CALIPER website (www.caliperdatabase.ca), which receives a large number of unique hits per month by physicians and laboratory professionals downloading the information. In order to improve access to CALIPER data and ensure effective knowledge translation, the team has recently developed a smartphone application for Apple and Android software to allow for rapid access to reference intervals by pediatric healthcare centres globally.

In the current presentation, I will review the recent worldwide initiatives in pediatric reference intervals, and discuss the concept and feasibility of common reference intervals and biological variability in children. I will also discuss the recently published CALIPER reference interval database. The CALIPER database is based on a multiethnic population examining the influence of ethnicity on laboratory reference intervals. Thus the database has proved to be of global benefit and is being adopted by hospital laboratories worldwide.

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Symposium Wednesday 14 June – REFERENCE INTERVALS IN CLINICAL CHEMISTRY

HARMONISATION OF ADULT REFERENCE INTERVALS IN AUSTRALASIA: AN EVIDENCE-BASED APPROACH

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Harmonisation of reference intervals (RIs) refers to use of the same or common RI across different platforms and/or assays for a specified analyte. It occurs optimally where there is sound calibration traceability and evidence from a between-method comparison shows that bias would not prevent use of a common RI.

An evidence-based harmonisation process requires a checklist approach to assess: 1) common laboratory usage and assay calibration traceability; 2) method differences (bias study); 3) evidence for selection of a common RI by searching the literature, lab surveys, local RI studies, and manufacturers' product information, data mining, and determining an acceptable bias goal; and 4) clinical implications of the RI (flagging rates). Validation of RIs by local laboratories can be by a simple validation using 20 normal subjects, or mining your laboratory's existing data. Surveillance of uptake is through the Royal College of Pathologists of Australasia Quality Assurance Programs (RCPAQAP).

Harmonisation workshops are held annually in Australia to discuss, select and agree upon common chemistry RIs. Harmonised RIs have been selected so far for 17 analytes in adults, nine analytes in children and four are proposed for pregnancy. Intervals for the Aussie Normals formal RI study are in general similar to those for the selected common RIs study but somewhat tighter as they are determined for one platform only. Surveillance by the RCPAQAP indicates a constantly increasing implementation of the common RIs within Australasia.

Harmonisation of RIs is a continuing project in Australia and New Zealand that is being led through the profession, namely the Australasian Association of Clinical Biochemists and RCPA. Harmonisation aims to create uniform interpretation of results and prevent misdiagnosis caused by a greater variation in RI than in the measurement result.

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Wednesday 14 June - ANTIBODIES AND MICROARRAYS FOR THE ANALYSIS OF BIOMARKERS

ALLERGY DIAGNOSIS BY MICROARRAY CHIP

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Allergen extracts are routinely applied for diagnostic and therapeutic purposes. These extracts are difficult to standardize regarding their allergen content as several allergens might be under-represented due to degradation, other non-allergenic components are present and there might be even contamination with allergens from other sources. Due to limitations of allergens extracts, molecular allergy diagnosis has been developed as an alternative to investigate specific IgE binding to purified molecules (natural as well as recombinant). Starting with the cloning of the first allergens in 1988, more than 2500 allergenic molecules have been identified so far. This huge number of allergens represents also one of the pitfalls of molecule-based allergy diagnosis. Thus, to profile patients´ IgE reactivities with such large number of allergens, multiplex (microarray) formats has become indispensable. The performance of allergen microarray chips to replace conventional extract-based diagnosis in allergy has been evaluated in several studies. The advantages and limitations of the technology will be discussed.

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Wednesday 14 June - ANTIBODIES AND MICROARRAYS FOR THE ANALYSIS OF BIOMARKERS

COMPLEMENT ANALYSIS: CLINICAL RELEVANCE, STANDARDIZATION AND QUALITY CONTROL

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Clinical and experimental evidence underlines the prominent role of complement in the pathogenesis of numerous inflammatory diseases including immune complex and autoimmune disorders. In recent years, complement analysis of body fluids and biopsies has gone far beyond C3 and C4, not only significantly enhancing our current understanding of the disease process, but also allowing for a more precise differential diagnosis and critical monitoring of complement-targeted therapy.

Analysis of functional activity (e.g. for the classical, alternative, or lectin pathways) and of individual complement proteins varies widely between laboratories because, except for a few proteins such as C3 and C4, there is a lack of well-characterized standard preparations and calibrated assays. In addition, there is a need for the standardization of the measurement of complement activation products, such as C3a ad sC5b-9, that are indispensable to determine whether clinically relevant complement activation has occurred in vivo. Finally, autoantibodies to complement proteins (e.g. anti-C1q), C3 and C4 convertases (C3 and C4 nephritic factor) or autoantibodies to regulatory proteins (e.g. anti-C1inhibitor, anti-factor H) are important in defining autoimmune processes and diseases based on complement dysregulation. To improve the quality of complement laboratory analysis a standardization committee (ICS, IUIS) has been formed to not only organise external quality assessment rounds but also to provide guidelines for modern complement analysis and standards for the development of international testing programs.

