Importance of Pathology testing and treatment

Pathology Lab, Roche Diagnostics

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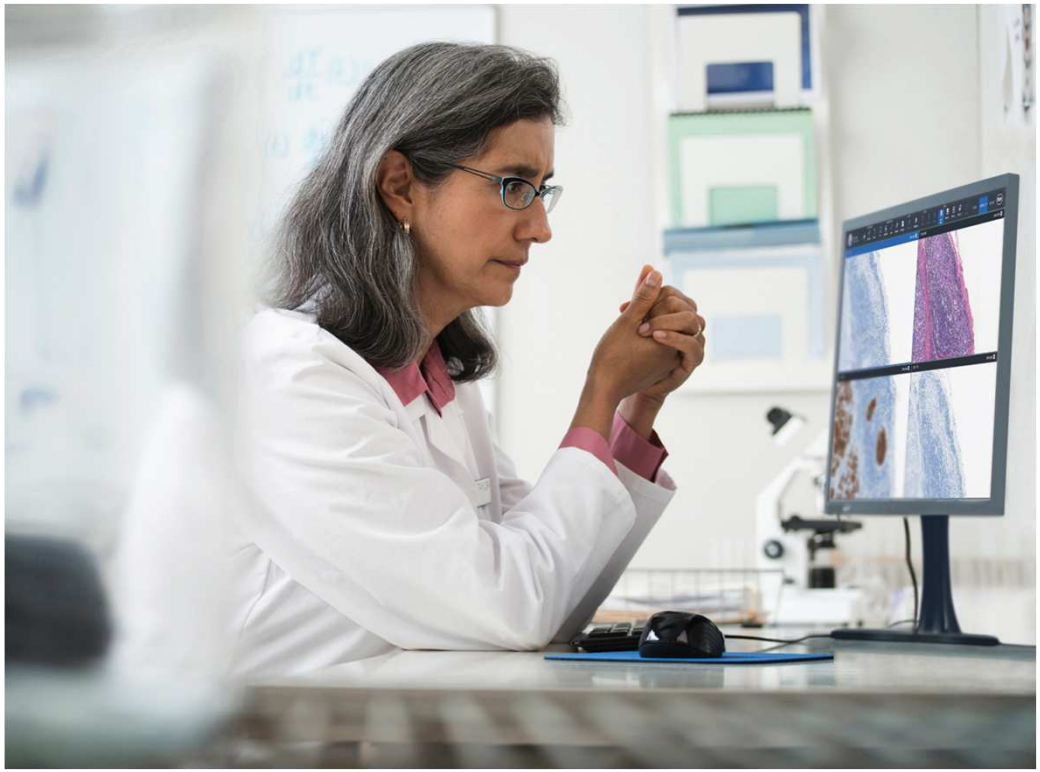
Agenda

- Quality in Roche
- EQA
- Importance of clinical validation
- CDx development
- Medical value
- Pipeline

Quality

Why quality is important



EQA programs have the following goals:

- validate the reliability of laboratory analyses
- verify the reliability of analytical methods
- inform the laboratories about the weaknesses of their processes

More than 26,000 IHC slides have been evaluated during the period 2003–2013; 15 – 300 laboratories have participated in each assessment. Overall, 71% of the staining results assessed have been evaluated as sufficient for diagnostic use, while 29% were judged insufficient. **Almost ONE EVERY THREE RESULTS IS INSUFFICIENT (NordiQC data)**[1]

The number of predictive biomarkers is increasing, driving life-changing therapeutic decision. Consistent high quality is paramount.

[1] *Nielsen S. External quality assessment for immunohistochemistry: experiences from NordiQC. Biotech Histochem. 2015 Jul;90(5):331-40. doi: 0.3109/10520295.2015.1033462. Epub 2015 Apr 22. PMID: 25901597.*

EQA participation

Roche cares about quality

Roche has been participating in External Quality Assessment programs since 1997

Our goal is to apply feedback from EQA schemes to improve the quality of our products and support healthcare professionals that are using Roche products.

Participate
Roche participates as any other participant

Review
EQAs review lab participation anonymously

Report
EQAs send report to participants (individual & global)

Analyse
Roche analyses results

Improve
EQA data is used for continuous improvement

EQA participation

Programs

EQA steps

This list includes all EQA modules Roche participates in and indicates what is conducted by participants versus what is assessed and scored by the EQA.

Pre-Analytic — EQA (Except for UK NEQAS CPT/H&E)

Analytic — Test: Participant / Read-out: Participant & EQA

Post-Analytic — Participant & EQA

		What participants send back to EQA			What EQA schemes assess		
	Module(s)	EQA Slide (or raw molecular files)	Read-out of EQA sample (score, genotype)	Interpretation of EQA sample	Slide staining quality	Read-out	Interpretation
Primary Staining							
UK NEQAS CPT	**H&E Module** (Tissue provided by the participant) **General Pathology Module**	✓	✗	✗	✓	✗	✗
afAQap	**H&E** (Tissue provided by the participant) **Special Stains**	✓	✗	✗	✓	✗	✗
Advanced Staining							
afAQap	IHC General	✓	✗	✗	✓	✗	✗
	ER/PR, HER2, Ki-67 & PD-L1	✓	✓	✗	✓	✓	✗
	HER2 ISH	✓	✓	✓	✗	✓	✓
ESP Lung	ALK, PD-L1, ROS1	✓	✓	✓	✓	✓	✓
NordiQC	General	✓	✗	✗	✓	✗	✗
	Breast	✓	✗	✗	✓	✗	✗
	HER2 ISH	✓	✓	✗	✓	✗	✗
	Companion	✓	✓	✗	✓	✗	✗
QuIP	Breast IHC & Ki-67	✓	✓	✗	✓	✓	✗
	Breast ISH	✓	✗	✓	✓	✗	✓
	Gastric IHC	✓	✓	✗	✓	✓	✗
	Gastric ISH	✓	✗	✓	✓	✗	✓
	PD-L1 (NSCLC, TNBC & Uro)	✓	✓	✗	✓	✓	✗
SEKK	PD-L1 (NSCLC, HNSCC, TNBC & Uro)	✗	✓	✗	✗	✓	✗
UK NEQAS ICC & ISH	Alimentary Tract Pathology	✓	✗	✗	✓	✗	✗
	Breast HER2 IHC	✓	✓	✗	✓	✗	✗
	Breast HER2 ISH Technical	✓	✓	✗	✓	✗	✗
	Breast HER2 ISH Interpretation	✓	✓	✓	✗	✓	✓
	Breast Pathology	✓	✓	✗	✓	✗	✗
	Gastric HER2 IHC	✓	✓	✗	✓	✗	✗
	General Pathology	✓	✗	✗	✓	✗	✗
	Head & Neck Pathology Module	✓	✓	✗	✓	✗	✗
	Ki-67 in Breast Module	✓	✓	✗	✓	✗	✗
	Lymphoid Pathology	✓	✗	✗	✓	✗	✗
	Mismatch Repair Proteins	✓	✗	✗	✓	✗	✗
	Neuropathology	✓	✗	✗	✓	✗	✗
	NSCLC ALK IHC	✓	✓	✗	✓	✗	✗
	NSCLC PD-L1 IHC	✓	✓	✗	✓	✗	✗
	NSCLC ROS1 IHC	✓	✓	✗	✓	✗	✗
	TNBC PD-L1 IHC	✓	✓	✗	✓	✗	✗

EQA participation

Results

Annual UK NEQAS scores from the Roche lab

Each year, participants in the UK NEQAS (the EQA with the highest number of modules and markers tested per year; data on file from EQA website), receive an annual score for each module. This annual score is the average of each mark obtained during the assessed year (the annual report-subscription runs from April Year N to March Year N+1). For each module, there are 4 runs per year. Table 3 shows the 2021 – 2022 scores obtained by the Roche EMEA-LATAM Research & QC lab.

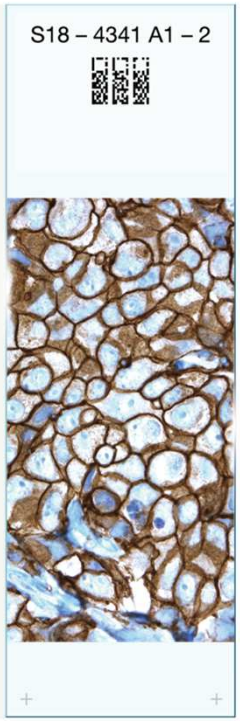
UK NEQAS modules	UK NEQAS Slide	In-house Slide
Alimentary Tract Pathology (GIST)	16.00/20	16.63/20
Breast HER2 IHC Pathology	16.50/20	16.75/20
Breast HER2 ISH – Technical	15.75/20	15.50/20
Breast Hormone Receptor – ER	16.25/20	14.50/20
Breast Hormone Receptor – PR	18.00/20	17.00/20
Gastric HER2 IHC	15.00/20	17.50/20
General Pathology	18.13/20	17.88/20
Lymphoid Pathology	18.14/20	18.00/20
Mismatch Repair (MMR) Proteins	15.50/20	15.63/20
Neuropathology	17.00/20	17.38/20
NSCLC ALK IHC	16.50/20	16.50/20
NSCLC PD-L1 IHC - SP263	17.50/20	17.75/20
NSCLC PD-L1 IHC - SP142	14.25/20	16.75/20

Table 3: Roche lab UK NEQAS ICC & ISH 2021–2022 yearly results (data on file from yearly UK NEQAS individual report).

Quality – consistent, superior performance

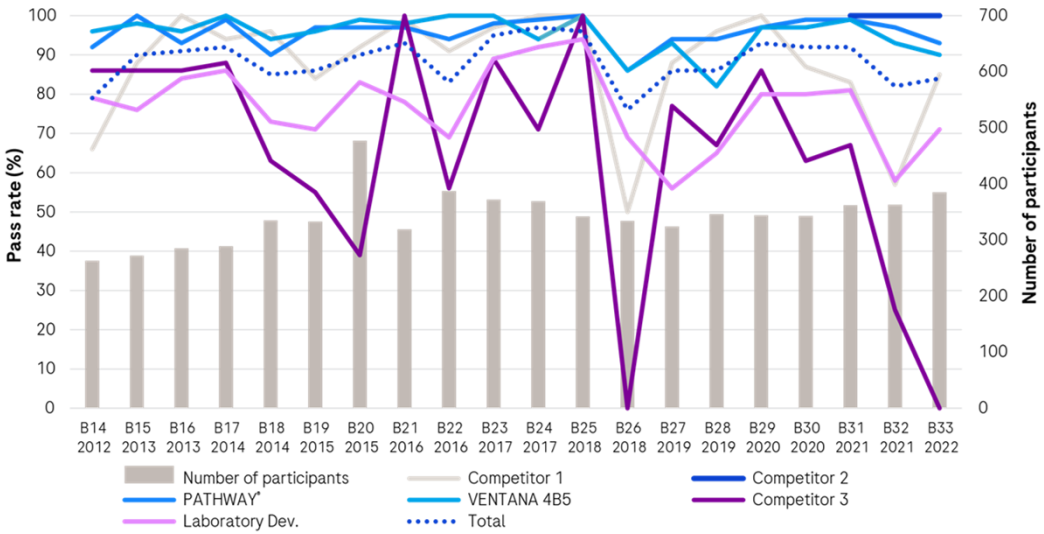
HER2 (4B5) antibodies illustrate brand reliability of Roche HMV assays

HER2 (4B5) antibodies show* proven consistency and performance



Pass rates* of the HER2 IHC assessments in the NordiQC breast cancer module 2012-2022

*Pass rates using vendor recommended protocol changes



* Data refers to PATHWAY, CONFIRM and VENTANA products
** Based on data from a leading external quality assessment scheme. Retrieved from Run B30 2020 http://www.nordiqc.com HercepTest data reflects clone SK001

Pathology education and training

Offering comprehensive tools to support pathologists

Stay at the forefront of predictive diagnostics through Roche Diagnostics' Pathology Education Portal

- We are committed to providing pathologists with up-to-date information, education and training that will advance knowledge and elevate confidence in results.
- The Pathology Education Portal equips pathologists with a comprehensive suite of educational tools to further explore and understand the newest horizons of pathology.
- Education modules include videos and interactive courses to aid in the interpretation of our assays.

https://education.ventana.com/*

Is your score the same as your colleague's?

