SLOVENSKI STANDARD
oSIST prEN ISO 18704:2024

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Molekularne diagnostične preiskave in vitro - Specifikacije za predpreiskovalne procese pregleda urina in drugih telesnih tekočin - Izolirana brezcelična DNK (ISO/DIS 18704:2024)

Molecular in vitro diagnostic examinations - Specifications for pre-examination processes for urine and other body fluids - Isolated cell free DNA (ISO/DIS 18704:2024)

Molekularanalytische in-vitro-diagnostische Verfahren - Spezifikationen für präanalytische Prozesse für Urin und andere Körperflüssigkeiten - Isolierte zellfreie DNA (ISO/DIS 18704:2024)

Analyses de diagnostic moléculaire in vitro - Spécifications relatives aux processus préanalytiques pour l'urine et d'autres liquides corporels - ADN libre extrait (ISO/DIS 18704:2024)

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

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT), see www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 212, *Medical laboratories and in vitro diagnostic systems*.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

Molecular in vitro diagnostics has enabled significant progress in medicine. Further progress has been achieved and is still expected by new technologies used to examine profiles of nucleic acids, proteins, and metabolites in human tissues and body fluids (e.g. genomic, epigenomic, transcriptomic, proteomic and metabolomic profiling). However, the profiles of these molecules can change drastically during specimen collection, transport, storage and processing. This can make the outcome from diagnostics or research unreliable or even result in failure because the subsequent examination will not measure the genuine cfDNA profile as it was in the patient, but a profile altered by the pre-examination process. Therefore, specifying, developing, verifying and validating preanalytical workflows has become an essential part of examination development[1].

Most of the DNA in the body is located within cells, but small amounts of DNA originating from cells can also be found outside of cells (extracellular DNA). 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 passing through glomerular filtration[2]. cfDNA from cancerous or malignant cells in urine have been associated with cancer specific sequences, epigenetic and structural changes[3],[4]. Urine is currently the most frequently used non-circulating body fluid for cfDNA examination because it is easily obtained from patients. Although urine is often described as the major specimen type, in this document the term body fluid is used for urine and other body fluids as defined in chapter 3.

Standardization of the entire workflow from specimen collection to the cfDNA examination is needed to minimize post-collection 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. Post collection microbial growth in the specimen can further enhance the degradation of the cfDNA, e.g. in urine and saliva. Furthermore, the isolation of cfDNA can lead to a cfDNA profile bias. Different methods to determine cfDNA yield and quality can lead to additional variations and impacts.

Studies have been undertaken to determine the pre-examination sources of these and other variables, as they can impact the cfDNA examination. This can compromise the specified examination performance characteristics, such as sensitivity, specificity, linearity and reproducibility. It can also impact the examination reliability which could lead to an erroneous examination result and misdiagnosis.

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;

— “should” indicates a recommendation;

— “may” indicates a permission;

— “can” indicates a possibility or a capability.

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

1 Scope

This document specifies requirements and provides recommendations for the pre-examination phase of cell free DNA (cfDNA) from body fluid specimens other than blood, including but not limited to the collection, handling, storage, transport, processing and documentation of human body fluids, such as urine, pleural effusions, ascites, cerebrospinal fluid (CSF), and saliva, intended for cfDNA examination. Processing includes multiple steps, such as centrifugation for specimen purification and isolation of cfDNA.

This document is applicable to medical laboratories, health institutions including facilities collecting and handling specimens, laboratory customers, in vitro diagnostic examination developers and manufacturers, biobanks, institutions and 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 document, 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 circulating cell free DNA (ccfDNA) from blood. These are not described in this document, but are covered in 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.

ISO 15189, *Medical laboratories — Requirements for quality and competence*

ISO 13485, *Medical devices — Quality management systems — Requirements for regulatory purposes*

3 Terms and definitions

For the purposes of this document, the terms and definitions given below apply.

For medical laboratories additional terms and definitions described in ISO 15189 apply.

For IVD developers and manufacturers additional terms and definitions described in ISO 13485 apply.

ISO and IEC maintain terminology 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 [5], [6] and [7].

[SOURCE: ISO 20166-1:2018, 3.1]

3.2
analyte
component represented in the name of a measurable quantity

[SOURCE: ISO 17511:2020, 3.1 — Deleted example.]

3.3
examination performance
analytical test performance
analytical performance
includes but is not limited to accuracy, precision, specificity, sensitivity and limit of detection of a test to examine the analyte of interest

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

[SOURCE: ISO 20184-1:2018, 3.4, modified — added specificity and limit of detection to the definition.]

3.4
ascites
abnormal buildup 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 [8].

3.5
body fluid
natural fluid or secretion that is produced by the body including, but not limited to, urine, saliva, semen, mucus, vaginal secretions, breast milk, amniotic fluid, cerebrospinal fluid (CSF), synovial fluid, ascites, pleural effusions and pericardial fluid

[SOURCE: ISO/TR 19591:2018, 3.23, modified — blood and faeces deleted, saliva, ascites and pleural effusion added.]

Note 1 to entry: For the purpose of this document blood is not included.

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: 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[9].

3.9
cfDNA profile
cell free DNA profile
amount of different *cfDNA* (3.8) molecules, present in a body fluid 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
collection facility
any area where a human specimen is collected, such as physician's office, patient's home, hospital and clinic

3.12
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 [8].

3.13
DNA
deoxyribonucleic acid
polymer of deoxyribonucleotides occurring in a double-stranded (dsDNA) or single-stranded (ssDNA) form

[SOURCE: ISO 22174:2005, 3.1.2]

3.14
DNA stabilizer
compound, solution or mixture that is designed to minimize degradation and fragmentation of cfDNA as well as release of genomic DNA from nucleated cells

3.15
examination
set of operations having the objective of determining the numerical 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: ISO 15189:2022, 3.8, modified — Term and definition are used here without the original notes; the term "text value" was removed.]

3.16
examination device manufacturer
entity that manufactures in vitro diagnostic or research examination devices, including measurement systems, instruments, reagents, and instructions for use for a specific examination (3.15)

[SOURCE: ISO 20166-4:2021, 3.16]