

**Organization Name: TUBITAK National Metrology Institute, TUBITAK UME**

**JCTLM Member status: National and Regional Member**

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**Period covered: 2022 – 2023**

## 1. Major achievement(s) in support of standardization in laboratory medicine

### ➤ The production of reference materials:

The following reference materials are on sale from TUBITAK UME web site “[https://rm.ume.tubitak.gov.tr/urun\\_listesi\\_en.aspx](https://rm.ume.tubitak.gov.tr/urun_listesi_en.aspx)”.

- UME CRM 1301: Chloramphenicol
- UME CRM 1308: 25-Hydroxy Vitamin D2 and 25-Hydroxy Vitamin D3 in lyophilized serum
- UME CRM 1314: Amino Acids in Plasma, Lyophilized
- UME CRM 1315: Organic Acids in Urine, Lyophilized
- UME RM 2019: SARS-CoV-2 RNA
- UME RM 2020: SARS-CoV-2 RNA Lyophilized

### ➤ Development of reference measurement methods

- Sensor Production for Different Virus Antigens or Antibody Proteins.  
In this project, it is aimed to develop/produce electrochemical sensor(s) for the determination of specific proteins of some viruses (e.g. yellow fever, influenza a, norovirus, parvovirus) in synthetic and/or real samples. Developments related to the project continue.
- Primary measurement methods were developed for quantification of DNA methylation.
- Primary measurement methods were developed for quantification amount-of-substance fraction of [HbA1c/(HbA1c+HbA0)] in Human Hemolysate.
- Primary measurement methods were developed for quantification of SARS-CoV-2 Monoclonal Antibody in Solution

➤ **Projects in the field of Laboratory Medicine:**

**EURAMET projects:**

Chemistry Group Laboratories have been collaborating in health related projects and contribute to the development of new measurements methods and production of new certified reference materials in Laboratory Medicine. TUBITAK UME Laboratories actively participated in the following EURAMET projects in the period of 2022-2023:

- JRP-h01- GenomeMET: Metrology for genomic profiling to support early cancer detection and precision medicine, 2023-2025
- JRP-h06- NEuroBioStand: Standardisation of measurements of neurodegenerative disease biomarkers, 2023-2025
- 18 HLT10- CardioMet: Providing the measurement infrastructure to allow quantitative diagnostic methods for biomarkers of coronary heart diseases, 2019–2022
- JNP: 18NET02- TraceLabMed: Support for a European Metrology Network on Traceability in Laboratory Medicine, 2019-2024
- QUIERO: Quantitative MR-based imaging of physical biomarkers, 2019–2022

The following EURAMET project proposals were supported and they will start in 2024.

- JRP-f11 – ProMET: Fundamental protein metrology to support the definition of measurands, analytical targets, and their associated measurement uncertainty, 2024-2026
- JRP-i19 – COMET: Manufacturing of commutable calibrators and quality control materials for standardization and post-market surveillance of IVD tests, 2024-2026

**National projects:**

- TUBITAK 2218- National Post-Doc Scholarship Program “The production of reference material for cell-free DNA (cfDNA) measurements: The standardization of recovery efficiency of cfDNA isolation which is used as a biomarker in the diagnosis and treatment of diseases”. 2022-2024.

➤ **The establishment of calibration (reference) measurement services.**

The following reference measurement services were offered in 2023 and listed under TUBITAK UME measurement services (Table 1).

Table 1. TUBITAK UME primary level measurement services offered in 2023.

