Summary of Safety and Performance

NanoTYPE Device Family

Omixon's reference number for the SSP:	**SSP-NanoTYPE-001**
Version:	**05**
Issue Date:	**19/06/2024**

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This Summary of Safety and Performance (SSP) is intended to provide public access to an up-to-date summary of the main aspects of the safety and performance of the device.

Section A. Summary of safety and performance for professional users

The following information is intended for professional users.
*Following this information there is a summary intended for patients/lay persons (please see **Section B**)*

The SSP is not intended to replace the Instructions For Use as the main document to ensure the safe use of the device, nor is it intended to provide diagnostic or therapeutic suggestions to intended users.

Abbreviations

EUDAMED	European database on medical devices according to the IVDR (see below)
GTIN	Global Trade Item Number, serves as UDI-DI (see below)
IFU	Instructions for Use
IVDR	Regulation (EU) 2017/746 of the European Parliament and of the Council on in vitro diagnostic medical devices
HLA	Human Leucocyte Antigen
KPL	Known Product Limitations
NGS	Next Generation Sequencing
ONT	Oxford Nanopore Technologies
PCR	Polymerase Chain Reaction
PMS	Post Market Surveillance
PMPF	Post-Market Performance Follow-Up
SSP	Summary of Safety and Performance
UDI	Unique Device Identification
UDI-DI	UDI device identifier ('UDI-DI') specific to a manufacturer and a device

1. Device Identification and General Information

1.1.	**Device Group Name**	NanoTYPE	**Trade name(s):** NanoTYPE 24/11 CE NanoTYPE 96/11 CE NanoTYPE 4x96/11 CE
1.2.	**Manufacturer**	**Name:** **Address:**	Omixon Biocomputing Ltd. H-1117 Budapest, Kaposvár u. 14-18., Hungary, EU
1.3.		**SRN*:**	HU-MF-000003018
1.4.	**Device Basic UDI-DI:**		599956578001TV
1.5.	**EMDN****	**Code:** **Description:**	W01030499 TISSUE TYPING REAGENTS - OTHER
1.6.	**Risk class of device**		**C**
1.7.	**The device is neither for near-patient testing nor a companion diagnostic.**		
1.8.	**Year of the first IVDR certificate:**		2024
1.9.	**Authorised representative**	**Name:** **SRN:**	N/A N/A
1.10.	**Notified Body**	**Name:** **SIN***:**	BSI Group The Netherlands B.V. 2797

*: Single registration number. **: European Medical Device Nomenclature. ***: Single identification number

2. Intended Purpose

2.1.	**Intended use:**	NanoTYPE is a family of qualitative in vitro diagnostic medical devices intended for the identification and definition of Class I (A, B, and C) and class II (DQA1, DQB1, DRB1, DRB3/4/5, DPA1, DPB1) genes of the Human Leukocyte Antigens (HLA) complex from human genomic DNA derived from human whole blood. It is a single-use, non-automated assay utilizing polymerase chain reaction (PCR) to amplify a list of targeted genes depending on the product configuration. The generated amplicons are intended for a downstream library preparation and sequencing by Oxford Nanopore Technologies reagents and platforms in order to generate data for high

			resolution HLA genotyping using the Omixon NanoTYPER software. The assay results are intended to provide an HLA profile of the tested individual which can be used as an aid in assessment of the HLA gene compatibility between the patient and the donor population for the transplantation purposes.
2.2.	**Patient**	**Population(s):**	Transplantation patients and donors
		Indications*:	N/A
2.3.		**Contra-indications**:**	Heparin therapy
2.4.	**Intended users:**		NanoTYPE is intended for in vitro diagnostic use by professional healthcare personnel, such as laboratory technicians and physicians, trained in the techniques of molecular and in vitro diagnostic procedures as well as in HLA typing in diagnostic laboratories either EFI or ASHI accredited or able to work according to EFI or ASHI specifications.

3. Device Description

3.1. Description of the Device

3.1.1. Conditions to Use the Device

The device is for laboratory testing.

3.1.2. Method Principle

NanoTYPE 24/11 is an HLA amplification kit. The kit allows the simultaneous amplification of 11 HLA loci (HLA-A, B, C, DQA1, DQB1, DPA1, DPB1, DRB1, and DRB3/4/5) and provides workflow instructions for subsequent ONT library preparation and sequencing step as well as software analysis for HLA genotyping.
All 11 loci are amplified in a single, long-range multiplex PCR. Amplicons are then tagged with barcodes, pooled together, purified, and linked to adapters. The final library is then loaded into the flow cell.
During the sequencing, a DNA fragment enters a nanopore. As it goes through the nanopore, each DNA base disrupts the electrical field with a specific signature and can be used as a single molecule detector. The deconvolution of the electrical signal is done using a basecaller converting the electric signal into a DNA sequence with a FASTQ output format. This FASTQ file is then imported into NanoTYPER software for genotyping.

3.2. Description of the Device Kit(s)

Device Trade Name: NanoTYPE 24/11 CE for 24 reactions per kit

Component					Regulatory Status	Basic UDI-DI
ID	Name	Description	Filling Volume [µl]	Σ*		
A11	PCR Enzyme (24)	Thermostable DNA Polymerase enzyme	35	24	Accessory	N/A
A12	PCR Buffer (24)	Buffer	150	24	Accessory	N/A
A13	dNTP Mixture (24)	Mixture of monomer molecule for DNA amplification / substrates of the PCR enzyme	60	24	Accessory	N/A
P206	HLA Multi Primer Mix 24/11 v2.1	Primer mixture / mixture of highly selective short DNA sequences for starting DNA amplification / substrates of the PCR enzyme	22	24	Accessory	N/A

