SLOVENSKI STANDARD
SIST-TS CEN/TS 16835-3:2015

01-december-2015

Molekularne diagnostične preiskave in vitro - Specifikacije za predpreiskovalne procese za vensko polno kri - 3. del: Iz plazme izolirani cirkulirajoči brezcelični DNA

Molecular in vitro diagnostic examinations - Specifications for pre-examination processes for venous whole blood - Part 3: Isolated circulating cell free DNA from plasma

Molekularanalytische in-vitro-diagnostische Verfahren - Spezifikationen für präanalytische Prozesse für venöses Vollblutproben - Teil 3: Aus Plasma isolierte zirkulierende zellfreie DNS

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Tests de diagnostic moléculaire in vitro - Spécifications relatives aux processus pré-analytiques pour le sang total veineux - Partie 3: ADN libre circulant extrait du plasma

Ta slovenski standard je istoveten z: **CEN/TS 16835-3:2015**

ICS:

11.100.10	Diagnostični preskusni sistemi in vitro	In vitro diagnostic test systems
11.100.30	Analiza krvi in urina	Analysis of blood and urine

SIST-TS CEN/TS 16835-3:2015 **en,fr,de**

2003-01.Slovenski inštitut za standardizacijo. Razmnoževanje celote ali delov tega standarda ni dovoljeno.

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TECHNICAL SPECIFICATION

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English Version

Molecular in vitro diagnostic examinations - Specifications for pre-examination processes for venous whole blood - Part 3: Isolated circulating cell free DNA from plasma

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This Technical Specification (CEN/TS) was approved by CEN on 31 August 2015 for provisional application.

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European foreword

This document (CEN/TS 16835-3:2015) 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 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 profile generated during the pre-examination process. Therefore, a standardization of the entire process from primary sample collection to circulating cell free DNA (ccfDNA) analysis is needed. Studies have been undertaken to determine the important influencing factors. This Technical Specification draws upon such work to codify and standardize the steps for circulating cell free DNA analysis from plasma prepared from human venous whole blood in what is referred to as the preanalytical phase.

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1 Scope

This Technical Specification recommends the handling, documentation and processing of venous whole blood specimens intended for circulating cell free DNA (ccfDNA) analysis during the preanalytical phase before a molecular assay is performed. This Technical Specification covers specimens collected by venous whole blood collection tubes. This Technical Specification is applicable to molecular *in vitro* diagnostic examinations (e.g. *in vitro* diagnostic laboratories, laboratory customers, *in vitro* diagnostics developers and manufacturers, institutions and commercial organizations performing biomedical research, biobanks, and regulatory authorities).

Blood ccfDNA profiles can change significantly after blood collection from the donor (e.g. release of genomic DNA from white blood cells, ccfDNA fragmentation and ccfDNA quantity change). Special measures need to be taken to secure good quality blood samples for ccfDNA analysis and storage.

Different dedicated measures need to be taken for preserving blood genomic DNA. These are not described in this Technical Specification. Blood genomic DNA is covered in CEN/TS 16835-2, *Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for venous whole blood — Part 2: Isolated genomic DNA*

NOTE CcfDNA obtained from blood by the procedures suggested in this document can contain DNA present in exosomes [3] [4].

DNA from pathogens present in blood is not covered by this Technical Specification.

2 Normative references

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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.

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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 kind of parameter testing or chemical manipulation for quantitative or qualitative analysis

3.3
ccfDNA
circulating cell free DNA
extracellular human DNA present in blood, serum and plasma

Note 1 to entry: ccfDNA can include DNA present in vesicles such as exosomes [3] [4].

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3.4
ccfDNA profile/s
circulating cell free DNA profile/s
amounts of different ccfDNA molecules, that are present in blood and plasma, that can be measured in the absence of any losses, inhibition and interference

3.5
cryo-precipitates
insoluble residue when frozen plasma is thawed

3.6
DNA
deoxyribonucleic acid
polymer of deoxyribonucleotides occurring in a double-stranded (dsDNA) or single-stranded (ssDNA) form

[SOURCE: EN ISO 22174:2005, 3.1.2]

3.7
pre-examination processes
preanalytical phase
preanalytical workflow
processes that start, in chronological order, from the clinicians' request and include the examination request, preparation and identification of the patient, collection of the primary sample(s), temporary storage, transportation to and within the analytical laboratory, aliquotting, retrieval, isolation of analytes, and end when the analytical examination begins

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

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

3.8
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.]

3.9
room temperature
temperature which is defined as 18 °C to 25 °C for the purposes of this document

3.10
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 words “reference material” were replaced by “sample material".]

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

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4 General considerations

For general statements on primary sample collection and handling (including avoidance of cross contaminations), see EN ISO 15189:2012, 5.2.6, 5.4.4. 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 sample stability and storage conditions, and analytical steps should be verified and validated (see EN ISO 15189).

Blood circulating cell free DNA profiles can change significantly after blood collection and plasma separation. The release of genomic DNA from white blood cells can change the ccfDNA profile significantly. This can impact the validity of the analytical test results. Additional post-collection effects can also occur e.g. ccfDNA fragmentation [5], [6], [7], [8]. These changes can vary individually in different donors' / patients' blood depending on pathophysiological conditions [5] [9], [10], [11].

The stability of the specific blood ccfDNA profile of interest should be investigated throughout the complete preanalytical workflow e.g. by applying the intended analytical test in time course studies reflecting the individual preanalytical workflow steps such as transport and storage.

Before or during the design of the analytical test system, it should be investigated and ensured that the blood ccfDNA profile/s intended to be analysed in the analytical test is/are not affected by the envisioned entire pre-analytical workflow.

If a commercial product is not used in accordance with the manufacturers' instructions, responsibility for its validation, verification, use and performance lies with the user.

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Safety regulations on facilities, transport and handling shall be considered (EN ISO 15189:2012, 5.2.3 and 5.4.5, and ISO 15190).

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5 Outside the laboratory

5.1 Primary venous whole blood collection manual

5.1.1 Information about the primary sample donor

The documentation should include, but is not limited to:

a) the primary donor / patient ID, which can be in the form of a code;

b) the health status and relevant lifestyle factors of the blood donor (e.g. healthy, gender, age, disease type, gestational age);

NOTE In particular e.g. cancer, inflammation, diabetes, hepatic disease, coronary disease, respiratory syndrome, trauma, after exhaustive exercise [5], in elderly patients suffering from acute or chronic disease, first trimester of pregnancy, placental disorders as pre-term labour, pre-eclampsia and malimplantation have been reported to affect both blood ccfDNA quantity and fragmentation [5], [9], [10], [11].

c) the information about medical treatment and special treatment prior to blood collection (e.g. anaesthetics, medications, fasting status);

d) the type and purpose of the proposed analytical test requested.

See also EN ISO 15189:2012, 5.4.4.