CADQAS digital interpretive proficiency tests

Roche is pleased to sponsor these proficiency test modules that are supporting quality and accurate interpretation of cancer diagnostic testing.

Registration is available through the QR code and/or link (https://cadqas.org/register/).

You can register independently to any of the modules.

Self-assessment is at your own pace, followed by a live discussion including an educational part. (see below for available modules and to save the date).

*For ex-US only

Interpretive proficiency testing harmonize inter-observer variability

Cancer Diagnostic Quality Assurance Services

CADQAS offers online Interpretive proficiency tests with live feedback QA sessions.

Roche sponsored
Free access

Register here

CIC
CADQAS
Ensuring quality cancer diagnostics

High medical value assays overview

Our focus on outcomes-driven innovation

Roche Diagnostics offers a menu of **more than 250 IHC/ISH assays in key disease states**

Our high medical value assays are **ready to use and fully automated** to streamline workflow and ensure patient safety

Consistent high quality and performance aids in accurate diagnosis

Our digital pathology software and image analysis algorithms **improve the pathologist workflow and diagnostic confidence**

Supporting pathologists with educational tools and resources through our Pathology Education Portal

Leader in personalised healthcare, guiding clinical decision-making and enabling targeted treatment strategies

Two decades of **global leadership in companion diagnostics** and 200+ partnerships with pharmaceutical and biotech companies

Robust pipeline of predictive diagnostics covering a number of disease areas, and **300+ ongoing clinical trials**

Importance of clinical validation in Precision Oncology

Our portfolio - how we build it

We bring together the best of many technologies

Ready-to-use reagents

Pre-diluted for consistent and reproducible results

Individual protocol dialability

To achieve optimal staining intensity for each marker

Fully automated

and optimised for use on BenchMark systems

Immunohistochemistry

OptiView DAB IHC Detection Kit
*ultra*View Universal DAB Detection
*ultra*View Universal Alkaline Phosphatase Red

Immunocytochemistry

CINtec® *PLUS* Cytology Kit

Cytochemistry

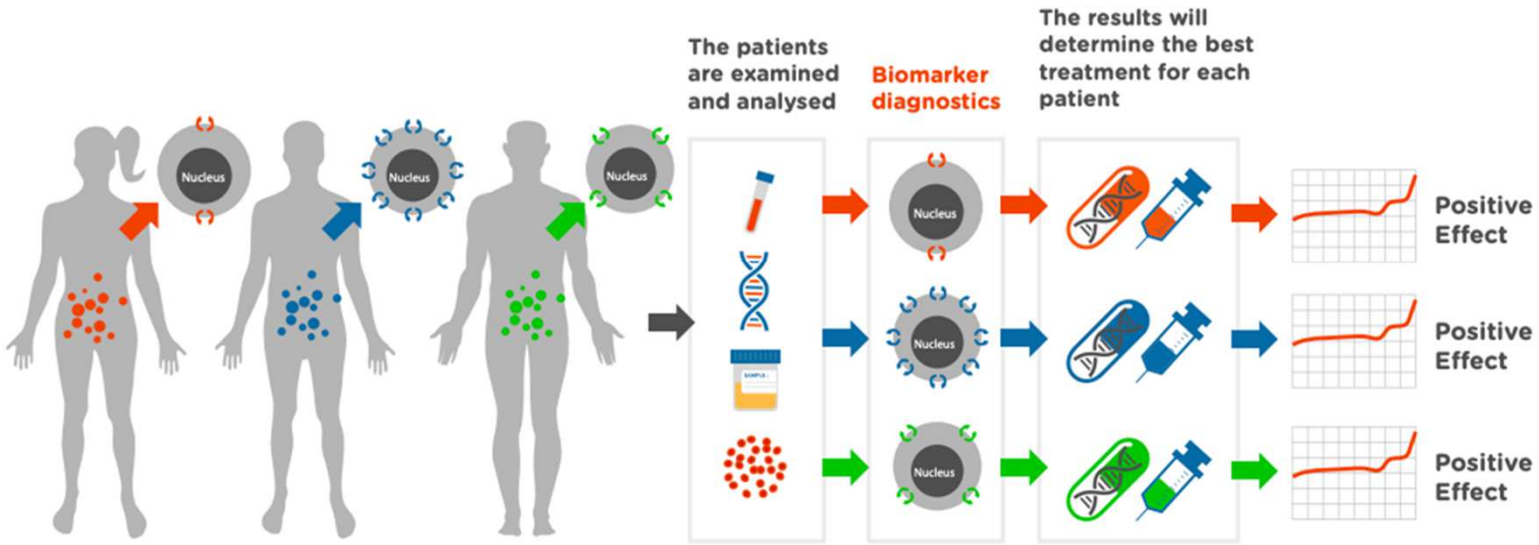
18 special stains assays

Brightfield *in situ* hybridization

VENTANA Silver ISH DNP Detection Kit
VENTANA Red ISH DIG Detection Kit
ISH iVIEW Blue Plus Detection Kit

What is Precision Medicine?

A healthcare approach that utilises molecular information, phenotypic and health data from patients to generate care insights to prevent or treat human disease resulting in improved health outcomes

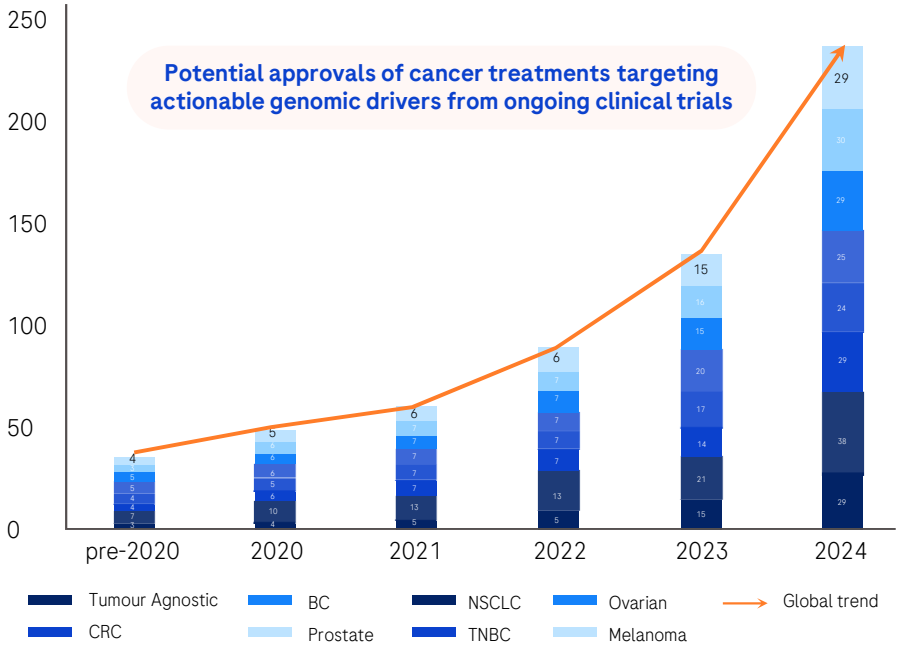


Biomarker is a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic

https://www.efpia.eu/about-medicines/development-of-medicines/precision-medicine/

Adapted from Federico Rojo Todo, MD, PhD at ECP 2023

Precision medicine as the paradigm change in oncology



1. Densen P. Trans Am Clin Climatol Assoc 2011;122:48–58; 2. World Health organisation. Global Observatory on Health R&D (2021) [internet: cited 2022 February] available from: https://www.who.int/observatories/global-observatory-on-health-research-and-development/monitoring/number-of-clinical-trials-by-year-country-who-region-and-income-group Accessed on 01 May 2023.; 3. PubMed.gov. Guideline search results available from: https://pubmed.ncbi.nlm.nih.gov/?term=clinical%20practice%20guideline&filter=pubt.guideline&filter=datesearch.y_5. Accessed on 01 May 2023.; 4. Densen P. Challenges and opportunities facing medical education. Trans Am Clin Climatol Assoc. 2011;122:48-58. PMID: 21686208; PMCID: PMC3116346.

Roche

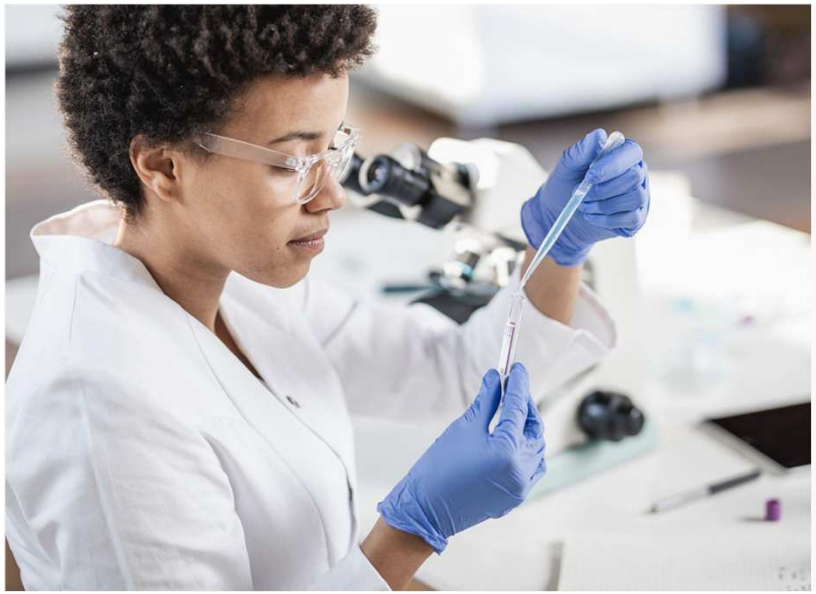
- Increasing number of available targeted therapies
- More than 14,500 clinical trials were initiated in Europe in 2021 [2]
- More than 6000 clinical practice guidelines have been published on PubMed since 2015 [3]
- Medical knowledge continues to grow exponentially [1,4]

A new approach is needed to transform this complexity into opportunities to improve patient care and give access to:

The right solution, for the right treatment, to the right patient at the right time.

Predictive biomarkers

From reagent development through global commercialization



Predictive biomarkers are measures of the likelihood of response or lack of response of a particular therapy, and allow identification of patients most likely to benefit from a given treatment, thus sparing other patients from toxicities of ineffective therapies.

