# *SCIENTIFIC DIVISION*

**66th MEETING**
**Conference Call: December 7, 2020 10th (3pm – 6pm CET)**

**MINUTES *(FINAL)***

| **Members:** | **Abbr.** | **Term and Time of Office** |
|---|---|---|
| Philippe GILLERY (FR) (Chair) | PG | 2nd 2020 01 - 2022 12 |
| Christa COBBAERT (NL) (Vice-Chair) | CC | 2nd 2020 01 - 2022 12 |
| Joseph PASSARELLI (US) (Secretary) | JP | 2nd 2018 01 - 2020 12 |
| Barnali Das (IN) | BD | 1st 2018 06 - 2020 12 |
| Konstantinos MAKRIS (GR) | KM | 2nd 2020 01 - 2022 12 |
| Mario PLEBANI (IT) | MP | 2nd 2020 01 - 2022 12 |
| Michael ROTTMANN (DE) (Corporate Rep.) | MR | 1st 2020 03 - 2022 12 |
| Karen PHINNEY (NIST Representative) | KP | Consultant |
| Heinz SCHIMMEL (JRC Observer) | HS | Observer |
| Ian YOUNG (UK) (Chair JCTLM) | IY | Consultant |
| Chris BURNS (UK) (NIBSC Representative) | CB | Consultant |
| Greg MILLER (US) (ICHCLR Representative) | GM | Observer |
| Yang Zhen (CN) (NIFDC Representative) | YZ | Observer |

**EXECUTIVE SUMMARY - SCIENTIFIC DIVISION 66th MEETING**
**Conference Call – December 7th (3pm - 6pm CET)**
**Present:** Philippe Gillery (Chair), Christa Cobbaert (Vice-Chair), Joe Passarelli (Secretary), Barnali Das, Konstantinos Makris, Mario Plebani (Members), Michael Rottmann (Corporate Representative), Karen Phinney (NIST Representative), Ian Young (SD Consultant/Chair JCTLM), and Greg Miller (ICHCLR Representative) were in attendance. Apologies received from Chris Burns (NIBSC Representative), and Heinz Schimmel (JRC Observer). No correspondence was received from Yang Zhen (NIFDC Representative).

**5.4 EUROPEAN FEDERATION of CLINICAL CHEMISTRY and LABORATORY MEDICINE (EFLM):**
The EFLM Science Committee and SD leadership once again agreed there should be close liaison and communication between the two groups. Professor Eric Kilpatrick is the EFLM SC chair. His third term is scheduled to conclude at the end of 2021. The Science Committee is responsible for scientific matters within EFLM and projects which further the scientific development of EFLM (except those specifically related to quality management, which are the responsibility of the Quality Management Committee). Activities of the Committee particularly focus on promotion of research that translates the scientific results of

clinical chemistry and laboratory medicine to clinical applications and improves patient outcomes through the appropriate use and interpretation of laboratory data in clinical practice. Within the EFLM SC, there are working groups on cardiac biomarkers, biological variation, test evaluation, personalized laboratory medicine and a number of others but the consensus of the SD is that these activities do not overlap with ours. The Working Group on Test Evaluation is chaired by CC who does not believe there is much overlap as the focus is more on how to generate clinical evidence rather than on analytical standardization.
PG has been in contact with the chair of the EFLM SC. Approaches to avoid overlap and work collaboratively continue to be discussed and explored.
A new Task Force that has been established to address the IVDR that goes into effect in May 2022: "EFLM Task Force on European Regulatory Affairs (TF-ERA)". Professors Michael Neumaier and Christa Cobbaert are interim co-chairs. TF-ERA is a multi-national Working Group interconnecting with diagnostic and clinical societies to assist in smooth transition of laboratory tests during the implementation phase of the EU IVDR.

### 6.1 WORLD HEALTH ORGANIZATION (WHO):

The WHO meeting occurs each autumn. PG attends and participates as the liaison from the SD. CB is a full member of the WHO Expert Committee on Biological Standardization (ECBS) and provides a complete update from the WHO to the SD. There was a call for public comment with respect to the WHO Model List of in Vitro Diagnostics - https://www.who.int/medical_devices/diagnostics/selection_in-vitro/selection_in-vitro-meetings/sage-ivd-2nd-meeting/en/.
The WHO is almost completely focused on COVID-19 for the time being until the pandemic situation subsides.

### 6.2 CLINICAL AND LABORATORY STANDARDS INSTITUTE (CLSI):

The link to these projects is under CPD: http://www.ifcc.org/ifcc-communications-publications-division-(cpd)/ifcc-publications/clsi-ifcc-joint-projects/.
The proposal to update the CLSI EP28 guidance document on reference ranges to reflect recent advances from IFCC C-RIDL and other content was not accepted due to the very large estimated size of the revised document. Instead, CLSI recently issued a call for nominations for the following document revision committees to essentially replace EP28:

- EP44—*Establishing Reference Intervals,* 4th Ed.
- EP45—*Verifying Reference Intervals in a Medical Laboratory,* 4th Ed.

The chair for C-RIDL was immediately informed of this new development.
The following new publications are planned for release through 2020:

- Revision to Collection of Capillary Blood Specimens (GP42)
- Collection, Transport, Preparation, and Storage of Specimens for Molecular Methods (MM13)
- Revision to the Reagent Stability Guidance Document (EP25)
- Revision to Point-of-Care Coagulation Testing and Anticoagulation Monitoring (POCT14)
- Revision to the Linearity Assessment Guidance Document (EP06)
- Revision to Collection, Transport, and Processing of Blood Specimens for Testing Plasma-Based Coagulation Assays (H21)
- Revision to the Qualitative Assay Performance Evaluation Guidance Document (EP12)

