SLOVENSKI STANDARD
SIST-TS CEN/TS 17390-3:2020

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Molekularne diagnostične preiskave in vitro - Specifikacije za predpreiskovalne procese za cirkulirajoče tumorske celice (CTC) v venski polni krvi - 3. del: Priprave za analitično barvanje CTC

Molecular in vitro diagnostic examinations - Specifications for pre-examination processes for circulating tumor cells (CTCs) in venous whole blood - Part 3: Preparations for analytical CTC staining

Molekularanalytische in-vitro-diagnostische Verfahren - Spezifikationen für präanalytische Prozesse für zirkulierende Tumorzellen (CTC) in venösen Vollblutproben - Teil 3: Vorbereitungen für die analytische CTC-Färbung

Analyses de diagnostic moléculaire in vitro - Spécifications relatives aux processus préanalytiques pour les cellules tumorales circulantes (CTC) du sang total veineux - Partie 3 : Préparations pour l'analyse par coloration des CTC

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EUROPEAN COMMITTEE FOR STANDARDIZATION
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European foreword

This document (CEN/TS 17390-3:2020) has been prepared by Technical Committee CEN/TC 140 “In vitro diagnostic medical devices”, the secretariat of which is held by DIN.

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. CEN shall not be held responsible for identifying any or all such patent rights.

CEN/TS 17390 consists of the following parts, under the general title *Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for Circulating Tumor Cells (CTCs) in venous whole blood*:

— *Part 1: Isolated RNA*

— *Part 2: Isolated DNA*

— *Part 3: Preparations for analytical CTC staining*

According to the CEN/CENELEC Internal Regulations, the national standards organisations of the following countries are bound to announce this Technical Specification: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Republic of North Macedonia, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey and the United Kingdom.

Introduction

Solid tumours release cells and bioanalytes into blood and other body fluids. This has opened the option of minimally-invasive tumour detection, diagnosis and characterization from venous whole blood (liquid biopsies). Liquid biopsies are expected to enable earlier detection and diagnosis of cancers and advance personalized patient treatment. These applications have become one of the fastest growing segments of the entire diagnostic market.

Circulating tumour cells (CTCs) in venous whole blood reflect the disease complexity that evolves during tumour progression, with distinct genetic, epigenetic and expression features. Besides the prognostic role of CTC identification and/or enumeration in cancer progression, CTC identification and analysis can improve e.g. disease outcome prediction, therapeutic guidance and post-treatment monitoring of the patient.

CTCs are now considered as a surrogate sample of tumour tissue, both in cancer early development and metastatic phase.

Molecular characterization of CTCs can provide for example a strategy for monitoring cancer genotypes during systemic therapies [1], identification of mechanisms of disease progression, identification of novel targets for treatment [2] and to select targeted therapies. Moreover, CTC single-cell sequencing is emerging as an important tool for tumour genomic heterogeneity analysis [3] [4] [5].

CTCs are fragile and tend to degrade within a few hours when collected in conventional blood collection tubes, e.g. EDTA containing tubes, without dedicated CTC stabilizers. CTCs are extremely rare, especially in early disease, e.g. less than 10 cells per 10 ml of blood, representing a ratio of approx. $1:10^7$ CTCs to white blood cells (WBCs). This low ratio represents a significant challenge to CTC enrichment required for identification and examination as tumour-derived cells.

Furthermore, CTC morphology and biomolecules can change during the pre-examination process. These can lead to changes in protein quantity, integrity, modification, conformation and localization within the cell. This can impact the validity and reliability of the examination result.

CTC examination usually requires a CTC enrichment step (e.g. based on biological properties, such as expression of surface molecules, or physical properties, such as size and density, of the CTCs or their combination) prior to cytomorphological examination or immunofluorescent staining. CTC enrichment technologies can provide CTCs attached on a solid surface, ready for cytological examination, or CTCs in suspension requiring extra processing steps prior to the examination. This can lead to potential cell loss. [6]

CTC enrichment is usually followed by their identification by conventional cytochemical or protein-targeted staining procedures that allow detection of the cell traits.

Standardization of all steps of the pre-examination process is required. This includes blood collection and stabilization, transport, storage, CTC enrichment, and CTC isolation (if required). A decision guideline for the critical steps of the pre-analytical workflow for CTC staining is provided in Annex A.

This document describes measures to standardize the pre-examination process to obtain appropriate CTC staining.

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 guidelines on the handling, storage, processing and documentation of human venous whole blood specimens intended for staining of circulating tumour cells (CTCs) during the pre-examination phase before a molecular examination is performed.

This document is applicable to molecular *in vitro* diagnostic examinations including laboratory developed tests 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.

This document does not cover pre-analytical workflow requirements for viable CTC cryopreservation and culturing.

NOTE 1 The requirements given in this document can also be applied to other circulating rare cells (e.g. fetal cells).

NOTE 2 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 15189:2012, *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 following terms and definitions apply.

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— IEC Electropedia: available at http://www.electropedia.org/

— ISO Online browsing platform: available at https://www.iso.org/obp

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 bibliographical references [7], [8] and [9].

