ICS 11.100.10 PREDBEŽNÁ SLOVENSKÁ TECHNICKÁ NORMA Apríl 2020

STN P	**Molekulárno-diagnostické vyšetrenia in vitro Špecifikácie predbežných vyšetrení cirkulujúcich nádorových buniek (CTC) v plnej krvi Časť 3: Prípravky na analytické farbenie CTC**	**STN P CEN/TS 17390-3** 85 1027

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

Táto norma obsahuje anglickú verziu európskej normy.
This standard includes the English version of the European Standard.

Táto norma bola oznámená vo Vestníku ÚNMS SR č. 03/20

Táto predbežná STN je určená na overenie. Pripomienky zasielajte ÚNMS SR najneskôr do januára 2022.

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English Version

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

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

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

This Technical Specification (CEN/TS) was approved by CEN on 27 October 2019 for provisional application.

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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*