SUMMARY OF SAFETY AND PERFORMANCE (SSP)

Software 6.1

TD-HER2DX_11_00 TECHNICAL DOCUMENTATION **Version** **3**

Written by:	Reviewed by:	Approved by:
Mercedes Marín (PDM)	Angeles Sebastián (COO)	Joel Parker (CSO)
Date: 26/03/2026 Signature	Date: 26/03/2026 Signature	Date: 26/03/2026 Signature

REVEAL GENOMICS S.L. Carrer Villarroel 170 Escala 2 Planta 5. 08036 Barcelona. Spain Tel. (+34) 93 227 54 00 Ext. 4829.
Email: info@reveal-genomics.com

CHANGE CONTROL

SSP revision	Date issued	Change description	Revision validated by the Notified Body (NB)
1	09/9/2024	Initial release of Summary of Safety and Performance (SSP). Pending revision by the NB.	☐ Yes Validation language: Non-applicable. ☒ No (only applicable for class C devices (IVDR, Article 48 (7)) for which the SSP is not yet validated by the NB)
2	30/9/2025	Updates applied in several sections: • 2.1.6 The type of specimen(s) required: clarified that HER2DX does not directly interact with human specimens, requires input data generated with nCounter® Analysis System (NanoString® Technologies); only FFPE samples validated; RNA quality criteria added (OD260/280 = 1.7–2.5; concentration ≥12.5 ng/µL); exclusion of post-treatment samples. • 2.1.7 Testing population: expanded to state no exclusions by sex, age (≥18), menopausal status, or hereditary risk in retrospective studies; emphasized not validated in <18 years; only treatment-naïve samples applicable. • 2.3 Limitations/contra-indications: reinforced limitations on pre-treatment samples, FFPE only, exclusion of frozen tissue, nCounter-only validated, RNA input quality requirements, pediatric population not supported. • 3.1 Description of the device: updated description of automated data processing	☐ Yes Validation language: Non-applicable. ☒ No (only applicable for class C devices (IVDR, Article 48 (7)) for which the SSP is not yet validated by the NB)

		pipeline (R-Service in Docker, JSON input/output, QC steps) with clearer description of cloud services and architecture roles. • 5.1 Residual risk and undesirable effects: new risk identifiers added (R072, R073, R074) covering corrupted RCC files, pre-analytical errors, and interobserver variability in T/N classification. • 6.3 Summary of performance data: substantially expanded with new clinical studies (Tolaney, Waks, Bueno-Muiño, Villacampa, Llombart-Cussac, Sanfeliu, Tarantino, Martínez-Saez, Lynce, Nozawa, etc.), including evidence tables, outcomes, claims, and indexed publications, strengthening clinical validation dataset.	
3	26/03/2026	Section 2.1: Intended purpose clarification. This change consists of a clarification of the Intended Purpose wording, without modification of device claims, algorithm, or clinical outputs, introducing the qualification of the device as a qualitative IVD MDSW and clarifying the target population, specimen type, and non-validated use conditions. Software version updated to 6.1 to reflect clarified wording of the Intended Purpose. Section 2.1: Information removed to description of the product Section 2,4 Reviewed information according last version of IFUV12	☐ Yes Validation language: Non-applicable. ☒ No (only applicable for class C devices (IVDR, Article 48 (7)) for which the SSP is not yet validated by the NB)

		Section 3: Description of the product aligned from previous Section 5.1: Residual risks reviewed, according indications of MDCG 2022-09 rev1 Section 6.3 list of studies are the same but only included the conclusion.	

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GLOSSARY

Acronym	Description
BC	Breast Cancer
CDM	Clinical Data Management
CHL	Clinical Hazard List
CP	Clinical Performance
CPR	Clinical Performance Report
ERBB2	Receptor tyrosine-protein kinase ERBB-2
EU	European Union
EBP	Evidence-Based Practice
FDA	U.S. Food and Drug Administration
FFPE	Formalin Fixed Paraffin Embedded
FFPET	Formalin-Fixed Paraffin-Embedded Tissue
FSCA	Field Safety Corrective Action
FSN	Field Safety Notice
GSPR	General Safety and Performance Requirements
H&E	Hematoxylin and Eosin
HER2	Human Epidermal Growth Factor Receptor 2
HER2+ BC	Human Epidermal Growth Factor Receptor 2 Positive Breast Cancer
IFU	Instructions for Use
ISO	International Standard Organization

Acronym	Description
IVD	*In vitro* diagnostic
IVDR	Regulation (EU) 2017/746 on IVD medical devices
LDT	Lab-Develop Test
LSSPR	Literature Search and Selection Protocol and Results
MDCG	Medical Device Coordination Group
MDSW	Medical Device Software
NB	Notified Body
NBOG	Notified Body Operations Group
OJEU	Official Journal of the European Union
pCR	Pathological Complete Response
PE	Performance Evaluation
PEP	Performance Evaluation Plan
PER	Performance Evaluation Report
PMPF	Post Market Performance Follow-up
PMS	Post-Market Surveillance
PRRC	Person Responsible for Regulatory Compliance
PSUR	Periodic Safety Update Report
QMS	Quality Management System
RNA	Ribonucleic Acid
SOTA	State-Of-The-Art

Acronym	Description
SSP	Summary of Safety and Performance
SRN	Single Registration Number
SV	Scientific Validity
SVR	Scientific Validity Report
TD	Technical Documentation
TPR	Technical Performance Report

SECTION 1.A OF MDCG 2022-09 – SSP FOR PROFESSIONAL USERS FOR DEVICES NOT INTENDED FOR SELF-TESTING

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 and has been established in accordance to section 1.A of the guidance of the Medical Device Coordination Group (MDCG) 2022/09 – *Summary of Safety and Performance Template*.

The SSP is not intended to replace the Instructions For Use (IFU) 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.

The following information is intended for professional users.

Document revision: 00.1

Date issued: 22-05-2024

Manufacturer's reference number for the SSP: SSP-HER2DX-EN 2024/05

1. DEVICE IDENTIFICATION AND GENERAL INFORMATION

1.1. Device trade name	HER2DX® Software
1.2. Manufacturer; name and address	**REVEAL GENOMICS, S.L.** • Location: Carrer Villarroel, 170 Escala 2 Planta 5; 08036 – Barcelona; Spain • Telephone: (+34) 93 2275400 ext: 4829 • E-mail: info@reveal-genomics.com
1.3. Manufacturer's single registration number (SRN)	**ES-MF-000039673**
1.4. Basic UDI-DI	**843702662 5HER2DX94**
1.5. European Medical Device Nomenclature (EMDN)	W010603 - MULTIPLE PARAMETERS - GENETIC TESTING
1.6. Risk class of device	**Rule C (Annex VIII, Rule 3)**
1.7. Indication whether it is a device for near-patient testing and/or a companion diagnostic	Not Applicable
1.8. Year when the device was first CE-marked under Regulation (EU) 2017/746	Non-applicable. First submission under Regulation (EU) 2017/746 of *In Vitro* Diagnostic (IVD) Medical Devices (IVDR)
1.9. Authorised representative if applicable; name and the SRN	Non-applicable. European Union manufacturer
1.10. Notified Body (NB)'s name and the NB's single identification number	**DEKRA Certification B.V.** NB number: 0344

2. INTENDED PURPOSE OF THE DEVICE

2.1. Intended purpose (elements in Annex II 1.1 (c))

HER2DX® Software is a qualitative in vitro diagnostics (IVD) medical device software (MDSW) intended to help healthcare professionals to optimally select the best treatment option for adult patients with early-stage HER2+ breast cancer; the software integrates genomic data -quantitative gene expression- obtained from formalin-fixed paraffin-embedded (FFPE) tumor tissue samples collected prior to systemic treatment, and clinical data - tumor size and lymph nodal involvement (nodal status)-, to provide information on the long-term risk of relapse (HER2DX® relapse risk score), on the likelihood of achieving a pathologic complete response (pCR) following neoadjuvant therapy (HER2DX® pCR likelihood score), and *ERBB2* mRNA expression levels (HER2DX® *ERBB2* mRNA score). The HER2DX® Software, designed as a web application, is intended to be operated exclusively by authorized and trained healthcare professionals. The device has not been validated for use in metastatic disease, HER2-negative tumors, or post-treatment samples.

2.2. Indication(s) and target population(s)

2.2.1. Indications

HER2DX® Software is an IVD MDSW is indicated in adult patients with early-stage HER2-positive breast cancer.

2.2.2. Target population(s)

Use of HER2DX® Software is indicated for adult patients with early-stage HER2+ breast cancer (see section 1.1.3.3.) and who, according to their doctor's judgement, need to be treated.

2.3. Limitations and/or contra-indications (e.g., relevant interferences, cross reactions)

- HER2DX® relapse risk score was developed from primary tumor specimens and staging was based on surgical pathology reports. This approach is different from the neoadjuvant setting where a core biopsy is the only available tissue and staging is based on imaging. Despite this limitation, HER2DX® Software performed well in core biopsies in the validation prognostic dataset, where all patients received neoadjuvant therapy and clinical staging was used instead of pathology reports.

- HER2DX® relapse risk score development is based on Short-HER cohort that was powered for a particular primary endpoint, which was to compare DFS between two arms distinguished by the duration of trastuzumab (i.e., 9 weeks versus 1 year). Due to the low sample size and number of events in each arm, this cohort was not used to evaluate the value of HER2DX® Software to predict the benefit from adjuvant trastuzumab according to its duration.

- Separately, several patient cohorts used for the clinical validation have a limited sample size.

- Some cohorts collected from trials do not follow standard treatment strategies, like the administration of letrozole as neoadjuvant treatment.

- The IVD MDSW HER2DX® Software cannot be considered in any case as a substitute for the physician's activity or for the required medical surveillance in any treatment to the patient. The healthcare professional must be a licensed physician specialist (mainly medical oncologists but also gynecologists, surgeons, radiologists, among others specialist responsible for prescribing treatment for patients with breast cancer) and they have the ultimate responsibility for all therapeutic decisions based on the patient diagnosis, medical history and family medical history, the indications of the treatment, concomitant medications, other individual characteristics of the patient, and a comprehensive interpretation of the report.

- The interpretation of HER2DX® software (including the Relapse risk score, pCR likelihood score and ERBB2 mRNA score) should be evaluated within the context of other clinicopathological factors and the patient's medical history.

- There is currently no evidence to support the use of HER2DX in patients under 18 years old, as all development and validation studies were conducted in adult populations.
- Only FFPE samples are validated. Frozen tissue is not supported for clinical use.
- Currently, only data derived from the nCounter® platform are validated. The use of alternative platforms is under investigation but not supported for clinical use.
- The performance of HER2DX® Software depends on the quality of the input data derived from FFPE tumor samples. Therefore, pre-analytical acceptance criteria for both tissue and RNA must be fulfilled to ensure a valid result. Tissue samples must meet minimum requirements, including tumor surface area ≥ 4 mm^2 and tumor cellularity ≥ 10%. A minimum number of sections is required depending on tumor size (e.g., one section if ≥100 mm^2, up to three sections for smaller tumor areas). In addition, RNA samples must meet minimum quality criteria, including RNA purity (OD260/280) between 1.7 and 2.5 and RNA concentration ≥ 12.5 ng/µL. Failure to meet these criteria may result in insufficient or unreliable gene expression data and, consequently, no reportable HER2DX® result.