[SOURCE: EN ISO 20166-3:2019, 3.1]

3.2
ambient temperature
unregulated temperature of the surrounding air

[SOURCE: EN ISO 20166-3:2019, 3.2]

3.3
analyte
component represented in the name of a measurable quantity

[SOURCE: EN ISO 17511:2003, 3.2, modified — EXAMPLE has been removed.]

3.4
analytical test performance
accuracy, precision, specificity 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, modified — "specificity" was added.]

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 in a vacuum which forces blood from the vein through the needle and into the tube

3.7
backflow
flow of a liquid opposite to the usual or desired direction

3.8
circulating tumor cells
CTCs
cells present in blood, which are derived from a primary and/or metastatic site of a tumor

3.9
diagnosis
identification of a disease from its signs and symptoms, where the diagnostic process can involve examinations 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

[SOURCE: EN ISO 20184-1:2018, 3.6]

3.10
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 CTC staining and include all kinds of parameter testing or chemical manipulation for quantitative or qualitative examination.

[SOURCE: EN ISO 15189:2012, 3.7, modified — Notes to entry 1 to 3 have been removed, Note 1 to entry has been added and "analytical test" has been added as a preferred term.]

3.11
examination performance
analytical test performance
analytical performance
ability of an examination procedure to measure or detect a particular analyte

Note 1 to entry: Analytical performance is determined from analytical performance studies used to assess the ability of an *in vitro* diagnostic examination procedure to measure or detect a particular analyte.

Note 2 to entry: Analytical performance includes such characteristics as analytical sensitivity, detection limit, analytical specificity (interference and cross-reactivity), trueness, precision and linearity.

[SOURCE: ISO/TS 17822-1:2014, 3.2, modified — "analytical test performance" and "analytical performance" have been added as preferred terms.]

3.12
examination manufacturer
analytical test manufacturer
group or company that provides the specific analytical test

3.13
immunocytochemistry
in situ detection technique that uses the principle of antibodies binding specifically to antigens in or on cells to detect the antigens (e.g. proteins) using brightfield microscopy

3.14
needle holder
barrel used in routine venipuncture procedures to hold the blood collection tube in place and to protect the phlebotomist from direct contact with blood

[SOURCE: EN ISO 20186-1:2019, 3.24]

3.15
pre-examination processes
preanalytical phase
preanalytical workflow
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 medical or pathology laboratory, 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 — "pre-analytical workflow" has been added as a preferred term, Note 1 to entry has been added and the definition has been extended.]

3.16
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 — Notes to entry 1 to 3 have been removed.]

3.17
proficiency testing
evaluation of participant performance against pre-established criteria by means of inter-laboratory comparisons

[SOURCE: EN ISO/IEC 17043:2010, 3.7, modified — Notes to entry 1 to 3 have been removed.]

3.18
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.

3.19
sample
one or more parts taken from a primary sample

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

3.20
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”.]

3.21
storage
prolonged interruption of the pre-analytical workflow of a sample or analyte respectively, or of their derivatives e.g., stained sections or tissue blocks, 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 20166-3:2019, 3.24]

3.22
validation
confirmation, throughout 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: EN ISO 9000:2015, 3.8.13, modified — Notes to entry 1 to 3 have been removed.]

3.23
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: EN ISO 9000:2015, 3.8.12, modified — Notes to entry 1 and 2 have been removed.]

3.24
workflow
series of activities necessary to complete a task

[SOURCE: EN ISO 20166-3:2019, 3.29]

4 General considerations

For general statements on medical laboratory quality management systems and in particular on specimen collection and handling (including avoidance of cross contaminations) see EN ISO 15189:2012, 4.2, 5.4.4, or EN ISO/IEC 17020:2012, 7.2 and 8. The requirements on laboratory equipment, reagents, and consumables according to EN ISO 15189:2012, 5.3 shall be followed; EN ISO 15189:2012, 5.5.1.2 and 5.5.1.3 and EN ISO/IEC 17020:2012, 6.2 can also apply.

All steps of a diagnostic workflow can influence the final analytical test result. Thus, the entire workflow including biomolecule stability and specimen and/or sample storage conditions shall be verified and validated. Workflow steps which cannot always be controlled shall be documented. A risk assessment of non-controllable workflow steps including their potential impact on the analytical test performance shall be performed and mitigation measures shall be established to enable the required analytical test performance.

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

During the whole pre-examination process precautions shall be taken to avoid cross contamination between different specimens/samples, e.g. by using single-use material whenever feasible or appropriate cleaning procedures between processing of different specimens/samples.

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

5 Outside the laboratory

5.1 Specimen collection

5.1.1 Information about the specimen donor/patient

The documentation shall include the ID of the specimen donor/patient, which can be in the form of a code.

The documentation should include, but is not limited to:

a) the relevant health status of the specimen donor/patient (e.g. healthy, disease type, concomitant disease, demographics (e.g. age and gender));

b) the information about medical treatment and special treatment prior to blood collection;

c) the type and purpose of the proposed examination requested;