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Wednesday 14 June - ANTIBODIES AND MICROARRAYS FOR THE ANALYSIS OF BIOMARKERS

MONOCLONAL ANTIBODIES FOR STUDYING LEUKOCYTE CELL-SURFACE MOLECULES

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CD molecules are cell surface molecules expressed on leukocytes and other cells of the immune system. CD nomenclature provides a unified designation system for mAbs, as well as for the cell surface molecules that they recognize. Human Leukocyte Differentiation Antigens (HLDA) Workshops have led to the characterization and formal designation of more than 400 molecules. CD molecules are routinely used as cell markers, allowing the identification and isolation of leukocyte populations and subsets. More recently, they have been recognized as invaluable tools for the treatment of cancer and autoimmune diseases. Bioinformatics studies indicate that only a fraction of the cell surface molecules, expressed by the cells of the immune system, have been characterized. Direct protein profiling, which reflects the actual levels of protein expression, is limited by the availability of high-quality mAbs against these molecules In recent years, a massive number of mAbs have been produced by academic groups and companies. However, a large number of these Abs remain poorly validated. Thus, the main goal of the HLDA Workshops is to continue with the characterization of cell surface molecules and the validation of mAbs against these molecules. Moreover, there are extensive gaps in our knowledge of CD molecule expression patterns, mainly because of the heterogeneity of the expression studies and the significant changes in flow cytometry technology over the last 30 years. We have recently launched a new project called CDMaps, whose objective is to accurately determine the expression patterns of the established CD molecules markers on all major blood and lymphoid tissue leukocyte subsets, using state-of-the-art multicolor flow cytometry, and to generate an online database of their expression profiles. This database will serve as a useful platform to increase our understanding of leukocyte biology and pathology as well as facilitate the identification of new disease biomarkers and therapeutic targets.

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Symposium Wednesday 14 June – INFECTION, ANTIMICROBIAL RESISTENCE AND MIGRATION

ANTIMICROBIAL RESISTANCE EXCHANGE BETWEEN HOSPITALS AND THE COMMUNITY –ROLE OF THE DIAGNOSTIC LAB

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Antibiotic Resistance is mainly advertized to be a problem mostly in hospitals, and antibiotic resistant bacteria are considered to be mainly isolated from patients hospitalized in ICUs.

However during the last years it has been increasingly recognized the importance of the general environment, including outpatients, rehabilitation centers, as well as the food chain and the urban sewer systems, as sources as well as vehicles for the development and spread of resistant bacteria.

Vancomicin resistant Enterococcus in Europe, MRSA in the Nederlands and elsewhere, the CTX-M ESBLs, in many parts of the world, the NDM-1 Carbapenemase in the Indian subcontinent, and lately the spread of the mcr-1 from the animal husbandry in China are examples of the spread of new resistance determinant through the food chain to humans.

Surveillance of the prevailing resistant mechanisms and the early identification of new genes as well as the understanding of the spread of high endemic bacterial clones harboring resistant mechanisms should be an integral part of any national and international Surveillance system.

Moreover the “one health approach”, the close communication among the (human) health system the veterinary system and the environment experts is also a prerequisite.

Above all the (human and veterinary) clinical laboratory in close collaboration with the reference centers and laboratories being the first to early recognize new resistance mechanisms, through the early recognition of changes in the local epidemiology as well as of discrepancies in the antibiogramme, must have the knowhow as well as the alertness to fulfill this important public health task.

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Debate Thursday 15 June - ANTIDOPING TESTING

ANTIDOPING TESTING: ARE WE THE DOPES?

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The clinical laboratory methods used to care for patients are often used in non-patient care settings. While using forensic testing to assess legal or criminal liability is generally accepted in our society, whether or not it makes sense for the clinical laboratory to assess fairness in sports is less obvious. Beyond the philosophical conundrum of how to define and enforce fairness, though, the logical, methodologic and practical issues with applying clinical laboratory approaches to athletic events are important to consider, yet few members of the public, or even athletes themselves, probably understand these problems. The main issues at stake in the argument over antidoping testing are as follows: thresholds for "positive" findings are often set as highly specific so as to avoid false declarations of guilt, but the concomitant decrement in sensitivity allows cheaters to evade detection; athletes and athletic federations can reap considerable, and sometimes astronomical, secondary gains from subverting the testing process or making sure that detection rates are low; Bayesian statistics necessitate that testing will be futile in athlete populations with high pre-test probabilities of malfeasance; antidoping testing infrastructures are corruptible, with recent clear evidence of state-sponsored tampering; and finally, there is substantial evidence that doping continues, and maybe even increases in prevalence, despite all efforts to fight it. In the face of these obstacles, might it be time for the clinical laboratory community to question its role in the quest for clean competitive sports? Completely abandoning antidoping efforts would undoubtedly send a message to some that society has given up on sports, and that cheating is now allowed, but continuing the status quo in our antidoping efforts and lending a veneer of credibility to what is an otherwise quixotic effort only stands to sully the reputation of our entire profession.

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Symposium Thursday 15 June - TOPICS OF LABORATORY MEDICINE IN BALKAN REGION

BIOMOLECULAR LABORATORY MARKERS IN CANCER MANAGEMENT

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The laboratory analysis is a compulsory supplement to clinical evaluation in making decisions upon diagnosis and treatment of cancer, one of the leading causes of death worldwide. The traditional biochemical laboratory protocols employed in diagnosis, prognosis and monitoring of malignant diseases include testing of soluble macromolecules as tumor markers and certain common parameters corresponding to the specific type of malignancy, but their limited reliability urges the necessity of identifying new biomarkers with higher specificity, sensitivity and predictability. Biomolecular/genetic testing is an emerging field within the scope of laboratory analysis with high clinical potential based on the assumption that revealing the genetic profile unique to each individual cancer may help predict the prognosis and select an appropriate treatment to target the changes in the specific tumor.