Predictive Biomarkers

Since HER2-driven therapies approval in 2000, several new targeted cancer medicines for which treatment decisions are to be guided by an IVD have been approved and introduced in the clinic, mainly in NSCLC and breast cancer indications

Short Indication	Biomarker	EU name	INN	Biomarker as essential in the therapeutic indication (4.1 of SmPC)	Biomarker testing in SmPC
Non small cell lung cancer	ALK	Xalkori	Crizotinib	ALK positive	4.2 and 4.4
		Zykadia	Ceritinib	ALK positive	4.2
		Alecensa	Alectinib	ALK positive	4.2
		Alunbrig	Brigatinib	ALK positive	4.2
		Lorviqua	Lorlatinib	ALK positive	4.2
	BRAF	Tafinlar	Dabrafenib	BRAFV600 mutation	4.2 and 4.4
		Mekinist	Trametinib	BRAFV600 mutation	4.2
	EGFR	Tagrisso	Osimertinib	EGFR exon 19 deletions or exon 21 (L858R) substitution mutations; activating EGFR mutations; EGFR T790M mutation positive	4.2 and 4.4
		Rybrevant	Amivantamab	EGFR Exon 20 insertion mutations	4.2
		Iressa	Gefitinib	Activating mutations of EGFR TK	4.4
		Tarceva	Erlotinib	EGFR activating mutations	4.2 and 4.4
		Giotrif	Afatinib	Activating EGFR mutation(s)	4.2 and 4.4
		Vizimpro	Dacomitinib	EGFR-activating mutations	4.2 and 4.4
		Cyramza	Ramucirumab	Activating EGFR mutations	4.2
	RET	Retsevmo	Selpercatinib	RET fusion-positive	4.2
		Gavreto	Pralsetinib	RET fusion-positive	4.2
	KRAS	Lumykras	Sotorasib	KRAS G12C mutation	4.2
	METex14	Tepmetko	Tepotinib	Alterations leading to METexon14 skipping	4.2 and 4.4
		Tabrecta	Capmatinib	Alterations leading to METexon14 skipping	4.2 and 4.4
	ROS1	Xalkori	Crizotinib	ROS1-positive	4.2 and 4.4
		Rozlytrek	Entrectinib	ROS1-positive	4.2
	PD-1/PD-L1	Keytruda	Pembrolizumab	PD-L1 with a ≥ 50% TPS; PD-L1 with a ≥ 1% TPS	4.2
		Libtayo	Cemiplimab	PD-L1 (in > 50% TC)	4.2
		Tecentriq	Atezolizumab	PD-L1 expression on > 50% of TC; PD-L1 expression ≥ 50% TC or ≥ 10% IC	4.2
		Imfinzi	Durvalumab	PD-L1 on ≥ 1% of TC	4.2
Breast cancer	BRCA1/2	Lynparza	Olaparib	Germline BRCA1/2-mutations	4.2
		Talzenna	Talazoparib	Germline BRCA1/2-mutations	4.2
	HER2	Herceptin	Trastuzumab	HER2 overexpression or HER2 gene amplification	4.2 and 4.4
		Tyverb	Lapatinib	Tumors overexpress HER2 (ErbB2)	4.2
		Perjeta	Pertuzumab	HER2-positive	4.2
		Kadcyla	Trastuzumab emtansine	HER2-positive	4.2
		Enhertu	Trastuzumab deruxtecan	HER2-positive	4.2
		Tukysa	Tucatinib	HER2-positive	N/a
		Phesgo	Pertuzumab–trastuzumab	HER2-positive	4.2
		Nerlynx	Neratinib	HER2-overexpressed/amplified	N/a
	PIK3CA	Piqray	Alpelisib	PIK3CA mutation	4.2
	PD-1/PD-L1	Tecentriq	Atezolizumab	PD-L1 expression ≥ 1%	4.2
Gastric cancer	HER2	Herceptin	Trastuzumab	HER2 overexpression as defined by IHC2+ and a confirmatory SISH or FISH result, or by an IHC 3+ result	4.2 and 4.4
	PD-1/PD-L1	Opdivo	Nivolumab	PD-L1 with a CPS ≥ 5	4.2
	dMMR/MSI-H	Keytruda	Pembrolizumab	MSI-H or dMMR	4.2

Short Indication	Biomarker	EU name	INN	Biomarker as essential in the therapeutic indication (4.1 of SmPC)	Biomarker testing in SmPC
Colorectal cancer	EGFR	Erbitux	Cetuximab	EGFR-expressing	N/a
	RAS	Erbitux	Cetuximab	RAS wild-type	4.2 and 4.4
		Vectibix	Panitumumab	RAS wild-type	4.2 and 4.4
	BRAF	Braftovi	Encorafenib	BRAF V600 mutation	4.4
	dMMR/MSI-H	Opdivo	Nivolumab	dMMR or MSI-H	4.2
		Keytruda	Pembrolizumab	MSI-H or dMMR	4.2
Melanoma	BRAF	Mekinist	Trametinib	BRAF V600 mutation	4.2 and 4.4
		Tafinlar	Dabrafenib	BRAF V600 mutation	4.2 and 4.4
		Zelboraf	Vemurafenib	BRAF V600 mutation-positive	4.2 and 4.4
		Cotellic	Cobimetinib	BRAF V600 mutation	4.2 and 4.4
		Mektovi	Binimetinib	BRAF V600 mutation	4.4
		Braftovi	Encorafenib	BRAF V600 mutation	4.4
	PD-1/PD-L1	Opdivo	Nivolumab	Low tumor PD-L1 expression	4.2 and 4.4
Head and neck cancer	PD-1/PD-L1	Keytruda	Pembrolizumab	PD-L1 with a CPS ≥ 1; PD-L1 with a ≥ 50% TPS	4.2
Hepatocellular cancer	AFP	Cyramza	Ramucirumab	Serum AFP of ≥ 400 ng/mL	4.2
Pancreas cancer	BRCA1/2	Lynparza	Olaparib	Germline BRCA1/2 mutations	4.2
Ovarian cancer	HRD	Lynparza	Olaparib	HRD positive status defined by either a BRCA1/2 mutation and/or genomic instability	4.2
	BRCA1/2	Lynparza	Olaparib	BRCA1/2-mutated (germline and/or somatic)	4.2
Esophageal (including gastro-esophageal junction) cancer	PD 1/PD L1	Keytruda	Pembrolizumab	PD L1 with a CPS ≥ 10	4.2
		Opdivo	Nivolumab	TC PD-L1 expression ≥ 1%; PD-L1 with a CPS ≥ 5	4.2
Prostate cancer	BRCA1/2	Lynparza	Olaparib	BRCA1/2-mutations (germline and/or somatic)	4.2
Acute lymphoblastic leukemia	CD22	Besponsa	Inotuzumab ozogamicin	CD22-positive	4.2
Endometrial cancer	dMMR/MSI-H	Jemperli	Dostarlimab	dMMR/MSI-H	4.2
		Keytruda	Pembrolizumab	MSI-H or dMMR	4.2
Cholangiocarcinoma	FGFR2	Pemazyre	Pemigatinib	FGFR2 fusion or rearrangement	4.2
Acute myeloid leukemia	FLT3	Rydapt	Midostaurin	FLT3 mutation-positive	4.2
		Xospata	Gilteritinib	FLT3 mutation	4.2
Solid tumors	NTRK	Vitrakvi	Larotrectinib	NTRK gene fusion	4.2
		Rozlytrek	Entrectinib	NTRK gene fusion	4.2
Small intestine or biliary cancer	dMMR/MSI-H	Keytruda	Pembrolizumab	MSI-H or dMMR	4.2
Urothelial cancer	PD 1/PD L1	Keytruda	Pembrolizumab	PD L1 with a CPS ≥ 10	4.2
		Opdivo	Nivolumab	TC PD-L1 expression ≥ 1%	4.2
		Tecentriq	Atezolizumab	PD-L1 expression ≥ 5%	4.2
Gastrointestinal stromal tumor	PDGFRA	Ayvakyt	Avapritinib	PDGFRA D842V mutation	4.2
Thyroid cancer	RET	Retsevmo	Selpercatinib	RET-mutant	4.2

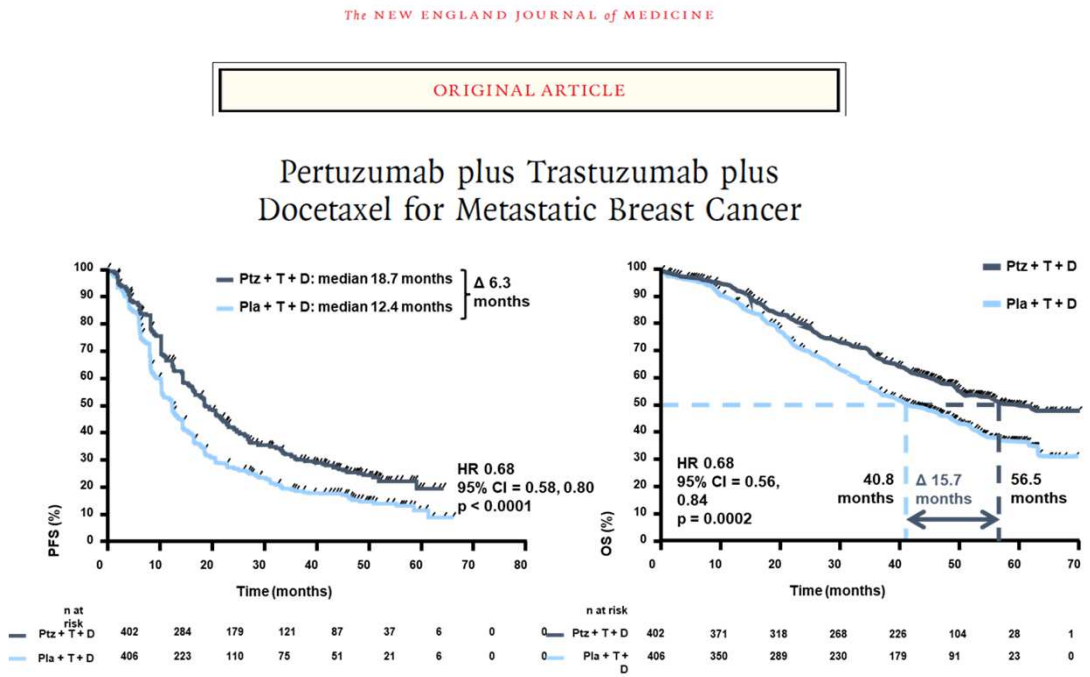
Verbaanderd, C et al. Clin Pharmacol Therap 2023

Adapted from Federico Rojo Todo, MD, PhD at ECP 2023

Predictive Biomarkers

Trastuzumab (Herceptin®) was the first medicinal product that was co-developed with a specific diagnostic assay.

