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Molekylärbiologisk diagnostik – Specifikationer för den preanalytiska processen för FFPE vävnad – Del 2: Isolerade proteiner

Molecular in vitro diagnostic examinations – Specifications for pre-examination processes for FFPE tissue – Part 2: Isolated proteins

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Molecular in vitro diagnostic examinations - Specifications for pre-examination processes for FFPE tissue - Part 2: Isolated proteins

Tests de diagnostic moléculaire in vitro - Spécifications pour les processus préanalytiques pour tissu FFPE - Partie 2: Protéines extraites

Molekularanalytische in-vitro-diagnostische Verfahren - Spezifikationen für präanalytische Prozesse für FFPE-Gewebeproben - Teil 2: Isolierte Proteine

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European foreword

This document (CEN/TS 16827-2:2015) has been prepared by Technical Committee CEN/TC 140 "*In vitro* diagnostic medical devices", the secretariat of which is held by DIN.

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Introduction

Molecular in vitro diagnostics has enabled a significant progress in medicine. Further progress is expected by new technologies analysing signatures of nucleic acids, proteins, and metabolites in human tissues and body fluids. However, the profiles and/or integrity of these molecules can change drastically during primary sample collection, transport, storage, and processing thus making the outcome from diagnostics or research unreliable or even impossible because the subsequent analytical assay will not determine the situation in the patient but an artificial molecular pattern generated during the pre-examination process.

Although originally thought as being impossible due to the crosslinking activities of formaldehyde, protein extraction techniques from formalin formalin fixed and paraffin embedded (FFPE) tissues have been much improved in recent years. Heat-induced reversal of formaldehyde-induced crosslinks has been demonstrated as an essential step in the protein extraction procedures [1], [2]. Currently, most investigators accept that proteins extracted from FFPE tissue are suitable for downstream proteomic analysis [3].

However, a standardization of the entire process from primary sample collection to protein analysis is needed. Studies have been undertaken to determine the important influencing factors. This Technical Specification draws upon such work to codify and standardise the steps for FFPE tissue with regard to protein analysis in what is referred to as the preanalytical phase.

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1 Scope

This Technical Specification gives recommendations for the handling, documentation and processing of FFPE tissue specimens intended for the analysis of extracted proteins during the preanalytical phase before a molecular assay is performed. This Technical Specification is applicable to molecular *in vitro* diagnostic examinations (e.g., *in vitro* diagnostic laboratories, laboratory customers, developers and manufacturers of *in vitro* diagnostics, institutions and commercial organizations performing biomedical research, biobanks, and regulatory authorities).

Protein profiles and protein-protein interactions in tissues can change drastically before and after collection (due to e.g., gene induction, gene down regulation, protein degradation). Protein species amounts can change differently in tissues from different donors / patients. The expression of genes can be influenced by the given treatment or intervention (surgery, biopsy), or drugs administered for anaesthesia or even treatment of concomitant disease as well as by the different environment conditions after the tissue removal from the body.

Furthermore, the formalin fixation and paraffin embedding process leads to modifications of the protein molecules, which can impact the validity and reliability of the analytical test results.

Therefore, it is essential to take special measures to minimize the described profile changes and modifications within the tissue for subsequent protein analysis.

This document is not applicable for protein analysis by immunohistochemistry.

2 Normative references

The following documents, in whole or in part, are normatively referenced in this document and are indispensable for its application. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

EN ISO 15189:2012, *Medical laboratories — Requirements for quality and competence (ISO 15189:2012, Corrected version 2014-08-15)*

ISO 15190, *Medical laboratories — Requirements for safety*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in EN ISO 15189:2012 and the following apply.

