



SLOVENSKI STANDARD

kSIST-TS FprCEN/TS 17742:2021

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Molekularne diagnostične preiskave in vitro - Specifikacije za predpreiskovalne procese za vensko polno kri - Iz plazme izolirana cirkulirajoča brezcelična RNK

Molecular in vitro diagnostic examinations - Specifications for pre-examination processes for venous whole blood - Isolated circulating cell free RNA from plasma

Molekularanalytische in-vitro-diagnostische Verfahren - Spezifikationen für präanalytische Prozesse für venöse Vollblutproben - Isolierte zirkulierende zellfreie RNA aus Plasma

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Ta slovenski standard je istoveten z: **FprCEN/TS 17742**

ICS:

11.100.10	Diagnostični preskusni sistemi in vitro	In vitro diagnostic test systems
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ICS 11.100.10

English Version

**Molecular in vitro diagnostic examinations - Specifications
for pre-examination processes for venous whole blood -
Isolated circulating cell free RNA from plasma**

Molekularanalytische in-vitro-diagnostische Verfahren
- Spezifikationen für präanalytische Prozesse für
venöse Vollblutproben - Isolierte zirkulierende
zellfreie RNA aus Plasma

This draft Technical Specification is submitted to CEN members for Vote. It has been drawn up by the Technical Committee CEN/TC 140.

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Recipients of this draft are invited to submit, with their comments, notification of any relevant patent rights of which they are aware and to provide supporting documentation.

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EUROPEAN COMMITTEE FOR STANDARDIZATION
COMITÉ EUROPÉEN DE NORMALISATION
EUROPÄISCHES KOMITEE FÜR NORMUNG

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European foreword

This document (FprCEN/TS 17742:2021) has been prepared by Technical Committee CEN/TC 140 “In vitro diagnostic medical devices”, the secretariat of which is held by DIN.

This document is currently submitted to the Vote on TS.

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FprCEN/TS 17742:2021 (E)

Introduction

Molecular *in vitro* diagnostics has enabled a significant progress in medicine. Further progress is expected by new technologies analysing profiles of nucleic acids, proteins, and metabolites in human tissues and body fluids. However, the profiles of these molecules can change drastically during the pre-examination process, including the specimen collection, transport, storage and processing.

Consequently, this makes the outcome from diagnostics or research unreliable or even impossible, as the subsequent examination might not determine the real situation in the patient, but an artificial profile generated during the pre-examination processes.

Besides cell free circulating nucleic acids, circulating tumour cells (CTCs) and other rare cells, cell free circulating RNA (ccfRNA) represents another key component of liquid biopsies. Therefore, there is a strongly increasing interest in emerging diagnostics and research in ccfRNA.

In blood, ccfRNA is composed of extracellular RNA present both in and outside of exosomes and other extracellular vesicles. The pre-examination process described in this document results in total ccfRNA isolated from blood plasma.

ccfRNA profiles and quantity can change significantly after blood collection, e.g. by release and/or uptake of RNA containing extracellular vesicles by cells present in the blood specimen as well as by ccfRNA degradation. Therefore, special measures have to be taken to secure good quality specimens for ccfRNA examination.

Standardization of the entire workflow from specimen collection to the ccfRNA examination is therefore needed. Studies have been undertaken to determine the important influencing factors. This document draws upon such work to codify and standardize the steps of ccfRNA examination in what is referred to as the pre-examination phase.

In this document, the following verbal forms are used:

- “shall” indicates a requirement;
- “should” indicates a recommendation;
- “may” indicates a permission;
- “can” indicates a possibility or a capability.

1 Scope

This document specifies requirements and recommendations for the pre-examination phase of circulating cell free RNA (ccfRNA) from venous whole blood specimens, including but not limited to the collection, handling, storage, processing and documentation of venous whole blood specimens intended for ccfRNA examination. This document covers specimens collected in venous whole blood collection tubes.

The pre-examination process described in this document results in circulating cell free RNA isolated from blood plasma without prior enrichment of exosomes and other extracellular vesicles.

This document is applicable to molecular *in vitro* diagnostic examinations performed by medical laboratories. It is also intended to be used by laboratory customers, *in vitro* diagnostics developers and manufacturers, biobanks, institutions and commercial organizations performing biomedical research, and regulatory authorities.

Different dedicated measures need to be taken during the pre-examination phase for isolated RNA from enriched exosomes and other extracellular vesicles enriched from venous whole blood and for cellular RNA isolated from venous whole blood. These are not described in this document but are covered in CEN/TS 17747, *Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for exosomes and other extracellular vesicles in venous whole blood — Isolated DNA, RNA and proteins*, and in EN ISO 20186-1, *Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for venous whole blood — Part 1: Isolated cellular RNA*.

NOTE International, national or regional regulations or requirements can also apply to specific topics covered in this document.

2 Normative references (standards.iteh.ai)

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. 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, *Medical laboratories - Requirements for quality and competence (ISO 15189)*

EN ISO 15190, *Medical laboratories — Requirements for safety (ISO 15190)*

3 Terms and definitions

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

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

- ISO Online browsing platform: available at <https://www.iso.org/obp>
- IEC Electropedia: available at <https://www.electropedia.org/>

3.1

aliquot

portion of a larger amount of homogenous material, assumed to be taken with negligible sampling error

Note 1 to entry: The term is usually applied to fluids. Tissues are heterogeneous and therefore cannot be aliquoted.

Note 2 to entry: The definition is derived from the Compendium of Chemical Terminology Gold Book. International Union of Pure and Applied Chemistry. Version 2.3.3., 2014; the PAC, 1990,62,1193 (Nomenclature for sampling in analytical chemistry (Recommendations 1990)) p. 1206; and the PAC 1990, 62, 2167 (Glossary of atmospheric chemistry terms (Recommendations 1990)) p. 2173.

