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List of NGS-Relevant Standardization Documents

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Background

Instand-NGS4P has prepared a list of relevant existing “published” and ongoing “in development” NGS-relevant standardization documents and projects within the International Standardization Organization (ISO) and the European Standardization Organization (CEN). Only the published documents can be applied to the product development within Instand-NGS4P.
In addition to the existing and ongoing projects, the Instand-NGS4P consortium is partnering with CEN/TC 140/WG 3 to develop a standardization document for the entire NGS workflow. Participation in the development of this standard is encouraged, and interested parties should contact their national standardisation body to enquire about nomination to the CEN/TC 140 Working Group 3.

The relevant published standards are listed below under the following topics:

1. Standards for specimen/sample pre-analytics (Lot 1a)
2. Standards for library preparation and NGS-analysis (Lot 1b and Lot 2)
3. Standards for NGS-data (Lot 3)

The scope of each document/project can be found in the Annex.

1. Standards for specimen/sample pre-analytics (Lot 1a)

The following projects cover the necessary pre-analytical steps which need to be performed before starting the analysis. Most of these standardization documents include detailed processes for specific specimen/sample types depending on the analytes of interest. Following these processes is key to preserving the target properties and analytes of the specimen/sample, and thus to obtain good quality samples for NGS analysis. If specimens/samples are obtained from a biobank, ISO 20387 covers additional general requirements (e.g., for traceability, documentation, handling, storage, information management and a quality management system) contributing to their quality attributes as well as the quality of their associated data. The relevant preanalytics requirements for NGS analysis are sufficiently covered in the following documents and can be referenced.

Published:

EN ISO 20166-1:2018, Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for formalin-fixed and paraffin-embedded (FFPE) tissue — Part 1: Isolated RNA

EN ISO 20166-3:2019, Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for formalin-fixed and paraffin-embedded (FFPE) tissue — Part 3: Isolated DNA

EN ISO 20184-1:2018, Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for frozen tissue — Part 1: Isolated RNA

EN ISO 20184-3:2021, Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for frozen tissue — Part 3: Isolated DNA

EN ISO 20186-1:2019, Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for venous whole blood — Part 1: Isolated cellular RNA

EN ISO 20186-2:2019, Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for venous whole blood — Part 2: Isolated genomic DNA

EN ISO 20186-3:2019, Molecular in-vitro diagnostic examinations — Specifications for pre-examination processes for venous whole blood — Part 3: Isolated circulating cell free DNA from plasma

ISO 4307:2021, Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for saliva – Isolated human DNA

CEN/TS 17390-1:2020, Molecular in vitro diagnostic examinations — for pre-examination processes for circulating tumor cells (CTCs) in venous whole blood — Part 1: Isolated RNA

CEN/TS 17390-2:2020, Molecular in vitro diagnostic examinations — for pre-examination processes for circulating tumor cells (CTCs) in venous whole blood — Part 2: Isolated DNA

ISO/TS 20658:2017 Medical laboratories — Requirements for collection, transport, receipt, and handling of samples

EN ISO 20387:2020, Biotechnology — Biobanking — General requirements for biobanking

2. Standards for library preparation and NGS-analysis (Lot 1b and 2)

Projects listed within this chapter are either directly relevant to the library preparation, NGS-analysis or to closely related components used in or needed for the NGS-analysis, such as nucleic acids.

Published:

None

Expected soon:

ISO/DIS 20397-1, Biotechnology — General Requirements for Massive Parallel Sequencing — Part 1: Nucleic acid and library preparation

Closely related :

ISO 20688-1:2020, Biotechnology — Nucleic acid synthesis — Part 1: Requirements for the production and quality control of synthesized oligonucleotides

3. Standards for NGS-data (Lot 3)

ISO projects listed within this chapter are related to data obtained either by NGS directly or within a specimen's/sample's life cycle including NGS. They give requirements for data collection, analysis, processing, storage, sharing, define data types, relationships, optionality, cardinalities and the bindings of particular terminology of the data, and thus contribute to the imteroperability of data. Interoperability of data is important for the exchange, traceability and comparability of data and their bigger picture (e.g., for the use in or comparison of studies or publications).