<b>Code</b>	<b>Measurement Service Name</b>
G3OK-4600	Determination of 3-epi-25-Hydroxyvitamin D3 in Serum
G3OK-4610	Determination of Vitamin 25-OH D2
G3OK-4620	Determination of Vitamin 25-OH D3
G3OK-5600	Determination of Cholesterol in Serum
G3OK-5700	Determination of Glucose in Serum
G3OK-5800	Determination of Creatinine in Serum
G3OK-6900	Determination of Urea and Uric Acid in Biological Matrix
G3IK-3301	Determination of As in Biological Materials
G3IK-3302	Determination of Pb in Biological Materials
G3IK-3303	Determination of Cr in Biological Materials
G3IK-3306	Determination of K in Human Serum
G3IK-3307	Determination of Ca in Human Serum
G3IK-3308	Determination of Mg in Human Serum
G3IK-3309	Determination of Fe in Human Serum
G3IK-3310	Determination of Selenomethionine in Human Serum
G3IK-3311	Determination of Cl in Serum
G3IK-3312	Determination of Cu in Serum
G3IK-3313	Determination of Na in Serum
G3IK-3314	Determination of P in Serum
G3IK-3315	Determination of Se in Serum
G3IK-3320	Determination of Hg in Biological Materials
G3IK-3321	Determination of Ni in Biological Materials
G3IK-3322	Determination of P in Biological Materials
G3IK-3323	Determination of Zn in Biological Materials
G3BA-2100	Determination of Relative Gene Expression Levels - Real Time PCR
G3BA-3100	Relative quantification of DNA methylation levels - RT PCR Melting Analysis
G3BA-4100	Absolute quantification of Plasmid DNA - Digital PCR instrument
G3BA-4210	Relative quantification of oncogenes (KRAS-G12D) - Digital PCR Instrument
G3BA-4220	Relative quantification of oncogenes (BRAF-V600E) - Digital PCR Instrument
G3BA-4230	Relative quantification of oncogenes (EGFR-?746-750) - Digital PCR Instrument
G3BA-4310	Absolute quantification of HIV virus - Digital PCR Instrument
G3BA-4320	Absolute quantification of SARS-CoV-2 virus - Digital PCR Instrument
G3BA-5100	Amino Acid Analysis For Pure Protein/Peptide - LC-ID-MS
G3BA-5300	Quantification of C-peptide/angiotensin - LC-ID-MS(n)
G3BA-5400	Quantification of Protein Concentration - HPLC
G3BA-5500	Quantification of Protein Concentration - ELISA
G3BA-5600	Quantification of Protein Concentration - PICA
G3BA-5700	Relative Quantification of HbA1c Protein - HPLC
G3BA-5800	Relative Quantification of HbA1c Protein- LC-ID-MS
G3BA-5900	Determination of Amylase Enzyme Activity
G3BA-6000	Complex Proteome Analysis - Relative Quantification (LFQ-TMT)
G3BA-6100	Identification of Post Translational Modifications
G3BA-6200	Peptide Fragmentation (HCD)
G3BA-6300	LC-MS/MS Method based protein identification

➤ **Outline of the measurement area(s)/measurands covered:**

**CCQM Measurement Comparison Studies**

TUBITAK UME Chemistry Group Laboratories have participated to several international measurement comparison studies related to the field of Laboratory Medicine between 2022 and 2023 (Table 2). More resources will be devoted to the development of new reference measurement methods in this field.

Table 2. CCQM international measurement comparison studies organized and participated by TUBITAK UME between 2022 and 2023.

<b>Comparison #</b>	<b>Comparison Name</b>
CCQM-K115c	Peptide Purity - Synthetic Glycated Hexapeptide of HbA1c (GE)
CCQM-K115.2018	Peptide Purity - Synthetic Hexapeptide of HbA0 (VE)
CCQM-K148.b	Mass fraction of oxytetracycline in oxytetracycline hydrochloride material
CCQM-K176	Breast Cancer Biomarker HER2 Copy Number Variation (CNV) Measurement
CCQM-K179	Mass fraction of oxytetracycline hydrochloride salt
CCQM-K180	Metranidazole in porcine muscle
CCQM-K181	SARS-CoV-2 RNA Copy number quantification
CCQM- P94.3:	Quantitative analysis of DNA methylation of a defined human genomic DNA region*
CCQM-P216	Quantification of SARS-CoV-2 Monoclonal Antibody in Solution
CCQM-P199	Measurement of HIV-1 RNA Copy Number Concentration
CCQM-P199.b	SARS-CoV-2 RNA Copy Number Quantification
CCQM-P219	Determination of the Amount-of-Substance Fraction of [HbA1c/(HbA1c+HbA0)] in Human Hemolysate
CCQM-P232	Fire Drill Influenza RNA copy number quantification*