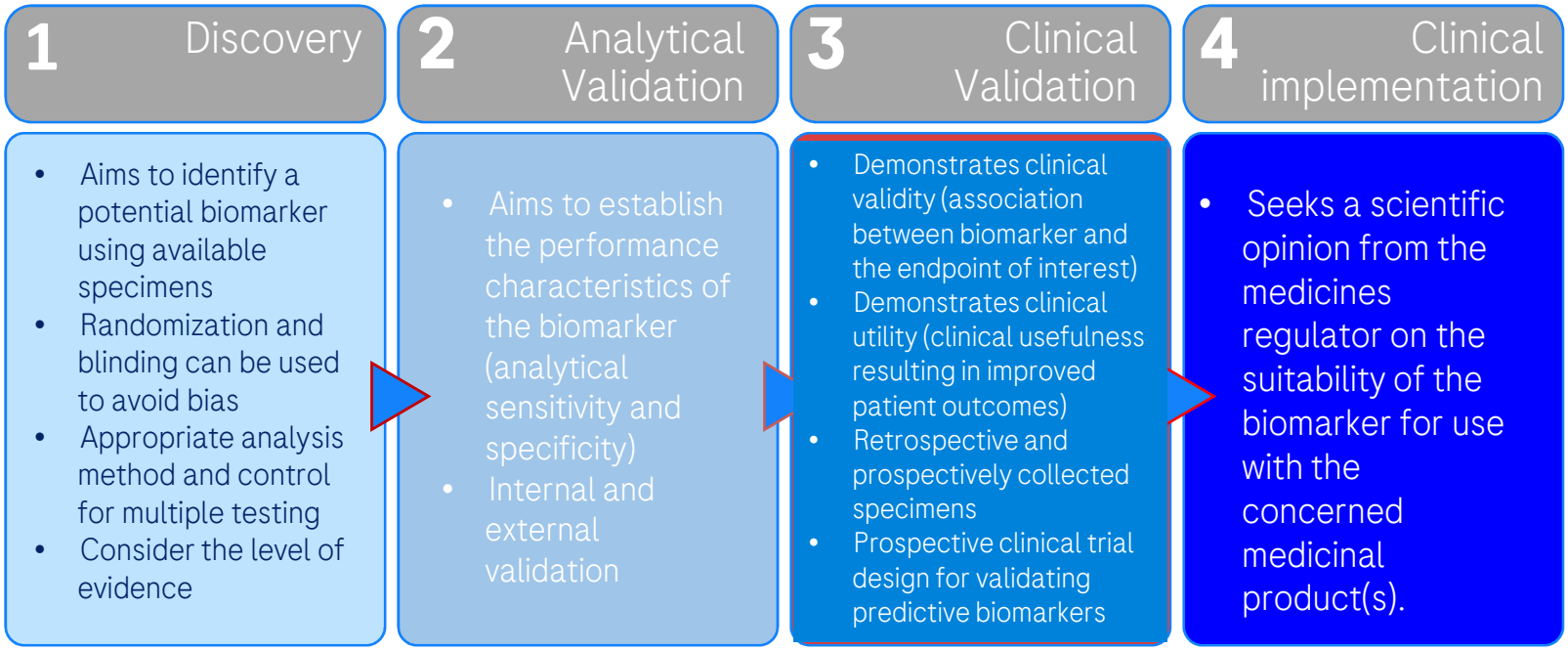
CLEOPATRA clinical trial: an example of rational transition from lab to patient based on a validated predictive biomarker



Pertuzumab (+ trastuzumab)	
✓ Known mechanism of action	✓ Complementary effects on HER2 with increased HER2/HER3 targeting
✓ Biomarker validated preclinically	✓ HER2
✓ Target inhibition	✓ Yes
✓ Downstream effects	✓ Yes
✓ Molecularly defined	✓ HER2+

Adapted from Federico Rojo Todo, MD, PhD at ECP 2023

Predictive biomarkers: long way to the clinics



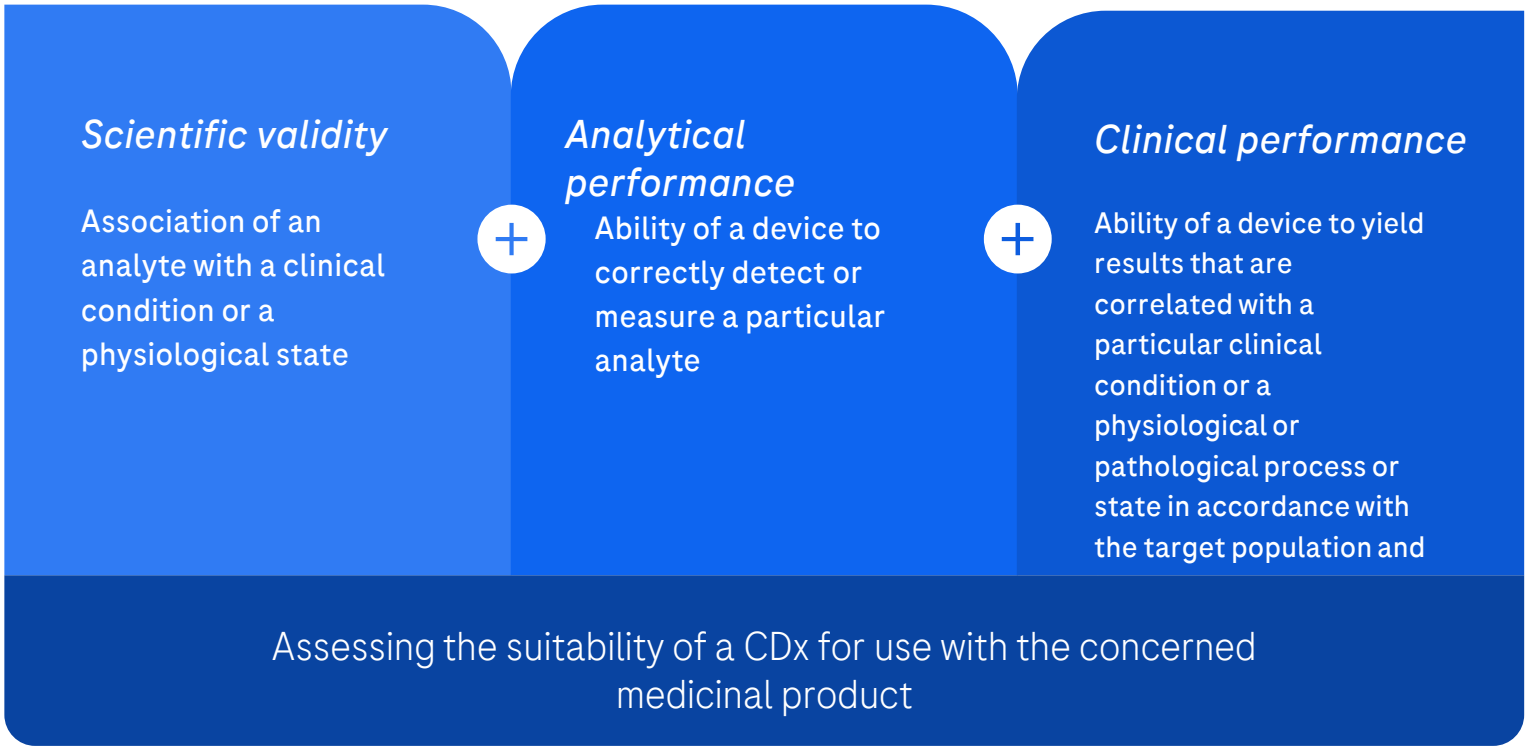
The high-evidence and quality data has to come from controlled clinical setting

- Clinical trials with prospective validation of the Biomarker of interest

From Ou, FS et al. J Thorac Oncol 2021

Adapted from Federico Rojo Todo, MD, PhD at ECP 2023

Considerations

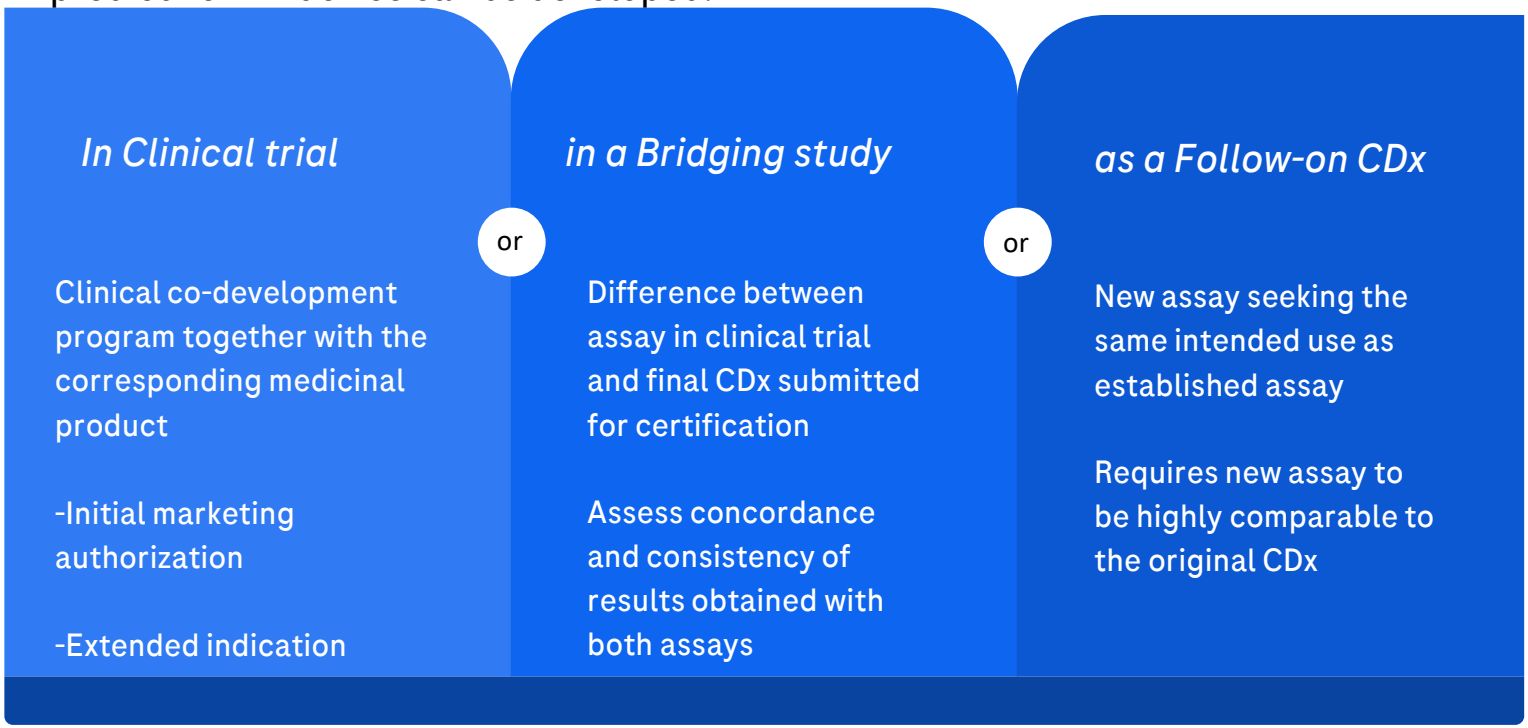


Verbaanderd, C et al. Clin Pharmacol Therap 2023 https://doi.org/10.1002/cpt.2928

Adapted from Federico Rojo Todo, MD, PhD at ECP 2023

To develop a CDx

A predictive IVD device can be developed:



Verbaanderd, C et al. Clin Pharmacol Therap 2023 https://doi.org/10.1002/cpt.2928

Adapted from Federico Rojo Todo, MD, PhD at ECP 2023

Validation and Verification: what do we need?

