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Molecular in vitro diagnostic examinations — Requirements and recommendations for pre-examination processes for urine and other body fluids — Isolated cell-free DNA

Analyses de diagnostic moléculaire in vitro — Exigences et recommandations relatives aux processus préanalytiques pour l'urine et d'autres liquides corporels — ADN libre extrait

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Foreword

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This document was prepared by Technical Committee ISO/TC 212, *Medical laboratories and in vitro diagnostic 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).

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Introduction

Molecular in vitro diagnostics has enabled significant progress in medicine. Further progress has been achieved and is still expected by new technologies used to examine profiles of nucleic acids, proteins, and metabolites in human tissues and body fluids (e.g. genomic, epigenomic, transcriptomic, proteomic and metabolomic profiling). However, the profiles of these molecules can change drastically during specimen collection, transport, storage and processing. This can make the outcome from diagnostics or research unreliable or even result in failure because the subsequent examination will not measure the genuine profile of nucleic acids, proteins or metabolites as it was in the patient, but a profile altered by the pre-examination process. Therefore, specifying, developing, verifying and validating preanalytical workflows has become an essential part of examination development.[21]

Most of the DNA in the body is located within cells, but small amounts of DNA originating from cells can also be found outside of cells (extracellular DNA). In case of circulating body fluids such as blood, this DNA is called circulating cell-free DNA (ccfDNA) and in case of non-circulating body fluids such as urine, saliva, cerebrospinal fluid, pleural effusion, ascites, and synovial fluid, the DNA is called cell-free DNA (cfDNA). cfDNA is of specific interest, as for example cfDNA in urine originates from cells from the genitourinary tract or from ccfDNA passing through glomerular filtration.[22] cfDNA from cancerous or malignant cells in urine have been associated with cancer specific sequences, epigenetic and structural changes.[23],[24] Urine is currently the most frequently used non-circulating body fluid for cfDNA examination because it is easily obtained from patients. Although urine is often described as the major specimen type, in this document the term body fluid is used for urine and other body fluids as defined in Clause 3.

Standardization of the entire workflow from specimen collection to the cfDNA examination is needed to minimize post-collection release of DNA from cells into the fluid and degradation of cfDNA in the specimen, which can change the original native cfDNA profile in the body fluid. Post collection microbial growth in the specimen can further enhance the degradation of the cfDNA, e.g. in urine and saliva. Furthermore, the isolation of cfDNA can lead to a cfDNA profile bias. Different methods to determine cfDNA yield and quality can lead to additional variations and impacts.

Studies have been undertaken to determine the pre-examination sources of these and other variables, as they can impact the cfDNA examination. The variables can compromise the specified examination performance characteristics, such as sensitivity, specificity, linearity and reproducibility. They can also impact the examination reliability which could lead to an erroneous examination result and misdiagnosis.

This document draws upon such work to codify and standardize the steps prior to cfDNA examination from body fluids in what is referred to as the pre-examination process.

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.