Device Trade Name: NanoTYPE 96/11 CE for 96 reactions per kit

Component					Regulatory Status	Basic UDI-DI
ID	Name	Description	Filling Volume [µl]	Σ*		
A14	PCR Enzyme (96)	Thermostable DNA Polymerase enzyme	140	96	Accessory	N/A
A15	PCR Buffer (96)	Buffer	600	96	Accessory	N/A

Component					Regulatory Status	Basic UDI-DI
ID	Name	Description	Filling Volume [µl]	Σ*		
A16	dNTP Mixture (96)	Mixture of monomer molecule for DNA amplification / substrates of the PCR enzyme	240	96	Accessory	N/A
P208	HLA Multi Primer Mix 96/11 v2.1	Primer mixture / mixture of highly selective short DNA sequences for starting DNA amplification / substrates of the PCR enzyme	90	96	Accessory	N/A

Device Trade Name: NanoTYPE 4x96/11 CE for 384 reactions per kit

Component (4 from each in this kit)					Regulatory Status	Basic UDI-DI
ID	Name	Description	Filling Volume [µl]	Σ*		
A14	PCR Enzyme (96)	Thermostable DNA Polymerase enzyme	140	96	Accessory	N/A
A15	PCR Buffer (96)	Buffer	600	96	Accessory	N/A
A16	dNTP Mixture (96)	Mixture of monomer molecule for DNA amplification / substrates of the PCR enzyme	240	96	Accessory	N/A
P208	HLA Multi Primer Mix 96/11 v2.1	Primer mixture / mixture of highly selective short DNA sequences for starting DNA	90	96	Accessory	N/A

Component (4 from each in this kit)					Regulatory Status	Basic UDI-DI
ID	Name	Description	Filling Volume [µl]	Σ*		
		amplification / substrates of the PCR enzyme				

*: Σ :No of reaction can be conducted

3.3. Previous Generation(s) or Variants of the Device

- NanoTYPE 24/11 RUO – Equivalent research use only product.
- NanoTYPE 24/11 CE – with HLA Multi Primer Mix 24/11 v2.0

3.4. Description of Any Accessories Which are Intended to Be Used in Combination with the Device

Other Devices:

Included:

NGS sequencer: Oxford Nanopore Technologies (ONT) MinION/GridION, specification is detailed in **Appendix C**

PCR Amplification: The NanoTYPE 24/11 CE was developed and validated on ABI Veriti 96-well thermocyclers with the following specification:

- PCR program used in an ABI 9600 emulation mode.

Liquid handling instruments:

- Micropipette capable of handling volumes of 1 to 1000 µL capacity,
- Multichannel pipette for handling volumes of 1-100 µL capacity.

DNA Quantitation: Qubit fluorometer (Thermo Fisher Scientific)

General laboratory equipment

- Magnetic stand for 1.5-2.0ml tubes
- Magnetic stand for 96-well PCR plates (optional)
- 96-well cooler rack or ice bucket with ice
- 1.5ml tube cooler rack or ice bucket with ice

			• Microplate centrifuge • Microtube centrifuge • Vortex • Timer
Other Articles:	**Excluded.**		Not identified.
	Included:	**NGS sequencing:**	• ONT MinION flow cell type R9.4.1 • ONT Rapid Barcoding Kit 96 (SQK-RBK110.96) • ONT Flow Cell Wash kit • MinKNOW software (sequencer's controlling software) specifications are detailed in **Appendix C**
		DNA Quantitation:	Qubit dsDNA BR Assay Kit
		Amplicon purification:	• ExoSAP-IT Express (Thermo Fisher Scientific) – if applicable • Molecular grade ethanol
		Consumables:	• Molecular grade water (DNase and RNase free) • General laboratory consumables
	Excluded.		Not identified.

3.5. Description of Any Other Devices and Products Which are Intended to Be Used in Combination with the Device

Other Medical Devices:	**Included:**	NanoTYPER™ (HLA genotyping software)
	Excluded.	Not identified.

4. Reference to Any Harmonised Standards and CS Applied

4.1. Common Specifications (CS)

- Common Specification are not determined.

4.2. Harmonized Standards

- EN ISO 13485:2016+A11:2021 – Medical devices - Quality management systems - Requirements for regulatory purposes (ISO 13485:2016)
- EN ISO 14971:2019/A11:2021 – Medical devices - Application of risk management to medical devices (ISO 14971:2019)
- EN ISO 15223-1:2021 – Medical devices - Symbols to be used with information to be supplied by the manufacturer - Part 1: General requirements (ISO 15223-1:2021)

4.2.1. Other Standards

- ISO 20916:2019 – In vitro diagnostic medical devices. Clinical performance studies using specimens from human subjects. Good study practice
- ISO/TR 20416:2020 – Medical devices. Post-market surveillance for manufacturers
- ISO 23640:2015 – In vitro diagnostic medical devices. Evaluation of stability of in vitro diagnostic reagents
- ISO 20417:2021 – Medical devices. Information to be supplied by the manufacturer
- CLSI EP12-A2:2008 Correction Oct 2021 User Protocol for Evaluation of Qualitative Test Performance

5. Risks and Warnings

5.1. Residual Risks and Undesirable Effects

- There is no unacceptable risk identified during Risk Management, however the Known Product Limitations of the devices are disclosed in **Section 5.3**.