### 6.22.1 Joint Committee on Traceability in Laboratory Medicine (JCTLM):

1) The biennial workshop of the JCTLM was held at the BIPM in Sèvres, Paris, on 2-3 December 2019. The workshop reviewed recent developments in traceability in laboratory

medicine and the impact that they are having on reducing between-method variability in the interests of better patient outcomes. For the first time the workshop included parallel sessions in order to accommodate the expanding activity in this important area of laboratory medicine. The proceedings can be accessed at www.bipm.org/en/committees/jc/jctlm/workshop-2019.html. Work is ongoing on a joint workshop with ICHCLR to be held (hopefully) in Paris in December 2021.
2) The International Council for Standardization in Haematology (ICSH) joined JCTLM as a new Executive Committee Member, effective December 2019. The aim of this was to increase awareness and strengthen the activities of JCTLM in haematology and coagulation. JCTLM would be open to other international organizations in complementary areas becoming Executive Members, and a process will be developed around the governance and facilitation of this.
3)The JCTLM review process conducted in 2019 resulted in 30 new entries in the JCTLM Database for available higher-order certified reference materials, as well as one new published reference measurement method, and ten new measurement services delivered by reference laboratories.
4) Professor Elvar Theodorssen has been appointed as chair of the WG for Traceability, Education and Promotion, taking over from Professor Graham Beastall.
5) Professor Mauro Panteghini will chair a new JCTLM Task Force on Reference Measurement System Implementation (TF-RMSI). The purpose of this group is to identify and describe available reference measurement systems (RMSs) and traceability chains in their entirety, based on the information present in JCTLM database; to illustrate the evolution of measurement uncertainty (MU) through the entire metrological traceability chains; by using appropriately derived analytical performance specifications (APS), to judge whether RMS components are fit for purpose; to identify those measurands for which further advancements to existing RMSs are needed or some components of the RMS are lacking**.**

### 6.22.2 Joint Committee for Guide in Metrology (JCGM):

**Report from Working Group 1 (GUM - Expression of Uncertainty in Measurement)**
Dr. Martin J.T. Milton is the Chairman of the JCGM. Dr. Graham White is acting as IFCC representative.
Correspondence was received requesting approval and / or comments to the Final Draft of GUM-6: (formerly numbered JCGM 103): Guide to the expression of uncertainty in measurement - Developing and using measurement models. Previously the SD provided comments to an earlier version and these responses can be found along with the Final Draft of GUM-6 at the following location on the JCGM webpages: https://www.bipm.org/cc/AllowedDocuments.jsp?cc=JCGM. The deadline for submission is November 10, 2020.
Comments received from all Member Organizations will be discussed at the next meeting of the JCGM Plenary which is planned for 7th December 2020 (visioconference) with the hope to find a consensus as to whether this Final Draft of GUM-6 can be published.
In principal, the SD approves the publication of the Final Draft of GUM-6.

**Report from Working Group 2 (VIM)**
Professor Gunnar Nordin is acting as IFCC representative. The fourth edition of the International Vocabulary of Metrology (VIM4) Working Draft (WD), as approved by JCGM/WG2 at the end of the June 2020 meeting, and then updated according to the

input from the Focus Groups that were established afterwards. Also comments received from WG2 members after the June 2020 meeting were taken into account. For ease of comparison, the changes with respect to the VIM3 are highlighted with yellow background for easier comparison;

- the bibliographical references are highlighted with red text;
- for avoiding ambiguities, the references to the identifiers of entries of previous VIM editions have been removed.

Some things are still to do, and in particular:

- French text;
- introductory texts;
- possible revision of the organization in chapters;
- references to VIM3 (and previous editions?) entries.

### 6.22.3 BUREAU INTERNATIONAL DES POIDS ET MESURES (BIPM) Consultative Committees

6.22.3.1 Consultative Committee for Amount of Substance: Metrology in Chemistry and Biology (CCQM):
The CCQM covers measurement standards and standardization in all branches of chemical and biological measurement science, and provides a forum where NMIs can be addressed collectively. A number of the CCQM WGs have programs in which a substantial portion of their activities is related to Laboratory Medicine, and notably for the Organic Analysis (OAWG) and Protein Analysis (PAWG) working groups. The OAWG has completed a comparison of metrology institutes with Vitamin D (D3 and D2) reference measurement procedure capabilities; this covered 7 institutes and will be published soon. The PAWG has mapped out a model system to look at the different types of pure peptide/protein with respect to different challenges for purity assessment, with the aim of running comparisons to demonstrate NMI measurement capabilities for values assigning primary reference materials for peptides/small proteins.
6.22.3.2 CC for Units (CCU): The IFCC is also a Member of the BIPM's CCU. At the last meeting in November, the proposals for definitions of 'unit', 'quantity' and 'quantity value' proposed by members of the WG-CMT, were reviewed and discussed. It was noted that there were many commonalities between these approaches and hope was to find consensus during the meeting. There was consensus that shorter definitions would lead to fewer issues with interpretation and that there was a need for clarification between addressing the abstract and the specific – since one definition may not be appropriate for both considerations. There was also an extensive discussion about ordinal quantities and how they should be considered in the definitions. Following the discussions, the WG-CMT reached consensus on the following definitions, the guiding principle being to keep the definitions as simple and general as possible:
**Quantity**: property of a phenomenon, body or substance that can be compared to others of the same kind.
**Unit:** quantity adopted by convention as a reference.
**Quantity value**: expression of a quantity in terms of a reference.
**NOTE:** A quantity value is typically the product of a number and a unit or a position on an ordinal scale.
These will be submitted to JCGM WG2 as soon as possible.

A Memo of Understanding was recently signed between the BIPM and IFCC to further enhance the cooperation via:
• Consultation on development of reference measurement systems
• Reciprocal representation (IFCC SD and CCQM, further possible)

• Exchange of information

### 6.31 JOINT RESEARCH CENTER (JRC)

The status of JRC reference materials activities are mostly covered under the respective Cs and WGs. The JRC continues to collaborate with numerous SD Cs/WGs on a variety of projects. These include:

Enzyme CRMs:

1. CRM for alpha-amylase: ERM-AD456/IFCC:
   This project was finalized and the CRM was released on 2 October 2019.

CRMs for autoimmune disorders:

1. CRM for IgG anti-B2GP (antiphospholipid syndrome (APS)): ERM-DA477/IFCC
2. CRM for IgG anti-GBM (vasculitis): ERM-DA484/IFCC
3. CRM for IgG and IgA anti tissue transglutaminase (Celiac disease)

CRMs for CSF proteins:

1. CRM for Aβ1-42 in CSF: ERM-DA480/IFCC, ERM-DA481/IFCC, ERM-DA482/IFCC
   The CRMs were released at the end of 2017. Re-calibration of commercial assays using the CRMs has been completed. A round-robin study is currently organized to see the effect of re-calibration on the measurement results for patient samples.
2. CRM for Aβ1-40 in CSF: ERM-DA480/IFCC, ERM-DA481/IFCC, ERM-DA482/IFCC
   Certification project on the existing CRMs: ERM-DA480/IFCC, ERM-DA481/IFCC and ERM-DA482/IFCC.
3. CRM for Tau project: Development of a reference system for Tau
4. Neurofilament light (Nfl): Project for the standardization of Nfl in blood (possibly in CSF).

