New regulations impact on academic research and patient care

Alberto Hernando-Calvo
Vall d´Hebron Barcelona Hospital Campus
Vall d´Hebron Institute of Oncology (VHIO)

Conflicts of interest

- **Consultant or Advisory Role:** Boehringer Ingelheim, Slingshot insights and Karger Publishers (all personal)
- **Research Funding:** Principal investigator in clinical trials from GSK, Bayer, Boehringer Ingelheim, CDR-life, Novartis and NEC Bio (all institution)
- **Grant support:** Gilead (institution)

Outline

- **Background: Precision oncology and EU IVDR regulation**
- **In-House developed IVDs**
- **IVDs in academic clinical trials**
- **Institutional experience with EU IVDR regulation**

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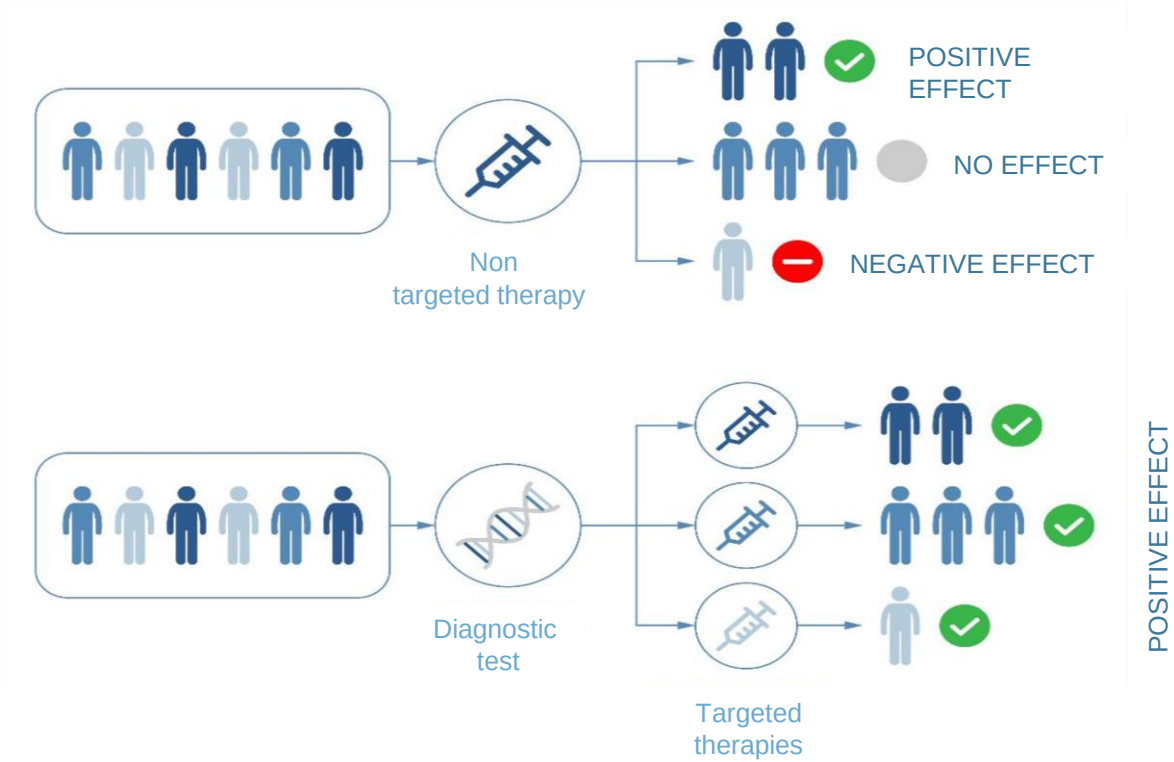
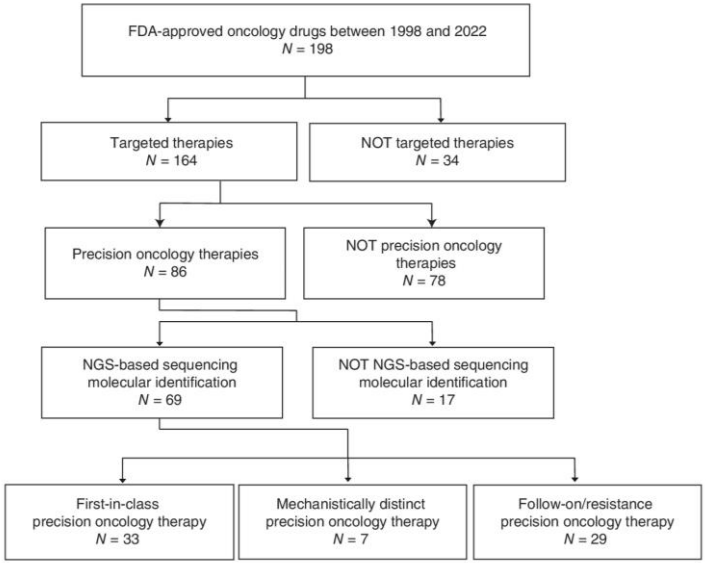
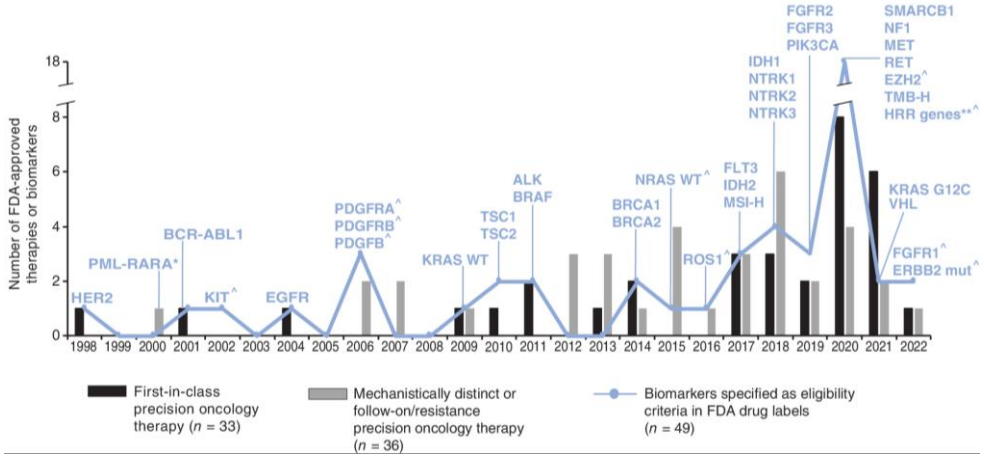
The paradigm of precision oncology