This work reviews the currently available genomic laboratory tests and highlights their clinical and scientific relevance. Implication of aberrant transcripts BCR-ABL and PML-RARα for the management of leukemias, detection of genetic and epigenetic aberrations associated with familial cancer syndromes (MMR gene defects in Lynch Syndrome), pharmacogenetic assays for HER2, EGFR, ALK, KRAS, BRAF, UGT1A1 testing for selection of appropriate most efficient and least toxic treatment of particular cancer types will be addressed, along with novel, recently identified markers with anticipated clinical impact.

The rapid development of high throughput technologies shifting singleplex towards multiplex testing, such as the next generation sequencing paired with bioinformatics which enable fast and affordable sequencing of the entire genome of an individual, will inevitably empower accelerated establishment of new biomolecular markers associated with the process of cancer initiation and progression. A comparative overview of the contemporary methodologies will be presented in the lecture. Multidisciplinary efforts should be made to implement the benefits from the technological advancement in the scientific process of new biomarker identification and translation of the research results into clinical practice, in order to provide best treatment for cancer patients in accordance with the principles of the precision medicine.

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Symposium Thursday 15 June - TOPICS OF LABORATORY MEDICINE IN BALKAN REGION

HOW TO ACHIEVE HARMONIZATION OF PREANALYTICAL PHASE?

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Laboratory diagnostics develop through different phases whichstart from test ordering (pre-preanalytical phase), collection of diagnostic specimens (preanalytical phase), sample analysis (analytical phase), results reporting (postanalytical phase) and interpretation (post-postanalytical phase). Pre-analytical errors account for up to 70% of all mistakes made in laboratory diagnostics, mostly because of problems in patient preparation and identification, sample collection and handling, interferences, transportation and storage. The most of the of pre-analytical errors are the result of non-standardized procedures and lack of harmonization. The improvement of this field of laboratory medicine is a great task and challenge for laboratory professionals. European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) through its Working Group Preanalytical Phase (WGPRE) draws attention about the need of harmonizationof the preanalytical phase and has aim to take the lead in catalyzing various international projects in this field. Beside the goal of EFLM WG PRE in promotion of the importance of the of preanalytical phase of laboratory medicine, EFLM WG PRE works on conduction of surveys to assess the current practices related to some preanalytical variables, definition of the best practices, production of recommendations for some critical activities and their implementation. Our major task for the future is to defineas and to implement many standards as possible. The compliance and cooperation is achieved through education of all stakeholders, starting from ourselves, medical doctors, nurses, laboratory technicians and patients. The educationand quality management of preanalytical phase is our responsibility which has been definedin the ISO 15189 standard for medical laboratories. The initials projects of EFLM WG PRE were survey of national guidelines, education and training on phlebotomy in European countries and observational study on compliance of blood sampling procedures with CLSI H3-A6 guidelines with aim to identify the most critical procedures which need urgent modification and improvement. The knowledge that only a minor part of European countries have their own written nationally accepted protocols (guidelines, recommendations) for venous blood sampling and the fact that the existing international guidelines and recommendations are not providing clear and unambiguous guidance for all steps during blood collection led to making EFLM WG-PRE Recommendation for venous blood sampling with the aim to provide a simple, condensed and evidence-based recommendation for the venous blood sampling. EFLM WG PRE also issued the articles with which draws attention to the importance on harmonization of fasting requirements for blood sampling, patient identification and tube labeling. Future activities of EFLM WG-PRE will be specifically address on all other preanalytical issues, such as paediatric and neonatal sampling, appropriate test selection and test profile requesting, sample handling, management of unsuitable specimens, transport and storage, application of quality indicatorsas well as organizing symposia, workshops, webinars or trainings. The EFLM WG-PRE emphasizes the importance of joint action of laboratory professionals, healthcare practitioners, manufacturers and standard writing bodies in supporting the development of universally applicable standards for the preanalytical phase and their worldwide implementation. One of the most important activities of EFLM WG PRE is also a collaboration with national societies as well as with other EFLM WGs: WG for Harmonization of the Total Testing Process, WG-Postanalytical Phase,WG Guidelines, WG-Accreditation and ISO/CEN standards on a rise awarness on significance of the preanalytical phase among all participants in the health care system which will be markedly reduce the potential risk of preanalytical errors and substantially improve patient safety.