5.2. Warnings And Precautions

5.2.1. Product safety

- The instructions in this document must be strictly and explicitly followed by qualified and properly trained personnel in order to ensure the proper and safe use of the product(s) described herein. All of the contents of this document must be fully read and understood prior to using such product(s).
- Failure to completely read and explicitly follow all of the instructions contained herein may result in damage to the product(s), injury to persons, including to users or others, and damage to other property. Omixon does not assume any liability arising out of the improper use of the product(s) described herein (including parts thereof or software) or any use of such product(s) outside the scope of the express written licenses or permissions granted by Omixon in connection with the customer's acquisition of such product(s).
- Good laboratory practice is essential for the proper execution of the test. Always separate pre and post-PCR steps in dedicated areas. Each workplace must be equipped with its own pipettes and the necessary auxiliary materials and equipment. Use only DNase-free consumables.
- When working with chemicals always wear: (1) suitable lab coat, (2) disposable gloves and (3) protective goggles.
- The chemical component overview of device reagents can be found in the relevant SDSs uploaded to the Product support website. For other components, please consult the appropriate Safety Data Sheets (SDSs) available from the specified product suppliers.
- Avoid unnecessarily long exposure of reagents to a temperature out of the storing conditions.
- Do not expose reagents to UV light.
- Do not reconstitute or dilute the reagents in volumes other than described in this IFU. Do not use less than the specified volume of the reagents. These activities can lead to performance errors.
- Do not use the product if any of its components are damaged (broken vials, loose caps, and so on).
- Do not use the product past the expiration date given on the label!
- Do not replace or mix device reagents with other manufacturer's products!
- Do not mix and match vials between kits. Vials from kits bearing different catalog or LOT numbers can NOT be used interchangeably.
- It is highly recommended to use different barcode sets for samples being processed in parallel for different sequencing runs and also for subsequent re-use of flow cells after washing.

- The user shall report any serious incident that has occurred in relation to the device to the manufacturer and the competent authority of the Member State in which the user and/or the patient is established.
- It is end user's responsibility to use the protocol for a time-critical applications.

5.2.2. Reagent and sample handling

- We recommend isolating human gDNA from whole blood. Do not collect blood in heparinized tubes. Do not use lipemic or hemolyzed samples or blood samples from patients undergoing heparin therapy. To ensure the quality and consistency of sample preparation, we recommend using a well-tested, commercially available DNA isolation kit.
- EDTA in gDNA elution buffer can inhibit PCR reaction so we recommend using elution buffer with only low EDTA content.
- We recommend storing the prepared gDNA for extended periods at temperatures of -20°C or less and avoid repetitive freeze/thaw of the gDNA as well to preserve its integrity and stability.
- When handling reagents or samples always wear: (1) suitable lab coat, (2) disposable gloves and (3) protective goggles.
- Discard used gloves into the hazardous waste bin!
- Wash your hands thoroughly after removing gloves!
- Treat samples, materials and instrumentation as potentially infectious!
- Avoid microbial contamination of reagents when removing aliquots from reagent vials!
- Use disinfectant to clean and disinfect the areas used during the processing of samples!
- Use, storage and disposal of kit components and samples, should be in accordance with the procedures defined by national safety guidelines and in accordance with country, federal, state and local regulations.
- Use of this product should be limited to personnel trained in PCR, NGS techniques and NGS data analysis.
- Due to the sensitivity of the device, a care should be taken when handling samples and materials to ensure that reagents and their mixtures are not contaminated.
- Keep Barcode plate and RAP-F adapter reagents on ice until its use.
- Temperature control and monitoring processes of the freezers must be in place and maintained regularly.
- It is always advisable to keep enough flow cells in stock to avoid delays in sample processing due to flow cells with insufficient pore count.

5.2.3. Performance

- For the best performance, use the following in the same workflow: (1) NanoTYPE 24/11 CE kit,(2) Omixon NanoTYPER™ CE software, and (3) the items in the Equipment, reagents,

and supplies section If other materials than the ones in the Equipment, reagents, and supplies section of the IFU are used, their verification and validation by the user is required.

- The recommended thermocycler is the ABI Veriti® instrument. When you program the thermocycler, set the ramp rate to resemble the ABI 9600 emulation mode, which is equal to a heating speed of +0.8°C/s and a cooling speed of -1.6°C/s.
- All instruments must be operated and maintained in accordance with good laboratory practice as defined by manufacturer's instructions and/or local laboratory rules (including calibration).
- For the best performance, the protocol requires 200 ng of gDNA per sample, and its quality should meet with 260/280 absorbance ratio values of 1.8-2.0 and 260/230 absorbance ratio values of 2.0-2.2. Values outside this range indicate impurities or the presence of contaminants (alcohol, salts, detergents, formaldehyde, heparin). It is critical to accurately determine the input DNA concentration. We highly recommend using a fluorometric method to accurately quantify DNA.
  The integrity of a DNA sample must be preserved as the initial amplification step requires a suitable amount of template material with more than 6.5 kilobases in length.
- In case the MinKNOW and NanoTYPER software are installed on the same computer do not perform basecalling and HLA genotyping at the same time, otherwise one of the processes may crash.
- The following reagents are known potential PCR inhibitors: EDTA, calcium, polysaccharide, isopropyl alcohol, ethanol, SDS, urea, guanidium salts and HOCl. If the concentrations of these substances exceed certain thresholds in the gDNA samples the performance of the PCR will be deteriorated. Use a wellestablished DNA extraction method to eliminate these substances from your gDNA samples.
- RNA may be a potential PCR inhibitor of gDNA amplification. Use RNAse treatment during the DNA extraction to eliminate any traces of RNA.
- NanoTYPE was successfully tested in combination with some of the most commonly used extraction methods. It is however user's responsibility to always validate his extraction method in combination with the assay to exclude interference with unknown interfering substances.

5.3. Other Relevant Aspects of Safety

Refer to the Known Product Limitations (KPL) document for known ambiguities, assay and software limitations of the NanoTYPE product family. The KPL is bundled with the IFU and also available on the Omixon website under the MyOmixon > Product downloads > NanoTYPER, or can be requested from Omixon Support.