Evolution of approvals for precision oncology drugs



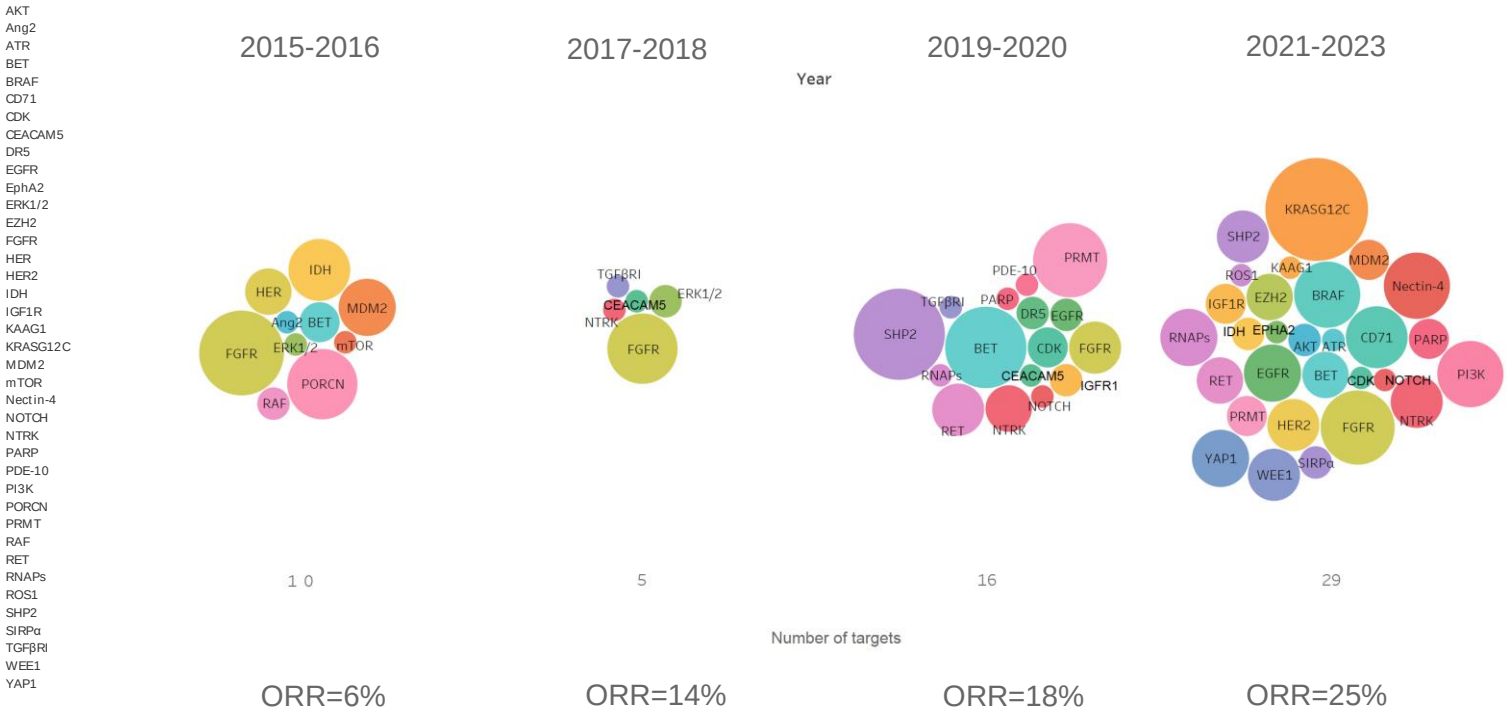
- 47,271 solid tumors sequenced with the MSK-IMPACT
- From 2017-2022, increase from 9% to 32% in the fraction of tumors harboring predictive biomarker of therapy response



