SLOVENSKI STANDARD
kSIST-TS FprCEN ISO/TS 7552-2:2024

01-september-2024

Nadomešča:
SIST-TS CEN/TS 17390-2:2020

Molekularne diagnostične preiskave in vitro - Specifikacije za predpreiskovalne procese za cirkulirajoče tumorske celice (CTC) v venski polni krvi - 2. del: Izolirana DNK (ISO/DTS 7552-2:2024)

Molecular in vitro diagnostic examinations - Specifications for pre-examination processes for circulating tumour cells (CTCs) in venous whole blood - Part 2: Isolated DNA (ISO/DTS 7552-2:2024)

Spezifikationen für präanalytische Prozesse für zirkulierende Tumorzellen (CTC) in venösen Vollblutproben - Teil 2: Isolierte DNA (ISO/DTS 7552-2:2024)

Titre manque - Partie 2: Titre manque (ISO/DTS 7552-2:2024)

Ta slovenski standard je istoveten z: **FpCEN ISO/TS 7552-2**

ICS:

11.100.10	Diagnostični preskusni sistemi in vitro	In vitro diagnostic test systems

kSIST-TS FprCEN ISO/TS 7552-2:2024 **en,fr,de**

FINAL DRAFT
Technical Specification

ISO/DTS 7552-2

Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for circulating tumour cells (CTCs) in venous whole blood —

Part 2: Isolated DNA

ISO/TC **212**

Secretariat: **ANSI**

Voting begins on:
2024-07-17

Voting terminates on:
2024-10-09

ISO/CEN PARALLEL PROCESSING

Reference number
ISO/DTS 7552-2:2024(en)

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Published in Switzerland

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Foreword

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This document was prepared by Technical Committee ISO/TC 212, *Clinical laboratory testing and in vitro diagnostic test systems*, in collaboration with the European Committee for Standardization (CEN) Technical Committee CEN/TC 140, *In vitro diagnostic medical devices*, in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

A list of all parts in the ISO 7552 series can be found on the ISO website.

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

Solid tumours release cells and bioanalytes into blood and other body fluids. This has opened the option of utilizing such body fluids (liquid biopsies) for a minimally-invasive procedure for tumour detection, diagnosis and characterization. Liquid biopsies can enable earlier detection and diagnosis of cancers and advance personalized patient treatment.[20,22]

These applications have become one of the fastest growing segments of the entire diagnostic market.

Circulating tumour cells (CTCs) in venous whole blood can reflect the disease complexity that evolves during tumour progression, with distinct genetic, epigenetic and gene expression biomarkers.[22]

Beside the prognostic role of CTC identification and enumeration in cancer progression, CTC molecular characterization can improve disease outcome prediction, therapeutic guidance and post-treatment monitoring of the patient.[20]

CTCs are now considered as a surrogate of tumour tissue in cancer early development, progression, and metastatic phase.[23]

Molecular characterization of CTCs can provide a strategy for monitoring cancer genotypes during systemic therapies,[24] identifying mechanisms of disease progression, identifying novel targets for biological treatment[25] and selecting targeted therapies.[20] Moreover, CTC single-cell sequencing is an important tool for tumour genomic heterogeneity analysis.[26-28] Molecular examination techniques such as qPCR, dPCR and sequencing methods including next generation sequencing (NGS) enable characterization of the CTC specific DNA features.

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 approximately $1:10^7$ CTCs to white blood cells (WBCs). This low ratio represents a significant challenge to CTC enrichment required for examination. Furthermore, co-enrichment of normal blood cells causes a dilution of CTCs. The challenge is to minimize the amount of co-enriched WBCs for subsequent accurate and sensitive detection of CTC specific genetic and epigenetic alterations, especially when dealing with minor tumour cell clones.

Special measures to remove the WBCs are necessary in order to obtain good quality DNA samples characterized by high purity and thus representative of the mutational pattern within the tumour.

Standardization includes all steps of the pre-examination process, including blood collection and stabilization, transport, storage, CTC enrichment, CTC isolation (if included), and DNA isolation. This pre-examination standardization is crucial to ensure reliable examination results in current clinical use and is also critical to develop new CTC based diagnostic examinations and to establish these in clinical healthcare.[29]

An illustration of critical steps of the CTC pre-analytical workflow is provided in Annex A.

This document describes special measures to obtain appropriate quality and quantity of DNA from CTC containing blood specimens for subsequent examination.

Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for circulating tumour cells (CTCs) in venous whole blood —

Part 2: Isolated DNA

1 Scope

This document specifies requirements and gives recommendations on the handling, storage, CTC enrichment and isolation, RNA isolation and storage, and documentation of venous whole blood specimens intended for the examination of DNA isolated from 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 the isolation of genomic DNA directly from venous whole blood containing CTCs. This is covered in ISO 20186-2.

This document does not cover the isolation of specific white blood cells and subsequent isolation of genomic DNA therefrom or the 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. foetal 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.

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

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 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.

[SOURCE: ISO 20166-3:2018, 3.1]

3.2
analyte
component represented in the name of a measurable quantity

[SOURCE: ISO 17511:2020, 3.1, modified — the example has been removed.]

3.3
backflow
flow of a liquid opposite to the usual or desired direction

3.4
blood collection set
intravenous device specialized for venipuncture consisting of a stainless steel beveled 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* (3.5).

3.5
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

3.6
circulating tumour cells
CTCs
cells present in blood, originating from a primary or metastatic site(s) of a tumour

3.7
closed system
non-modifiable system provided by the vendor including all necessary components for the analysis (i.e. hardware, software, procedures and reagents)

[SOURCE: ISO 20186-2:2019, 3.6]

3.8
CTC enrichment
method that is able to increase the ratio of *CTCs* (3.6) to other cells including white blood cells in a *sample* (3.21)

3.9
CTC isolation
method resulting in a *sample* (3.21) containing *CTCs* (3.6) without any other cell type

3.10
deoxyribonucleic acid
DNA
polymer of deoxyribonucleotides occurring in a double-stranded (dsDNA) or single-stranded (ssDNA) form

[SOURCE: ISO 22174:2005, 3.1.2]

3.11
deoxyribonucleic acid proficiency testing program
DNA PT program
proficiency testing (3.19) for DNA based *examinations* (3.13)