SLOVENSKI STANDARD
SIST-TS CEN/TS 17742:2022

01-junij-2022

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

Analyses de diagnostic moléculaire in vitro — Spécifications relatives auc processus préanalytiques pour le sang total veineux — ARN libre circulant extrait du plasma

Ta slovenski standard je istoveten z: **CEN/TS 17742:2022**

ICS:

11.100.10	Diagnostični preskusni sistemi in vitro	In vitro diagnostic test systems

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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

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EUROPEAN COMMITTEE FOR STANDARDIZATION
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CEN-CENELEC Management Centre: Rue de la Science 23, B-1040 Brussels

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European foreword

This document (CEN/TS 17742:2022) 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 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 circulating cell free DNA (ccfDNA), circulating tumour cells (CTCs) and other rare cells, circulating cell free 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,[1] *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

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)*

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 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/

[1] Under preparation. Stage at the time of publication: FprCEN/TS 17747.

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.

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: 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 bevelled 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

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.]

3.14
examination manufacturer
analytical test manufacturer
entity that manufactures and/or produces a specific analytical test

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]]

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 20184-1:2018, 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.]