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Symposium Thursday 15 June - TOPICS OF LABORATORY MEDICINE IN BALKAN REGION

IN VITRO DIAGNOSTICS AND EVOLVING REGULATORY CHALLENGES IN LABORATORY MEDICINE

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In vitro diagnostics (IVDs) provides objective information as a basis for better decisions in the management of diseases and appropriate and cost-effective treatment. IVDs have a broad scope ranging from sophisticated technologies at the cutting edge of research and development performed in clinical laboratories to simple self-test. About 60% of the information held on the patient record comes from diagnostic tests influencing the majority of clinical decisions, yet IVD sales represent only around 1-2% of the total healthcare expenditure. Clinicians are under increasing pressure for better clinical outcomes, and IVDs contribute positively to the quality of health care through screening, diagnosis, monitoring therapy, assessment of medical interventions and therapy. IVDs are a clear and rational investment in health care. Resource allocation in health care increasingly requires evidence of effectiveness/benefit. IVD testing provides objective evidence that is needed to assess medical treatments. Early and correct diagnosis ensures subsequent treatment relevant and cost-effective. Increased testing cannot significantly increase costs of health care; instead allowing earlier and more correct treatment, it decreases the costs of healthcare expenditure. IVDs provide objective information supporting "Evidence Based Medicine" which constitutes a basis for accurate and fast diagnosis. Accurate and fast diagnosis with the help of IVDs leads to appropriate and more effective therapy, targets drug treatments according to patient's response, causes reduction of morbidity, provides risk prediction and reduction, allows improved compliance, monitors recovery from disease and effects of treatment which allow for reassessment and updating of therapy, shortens length of hospital stay, lowers risk of hospital infection, and improves the quality of life of patients. IVD technology allows self-testing and provides genetic data about disease risk factors. Pharmaceuticals can be selected according to the genetic properties of patients for drug therapy which is the basis of Personalized Medicine.The healthcare authorities and policy makers should consider the expectations of IVD sector in deciding the new regulations and new policies for mutual interests and benefits.

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Symposium Thursday 15 June - TOPICS OF LABORATORY MEDICINE IN BALKAN REGION

MICRORNAS EXPRESSED DURING VIRAL INFECTION: BIOMARKER POTENTIAL AND THERAPEUTIC CONSIDERATIONS

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The discovery of small regulatory non-coding RNAs has been an exciting advance in the field of genomics. MicroRNAs (miRNAs) are short sequences of non-coding RNA which regulate gene expression at the post transcriptional level either through translation repression or mRNA degradation. Viruses utilize this fine tune expression mechanism, either by encoding their own miRNAs or by affecting the host's miRNA expression profile for their own benefit. . The altered expression of miRNA level in an infected human can be identified by the use of advanced diagnostic tools. The use of miRNA as an emerging tool for the identification of the human infectious disease is discussed. Several miRNAs have been reported as a molecular biomarkers in infectious diseases caused by viruses of clinical importance, namely, herpesviruses, polyomaviruses, hepatitis B virus, hepatitis C virus, human papillomavirus, and human immunodeficiency virus. The discovery of circulating miRNA in the blood of infected patients has the potential to become a powerful, non-invasive biomarker in coming future and may have a key role in early diagnosis of infection.

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Symposium Thursday 15 June - TOPICS OF LABORATORY MEDICINE IN BALKAN REGION

PROGNOSTIC VALUE OF LABORATORY MARKERS IN HEMODIALYSIS PATIENTS

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Chronic kidney disease (CKD) is a global health problem with a continuously increasing prevalence. Reduced renal function leads to an increase in various damaging substances as well as a decrease in protective ones. Pathophysiology of this disease leads to a toxic internal environment that predisposes the development of complications such as vascular disease, protein-energy wasting, osteoporosis, premature aging and malaise. Dialysis itself has some adverse side effects. It induces further loss of residual renal function, loss of nutrients and proteins into dialysate, hyper-metabolism, inflammation additionally contributed by central dialysis catheters, depression, loss of appetite etc.

End-stage renal disease (ESRD) is a condition with a unique risk factor profile and prognosis, risk stratification and monitoring of treatment differ to a great extent from the general population. The most studded in this population are prognostic values of different biomarkers by four currently applied criteria: accuracy, simplicity, cost-effectiveness and relevance of the provided information. Laboratory biomarkers relevant to the prognosis of cardiovascular diseases, myocardial injury and dysfunction, chronic kidney disease related mineral and bone disorder, protein energy wasting, inflammation, as well as biomarkers common for various ESRD related disorders have been intensively investigated. The multimarker approach (simultaneous assessment of different parameters which have individual prognostic value by statistical models) is promising field to be evaluated in large cohorts.

All biochemical markers performed by laboratories up to date haven't had sufficient testing to be used as useful additional tool to other prognostic factors or to monitor effects or guide the therapy. One of promising fields is multimarker approach especially in prediction of all-cause and cardiovascular mortality. Nevertheless, laboratory markers are powerful tool in characterization of etiology and pathophysiology of all stages of CKD and have potential to improve risk stratification and provide additional help in therapy guidance.

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Symposium Thursday 15 June - ADVANCES IN MASS SPECTROMETRIC APPLICATIONS

HIGH RESOLUTION MASS SPECTROMETRY ANALYSIS FOR NEW PSYCHOACTIVE SUBSTANCES

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The existence of "designer drugs" has been known for several decades, but is more recently termed new psychoactive substances (NPS). The reason for these new compounds to be manufactured and used is because they are not yet regulated and can be sold open as "legal" alternatives to narcotics. In the last decade the influx of the NPS has become alarming with nearly 2 new detected substances each week in Europe reported from the monitoring centre EMCDDA. This has put a challenge to forensic and clinical toxicology laboratories to adopt methodology to this situation.

