SLOVENSKI STANDARD
SIST-TS CEN/TS 17626:2021

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Molekularne diagnostične preiskave in vitro - Specifikacije za predpreiskovalne procese za vzorce človeškega tkiva - Izolirana mikrobiom DNA

Molecular in vitro diagnostic examinations - Specifications for pre-examination processes for human specimen - Isolated microbiome DNA

Molekularanalytische in-vitro-diagnostische Verfahren - Spezifikationen für präanalytische Prozesse für menschliche Proben - Isolierte Mikrobiom-DNA

Analyses moléculaires de diagnostic in vitro - Spécifications relatives aux processus préanalytiques pour les échantillons humains - ADN du microbiote isolé

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Molecular in vitro diagnostic examinations - Specifications for pre-examination processes for human specimen - Isolated microbiome DNA

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European foreword

This document (CEN/TS 17626:2021) 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 significant progress in medicine. Further progress is expected using new technologies analysing the microbiome (e.g. bacteria, fungi, viruses, yeasts, archaea) in human specimens.

The human microbiome has come into focus in many medical disciplines such as gastroenterology, dermatology, or gynaecology as a potential biomarker for diagnosis and management of diseases, and even as a therapeutic agent. Technologies analysing microbiome DNA such as shotgun metagenome or amplicon-based sequencing (e.g. 16S or 18S rRNA gene sequencing) have accelerated this process and are being increasingly performed in research and clinical practice.

However, the human microbiome profile can change drastically during the pre-examination process, which includes the specimen collection, transport, storage, and processing. These changes can, for example, be due to contamination of specimens with microbial cells or DNA from other sources than the sampling site or due to undesired growth and/or instability of individual microorganisms and viruses. Consequently, this makes the outcome from diagnostics or research unreliable or even impossible because the subsequent microbiome DNA examination might not determine the real situation in the patient but an artificial profile generated during the pre-examination processes. Therefore, special measures have to be taken to secure the stability of the microbiome profile.

Specimens for microbiome analysis are often collected by donors/patients. Therefore, dedicated measures are needed for informing donors/patients about and preparing them for the collection, storage and transport of specimens, and to check the compliance with the instructions, in order to reduce specimen variability.

In addition, isolation of microbiome DNA, which is representative in composition of the *in vivo* microbiome of the respective body site, is critical. This can be especially challenging e.g. due to different lysis requirements of the microorganisms (e.g. Gram-negative versus Gram-positive bacteria, or versus fungi) as well as inhibitory compounds (e.g. PCR inhibitors) in the specimen, which can impact the examination if not removed during the DNA isolation. The presence of high amounts of human host DNA, in addition to DNA introduced by reagents such as remnant plasmid DNA from generation of recombinant enzymes and/or DNA isolation kits, can further impact the examination result.

Therefore, standardization of the entire pre-examination workflow from specimen collection to the microbiome DNA examination is needed.

Studies have been undertaken to determine the important influencing factors. This document draws upon such work to codify and standardize the steps for microbiome DNA 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 gives recommendations for the pre-examination phase of human specimens, such as stool, saliva, skin and urogenital specimens, intended for microbiome DNA examination. The pre-examination phase includes but is not limited to specimen collection, handling, transport, storage, processing, isolation of DNA, and documentation.

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 are taken for pre-examination processes for infectious disease examination (e.g. targeted pathogen identification) and for microbiome DNA examination from tissue (e.g. biopsies). These are outside of the scope of this document.

Different dedicated measures are taken for pre-examination processes for saliva for human genomic DNA examination. These are not described in this document but are covered in CEN/TS 17305, *Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for saliva — Isolated DNA*.

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*

ISO/TS 20658, *Medical laboratories — Requirements for collection, transport, receipt, and handling of samples*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in EN ISO 15189 and the following ones 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 homogeneous material, assumed to be taken with negligible sampling error

Note 1 to entry: The term is usually applied to fluids.

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

3.3
analyte
component represented in the name of a measurable quantity

[SOURCE: EN ISO 17511:2003]

3.4
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]

3.5
deoxyribonuclease
DNase
enzyme that catalyzes the degradation of DNA [3.4] into smaller components

3.6
deviation
departure from an approved instruction, procedure and/or method

[SOURCE: EN ISO 15378:2017, 3.7.5 modified — The words “approved (3.7.1) standard operating procedure (SOP) (3.7.10)” have been replaced by “instruction, procedure and/or method”.]

3.7
diagnosis
identification of a health or disease state from its signs and/or symptoms, where the diagnostic process can involve examinations [3.8] and tests for classification of an individual's condition into separate and distinct categories or subclasses that allow medical decisions about treatment and prognosis to be made

3.8
examination
analytical test
set of operations with the objective 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 [3.3] and include all kinds of parameter testing or chemical manipulation for quantitative or qualitative examination.

[SOURCE: EN ISO 15189:2012, 3.7, modified — The term and definition are used here without the original Notes.]