Correctness

Accuracy

- Comparison with known results from validated tests (reference samples, validated samples)
- Comparison with other validated technique (e.g. ISH vs PCR), other validated instrument or reagents
- EQC or interlab comparison

Precision:

- Repeatability: intra/within runs
- Intermediate precision: inter/between runs
- Reproducibility: inter-lab reproducibility

Robustness

what influences result?
Ischemic time, fixation time, section thickness, stability antigen stability reagents, decal…

Sensitivity

- Analytical: detection limit of biomarker
- Diagnostic: evaluation of true positive staining

Specificity

- Analytical: ability to detect antigen without interferences or cross reactions
- Diagnostic: evaluation of true negative staining

Overall concordance

- Analytical: the degree of agreement between new test and reference (Correctness)
- Diagnostic: evaluation of TP and TN staining vs total (Concordance)

Performance characteristics:

Readout

- Training of pathologists in e.g using scoring systems
- Readout from different pathologists vs expected results known cases/controls, verified by expert panels
- Determine diagnostic sensitivity & specificity for different pathologists
- Compare results pathologists vs formulated acceptance criteria (>90% concordance)
- Inter-observer tuning between pathologists vs expected results

Ongoing validation

- IQC
- EQC/proficiency testing
- Interobserver periodically reviewed
- Education
- Correlation studies

From Ou, FS et al. J Thorac Oncol 2021

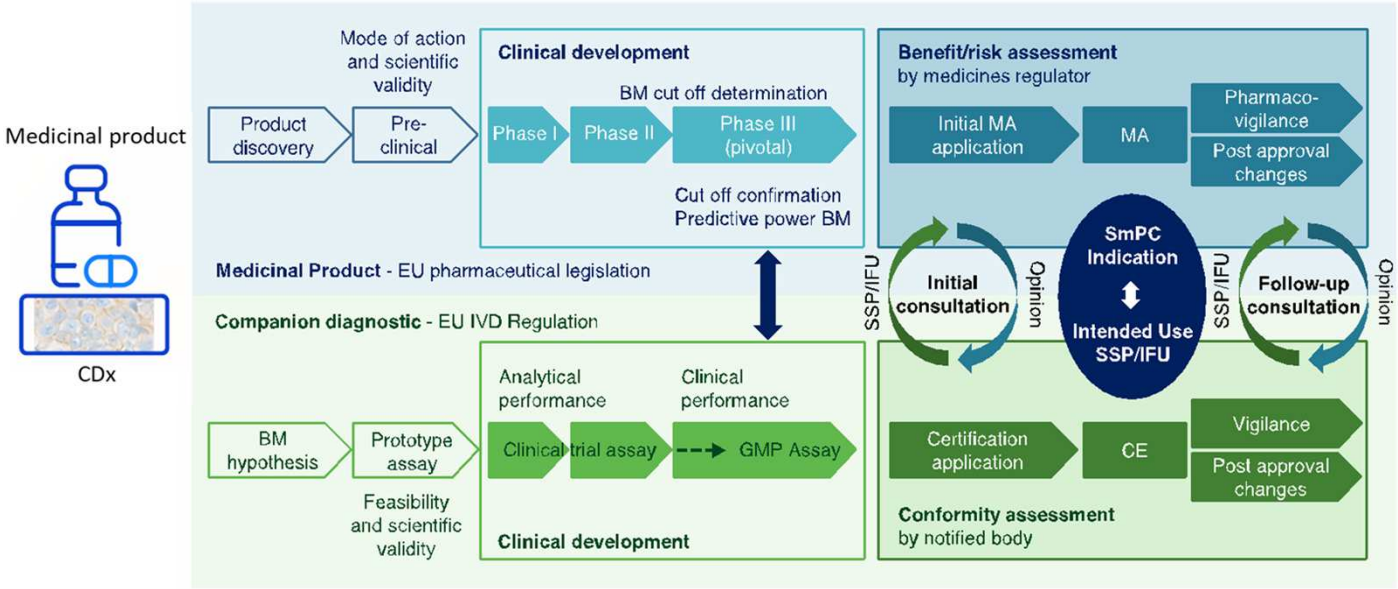
Adapted from Federico Rojo Todo, MD, PhD at ECP 2023

CDx approval in Europe

Interplay between the Clinical Trial Regulation (EU) No. 536/2014 (CTR) and the IVDR

Notified body seeks a scientific opinion from the ***medicines regulator*** on

Suitability of the **CDx** for use with the concerned medicinal product(s)



The IVDR introduces a link between the assessment of a CDx and the corresponding medicinal product by a medicines regulator.

BM, biomarker; CDx, companion diagnostics; CE, European conformity; EU, European Union; GMP, good manufacturing practice; IFU, instructions for use; IVD, in vitro diagnostic tests; IVDR, In Vitro Diagnostic Regulation; MA, marketing authorization; SmPC, summary of product characteristics; SSP, summary of safety and performance.

Verbaanderd, C et al. Clin Pharmacol Therap 2023

Adapted from Federico Rojo Todo, MD, PhD at ECP 2023

Verification and Validation of biomarkers

Verification: Confirmation by providing objective evidence that a test fulfils specifications (specific demands) or specified performance characteristics/parameters.
Which implies :
- Specific demands/performance characteristics are defined and validated by manufacturer
- Verification of performance characteristics performed by lab

Validation: Demonstrate by means of objective evidence that performance-characteristics fulfill predefined criteria or specific demands for a certain purpose or intended use.
Which implies :
- Validation performed by “manufacturer”
- (Full) validation done by the lab

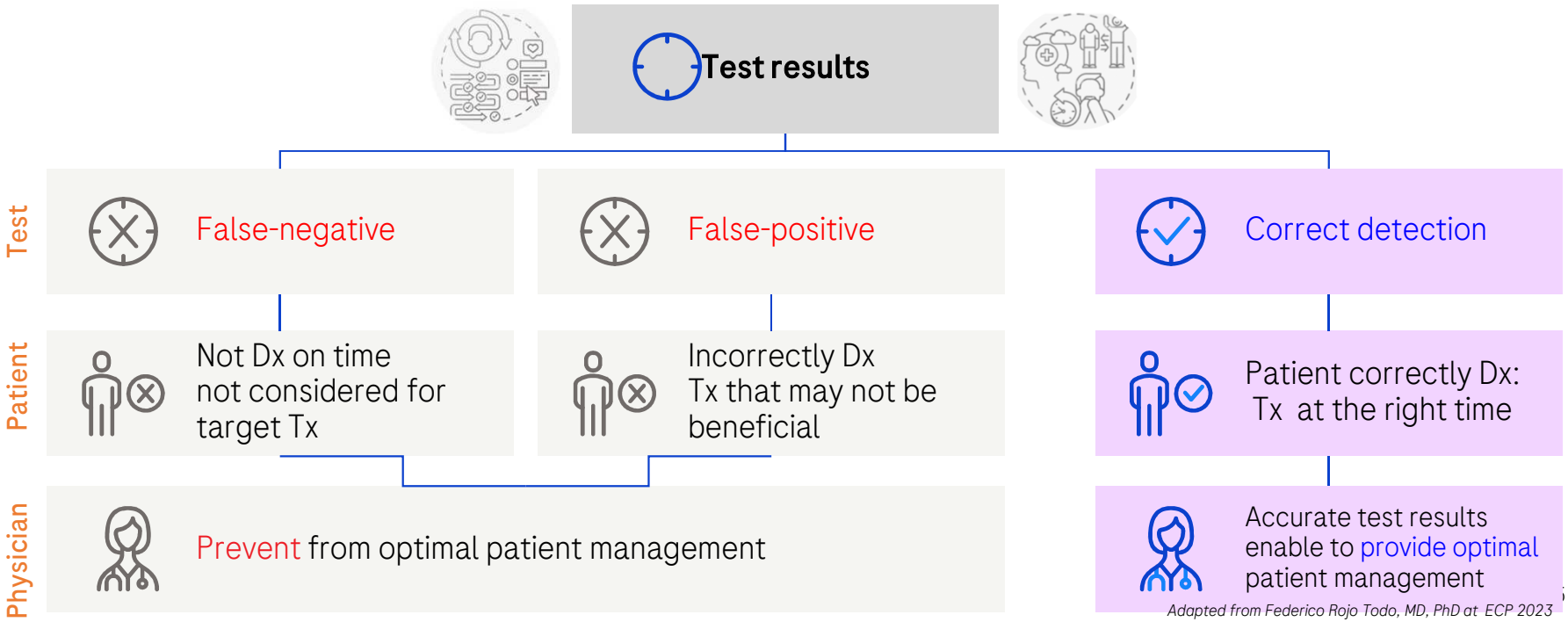
Objective evidence: Tests performed and evaluated needs to be demonstrated and documented
- raw data and assay evaluation, predetermined performance and acceptance criteria can be traced back

Verbaanderd, C et al. Clin Pharmacol Therap 2023

Adapted from Federico Rojo Todo, MD, PhD at ECP 2023

Clinical impact of validation/verification process in biomarkers

Ensure overall performance and safety of tests to avoid potential harms related to analytical false positive or false negative results



Adapted from Federico Rojo Todo, MD, PhD at ECP 2023

Clinical impact of using differently validated biomarkers

The HER2-low example in breast cancer

Clinical data using different IHC tests[1]

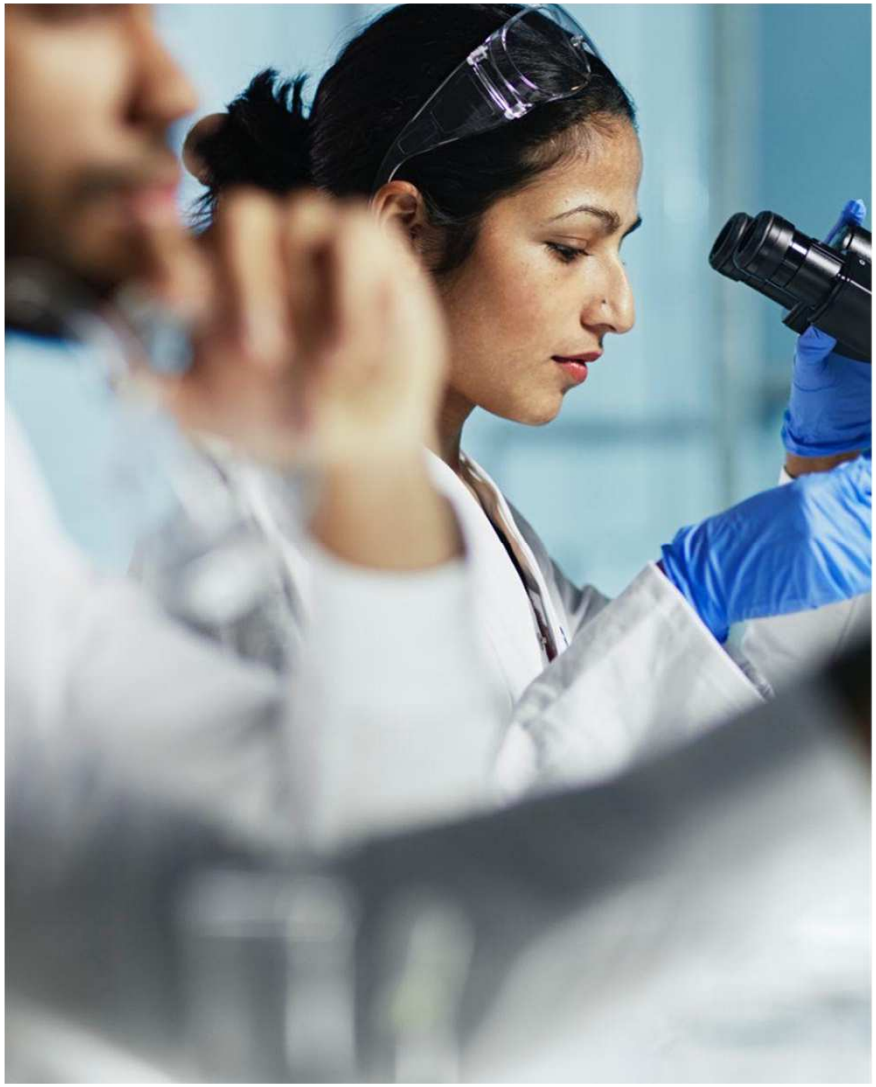
Different IHC assays have different ranges of sensitivity

		Roche HER2 4B5				
HercepTest (DG44)		0	1+	2+	3+	Total
	0	35	0	0	0	35
	1+	17	8	0	0	25
	2+	4	12	13	1	30
	3+	0	0	2	27	29
	Total	56	20	15	28	119

Results outside of clinical evidence for benefit/risk

Need to adhere to clinically validated assays when assessing therapy eligibility for patients

[1]Rüschoff *et al. Virchows Arch.* 2022;481(5):685-694.
HER2: Human epidermal growth factor receptor 2. IHC: Immunohistochemistry.