CRM for Thalassemia:

1. CRM for HbA2: ERM-DA485/IFCC and ERM-DA486/IFCC
   The calibrant materials have been processed and they will be value-assigned in the coming months. The processing of the CRMs is planned for autumn 2019.

CRM for apolipoproteins:

1. CRM for Apoliprotein(a) apo(a): and the apolipoproteins A-I, B100, C-I, C-II, C-III and E. All is under development.

### 6.33 NATIONAL INSTITUTE OF BIOLOGICAL STANDARDS AND CONTROL (NIBSC)

**Introduction:**

NIBSC has been heavily involved in the UK and global response to Covid19 since February/March 2020. Many work programmes are on hold until further notice, but medicines-testing activities and standardization activity continues. WHO have deviated from their usual process of holding one ECBS meeting per year and have held two additional extraordinary ECBS meetings in 2020. Before the usual meeting in October, committee members met in August and agreed the establishment of a number of standards and reference materials as well as discussing important guidelines related to Covid19. Furthermore, ECBS will also meet on December 9th and 10th.

Outputs that may be relevant to the work of the IFCC SD:

**International Standards established:**

- 1st WHO Reference Reagent for Anti-Malaria (*Plasmodium vivax*) human plasma:
- 2nd WHO International Standard Insulin-like growth factor-1:
- 6th WHO International Standard for human chorionic gonadotrophin (hCG):
- 1st WHO reference reagent for anti-HPA-15b IgG antibodies:
- 1st WHO IS for Herpes Simplex Virus (HSV) Nucleic Acid Amplification Techniques (NAT):

- 1st WHO IS for West Nile Virus (WNV) RNA for Nucleic Acid Amplification Techniques (NAT):

In addition to this work, two important International Standards will be established in December's meeting:

**WHO International Standards for COVID-19 (for rapid submission – Dec 2020):**

SARS-CoV-2 RNA standard - Standardization of diagnostic assays based on nucleic acid amplification techniques (NAT) for identification of COVID-19 infection by Clinical and public health laboratories, Vaccine manufacturers - Vaccine studies, Assay Kit manufacturers Research laboratories. Materials - Inactivated SARS-CoV-2 virus and SARS-CoV-2 RNA packaged inside lentiviral particles. A research reagent has been made available in NIBSC catalogue (19/304); feedback was positive.

SARS-CoV-2 antibody standard - Serological assays are needed to understand the real impact of COVID-19, as most of the cases with mild symptoms are undetected. **COVID-19** antibody standard is needed for serological assay development, evaluation of vaccine efficacy, and for epidemiological studies. Material is a Pool of plasma/serum from convalescent individuals.

### 6.37 NATIONAL INSTITUTE FOR STANDARDS AND TECHNOLOGY (NIST):

The status of NIST reference materials activity is mostly covered under the respective C's and WGs.

In addition, the NIST website (www.nist.gov) can provide information on materials and services available today.

The most relevant projects to the IFCC and SD are:

1. cardiac troponin I
2. human insulin-like Growth Factor 1
3. potential standards for COVID

NIST's lab activities remain limited because of the COVID-19 pandemic but work continues. NIST has developed a Research Grade Test Material (RGTM) comprised of synthetic SARS-CoV-2 RNA fragments, and that material is currently being evaluated by end users. NIST is also pursuing development of reference materials for serology tests.

## 8.2 MAIN ACTIVITIES OF COMMITTEES:

### 8.2.6 C-NOMENCLATURE, PROPERTIES AND UNITS (C-NPU):

As a reminder, in 2014 a formal agreement between IFCC and IUPAC was put in place. Wikipedia presence for the NPU was created 2015 (edited by the chair with input from many NPU members). The Wikipedia entry is a useful introduction: (https://en.wikipedia.org/wiki/NPU_terminology) and the NPU Website is performing well. The NPU Steering Committee continues to provide governance for the NPU terminology through representation from key stakeholders consisting of IFCC, IUPAC and National Release Centre representative, while the C-NPU functions as the technical and scientific expert committee.

A proposal of the start of a Laboratory Information Model was made. In the presentation, it was suggested that the outcome of a Laboratory Information Model should be a laboratory result overview, in which quantity results from different labs can be highlighted to show which results can be compared. The model should also be committed to other purposes such as billings and AI. Before commencing this work, the Steering Committee has suggested that a survey of a laboratory information model in use in any countries be made. The chair sent a survey to the attendees after the last C meeting.

It was suggested that a publication should be commenced in which 5 most essential issues are highlighted. The C-NPU will discuss how to approach this with help of voluntaries.

**8.2.11 C-MOLECULAR DIAGNOSTICS (C-MD)**:
Due to the Corona pandemic and the numerous tests and procedural changes and innovations that had to be made by many members, only a few points for the C-MD have been implemented in the last weeks. This includes the successful publication of the C-MD in CCLM:
IFCC Paper Deborah A. Payne, Graciela Russomando, Mark W. Linder, Katarina Baluchova, Tester Ashavaid, Werner Steimer and Parviz Ahmad-Nejad*, the IFCC Committee for Molecular Diagnostics (C-MD) External quality assessment (EQA) and alternative assessment procedures (AAPs) in molecular diagnostics: findings of an international survey: Clin Chem Lab Med 2020; aop
In addition, the list of molecular diagnostics centers and the application form for these has been revised. A new call for Molecular Diagnostic Network and Expert Laboratories was initiated. After reviewing within the Committee, several new laboratories were recommended. This led to continuous update of the webspace (EQA list, guidelines).
During the 10th „Beginners' Course in Molecular Diagnostics" in La Paz, Bolivia from March 1st – 6th, 2020 the chair introduced the C-MD and gave a presentation addressing the present C-MD web resources
In Oct 2020: submitted the latest manuscript „Current and Future Challenges in Quality Assurance in Molecular Diagnostics" to CCA (special issue)
In Dec 2020: virtual presentation at the AACC 2020 conference.