Suehnholz SP et al. Cancer Discov. 2024.

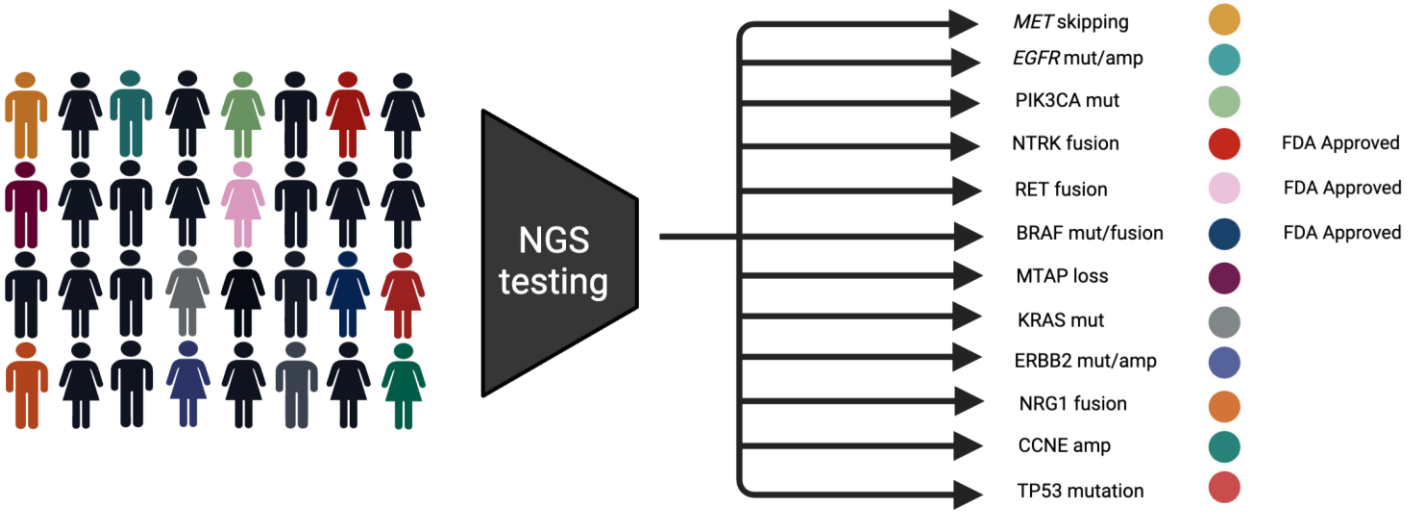
Expansion of actionable targets: Vall d´Hebron experience

- Patients enrolled in early phase trials testing targeted therapies
- N=261



Rossi A et al. Manuscript in preparation. Please do not share

Novel targets disrupting the clinical arena



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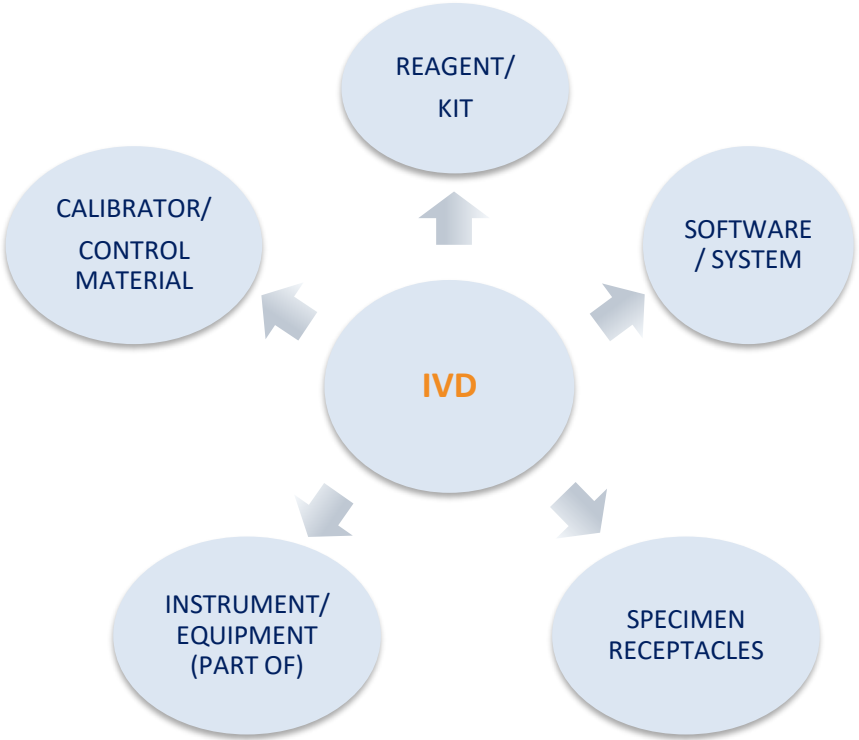
In vitro diagnostic device (IVD) definition