CDx development

Strength behind the science: our product development journey

Multidisciplinary centers of excellence drive medical value

1. Technology & Applied Research

Molecular biologists, chemists & engineers focus on developing technologies that will drive our future breakthrough innovations.

2. Clinical Development & Medical Affairs

Our team of MDs, PhDs & other professionals ensure product development is informed by the latest medical and scientific developments and discoveries.

3. Market Access

Ensures patients around the world have access to our diagnostic solutions through powerful partnerships with public & private global healthcare providers.

One test, one solution

Open collaboration approach to partnering leads to increased uptake

Non-exclusive model offers benefits for

Labs and clinicians

- Limits oncologist confusion
- Limits pathologist confusion
- Limits lab confusion

Pharma partners

- Allows drugs to compete on their own merit
- Open access to large library of IUO assays
- Focus on flexibility and customization

Patients

- Access to a broad range of therapies
- Minimizes patient risk (ensuring the correct test is ordered for the appropriate therapy)

Rigorous assay development discipline

Comprehensive, end-to-end process maximizes probability of success

Reagent development

- Custom antibody development
- RUO reagent development with DISCOVERY platforms for innovative new products

Prototype assay development

- Biomarker discovery for early phase clinical trials in Roche CAP/CLIA laboratory
- Robust prototype development using multiple technologies to inform clinical decisions for new drug compounds

Assay validation

- Collaboration with laboratories to validate new assays for use in clinical trials

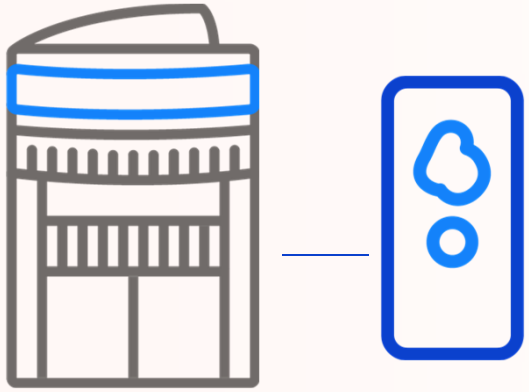
Scoring algorithm development

- Team of in-house pathologists determines scoring algorithms
- Robust pathology training programs

Vigorous clinical trials and data

- Collaboration with laboratories to execute clinical trials
- Ensure robust data for best chance of success
- Prepare laboratories for launch of new assays

Each assay is optimised as a complete, fully automated system



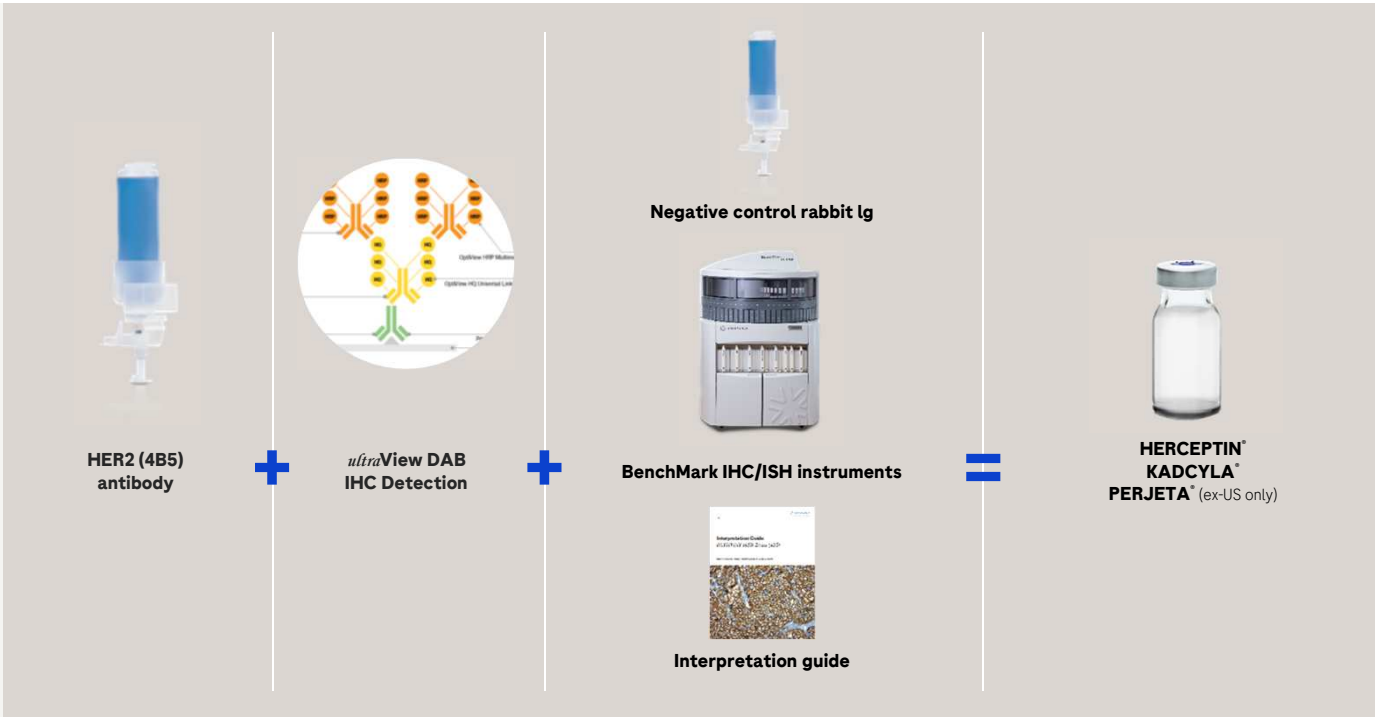
Multiple components comprise the full assay system

- Interpretation guide
- Software
- BMK staining platform
- Detection & ancillaries
- Antibody dispenser

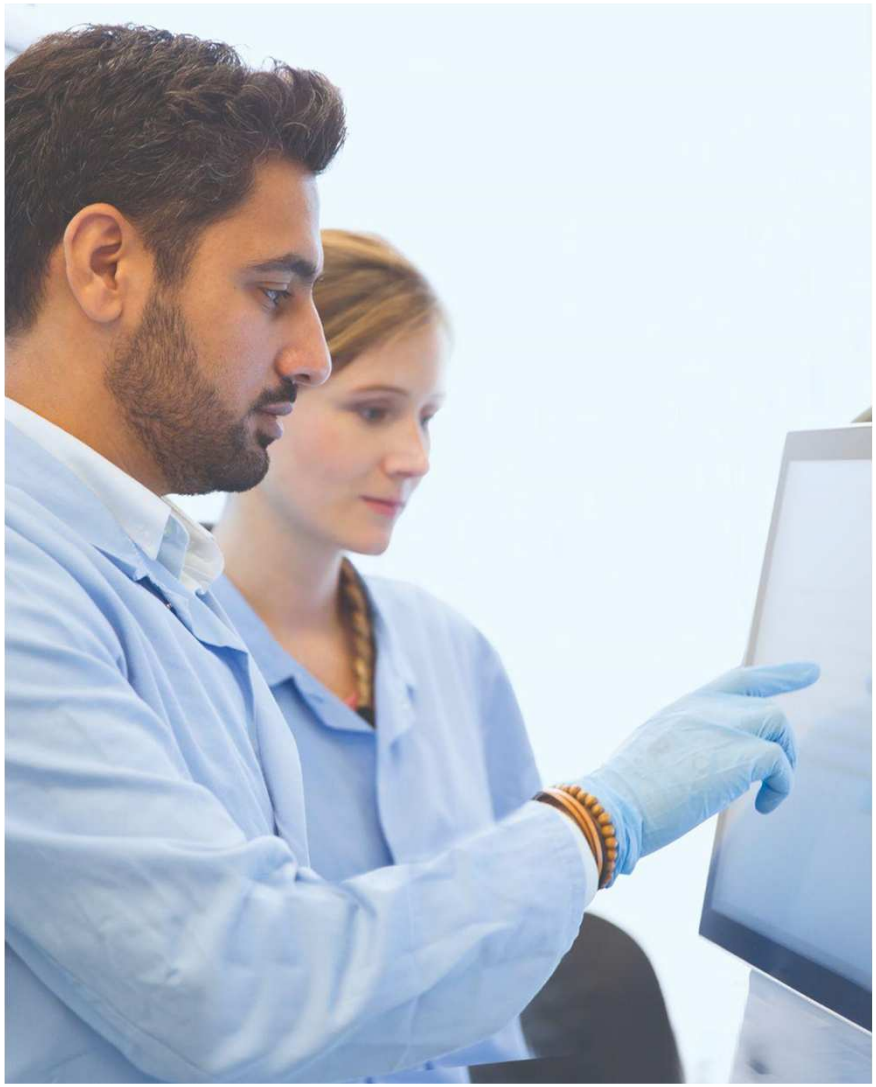
Each assay is approved as a complete, fully automated system

Example: VENTANA HER2 (4B5) Assay

The VENTANA HER2 (4B5) Assay is US FDA approved and CE IVD marked as a complete system[1,2] to identify breast cancer patients and pinpoint targeted therapy options



[1] Roche VENTANA anti-HER2/neu (4B5) Rabbit Monoclonal Primary Antibody Package Insert, 2019
[2] Roche PATHWAY anti-HER2/neu (4B5) Rabbit Monoclonal Primary Antibody Package Insert, 2012



