
Molekularne diagnostične preiskave in vitro - Specifikacije za postopke pred pregledom urina in drugih telesnih tekočin - Izolirana prosta celična DNK

Molecular in vitro diagnostic examinations - Specifications for pre-examination processes for urine and other body fluids - Isolated cell free DNA

Molekularanalytische in-vitro diagnostische Verfahren - Spezifikationen für präanalytische Prozesse für Urin und andere Körperflüssigkeiten - Isolierte zellfreie DNA

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ICS:

11.100.10	Diagnostični preskusni sistemi in vitro	In vitro diagnostic test systems
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**Molecular in vitro diagnostic examinations - Specifications
for pre-examination processes for urine and other body
fluids - Isolated cell free DNA**

Molekularanalytische in-vitro-diagnostische Verfahren
- Spezifikationen für präanalytische Prozesse für Urin
und andere Körperflüssigkeiten - Isolierte zellfreie
DNA

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 17811:2022) 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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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 specimen 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.

Most of the DNA in the body is located within cells, but a small amount of nucleic acids can also be found outside of cells, so called cell-free DNA (cfDNA). In case of circulating body fluids such as blood, this DNA is called circulating cell-free DNA (ccfDNA) and in case of non-circulating body fluids such as urine, saliva, cerebrospinal fluid, pleural effusion, ascites, and synovial fluid, the DNA is called cell-free DNA (cfDNA). cfDNA is of specific interest, as for example cfDNA in urine originates from cells from the genitourinary tract or from ccfDNA in circulation passing through glomerular filtration [1]. cfDNA from cancerous or malignant cells in urine have been associated with cancer specific sequences, epigenetic and structural changes [2], [3].

Standardization of the entire workflow from specimen collection to the cfDNA examination is needed to minimize release of DNA from cells into the fluid, and degradation of cfDNA in the specimen, which can change the original native cfDNA profile in the body fluid after specimen collection. Post collection microbial growth in the specimen can further enhance the degradation of the cfDNA, e.g. in urine and saliva. Studies have been undertaken to determine the important influencing factors as they can impact the sensitivity and reliability of cfDNA examination from urine and other body fluids.

This document draws upon such work to codify and standardize the steps for cfDNA examination from body fluids in what is referred to as the pre-examination phase.

In this document, the following verbal forms are used:

- “shall” indicates a requirement; [kSIST-TS FprCEN/TS 17811:2022](https://standards.iteh.ai/catalog/standards/sist/2814a6fb-a77c-43a9-8760-e50efa04b3c7/ksist-ts-fprcen-ts-17811-2022)
- “should” indicates a recommendation; <https://standards.iteh.ai/catalog/standards/sist/2814a6fb-a77c-43a9-8760-e50efa04b3c7/ksist-ts-fprcen-ts-17811-2022>
- “may” indicates a permission;
- “can” indicates a possibility or a capability.

1 Scope

This document specifies requirements and gives recommendations on the handling, storage, processing and documentation of body fluids specimens intended for human cfDNA examination during the pre-examination phase before a molecular examination is performed.

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

Dedicated measures that need to be taken for cytohistological analysis of body fluid derived nucleated cells are not described in this technical specification. Neither are measures for preserving and handling of pathogens, and other bacterial or whole microbiome DNA in body fluids described.

Different dedicated measures need to be taken for preserving ccfDNA from other body fluids such as blood, lymph and others. These are not described in this document. ccfDNA from blood is covered in EN ISO 20186-3.

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)*

3 Terms and definitions

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

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 [4], [5] and [6].

3.2

ambient temperature

Unregulated temperature of the surrounding air

3.3

analyte

component represented in the name of a measurable quantity

[SOURCE: EN ISO 17511:2021, 3.1 — Deleted example.]

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3.4

analytical test performance**analytical performance****examination 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]

3.5

ascites

abnormal build-up of fluid in the abdomen that can cause swelling

Note 1 to entry: In late-stage cancer, tumour cells can be found in the fluid in the abdomen.