EU 2017/746: Art 2(2)

Any device intended to be used in vitro for the examination of human specimens for the purpose of providing information about:

- physiological or pathological processes
- congenital physical or mental impairments
- predisposition to diseases
- Determine the safety/compatibility with recipients
- **to predict treatment response**
- **to define or monitoring therapeutic measures**

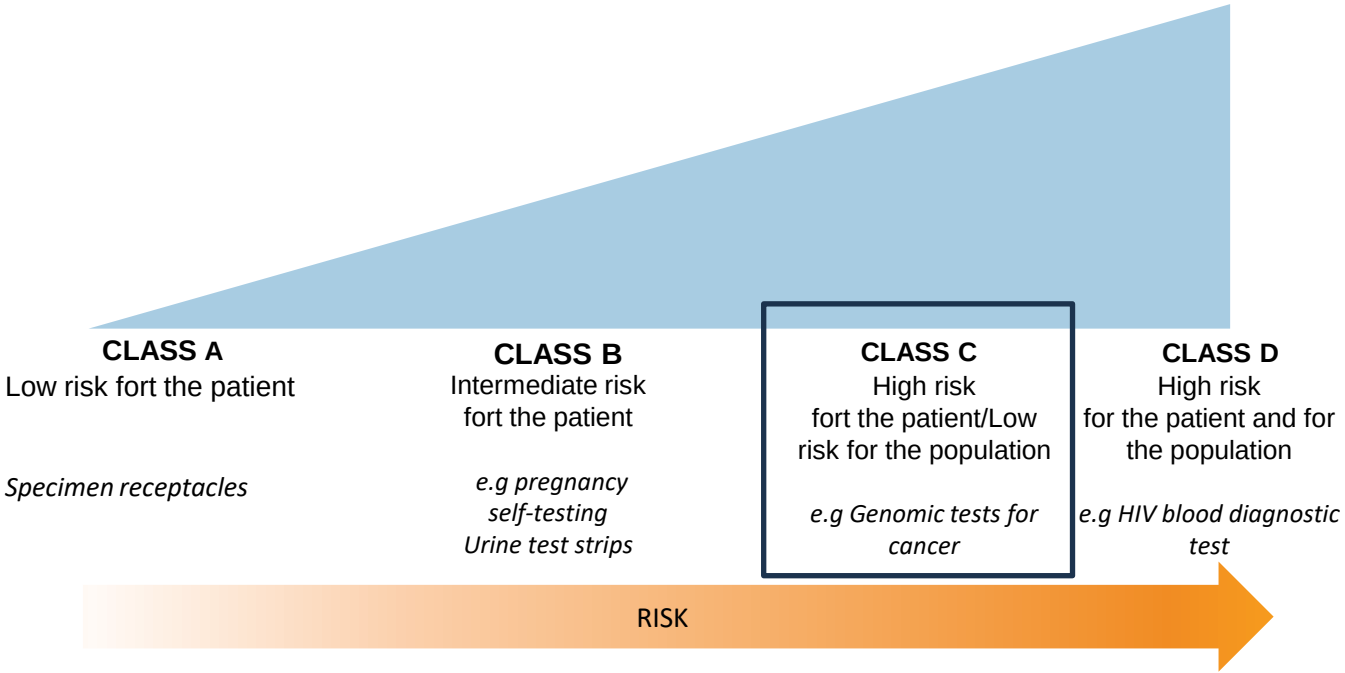


Courtesy of Deborah Lo Giacco

In vitro diagnostic device (IVD) categorization

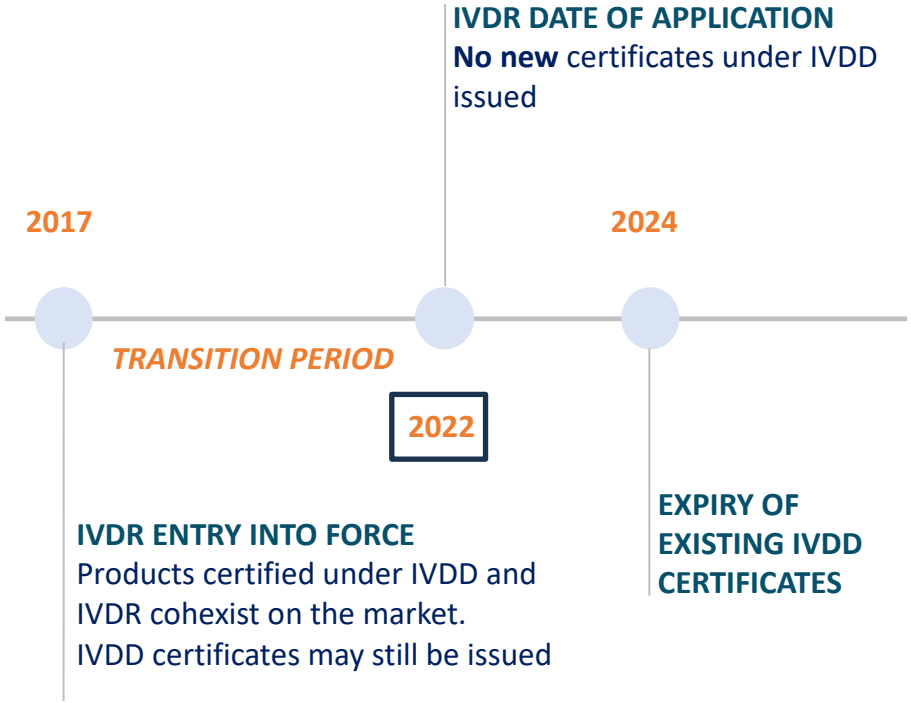
Union regulatory framework for In vitro DIAGNOSTIC MEDICAL DEVICES (IVD)

Devices shall be divided into classes A, B, C and D, taking into account the intended purpose and their inherent risks