The STRIDA project is a collaboration between our clinical drug testing laboratory and the Swedish Poison Information Centre since 2010, and aims to document intoxications from NPS occurring all over the country. The STRIDA project originally used a method for NPS analysis in urine based on simple dilution and LC-MS/MS in SRM mode. In order to more easily include new analytes into the method an alternative approach was introduced which is still using dilution of urine but monitored the analytes using LC-HRMS in XIM mode. The method features are as follows; 6 minutes total analysis time and a C18 reversed phase chromatographic gradient system. The mass spectrometer is set to monitor positive ions in electrospray ionization mode. Mass the range is 100-650 amu and the resolution set to 70.000 at m/z 200. To achieve this, a Thermo Scientific Q Exactive instrument is used.

So far the method has been used for investigating about 3000 intoxication cases and has also been employed as a routine drug testing method with ~25.000 samples being analysed to date. Results from these investigations and the experience of routine use, as well as data for method performance will be presented.

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Symposium Thursday 15 June - ADVANCES IN MASS SPECTROMETRIC APPLICATIONS

LC-MS/MS ANALYSIS OF STEROIDS IN THE CLINICAL LABORATORY

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Liquid chromatography- tandem mass spectrometry (LC-MS/MS) is a powerful tool that is changing the way we analyse steroids in the clinical laboratory. It offers positive compound identification to enable the unequivocal identification of a compound free from interference. LC-MS/MS is already opening up the field of steroid analysis in endocrinology and is providing new applications for individual steroids and panels of steroids in different clinical conditions. LC-MS/MS is now well accepted technology and is increasingly being used to replace problematic immunoassay methods because of greater sensitivity and specificity. Improved sample preparation, modern chromatography methods and sensitive, faster scanning mass spectrometers have all played a role in improving LC-MS/MS. LC-MS/MS is also playing a key role in improving the quality of assays through the development of reference measurement procedures, characterisation of reference materials and multi-site calibration programmes. There is increasing interest in multiplexing steroid assays into panels of diagnostic tests to aid and improve the diagnosis and monitoring of disease. LC-MS/MS is not without problems and issues regarding calibration, internal standards and matrix effects will be discussed.

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Symposium Thursday 15 June - ADVANCES IN MASS SPECTROMETRIC APPLICATIONS

QUALITY ASSURANCE AND STANDARDIZATION IN CLINICAL APPLICATION OF MASS SPECTROMETRY

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Thanks to highly specific analyte detection and potentially complete compensation for matrix variables based on the principle of stable isotope derivative internal standardization, mass spectrometry methods allow the development of diagnostic tests of outstanding analytical quality. However, these features per se do not guarantee reliability of tests. A wide range of factors can introduce analytical errors and inaccuracy due to the extreme complexity of the technologies involved (e.g., in-source transformation of conjugate metabolites, interference by isobaric compounds, use of inappropriate isotopically labelled internal standards, but also identification errors during complex sample preparation procedures). Furthermore, it can be expected that the application patterns of MS methods in diagnostic laboratories will change substantially during the coming years – with presumably less specialized laboratories implementing mass spectrometry. Introduction of fully automated analyzer solutions will potentially require some compromises between convenience of operation, sample throughput and analytical performance. Structured and careful quality and risk management is therefore a crucial challenge to translate the analytical power of mass spectrometry into actionable and reliable results for individual patients' care and to maintain the degree of reliability that is expected from MS methods in clinical pathology. The presentation discusses whether specific quality assurance tools should be applied for MS-based diagnostic tests and whether these tools should differ from those applied for optical- and affinity-based standard tests. Both pre-implementation strategies and surveillance of assays with assessment of metadata in routine testing are addressed.

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Symposium Thursday 15 June - ADVANCES IN MASS SPECTROMETRIC APPLICATIONS

WHEN HIGH-TECH MEETS THE NEEDS OF ROUTINE LABORATORY TESTING

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As predicted, mass spectrometry (MS) continues to play a major and increasing role in laboratory medicine (Wallemacq P, Clin Biochem 49 (2016) 945-6). Most large laboratories have now implemented MS in their routine practice, and clinical applications keep expanding in almost all areas of laboratory medicine (clinical chemistry, therapeutic drug monitoring/toxicology, metabolic diseases/neonatal screening, endocrinology, cardiac markers, microbiology, etc..). Such spectacular success may be explained by the economic pressure laboratories have to face, together with the need for higher efficiency (high throughput, multiplexing…), improved analytical and medical perfomances, as well as by the manufacturers progresses during the last decade. Larger dynamic analytical ranges, better sensitivity and analytical specificity (e.g absence of antibodies interferences, of metabolites cross-reactivity, of hook effect etc…), and the availability of a larger number of applications, commercial kits and deuterated isotopes, are the frequent reported advantages of MS over traditional methods. Scientific associations and manufacturers now promote validation guidelines in the development of MS methods, stressing the importance of a careful validation process, including for instance the ion suppression or matrix effects assessment. One of the most exciting progresses in MS is in relation with proteomics, metabolomics and other « omic » analyses. Other progresses have been observed with the MALDI-TOF in microbiology but also with applications in pathology laboratories to identify proteins or lipids in tissue sections avoiding conventional histology staining. Interest for full automated MS systems has been repeatedly raised in the past. MS manufacturers are now very close to the production of such full automated platforms developed to be integrated in core laboratories with random access, sample handling, and full process with bidirectional interfacing to the laboratory information system (LIS).