- Validation datasets included only samples obtained prior to systemic treatment, in order to avoid confounding transcriptomic signatures. Therefore, HER2DX® Software should not be applied to post-treatment samples.
- Only 12 samples can be run at a time, which includes 10 samples and 2 reference controls.

3. DESCRIPTION OF THE DEVICE

3.1. Description of the device, including the conditions to use the device (e.g., laboratory, near-patient testing)

HER2DX® Software is an in vitro diagnostic (IVD) medical device software (MDSW) developed by REVEAL GENOMICS, S.L. to provide both prognostic (estimating the risk of recurrence) and predictive (estimating the likelihood of treatment response) information for patients with early-stage HER2-positive breast cancer. By analyzing gene expression and clinicopathological data, the software estimates the risk of disease recurrence and the likelihood of achieving a pathological complete response (pCR) to systemic therapy. This integrated information supports clinicians in tailoring the intensity of treatment according to individual risk and likelihood of treatment response, helping to avoid unnecessary toxicity and preserve quality of life in low-risk patients, while identifying those who may benefit from more intensive therapy. HER2DX® is intended for use by qualified healthcare professionals and does not replace clinical judgment. Final treatment decisions remain under the responsibility of the treating physician, based on the patient's full clinical context.

HER2DX® Software is a qualitative MDSW that generates three patient-specific scores by processing gene expression data and clinicopathological variables. The scores are computed through a fixed, pre-trained algorithm that integrates the expression levels of 27 genes, grouped into four biologically defined gene expression signatures, and combines them with two clinicopathological variables, tumor size (T) and nodal status (N). all of which are weighted according to their relative prognostic and predictive contribution. These scores are output as continuous values (1 to 99), and interpreted categorically based on predefined clinical thresholds:

- **Gene signatures**: The 27 gene variables included in HER2DX® Software supervised learning algorithm are split into 4 gene expression signatures capturing various biological processes including immune infiltration, tumor cell proliferation, luminal differentiation, and the expression of the HER2 amplicon, giving rise to single scores. The 4 gene expression signatures are as follows:
    - The immune signature selected for HER2DX® Software was the 14-gene immunoglobulin (IGG) module (i.e., *CD27, CD79A, HLA-C, IGJ, IGKC, IGL, IGLV3-25, IL2RG, CXCL8, LAX1, NTN3, PIM2, POU2AF1 and TNFRSF17*), previously identified by unsupervised clustering of human breast tumors. The IGG signature has previously shown strong independent prognostic value in a large breast cancer dataset (N= 550), where patients did not receive adjuvant systemic therapy. [1]

  The other three gene signatures were identified from unsupervised clustering of the Short-HER HER2-positive dataset using data from 187-breast cancer-related genes.

The genes selected were obtained from highly correlated gene clusters (correlation coefficient > 0.80);

- The tumor cell proliferation signature includes 4 genes (i.e., *EXO1*, *ASPM*, *NEK2* and *KIF23*),
- The luminal differentiation signature includes 5 genes (i.e., *BCL2*, *DNAJC12*, *AGR3*, *AFF3* and *ESR1*), and
- The HER2 amplicon signature includes 4 genes located in the 17q11-12 chromosome (i.e., *ERBB2*, *GRB7*, *STARD3* and *TCAP*).

For each signature, the mean gene expression is calculated for each patient.

- **Clinical variables:**
  - Tumor size (T): size and/or extent of the main tumor. It is measured in cm being T1 (0-2 cm), T2 (2-5 cm), T3 (>5 cm), and T4 (tumor has broken through skin or attached to chest wall).
  - Nodal status (N):
    - Clinical Nodal status (cN): N0 (axillary and other nearby lymph nodes have no cancer), N1 (axillary lymph nodes have cancer, but can be moved around N2), axillary lymph nodes have cancer and are matted together or fixed to other structures (such as the chest wall) OR internal mammary nodes have cancer, but axillary lymph nodes don't appear to have cancer), N3 (infraclavicular (under the clavicle) nodes have cancer (axillary lymph nodes may or may not have cancer) OR internal mammary nodes and axillary lymph nodes have cancer OR supraclavicular (above the clavicle) nodes have cancer (axillary lymph nodes may or may not have cancer)).
    - Pathological Nodal status (pN): lymph node affectation being N0 (axillary and other nearby lymph nodes have no cancer or only have isolated tumor cells (individual cancer cells), when looked at under a microscope), N1 (micrometastases OR 1–3 axillary lymph nodes have cancer), N2 (4–9 axillary lymph nodes have cancer OR internal mammary nodes have cancer, but axillary lymph nodes don't have cancer) and N3 (10 or more axillary lymph nodes have cancer OR infraclavicular (under the clavicle) nodes have cancer OR internal mammary nodes have cancer plus 1 or more axillary lymph nodes have cancer OR 4 or more axillary lymph nodes have cancer plus internal mammary nodes have cancer or

micrometastases found on sentinel node biopsy OR supraclavicular (above the clavicle) nodes have cancer).

- **Numerical scores**:
    - **HER2DX® Relapse risk score**: this score provides the patient's long-term risk of recurrence during follow-up at 10 years after (neo)adjuvant chemotherapy. Patients are classified as low risk (score from 1 to 49), or high risk (50 to 99) (Table 1).
    - **HER2DX® pCR likelihood score**: this score provides the patient´s probability of achieving a pathological Complete Response (pCR) if treated with neoadjuvant therapy. Patients are classified as low, medium or high probability. It is categorized into low probability of pCR (score from 1 to 32), moderate probability of pCR (33 to 67), and high probability of pCR (68 to 99) (Table 1).
    - **HER2DX® *ERBB2* mRNA score**: this score provides levels of *ERBB2* gene expression and this feature is linked to the tumor's responsiveness to anti-HER2 targeting in the absence of standard chemotherapy. Patients are classified as low (score from 1 to 32), medium (33 to 50), or high levels (51 to 99) (Table 1).

All three HER2DX® scores (the relapse risk score, pCR likelihood score, and ERBB2 mRNA score) are prognostic and/or predictive in nature, expressed as percentiles (1 to 99) and categorized into low, medium (for pCR likelihood and *ERBB2* mRNA scores), or high levels.

Table 1: HER2DX® Software score groups by score range

HER2DX Score	Score Range	Group
Relapse risk score	1-49 50-99	Low High
pCR likelihood score	1-32 33-67 68-99	Low Medium High
ERBB2 mRNA score	1 – 32 33-50 51-99	Low Medium High

The **HER2DX® Relapse risk score** is based on 3 gene expression-based signatures (immune, tumor cell proliferation, and luminal differentiation), together with tumor stage (T1 vs. T2-4) and nodal status (N0 vs. N1 vs. N2-3).
The HER2DX® Relapse risk score is indicative of patient outcomes in HER2+ breast cancer. A statistically significant overexpression of genes within the immune and luminal signatures

correlates with a good prognosis, whereas a significant overexpression of the proliferation signature, coupled with nodal status N1-3 and/or tumor status T2-4, is indicative of a poor prognosis.

The **HER2DX® pCR likelihood score** is based on 4 gene expression-based signatures (immune, tumor cell proliferation, HER2 amplicon, and tumor cell luminal differentiation), together with tumor size (T1 vs. T2-4) and nodal status (N0 vs. N1-3). Furthermore, the HER2DX® pCR likelihood score is associated with predictive responses to anti-HER2 therapies. Specifically, a significant overexpression of the immune, proliferation, and HER2 amplicon signature is associated with a complete pathological response (pCR), suggesting a positive response to treatment. In contrast, overexpression of the luminal signature, along with nodal status N1-3 and/or tumor status T2-4, suggests that the patient is likely a non-responder to anti-HER2 therapies.

The **HER2DX® *ERBB2* mRNA score** is based on the individual expression of the *ERBB2* gene.

Once the individual patient's three scores are calculated, they are extrapolated by referencing to databases that store the outcomes collected during the test's development phase. These databases serve as the foundation for the algorithm, which relies on them in the final step to compute the three numerical scores, presented as percentiles (ranging from 1 to 99) and categorized into low, medium (for pCR likelihood and *ERBB2* mRNA scores), or high levels.

Genomic data play a pivotal role in the determining the scores, providing substantial added value to the diagnostic test, surpassing the significance of the two clinical variables. On average, the contribution to the two scores comprises 60% from genomic data and 40% from clinical variables (T and N).

The input to HER2DX® Software is the patient's genomic information and two clinicopathological variables (T and N). The patient's genomic information is obtained from a sample of the tumor that is sent to a laboratory for its genomic analysis. The samples can be collected by biopsy or surgical procedures, and they must not be previously exposed to any systemic therapies. In the laboratory, the RNA of the tumor sample is extracted and purified to perform a gene expression analysis of 192 set of genes (187 breast cancer-related genes and 5 housekeeping genes) using the nCounter® Analyses System (NanoString® Technologies, Seattle, USA).

The HER2DX® Software evaluates results from the exogenous (positive controls and negative controls), endogenous controls (housekeepers), and synthetic RNA samples to evaluate assay quality and sample quality of each run prior to issuing a test report.

RNA sample quality consists of positive control probes targeting exogenous RNA sequences, synthetic exogenous RNA sequences homologous to the positive controls, and

negative probes targeting exogenous RNA sequences that are not included as synthetic targets in the reaction. Linearity and Limit of Detection for the positive controls is performed for each sample. Additional sample-level controls include evaluation of the average housekeeping gene counts and each targeted breast cancer related gene count to ensure that a suitable amount of measurable RNA was input to obtain accurate results from the test algorithm.

Batch controls consist of two synthetic RNA reference samples included in every assay run to monitor the efficiency and consistency of the analytical process.. The RNA sequences were synthesized by Integrated DNA Technologies (IDT); however, the RNA-SINT reference controls used in the HER2DX workflow are prepared and qualified by the manufacturer at predefined concentrations to ensure consistent assay performance across runs. These synthetic RNAs are designed according to a customized sequence including the HER2DX gene panel and housekeeping genes and are used as assay-specific quality control materials within the HER2DX analytical workflow. Gene expression measured obtained from these controls are evaluated as part of the quality control procedures applied to the gene expression data prior to interpretation by the HER2DX® Software.

HER2DX® Software based on the input of the 27 genes generates 4 different gene signatures. These signatures capture various biological processes: immune infiltration, tumor cell proliferation, luminal differentiation, and expression of the HER2 amplicon (see section 1.1.3.1.). The scanner component of the nCounter Analysis System generates the raw data into RCC files. These files, together with two clinicopathological parameters (T and N), constitue the input data data analyzed by the HER2DX® Software.