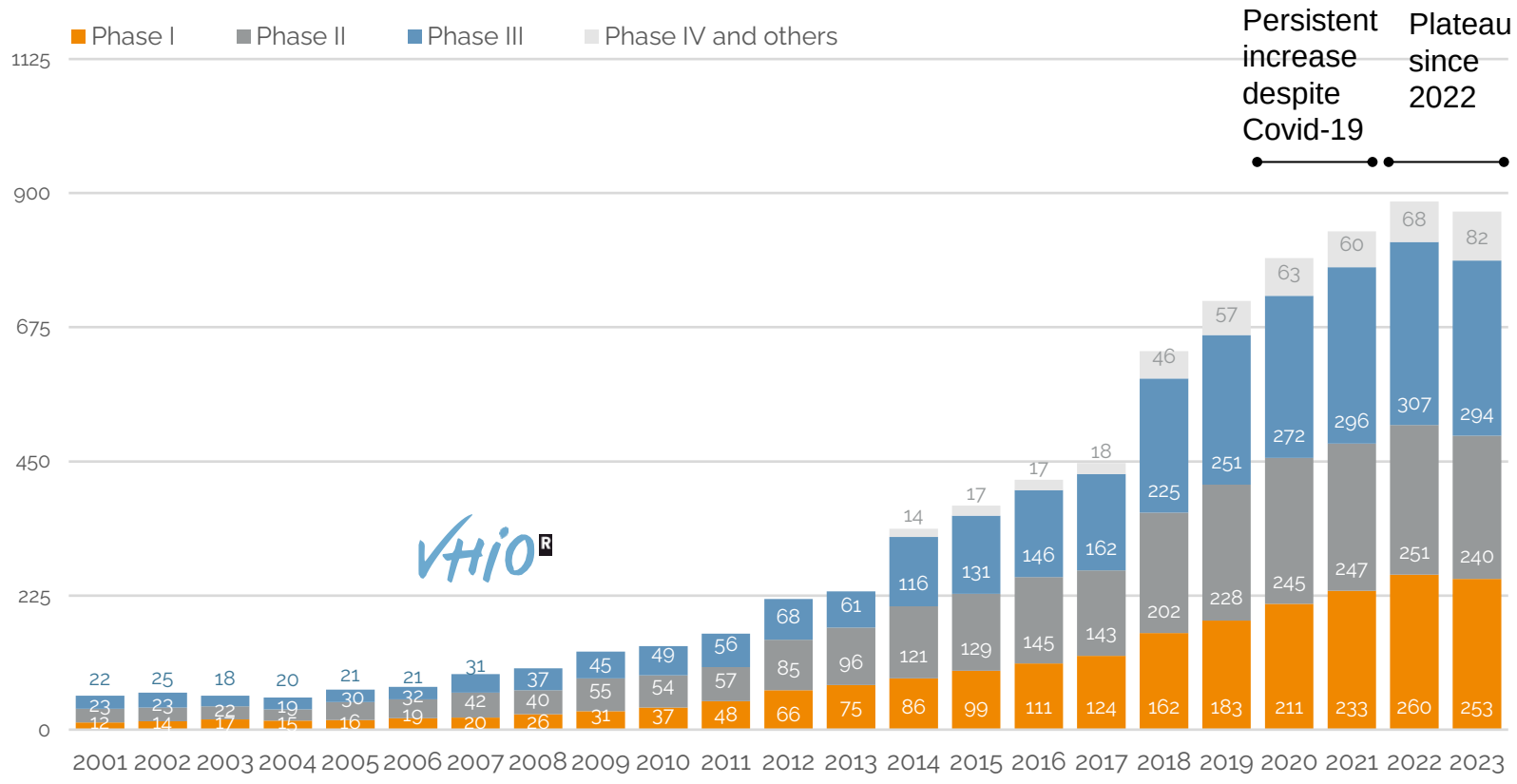
Courtesy of Deborah Lo Giacco

IVDR regulation: Timeline

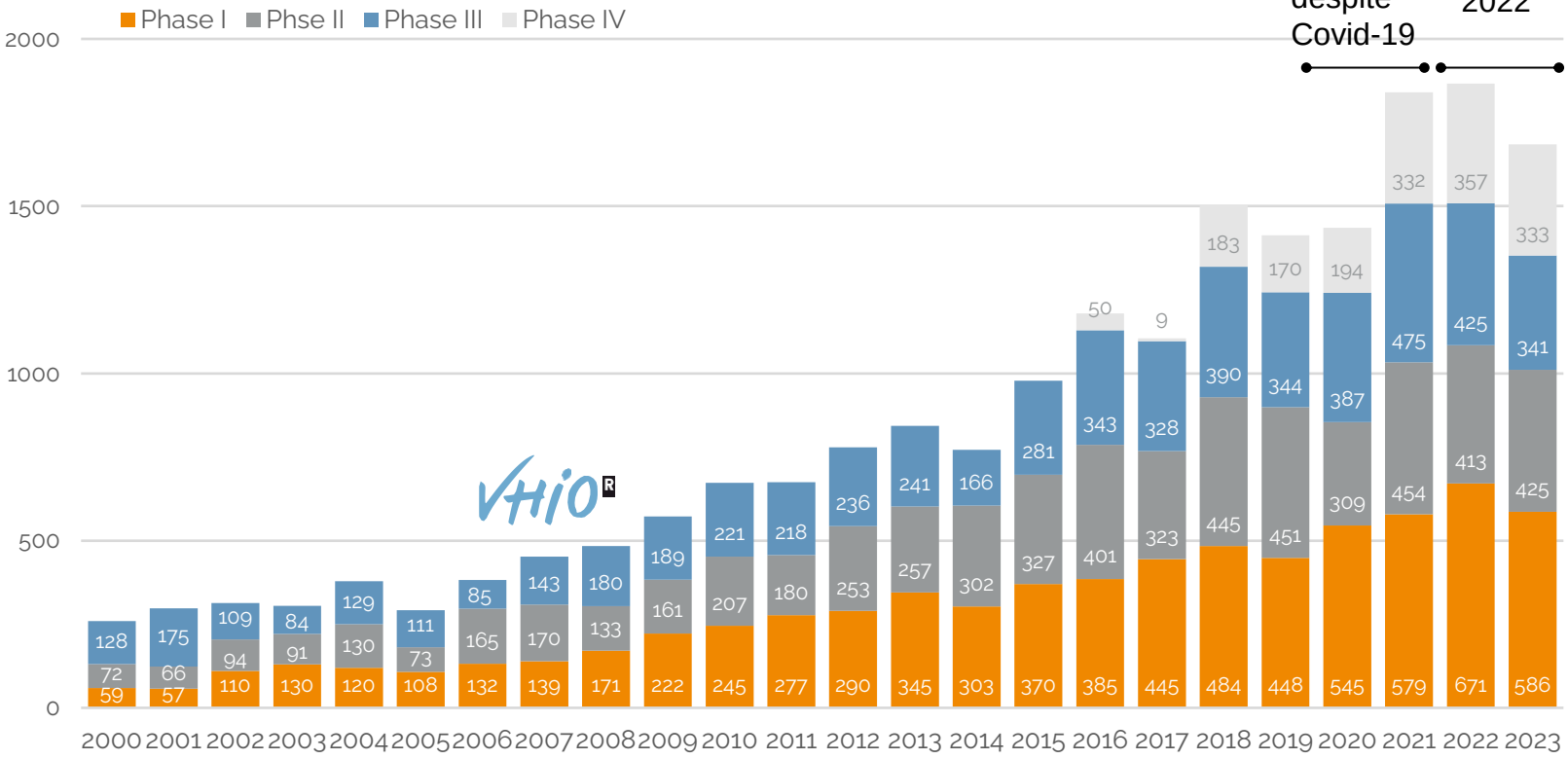


Courtesy of Deborah Lo Giacco

Active clinical trials per year: Distribution by phase



Patients included in clinical trials, by phase



IVDR regulation in clinical trials: EFPIA Survey

- **Hypothesis**: There is a negative impact of IVDR on clinical trials using IVD due to lack of coordination and clarity for performance studies
- EFPIA survey evaluated:

  1-Time to clinical trial launch and study initiation is impacted
  2-Patients may have reduced access to trials
  3-Delays in access to novel therapies
  4-Impact in other academic initiatives

- Out of **21 of 32** companies responded
- **6-12 months** delay frequently reported
- **48%** responders estimating 6-12 months delay to continue for over three years
- **>15.000** cancer patients could be impacted in 3 years time

https://efpia.eu/media/677143/efpia_ivdr-survey-slides.pdf

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- IVDs in academic clinical trials
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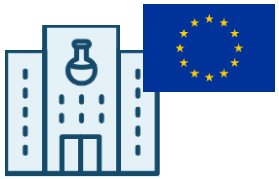
IVDR Article 5(5): IN-HOUSE DEVELOPED IVD

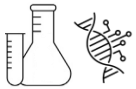