**8.2.23 C-TRACEABILITY IN LABORATORY MEDICINE (C-TLM)**:
The committee had its annual (virtual) meeting on November 12, 2020. All members and consultants were present. Major point of discussion were the RELA 2020 results of HbA1c. The results of the participants were divided into two collectives. The C is looking for the reason and is in the process of contacting the participants. At first glance, the comparison of the calibrators shows no indication that this could be the reason for deviation. The samples of RELA2020 will be sent out in addition to the samples of RELA 2021 to investigate whether the outcome can be repeated.
The next RELA survey (RELA 2021) has been announced and approximately 680 orders have been received to date. The dispatch of samples is currently underway.
The RELA procedure manual has to be revised and limits of equivalence for new measurands will be added. This will be an additional project for 2021.
It is planned to conduct RELA surveys in parallel with CCQM comparison studies of NMIs for HbA1c and enzymes, respectively. The coordinators of NMIs contacted the chair of C-TLM to discuss the design and organization of both projects. These projects will be pending, however, the effects of the pandemic on progress cannot yet be estimated. Nevertheless, it would be an important step to demonstrate the implementation of metrological traceability.
It is standard for the IFCC HbA1c Network to organize two intercomparison studies a year. Due to the pandemic the first study has been postponed to a later date. The HbA1c network will continue its activities in 2021.

**8.2.24 C-REFERENCE INTERVALS AND DECISION LIMITS (C-RIDL)**:
The SD discussed the new project of Prof Khosrow Adeli (IFCC President) that aims to create a website and database of regional reference intervals from all over the world - IFCC Reference Interval Database (A Global Resource for Clinical Laboratories around the

World). A new Task Force has been formed. C-RIDL will support this project to evaluate the studies to create this website.
Regarding the proposal to revise the CLSI document EP28 (guidance to establish reference intervals), Professor Yesim Ozarda, the vice chair of the proposed revision and chair of C-RIDL confirmed that the CLSI Consensus Council once again rejected the revised project plan. The major concern was the eventual length of the guidance document, which was deemed too long. According to the feedback received, the project has to be split into two parts; 1) verification of the reference intervals and 2) multicenter trials to establish reference intervals.
Interesting and in the interim, CLSI issued a call for volunteers in November that appears to address this very issue:

1. A document development committee for a document revision: EP44—*Establishing Reference Intervals,* 4th Ed.
2. A document development committee for a document revision: EP45—*Verifying Reference Intervals in a Medical Laboratory,* 4th Ed.

It is unknown at this time whether there is the intention to include the methodology of using real world data in either document. The SD immediately informed that chair to encourage her to consider joining the committee for EP44 and/or EP45. The hope is to include real world data and to gain alignment with the activities of C-RIDL.

**8.2.25 C-STANDARDIZATION OF THYROID FUNCTION TESTS (C-STFT)**:
Establishing a system to maintain traceability of free thyroid hormone and TSH measurements has been completed and now the focus is on implementation:
**Laboratory Network for fT4 RMP:**
The Network is necessary to ensure consistency in measurements over time performed by the conventional RMP for fT4. Furthermore, the network will provide measurement capacity as high need for reference measurements is anticipated, and will ensure consistency of national or regional standardization efforts.

- 2nd interlaboratory comparison study ongoing. This study includes samples from patients with thyroid disorders as well as samples from healthy donors. In addition, it contains standard solutions for potential use as calibrators. A second study is ongoing with individuals that have thyroid disorders.
- Completion of the study has been delayed due to COVID-19 and is anticipated to be finished in Spring 2021

**TSH Harmonization:**
The IFCC C-STFT is the only organization providing an ISO 17511 compliant traceability chain for TSH by maintaining a harmonization sample panel generated using a generally recognized harmonization protocol. The current harmonization panel is kept at NIBSC.

- It is anticipated that the current harmonization sample panel (single donor) will be exhausted within 2 years. C-STFT is ensuring consistency in assay harmonization over time by developing a follow harmonization sample panel.

**Education of stakeholders about the new reference system and its impact on patient data:**
The implementation of harmonization of TSH occurred without any notable problems in Japan. Therefore, it is assumed that similar efforts in other regions will occur in the same manner. Concerns have been raised about the impact of fT4 standardization. These concerns were raised mainly by IVD manufacturers. C-STFT is addressing these concerns by helping national or regional groups with educational activities.

IFCC C-STFT work will be mentioned at the 2020 AACC meeting.

### 8.2.26 C-HARMONIZATION OF AUTOIMMUNE TESTS (C-HAT):

The committee is facing a similar issue as C-STFT with implementation of harmonized assays systems in that there is the need to work with manufacturers and the FDA and other regulatory agencies worldwide.
The main development has been in the interaction with NIBSC and the WHO to progress the anti B2GP1 material. They have been unable to value assign in mass units due to the poor commutability of the purified preparation that was to be use for the value assignment process. The reference material itself is commutable. Their only option was to work with the WHO and provide values in arbitrary units. The WHO ECBS have now officially approved the B2GPI IgG autoantibody standard project: BS2396: WHO 1st International Standard for Anti-β2GPI IgG antibodies. In the next meeting of the WHO in October 2021, a detailed report will be presented with all relevant information about the material (commutability, stability etc.).
There were also some comments from the US CBER FDA representative:
The FDA is supportive of the proposal and have a few comments for consideration: The field of autoantibodies, where individual patients cannot be assumed to be qualitatively or quantitatively similar, or to produce consistent assay estimates between assay methods, imposes severe limitations on what can be achieved in terms of standardization.
Because the proposed preparation is comprised of polyclonal antibodies, it is unlikely this IS will be able to standardize (i.e. be comparable through metrological traceability) the existing assays. These assays are based on different master calibrator(s) and utilize a variety of methodologies that do not always produce comparable results to each other. It is not known if the proposed IS will be used as a metrologically traceable reference material for new assays. With careful consideration, this preparation may be helpful in harmonizing results across different methods or across manufacturers' tests.