3.9
examination manufacturer
analytical test manufacturer
entity that manufactures and/or produces the specific analytical test [3.8]

3.10
examination performance
analytical test performance
accuracy, precision, and sensitivity of a test to measure the analyte [3.3] of interest

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

3.11
homogeneous
uniform in structure and composition

3.12
interfering substances
endogenous substances of a specimen [3.26]/sample [3.25] or exogenous substances (e.g. stabilization reagent [3.28]) that can alter an examination result

3.13
laboratory developed procedure
modified commercially available in vitro diagnostic device or fully in house developed procedure

3.14
microbial biomass
measure of the mass (amount) of microbiome [3.15] in a specimen [3.26]/sample [3.25]

3.15
microbiome, human
entire community of all commensal, symbiotic and pathogenic microorganisms [3.18] and viruses inside and on specific human body sites in a particular environment/habitat

[SOURCE: [1][2][3][4]]

3.16
microbiome DNA
microbial DNA
DNA [3.4] of the microorganisms [3.18] and DNA viruses comprising the human microbiome [3.15]

3.17
microbiome DNA profile
microbial DNA profile
amounts of DNA molecules from the microbiome [3.15] that are present in a specimen [3.26]/sample [3.25] and can be measured in the absence of any losses, inhibition or interference

3.18
microorganisms
entity of microscopic size, encompassing bacteria, archaea, single celled eukaryotes (incl. fungi, protozoa), and phages

[SOURCE: [1][2]]

3.19
nonconformity
non-fulfillment of a requirement

[SOURCE: EN ISO 9000:2015, 3.6.9, modified — Note 1 to entry deleted.]

3.20
pre-examination processes
pre-analytical workflow
pre-examination phase
pre-analytical 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 specimen(s) [3.24], transportation to and within the medical laboratory, isolation of analytes [3.3], and ends when the examination [3.8] 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 has been added, the words "primary sample(s)" have been replaced by "specimen(s)" and more details have been included.]

3.21
primary collection device
tool specifically intended by a manufacturer to obtain or obtain and contain or obtain, contain and preserve a specimen [3.26] from the donor/patient

[SOURCE: EN ISO 18113-1:2009, 3.55, Modified – Notes to entry have been deleted, "apparatus" has been changed to "tool, "to obtain or obtain and contain" has been added, "for *in vitro* diagnostic examination" has been deleted.]

3.22
secondary collection device
container into which the specimen [3.26] is transferred from or together with the primary collection device [3.21]

3.23
proficiency test
evaluation of participant performance against pre-established criteria by means of inter-laboratory comparisons

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

3.24
room temperature
for the purposes of this document, temperature in the range of 18 °C to 25 °C

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

3.25
sample
one or more parts taken from a specimen [3.26]

[SOURCE: EN ISO 15189:2012, 3.24, modified — The words “primary sample(s)” have been replaced by “specimen(s)” and the example has been omitted.]

3.26
specimen
primary sample
discrete portion of a body fluid, breath, hair, stool, or biological material mechanically taken off body or organ surfaces (e.g. by swabs, brushes, tapes, spatulas or blades) or tissue taken for examination of one or more quantities or properties assumed to apply for the whole

[SOURCE: EN ISO 15189:2012, 3.16, modified — Notes to entry have been omitted.]

3.27
stability
ability of a specimen [3.26]/sample [3.25] 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 analyte for the purpose of this document is DNA.

[SOURCE: ISO Guide 30:2015, 2.1.15, modified — The words “reference material” have been replaced by “specimen/sample material”.]

3.28
stabilizers
stabilization reagents
microbiome DNA stabilizers
compounds, solutions or mixtures that are designed to minimize changes of the microbiome DNA profile [3.17] in a specimen [3.26] or sample [3.25] (by inhibition of undesired growth or decline of microorganisms [3.18] and viruses, and/or of degradation and fragmentation of DNA [3.4])

3.29
storage
maintenance of biological material under conditions appropriate for intended use

3.30
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 3 to entry have been omitted.]

3.31
verification
confirmation, through provision of objective evidence, that specified requirements have been fulfilled

Note 1 to entry: The term "verified" is used to designate the corresponding status.

Note 2 to entry: Confirmation can comprise activities such as:

— performing alternative calculations;

— comparing a new design specification with a similar proven design specification;

— undertaking tests and demonstrations; and

— reviewing documents prior to issue

[SOURCE: ISO 9000:2015, 3.8.12, modified — Note 1 and 2 to entry have been omitted. New Note 2 to entry has been added.]

3.32
workflow

series of activities necessary to complete a task

[SOURCE: ISO 20166-1:2018, 3.30]

4 General considerations

For general statements on medical laboratory quality management systems and in particular on specimen collection, reception and handling (including avoidance of cross contaminations), see EN ISO 15189, EN ISO/IEC 17025 or EN ISO/IEC 17020. The requirements on laboratory equipment, reagents, and consumables according to EN ISO 15189 shall be followed; EN ISO/IEC 17025 and EN ISO/IEC 17020 can also apply.

All steps of the pre-examination, examination and post-examination processes (i.e. the entire workflow) can influence the diagnosis or research study results.

Thus, this entire workflow shall be specified, verified and validated during the development of the examination, including *in vitro* diagnostic (IVD) medical devices. This includes specifically all pre-examination process steps such as the examination request, preparation and identification of the patient, collection of the primary sample(s), transportation to and within the medical laboratory, storage and isolation of analytes. This shall also include determination of and information on the stability of the specimen within the timeframe between taking the specimen and its analysis and storage conditions such as duration, temperature limits and freeze/thaw cycles.

The microbiome profile can change drastically during the pre-examination phase [5][6][27][28]. Microbiome composition and densities are influenced by lifestyle conditions [7] and treatment of the sampling site prior to specimen collection, and strongly differ depending on the body site and disease