THE HEALTH INSTITUTION PARTIAL EXEMPTION

To address the specific needs of target patient groups which cannot be met, or cannot be met at the appropriate level of performance, by an equivalent CE-marked device ***(MDCG 2023-1)***



→ WITHIN EU HEALTH INSTITUTIONS
→ ON A NON-INDUSTRIAL SCALE

IN-HOUSE DEVELOPED TEST



NEW DEVICE DEVELOPED INTERNALLY

Manufacturing
- From raw materials
- From part of a device
- Combining existing devices
- Modyfing existing devices

(CE MARKED) IVD USED OFF-LABEL

Using
- Physical
- Remote (MDSW)*

RUO DEVICES FOR DIAGNOSTICS

* Provided it is not made available to another legal entity

Courtesy of Deborah Lo Giacco

IVDR Article 5(5): When It Is Not Applicable

Health Institutions
NOT Established in EU

Non-health care entities

Restrictions by a
National Competent
Authority

BY 31 DECEMBER 2030
(EU) 2024/1860 June 2024)

The IVD is used outside
the health institution

An equivalent
CE-marked device
exists on the market

Courtesy of Deborah Lo Giacco

IVDR Article 5(5): Requirements

- **Compliance with the General Safety & Performance Requirements (GSPRs)**

A. General requirements

-Risk management
-Performance, clinical evidence
-Safety and reliability
-Elimination of risks

B. Design and manufacturing