### 8.2.27 C-BONE METABOLISM (C-BM):

**PTH standardization:**
Dr. Vincent Delatour (VD) presented the results of the commutability study to the rest of the C. Prof. Cathie Sturgeon (CS) is preparing new pools that will be tested by as many methods as possible in Prof. Etienne Cavalier's (EC's) lab. Samples should be received in December 2020 or January 2021.
**Liaison with other societies:**
The C-BM is already endorsed by the IFCC. EC has contacted K-DIGO representatives, but K-DIGO does not endorse any other initiative. EC is in contact with the ERA-EDTA to try to set up a joint ERA-EDTA-IOF-IFCC Committee.
Update: The Council of ERA-EDTA (European Renal Association-European Dialysis and Transplantation Association) has accepted to endorse the Committee and Standardization project.
**Bone markers assays:**
**PINP:**
EC and VD have designed a commutability study by enriching various matrices with PINP provided by IDS. Methodology is the same as the one used for PTH. The Roche Universal Diluent has been found to be commutable for IDS, Roche and Orion PINP assays. Results of the commutability study have been presented to the other C members and a new set of samples have been analyzed at EC's lab to analyze the commutability. VD is currently analyzing these results. Future studies will evaluate the opportunity to develop a RMP for PINP and to prepare commutable standard to calibrate the assays (with the help of the LNE).

**CTX:**
EC has proposed a new version of the manuscript. This version has been approved by all authors (and had already been analyzed by the SD). He has sent it to IDS and Roche and will submit it by the end of 2020.
**Other bone biomarkers:**
Different other biomarkers have been measured in Liege to evaluate their biological variation: osteocalcin, FGF-23 and uCuP-MGP. The manuscript has been accepted in Osteoporosis International.
Vitamin D metabolites assay standardization:
The manuscript on measurement uncertainty has been submitted and is currently under review. It is planned to complete the study in pregnant women in 2021.

## 8.3 MAIN ACTIVITIES OF WORKING GROUPS:

### 8.3.35 WG - STANDARDISATION OF HEMOGLOBIN A2 (WG-HbA2):

A joint committee with ICSH (The International Council for Standardization in Hematology) is being formed. The following is a short update of the current status of activities:
1) The roadmap for the standardization of HbA2 has been published, and now a set of actions to diffuse it to the stakeholders (mainly manufacturers and clinical societies) has to be undertaken. Personal e-mails to the various opinion leaders among the manufacturers have been already sent. A possible short news in the eJIFCC will also be prepared. Dr. Kees Harteveld is going to communicate the information among the International Committee for the Standardization in Hematology.
2) The purity and the content of the primary reference materials (i.e. the recombinant hemoglobins A0 and A2) has been verified at the JRC and at the PTB.
3) The calibrators (i.e. mixtures of the purified Hbs) will be prepared and distributed to the IFCC reference laboratories (2 in Europe and 2 in China) in order that they practice the reference measurement procedure.
4) The raw materials (i.e. the stabilized frozen hemolysates) to prepare the final lyophilized Certified Reference Materials (CRMs) have been prepared at the JRC and stored at -80 °C awaiting lyophilization.

### 8.3.36 WG - STAND. OF CARBOHYDRATE-DEF. TRANSFERRIN (WG-CDT):

The following is a summary and a description of the current focus of this WG:
The WG continues to raise awareness of the IFCC approved RMP through online meetings and electronic communications when approached by current CDT users still hesitant to switch from classic to CDTIFCC**.** In addition, actively seeks further participants globally as candidate laboratories with progression to network status through participation in the annual IFCC CDT blind study.
Sustainability and performance of network laboratories and participating commercial manufacturers are assessed by the yearly distribution of IFCC calibrators, controls and blind samples from Dr. Weykamp's MCA NL laboratory section now overseen by Dr. Carla Siebelder.
The 2020 Cycle took place during the first quarter of this year with participants' results submitted by end May. There were five successful IFCC networked laboratories this year, with one candidate lab yet to improve in performance and one manufacturer who has yet to pass the blind study
Cycle of blind IFCC samples will take place during late spring / early summer 2021, following prior requests which will be sent to all prospective participants (network labs and manufacturers). Results will be presented and discussed during the WG CDT meeting anticipated during the EuroMedlab Munich event.

Most participating commercial CDT manufacturers have achieved positive results towards CDTIFCC and have launched respective assays. A further CDT manufacturer participated in the standardization process and passed this year's blind study. WG members have also been in discussion with another manufacturer towards reviewing their approach to improve alignment closer to CDTIFCC. It is planned to continue to assist the remaining commercial participants in successfully achieving the CDTIFCC goal.

### 8.3.39 WG – STAND. OF ALBUMIN ASSAYS IN URINE (WG-SAU):

All activities of the WG-SAU are a joint effort with the National Institute of Diabetes and Digestive and Kidney Diseases Laboratory Working Group - LWG (previously of the National Kidney Disease Education Program).

The focus of the LWG is to develop higher order references to support metrological traceability of urine albumin measurements according to the requirements of ISO 17511. The final goal is standardization of all clinical laboratory measurement procedures to produce equivalent results for urine albumin, urine creatinine and the albumin/creatinine ratio. Higher order references for urine creatinine are currently available.

**NIST Reference Materials for urine albumin:**

Standard Reference Material SRM 2925 Pure Albumin became available for purchase from NIST in 2020.

SRM 3666 Albumin in Frozen Human Urine:

Samples at 4 concentrations have been prepared from human urine, vialed and preliminary values determined using a clinical laboratory measurement procedure. Next steps are to do certification of the materials and assign values for urine albumin and creatinine using the NIST candidate reference measurement procedures.

**Reference Measurement Procedures (RMP) for Urine Albumin based on isotope dilution mass spectrometry (IDMS):**

**NIST:**

The NIST candidate RMP has been characterized and published (Beasley-Green A, Burris NM, Bunk DM, Phinney KW. Multiplexed LC-MS/MS assay for urine albumin. J Proteome Res 2014;13:3930-9). Requirements for the JCTLM submission are being reviewed, and validation studies with the Mayo Clinic and UMN are ongoing.

**University of Minnesota and Mayo Clinic:**

Both laboratories are setting up the same candidate RMP originally developed at the Mayo Clinic (Seegmiller JC, Barnidge DR, Burns BE, Larson TS, Lieske JC, Kumar R. Quantification of urinary albumin by using protein cleavage and LC-MS/MS. Clin Chem 2009;55:1100-7; Lieske JC, Bondar O, Miller WG, Bachmann LM, Narva AS, Itoh Y, Zegers I, Schimmel H, Phinney K, Bunk DM. A reference system for urinary albumin: current status. Clin Chem Lab Med 2013;51:981-9). The calibration of the RMPs at UNM and Mayo is being established to be traceable to the NIST 2995 primary reference material. The analytical performance characterization has largely been completed. The main remaining item is to investigate the replication of measurements needed to reduce the imprecision to 2-4% CV that will be suitable for use in the calibration hierarchies of clinical laboratory measurement procedures to meet the specifications set by the LWG program (Miller WG, Seegmiller JC, Lieske JC, Narva AS, Bachmann LM. Standardization of Urine Albumin Measurements: Status and Performance Goals. J Applied Lab Med 2017;2:423-9).