HER2DX® Software has been validated retrospectively across more than 2,000 patients with HER2+ breast cancer, including tumor samples from phase II and III clinical trials.[2–9]

Thus, HER2DX® Software is intended to help healthcare professionals to optimize the treatment selection for patients with early-stage HER2+ breast cancer. Specifically, HER2DX® Software is used to guide both neoadjuvant and adjuvant treatment. The healthcare professionals who use HER2DX® Software must be medical oncologists but also gynecologists, surgeons, radiologists, among others specialist responsible for deciding on the oncology treatment for patients. These professionals are the ones who order the use of the HER2DX® Software, when they deem it appropriate and in accordance with professional guidelines,[10] to obtain the report with the above-mentioned patient-specific data (numerical scores) and who interpret the results as an aid to select the best treatment option for the patients. HER2DX® Software is operated by healthcare professional who are properly trained to use it. HER2DX® Software is not conclusive or prescriptive for use of any specific treatment or therapeutic product.

The European Medical Device Nomenclature (EMDN) will be the nomenclature of use by manufacturers when registering their medical devices in the European Database on Medical Devices (EUDAMED). Founded on pre-established criteria and requirements and based on

orientations provided by the Medical Device Coordination Group (MDCG), the European Commission decided in favour of the use of the "*Classificazione Nazionale Dispositivi medici*" (CND) from Italy as the basis for the EMDN. Regulation (EU) 2017/2185 also establishes a list of codes and corresponding types of medical devices for the purpose of specifying the scope of the designation as notified bodies.

HER2DX® Software, which is an IVD MDSW, pertains to the following subcategories in accordance with the EMDN nomenclature and the subcategories of Regulation (EU) 2017/2185 for medical devices (including IVD medical devices):

- **EMDN (CND):**
  - **W02069092** – VARIOUS SAMPLE PROCESSING INSTRUMENTS – IVD MEDICAL DEVICE SOFTWARE
- **IVR**:
  - **IVR 0301** Devices intended to be used in screening, diagnosis, staging or monitoring of cancer
- **IVS**:
  - **IVS 1009** - Software that are devices in themselves including software apps, software for data analysis, and for defining or monitoring therapeutic measures.
- **IVT**:
  - **IVT 2010** - *In vitro* diagnostic devices manufactured using electronic components including communication devices.
- **IVP**:
  - **IVP 3011** - *In vitro* diagnostic devices which require knowledge regarding molecular biological testing including nucleic acid assays and next generation sequencing (NGS).
- **IVD**:
  - **IVD 4009** - *In vitro* diagnostic devices which require knowledge regarding molecular biology / diagnostics.

3.2. In case the device is a kit, description of the components (including regulatory status of components, for example, IVDs, medical devices and any Basic UDI-DIs)

Non-applicable. HER2DX® Software does not directly require any type of specimen collection and transport materials. It is an approach that needs as inputs the genomic data obtained from the tumor sample gene expression analyses, and the patient's tumor clinicopathological T and N information.

3.3. A reference to previous generation(s) or variants if such exists, and a description of the differences

The first generation of the IVD MDSW is HER2DX® Software, which is considered an *in-house* Lab-Develop Test (LDT) fulfilling the conditions set in Article 5 (5) of IVDR, since it is manufactured and used within REVEAL GENOMICS, S.L. as the legally approved manufacturer.

At this time, changes due to commercial decisions has been taken, and the regulatory strategy for putting into the market HER2DX® 2.0 as an LDT used *in-house* is to be terminated once the CE Marking according to IVDR will be obtained. Thus, HER2DX® Software will be able to be commercialized without restrictions.

The control of HER2DX® Software released versions and their changes are documented in the register **FORM-RG-RES-006** *MDSW Release and installation report HER2DX®.*

3.4. Description of accessories which are intended to be used in combination with the device

HER2DX® Software is designed to be used by qualified healthcare professionals in accordance with professional guidelines and is not conclusive or prescriptive for labeled use of any specific therapeutic product. The action planned and its function can be efficiently assessed by the user, with no other products or reagents needed.

REVEAL GENOMICS, S.L. has no intention of providing an accessory for this device and its use will be managed by the user. To consider if an accessory is placed or not, the definition for "*accessory for an in vitro diagnostic medical device*" referred in Article 2 (4) of IVDR has been taken into account:

> *"means an article which, whilst not being itself an in vitro diagnostic medical device, is intended by its manufacturer to be used together with one or several particular in vitro diagnostic medical device(s) to specifically enable the in vitro diagnostic medical device(s) to be used in accordance with its/their intended purpose(s) or to specifically*

and directly assist the medical functionality of the in vitro diagnostic medical device(s) in terms of its/their intended purpose(s)".

In conclusion, REVEAL GENOMICS, S.L. does not intend to provide an accessory for this device, and its use following its intended purpose (see section 2.1.) and mode of action (see section 2.1.1) will be managed by the user.

3.5. Description of any other devices and products which are intended to be used in combination with the device

Not applicable. The IVD MDSW HER2DX® is a stand-alone software in its own right that does not need to be used in combination with other device(s) to enable its use in accordance with its intended purpose.

4. REFERENCE TO HARMONISED STANDARDS AND COMMON SPECIFICATIONS (CS) APPLIED

A list with all applied CS, international standards harmonised under the medical device Directives and/or the IVDR, and the sources of relevant approved drug labels are provided below:

- **EN ISO 13485:2016/A11:2021** — Medical Devices - Quality management systems - Requirements for regulatory purposes
- **EN ISO 14971:2019/A11:2021** — Application of risk management to medical devices
- **EN ISO 15223-1:2021** — Medical devices - Symbols to be used with information to be supplied by the manufacturer - Part 1: General requirements
- **EN ISO 20417:2021** — Medical devices - Information to be supplied by the manufacturer
- **EN 13612:2002/AC:2002** — Performance evaluation of *in vitro* diagnostic medical devices
- **ISO 20916:2019** - *In vitro* diagnostic medical devices — Clinical performance studies using specimens from human subjects — Good study practice
- **EN 62304:2006/A1:2015** — Medical device software - Software life-cycle processes
- **EN 82304-1:2017** — Health Software - Part 1: General requirements for product safety
- **EN 62366-1:2015/A1:2020** — Medical devices - Part 1: Application of usability engineering to medical devices
- **EN IEC 81001-5-1:2022** — Health software and health IT systems safety, effectiveness and security - Part 5-1: Security - Activities in the product life cycle

5. RISK AND WARNINGS

5.1. Residual risk and undesirable effects for the device

The information from risk management is controlled under the ISO 14971:2019/A11:2021 requirements.

The residual risks to be considered in relation to the intended purpose of the IVD MDSW HER2DX® Software are listed in the table below.

Table 1. List of the residual risks of the IVD MDSW HER2DX® Software.

No other documentation is provided by REVEAL GENOMICS, S.L. that differs from the documents attached in the current annex of the Technical Documentation for IVD MDSW HER2DX® Software, as well as the information also available on its website: https://www.reveal-genomics.com/.

Risk Identifier	Hazard (n.n)	Hazard Identifier	Residual Risk Advice or Other Recommendations (Indications, contra-indications and warnings to be included in the label and IFU (IS risk
R008	3.7.	Use by untrained / unexperienced personnel	· "Warnings: For healthcare professional use only." (TD-HER2DX_02_01_Label_HER2DX). . "The HER2DX® Software is intended to be operated exclusively by authorized and trained healthcare professionals. Usage of the HER2DX® Software by an untrained healthcare professional or unauthorized user may lead to wrongfully handled or interpreted health information." (TD-HER2DX_02_02-IFU, section Warnings and Precautions) · "After using HER2DX®, always log out from your session to avoid access by a non-authorized user" (TD-HER2DX_02_02-IFU, section Warnings and Precautions)

Risk Identifier	Hazard (n.n)	Hazard Identifier	Residual Risk Advice or Other Recommendations (Indications, contra-indications and warnings to be included in the label and IFU (IS risk
R009	3.8	Reasonably foreseeable misuse or unsafe use	· "Warnings: For healthcare professional use only." (TD-HER2DX_02_01_Label_HER2DX) TD-HER2DX_02_02-IFU, section Warnings and Precautions: . The HER2DX® Software is not indicated for breast cancer diagnostic purposes. . The HER2DX® Software is only indicated for patients with early-stage HER2+ breast cancer. · "HER2DX® Results shall be taken in the context of other relevant clinico-pathological factors and standard practice of medicine." .The HER2DX® Software is intended to be operated exclusively by authorized and trained healthcare professionals. Usage of the HER2DX® Software by an untrained healthcare professional or unauthorized user may lead to wrongfully handled or interpreted health information. . If a patient's tumor size category is entered into the software incorrectly, the pCR likelihood score and relapse risk score classification may be adversely affected (e.g. shifted pCR likelihood score and relapse risk score and misclassification).

Risk Identifier	Hazard (n.n)	Hazard Identifier	Residual Risk Advice or Other Recommendations (Indications, contra-indications and warnings to be included in the label and IFU (IS risk
			. If a patient's nodal status is entered into the software incorrectly, the patient's test results may be reported incorrectly (e.g. shifted pCR likelihood score and relapse risk score and misclassification). . Always verify that the results of the report you select correspond to the right patient. Warnings and precautions (report): • Results should be taken in the context of other relevant clinico-pathological factors and standard practice of medicine. • The provided clinicopathological information, tumor and nodal status, must be accurate. Incorrect data might adversely affect the classification of the Relapse risk score and the pCR likelihood score. Limitations of the procedure: • HER2DX® Relapse risk score was developed from primary tumor specimens and staging was based on surgical pathology reports. This approach is different from the neoadjuvant setting where a core biopsy is the only available tissue and staging is based on imaging. Despite this limitation, HER2DX® Software performed well in core biopsies in the

Risk Identifier	Hazard (n.n)	Hazard Identifier	Residual Risk Advice or Other Recommendations (Indications, contra-indications and warnings to be included in the label and IFU (IS risk
			validation prognostic dataset, where all patients received neoadjuvant therapy and clinical staging was used instead of pathology reports. •HER2DX® Relapse risk score development is based on Short-HER cohort that was powered for a particular primary endpoint, which was to compare DFS between two arms distinguished by the duration of trastuzumab (i.e., 9 weeks versus 1 year). Due to the low sample size and number of events in each arm, this cohort was not used to evaluate the value of HER2DX® Software to predict the benefit from adjuvant trastuzumab according to its duration. •Separately, several patient cohorts used for the clinical validation have a limited sample size. •Some cohorts collected from trials do not follow standard treatment strategies, like the administration of letrozole as neoadjuvant treatment. The interpretation of HER2DX® Software (including the Relapse risk score, pCR likelihood score and ERBB2 mRNA score) should be evaluated within the context of other clinicopathological factors and the patient's medical history. • The IVD MDSW HER2DX® Software cannot be considered in any case as a substitute for the physician's activity or for the required medical surveillance in any treatment to the patient. The healthcare professional must be a licensed physician specialist (mainly medical oncologists but also gynecologists, surgeons, radiologists, among others specialist

Risk Identifier	Hazard (n.n)	Hazard Identifier	Residual Risk Advice or Other Recommendations (Indications, contra-indications and warnings to be included in the label and IFU (IS risk
			responsible for prescribing treatment for patients with breast cancer) and they have the ultimate responsibility for all therapeutic decisions based on the patient diagnosis, medical history and family medical history, the indications of the treatment, concomitant medications, other individual characteristics of the patient, and a comprehensive interpretation of the report. • There is currently no evidence to support the use of HER2DX in patients under 18 years old, as all development and validation studies were conducted in adult populations. • Only FFPE samples are validated. Frozen tissue is not supported for clinical use. • Currently, only data derived from the nCounter® platform are validated. The use of alternative platforms is under investigation but not supported for clinical use. • The performance of HER2DX® Software depends on the quality of the input data derived from FFPE tumor samples. Therefore, pre-analytical acceptance criteria for both tissue and RNA must be fulfilled to ensure a valid result. Tissue samples must meet minimum requirements, including tumor surface area ≥ 4 mm^2 and tumor cellularity ≥ 10%. A minimum number of sections is required depending on tumor size (e.g., one section if ≥100 mm^2, up to three sections for smaller tumor areas). In addition, RNA samples must meet minimum quality criteria, including RNA purity (OD260/280) between 1.7 and 2.5 and RNA concentration ≥ 12.5 ng/µL.