FprCEN/TS 17742:2021 (E)**3.2****ambient temperature**

unregulated temperature of the surrounding air

[SOURCE: EN ISO 20166-1:2018, 3.2]

3.3**analyte**

component represented in the name of a measurable quantity

[SOURCE: EN ISO 17511:2020, 3.2, modified — Deleted Example.]

3.4**backflow**

flow of a liquid opposite to the usual or desired direction

3.5**blood collection set**

intravenous device specialized for venipuncture consisting of a stainless steel beveled needle and tube (tubing) with attached plastic wings and fitting connector

Note 1 to entry: The connector attaches to an additional blood collection device, e.g. a blood collection tube.

3.6**blood collection tube**

tube used for blood collection, usually with a vacuum which forces blood from the vein through the needle into the tube

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3.7**circulating cell free DNA****ccfDNA**

extracellular human DNA present in blood and plasma

Note 1 to entry: ccfDNA includes DNA present in extracellular vesicles such as exosomes.

3.8**circulating cell free RNA****ccfRNA**

extracellular human RNA present in blood and plasma

Note 1 to entry: ccfRNA includes RNA present in extracellular vesicles such as exosomes.

3.9**circulating cell free RNA profile****ccfRNA profile**

amount of different ccfRNA molecules, present in blood and plasma that can be measured in the absence of any losses, inhibition and interference

3.10**closed system**

non-modifiable system provided by the vendor including all necessary components for the examination (i.e. hardware, software, procedures and reagents)

3.11**deoxyribonucleic acid****DNA**

polymer of deoxyribonucleotides occurring in a double-stranded (dsDNA) or single-stranded (ssDNA) form

[SOURCE: EN ISO 22174:2005, 3.1.2]

3.12**deoxyribonuclease****DNase**

enzyme that catalyzes the degradation of DNA into smaller components

3.13**examination****analytical test**

set of operations having the object of determining the value or characteristics of a property

Note 1 to entry: Processes (i.e. set of operations) that start with the isolated analyte and include all kinds of parameter testing or chemical manipulation for quantitative or qualitative examination.

[SOURCE: EN ISO 15189:2012, 3.7, modified — Term and definition are used here without the original notes; an additional preferred term was added.]

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3.14**examination manufacturer****analytical test manufacturer**

entity that manufactures and/or produces a specific analytical test

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3.15**examination performance****analytical test performance****analytical performance**

accuracy, precision, and sensitivity of a test to measure the analyte of interest

Note 1 to entry: Other test performance characteristics such as robustness, repeatability can apply as well.

[SOURCE: EN ISO 20184-1:2018, 3.4]

3.16**extracellular vesicle****EV**

particle naturally released from the cell that is delimited by a lipid bilayer and cannot replicate, i.e. does not contain a functional nucleus

EXAMPLE Exosomes, endosomes, oncosomes, apoptotic bodies

[SOURCE: [13]]

FprCEN/TS 17742:2021 (E)**3.17****interfering substance**

endogenous or exogenous substance in clinical specimens/samples that can alter an examination result

Note 1 to entry: Examples of endogenous substances are blood components and acidic polysaccharides.

Note 2 to entry: Examples of exogenous substances are talc and anticoagulant.

3.18**laboratory developed procedure**

modified commercially available *in vitro* diagnostic device or fully in house developed procedure

3.19**needle holder**

barrel used in routine venepuncture procedures to hold the blood collection tube in place and to protect the phlebotomist from direct contact with blood

3.20**pre-examination process****preanalytical phase****preanalytical workflow****pre-examination phase**

process that starts, in chronological order, from the clinician's request and includes the examination request, preparation and identification of the patient, collection of the primary sample(s), transportation to and within the medical laboratory, storage, isolation of analytes, and ends when the analytical examination begins

Note 1 to entry: The pre-examination phase includes preparative processes, e.g. RNA isolation procedures, which influence the outcome of the intended examination.

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

3.21**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 are used here without the original notes.]

3.22**ribonucleic acid****RNA**

polymer of ribonucleotides occurring in a double-stranded or single-stranded form

[SOURCE: EN ISO 22174:2005, 3.1.3]

3.23**ribonuclease****RNase**

enzyme that catalyses the degradation of RNA into smaller components

3.24**room temperature**

temperature in the range of 18 °C to 25 °C

Note 1 to entry: Local or national regulations can have different definitions.

[SOURCE: EN ISO 20166-1:2018, 3.22]

3.25**sample**

one or more parts taken from a primary sample

[SOURCE: EN ISO 15189:2012, 3.24, modified — Example has been removed.]

3.26**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 30:2015, 2.1.15, modified — The phrase “reference material” has been replaced by “sample material”.]

3.27**storage**

prolonged interruption of the pre-analytical workflow of a sample or analyte respectively, or of their derivatives, under appropriate conditions in order to preserve their properties

Note 1 to entry: Long-term storage typically occurs in laboratory archives or in biobanks.

[SOURCE: EN ISO 20184-1:2017/2018, 3.21, modified — Example has been removed.]

3.28**validation**

confirmation, through the provision of objective evidence, that the requirements for a specific intended use or application have been fulfilled

Note 1 to entry: The term “validated” is used to designate the corresponding status.

[SOURCE: ISO 9000:2015, 3.8.13, modified — Note 1 and Note 3 have been omitted.]

3.29**venous whole blood**

blood collected after directly puncturing a vein, usually with a needle and syringe, or other collection device