5.3.1. Ambiguities Due to Assay Design

Locus	Ambiguous allele group
HLA-DPB1	02:01:02/1315:01
	04:01:01/1300:01/1321:01/1322:01
	05:01:01/1273:01/05:01:16
	13:01:01/107:01
	39:01:01/39:01:02
	105:01:01/1072:01/665:01:01
	296:01/1286:01
	584:01:01/584:01:02
HLA-DRB1	01:01:01/01:100/01:01:35
	03:01:01/03:01:31/03:147
	08:01:01/08:105
	09:01:02/09:31:02
	10:01:01/10:38Q
	12:01:01/12:10
	13:01:01/13:01:34
	14:25:01/14:25:02
	14:54:01/14:216/14:243
	15:01:01/15:204
	15:02:01/15:140/15:149
	15:03:01/15:185
	16:02:01/16:64
HLA-DRB3	01:01:02/01:62:01
	02:02:01/02:144/02:167/02:168
HLA-DRB4	01:01:01/01:156
	01:03:01:02N/01:03:01:13N

5.3.2. Assay Limitations

HLA-DQB1*03:276N and HLA-DRB4*03:01N are not amplified due to the deletion of the forward primer site. The following allele groups may show low amplification, and very rarely (with a ~1% chance) allele dropouts may occur: HLA-DQB1*03:01, HLA-DQB1*03:03, HLA-DQB1*04:02, HLA-DRB1*04, HLA-DRB1*07:01.

5.3.3. Ambiguities Due to the Limitations of the Sequencing Technology

Certain null and alternatively expressed alleles are not reported if a normally expressed allele match was found. The following well-documented null alleles are affected by this limitation, and the listed normally expressed alleles are reported:

- HLA-A*01:01:81/HLA-A*01:15N
- HLA-B*37:01:01/HLA-B*37:42N
- HLA-C*02:02:02/HLA-C*02:92N
- HLA-C*05:248/HLA-C*05:99N
- HLA-DRB1*07:01:01/HLA-DRB1*07:26N

5.3.4. Summary of Any Field Safety Corrective Action

- Not Applicable.

6. Summary of Performance Evaluation and Post-Market Performance Follow-Up (PMPF)

6.1. Summary of Scientific Validity of the Analyte

Based on the assessment of the available information, application of the human genomic DNA as an analyte is scientifically valid in both hematopoietic stem cell transplantation and solid organ transplantation with 11 loci determination and with low, intermediate, and high resolution for donor/recipient HLA matching. Venous blood as the claimed sample type is a scientifically valid source of human genomic DNA.

6.2. Summary of Performance Data from Equivalent Device(s)

Not Applicable.

6.3. Summary of Performance Data from Studies Conducted Prior to CE-Marking

Analytical Performance	**Trueness:**		99.50 %	
	Repeatability:		100.0 %	
	Reproducibility:	**Lot-to-Lot:**	99.73 %	
		Operator-to-Operator:	100.0 %	
		Equivalency of sample setups:	multi vs. single:	99.8 %
			12 vs. 4:	100.0 %
			12 vs. 24:	100.0 %
	Accuracy:		99.96 %	
Stability	**In-use Open:**		>6 hours	
	In-use Closed:		>6 hours	
	Shelf life:		12 months (interim)	
	Transport stability:		No deterioration and leakage under the defined shipping condition.	
Interference	**DNA Isolation kits**		Will be determined in a PMPF Study	
	Interfering substances: may cause interference above given concentration limit		• EDTA above 0.5 mM • Calcium above 2.0 mM • Polysaccharide above 60.0 ng/µL • Isopropyl alcohol above 1% (v/v) • Ethanol above 1% (v/v) • SDS above 1% (v/v) • Urea above 0.005% (w/v) • Guanidium salts above 20 mM • HOCl above 100 µM	
Clinical Performance	**Positive Percentage Agreement:**		99.44%	
	Negative Percentage Agreement:		99.98%	
Technical Features	**Total amplification time:**		<3 hours	
	Amplicon concentration	**Routine protocol:**	>37 ng/µl	
		Single protocol:	>37 ng/µl	

6.3.1. Locus Level Clinical Performance Parameters

6.3.1.1. Positive Percentage Agreement

Locus	Routine and single protocols [%]	Single sample protocol [%]
HLA-A	100.0	100.0
HLA-B	99.61	100.0
HLA-C	100.0	100.0
HLA-DPA1	100.0	100.0
HLA-DPB1	100.0	100.0
HLA-DQA1	99.48	97.73
HLA-DQB1	98.03	97.73
HLA-DRB1	99.74	100.0
HLA-DRB3	98.82	100.0
HLA-DRB4	98.56	95.45
HLA-DRB5	99.61	100.0
Cumulative PPA	99.44	99.90

6.3.1.2. Negative Percentage Agreement

Locus	Routine and single protocols [%]	Single sample protocol [%]
HLA-A	100.0	100.0
HLA-B	99.99	100.0
HLA-C	100.0	100.0
HLA-DPA1	100.0	100.0
HLA-DPB1	100.0	100.0
HLA-DQA1	99.98	99.77
HLA-DQB1	99.91	99.77
HLA-DRB1	99.99	100.0
HLA-DRB3	99.83	100.0
HLA-DRB4	99.64	97.73
HLA-DRB5	99.90	100.0
Cumulative PPA	99.98	99.90

6.3.1.3. Locus Level Analytical Performance Parameters

Locus	Trueness [%]	Accuracy [%]	Precision [%]					
			Repeatability	Reproducibility				
				Lot-to-Lot	Operator-to-Operator	Equivalency of sample setups		
						Multi-Sample vs. Single-Sample	12 Sample vs. 24 Sample	12 Sample vs. 4 Sample
HLA-A	99.48	99.98	100.0	100.00	100.0	100.0	100.0	100.0
HLA-B	99.48	99.98	100.0	100.00	100.0	100.0	100.0	100.0
HLA-C	99.74	99.98	100.0	100.00	100.0	100.0	100.0	100.0
HLA-DPA1	99.47	99.90	100.0	100.00	100.0	98.1	98.1	98.1
HLA-DPB1	99.22	99.94	100.0	99.60	100.0	100.0	100.0	100.0
HLA-DQA1	98.95	98.88	100.0	98.77	100.0	100.0	100.0	100.0
HLA-DQB1	99.22	99.91	100.0	100.00	100.0	100.0	100.0	100.0
HLA-DRB1	99.74	99.99	100.0	100.00	100.0	100.0	100.0	100.0
HLA-DRB3	99.21	99.74	100.0	98.73	100.0	100.0	100.0	100.0
HLA-DRB4	100.00	100.00	100.0	100.00	100.0	100.0	100.0	100.0
HLA-DRB5	100.00	100.00	100.0	100.00	100.0	100.0	100.0	100.0
Cumulative	99.50	99.96	100.0	99.73	100.0	100.0	100.0	100.0

6.4. Summary of Performance Data from Other Sources

Not Applicable.