Risk Identifier	Hazard (n.n)	Hazard Identifier	Residual Risk Advice or Other Recommendations (Indications, contra-indications and warnings to be included in the label and IFU (IS risk
			Failure to meet these criteria may result in insufficient or unreliable gene expression data and, consequently, no reportable HER2DX® result. • Validation datasets included only samples obtained prior to systemic treatment, in order to avoid confounding transcriptomic signatures. Therefore, HER2DX® Software should not be applied to post-treatment samples. • Only 12 samples can be run at a time, which includes 10 samples and 2 reference controls.
R010	3.13	Misinterpretation of results	· "Warnings: For healthcare professional use only." (TD-HER2DX_02_01_Label_HER2DX) · "HER2DX® Results shall be taken in the context of other relevant clinico-pathological factors and standard practice of medicine." (TD-HER2DX_02_02-IFU, section Warnings and Precautions)

Risk Identifier	Hazard (n.n)	Hazard Identifier	Residual Risk Advice or Other Recommendations (Indications, contra-indications and warnings to be included in the label and IFU (IS risk
R011	4.1	Mistakes and errors of judgement	User error in interpreting the presented data (e.g., extrapolation of results to other treatments, use the IVD MDSW as a diagnostic tool, use the IVD MDSW as a prescription of incorrect treatment by misinterpreting the scores, prescribing a overtreatment or undertreatment, etc.). The user does not take into account that the device translates information of gene expression along with tumor size and nodal status and interprets the results as an absolute "truth", without considering other patient's characteristics. Incorrect or inefficient use of the IVD MDSW leading to incorrect or inefficient treatment selection and patient follow-up. Inclusion of related warnings and precautions in IFUs. · "Warnings: For healthcare professional use only." (TD-HER2DX_02_01_Label_HER2DX) TD-HER2DX_02_02-IFU, section Warnings and Precautions · "HER2DX® Results should be taken in the context of other relevant clinico-pathological factors and standard practice of medicine." . The HER2DX® Software is not indicated for breast cancer diagnostic purposes. . The HER2DX® Software is only indicated for patients with early-stage HER2+ breast cancer. . If a patient's tumor size category is entered into the software incorrectly,

Risk Identifier	Hazard (n.n)	Hazard Identifier	Residual Risk Advice or Other Recommendations (Indications, contra-indications and warnings to be included in the label and IFU (IS risk
			the pCR likelihood score and relapse risk score classification may be adversely affected (e.g. shifted pCR likelihood score and relapse risk score and misclassification). . If a patient's nodal status is entered into the software incorrectly, the patient's test results may be reported incorrectly (e.g. shifted pCR likelihood score and relapse risk score and misclassification). Limitations of the procedure: • The interpretation of HER2DX® Software (including the Relapse risk score, pCR likelihood score and ERBB2 mRNA score) should be evaluated within the context of other clinicopathological factors and the patient's medical history. • The IVD MDSW HER2DX® Software cannot be considered in any case as a substitute for the physician's activity or for the required medical surveillance in any treatment to the patient. The healthcare professional must be a licensed physician specialist (mainly medical oncologists but also gynecologists, surgeons, radiologists, among others specialist responsible for prescribing treatment for patients with breast cancer) and they have the ultimate responsibility for all therapeutic decisions based on the patient diagnosis, medical history and family medical history, the indications of the treatment, concomitant medications, other individual characteristics of the patient, and a comprehensive interpretation of the report.

Risk Identifier	Hazard (n.n)	Hazard Identifier	Residual Risk Advice or Other Recommendations (Indications, contra-indications and warnings to be included in the label and IFU (IS risk
			• There is currently no evidence to support the use of HER2DX in patients under 18 years old, as all development and validation studies were conducted in adult populations. • Only FFPE samples are validated. Frozen tissue is not supported for clinical use. • Currently, only data derived from the nCounter® platform are validated. The use of alternative platforms is under investigation but not supported for clinical use. • The HER2DX® Software requires RNA samples meeting minimum input quality criteria: RNA purity (OD260/280) between 1.7 and 2.5, and RNA concentration ≥12.5 ng/µL. • Validation datasets included only samples obtained prior to systemic treatment, in order to avoid confounding transcriptomic signatures. Therefore, HER2DX® Software should not be applied to post-treatment samples. • Only 12 samples can be run at a time, which includes 10 samples and 2 reference controls.

Risk Identifier	Hazard (n.n)	Hazard Identifier	Residual Risk Advice or Other Recommendations (Indications, contra-indications and warnings to be included in the label and IFU (IS risk
R013	4.3	Slips and distractions (mental or physical)	The healthcare professional selects a wrong patient report not corresponding to the patient and acts upon it. Incorrect or inefficient treatment selection and patient follow-up. Inclusion of related warnings and precautions in IFUs. - The report contains the information of the Lab ID and HER2DX ID in the Header TD-HER2DX_02_02-IFU, section Warnings and Precautions · "HER2DX® Results should be taken in the context of other relevant clinico-pathological factors and standard practice of medicine." . If a patient's tumor size category is entered into the software incorrectly, the pCR likelihood score and relapse risk score classification may be adversely affected (e.g. shifted pCR likelihood score and relapse risk score and misclassification). . If a patient's nodal status is entered into the software incorrectly, the patient's test results may be reported incorrectly (e.g. shifted pCR likelihood score and relapse risk score and misclassification). . Always verify that the results of the report you select correspond to the right patient.

R014	4.3	Slips and distractions (mental or physical)	· "Warnings: For healthcare professional use only." (TD-HER2DX_02_01_Label_HER2DX) TD-HER2DX_02_02-IFU, section Warnings and Precautions · "HER2DX® Results shall be taken in the context of other relevant clinico-pathological factors and standard practice of medicine." .The HER2DX® Software is intended to be operated exclusively by authorized and trained healthcare professionals. Usage of the HER2DX® Software by an untrained healthcare professional or unauthorized user may lead to wrongfully handled or interpreted health information. . If a patient's tumor size category is entered into the software incorrectly, the pCR likelihood score and relapse risk score classification may be adversely affected (e.g. shifted pCR likelihood score and relapse risk score and misclassification). . If a patient's nodal status is entered into the software incorrectly, the patient's test results may be reported incorrectly (e.g. shifted pCR likelihood score and relapse risk score and misclassification). . Always verify that the results of the report you select correspond to the right patient. Warnings and precautions (report):

			• Results should be taken in the context of other relevant clinico-pathological factors and standard practice of medicine. • The provided clinicopathological information, tumor and nodal status, must be accurate. Incorrect data might adversely affect the classification of the Relapse risk score and the pCR likelihood score.

R015	4.3	Slips and distractions (mental or physical)	· "Warnings: For healthcare professional use only." (TD-HER2DX_02_01_Label_HER2DX) TD-HER2DX_02_02-IFU, section Warnings and Precautions · "HER2DX® Results shall be taken in the context of other relevant clinico-pathological factors and standard practice of medicine." .The HER2DX® Software is intended to be operated exclusively by authorized and trained healthcare professionals. Usage of the HER2DX® Software by an untrained healthcare professional or unauthorized user may lead to wrongfully handled or interpreted health information. . If a patient's tumor size category is entered into the software incorrectly, the pCR likelihood score and relapse risk score classification may be adversely affected (e.g. shifted pCR likelihood score and relapse risk score and misclassification). . If a patient's nodal status is entered into the software incorrectly, the patient's test results may be reported incorrectly (e.g. shifted pCR likelihood score and relapse risk score and misclassification). . Always verify that the results of the report you select correspond to the right patient.

			Warnings and precautions (report): • Results should be taken in the context of other relevant clinico-pathological factors and standard practice of medicine. • The provided clinicopathological information, tumor and nodal status, must be accurate. Incorrect data might adversely affect the classification of the Relapse risk score and the pCR likelihood score.

R016	4.3	Slips and distractions (mental or physical)	· "Warnings: For healthcare professional use only." (TD-HER2DX_02_01_Label_HER2DX) TD-HER2DX_02_02-IFU, section Warnings and Precautions · "HER2DX® Results shall be taken in the context of other relevant clinico-pathological factors and standard practice of medicine." .The HER2DX® Software is intended to be operated exclusively by authorized and trained healthcare professionals. Usage of the HER2DX® Software by an untrained healthcare professional or unauthorized user may lead to wrongfully handled or interpreted health information. . If a patient's tumor size category is entered into the software incorrectly, the pCR likelihood score and relapse risk score classification may be adversely affected (e.g. shifted pCR likelihood score and relapse risk score and misclassification). . If a patient's nodal status is entered into the software incorrectly, the patient's test results may be reported incorrectly (e.g. shifted pCR likelihood score and relapse risk score and misclassification). . Always verify that the results of the report you select correspond to the right patient.

			Warnings and precautions (report): • Results should be taken in the context of other relevant clinico-pathological factors and standard practice of medicine. • The provided clinicopathological information, tumor and nodal status, must be accurate. Incorrect data might adversely affect the classification of the Relapse risk score and the pCR likelihood score.