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Symposium Thursday 15 June - ETHICAL ISSUES IN LABORATORY MEDICINE

A PRIMER IN BIOMEDICAL ETHICS

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Biomedical ethics relates to moral values and judgments as they apply to medicine. Laboratory medicine, just as other areas of medicine, is obliged to adhere to high ethical standards. Specific issues that challenge laboratory professionals include: confidentiality, screening tests, direct to consumer testing, residual specimen use, add on testing, and research/publication ethics. However, ethical issues have been given limited attention by professionals in laboratory medicine.

This presentation will review the history of biomedical ethics, and describe the core principles of modern biomedical ethics including: autonomy, beneficence (non-maleficence) and justice. In addition, the specific application of biomedical ethics will be applied to laboratory medicine in the pre-analytical, analytical and post-analytical phases.

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Symposium Thursday 15 June - ETHICAL ISSUES IN LABORATORY MEDICINE

ETHICS IN LABORATORY MEDICINE: CLINICAL CASE STUDIES

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Medical ethics, based on the principles of autonomy, beneficence (non-maleficence) and justice, are applicable to the practice of laboratory medicine. In the pre analytical phase ethical concerns may arise from the collection of extra samples above that ordered, correctly following the ordering requisition and sexual harassment during the collection process. In the analytical phase ethical concerns may arise from the finding of an inappropriate result, such as the presence of sperm in urine of young females, and subsequent follow up in these situations. In the post analytical phase the handling of samples once analyzed may give rise to ethical concerns such as the use of residual samples for unrelated testing. In general laboratory operation the vendor/laboratory relationship may cause ethical concerns, such as the provision of lunch/dinner, during the installation/training period of a new analyzer.

This case-based presentation will illustrate real-life situations that have occurred in the speaker's experience. Cases will be presented in the context of the underlying ethical principles along with approaches that management can take to aid in the resolution of the ethical conflicts

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Symposium Thursday 15 June - ETHICAL ISSUES IN LABORATORY MEDICINE

PUBLICATION ETHICS

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Over the past decade, we have been witnessing an increased reporting of misconduct in scientific publishing. Such unethical behavior undermines the credibility of the scientific institution and erodes the general public trust in our community. Editors, authors, and reviewers have the obligation of assuring both the scientific community and the public at large that the conducted research has been evaluated and reported according to the highest ethical standards. The editors are responsible for overseeing the entire evaluation process of the manuscript; the authors are required to conduct their research and report their findings ethically and without committing transgressions such as fraud, plagiarism, and falsification or fabrication of data; and reviewers are expected to provide an impartial, fair, and timely assessment of the manuscript.

This presentation will review the status of scientific publishing and the incident of reporting misconduct as well as the roles of authors, reviewers, and editors in assuring the ethical reporting of scientific findings.

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Symposium Thursday 15 June - EXTERNAL QUALITY ASSURANCE - JUST A NECESSARY EVIL OR A VALUABLE TOOL IN LABORATORY MANAGEMENT

EQA OF POINT-OF-CARE TESTING, IS IT NECESSARY?

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It has been advocated that POC instruments are so easy and so robust that quality control should not be necessary. However, numerous publications have shown that use of POC instruments can jeopardise patient safety because of errors occurring both in the pre-examination, the examination and the post-examination process. An External quality assurance (EQA) program for POC testing should therefore take into account all of these aspects. In principle EQA of POC testing is similar to EQA for larger hospital laboratories, but it is important to underline that the participants are different. The participants are usually health care personnel with little or no knowledge of laboratory medicine. The EQA provider has must therefore be able to convince the participants that participation in EQA schemes is important. The workload connected with the EQA should be reasonable and the feedback reports must be understandable. The EQA organiser should prioritize to offer help and guidance to the participants when needed. It is also important that EQA for POC testing addresses the pre-examination, the examination and the post-examination processes, and that schemes for measurement procedures using interval or ordinal scale are offered. The present paper will address practical aspects of EQA for POC testing.

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EXTERNAL QUALITY CONTROL IN EUROPE: THE BENEFITS FOR LABORATORIES

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External quality assessment (EQA) is an indispensable part of the laboratories total quality management system. EQA is organised by independent EQA providers and their major focus is on participant performance assessment related to accuracy.

Laboratories, and as such also patient care, advance from participating in EQA programmes operating according to the state-of-the-art knowledge on the role of EQA in quality assessment and quality improvement. To provide a forum for co-operation and exchange of knowledge on quality-related matters in laboratory medicine, an European Organisation for External Quality Assurance Providers in Laboratory Medicine (EQALM) was founded in 1996. Currently EQA providers from 29 European countries and 6 countries from outside Europe are member of EQALM.

EQALM is active in scientific and educational activities in different fields such as survey frequency, haematology, haemostasis, microbiology, nomenclature, virtual microscopy, traceability, accreditation, and quality assurance of the total testing process.

In addition, EQALM represent the EQA providers in laboratory medicine at European level vis-à-vis political, professional, scientific and other bodies, including patients' organisations. To this end EQALM promotes activities such as organizing meetings with scientific and practical themes for members and other interested parties, issuing scientific publications, developing EQA projects and representing laboratory medicine EQA activities within other organisations and networks.

Several examples of EQALM activities will be presented specially in relation to the benefit for laboratories in their quality management.