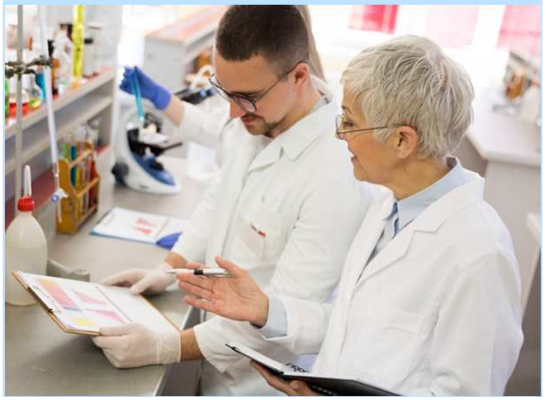
Process & timeline

CDx development & co-launch strategy

From reagent development through global commercialization

1
Early stage

2
Late stage



3
Launch & commercialization

CDx development & co-launch strategy

From reagent development through global commercialization

1 Early stage

Design and develop robust assay with in-house clinical testing on pharmaceutical partner's patient tissue samples

- Antibody development
- Biomarker testing
- Prototype assay validation

2 Late stage

Develop assay kit, scoring algorithm, control slides and training materials

- Assay validation and verification
- Pivotal trial support with an IUO assay
- Deep experience and relationships with multiple CRO partners
- Regulatory planning and submission

3 Launch & commercialization

Traditional and accelerated adoption models

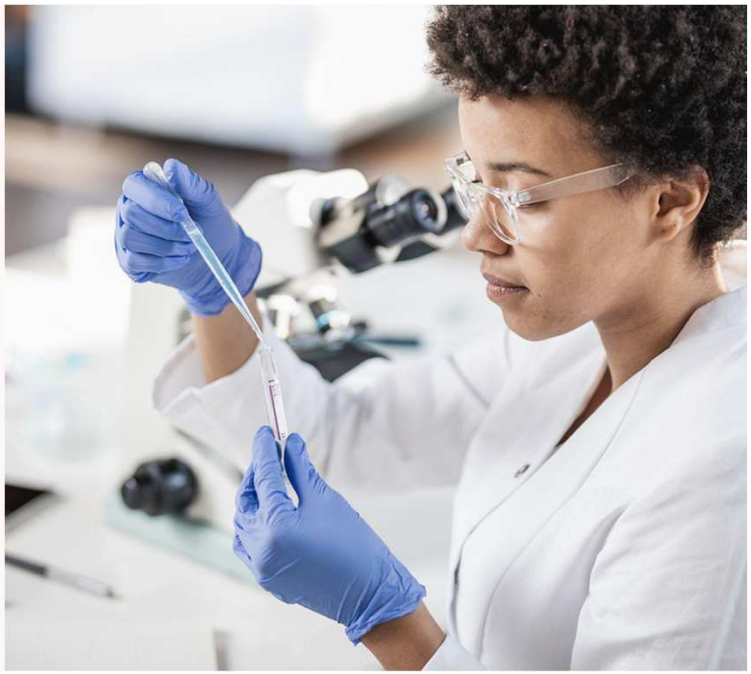
- Biomarker awareness and evidence generation
- Day one readiness
- Launch excellence
- Rapid adoption

Early stage development

1

Design and develop robust assay with in-house clinical testing on pharmaceutical partner's patient tissue samples

- Antibody development
- Biomarker testing
- Prototype assay validation



Early stage development – pharma services

Comprehensive approach enables seamless transition to IVD development

Assay development

- RPA and LDT development and validation
- Prevalence and research studies

Clinical Science management

- Professional project management organization, acting as study team point of contact
- Study support and execution

CAP/CLIA laboratory

- Three CAP/CLIA certified labs in Tucson, Santa Clara, and Europe
- 200+ active clinical trials; managing 50+ IVD global registration studies
- Partnership with CAP-accredited lab in China

Data management

- Data formatting and transfers
- Summary report of assay performance

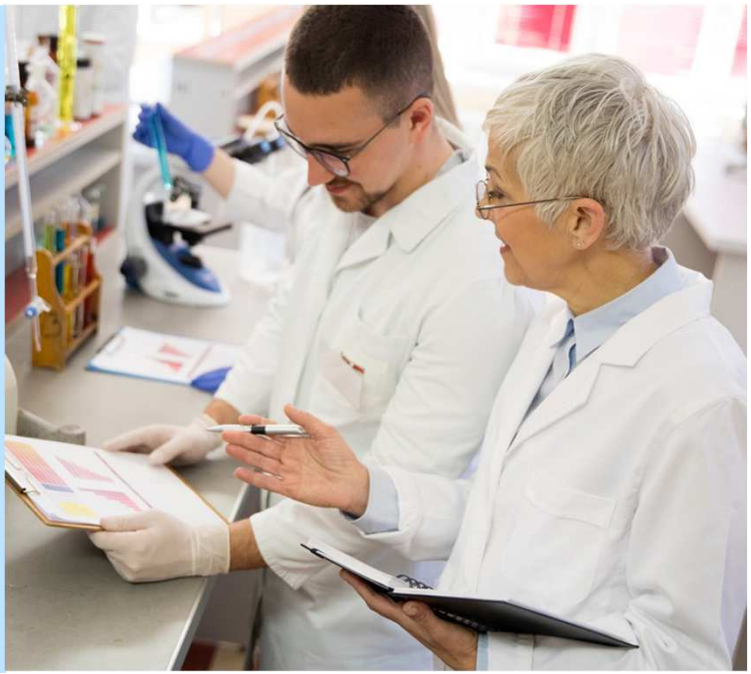
Proven model used for 15+ years with more than 70 pharma partners

Late stage development

2

Develop assay kit, scoring algorithm, control slides and training materials

- Assay validation and verification
- Pivotal trial support with an IUO assay
- Deep experience and relationships with multiple CRO partners
- Regulatory planning and submission



Global clinical expertise

Access to extensive, well-established network of thought leaders

Accelerated adoption strategy and visibility for our partners includes:

- Delivery of knowledge and expertise to our pharmaceutical partners
- Incorporation of critical information into disease state panels to build awareness
- Management of samples from across the globe regardless of study type
- Industry leadership through pathologist education, KOL study initiation and publication strategy
- Access to local lab leaders worldwide

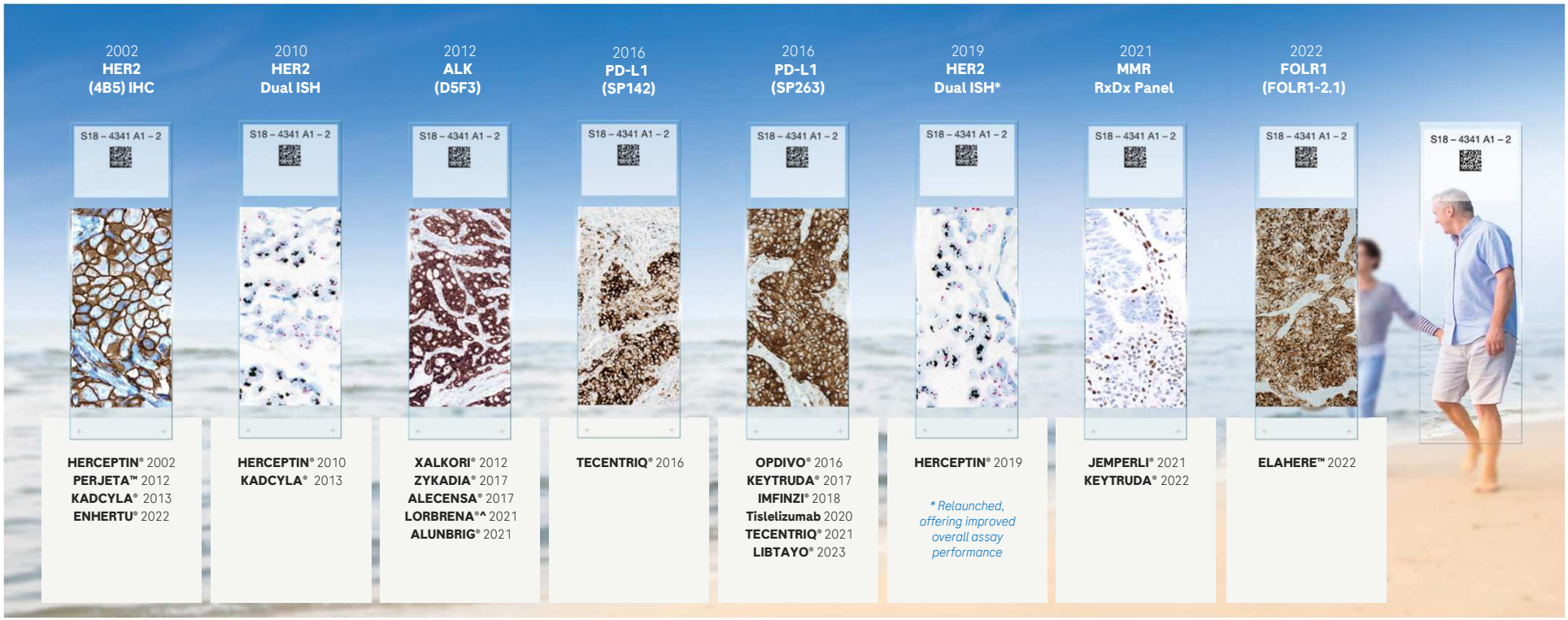
Launch and commercialization

3

Traditional and accelerated adoption models

- Biomarker awareness and evidence generation
- Day one readiness
- Launch excellence
- Rapid adoption

Identify more patients for the right drug at the right time

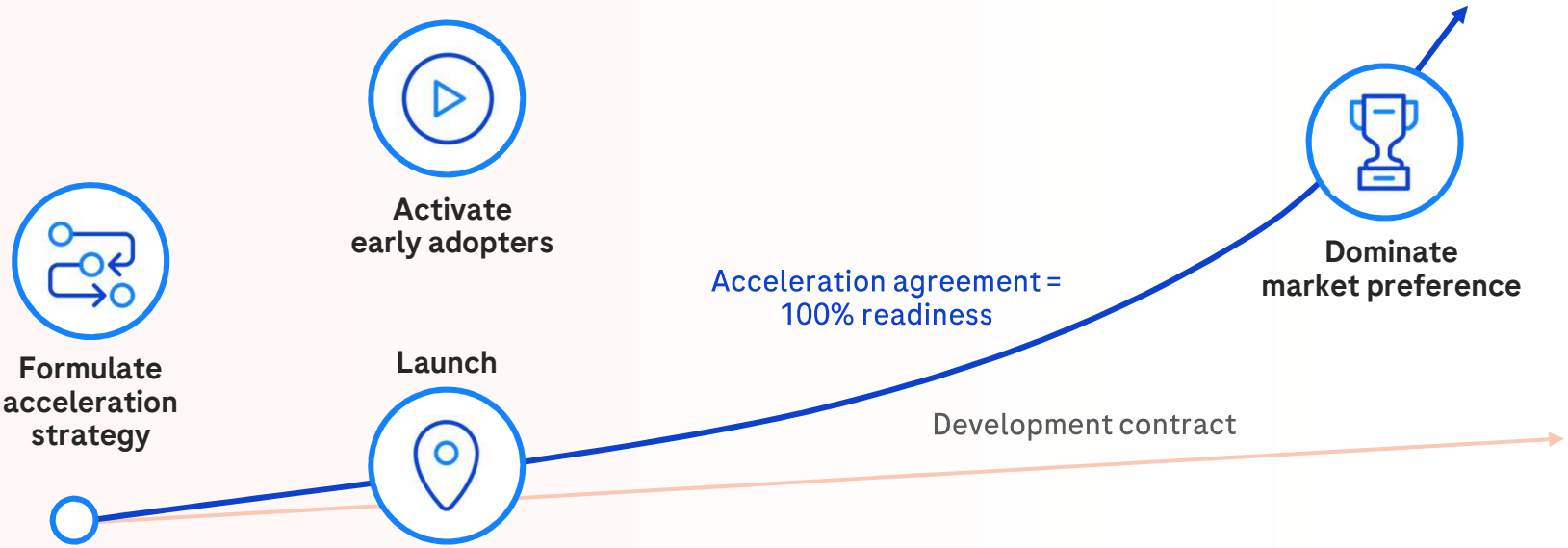


Timeline illustrative of first launch dates and label additions.
Approved indications and therapies may vary by geography.