R017	4.3	Slips and distractions (mental or physical)	· "Warnings: For healthcare professional use only." (TD-HER2DX_02_01_Label_HER2DX) TD-HER2DX_02_02-IFU, section Warnings and Precautions · "HER2DX® Results shall be taken in the context of other relevant clinico-pathological factors and standard practice of medicine." .The HER2DX® Software is intended to be operated exclusively by authorized and trained healthcare professionals. Usage of the HER2DX® Software by an untrained healthcare professional or unauthorized user may lead to wrongfully handled or interpreted health information. . If a patient's tumor size category is entered into the software incorrectly, the pCR likelihood score and relapse risk score classification may be adversely affected (e.g. shifted pCR likelihood score and relapse risk score and misclassification). . If a patient's nodal status is entered into the software incorrectly, the patient's test results may be reported incorrectly (e.g. shifted pCR likelihood score and relapse risk score and misclassification). . Always verify that the results of the report you select correspond to the right patient.

			Warnings and precautions (report): • Results should be taken in the context of other relevant clinico-pathological factors and standard practice of medicine. • The provided clinicopathological information, tumor and nodal status, must be accurate. Incorrect data might adversely affect the classification of the Relapse risk score and the pCR likelihood score. .

Risk Identifier	Hazard (n.n)	Hazard Identifier	Residual Risk Advice or Other Recommendations (Indications, contra-indications and warnings to be included in the label and IFU (IS risk
R023	5.1.	Inappropriate benefit characteristics to the intended purpose	· "Warnings: Not indicated for breast cancer diagnostic purposes." (TD-HER2DX_02_01_Label_HER2DX) TD-HER2DX_02_02-IFU, section Warnings and Precautions: . The HER2DX® Software is not indicated for breast cancer diagnostic purposes. . The HER2DX® Software is only indicated for patients with early-stage HER2+ breast cancer. Limitations of the procedure: • HER2DX® Relapse risk score was developed from primary tumor specimens and staging was based on surgical pathology reports. This approach is different from the neoadjuvant setting where a core biopsy is the only available tissue and staging is based on imaging. Despite this limitation, HER2DX® Software performed well in core biopsies in the validation prognostic dataset, where all patients received neoadjuvant therapy and clinical staging was used instead of pathology reports. •HER2DX® Relapse risk score development is based on Short-HER cohort that was powered for a particular primary endpoint, which was to

Risk Identifier	Hazard (n.n)	Hazard Identifier	Residual Risk Advice or Other Recommendations (Indications, contra-indications and warnings to be included in the label and IFU (IS risk
			compare DFS between two arms distinguished by the duration of trastuzumab (i.e., 9 weeks versus 1 year). Due to the low sample size and number of events in each arm, this cohort was not used to evaluate the value of HER2DX® Software to predict the benefit from adjuvant trastuzumab according to its duration. •Separately, several patient cohorts used for the clinical validation have a limited sample size. •Some cohorts collected from trials do not follow standard treatment strategies, like the administration of letrozole as neoadjuvant treatment. • The interpretation of HER2DX® Software (including the Relapse risk score, pCR likelihood score and ERBB2 mRNA score) should be evaluated within the context of other clinicopathological factors and the patient's medical history. • The IVD MDSW HER2DX® Software cannot be considered in any case as a substitute for the physician's activity or for the required medical surveillance in any treatment to the patient. The healthcare professional must be a licensed physician specialist (mainly medical oncologists but also gynecologists, surgeons, radiologists, among others specialist responsible for prescribing treatment for patients with breast cancer) and they have the ultimate responsibility for all therapeutic decisions based on the patient diagnosis, medical history and family medical history, the indications of the treatment, concomitant medications, other individual

Risk Identifier	Hazard (n.n)	Hazard Identifier	Residual Risk Advice or Other Recommendations (Indications, contra-indications and warnings to be included in the label and IFU (IS risk
			characteristics of the patient, and a comprehensive interpretation of the report. • There is currently no evidence to support the use of HER2DX in patients under 18 years old, as all development and validation studies were conducted in adult populations. • Only FFPE samples are validated. Frozen tissue is not supported for clinical use. • Currently, only data derived from the nCounter® platform are validated. The use of alternative platforms is under investigation but not supported for clinical use. • The performance of HER2DX® Software depends on the quality of the input data derived from FFPE tumor samples. Therefore, pre-analytical acceptance criteria for both tissue and RNA must be fulfilled to ensure a valid result. Tissue samples must meet minimum requirements, including tumor surface area ≥ 4 mm^2 and tumor cellularity ≥ 10%. A minimum number of sections is required depending on tumor size (e.g., one section if ≥100 mm^2, up to three sections for smaller tumor areas). In addition, RNA samples must meet minimum quality criteria, including RNA purity (OD260/280) between 1.7 and 2.5 and RNA concentration ≥ 12.5 ng/µL. Failure to meet these criteria may result in insufficient or unreliable gene expression data and, consequently, no reportable HER2DX® result.

Risk Identifier	Hazard (n.n)	Hazard Identifier	Residual Risk Advice or Other Recommendations (Indications, contra-indications and warnings to be included in the label and IFU (IS risk
			• Validation datasets included only samples obtained prior to systemic treatment, in order to avoid confounding transcriptomic signatures. Therefore, HER2DX® Software should not be applied to post-treatment samples. • Only 12 samples can be run at a time, which includes 10 samples and 2 reference controls.

R029	5.11.	False representation of results	· "Warnings: For healthcare professional use only." (TD-HER2DX_02_01_Label_HER2DX) TD-HER2DX_02_02-IFU, section Warnings and Precautions: · "HER2DX® Results shall be taken in the context of other relevant clinico-pathological factors and standard practice of medicine." .The HER2DX® Software is intended to be operated exclusively by authorized and trained healthcare professionals. Usage of the HER2DX® Software by an untrained healthcare professional or unauthorized user may lead to wrongfully handled or interpreted health information. . If a patient's tumor size category is entered into the software incorrectly, the pCR likelihood score and relapse risk score classification may be adversely affected (e.g. shifted pCR likelihood score and relapse risk score and misclassification). . If a patient's nodal status is entered into the software incorrectly, the patient's test results may be reported incorrectly (e.g. shifted pCR likelihood score and relapse risk score and misclassification). . Always verify that the results of the report you select correspond to the right patient.

			Warnings and precautions (report): • Results should be taken in the context of other relevant clinico-pathological factors and standard practice of medicine. • The provided clinicopathological information, tumor and nodal status, must be accurate. Incorrect data might adversely affect the classification of the Relapse risk score and the pCR likelihood score. Limitations of the procedure: • HER2DX® Relapse risk score was developed from primary tumor specimens and staging was based on surgical pathology reports. This approach is different from the neoadjuvant setting where a core biopsy is the only available tissue and staging is based on imaging. Despite this limitation, HER2DX® Software performed well in core biopsies in the validation prognostic dataset, where all patients received neoadjuvant therapy and clinical staging was used instead of pathology reports. •HER2DX® Relapse risk score development is based on Short-HER cohort that was powered for a particular primary endpoint, which was to compare DFS between two arms distinguished by the duration of trastuzumab (i.e., 9 weeks versus 1 year). Due to the low sample size and number of events in each arm, this cohort was not used to evaluate the value of HER2DX® Software to predict the benefit from adjuvant trastuzumab according to its duration.

			•Separately, several patient cohorts used for the clinical validation have a limited sample size. •Some cohorts collected from trials do not follow standard treatment strategies, like the administration of letrozole as neoadjuvant treatment. • The interpretation of HER2DX® Software (including the Relapse risk score, pCR likelihood score and ERBB2 mRNA score) should be evaluated within the context of other clinicopathological factors and the patient's medical history. • The IVD MDSW HER2DX® Software cannot be considered in any case as a substitute for the physician's activity or for the required medical surveillance in any treatment to the patient. The healthcare professional must be a licensed physician specialist (mainly medical oncologists but also gynecologists, surgeons, radiologists, among others specialist responsible for prescribing treatment for patients with breast cancer) and they have the ultimate responsibility for all therapeutic decisions based on the patient diagnosis, medical history and family medical history, the indications of the treatment, concomitant medications, other individual characteristics of the patient, and a comprehensive interpretation of the report. • There is currently no evidence to support the use of HER2DX in patients under 18 years old, as all development and validation studies were conducted in adult populations.

			• Only FFPE samples are validated. Frozen tissue is not supported for clinical use. • Currently, only data derived from the nCounter® platform are validated. The use of alternative platforms is under investigation but not supported for clinical use. • The performance of HER2DX® Software depends on the quality of the input data derived from FFPE tumor samples. Therefore, pre-analytical acceptance criteria for both tissue and RNA must be fulfilled to ensure a valid result. Tissue samples must meet minimum requirements, including tumor surface area ≥ 4 mm^2 and tumor cellularity ≥ 10%. A minimum number of sections is required depending on tumor size (e.g., one section if ≥100 mm^2, up to three sections for smaller tumor areas). In addition, RNA samples must meet minimum quality criteria, including RNA purity (OD260/280) between 1.7 and 2.5 and RNA concentration ≥ 12.5 ng/µL. Failure to meet these criteria may result in insufficient or unreliable gene expression data and, consequently, no reportable HER2DX® result. • Validation datasets included only samples obtained prior to systemic treatment, in order to avoid confounding transcriptomic signatures. Therefore, HER2DX® Software should not be applied to post-treatment samples. • Only 12 samples can be run at a time, which includes 10 samples and 2 reference controls. Warnings and precautions (report):

			• Results should be taken in the context of other relevant clinico-pathological factors and standard practice of medicine. • The provided clinicopathological information, tumor and nodal status, must be accurate. Incorrect data might adversely affect the classification of the Relapse risk score and the pCR likelihood score. Limitations of the procedure: • The interpretation of HER2DX® Software (including the Relapse risk score, pCR likelihood score and ERBB2 mRNA score) should be evaluated within the context of other clinicopathological factors and the patient's medical history. • The IVD MDSW HER2DX® Software cannot be considered in any case as a substitute for the physician's activity or for the required medical surveillance in any treatment to the patient. The healthcare professional must be a licensed physician specialist (mainly medical oncologists but also gynecologists, surgeons, radiologists, among others specialist responsible for prescribing treatment for patients with breast cancer) and they have the ultimate responsibility for all therapeutic decisions based on the patient diagnosis, medical history and family medical history, the indications of the treatment, concomitant medications, other individual characteristics of the patient, and a comprehensive interpretation of the report.

			• There is currently no evidence to support the use of HER2DX in patients under 18 years old, as all development and validation studies were conducted in adult populations. • Only FFPE samples are validated. Frozen tissue is not supported for clinical use. • Currently, only data derived from the nCounter® platform are validated. The use of alternative platforms is under investigation but not supported for clinical use. • The HER2DX® Software requires RNA samples meeting minimum input quality criteria: RNA purity (OD260/280) between 1.7 and 2.5, and RNA concentration ≥12.5 ng/µL. • Validation datasets included only samples obtained prior to systemic treatment, in order to avoid confounding transcriptomic signatures. Therefore, HER2DX® Software should not be applied to post-treatment samples. • Only 12 samples can be run at a time, which includes 10 samples and 2 reference controls.

