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

Part 1: Isolated RNA

DTS stage

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Foreword

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

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Introduction

Solid tumorstumours 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 tumortumour detection, diagnosis and characterization. Liquid biopsies can enable earlier detection and diagnosis of cancers and advance personalized patient treatment.[20,21] [1,2].

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

Circulating tumortumour cells (CTCs) in venous whole blood can reflect the disease complexity that evolves during tumortumour progression, with distinct genetic, epigenetic and gene expression biomarkers.[41] [3].

Besides the prognostic role of CTC identification and/or enumeration in cancer progression, CTC molecular characterization can improve e.g. disease outcome prediction, therapeutic guidance and post-treatment monitoring of the patient.[39] [1].

CTCs are now considered as a surrogate of tumortumour tissue in cancer early development, progression and metastatic phase[23] [4].

Molecular characterization of CTCs can provide for example a strategy for monitoring cancer genotypes during systemic therapies,[24] [5], identification of identifying mechanisms of disease progression, identification ofidentifying novel targets for biological treatment[25] [6] and to selectselecting targeted therapies[39] [1].

Moreover, CTC single-cell sequencing is emerging as an important tool for tumortumour genomic heterogeneity analysis.[26-28] [7-9] 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.approximately 1:10^7 CTCs to white blood cells (WBCs). This low ratio represents a significant challenge to CTC enrichment required for examination.

RNA profiles of CTCs resemble gene expression profiles of tumorstumours. For RNA profile analysis, measures need to be taken to get rid ofremove the WBCs are necessary in order to obtain sufficiently enriched CTC-specific RNA.

RNA profiles can change significantly after blood collection, during CTC enrichment and isolation. Therefore, special measures need to be takenare necessary to obtain CTC samples of adequate quality CTC samples and isolated RNA of appropriate quality isolated RNA for ensuring the specified RNA examination performance.[29] [10].

Standardization ofincludes all steps of the pre-examination process is required. This includes, including blood collection and stabilization, transport, storage, CTC enrichment, CTC isolation (if requiredincluded), and RNA 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.[30] (11)

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

This document describes special measures that need to be taken to obtain appropriate quality and quantity of RNA from CTC-containing blood specimens for subsequent examination.

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

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

Part 1: Isolated RNA

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 RNA 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 cellular RNA directly from venous whole blood containing CTCs. This is covered in ISO 20186-1~~, *Molecular in vitro diagnostic examinations - Specifications for pre-examination processes for venous whole blood - Part 1: Isolated cellular RNA*~~.

This document does not cover the isolation of specific white blood cells and subsequent isolation of cellular RNA therefrom. 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. 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*

~~ISO 14971, *Medical devices — Application of risk management to medical devices*~~

~~ISO 35001, Biorisk management for laboratories and other related organisations~~

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 15189 and the following 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 References [12], [13] and [14].~~

[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 — ~~EXAMPLE~~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)~~).

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 tumor cells
CTCs
cells present in blood, originating from a primary ~~and/~~or metastatic site(s) of a tumor

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~~(3.6)~~) to other cells including white blood cells in a *sample* (3.24 ~~(3.24)~~)

3.9
CTC isolation
method resulting in a *sample* (3.24~~(3.24)~~) containing *CTCs* (3.6~~(3.6)~~) without any other cell ~~types~~type

3.10
deoxyribonuclease
DNAse
enzyme that catalyzes the degradation of DNA into smaller components

[SOURCE: ISO 20186-1:~~2018~~2019, 3.11]

3.11
diagnosis
identification of health or a disease state from its signs and~~/or~~ symptoms, where the diagnostic process can involve *examinations* (3.12~~(3.12)~~) 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: ISO 20184-1:2018, 3.6]

3.12
examination
analytical test
set of operations having the objective of determining the numerical value, text value or characteristics of a property

Note 1 to entry: ~~Processes~~ An examination includes the processes that start with the isolated *analyte* (3.2~~[3.2]~~) and include all kinds of parameter testing or chemical manipulation for quantitative or qualitative examination.

[SOURCE: ISO 15189:2022, 3.8, modified — the original Notes to entry ~~1 to 3~~ have been removed, and a new Note 1 to entry has been added ~~and "; "~~analytical test~~""~~ has been added as a preferred term.]

3.13
examination performance
analytical test performance
analytical performance
ability of an *examination* (3.12~~(3.12)~~) procedure to measure or detect a particular *analyte* (3.2~~(3.2)~~)

Note 1 to entry: Analytical performance is determined from analytical performance studies used to assess the ability of an in vitro diagnostic examination ~~(3.12)~~ procedure to measure or detect a particular analyte ~~(3.2).~~ .

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 20186-3:2019, 3.11]

3.14
manufacturer
entity that is legally responsible for manufacturing a specific *workflow* (3.29~~(3.29)~~) component

Note 1 to entry: For the purpose of this document, manufacturers can be *examination* (3.12~~(3.12)~~) manufacturers, collection device manufacturers, *CTC enrichment* (3.8~~(3.8)~~) and isolation manufacturers, nucleic acid isolation manufacturers.

3.15
needle holder
barrel used in routine venipuncture procedures to hold the *blood collection tube* (3.5~~(3.5)~~) in place and to protect the phlebotomist from direct contact with blood

[SOURCE: ISO 20186-1:2019, 3.16]