Published:

ISO 20397-2:2021, Biotechnology — General requirements for massively parallel sequencing — Part 2: Methods to evaluate the quality of sequencing data

ISO/TR 3985:2021, Health informatics — Data elements and their metadata for describing structured clinical genomic sequence information in electronic health records

ISO/TS 22692:2020, Genomics Informatics — Quality control metrics for DNA sequencing

ISO/TR 3985:2021, Development of International Standards in Biotechnology — Data Publication — Preliminary Considerations and Concepts

Annex: Scope of listed projects

1. Standards for specimen/sample pre-analytics

Project number	Title	Committee
EN ISO 20166-1:2018	Molecular in vitro diagnostic examinations - Specifications for pre-examination processes for formalin-fixed and paraffin-embedded (FFPE) tissue - Part 1: Isolated RNA (ISO 20166-1:2018)	ISO/TC 212 and CEN/TC 140
Scope	This document gives guidelines on the handling, documentation, storage and processing of formalinfixed and paraffin-embedded (FFPE) tissue specimens intended for RNA examination during the preexamination phase before a molecular assay is performed. This document is applicable to molecular in vitro diagnostic examinations including laboratory developed tests performed by medical laboratories and molecular pathology 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. NOTE International, national or regional regulations or requirements can also apply to specific topics covered in this document.	

Project number	Title	Committee
EN ISO 20166-3:2019	Molecular in vitro diagnostic examinations - Specifications for pre-examination processes for formalin-fixed and paraffin-embedded (FFPE) tissue - Part 3: Isolated DNA (ISO 20166-3:2018)	ISO/TC 212 and CEN/TC 140
Scope	This document gives guidelines on the handling, documentation, storage and processing of formalinfixed and paraffin-embedded (FFPE) tissue specimens intended for DNA examination during the preexamination phase before a molecular assay is performed. This document is applicable to molecular in vitro diagnostic examinations including laboratory developed tests performed by medical laboratories and molecular pathology 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. NOTE International, national or regional regulations or requirements can also apply to specific topics covered in this document.	

Project number	Title	Committee
EN ISO 20184-1:2018	Molecular in vitro diagnostic examinations - Specifications for pre-examination processes for frozen tissue - Part 1: Isolated RNA (ISO 20184-1:2018)	ISO/TC 212 and CEN/TC 140
Scope	This document gives guidelines on the handling, documentation, storage and processing of frozen tissue specimens intended for RNA examination during the pre-examination phase before a molecular assay is performed. This document is applicable to any molecular in vitro diagnostic examination performed by medical laboratories and molecular pathology laboratories that evaluate RNA extracted from frozen tissue. It is also intended to be used by laboratory customers, in vitro diagnostics developers and manufacturers, biobanks, institutions and commercial organisations performing biomedical research, and regulatory authorities. Tissues that have undergone chemical stabilization pre-treatment before freezing are not covered in this document. NOTE International, national or regional regulations or requirements can also apply to specific topics covered in this document.	

Project number	Title	Committee
EN ISO 20184-3:2021	Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for frozen tissue — Part 3: Isolated DNA	ISO/TC 212 and CEN/TC 140
Scope	This document specifies requirements and gives recommendations for the handling, storage, processing, and documentation of frozen tissue specimens intended for DNA examination 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 and molecular pathology laboratories that evaluate DNA isolated from frozen tissue. 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. Tissues that have undergone chemical stabilization pre-treatment before freezing are not covered in this document. NOTE International, national, or regional regulations or requirements can also apply to specific topics covered in this document.		

Project number	Title	Committee
EN ISO 20186-1:2019	Molecular in vitro diagnostic examinations - Specifications for pre-examination processes for venous whole blood - Part 1: Isolated cellular RNA (ISO 20186-1:2019)	ISO/TC 212 and CEN/TC 140
Scope	This document gives guidelines on the handling, storage, processing and documentation of venous whole blood specimens intended for cellular RNA examination during the pre-examination phase before a molecular assay is performed. This document covers specimens collected in venous whole blood collection tubes. This document is applicable to any molecular in vitro diagnostic examination 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 are taken for stabilizing blood cell free circulating RNA and RNA in exosomes circulating in blood. These are not described in this document. Different dedicated measures are taken for collecting, stabilizing, transporting and storing capillary blood as well as for collecting and storing blood by paper based technologies or other technologies generating dried blood. These are not described in this document. This document does not cover the isolation of specific blood cells and subsequent isolation of cellular RNA therefrom. RNA in pathogens present in blood is not covered by this document.		

Project number	Title	Committee
EN ISO 20186-2:2019	Molecular in vitro diagnostic examinations - Specifications for pre-examination processes for venous whole blood - Part 2: Isolated genomic DNA (ISO 20186-2:2019)	ISO/TC 212 and CEN/TC 140
Scope	This document gives guidelines on the handling, storage, processing and documentation of venous whole blood specimens intended for genomic DNA examination during the pre-examination phase before a molecular examination is performed. This document covers specimens collected in venous whole blood collection tubes. This document is applicable to any molecular in vitro diagnostic examination 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 are taken for stabilizing blood cell free circulating DNA, which are not described in this document. NOTE Circulating cell free DNA in blood is covered in ISO 20186-3. Different dedicated measures are taken for collecting, stabilizing, transporting and storing capillary blood as well as for collecting and storing blood by paper based technologies or other technologies generating dried blood. These are not described in this document. This document does not cover the isolation of specific blood cells and subsequent isolation of genomic DNA therefrom. DNA in pathogens present in blood is not covered by this document.		