\*In progress

➤ **Listing of the relevant technical/scientific publications:**

- Öztug, M., Saban, E., Küçük, M., Isleyen, A., & Akgöz, M. "Development of UME CRM 1008: certified reference material for C-reactive protein". (2023). Doi.org/10.21203/rs.3.rs-3120831/v1
- Daniel Burke, Alison S. Devonshire, Leonardo B. Pinheiro, Gerwyn M. Jones, Kate R. Griffiths, Ana Fernandez Gonzalez, Michael Forbes-Smith, Jacob McLaughlin, Kerry R. Emslie, Christopher Weidner, Joachim Mankertz, John E. Leguizamon, Marcelo Neves de Medeiros, Roberto Becht Flatschart, Antonio M. Saraiva, Paulo Jose Iwakami Beltrao, Carla Divieto, Laura Revel, Young-Kyung Bae, Lianhua Dong, Chunyan Niu, Xia Wang, Sasithon Temisak, Sachie Shibayama, Burhanettin Yalcinkaya, Muslum Akgoz, Rainer Macdonald, Annabell Plauth, Jim Huggett. "Standardisation of cell-free DNA measurements: An International Study on Comparability of Low Concentration DNA Measurements using cancer variants". (2023) BioRxiv 2023.09.06.554514, doi.org/10.1101/2023.09.06.554514
- Ascioğlu, M., Oztug Kilinc, M., Karaguler, N.G. "Development of an ID-LC-MS/MS Method Using Targeted Proteomics for Quantifying Cardiac Troponin I in Human Serum", *Clinical Proteomics*, (2023), 20:1
- Mi, W., Josephs, R., Melanson, J., Dai, X., Wang, Y., Zhai, R., Chu, Z., Fang, X., Thibeault, M., Stocks, B., Meija, J., Bedu, M. "PAWG Pilot Study on Quantification of SARS-CoV-2 Monoclonal Antibody - Part 2", *Metrologia*, (2023), 60:1A
- Olgaç, N., Karakuş, E., Şahin, Y., Liv, L. Electrochemical biosensing of cortisol in a hormone tablet and artificial bodily fluids, *Diamond and Related Materials*, 132 (2023), 109622. <https://doi.org/10.1016/j.diamond.2022.109622>
- Josephs, R., Liu, Q., Martos, G., Bedu, M. "CCQM-K115.2018 Key Comparison Study on Peptide Purity - Hexapeptide of HbA0", *Metrologia*, 59, 1A (2022), DOI 10.1088/0026-1394/59/1A/08013
- Olgaç, N., Şahin, Y., Liv, L. Development and characterisation of cysteine-based gold electrodes for the electrochemical biosensing of the SARS-CoV-2 spike antigen, *Analyst*. 147 (2022) 4462–4472. <https://doi.org/10.1039/D2AN01225A>
- Josephs, R., Qinde, L., Martos, G., Bedu, M., Daireaux, A., Tiphaine, C., Westwood, S., Wielgosz, R., Nammoonnoy, J., Zhang, W., Yong, S., Liu, H., Yizhao, C., Ng, C., Ting, L., Wang, J., Leung, H., Teo, T., Gong, X., Dai, X., Un, I., Bilsel, M., Oztug Kilinc, M., Saban, E., Akgoz, M. "CCQM-P55.2.2018 Pilot Study on Peptide Purity - Hexapeptide of HbA0", *Metrologia*, 59, 1A, (2022), DOI 10.1088/0026-1394/59/1A/08014
- Josephs, R., Liu, Q., Martos, G., Bedu, M., Daireaux, A., Choteau, T., Westwood, S., Wielgosz, R., Nammoonnoy, j., Zhang, W., Yong, S., Liu, H., Chen, Y., Ng, C., Lu, T., Un, I., Bilsel, M., Oztug Kilinc, M., Saban, E., Akgoz, M. "Pilot Study on Peptide Purity - Glycated Hexapeptide of HbA1c", *Metrologia*, 59, 1A, (2022), DOI 10.1088/0026-1394/59/1A/08007
- Liv, L., Yener, M., Çoban, G., Can, Ş.A. Electrochemical biosensing platform based on hydrogen bonding for detection of the SARS-CoV-2 spike antibody. *Analytical and Bioanalytical Chemistry*, 414 (2022) 1313-1322. <https://doi.org/10.1007/s00216-021-03752-3>
- Liv, L., Kayabay, H. An Electrochemical Biosensing Platform for the SARS-CoV-2 Spike Antibody Detection Based on the Functionalised SARS-CoV-2 Spike Antigen Modified Electrode, *ChemistrySelect*. 7 (2022) e202200256. <https://doi.org/https://doi.org/10.1002/slct.202200256>
- Liv, L., Baş, A. Discriminative electrochemical biosensing of wildtype and omicron variant of SARS-CoV-2 nucleocapsid protein with single platform, *Analytical Biochemistry*, 657 (2022) 114898. <https://doi.org/10.1016/j.ab.2022.114898>