R030	5.11.	False representation of results	Limitations of the procedure: • HER2DX® Relapse risk score was developed from primary tumor specimens and staging was based on surgical pathology reports. This approach is different from the neoadjuvant setting where a core biopsy is the only available tissue and staging is based on imaging. Despite this limitation, HER2DX® Software performed well in core biopsies in the validation prognostic dataset, where all patients received neoadjuvant therapy and clinical staging was used instead of pathology reports. •HER2DX® Relapse risk score development is based on Short-HER cohort that was powered for a particular primary endpoint, which was to compare DFS between two arms distinguished by the duration of trastuzumab (i.e., 9 weeks versus 1 year). Due to the low sample size and number of events in each arm, this cohort was not used to evaluate the value of HER2DX® Software to predict the benefit from adjuvant trastuzumab according to its duration. •Separately, several patient cohorts used for the clinical validation have a limited sample size. •Some cohorts collected from trials do not follow standard treatment strategies, like the administration of letrozole as neoadjuvant treatment. • The interpretation of HER2DX® Software (including the Relapse risk score, pCR likelihood score and ERBB2 mRNA score) should be evaluated

			within the context of other clinicopathological factors and the patient's medical history. • The IVD MDSW HER2DX® Software cannot be considered in any case as a substitute for the physician's activity or for the required medical surveillance in any treatment to the patient. The healthcare professional must be a licensed physician specialist (mainly medical oncologists but also gynecologists, surgeons, radiologists, among others specialist responsible for prescribing treatment for patients with breast cancer) and they have the ultimate responsibility for all therapeutic decisions based on the patient diagnosis, medical history and family medical history, the indications of the treatment, concomitant medications, other individual characteristics of the patient, and a comprehensive interpretation of the report. • There is currently no evidence to support the use of HER2DX in patients under 18 years old, as all development and validation studies were conducted in adult populations. • Only FFPE samples are validated. Frozen tissue is not supported for clinical use. • Currently, only data derived from the nCounter® platform are validated. The use of alternative platforms is under investigation but not supported for clinical use.

			• The HER2DX® Software requires RNA samples meeting minimum input quality criteria: RNA purity (OD260/280) between 1.7 and 2.5, and RNA concentration ≥12.5 ng/µL. • Validation datasets included only samples obtained prior to systemic treatment, in order to avoid confounding transcriptomic signatures. Therefore, HER2DX® Software should not be applied to post-treatment samples. • Only 12 samples can be run at a time, which includes 10 samples and 2 reference controls.

R031	5.11.	False representation of results	"Warnings: For healthcare professional use only." (TD-HER2DX_02_01_Label_HER2DX) TD-HER2DX_02_02-IFU, section Warnings and Precautions: · "HER2DX® Results shall be taken in the context of other relevant clinico-pathological factors and standard practice of medicine." .The HER2DX® Software is intended to be operated exclusively by authorized and trained healthcare professionals. Usage of the HER2DX® Software by an untrained healthcare professional or unauthorized user may lead to wrongfully handled or interpreted health information. . If a patient's tumor size category is entered into the software incorrectly, the pCR likelihood score and relapse risk score classification may be adversely affected (e.g. shifted pCR likelihood score and relapse risk score and misclassification). . If a patient's nodal status is entered into the software incorrectly, the patient's test results may be reported incorrectly (e.g. shifted pCR likelihood score and relapse risk score and misclassification). . Always verify that the results of the report you select correspond to the right patient.

			Warnings and precautions (report): • Results should be taken in the context of other relevant clinico-pathological factors and standard practice of medicine. • The provided clinicopathological information, tumor and nodal status, must be accurate. Incorrect data might adversely affect the classification of the Relapse risk score and the pCR likelihood score. Limitations of the procedure: • HER2DX® Relapse risk score was developed from primary tumor specimens and staging was based on surgical pathology reports. This approach is different from the neoadjuvant setting where a core biopsy is the only available tissue and staging is based on imaging. Despite this limitation, HER2DX® Software performed well in core biopsies in the validation prognostic dataset, where all patients received neoadjuvant therapy and clinical staging was used instead of pathology reports. •HER2DX® Relapse risk score development is based on Short-HER cohort that was powered for a particular primary endpoint, which was to compare DFS between two arms distinguished by the duration of trastuzumab (i.e., 9 weeks versus 1 year). Due to the low sample size and number of events in each arm, this cohort was not used to evaluate the value of HER2DX® Software to predict the benefit from adjuvant trastuzumab according to its duration.

			•Separately, several patient cohorts used for the clinical validation have a limited sample size. •Some cohorts collected from trials do not follow standard treatment strategies, like the administration of letrozole as neoadjuvant treatment. • The interpretation of HER2DX® Software (including the Relapse risk score, pCR likelihood score and ERBB2 mRNA score) should be evaluated within the context of other clinicopathological factors and the patient's medical history. • The IVD MDSW HER2DX® Software cannot be considered in any case as a substitute for the physician's activity or for the required medical surveillance in any treatment to the patient. The healthcare professional must be a licensed physician specialist (mainly medical oncologists but also gynecologists, surgeons, radiologists, among others specialist responsible for prescribing treatment for patients with breast cancer) and they have the ultimate responsibility for all therapeutic decisions based on the patient diagnosis, medical history and family medical history, the indications of the treatment, concomitant medications, other individual characteristics of the patient, and a comprehensive interpretation of the report. • There is currently no evidence to support the use of HER2DX in patients under 18 years old, as all development and validation studies were conducted in adult populations.

			• Only FFPE samples are validated. Frozen tissue is not supported for clinical use. • Currently, only data derived from the nCounter® platform are validated. The use of alternative platforms is under investigation but not supported for clinical use. • The performance of HER2DX® Software depends on the quality of the input data derived from FFPE tumor samples. Therefore, pre-analytical acceptance criteria for both tissue and RNA must be fulfilled to ensure a valid result. Tissue samples must meet minimum requirements, including tumor surface area ≥ 4 mm^2 and tumor cellularity ≥ 10%. A minimum number of sections is required depending on tumor size (e.g., one section if ≥100 mm^2, up to three sections for smaller tumor areas). In addition, RNA samples must meet minimum quality criteria, including RNA purity (OD260/280) between 1.7 and 2.5 and RNA concentration ≥ 12.5 ng/µL. Failure to meet these criteria may result in insufficient or unreliable gene expression data and, consequently, no reportable HER2DX® result. • Validation datasets included only samples obtained prior to systemic treatment, in order to avoid confounding transcriptomic signatures. Therefore, HER2DX® Software should not be applied to post-treatment samples. • Only 12 samples can be run at a time, which includes 10 samples and 2 reference controls.

R032	5.11.	False representation of results	Limitations of the procedure: • HER2DX® Relapse risk score was developed from primary tumor specimens and staging was based on surgical pathology reports. This approach is different from the neoadjuvant setting where a core biopsy is the only available tissue and staging is based on imaging. Despite this limitation, HER2DX® Software performed well in core biopsies in the validation prognostic dataset, where all patients received neoadjuvant therapy and clinical staging was used instead of pathology reports. •HER2DX® Relapse risk score development is based on Short-HER cohort that was powered for a particular primary endpoint, which was to compare DFS between two arms distinguished by the duration of trastuzumab (i.e., 9 weeks versus 1 year). Due to the low sample size and number of events in each arm, this cohort was not used to evaluate the value of HER2DX® Software to predict the benefit from adjuvant trastuzumab according to its duration. •Separately, several patient cohorts used for the clinical validation have a limited sample size. •Some cohorts collected from trials do not follow standard treatment strategies, like the administration of letrozole as neoadjuvant treatment. • The interpretation of HER2DX® Software (including the Relapse risk score, pCR likelihood score and ERBB2 mRNA score) should be evaluated

			within the context of other clinicopathological factors and the patient's medical history. • The IVD MDSW HER2DX® Software cannot be considered in any case as a substitute for the physician's activity or for the required medical surveillance in any treatment to the patient. The healthcare professional must be a licensed physician specialist (mainly medical oncologists but also gynecologists, surgeons, radiologists, among others specialist responsible for prescribing treatment for patients with breast cancer) and they have the ultimate responsibility for all therapeutic decisions based on the patient diagnosis, medical history and family medical history, the indications of the treatment, concomitant medications, other individual characteristics of the patient, and a comprehensive interpretation of the report. • There is currently no evidence to support the use of HER2DX in patients under 18 years old, as all development and validation studies were conducted in adult populations. • Only FFPE samples are validated. Frozen tissue is not supported for clinical use. • Currently, only data derived from the nCounter® platform are validated. The use of alternative platforms is under investigation but not supported for clinical use. • The performance of HER2DX® Software depends on the quality of the input data derived from FFPE tumor samples. Therefore, pre-analytical acceptance criteria for both tissue and RNA must be fulfilled to ensure a

			valid result. Tissue samples must meet minimum requirements, including tumor surface area ≥ 4 mm^2 and tumor cellularity ≥ 10%. A minimum number of sections is required depending on tumor size (e.g., one section if ≥100 mm^2, up to three sections for smaller tumor areas). In addition, RNA samples must meet minimum quality criteria, including RNA purity (OD260/280) between 1.7 and 2.5 and RNA concentration ≥ 12.5 ng/µL. Failure to meet these criteria may result in insufficient or unreliable gene expression data and, consequently, no reportable HER2DX® result. • Validation datasets included only samples obtained prior to systemic treatment, in order to avoid confounding transcriptomic signatures. Therefore, HER2DX® Software should not be applied to post-treatment samples. • Only 12 samples can be run at a time, which includes 10 samples and 2 reference controls.

R041	6.12.	Filling failures	See hazard 4.3. (R013, R014, R015, R016, R017) and 4.5. (R019, R020)

R072	6.16	Invalid or corrupted RCC file	· "Warnings: For healthcare professional use only." (TD-HER2DX_02_01_Label_HER2DX) TD-HER2DX_02_02-IFU, section Warnings and Precautions: .The HER2DX® Software is intended to be operated exclusively by authorized and trained healthcare professionals. Usage of the HER2DX® Software by an untrained healthcare professional or unauthorized user may lead to wrongfully handled or interpreted health information. . Manual modification of RCC files is strictly forbidden. Any change performed by the end-user may lead to unexpected, incorrect, or inaccurate results, which will adversely affect the analysis and the report generated by the application.

R074	7.6	Interobserver variability in T/N classification	might adversely affect the classification of the Relapse risk score and the pCR likelihood score. Limitations of the procedure: • The interpretation of HER2DX® Software (including the Relapse risk score, pCR likelihood score and ERBB2 mRNA score) should be evaluated within the context of other clinicopathological factors and the patient's medical history. • The IVD MDSW HER2DX® Software cannot be considered in any case as a substitute for the physician's activity or for the required medical surveillance in any treatment to the patient. The healthcare professional must be a licensed physician specialist (mainly medical oncologists but also gynecologists, surgeons, radiologists, among others specialist responsible for prescribing treatment for patients with breast cancer) and they have the ultimate responsibility for all therapeutic decisions based on the patient diagnosis, medical history and family medical history, the indications of the treatment, concomitant medications, other individual characteristics of the patient, and a comprehensive interpretation of the report. • There is currently no evidence to support the use of HER2DX in patients under 18 years old, as all development and validation studies were conducted in adult populations.