6.5. Overall Summary of the Performance and Safety

According to the **Analytical Performance** of the Omixon NanoTYPE 24/11 CE, the products of the NanoTYPE device group fulfilled the **Design Verification** requirements.
The **Clinical Performance** of Omixon NanoTYPE 24/11 CE was determined with all **Clinical Performance parameters** and **Technical Features** defined in the objectives of the Studies, and the **Scientific Validity** was demonstrated.
According to the **Performance Evaluation** the Omixon NanoTYPE 24/11 CE is

- compliant with the relevant general safety and performance requirements with respect to clinical performance,
- safe and effective for its intended use.

6.6. Ongoing or Planned Post-Market Performance Follow-Up

According to the PMSP-NT2411CE-001 *PMSP for NanoTYPE 24_11* CE_v2 ***Post Market Surveillance Plan*** of the Device the following **Post-Market Performance Follow-Up** activities are planned for assessing direct information about safety and performance of the device:

- *PMPFP- NT2411CE-001 PMPFP for NanoTYPE 24_11 CE_v2.pdf*, including
    - an **Interfering Substance Study** as **PMPF Study** planned in ISSP-NT2411CE-002 *Interfering Substance Study Plan for NanoTYPE 24_11 CE_v01.pdf.*
    - PMPF Study on the failure rate of ONT flow cells.
    - PMPF Study on the device performance after IMGT database update as determined in Study Plan: IMGT/HLA 0.00.0 study design Confluence page: https://confluence.omixon.com/pages/viewpage.action?pageId=105055392

7. Metrological Traceability of Assigned Values

7.1. Explanation of the Unit of Measurement

Not Applicable.

7.2. Applied Reference Materials and/or Reference Measurement Procedures Used for Calibration

- Reference Material / Calibrator is Not Applicable.
- Reference Method is Not Applicable.

8. Suggested Profile and Training for Users

Profile is Not Applicable.
Training with predefined training material is available in connection with the required training of the NanoTYPER IVD Medical Device Software as NanoTYPE CE training presentation.

Section B. Summary of safety and performance for patients/lay persons

This Summary of Safety and Performance (SSP) is intended to provide public access to an updated summary of the main aspects of the safety and performance of the device not intended for self-testing. The information presented below is intended for patients or lay persons. A more extensive summary of the safety and performance prepared for healthcare professionals is found in the first part of this document, ***Section A****.*

The SSP is not intended to give general advice on the diagnosis and/or treatment of a medical condition. Please contact your healthcare professional in case you have questions about your medical condition or about the use of the device in your situation.
The SSP is not intended to replace the Instructions For Use to provide information on the safe use of the device.

Abbreviations

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1. Device identification and general information

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1.2.	**Manufacturer**	**Name:**	Omixon Biocomputing Ltd.
		Address:	H-1117 Budapest, Kaposvár u. 14-18., Hungary, EU
1.3.	**Device Basic UDI-DI:**		599956578001TV
1.4.	**Risk class of device**		**C**
1.5.	**Year of the first IVDR certificate:**		N/A

2. Intended Purpose

2.1.	**Intended use:**	NanoTYPE is a family of qualitative in vitro diagnostic medical devices intended for the identification and definition of Class I (A, B, and C) and class II (DQA1, DQB1, DRB1, DRB3/4/5, DPA1, DPB1) genes of the Human Leukocyte Antigens (HLA) complex from human genomic DNA derived from human whole blood. It is a single-use, non-automated assay utilizing polymerase chain reaction (PCR) to amplify a list of targeted genes depending on the product configuration. The generated amplicons are intended for a downstream library preparation and sequencing by Oxford Nanopore Technologies reagents and platforms in order to generate data for high resolution HLA genotyping using the Omixon NanoTYPER software. The assay results are intended to provide an HLA profile of the tested individual which can be used as an aid in assessment of the HLA gene compatibility between the patient and the donor population for the transplantation purposes.

2.2.	**Patient**	**Population(s):**	Transplantation patients and donors
		Indications*:	N/A
2.3.		**Contra-indications**:**	Heparin therapy
2.4.	**Intended users:**		NanoTYPE is intended for in vitro diagnostic use by professional healthcare personnel, such as laboratory technicians and physicians, trained in the techniques of molecular and in vitro diagnostic procedures as well as in HLA typing in diagnostic laboratories either EFI or ASHI accredited or able to work according to EFI or ASHI specifications.

3. Device Description

3.1. General Description of the Device

The device is for laboratory testing.

3.2. How The Device is Achieving its Intended Purpose

NanoTYPE 24/11 is an HLA amplification kit. The kit allows the simultaneous amplification of 11 HLA loci (HLA-A, B, C, DQA1, DQB1, DPA1, DPB1, DRB1, and DRB3/4/5) and provides workflow instructions for subsequent ONT library preparation and sequencing step as well as software analysis for HLA genotyping.
All 11 loci are amplified in a single, long-range multiplex PCR. Amplicons are then tagged with barcodes, pooled together, purified, and linked to adapters. The final library is then loaded into the flow cell.
During the sequencing, a DNA fragment enters a nanopore. As it goes through the nanopore, each DNA base disrupts the electrical field with a specific signature and can be used as a single molecule detector. The deconvolution of the electrical signal is done using a basecaller converting the electric signal into a DNA sequence with a FASTQ output format. This FASTQ file is then imported into NanoTYPER software for genotyping.