Project number	Title	Committee
EN ISO 20186-3:2019	Molecular in-vitro diagnostic examinations - Specifications for pre-examination processes for venous whole blood - Part 3: Isolated circulating cell free DNA from plasma (ISO 20186-3:2019)	ISO/TC 212 and CEN/TC 140
Scope	This document provides recommendations and requirements on the handling, storage, processing and documentation of venous whole blood specimens intended for circulating cell free DNA (ccfDNA) examination during the pre-examination phase before an analytical test is performed. This document covers specimens collected in venous whole blood collection tubes. This document is applicable to any molecular in vitro diagnostic examination 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 are taken for stabilizing blood genomic DNA, which are not described in this document. Blood genomic DNA is covered in ISO 20186-2. Different dedicated measures are taken for preserving DNA in circulating exosomes, which are not described in this document. NOTE ccfDNA obtained from blood by the procedures cited in this document can contain DNA originally present in exosomes [8][9]. DNA in pathogens present in blood is not covered by this document.		

Project number	Title	Committee
CEN/TS 17305:2019, ISO 4307:2021	Molecular in vitro diagnostic examinations – Specifications for pre-examination processes for saliva – Isolated human DNA	ISO/TC 212 and CEN/TC 140
Scope	This document gives requirements on the handling, storage, processing and documentation of saliva specimens intended for human DNA examination during the pre-examination phase before a molecular examination is performed. This document is applicable to molecular in vitro diagnostic examination 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 organisations performing biomedical research, and regulatory authorities. Dedicated measures that need to be taken for saliva collected on absorbing material or by mouth washes are not described in this technical specification. Neither are measures for preserving and handling of native saliva cell-free DNA, pathogens, and other bacterial or whole microbiome DNA in saliva described. NOTE International, national or regional regulations or requirements can also apply to specific topics covered in this document.		

Project number	Title	Committee
CEN/TS 17390-1:2020	Molecular in vitro diagnostic examinations — for pre-examination processes for circulating tumor cells (CTCs) in venous whole blood — Part 1: Isolated RNA	CEN/TC 140
Scope	This document gives guidelines on the handling, storage, processing and documentation of venous whole blood specimens intended for the examination of human cellular RNA isolated from Circulating Tumor 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 EN ISO 20186-1. This document does not cover the isolation of specific blood cells and subsequent isolation of cellular RNA therefrom. RNA in pathogens present in blood is not covered by this document. NOTE International, national or regional regulations or requirements can also apply to specific topics covered in this document.		

Project number	Title	Committee
CEN/TS 17390-2:2020	Molecular in vitro diagnostic examinations — for pre-examination processes for circulating tumor cells (CTCs) in venous whole blood — Part 2: Isolated DNA	CEN/TC 140
Scope	This document gives guidelines on the handling, storage, processing and documentation of venous blood specimens intended for the examination of human genomic DNA isolated from Circulating Tumor 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 specific blood cells and subsequent isolation of genomic DNA therefrom. DNA in pathogens present in blood is not covered by this document. NOTE International, national or regional regulations or requirements can also apply to specific topics covered in this document.	

Project number	Title	Committee
ISO/TS 20658:2017, ISO/AWI 20658:2020	Medical laboratories – Requirements for collection, transport, receipt, and handling of samples	ISO/TC 212
Scope	This document specifies requirements and good practice recommendations for the collection, transport, receipt and handling of samples intended for medical laboratory examinations. This document is applicable to medical laboratories and other medical services involved in laboratory pre-examination processes that include the examination request, patient preparation and identification, sample collection, transport, receipt and storage. It may also be applicable to some biobanks. This document does not apply to blood and blood products intended for transfusion.	

Project number	Title	Committee
EN ISO 20387:2020	Biotechnology – Biobanking – General requirements for biobanking (ISO 20387:2018)	ISO/TC 276, CEN/CENELEC JCT 1
Scope	This document defines best practice that (1) respects the existing standardization efforts of life sciences research communities, (2) normalizes key aspects of data description particularly at the level of the biology being studied (and shared) across the life sciences communities, (3) ensures that data is "findable" and useable by other researchers and (4) provides concrete guidance and metrics for judging the applicability of a particular data sharing plan. This document is applicable to domains in life sciences including biotechnology, genomics (including massively parallel nucleotide sequencing, metagenomics, epigenomics and functional genomics), transcriptomics, translatomics, proteomics, metabolomics, lipidomics, glycomics, enzymology, immunochemistry, life science imaging, synthetic biology, systems biology, systems medicine and related fields.	