Note 2 to entry: Ascites also occurs in patients with liver disease.

Note 3 to entry: This definition was derived from [7].

3.6

body fluid collection device

tube or other container in which the body fluid (e.g. urine) specimen is collected

3.7

ccfDNA**circulating cell free DNA**

extracellular human DNA present in blood and plasma

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

[SOURCE: EN ISO 20186-3:2019, 3.5]

3.8

cfDNA**cell free DNA**

extracellular human DNA present in body liquids such as urine

Note 1 to entry: cfDNA can include DNA present in vesicles such as exosomes [8].

3.9

cfDNA profile**cell free DNA profile**

amount of different cfDNA molecules, that are present in a body liquid, 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 analysis (i.e., hardware, software, procedures and reagents)

3.11**CSF****cerebrospinal fluid**

fluid that flows in and around the hollow spaces of the brain and spinal cord, and between two of the meninges (the thin layers of tissue that cover and protect the brain and spinal cord)

Note 1 to entry: Cerebrospinal fluid is made by tissue called the choroid plexus in the ventricles (hollow spaces) in the brain.

Note 2 to entry: This definition was derived from [7].

3.12**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]

3.13**DNA stabilizers**

compounds, solutions or mixtures that are designed to minimize degradation and fragmentation of cfDNA as well as release of genomic DNA from nucleated cells

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

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

Note 1 to entry: Processes that start with the isolated measurand 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 term was added.]

3.15**examination manufacturer****analytical test manufacturer**

entity that manufactures and/or produces a specific analytical test

[SOURCE: FprCEN/TS 17747:2021, 3.9 — Deleted Note.]

3.16**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]

FprCEN/TS 17811:2022 (E)**3.17****genomic DNA****gDNA**

genomic DNA present in nucleated cells

3.18**homogenous**

uniform in structure and composition

3.19**interfering substances**

endogenous or exogenous substances (e.g. stabilization solution) that can be present in specimens and that can alter an examination result

3.20**microorganisms**

entity of microscopic size, encompassing bacteria, fungi, protozoa and viruses

[SOURCE: ISO 18362:2016, 3.18]

3.21**pleural effusion**

abnormal collection of fluid between the thin layers of tissue (pleura) lining the lung and the wall of the chest cavity

Note 1 to entry: This definition was derived from [7].

3.22**pre-examination processes****pre-analytical phase****pre-analytical workflow****pre-examination phase**

processes that start, in chronological order, from the clinician's request and include the examination request, preparation and identification of the patient, collection of the primary sample(s), transportation to and within the analytical laboratory, storage, isolation of analytes, and end when the analytical examination begins

Note 1 to entry: The pre-examination phase includes preparative processes that 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.]

3.23**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.]

3.24**proficiency test**

evaluation of participant performance against pre-established criteria by means of inter-laboratory comparisons

[SOURCE: EN ISO/IEC 17043:2010, 3.7, modified — Term and definition are used here without the original notes.]

3.25**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]

3.26**sample**

one or more parts taken from a primary sample

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

3.27**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

Note 1 to entry: The measurand constituent for the purpose of this document is isolated DNA.

[SOURCE: ISO Guide 30:2015, 2.1.15, modified — The words “reference material” were replaced by “sample material”.] <https://standards.iteh.ai/catalog/standards/sist/2814a6fb-a77c-45a9-8760-e50efa04b3c7/ksist-ts-fprcen-ts-17811-2022>

3.28**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: ISO 20184-1:2018, 3.21, modified — Example has been removed.]

3.29**synovial fluid**

transparent, sticky liquid produced in joints (i.e. places where two bones are connected) that allows the bones and tendons to move smoothly

Note 1 to entry: In pathological situations the collected synovial fluid can have a different colour.

Note 2 to entry: This definition was derived from [9].