3.3. Description of the Kit(s)

Device Trade Name: NanoTYPE 24/11 CE for 24 reactions per kit

Component				Regulatory Status	Basic UDI-DI
ID	Name	Description	No of Reactions		
A11	PCR Enzyme (24)	Thermostable DNA Polymerase enzyme	24	Accessory	N/A
A12	PCR Buffer (24)	Buffer	24	Accessory	N/A
A13	dNTP Mixture (24)	Mixture of monomer molecule for DNA amplification / substrates of the PCR enzyme	24	Accessory	N/A
P206	HLA Multi Primer Mix 24/11 v2.1	Primer mixture / mixture of highly selective short DNA sequences for starting DNA amplification / substrates of the PCR enzyme	24	Accessory	N/A

Device Trade Name: NanoTYPE 96/11 CE for 96 reactions per kit

Component				Regulatory Status	Basic UDI-DI
ID	Name	Description	No of Reactions		
A14	PCR Enzyme (96)	Thermostable DNA Polymerase enzyme	96	Accessory	N/A
A15	PCR Buffer (96)	Buffer	96	Accessory	N/A

Component				Regulatory Status	Basic UDI-DI
ID	Name	Description	No of Reactions		
A16	dNTP Mixture (96)	Mixture of monomer molecule for DNA amplification / substrates of the PCR enzyme	96	Accessory	N/A
P208	HLA Multi Primer Mix 96/11 v2.1	Primer mixture / mixture of highly selective short DNA sequences for starting DNA amplification / substrates of the PCR enzyme	96	Accessory	N/A

Device Trade Name: NanoTYPE 4x96/11 CE for 384 reactions per kit

Component (4 from each in this kit)				Regulatory Status	Basic UDI-DI
ID	Name	Description	No of Reactions		
A14	PCR Enzyme (96)	Thermostable DNA Polymerase enzyme	96	Accessory	N/A
A15	PCR Buffer (96)	Buffer	96	Accessory	N/A
A16	dNTP Mixture (96)	Mixture of monomer molecule for DNA amplification / substrates of the PCR enzyme	96	Accessory	N/A
P208	HLA Multi Primer Mix 96/11 v2.1	Primer mixture / mixture of highly selective short DNA sequences for starting DNA amplification / substrates of the PCR enzyme	96	Accessory	N/A

3.4. Description of Any Accessories Which are Intended to Be Used in Combination with the Device

Other Devices:	**Included:**	**NGS sequencer:**	Oxford Nanopore Technologies (ONT) MinION/GridION, specification is detailed in Appendix C
		PCR Amplification:	The NanoTYPE 24/11 CE was developed and validated on ABI Veriti 96-well thermocyclers with the following specification: PCR program used in an ABI 9600 emulation mode.
		Liquid handling instruments:	Micropipette capable of handling volumes of 1 to 1000 µL capacity, Multichannel pipette for handling volumes of 1-100 µL capacity.
		DNA Quantitation:	Qubit fluorometer (Thermo Fisher Scientific)
		General laboratory equipment	Magnetic stand for 1.5-2.0ml tubes Magnetic stand for 96-well PCR plates (optional) 96-well cooler rack or ice bucket with ice 1.5ml tube cooler rack or ice bucket with ice Microplate centrifuge Microtube centrifuge Vortex Timer
	Excluded:		Not identified.
Other Articles:	**Included:**	**NGS sequencing:**	ONT MinION flow cell type R9.4.1 ONT Rapid Barcoding Kit 96 (SQK-RBK110.96) ONT Flow Cell Wash kit MinKNOW software (sequencer's controlling software) specifications are detailed in Appendix C
		DNA Quantitation:	Qubit dsDNA BR Assay Kit
		Amplicon purification:	ExoSAP-IT Express (Thermo Fisher Scientific) – if applicable Molecular grade ethanol
		Consumables:	Molecular grade water (DNase and RNase free) General laboratory consumables
	Excluded:		Not identified.

3.5. Description of Any Other Devices and Products Which are Intended to Be Used in Combination with the Device

Other Medical Devices:	**Included:**	NanoTYPER™ (HLA genotyping software)
	Excluded.	Not identified.

4. Risks and Warnings

Contact your healthcare professional if you are concerned about the use of the device or about the results.
This document is not intended to replace a consultation with your healthcare professional, if needed.

4.1. How Potential Risks Have Been Controlled or Managed

Omixon Ltd. applies a procedure integrated into the company's quality management system to control risk management. Risk management is performed to evaluate

- the safety of the IVD Medical Devices related to the patient, the user and other persons and
- the impacts of proposed changes to both processes and products to such safety.

Risk management encompasses risk analysis, risk evaluation, risk control during Design and Development, production and post market activities throughout the life cycle of an IVD product. As for all IVD medical Devices produced by Omixon Ltd. a risk management file containing the records of the risk management related to all identified risks is established and maintained for the NanoTYPE device.
Omixon eliminates or reduces risks as far as possible without adversely affecting the benefit-risk ratio and make all efforts to keep any residual risk as low as possible. Any remaining risks will be weighed against the benefits that the product has for the patient.
Omixon will inform the user or other persons of any residual risks in the IFU and/or KPL.

4.2. Residual Risks and Undesirable Effects

- There is no unacceptable risk identified during Risk Management, however the Known Product Limitations of the devices are disclosed in **Section 4.4**.