**Urinary Albumin LC-MS/MS Candidate Reference Measurement Procedure:**

Throughout 2019 a potential urinary albumin reference measurement procedure (RMP) was validated using calibrators and controls. This work was performed to understand the imprecision of the assay and what would be needed in order to potentially meet performance specifications for a reference measurement procedure. Given the findings

from this validation study it was agreed upon through consensus by the NKDEP-LWG it would be necessary to perform replication to improve imprecision < 5 %CV.

### 8.3.40 WG – STAND. OF PREGNANCY-ASS. P-PROTEIN A (WG-PAPPA):

The WG main goal is to harmonize the PAPP-A measurements of the various methods commercially available:

a) To establish well-characterized reference materials
b) To characterize different antibody combinations (reference assays and company assays) with these materials in different matrices
c) Assays detect different forms of PAPP-A similarly to test reference materials in different matrices with commercial assays
    - Recombinant PAPP-A - ***not suitable***
    - Endogenous PAPP-A purified from retroplacental blood - ***not suitable***
    - Pooled 2nd trimester or 3rd trimester serum – ***suitable***
d) to select, manufacture and validate reference material NIST SRM 1949

**Companies actively participating:**

- Beckman Coulter
- Perkin-Elmer
- Roche Diagnostics
- Siemens Healthineers
- Thermo Fisher (B.R.A.H.M.S.)

**Plans:**

- Confirmation of commutability of SRM 1949
- Value assignment (average of commercial assays using mIU/L)

**Part A – University of Turku**

- Initial concentration for the 4 pools/products of SRM 1949 determined at the University of Turku
- The suitable pool(s) identified, dilution scheme designed, aliquots prepared

**Part B - Companies**

- Each company will be given
    - 2 vials of chosen SRM 1949 products -> 4 dilutions prepared of each vial according to instructions
    - 5 pools of 1st trimester serum (to secure commutability)
    - 2 samples of premade SRM 1949 dilutions
        - *15 samples in total*
- 15 samples in total analysed 5 times as duplicates (one method / company)
- Results sent to the University of Turku for analysis

### 8.3.41 WG – GROWTH HORMONE (WG-GH)

The overall goal of the WG-GH is to achieve standardization of growth hormone through secondary reference materials and a reference measurement procedure.
A long recognized problem in the reliable measurement of GH is the lack of standardization of different assays that are currently used. 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 in different matrices.
To address these issues, the WG is currently organizing a commutability study at two reference laboratories using LCMS/MS. The difference in bias will be compared with a pre-determined criterion based on medically relevant differences. The goal is to determine how

close the bias of a RM (reference material) and the CS (clinical representative samples) are to each other. A RM is commutable if the systematic difference, or bias, for the RM and the average bias for the CS between two measurement procedures (dRM), at the RM level, is within an agreed criterion. A maximum of dRM, named the commutability criterion (C), is already decided.
Once the reference material and reference measurement procedure is finalized the following commercial assay will be studied:

| | |
|---|---|
| Siemens | Immulite 2000/XP |
| DiaSorin | Liaison |
| BeckmanCoulter | Access/DXi |
| IDS | Isys |
| Roche | Cobas/Elecsys |

### 8.3.42 WG – STANDARDIZATION OF INSULIN ASSAYS (WG-SIA)

This is a joint project between ADA/EASD and IFCC. The overall goal of the WG is to establish a reference system for serum/plasma insulin measurement to achieve standardization of all commercial methods to assay insulin.
Current status:
1. Ongoing development and validation of MS/MS method for intact insulin at University of Minnesota. Significant progress has been made following prioritization and financial support for development of the LC-MS/MS insulin assay at the University of Minnesota.
2. Continued collaboration with other laboratories (Quest Diagnostics, Mayo Clinic) developing insulin methods by mass spectrometry and sustained efforts to evolve reference method procedures in these laboratories.
3. In collaboration with the College of American Pathologists (CAP), established criteria for ongoing accuracy based evaluation of serum pools for testing of insulin, C-peptide, and glucose.
4. Continued collaboration with NIBSC to evaluate the insulin candidate reference material which will ultimately be utilize to calibrate the mass spec method and establish it as a higher order reference method.
Future Plans and activities:
1. Implement accuracy based proficiency testing survey using serum pools for insulin (and c-peptide) via the College of American Pathologists; results will allow for assessment of comparability of results across assays, using a commutable matrix, as the WG moves towards standardization or harmonization.
2. Working group report or peer-reviewed publication regarding either insulin/c-peptide serum pool data across hundreds of laboratories/assays and/or lack of harmonized conversion factor across insulin assays.

### 8.3.43 WG – STANDARDIZATION OF TROPONIN I (WG-TNI)

Unfortunately, the WG-TNI activities have been significantly delayed due to COVID-19, especially given the severity in the United States.
The WG collected all of the cardiac troponin I (cTnI) samples from Myocardial Infarction patients that are needed to produce the commutable reference material (RM) 8121 (SRM 2922). Development of this material has been in close collaboration with NIST. High cTnI samples will be blended with heparinized plasma from healthy individuals. The WG was just about to initiate blood collection from the healthy individuals when the COVID-19 crisis forced the university to bring a hard stop to activities. Thus, the WG-TNI project to develop RM 8121 in collaboration with NIST has been unavoidably delayed.
Ongoing activities:

- NIST is actively evaluating commercial vendors that will blend RM 8121 (SRM 2922) at the specified series of concentrations.
- The chair worked with NIST to develop a submission for funding that will help cover the costs of screening and recruiting the healthy individuals who will donate units of heparinized blood for production of the plasma that will be used for blending with high cTnI samples.
- The abstract for the pilot study was submitted to the AACC and has been selected for oral presentation at the Annual Meeting to be conducted in Chicago, IL in December.