			• Only FFPE samples are validated. Frozen tissue is not supported for clinical use. • Currently, only data derived from the nCounter® platform are validated. The use of alternative platforms is under investigation but not supported for clinical use. • The performance of HER2DX® Software depends on the quality of the input data derived from FFPE tumor samples. Therefore, pre-analytical acceptance criteria for both tissue and RNA must be fulfilled to ensure a valid result. Tissue samples must meet minimum requirements, including tumor surface area ≥ 4 mm^2 and tumor cellularity ≥ 10%. A minimum number of sections is required depending on tumor size (e.g., one section if ≥100 mm^2, up to three sections for smaller tumor areas). In addition, RNA samples must meet minimum quality criteria, including RNA purity (OD260/280) between 1.7 and 2.5 and RNA concentration ≥ 12.5 ng/µL. Failure to meet these criteria may result in insufficient or unreliable gene expression data and, consequently, no reportable HER2DX® result. • Validation datasets included only samples obtained prior to systemic treatment, in order to avoid confounding transcriptomic signatures. Therefore, HER2DX® Software should not be applied to post-treatment samples. • Only 12 samples can be run at a time, which includes 10 samples and 2 reference controls. . If a patient's nodal status is entered into the software incorrectly, the patient's test results may be reported incorrectly (e.g. shifted pCR likelihood score and relapse risk score and misclassification).

			. Always verify that the results of the report you select correspond to the right patient. Warnings and precautions (report): • Results should be taken in the context of other relevant clinico-pathological factors and standard practice of medicine. • The provided clinicopathological information, tumor and nodal status, must be accurate. Incorrect data might adversely affect the classification of the Relapse risk score and the pCR likelihood score. Limitations of the procedure: • The interpretation of HER2DX® Software (including the Relapse risk score, pCR likelihood score and ERBB2 mRNA score) should be evaluated within the context of other clinicopathological factors and the patient's medical history. • The IVD MDSW HER2DX® Software cannot be considered in any case as a substitute for the physician's activity or for the required medical surveillance in any treatment to the patient. The healthcare professional must be a licensed physician specialist (mainly medical oncologists but

			also gynecologists, surgeons, radiologists, among others specialist responsible for prescribing treatment for patients with breast cancer) and they have the ultimate responsibility for all therapeutic decisions based on the patient diagnosis, medical history and family medical history, the indications of the treatment, concomitant medications, other individual characteristics of the patient, and a comprehensive interpretation of the report. • There is currently no evidence to support the use of HER2DX in patients under 18 years old, as all development and validation studies were conducted in adult populations. • Only FFPE samples are validated. Frozen tissue is not supported for clinical use. • Currently, only data derived from the nCounter® platform are validated. The use of alternative platforms is under investigation but not supported for clinical use. • The HER2DX® Software requires RNA samples meeting minimum input quality criteria: RNA purity (OD260/280) between 1.7 and 2.5, and RNA concentration ≥12.5 ng/µL. • Validation datasets included only samples obtained prior to systemic treatment, in order to avoid confounding transcriptomic signatures. Therefore, HER2DX® Software should not be applied to post-treatment samples.

			• Only 12 samples can be run at a time, which includes 10 samples and 2 reference controls.

5.2. Warnings and precautions

All warnings and precautions pertaining to the IVD MDSW are presented in the IFU and/or label of the device.

1. The HER2DX® Software is a stand-alone software in its own right which does not need to be used in combination with other device(s) to enable its use in accordance with its intended purpose. Results should be taken in the context of other relevant clinico-pathological factors and standard practice of medicine.
2. The HER2DX® Software is not indicated for breast cancer diagnostic purposes.
3. The HER2DX® Software is only indicated for patients with early-stage HER2+ breast cancer. (not validated in metastatic disease or HER2-negative tumors).
4. The HER2DX® Software is intended to be operated exclusively by authorized and trained healthcare professionals. Usage of the **HER2DX® Software** by an untrained healthcare professional or unauthorized user may lead to wrongfully handled or interpreted health information.
5. The accuracy of the HER2DX® scores depends on the correct classification of tumor size and nodal status. These clinical-pathological variables must be assessed following the latest edition of the AJCC/UICC TNM staging system.
6. If a patient's tumor size category is entered into the software incorrectly, the pCR likelihood score and relapse risk score classification may be adversely affected (e.g. shifted pCR likelihood score and relapse risk score and misclassification).
7. If a patient's nodal status is entered into the software incorrectly, the patient's test results may be reported incorrectly (e.g. shifted pCR likelihood score and relapse risk score and misclassification).
8. Always verify that the results of the report you select correspond to the right patient.
9. After using Software HER2DX®, always log out from your session to avoid access by a non-authorized user.
10. Users should be aware that any serious incidents related to the device must be promptly reported to both the manufacturer and the competent authority of the Member State in which the user and/or the patient is located.
11. Users should be aware that it is their responsibility to identify, analyze, evaluate and control any potential risks and hazards in relation to the access and usage of the HER2DX® Software. For potential hazards and its consequences, see chapter *7.9. Hazardous situations resulting from IT-network failure*.
12. Manual modification of RCC files is strictly forbidden. Any change performed by the end-user may lead to unexpected, incorrect, or inaccurate results, which will adversely affect the analysis and the report generated by the application.

Limitations

- The interpretation of HER2DX® software (including the Relapse risk score, pCR likelihood score and *ERBB2* mRNA score) should be evaluated within the context of other clinicopathological factors and the patient's medical history.

- The IVD MDSW HER2DX® Software cannot be considered in any case as a substitute for the physician's activity or for the required medical surveillance in any treatment to the patient. The healthcare professional must be a licensed physician specialist (mainly medical oncologists but also gynecologists, surgeons, radiologists, among others specialist responsible for prescribing treatment for patients with breast cancer) and they have the ultimate responsibility for all therapeutic decisions based on the patient diagnosis, medical history and family medical history, the indications of the treatment, concomitant medications, other individual characteristics of the patient, and a comprehensive interpretation of the report.
- There is currently no evidence to support the use of HER2DX in patients under 18 years old, as all development and validation studies were conducted in adult populations.
- Only FFPE samples are validated. Frozen tissue is not supported for clinical use.
- Currently, only data derived from the nCounter® platform are validated. The use of alternative platforms is under investigation but not supported for clinical use.
- The performance of HER2DX® Software depends on the quality of the input data derived from FFPE tumor samples. Therefore, pre-analytical acceptance criteria for both tissue and RNA must be fulfilled to ensure a valid result. Tissue samples must meet minimum requirements, including tumor surface area ≥ 4 mm^2 and tumor cellularity ≥ 10%. A minimum number of sections is required depending on tumor size (e.g., one section if ≥100 mm^2, up to three sections for smaller tumor areas). In addition, RNA samples must meet minimum quality criteria, including RNA purity (OD260/280) between 1.7 and 2.5 and RNA concentration ≥ 12.5 ng/µL. Failure to meet these criteria may result in insufficient or unreliable gene expression data and, consequently, no reportable HER2DX® result.
- Validation datasets included only samples obtained prior to systemic treatment, in order to avoid confounding transcriptomic signatures. Therefore, HER2DX® Software should not be applied to post-treatment samples.
- Only 12 samples can be run at a time, which includes 10 samples and 2 reference controls.

5.3. Other relevant aspects of safety, including a summary of any field safety corrective action (FSCA including FSN), if applicable

There are no other relevant aspects that should be described. The IVD MDSW has not any Field Safety Corrective Action (FSCA), including Field Safety Notice (FSN) or other safety concern actions.

6. SUMMARY OF PERFORMANCE EVALUATION AND POST-MARKET PERFORMANCE FOLLOW-UP (PMPF)

6.1. Summary of scientific validity of the device

REVEAL GENOMICS, S.L. has determined different data sources to obtain the scientific validity of HER2DX® as established on:

(1) PubMed
(2) Cochrane.

Following revision of the pertinent data, the scientific validity of IVD MDSW HER2DX® Software can be fully and successfully established and corresponds with the clinical indications and claims defined in its intended purpose.

HER2DX® Software is found to remain adequately aligned with the current state-of-the-art (SOTA) and to be in compliance with the requirement related with the demonstration of the scientific validity determination (requirement have been detected as applicable as per the obligations to the manufacturers shown in the Annex XIII Part A (1.2.1.) of the IVDR.

Last, the gained experience from several years as considered an *in-house* Lab-Develop Test (LDT) must be also highlighted. This historical data and the REVEAL GENOMICS, S.L. technological expertise is also established as effective and safe in order to provide the output desired from its IVD MDSW in its own.

6.2. Summary of performance data from the equivalent device, if applicable

The following list shows candidates for equivalence (i.e., presumed candidates) of HER2DX® Software.

- Oncotype DX Breast Recurrence Score® (EXACT SCIENCES)
- EndoPredict® (Myriad)
- MammaPrint® (Agendia)
- Prosigna® (Veracyte)
- Breast Cancer Test® (Cellanyx)

The systematic review of the literature of these similar products is collected and evaluated with the **TD-HER2DX_08_01 - SOTA-LSSPR**, which defines the appropriate intervention as the use of IVD-MDSW-based for diagnosis of breast cancer, prognostic and predictive of

treatment response. International medical guidelines and reviews regarding breast cancer treatment and unmet clinical needs were also included.

In summary, several IVD-MDSW-based decision support tools with a common core of the integration of molecular data with clinical parameters, as well as unique combinations of other genes (and variants), have been developed to provide prognosis and predictive information to patients with breast cancer disease. Among these tools, HER2DX® Software stands out as the only one specifically designed for patients with HER2-positive breast cancer. This subtype of breast cancer, characterized by the overexpression of the HER2 protein, often requires targeted therapeutic strategies. HER2DX® Software addresses this need by combining molecular data with clinical information. This integration allows for more accurate prognostic assessments of patients with this disease subtype.

For a complete list of the studies including IVD-MDSW-based decision support tools found through the literature review for the purpose of the SOTA determination (**TD-HER2DX_08_01 - SOTA-LSSPR**) see **Table 3**.