3.1
ambient temperature
unregulated temperature of the surrounding air

3.2
analytical phase
processes that start with the isolated analyte and include all kinds of parameter testing or chemical manipulation for quantitative or qualitative analysis

3.3
cold ischemia
condition after removal of the tissue from the body until its stabilization or fixation

3.4
FFPE
formalin fixation and paraffin embedding

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3.5
FFPE tissues
formalin fixed and paraffin embedded tissues

3.6
formalin
saturated formaldehyde solution containing a mas fraction of 37 % (corresponding to a volume fraction of 40 %) formaldehyde, termed 100 % formalin

3.7
formalin fixation
treatment of a sample with standard buffered formalin solution for stabilization

3.8
pre-examination processes
preanalytical phase
preanalytical workflow
processes that start, in chronological order, from the clinician's request and include the examination request, preparation and identification of the patient, surgical procedure, collection of the primary sample(s), temporary storage, transportation to and within the analytical laboratory, aliquoting, retrieval, isolation of analytes, and end when the analytical examination begins

[SOURCE: EN ISO 15189:2012, definition 3.15, modified — An additional term was added and more details were included.]

Note 1 to entry: The preanalytical phase may include preparative processes that may influence the outcome of the intended examination.

3.9
primary sample
specimen
discrete portion of a body fluid, breath, hair or tissue taken for examination, study or analysis of one or more quantities or properties assumed to apply for the whole

[SOURCE: EN ISO 15189:2012, 3.16, modified — The term and definition is used here without the original notes.]

3.10
protein
type of biological macromolecules composed of one or more chains with a defined sequence of amino acids connected through peptide bonds

3.11
protein profile
amounts of the individual protein molecules that are present in a sample and that can be measured in the absence of any losses, inhibition and interference

3.12
protein species
amounts of a chemically clearly-defined protein corresponding to one spot on a high-performance 2-dimensional gel electrophoresis pattern

[SOURCE: Jungblut *et. al.*1996]

3.13
PTM
post translational modifications
chemical alterations to a primary protein structure, often crucial for conferring biological activity on a protein

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[SOURCE: Encyclopedia of Psychopharmacology, 2010]

3.14
room temperature
temperature which is defined as 18 °C to 25 °C for the purposes of this document

3.15
sample
one or more parts taken from a primary sample

[SOURCE: EN ISO 15189:2012, 3.24, modified — The example was not taken over.]

3.16
stability
ability of a sample material, when stored under specified conditions, to maintain a stated property value within specified limits for a specified period of time

[SOURCE: ISO Guide 30:1992, 2.7]

Note 1 to entry: The measured constituent for the purpose of this document is RNA.

3.17
standard buffered formalin solution
10 % formalin solution containing a mass fraction of 3,7 % (corresponding to a volume fraction of 4 %) formaldehyde buffered to pH 6,8 to pH 7,2

Note 1 to entry: Standard buffered formalin solutions often contain methanol to inhibit oxidation and polymerization of formaldehyde.

3.18
warm ischemia
warm Ischemia is the condition where the tissue is deprived of its normal blood supply containing oxygen and nutrients while the tissue is at body temperature

4 General considerations

For general statements on primary sample collection and handling (including avoidance of cross contaminations) see EN ISO 15189:2012, 5.4.4, 5.2.6. Consumables including kits shall be verified before use in examination (see EN ISO 15189:2012, 5.3.2.3); EN ISO 15189:2012, 5.5.1.2 and 5.5.1.3 can also apply.

As all steps of a diagnostic workflow can influence the final analytical performance, the entire workflow comprising the preanalytical steps, including information on biomolecule stability and storage conditions, and analytical steps should be verified and validated (see EN ISO 15189).

The stability of the specific protein(s) of interest and their posttranslational modifications (if important for the assay) should be investigated throughout the complete preanalytical workflow prior to the development and implementation of an analytical test.

Before tissues are fixed in standard buffered formalin solution, protein amounts, conformations and binding status can change e.g. by protein degradation and altered synthesis following gene induction, gene down regulation, RNA degradation, and changes of the biochemical pathway and energy status. These effects depend on the duration of warm and cold ischemia and the ambient temperature before formalin fixation. In addition, the described effects can vary in tissues from different donors / patients.

Generally, the longer the warm and cold ischemia times and the higher the ambient temperature before fixation the tissue specimen, the higher is the risk that changes in the protein profile can occur.