-Safety
-Software and cybersecurity
-Sterility and hygiene
-Labeling and instructions

C. Performance evaluation and post market surveillance (PMS)

Name of health institution:

Address:

-the health institution- declares that the devices described in the accompanying table are only manufactured and used in *-the health institution-* and do meet the applicable general safety and performance requirements (GSPR) of the medical devices Regulation (EU 2017/745) or of the *in vitro* diagnostic medical devices Regulation (EU 2017/746). A reasoned justification is provided in case applicable general safety and performance requirements are not fully met.

Table of in-house devices:

Device identification (e.g. name, description, reference number)	Device type (IVD/ MD)	Risk class of the device[2]	Intended purpose	Applicable GSPR fully met? (Y/N)	Information on and justification for applicable GSPR that are not fully met (using the numbering as in Annex I of the IVDR/MDR)

Courtesy of Deborah Lo Giacco

MDCG 2023-1

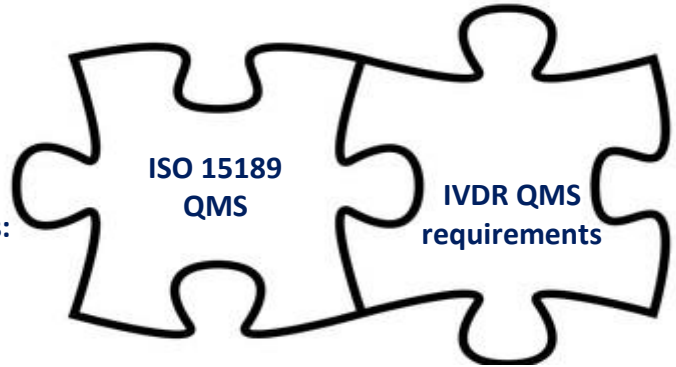
IVDR Article 5(5): Requirements

- **Appropriate quality management system (QMS)**
- **The laboratory must be compliant* with EN ISO 15189**

EN ISO 15189 QMS alone is not enough!