2. Standards for library preparation and NGS-analysis

Project number	Title	Committee
ISO/DIS 20397-1	Biotechnology — General Requirements for Massive Parallel Sequencing — Part 1: Nucleic acid and library preparation	ISO/TC 276
Scope	This document provides general requirements and guidance for quality assessments of nucleic acid samples, and general guidelines for library preparations and library quality assessments prior to sequencing and data generation.	

Project number	Title	Committee
ISO 20688-1:2020	Biotechnology — Nucleic acid synthesis — Part 1: Requirements for the production and quality control of synthesized oligonucleotides	ISO/TC 276
Scope	This document specifies minimum requirements for the production and quality control of synthesized oligonucleotides (nominally up to 250 bases). This document also describes general quality attributes for synthesized oligonucleotides as well as common methods for evaluating quality attributes.	

3. Standards for NGS-data

ISO projects listed within this chapter are related to data obtained either by NGS directly or within a specimen's/sample's life cycle including NGS. They give requirements for data collection, analysis, processing, storage, sharing, define data types, relationships, optionality, cardinalities and the bindings of particular terminology of the data, and thus contribute to the imteroperability of data. Interoperability of data is important for the exchange, traceability and comparability of data and their bigger picture (e.g., for the use in or comparison of studies or publications). ISO 20397-2 covers most of the needed requirements for NGS data analysis in cancer diagnostics and will be a good reference for a diagnostic NGS-workflow.

Project number	Title	Committee
ISO 20397-2:2021	Biotechnology — General requirements for massively parallel sequencing — Part 2: Methods to evaluate the quality of sequencing data	ISO/TC 276
Scope	This document specifies the general requirements and recommendations for quality assessments and control of MPS data. It covers post raw data generation procedures, sequencing alignments, and variant calling. This document also gives general guidelines for validation and documentation of MPS data. This document does not apply to any processes related to de novo assembly.	

Project number	Title	Committee
ISO/TS 20428:2017	Health informatics — Data elements and their metadata for describing structured clinical genomic sequence information in electronic health records	ISO/TC 215
Scope	ISO/TS 20428 defines the data elements and their necessary metadata to implement a structured clinical genomic sequencing report and their metadata in electronic health records particularly focusing on the genomic data generated by next generation sequencing	

	technology. This document - defines the composition of a structured clinical sequencing report (see Clause 5), - defines the required data fields and their metadata for a structured clinical sequencing report (see Clause 6), - defines the optional data (see Clause 7), - covers the DNA-level variation from human samples using whole genome sequencing, whole exome sequencing, and targeted sequencing (disease-targeted gene panels) by next generation sequencing technologies. Though whole transcriptome sequencing and other technologies are important to provide better patient care and enable precision medicine, this document only deals with DNA-level changes, - covers mainly clinical applications and clinical research such as clinical trials and translational research which uses clinical data. However, the necessary steps such as de-identification or consent from patient should be applied. The basic research and other scientific areas are outside the scope of this document, - does not cover the other biological species, i.e. genomes of viruses and microbes, and - does not cover the Sanger sequencing methods.

Project number	Title	Committee
ISO/TS 22692:2020	Genomics Informatics — Quality control metrics for DNA sequencing	ISO/TC 215/SC 1
Scope	This Technical Specification identifies quality metrics for the detection of DNA variants using next generation sequencing (NGS) technology. For the safety of NGS based applications, it is necessary to review the metrics of the whole data production process. This includes the quality-related data for the entire process of the NGS of DNA of all human-originated specimens, including DNA extraction, library preparation, sequencing, and data processing. It also defines the data types, relationships, optionality, cardinalities and the bindings of particular terminology of the data. In summary, this TS is intended to serve as a catalogue of sequencing data elements necessary to address quality metrics for various clinical applications. This document is not intended for • Sequencing methods other than NGS, such as the Sanger sequencing; • Targets other than genome, such as transcriptome or proteome; and • Specimens of species other than human.		

Project number	Title	Committee
ISO/TR 3985:2021	Development of International Standards in Biotechnology — Data Publication — Preliminary Considerations and Concepts	ISO/TC 276
Scope	This document defines best practice that (1) respects the existing standardization efforts of life sciences research communities, (2) normalizes key aspects of data description particularly at the level of the biology being studied (and shared) across the life sciences communities, (3) ensures that data is "findable" and useable by other researchers and (4) provides concrete guidance and metrics for judging the applicability of a particular data sharing plan. This document is applicable to domains in life sciences including biotechnology, genomics (including massively parallel nucleotide sequencing, metagenomics, epigenomics and functional genomics), transcriptomics, translatomics, proteomics, metabolomics, lipidomics, glycomics, enzymology, immunochemistry, life science imaging, synthetic biology, systems biology, systems medicine and related fields.		