4.3. Warnings And Precautions

4.3.1. Product safety

- The instructions in this document must be strictly and explicitly followed by qualified and properly trained personnel in order to ensure the proper and safe use of the product(s) described herein. All of the contents of this document must be fully read and understood prior to using such product(s).
- Failure to completely read and explicitly follow all of the instructions contained herein may result in damage to the product(s), injury to persons, including to users or others, and damage to other property. Omixon does not assume any liability arising out of the improper use of the product(s) described herein (including parts thereof or software) or any use of such product(s) outside the scope of the express written licenses or permissions granted by Omixon in connection with the customer's acquisition of such product(s).
- Good laboratory practice is essential for the proper execution of the test. Always separate pre and post-PCR steps in dedicated areas. Each workplace must be equipped with its own pipettes and the necessary auxiliary materials and equipment. Use only DNase-free consumables.
- When working with chemicals always wear: (1) suitable lab coat, (2) disposable gloves and (3) protective goggles.
- The chemical component overview of device reagents can be found in the relevant SDSs uploaded to the Product support website. For other components, please consult the appropriate Safety Data Sheets (SDSs) available from the specified product suppliers.
- Avoid unnecessarily long exposure of reagents to a temperature out of the storing conditions.
- Do not expose reagents to UV light.
- Do not reconstitute or dilute the reagents in volumes other than described in this IFU. Do not use less than the specified volume of the reagents. These activities can lead to performance errors.
- Do not use the product if any of its components are damaged (broken vials, loose caps, and so on).
- Do not use the product past the expiration date given on the label!
- Do not replace or mix device reagents with other manufacturer's products!
- Do not mix and match vials between kits. Vials from kits bearing different catalog or LOT numbers can NOT be used interchangeably.
- It is highly recommended to use different barcode sets for samples being processed in parallel for different sequencing runs and also for subsequent re-use of flow cells after washing.
- The user shall report any serious incident that has occurred in relation to the device to the manufacturer and the competent authority of the Member State in which the user and/or the patient is established.
- It is end user's responsibility to use the protocol for a time-critical applications.

4.3.2. Reagent and sample handling

- We recommend isolating human gDNA from whole blood. Do not collect blood in heparinized tubes. Do not use lipemic or hemolyzed samples or blood samples from patients undergoing heparin therapy. To ensure the quality and consistency of sample preparation, we recommend using a well-tested, commercially available DNA isolation kit.
- EDTA in gDNA elution buffer can inhibit PCR reaction so we recommend using elution buffer with only low EDTA content.
- We recommend storing the prepared gDNA for extended periods at temperatures of -20°C or less and avoid repetitive freeze/thaw of the gDNA as well to preserve its integrity and stability.
- When handling reagents or samples always wear: (1) suitable lab coat, (2) disposable gloves and (3) protective goggles.
- Discard used gloves into the hazardous waste bin!
- Wash your hands thoroughly after removing gloves!
- Treat samples, materials and instrumentation as potentially infectious!
- Avoid microbial contamination of reagents when removing aliquots from reagent vials!
- Use disinfectant to clean and disinfect the areas used during the processing of samples!
- Use, storage and disposal of kit components and samples, should be in accordance with the procedures defined by national safety guidelines and in accordance with country, federal, state and local regulations.
- Use of this product should be limited to personnel trained in PCR, NGS techniques and NGS data analysis.
- Due to the sensitivity of the device, a care should be taken when handling samples and materials to ensure that reagents and their mixtures are not contaminated.
- Keep Barcode plate and RAP-F adapter reagents on ice until its use.
- Temperature control and monitoring processes of the freezers must be in place and maintained regularly.
- It is always advisable to keep enough flow cells in stock to avoid delays in sample processing due to flow cells with insufficient pore count.

4.3.3. Performance

- For the best performance, use the following in the same workflow: (1) NanoTYPE 24/11 CE kit,(2) Omixon NanoTYPER™ CE software, and (3) the items in the Equipment, reagents, and supplies section If other materials than the ones in the Equipment, reagents, and supplies section of the IFU are used, their verification and validation by the user is required.

- The recommended thermocycler is the ABI Veriti® instrument. When you program the thermocycler, set the ramp rate to resemble the ABI 9600 emulation mode, which is equal to a heating speed of +0.8°C/s and a cooling speed of -1.6°C/s.
- All instruments must be operated and maintained in accordance with good laboratory practice as defined by manufacturer's instructions and/or local laboratory rules (including calibration).
- For the best performance, the protocol requires 200 ng of gDNA per sample, and its quality should meet with 260/280 absorbance ratio values of 1.8-2.0 and 260/230 absorbance ratio values of 2.0-2.2. Values outside this range indicate impurities or the presence of contaminants (alcohol, salts, detergents, formaldehyde, heparin). It is critical to accurately determine the input DNA concentration. We highly recommend using a fluorometric method to accurately quantify DNA.
  The integrity of a DNA sample must be preserved as the initial amplification step requires a suitable amount of template material with more than 6.5 kilobases in length.
- In case the MinKNOW and NanoTYPER software are installed on the same computer do not perform basecalling and HLA genotyping at the same time, otherwise one of the processes may crash.
- The following reagents are known potential PCR inhibitors: EDTA, calcium, polysaccharide, isopropyl alcohol, ethanol, SDS, urea, guanidium salts and HOCl. If the concentrations of these substances exceed certain thresholds in the gDNA samples the performance of the PCR will be deteriorated. Use a wellestablished DNA extraction method to eliminate these substances from your gDNA samples.
- RNA may be a potential PCR inhibitor of gDNA amplification. Use RNAse treatment during the DNA extraction to eliminate any traces of RNA.
- NanoTYPE was successfully tested in combination with some of the most commonly used extraction methods. It is however user's responsibility to always validate his extraction method in combination with the assay to exclude interference with unknown interfering substances.

4.4. Other Relevant Aspects of Safety

Refer to the Known Product Limitations (KPL) document for known ambiguities, assay and software limitations of the NanoTYPE product family. The KPL is bundled with the IFU and also available on the Omixon website under the MyOmixon > Product downloads > NanoTYPER, or can be requested from Omixon Support.