6.3. Summary of performance data from conducted studies of the device prior to CE-marking

Indexed Publications	**Prat A et al. Development and validation of the new HER2DX assay for predicting pathological response and survival outcome in early-stage HER2-positive breast cancer. EBioMedicine. 2022 Jan:75:103801. doi: 10.1016/j.ebiom.2021.103801. PMID: 34990895.**
Conclusion	HER2DX tests provide accurate estimates of the risk of recurrence, and the likelihood to achieve a pCR, in early-stage HER2-positive breast cancer.
Indexed Publications	Guarneri V et al. HER2DX genomic test in HER2-positive/hormone receptor-positive breast cancer treated with neoadjuvant trastuzumab and pertuzumab: A correlative analysis from the PerELISA trial. EBioMedicine. 2022 Nov;85:104320. doi: 10.1016/j.ebiom.2022.104320. PMID: 36374768.
Conclusion	HER2DX® pCR likelihood score predicts response in patients following neoadjuvant letrozole in combination with dual HER2 blockade with trastuzumab and pertuzumab (chemotherapy free regimen) in early-stage HER2-positive/hormone receptor-positive breast cancer.
Indexed Publications	Tolaney S et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer: final 10-year analysis of the open-label, single-arm, phase 2 APT trial. Lancet Oncol. 2023 Mar;24(3):273-285. doi: 10.1016/S1470-2045(23)00051-7. PMID: 36858723.
Conclusion	The HER2DX® genomic tool might help to refine the in patients with HER2-positive breast cancer with small (≤3 cm), node negative tumors,

	and Eastern Cooperative Oncology Group (ECOG) performance status of 0–1.
Indexed Publications	Waks AG et al. Assessment of the HER2DX Assay in Patients With ERBB2-Positive Breast Cancer Treated With Neoadjuvant Paclitaxel, Trastuzumab, and Pertuzumab. JAMA Oncol. 2023 Jun 1;9(6):835-840. doi: 10.1001/jamaoncol.2023.0181. PMID: 37103927
Conclusion	HER2DX® pCR likelihood score assay could predict pCR following treatment with deescalated neoadjuvant paclitaxel with trastuzumab and pertuzumab in patients with early-stage HER2-positive BC. The HER2DX® pCR likelihood score might guide therapeutic decisions by identifying patients who are candidates for deescalated or escalated approaches.
Indexed Publications	Bueno-Muiño C, et al. Assessment of a Genomic Assay in Patients With ERBB2-Positive Breast Cancer Following Neoadjuvant Trastuzumab-Based Chemotherapy With or Without Pertuzumab. JAMA Oncol. 2023 Jun 1;9(6):841-846. doi:10.1001/jamaoncol.2023.0187. PMID: 37103916
Conclusion	HER2DX® predicted pCR following neoadjuvant trastuzumab-based chemotherapy with or without pertuzumab. This assay could guide therapeutic decisions regarding the use of neoadjuvant pertuzumab.
Indexed Publications	Villacampa G et al. Association of HER2DX with pathological complete response and survival outcomes in HER2-positive breast cancer. Ann Oncol. 2023 Sep;34(9):783-795. doi: 10.1016/j.annonc.2023.05.012. PMID: 37302750.
Conclusion	HER2DX® pCR likelihood score and relapse-risk score might help identify ideal candidates to receive neoadjuvant dual HER2 blockade in combination with a single taxane in early-stage HER2þ breast cancer.
Indexed Publications	Llombart-Cussac A et al. Validation of a genomic assay in early-stage HER2+ breast cancer (BC) treated with trastuzumab and pertuzumab (HP): a correlative analysis from PHERGain phase II trial. ESMO 2023. Ann of Oncol. Abstract| volume 34, supplement 2, s240-s241, october 2023 DOI:https://doi.org/10.1016/j.annonc.2023.09.2874
Conclusion	HER2DX® predicts pCR following neoadjuvant HP-based therapy (with or without chemotherapy) and identifies pts with a higher risk of recurrence. This assay might help individualize HP-based therapy in early HER2+ BC.
Indexed Publications	Sanfeliu E et al. Independent validation of HER2DX ERBB2 mRNA score to predict HER2-positive (HER2+), HER2-low and HER2-0 status in breast cancer. Annals of Oncology (2023) 8 (1suppl_4): 101218-101218. 10.1016/esmoop/esmoop101218.
Conclusion	The standardized HER2DX® Software *ERBB2* mRNA score predicts the clinical status of HER2 (positive, low and zero) in BC.

Indexed Publications	Tarantino P et al. Adjuvant Trastuzumab Emtansine Versus Paclitaxel Plus Trastuzumab for Stage I Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: 5-Year Results and Correlative Analyses From ATEMPT. J Clin Oncol. 2024 Jun 27:JCO2302170. doi: 10.1200/JCO.23.02170.
Conclusion	A high HER2DX risk score predicted a higher risk of recurrence in ATEMPT.
Indexed Publications	Villacampa G et al. HER2DX and survival outcomes in early-stage HER2-positive breast cancer: an individual patient-level meta-analysis. Lancet Oncol. 2025 Aug;26(8):1100-1112. doi: 10.1016/S1470-2045(25)00276-1.
Conclusion	HER2DX provides clinically meaningful prognostic stratification in early-stage HER2-positive breast cancer, beyond standard clinical–pathological variables and pathological response. These results support its use in tailoring treatment intensity and guiding clinical decision making.
Indexed Publications	Martínez-Saez O et al.. Clinical decision impact of HER2DX, an algorithm-powered genomic diagnostic in early-stage HER2-positive breast cancer: results from a prospective real-world study. ESMO Real World Data and Digital Oncology. Volume 8, June 2025.
Conclusion	HER2DX impacts clinical management in stage I–III HER2-positive BC by supporting treatment adjustments, enhancing physician confidence, maintaining pCR rates, and reducing health care costs.
Indexed Publications	Martínez-Saez O et al.. Clinical decision impact of HER2DX, an algorithm-powered genomic diagnostic in early-stage HER2-positive breast cancer: results from a prospective real-world study. ESMO Real World Data and Digital Oncology. Volume 8, June 2025.
Conclusion	HER2DX impacts clinical management in stage I–III HER2-positive BC by supporting treatment adjustments, enhancing physician confidence, maintaining pCR rates, and reducing health care costs.
Indexed Publications	Lynce F et al.. HER2DX in HER2-positive inflammatory breast cancer: correlative insights and comparative analysis with noninflammatory breast cancers. ESMO Open. 2025 Feb;10(2):104100. doi: 10.1016/j.esmoop.2024.104100.
Conclusion	The HER2DX pCR score could predict pCR in stage III HER2-positive IBC following treatment with deescalated neoadjuvant systemic therapy and in stage III HER2-positive non-IBC. Elevated pCR rates in HER2-positive IBC with high HER2DX pCR scores suggest there may be a role for treatment de-escalation in these patients and confirmatory studies are justified.

Indexed Publications	Nozawa et al.. HER2DX in older patients with HER2-positive early 1 breast cancer: extended follow-up from the RESPECT trial of trastuzumab ± chemotherapy. Nature Medicine 2025
Conclusion	HER2DX provides prognostic information in older patients with HER2-positive early breast cancer and may help guide chemotherapy decisions.
Indexed Publications	Martínez-Sáez O, Marín-Aguilera M, Cejalvo JM, et al. Central Reassessment of HER2 Status in HER2-Positive Tumors Identified as ERBB2-Low by the HER2DX® Genomic Test. ESMO Breast Cancer Congress 2025. Annals of Oncology (2025) 10 (suppl_4)
Conclusion	Despite the limited sample size, this is the first study to demonstrate that most HER2+ tumors classified as ERBB2-low by HER2DX are reclassified as HER2-negative upon central reassessment. The HER2DX ERBB2 score may serve as a valuable tool to refine or confirm HER2 status. In patients with HER2DX ERBB2-low disease, reassessment of HER2 status using IHC/ISH should be considered, particularly if the initial testing was conducted at a different laboratory. More correlative data will be presented at the conference.

6.4.Summary of performance data from other sources, if applicable

Not applicable.

6.5.An overall summary of the performance and safety

From the searches conducted as described in the subsections above, it is concluded that:

- REVEAL GENOMICS, S.L. has successfully obtained a complete set of the most relevant documents and clinical data available relevant to HER2DX® Software at this time, including both favourable and unfavourable, to address all objectives set out in its Performance Evaluation Plan (PEP)
- The searches conducted include scientific articles, regulatory agency reports, manufacturer internal documents and instructions for use. This information provides extensive clinical data about safety and performance of HER2DX® Software as well as other similar devices.

6.6. Ongoing or planned post-market performance follow-up

According to the information provided in the Performance Evaluation Report (PER), the medium/long-term safety and clinical performance of HER2DX® Software in accordance with

its intended purpose are already known from the clinical performance studies and well as the previous experience on the market of the use of this IVD MDSW.

Therefore, the IVD MDSW HER2DX® Software is found as adequate to be placed on the market according to the requirements set as per the PEP.

Nevertheless, HER2DX® Software is as a class C IVD medical device. Therefore, in accordance with Article 81 and Annex XIII part B of the IVDR, REVEAL GENOMICS, S.L. plans to issue a PMPF plan and report yearly and as part of the Post-Market Surveillance (PMS) activities of HER2DX® Software, established in the PMS plan. The PMS activities are to be documented in the corresponding Post-Market Safety Update Report (PSUR) and included in the Technical Documentation of HER2DX® Software.

According to the clinical experience-based data and the scientific validity demonstration on the PER included in the Technical Documentation of HER2DX® Software (and summarized in the previous sections), REVEAL GENOMICS, S.L. currently considers not necessary to conduct new PMPF studies for the device. However, both a prospective observational decision impact study and a prospective randomized clinical trial (DEFINITIVE trial) are being conducted and more clinical evidence will be collected.

7. METROLOGICAL TRACEABILITY OF ASSIGNED VALUES

7.1. Explanation of the unit of measurement, if applicable

Not applicable. The IVD MDSW HER2DX® Software is not a metrological product.

7.2. Identification of applied reference materials and/or reference measurement procedures of higher order used by the manufacturer for the calibration of the device - Expected values in normal and affected populations

Not applicable. The IVD MDSW HER2DX® Software is not a metrological product and therefore it does not need reference materials and/or reference measurement procedures for its calibration, neither by the manufacturer nor for the intended user. However, HER2DX® Software as an IVD MDSW, does require maintenance by the manufacturer, which includes preventive and adaptative maintenance tasks involved in the monitoring and adaptation to changing technologies and policies and rules affecting software products (e.g., operating systems changes, programming language version updates, cloud storage, etc.) and corrective maintenance tasks (e.g., bug fixing).

8. SUGGESTED PROFILE AND TRAINING FOR USERS

HER2DX® Software is an online IVD MDSW, available and placed on the market in a unique configuration, which is web application on a web server. Its intended users are qualified healthcare professionals that are always authenticated and authorized to use the IVD MDSW and will access HER2DX® Software by using web browser.

The training process for HER2DX® Software is designed to ensure that all users acquire the necessary knowledge and skills to operate the application efficiently and securely. The training is comprehensive and covers various essential aspects, including general introduction to the software, usage of key functionalities, warnings and precautions, quality controls, and troubleshooting (TD-HER2DX_12_08 User Training HER2DX Software).
Upon completion, users must pass an evaluation to certify their proficiency, ensuring their ability to handle real-world scenarios effectively. Training records are maintained and updated regularly to reflect software updates, with each user receiving a certificate upon successful completion (TD-HER2DX_12_05 MDSW Training certification). Additionally, a detailed record of all production users is maintained in the document TD-HER2DX_12_02 User Access HER2DX.