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HOW TO ASSESS MY EQA SAMPLE, POSSIBILITIES AND LIMITATIONS

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External Quality Assessment (EQA) is a tool used by laboratories, regulatory bodies, standardization programs and IVD manufacturers to assess measurement procedure performance. Optimal effectiveness is achieved when the EQA samples are commutable with clinical samples. Commutable means that measured values for an EQA sample and for clinical samples have the same relationship among different measurement procedures. Commutable EQA samples allow a laboratory to verify that its results are traceable to reference systems and/or in agreement with other laboratories measuring the same analyte. Commutable samples also allow surveillance that a measurement procedure meets the calibration traceability and precision goals necessary for results to be fit for their intended purpose in medical decisions. Non-commutable samples are used in EQA programs for reasons such as cost and availability but interpretation of results is limited to assessing agreement with other measurement procedures of the same type and frequently only when from the same IVD manufacturer.

EQA with commutable samples has an important role to support harmonization protocols to achieve equivalent results among different measurement procedures. A harmonization protocol refers to an international consensus approach to assign values to IVD manufacturer's working calibrators such that calibration traceability to the protocol achieves equivalent results when there is no certified reference material or reference measurement procedure available. EQA provides a surveillance tool to determine the need for harmonization and to verify the effectiveness of a harmonization protocol.

Challenges in EQA include preparation and validation that samples are commutable and that replacement batches remain commutable and thus suitable for use. Recommendations on these issues are being developed by the IFCC Working Group on Commutability.

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IFCC Symposium Thursday 15 June - THE LIQUID BIOPSY APPROACH: FOLLOWING THE TUMOR IN PERIPHERAL BLOOD

BLOOD-BASED MONITORING OF MELANOMA EARLY STAGE AND BRAIN METASTASIS PATIENTS IDENTIFIES TUMOR EVOLUTION AND SUBCLONAL DRIVER GENE MUTATIONS

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The aggressiveness of metastatic melanoma combined with the increasing number of new therapies necessitates close monitoring of disease progression to improve treatment decisions. Blood-based biopsies enable frequent tumor profiling in anatomically difficult sites (i.e. melanoma brain metastasis (MBM) and capture of tumor heterogeneity. However, their poor sensitivities in profiling early-stage cancers and infrequent follow-ups have limited its clinical utility. Using a single-molecule next generation sequencing (smNGS) approach to detect clinically-relevant cell-free DNA (cfDNA) mutations (mts) and copy number amplifications (CNA), we strategically evaluated the utility of blood biopsies using melanoma patients with follow-up during disease progression. We assessed 153 blood samples from melanoma patients using our comprehensive 70-gene panel smNGS approach. We detected cfDNA genomic aberrations in pre-operative AJCC stage III melanoma patients with good concordance to matched tumor. cfDNA mts analysis was performed in 98 serial bleeds collected from 12 melanoma patients prior to curative surgery and throughout disease progression (every 2-4 months). cfDNA mts levels correlated with tumor burden ($p = 0.019$). cfDNA mts analysis enabled earlier detection of recurrence with a median lead time of 9.5 mos over the serum LDH (95% CI: 3.5-16.0 mos, $p = 0.01$). Patients with compared to those without CNA in EGFR or MET were significantly associated with a shorter disease-free survival (DFS; 5.3 mos vs 13.5 mos; $p = 0.0032$) and overall survival (OS; 20.7 mos vs 31.0 mos; $p = 0.019$). Most importantly because regional and distant metastasis sites were also serially profiled, our cfDNA mts analysis revealed capture of tumor heterogeneity and subclonal mts that became dominant recurrence. Interestingly, pre-operative blood of MBM patients ($n = 23$) contained detectable cfDNA genomic aberrations in patients using an expanded 70-gene panel. Through utilizing different patients with clinically-relevant follow-up, this study demonstrates applications of melanoma blood biopsies in monitoring detection of recurrence of early-stage disease, tumor progression, and the first to demonstrate capture of tumor evolution and heterogeneity in melanoma blood biopsies. Furthermore, our study being the largest MBM cohort tested to date indicates potential for blood biopsy monitoring in MBM patients.

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IFCC Symposium Thursday 15 June - THE LIQUID BIOPSY APPROACH: FOLLOWING THE TUMOR IN PERIPHERAL BLOOD

CLINICAL SIGNIFICANCE OF CTCS DETECTION AND MOLECULAR CHARACTERIZATION IN BREAST CANCER.