**8.3.49 WG – CSF PROTEINS (WG-CSF):**

The WG is in contact with NMIs for the standardization of the Tau proteins. There seems to be some coordinated activities. So far, the following have been accomplished:
- Two RMPs for CSF amyloid β 1-42 have been published and approved by the JCTLM (C12RMP1 and C11RMP9).
- A method for measurement of CSF amyloid β 1-40 by SRM has been published and validation of a RMP is ongoing.
- Mass spectrometric methods for measurement of CSF tau have been developed by several work group members.
- Three CRMs for CSF amyloid β 1-42 have been developed (ERM®-DA480/IFCC, ERM®-DA481/IFCC and ERM®-DA482/IFCC).
- Collection of CSF for development of CRMs for tau is ongoing.
- Round-Robin study of CSF-amyloid beta 1-42/1-40 ratio RMPs by mass spectrometry is in the planning stage.
- Round-Robin study of CSF tau RMPs by mass spectrometry is being planned.
- There has been reluctance by industry to adopt the new reference system and the WG has prepared training materials and trying to move this forward.

**8.3.51 WG – COMMUTABILITY IN METROLOGICAL TRACEABILITY (WG-CMT)**

The WG-CMT (WG on commutability in metrological traceability) was started in January 2020 to carry on work from the previous WG on Commutability. The WG published a paper in June 2020 “Miller WG, Budd J, Greenberg N, Weykamp C, Althaus H, Schimmel H, Panteghini M, Delatour V, Ceriotti F, Keller T, Hawkins D, Burns C, Rej R, Camara JE, MacKenzie F, van der Hagen E, Vesper H, for the IFCC Working Group on Commutability. IFCC Working Group Recommendations for Correction of Bias Caused by Noncommutability of a Certified Reference Material Used in the Calibration Hierarchy of an End-User Measurement Procedure. Clin Chem 2020;66:769-78. The paper was accompanied by an editorial “Mackay LG. Further Recommendations on Commutability Assessment. Clin Chem 2020;66:749-50.

The WG-CMT is currently developing recommendations for a criterion to use when assessing commutability of CRMs, trueness controls and EQA materials. The criterion should be related to maximum allowable uncertainty for a measurement procedure (MAU). Both MAU and the fraction that can be allocated to a commutability specification are challenging to clearly define. The criterion for a CRM and for an EQA material will be different. The WG held 8 Zoom meetings in 2020 and will continue in 2021. Additional topics planned to be addressed in the future include how to verify commutability for a replacement batch of a reference material, and how to use a CRM in the calibration hierarchy for a measurement procedure for which the sample matrix is not intended. Developing the criteria for assessing commutability is proving a bit more complicated but progressing.

### 8.3.53 WG – IMMUNOSUPPRESIVE DRUGS (WG-ID):

The WG is devoted to the establishment of candidate reference procedures and reference materials for immunosuppressive drugs (ISDs) such as cyclosporine, sirolimus, tacrolimus, everolimus, and mycophenolic acid (MPA).
The WG came to several agreements, which will serve as basis of future undertakings:
- There is a definitive need to bridge the traceability gap between primary and secondary reference materials and the industrial master calibrators.
- At least two quality levels of procedures must be provided to allow on the one hand the characterization of highest order reference materials and on the other hand, to support industry and other stakeholders with measurement platforms allowing to characterize sample cohorts of different study settings (e.g. instrument comparison studies ...).
- JCTLM listing of reference methods and materials is a must for the WG outcome to be successful.
- qNMR is most likely the key technology to provide reference materials of unmet quality and that any reference measurement procedure must be published such, that a sufficiently qualified laboratory is in the position to participate in a reference measurement network to be defined as ultimate goal of our initiative.

Dr. Loralie Langman as Past President of the IATDMCT and member of WG-ID took up the task to establish a link between IFCC and IATDMCT. Consequently a "memorandum of understanding" to extend the WG-ID to an IFCC-IATDMCT joint WG was prepared. This memorandum is already signed by the IFCC and is awaiting signature from the IATDMCT.
It is envisioned to organize joint presentations with the C-TLM, since JCTLM registration of established materials and methods is a central milestone of the WG-ID work. Furthermore, the WG plans to make a presentation at the IATDMCT conference 2021 in Banff – hopefully this will be the inauguration meeting of the IFCC-IATDMCT joint WG.

### 8.3.54 WG – APOLIPOPROTEINS BY MASS SPECTROMETRY (WG-APO MS):

**Reference Measurement Procedure:**

The WG set two major goals for 2020: the optimization of the LC-MS measurement method, including further evaluation of harmonization and proof of equimolar digestion of apo(a). Work has been initiated on both topics, but efforts have been hampered by the COVID-19 crisis.
Major accomplishments WG APO-MS 2020:

- Publication of a paper describing the conceptual outline of the candidate reference measurement system that is under development by the WG.
- Procurement of recombinant apo(a) material as a candidate secondary reference material and of synthetic peptides for apos A-I, B, C-I, C-II, C-III and E as candidate primary reference materials.
- Optimization of the candidate reference measurement procedure with regard to the peptides, internal standards and the LC-gradient used; initial precision experiments were performed and a common standard operating procedure was developed. A manuscript on this -harmonized- method is in preparation.
- Organization of a first commutability study to evaluate the potential of apo(a) secondary reference materials. The first results of this commutability study are expected in Q1 2021.
- First experiments to assess equimolarity of apo(a) digestion in the candidate reference measurement procedure. These experiments will be continued for apo(a), and started for apos A-I and B in 2021.

### 8.3.55 WG – PANCREATIC ENZYMES (WG-PE):

Development of a primary reference method for pancreatic amylase in serum:

- Organizing of certain reagents provided from Roche for interlab comparison
- Organizing of EQA material prepared and provided from Dr. Cas Weykamp for interlab comparison
- Preparation and provision of patient pools from the laboratory of Dr. Grote Koska for interlab comparison
- Measurement performed/finalized at Spanish site (F. Canalias)
- Measurement performed/finalized at the site of Dr. Grote Koska
- International survey with respect to lipase vs. (pancreatic) amylase: questions set up, survey planned for beginning of next year.

Development of a primary reference method for pancreatic Lipase in Serum:
No further activity is planned prior to the completion of the RMP of pancreatic lipase.
Certification of reference materials for enzymes being performed at the JRC:
In 2019 characterization studies of the new ERM reference material ERM AD456/IFCC of pancreatic amylase were performed by well-respected sites of WG-PE and others. Stability studies were performed in the calibration laboratory in Hannover for EC-JRC. The material is now released and available.
In 2020 investigations to monitor stability are being performed in the RfB-calibration laboratory in Hannover (Dr. Grote-Koska). Future activities are depending on the needs of the JRC. So far no plans are decided.