^LORVIQUA® in CE marked countries

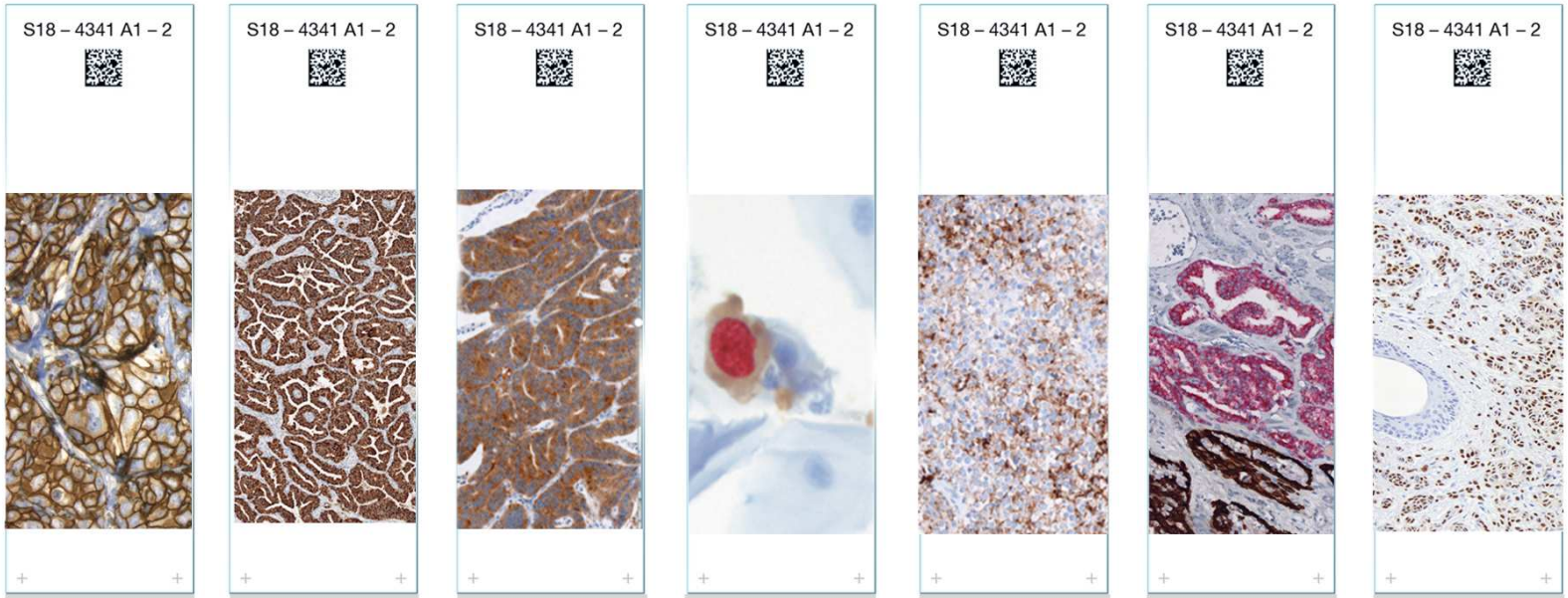
Acceleration strategy

Day one readiness and patient access



Medical Value

250+ diagnostic solutions across key disease states



The power of the predictive assay

The right therapy, for the right patient, at the right time

A predictive assay identifies patients who are more likely to benefit from a specific therapy, aiding in effective treatment decisions for the individual.

Before personalised healthcare, an average of only 25% of patients responded to their cancer chemotherapy[1]

Today, up to **80% of patients** respond to their targeted therapies[2,3]

[1] Spear, B. et al. Clinical application of pharmacogenetics. TRENDS in Molecular Medicine. 2001:(7)5:201-204.
[2] Peters., S et al. Alectinib versus Crizotinib in untreated ALK-positive non-small-cell lung cancer, N Engl J Med 2017; 377:829-838 https://www.nejm.org/doi/full/10.1056/NEJMoa1704795
[3] Kato, S. Real-world data from a molecular tumor board demonstrates improved outcomes with a precision N-of-One strategy. Nature Communications. (2020) 11:4965.

Pipeline

High medical value assays at Roche

Experience, expertise and investment

65+

ongoing **collaborative agreements for IVD development**

85+

pharma partners

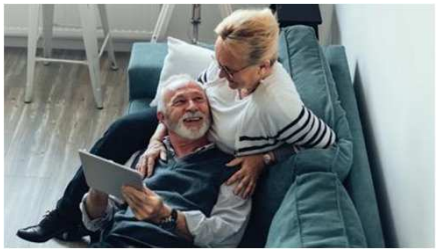
300+

ongoing clinical trials supported each year

20+

experience developing predictive diagnostics

years



3.5

million

patients tested with our HER2, ALK and PD-L1 companion diagnostic tests annually*

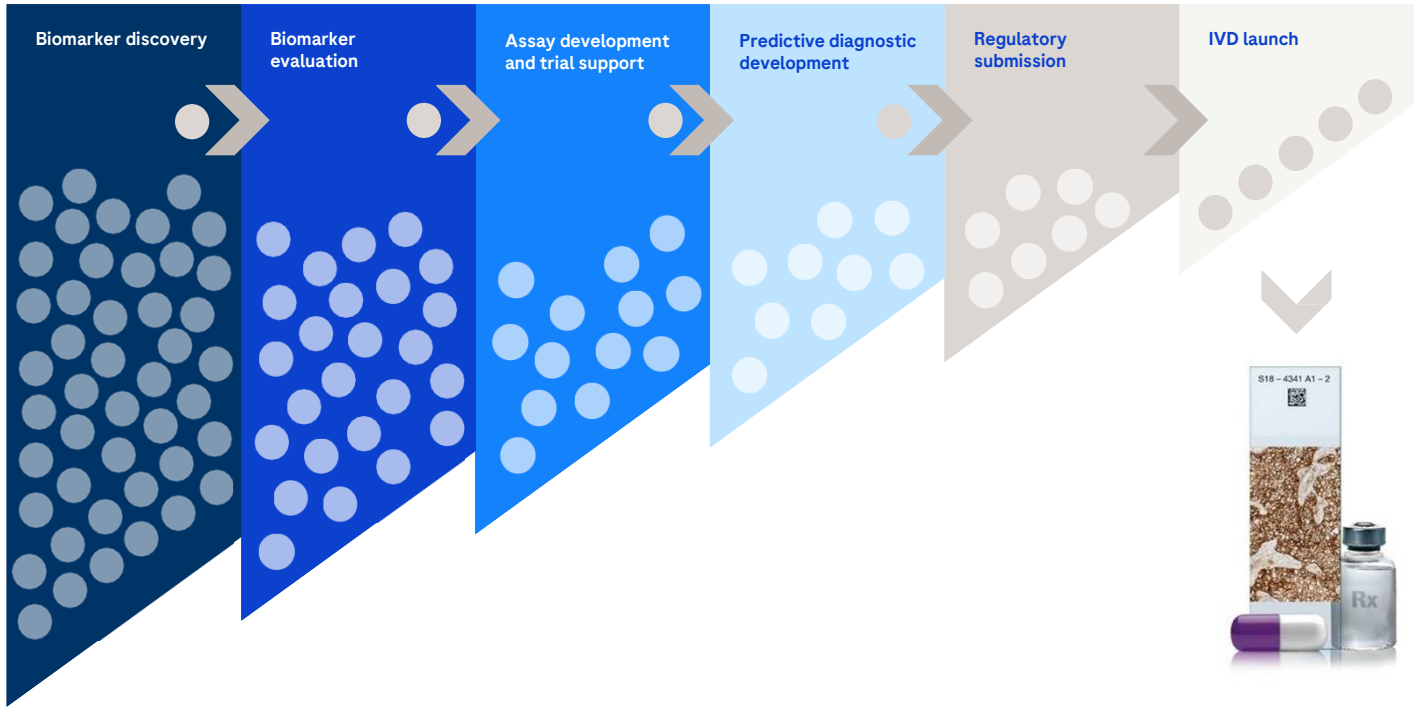
* Estimated number of unique patients based on total 2022 sales volume

Building a robust pipeline of predictive diagnostics

Continued expansion in medical value across 12+ disease states

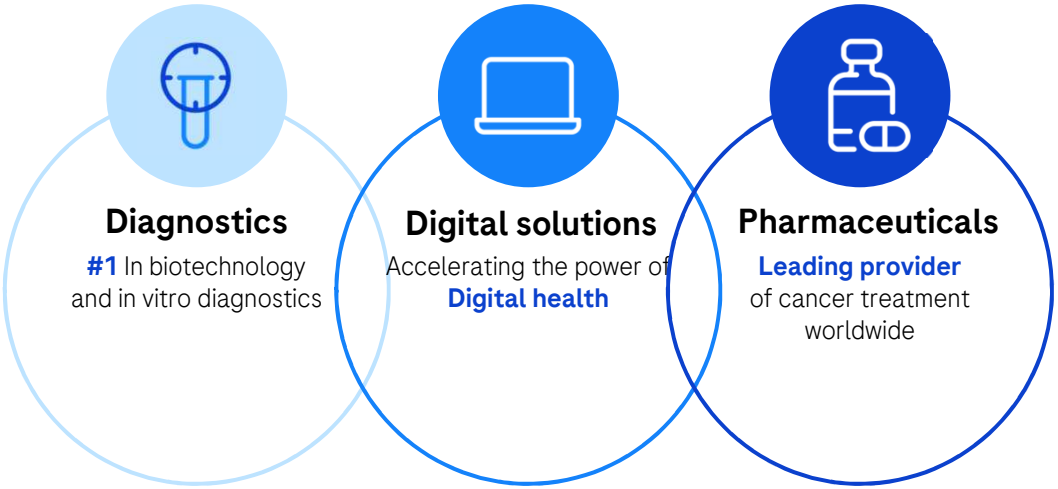
Biomarkers of interest*

ATM
B7H3
B7H4
CD73
CEA
CLDN6
CLDN18.2
FOLR1
FOXP3
HER3
HPV16 mRNA
LAG-3
MMR
MUC1
MUC16
PTEN
TIGIT
TIM-3
TROP2



*Biomarkers shown represent actual projects but are not a complete list

An integrated solutions approach that fulfils the promise of precision oncology



With our combined strengths in pharmaceuticals, diagnostics and digital solutions, we are continually expanding our understanding of how cancer operates.

We believe that we can bring value to more patients by leveraging solutions along the patient journey - from testing to personalized therapies.

This is what our Integrated Approach means: partnering with HCPs, using our respective expertise and breadth of solutions to improve patient care together, along the entire patient journey.

Thank you for your attention

www.roche.de

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