## 2. Planned activity(ies) in support of standardization in laboratory medicine

### ➤ R&D project(s) and/or programme(s)

TUBITAK UME Chemistry Group Laboratories collaborate with public and private institutions to develop measurement procedures in the field scientific metrology.

In Bioanalysis Laboratory, the levels of biological molecules such as bacterial or eukaryotic genomic DNA and genomic mutations are measured with digital PCR systems considered as reference measurement system. In case of new infectious diseases or other variants of SAR-CoV-2 emerges, new measurement methods and reference materials will be developed for measuring these viruses.

For quantitative measurement of DNA methylation, a new CCQM measurement comparison was organized in collaboration with KRISS under NAWG.

The measurements of small biological molecules such as amino acids, organic acids, hormones, lipids, antibiotics, pesticides and other metabolites are carried out by Organic Chemistry Laboratory which utilizes the quantification power of qNMR as a new reference measurement system in addition to the classical primary reference measurement methods.

Inorganic Chemistry Laboratory develops new measurement methods with the use of a new clean laboratory and new state-of-the-art instruments.

HbA1c proficiency testing (EurA1c) has been carried out by IFCC since 2016 and we will continue to contribute to this study in the following years.

After establishing measurement capabilities further, priority will be given to the preparation of more certified reference materials according to the needs of clinical laboratories in Turkey (Table 3).

Table 3. Certified Reference Materials Preparation Planning at TUBITAK UME, 2022-2023.

<b>Date of Release</b>	<b>Description of CRM or RM</b>
2024	HbA1c CRM
2024	C-Reactive Protein CRM
Planning	DNA methylation CRMs
Planning	Elements in serum (2024-2025)
Planning	Elements in whole blood (2024-2025)
Planning	Elements in urine (2024-2025)

➤ **EURAMET projects:**

The following EURAMET projects will be completed or continued as outlined in the project proposals and new measurement methods and/or new CRMs/RMs will be produced.

- JRP-f11 – ProMET: Fundamental protein metrology to support the definition of measurands, analytical targets, and their associated measurement uncertainty, 2024-2026
- JRP-i19 – COMET - Manufacturing of commutable calibrators and quality control materials for standardization and post-market surveillance of IVD tests, 2024-2026
- JRP-h01- GenomeMET: Metrology for genomic profiling to support early cancer detection and precision medicine, 2023-2025
- JRP-h06-NEuroBioStand - Standardisation of measurements of neurodegenerative disease biomarkers, 2023-2025
- 18NET02 TraceLabMed - Support for a European Metrology Network on Traceability in Laboratory Medicine, 2019-2024
- QUIERO - Quantitative MR-based imaging of physical biomarkers, 2019-2022

➤ **CCQM Measurement Comparison Studies:**

TUBITAK UME Chemistry Group Laboratories have been planning to attend to the following CCQM measurement comparison studies (Table 4).

Table 4. CCQM international measurement comparison studies planned between 2024 and 2025.