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Breast cancer affects each year thousands of women and it is among the most common cause of morbidity and mortality in the Western Countries. The majority of death are due to metastatic disease established after treatment of primary disease. The improved understanding of breast cancer biology demonstrated that this is a heterogeneous malignancy characterized by specific genomic abnormalities and differences in clinical behavior, response to endocrine therapies and chemotherapy along with specific patterns of recurrence. Metastatic breast cancer (MBC) is usually treated with palliative intent and improvement in symptoms and disease control varies in the individual patients and in different disease subtypes. The detection of circulating tumor cells (CTCs) in the peripheral blood of patients with primary and MBC is associate with strong prognostic significance and higher rate of metastatic spread irrespective of disease subtype suggesting the need for further molecular evaluations. Moreover, the identification of CTCs clusters seemed to provide additional information about the metastatic potential in the individual patient. CTCs molecular analysis revealed subtype specific common mutations such as PI3KCA and ESR1 in luminal subtype along with ER expression, TP53 and EGFR mutations with PDL-1 expression in triple negative breast cancer (TNBC) and HER2 expression, amplification and gene mutations in HER2-subtype and Luminal B disease. Furthermore, CTCs characterization combined with circulating cell-free DNA (ctDNA) provided a more comprehensive understanding of disease heterogeneity and advanced the possibility for performing a longitudinal molecular monitoring of patients undergoing disease subtype specific therapies. CTCs and ctDNA also termed “liquid biopsies” offer real-time complementary molecular information that must be used prospectively to tailor and monitor treatment efficacy in the individual patient. The combination of sensitive blood-based diagnostics with novel targeted therapies is advancing our ability for personalized treatment in breast cancer.

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CTC ANALYSIS: AN OVERVIEW OF CTC ISOLATION, DETECTION AND MOLECULAR CHARACTERIZATION TECHNOLOGIES

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"Liquid biopsy" has a high potential to give detailed information on tumor genome evolution over time, through simple blood draws that can be used for serial monitoring of the patients. This is a strong advantage towards the classic biopsy approach that is not allowing monitoring of primary tumors evolution during time, while sampling of metastatic sites is not always possible for practical reasons. Liquid biopsy has a strong potential to be translated into individualized targeted treatments. The liquid biopsy approach is based on the extraction of molecular information on the primary tumor by analyzing in detail tumor-derived genetic material from: Circulating Tumor Cells (CTC), cell free circulating tumor DNA (ctDNA), circulating miRNAs and exosomes. A variety of analytical systems are continuously been developed for liquid biopsy analysis. Especially molecular assays based on the nucleic acid analysis in CTCs like RT-qPCR, multiplex RT-qPCR, and next generation sequencing technologies are very powerful since they can be automated and high throughput. Quality control and standardization in liquid biopsy analysis is very important for the incorporation of this breakthrough concept into prospective clinical trials testing its clinical utility. Especially CTC molecular characterization at the single cell level holds considerable promise for the identification of therapeutic targets and resistance mechanisms in CTCs as well as for the stratification of patients and real-time monitoring of systemic therapies. This lecture will be mainly focused on the recent advances in the field and its clinical applications in many types of solid cancer.

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LIQUID BIOPSY: BLOOD-BASED DETECTION AND CHARACTERIZATION OF CIRCULATING TUMOR CELLS

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Sensitive methods have been developed to capture circulating tumor cells (CTCs) in the peripheral blood at the single cell level in cancer patients (Alix-Panabieres & Pantel, Nature Rev Cancer 2014). The analysis of CTCs may provide clinically relevant information as "liquid biopsy" (Alix-Panabieres & Pantel, Cancer Discovery, 2016). At present, most CTC assays rely on epithelial markers and miss CTCs undergoing an epithelial-mesenchymal transition (EMT). New markers that are not downregulated during EMT (e.g., plastin-3) might overcome this important limitation. CTC enumeration and characterization with certified systems provides reliable information on prognosis and may serve as liquid biopsy to identify therapeutic targets or mechanisms of resistance on metastatic cells such as mutations in KRAS or expression of the androgen receptor variant 7. Metastatic cells might have unique characteristics that can differ from the bulk of cancer cells in the primary tumor currently used for stratification of patients to systemic therapy. Moreover, monitoring of CTCs before, during and after systemic therapy (e.g., chemotherapy, hormonal therapy, antibody therapy) might provide unique information for the future clinical management of the individual cancer patient and might serve as surrogate marker for response to therapy. In the context of recent success in antibody-mediated blockade of immune checkpoint control molecules, expression of the PD-L1 on CTCs might be of interest as potential predictive marker. Functional characterization using specialized in vitro and in vivo test systems has started, which might provide novel insights into the biology of CTCs and serve as models for drug testing. In conclusion, the molecular and functional analysis of CTCs can be used as companion diagnostics to improve the stratification of therapies and to obtain insights into therapy-induced selection of cancer cells. Validation of liquid biopsy assays is essential and is currently being performed by the EU/IMI consortium CANCER-ID (www.cancer-id.eu).

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Thursday 15 June - A MEDITERRANEAN-LEADING PLATFORM FOR COLLABORATION AND INNOVATION IN LAB MEDICINE

THE FIFBCML: A MEDITERRANEAN-LEADING PLATFORM FOR COLLABORATION AND INNOVATION IN LAB MEDICINE

B. Gouget [1], M. Touimi Ben Jelloun [1]
[1]*on behalf of the FIFBCML-EB*

The session will provide a substantive overview of keys areas in the scientific and managerial aspects of Lab medicine in the French speaking countries and will offer opinions on the impact of new technologies, economic factors and social development that may play a role in shaping the future of lab medicine.

The topics covered by the FIFBCML representatives (Algeria, France, Lebanon Morocco, Tunisia) will range from comparative typologies of medical biology systems to the future of lab medicine and its sub specialities , from the changing role of the specialist in laboratory medicine to the impact of genomic, precision medicine and information technologies, from consolidation in private labs and/or in hospital and University practices to the shift of POCT, from quality management reforms with the implementation of the accreditation to the harmonization of the training in Euro-Mediterranean countries.