The biennial activity report from the Joint Research Centre (JRC)

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

During the past two years the JRC has produced certified reference materials (CRMs) for biomarkers in various clinical fields:

a. Proteins in cerebrospinal fluid (CSF)

To support measurement standardisation of biomarkers for the early detection of Alzheimer's disease, the JRC released a panel of three pooled CSF materials with different levels of amyloid-β 1-42 (Aβ1-42). This project was done in close collaboration with the working group of the International Federation of Clinical Chemistry (IFCC) on CSF proteins. The CRMs, ERM-DA480/IFCC, ERM-DA481/IFCC and ERM-DA482/IFCC, were characterised with reference measurement procedures (RMPs) based on isotope dilution mass spectrometry. The certification report is available on-line.

The certification of Amyloid β1-42 in CSF in ERM®-DA480/IFCC, ERM®-DA481/IFCC and ERM®-DA482/IFCC, 2017, EUR 28691 EN, ISBN 978-92-79-70556-4 (PDF), ISSN 1831-9424 (online), doi: 10.2760/621427 available via https://crm.jrc.ec.europa.eu/

The intended use of the CRMs is either calibration or quality control of various methods measuring Aβ1-42 in CSF including commercial immunoassays. Commutability of the CRMs for these methods is therefore essential. A commutability study was performed and the results showed that the CRMs are commutable for various methods. This study and its outcome were described in the following publication:

Andreasson U, Kuhlmann J, Pannee J, et al., Commutability of the certified reference materials for the standardization of β-amyloid 1-42 assay in human cerebrospinal fluid: lessons for tau and β-amyloid 1-40 measurements. Clin Chem Lab Med. 2018;56(12):2058-2066

These CRMs are listed as higher order reference materials for Aβ1-42 in human CSF by the JCTLM.

After the release of the CRMs several commercial immunoassays were re-calibrated and a round-robin study is currently organized to see the effect of re-calibration on the measurements of patient samples. An article on the release of the CRMs and the re-calibration of commercial immunoassays will be published in the journal of the Alzheimer Association: Alzheimer's and Dementia.

b. Autoimmune disorders

For the development of CRMs in the field of autoimmune disorders the JRC collaborates with the IFCC Scientific Division Committee on Harmonization of Autoimmune Tests. Recently, a CRM was produced for immunoglobulin G autoantibodies against proteinase 3 anti-neutrophil cytoplasmic (IgG PR3 ANCA). These autoantibodies can be present in patients with small vessel–associated vasculitis. The intended use of the CRM is primarily calibration of immunoassay-based *in vitro* diagnostic devices. Several candidate materials were tested for their commutability in a dedicated study. Based on the results of this study the final format of the CRM was selected. The CRM, called ERM-DA483/IFCC, was produced from a plasmapheresis sample of a patient diagnosed with vasculitis and certified for the mass concentration of IgG PR3 ANCA. The certification report is available online and one related article has been published in a peer-reviewed journal:

The certification of the mass concentration of immunoglobulin G proteinase 3 anti-neutrophil cytoplasmic autoantibodies (IgG PR3 ANCA) in human serum: ERM® - DA483/IFCC, 2017, EUR 28537 EN, ISBN 978-92-79-66974-3, ISSN 1831-9424, doi: 10.2760/373057 available via https://crm.jrc.ec.europa.eu/

Monogioudi E, Sheldon J, Meroni PL, et al., Certified reference material against PR3 ANCA IgG autoantibodies. From development to certification, Clinical Chemistry and Laboratory Medicine, 2019;57(8):1197-1206 doi: 10.1515/cclm-2018-1095.

This CRM is listed as a higher order reference material for IgG PR3 ANCA in human serum by the JCTLM.

c. Enzymes

Building on a long tradition in the development of CRMs for the catalytic activity concentration of enzymes, the JRC produced a new CRM for α-amylase. First, a commutability study was performed with several commercial methods and the primary reference measurement procedure (PRMP) for the catalytic activity of α-amylase to identify the most suitable matrix. This study was designed and analysed according to the guidelines of the IFCC working group on commutability. The results of this study have been published.