<b>Comparison #</b>	<b>Comparison Name</b>
CCQM-K159	Free Amino Acids in Plasma
CCQM-K/P	Purity assessment of primary reference materials for Parathyroid Hormone
CCQM- K/P	Purity assessment of primary reference materials for Cyclosporine
CCQM- K/P	Purity assessment of primary reference materials for hCMV
CCQM-K186/P238	Quantification of Total Haemoglobin in Blood
CCQM-K/P	17β-Estradiol in Human Serum

### 3. Promoting traceability in laboratory medicine

#### ➤ Technical/scientific publications:

- Yurek E, Yavuz BG, Tanoglu EG, Gurkas E, Altundag I, Yalcinkaya B, Yilmaz E, Colak S. “The Effect of the ABCB1(MDR-1) C3435T Polymorphism in Turkish Patients with Aspirin Resistance in Acute Ischemic Stroke”. *Transl Stroke Res.* (2023) doi: 10.1007/s12975-023-01175-z
- Altundag, I., Guzel Tanoglu, E., Genc Yavuz, B., Yalcinkaya, B., Yurek, E., Colak, S. “The effect of ALPL Gene Polymorphism on the Development of Urolithiasis in the Turkish Population”, *Urolithiasis*, 51:1 (2023) DOI: 10.1007/s00240-022-01396-1
- Oztug M., Yalcinkaya M. “Development and validation of an HPLC-UV method for purity determination of DNA”. *Medicine Science* (2023), 12, 3, 876-82.
- Yalcinkaya, B., Tastekin, D., Guzelbulut, F., Akgoz, M., Pence, S. "Quantification of Cell-Free Circulating Mitochondrial DNA Copy Number Variation in Hepatocellular Carcinoma", *Revista da Associacao Medica Brasileira*, 68:9 (2022): 1161-1165
- Karaboce, B., Saban, E., Boyuk, A.A., Durmus, H.O., Hamid, R., Bas, A. "Inactivation of viruses on surfaces by infrared techniques", *International Journal of Thermal Sciences*, 179, doi.org/10.1016/j.ijthermalsci.2022.107595, (2022)

#### ➤ Congress Presentations:

- Taslak, H., Yalcinkaya, B. "Development of ddPCR Assay for Accurate Measurement of HER2 Copy Number Variation", 2022 Medical Technologies Congress (TIPTEKNO 2022), Antalya, 31 October-2 November 2022, DOI:10.1109/TIPTEKNO56568.2022.9960209, (2022), 1-3.
- Kaş B., Akyürek S., “Optimization Study for DNA Methylation Quantitation by HRM Analysis for DAPK1 and MGMT Genes” TBS International Biochemistry Congress 33<sup>rd</sup> National Biochemistry Congress Çeşme İzmir, Turkey 26-30 October 2022
- B. Yalcinkaya, H. Taslak, B. Gurel Gokmen, M. Gurboga, O. Bingol Ozakpinar, T. Tunali Akbay, Does digested breast milk have an effect on breast cancer? FEBS 2023 47<sup>th</sup> FEBS Congress P-04.1-32, Tours France
- H. TASLAK, B. Yalcinkaya, B. Gurel Gokmen, M. Gurboga, O. Bingol Ozakpinar, T. Tunali Akbay, In silico and in vitro analysis of the therapeutic potential of breast milk bioactive peptides on MALAT1 expression in MCF-7 breast cancer cell line. FEBS 2023 47th FEBS Congress P-04.1-33, Tours France

#### 4. Reference laboratory networks /collaborations focusing on developing /implementing reference measurement systems

➤ **JCTLM Activities**

TUBITAK UME became a member to JCTLM in 2012 and has actively participated to the JCTLM Members' and Stakeholders' Meetings since 2012. Biennial report was also submitted to JCTLM Executive Committee in 2021.

➤ **CCQM Activities**

As a member of CCQM, TUBITAK UME Chemistry Group scientists attended and actively contributed to OAWG, IAWG, NAWG, PAWG, CAWG, EAWG and SAWG meetings in 2022 and 2023.

Merve OZTUĞ is also a member of PAWG Focus Group 1 (SI Value Assignment of Purity) and PAWG Focus Group 2 (SI-traceable determination of peptides and proteins in complex matrices).

➤ **EMN: TraceLabMed:** European Metrology Network - Traceability in Laboratory Medicine, 2019 - 2024

➤ **EurA1c: The European HbA1c Trial "EQA Program"**

In 2016, the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) Committee Education in the Use of Biomarkers in Diabetes (C-EUBD) started a proficiency testing program for standardization of HbA1c measurements (EurA1c) throughout Europe. TUBITAK UME has also attended to these proficiency tests in 2022 and 2023.

#### 5. Open questions and suggestions to be addressed by JCTLM