4.4.1. Ambiguities Due to Assay Design

Locus	Ambiguous allele group
HLA-DPB1	02:01:02/1315:01
	04:01:01/1300:01/1321:01/1322:01
	05:01:01/1273:01/05:01:16
	13:01:01/107:01
	39:01:01/39:01:02
	105:01:01/1072:01/665:01:01
	296:01/1286:01
	584:01:01/584:01:02
HLA-DRB1	01:01:01/01:100/01:01:35
	03:01:01/03:01:31/03:147
	08:01:01/08:105
	09:01:02/09:31:02
	10:01:01/10:38Q
	12:01:01/12:10
	13:01:01/13:01:34
	14:25:01/14:25:02
	14:54:01/14:216/14:243
	15:01:01/15:204
	15:02:01/15:140/15:149
	15:03:01/15:185
	16:02:01/16:64
HLA-DRB3	01:01:02/01:62:01
	02:02:01/02:144/02:167/02:168
HLA-DRB4	01:01:01/01:156
	01:03:01:02N/01:03:01:13N

4.4.2. Assay Limitations

HLA-DQB1*03:276N and HLA-DRB4*03:01N are not amplified due to the deletion of the forward primer site. The following allele groups may show low amplification, and very rarely (with a ~1%

chance) allele dropouts may occur: HLA-DQB1*03:01, HLA-DQB1*03:03, HLA-DQB1*04:02, HLA-DRB1*04, HLA-DRB1*07:01.

4.4.3. Ambiguities Due to The Limitations of the Sequencing Technology

Certain null and alternatively expressed alleles are not reported if a normally expressed allele match was found. The following well-documented null alleles are affected by this limitation, and the listed normally expressed alleles are reported:

- HLA-A*01:01:81/HLA-A*01:15N
- HLA-B*37:01:01/HLA-B*37:42N
- HLA-C*02:02:02/HLA-C*02:92N
- HLA-C*05:248/HLA-C*05:99N
- HLA-DRB1*07:01:01/HLA-DRB1*07:26N

4.5. Summary of Any Field Safety Corrective Action

- Not Applicable.

5. Summary of Performance Evaluation and Post-Market Performance Follow-Up (PMPF)

5.1. Summary of Scientific Validity of the Analyte

When matching donors and recipients for transplants, we check if their genes match up well. Clinicians used information about persons DNA, measured by NanoTYPE 24/11 CE, to confirm it's a good method for both bone marrow and organ transplants like kidney or heart. It helps figure out if they are a good match for 11 specific genes. This method can tell us how well they match with three levels of accuracy – low, medium, or high. They used blood samples, which works well for this.

5.2. Overall Summary of the Performance and Safety

According to the **Analytical Performance** of the Omixon NanoTYPE 24/11 CE, the the products of the NanoTYPE device group fulfilled the **Design Verification** requirements.
The **Clinical Performance** of Omixon NanoTYPE 24/11 CE was determined with all **Clinical Performance parameters** and **Technical Features** defined in the objectives of the Studies, and the **Scientific Validity** was demonstrated.
According to the **Performance Evaluation** the Omixon NanoTYPE 24/11 CE is

- compliant with the relevant general safety and performance requirements with respect to clinical performance,
- safe and effective for its intended use.

5.3. Summary of Performance Data from Studies Conducted Prior to CE-Marking

Analytical Performance	**Trueness:**		99.50 %	
	Repeatability:		100.0 %	
	Reproducibility:	**Lot-to-Lot:**	99.73 %	
		Operator-to-Operator:	100.0 %	
		Equivalency of sample setups:	multi vs. single:	99.8 %
			12 vs. 4:	100.0 %
			12 vs. 24:	100.0 %
	Accuracy:		99.96 %	
Stability	**In-use Open:**		>6 hours	
	In-use Closed:		>6 hours	
	Shelf life:		12 months (interim)	

	Transport stability:		No deterioration and leakage under the defined shipping condition.
Interference	**DNA Isolation kits:**		Will be determined in a PMPF Study
	Interfering substances: may cause interference above given concentration limit		• EDTA above 0.5 mM • Calcium above 2.0 mM • Polysaccharide above 60.0 ng/µL • Isopropyl alcohol above 1% (v/v) • Ethanol above 1% (v/v) • SDS above 1% (v/v) • Urea above 0.005% (w/v) • Guanidium salts above 20 mM • HOCl above 100 µM
Clinical Performance	**Positive Percentage Agreement:**		99.44%
	Negative Percentage Agreement:		99.98%
Technical Features	**Total amplification time:**		<3 hours
	Amplicon concentration	**Routine protocol:**	>37 ng/µl
		Single protocol:	>37 ng/µl

5.4. Summary of Performance Data from Equivalent Device(s) and/ or Other Sources

Not Applicable.

5.5. Ongoing or Planned Post-Market Performance Follow-Up

According to the ***Post Market Surveillance Plan*** of the Device the following **Post-Market Performance Follow-Up Studies** are planned for assessing direct information about safety and performance of the NanoTYPE 24/11 CE:

- an **Interfering Substance Study**.
- PMPF Study on the failure rate of ONT flow cells.
- PMPF Study on the device performance after IMGT database update.

6. Suggested Profile and Training for Users

Profile is Not Applicable.
Training with predefined training material is available in connection with the required training of the models of the NanoTYPE device group as NanoTYPE CE training presentation.

Revision History by NB

SSP			Validated by NB	
Revision No.	Issue Date	Change	Yes / validation language	No*
01	25/03/2024	First Issue	☒ English	☐
02	25/06/2024	Updated issue with accepted changes submitted at 05/06/2024	☐	☒

*: only applicable for class C (IVDR, Article 48 (7)) for which the SSP is not yet validated by the NB). Checked symbol: X, unchecked symbol: ☐