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Molecular in vitro diagnostic examinations - Specifications for pre-examination processes for venous whole blood - Isolated circulating cell free RNA from plasma

Molekularanalytische in-vitro-diagnostische Verfahren - Spezifikationen für präanalytische Prozesse für venöse Vollblutproben - Isolierte zirkulierende zellfreie RNA aus Plasma

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European foreword

This document (CEN/TS 17742:2022) 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.

Any feedback and questions on this document should be directed to the users’ national standards body. A complete listing of these bodies can be found on the CEN website.

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.

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Introduction

Molecular *in vitro* diagnostics has enabled a significant progress in medicine. Further progress is expected by new technologies analysing profiles of nucleic acids, proteins, and metabolites in human tissues and body fluids. However, the profiles of these molecules can change drastically during the pre-examination process, including the specimen collection, transport, storage and processing.

Consequently, this makes the outcome from diagnostics or research unreliable or even impossible, as the subsequent examination might not determine the real situation in the patient, but an artificial profile generated during the pre-examination processes.

Besides circulating cell free DNA (ccfDNA), circulating tumour cells (CTCs) and other rare cells, circulating cell free RNA (ccfRNA) represents another key component of liquid biopsies. Therefore, there is a strongly increasing interest in emerging diagnostics and research in ccfRNA.

In blood, ccfRNA is composed of extracellular RNA present both in and outside of exosomes and other extracellular vesicles. The pre-examination process described in this document results in total ccfRNA isolated from blood plasma.

ccfRNA profiles and quantity can change significantly after blood collection, e.g. by release and/or uptake of RNA containing extracellular vesicles by cells present in the blood specimen as well as by ccfRNA degradation. Therefore, special measures have to be taken to secure good quality specimens for ccfRNA examination.

Standardization of the entire workflow from specimen collection to the ccfRNA examination is therefore needed. Studies have been undertaken to determine the important influencing factors. This document draws upon such work to codify and standardize the steps of ccfRNA 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.

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1 Scope

This document specifies requirements and recommendations for the pre-examination phase of circulating cell free RNA (ccfRNA) from venous whole blood specimens, including but not limited to the collection, handling, storage, processing and documentation of venous whole blood specimens intended for ccfRNA examination. This document covers specimens collected in venous whole blood collection tubes.

The pre-examination process described in this document results in circulating cell free RNA isolated from blood plasma without prior enrichment of exosomes and other extracellular vesicles.

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 need to be taken during the pre-examination phase for isolated RNA from enriched exosomes and other extracellular vesicles enriched from venous whole blood and for cellular RNA isolated from venous whole blood. These are not described in this document but are covered in CEN/TS 17747,[1] *Molecular in vitro diagnostic examinations - Specifications for pre-examination processes for exosomes and other extracellular vesicles in venous whole blood - Isolated DNA, RNA and proteins*, and in EN ISO 20186-1, *Molecular in vitro diagnostic examinations - Specifications for pre-examination processes for venous whole blood - Part 1: Isolated cellular RNA*.

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*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in EN ISO 15189 and the following 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/

[1] Under preparation. Stage at the time of publication: FprCEN/TS 17747.

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