Deprez L, Toussaint B, Zegers I, et al., Commutability Assessment of Candidate Reference Materials for Pancreatic α-Amylase. Clin Chem. 2018;64(8):1193-1202. doi: 10.1373/clinchem.2018.289744.

Afterwards, ERM-AD456/IFCC was produced taking into account the outcome of the commutability study. The CRM consists of human pancreatic α–amylase in a buffered solution containing human serum albumin. The certified value was obtained through an interlaboratory comparison study with 11 expert laboratories applying the PRMP for the catalytic activity of α–amylase at 37 °C as established by the IFCC. The main purpose of this CRM is to assess method performance of the PRMP but, in addition, the material can also be used as trueness control or external quality control material for commercial measurement systems if commutability has been proven for the assay concerned. The certification report is available on-line.

The certification of the catalytic activity concentration of alpha-amylase in ERM®-AD456/IFCC. EUR 29857 EN, ISBN 978-92-76-11236-5 (PDF), ISSN 1831-9424 (online) doi:10.2760/740548621427, available via https://crm.jrc.ec.europa.eu/

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

In the upcoming years, the JRC will continue the development of CRMs for biomarkers in various clinical fields:

a. Proteins in CSF

The existing CRMs ERM-DA480/IFCC, ERM-DA481/IFCC and ERM-DA482/IFCC may also be certified for their concentration of amyloid-β 1-40 (Aβ 1-40). In case those CRM are not suitable for the certification of Aβ 1-40 a new CRM will be developed.

The JRC will also support the development of an RMP for Tau in CSF which is done within the IFCC WG on CSF proteins. When the RMP is available the JRC intends to produce a CRM for tau in CSF.

b. Autoimmune disorders

The production of a CRM for IgG autoantibodies targeting glomerular basement membrane (anti-GBM) has started.

In addition, the JRC also plans to start the production of a CRM for IgG and IgA antibodies targeting tissue transglutaminase.

c. Apolipoproteins

The JRC supports the development of an LC-MS/MS-based RMP for a panel of clinically relevant serum apolipoproteins (apo) A-I, B, C-I, C-II , C-III, E and apo (a) which is done within the IFCC working group on Apolipoproteins by Mass Spectrometry. When the RMP is available the JRC plans to produce matrix CRMs for the above mentioned analytes.

d. HbA2

The JRC has started with the development of two CRMs for haemoglobin A2 in collaboration with the members of the IFCC working group on standardisation of haemoglobin A2 (WG-HbA2).

3. Promoting traceability in laboratory medicine

In addition to the publications mentioned above, the following manuscripts were also published:

Monogioudi E, Zegers I, Certified Reference Materials and their need in diagnosis of autoimmune disease, Mediterranean Journal of Rheumatology, 2019;30(1):26-32

Monogioudi E, Martos G, Hutu DP, et al., Standardisation of autoimmune testing – is it feasible? Clinical Chemistry and Laboratory Medicine, 2018; 56(10): 1734-1742

Staff members of the JRC also gave presentations at various congresses including:

"CRMs for protein In-vitro Diagnostics" given by I. Zegers at The Protein and Peptide Therapeutics and Diagnostic workshop (PPTD), 10-12 October 2018, Chendu , China

"New approach for assessing commutability of reference materials for clinical measurements" given by L. Deprez at International Symposium on Biological and Environmental Reference Materials (BERM), 24-26 September 2018, Berlin, Germany

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

A staff member of the JRC is an observer in the Executive Committee of the Scientific Division of the IFCC.

Several staff members of the JRC are members or consultants in the following IFCC working groups:

- CSF-Proteins (WG-CSF)
- Apolipoproteins by Mass Spectrometry (WG-APO MS)
- Commutability (WG-C)
- Fecal Immunochemical Testing (WG-FIT)

In addition, the JRC supports the IFCC Scientific Division Committee on Harmonization of Autoimmune Tests (C-HAT), the working group on Standardisation of Haemoglobin A2 (WG-HbA2) and the working group on Pancreatic Enzymes (WG-PE) by the production of CRMs as mention before.