### 8.3.56 WG – FECAL IMMUNOCHEMICAL TESTING (WG-FIT):

Given the COVID-19 pandemic, work is mostly through emails and also via WG sub-groups. Each meeting is highly attended by approximately 20 members including four manufacturers and work continues in spite of the current situation. A virtual conference is planned at the end of October which will focus on discussing the harmonization studies of FIT methods. It was previously confirmed that standardization will not be possible and a sub-group of the FIT-WG has drawn up a harmonization protocol. The final protocol is now with the manufacturers for approval and the hope is to start the harmonization work in October with it being completed (all going well) by December 2020. A great deal of work has been done to develop the RM (reference material) with the JRC in the lead and in the end material from Japan has been chosen. Four manufactures will perform the study and first run their methods and then recalibrate with the chosen RM.
Two papers were recently published which relate to the activities of the FIT-WG concerning independent IQC and suitable EQA material;

- One relates to the lack of availability of third party IQC. During one of the FIT-WG meetings all manufacturers agreed that the WG could test each manufacturer IQC on the other analysers. Once the IQC work on all analysers is complete is to then see if the manufacturers are willing to market their IQC independent of the FIT method until there is the possibility of 3rd party IQC:
    - Letter to the Editor Carolyn Piggott*, Zinab Shugaa and Sally C. Benton Independent internal quality control (IQC) for faecal immunochemical tests (FIT) for haemoglobin: use of FIT manufacturers' IQC for other FIT systems (Clin Chem Lab Med 2020; aop)
- EQA is challenging for FIT because of the pre-analytical variability and the WG members had a lot of discussion as to what an ideal EQA should be for FIT. A paper recently published that looks at different type of EQA material:
    - Shane O'Driscoll, Carolyn Piggott, Helen Bruce and Sally C. Benton* An evaluation of ten external quality assurance scheme (EQAS) materials for the

faecal immunochemical test (FIT) for haemoglobin (Clin Chem Lab Med 2020; aop; published online August 7, 2020)

### 8.3.57 WG – CELL FREE DNA AND RELATED CIRCULATING BIOMARKERS (WG-cfDNA):

The WG has reached out for corporate member sponsorships to enable face-to-face meetings.

Terms of Reference:

- To identify and provide guidance on preanalytical and analytical aspects for obtaining good and reproducible results for cfDNA and related circulating biomarkers for clinical use, and to guide the correct clinical implementation of these biomarkers.

Current projects:

- Defining pre-analytical aspects / drafting guideline
- Defining minimal analytical performance
- Setting up proficiency testing for cfDNA
- Organizing international workshops
- Defining grant proposals to address unmet needs

The chair and WG have prepared a paper about the pre-analytical aspects and the paper is currently being reviewed by the WG. The chair believes the WG members will provide expertise in lung cancer, organ rejection, and other broad areas (such as exosomes). The WG also plans to be involved early on with NMIs.

### 8.3.58 WG – PROCALCITONIN (WG-PCT):

The following is the status of WG-PCT to date:

**Development of candidate reference method for PCT by mass spectrometry**:

Sample preparation optimization was pursued with the objective to improve the method's sensitivity. The limit of quantification is now 0.25 ng/mL. Method validation is now completed and is the subject of two scientific publications. The first paper was submitted to analytical and bioanalytical chemistry in Dec 2020. The second publication is under preparation and will be submitted by end 2020 or early 2021.

**EQA Survey**:

Ten external quality assessment scheme (EQAS) providers from eight different countries were approached to share results of their PCT EQAS. From 2014 to 2020, 2220 routine laboratories conducted 27500 PCT measurements using 137 EQA materials which PCT concentration ranged from 0.05 ng/mL to 43.66 ng/mL (median 3.02 ng/mL). The mean between lab CV% is 15.6% but greatly varied across EQA Schemes. As commutability of EQA materials was not evaluated, it can be speculated that differences in estimates of between lab agreement is (at least partially) due to variable commutability levels of the EQA materials. This confirms the need to evaluate commutability of EQA materials before a conclusion can be made regarding the need to improve comparability of PCT assays. EQA providers will be invited sharing their materials to include these in the commutability study that will be organized in 2021.

**Commutability study**:

Due to the coronavirus crisis, collection of large single donation in the lab of Prof Tsatsanis was stopped between March and May and then resumed in June. So far, 23 large single donations were collected but only 10 of these have a volume sufficient to be measured by all immunoassays. In parallel, small single donations (leftovers) were collected with the objective to prepare pools that will be used as EQA materials which commutability will be evaluated. Samples collection will soon be expanded thanks to partners of EMPIR project SEPTIMET.

### 8.3.59 WG – CONTINUOUS GLUCOSE MONITORING (WG-CGM):

The WG is preparing work packages and publications as follows;

**Work package 1 (WP 1): Establish a Traceability Chain to a Defined Measurand:**

On-going e-mail conversation with discussions about background information and the methods, answers about WP-1 were sent to the members of the WG, a consensus document with the corresponding answers was prepared.

**Work package 2 (WP 2): CGM Analytical Performance: Procedures & Metrics:**

On-going e-mail conversation, answers about WP-2 were sent to the members of the WG, answers are still being collected and a consensus document will be prepared.

**Work package 3 (WP 3): Work with ISO on a New CGM Guideline:**

Internal discussions via conference calls and via e-mail conversation are planned for next year.

Submission of two publications ("Standardization process of continuous glucose monitoring: traceability and performance. Submitted to Clinica Chimica Acta, 2020" and "Continuous Glucose Monitoring – What should be optimized and considered in the future? Scientific short, submitted to American Association for Clinical Chemistry (AACC), 2020")

Talks / lectures about the work of the IFCC-WG-CGM were given by G. Freckmann at various online events (e.g. DDG German Diabetes Association Nov. 2020, DTM / Diabetes Technology Meeting Nov. 2020 or AACC Dec. 2020).

## 8.19 MEETINGS

8.16.66 66th SD Meeting – December 7, 2020 via extended web conference call

8.16.67 67th SD Meeting – TBD; likely in April / May 2021 either virtual or in person in Milano at the IFCC offices.

8.16.68 68th SD Meeting – to be held in Munich, Germany in conjunction with EuroMedLab 2021 (28 Nov. – 2 Dec.).