→ **Technical Requirements:**
- Personnel
- Equipment
- …..

→ **Management Requirements:**
- Document control
- Audits
- Continual improvement
- ….



→ **Compliance with GSPRs**

→ **Post Market Surveillance (PMS)**

***Compliance with EN ISO 15189**

- **Accreditation**
- **Other means of compliance**

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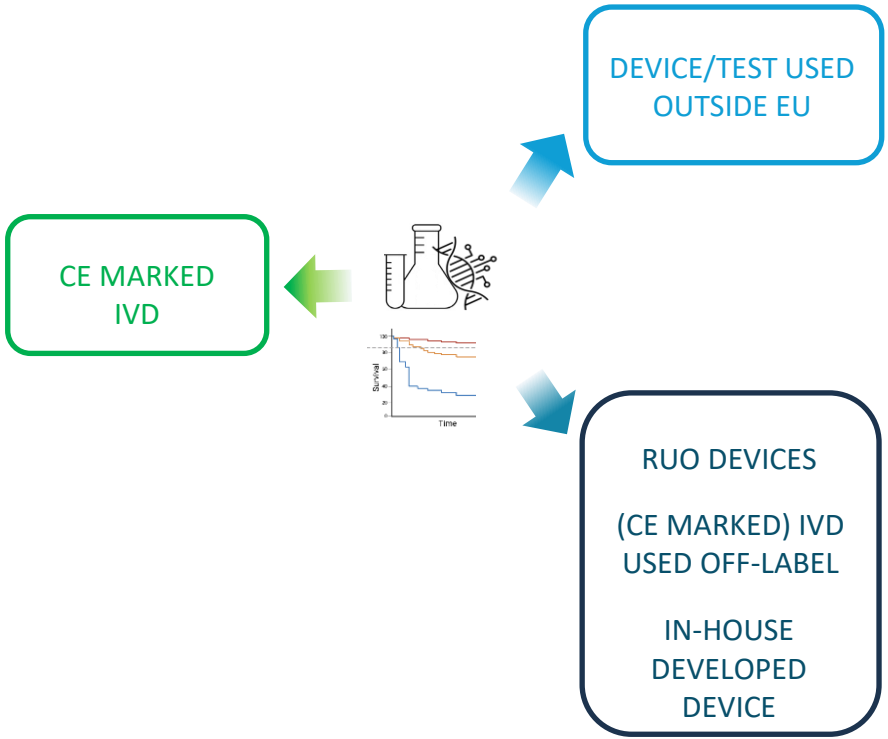
Devices in European Clinical Trials: IVDR compliance roadmaps



Option 1:
In-House IVD
(Art 5.5 IVDR)

Option 2:
IVD for performance study
(Art 57, 58 Annex XIII, XIV)

Courtesy of Deborah Lo Giacco

IVDR Compliance Options for EU Clinical Trials

Option 1: In-House IVD, the health institution partial exemption

ADVANTAGES

1-Exemption from most IVDR provisions
IVDR Article 5(5) applicable

2-Centralization of testing: uniformity, operational agility, high quality results
Samples can be shared and analyzed by EN ISO 15189 compliant lab

3-Flexibility for IVD up-date
EN ISO 15189 QMS allows (No substantial) modifications to the IVD

LIMITATIONS

1-Only applicable to health institutions established in the EU.

2-Compliance monitored and enforced by the national competent authority of each member state
Potential different national interpretations

3-No equivalent CE-IVD available on the market (By December 2030)

4-Complete IVD performance evaluation required
Full validation of IHDs is required, but limitations in clinical performance and clinical valiatiy data make it difficult to assess their effectiveness before clinical trial initiation

Courtesy of Deborah Lo Giacco

Option 2: IVD for clinical performance study

To establish the **IVD CLINICAL PERFORMANCE:**
How good the test is in providing results on the clinical condition? Sensitivity, specificity, PPV, NPV..

ADVANTAGES

1-Exemption from most IVDR provisions
IVDR Articles 57 and 58 and Annexes XIII and XIV

2-Only option for IVD tests in EU clinical trials to be used in Non-EU laboratories

3-Promotes the development of new IVDs:
The only option for IVDs for which clinical performance has not yet been demonstrated

LIMITATIONS

1-Interventional performance evaluation studies require competent Authority Review and Approval:
Formal application to competent authority needed

2-Long approval timelines:

-No harmonized procedure for application in place
-Each member state can interpret the applicable provisions and add extra requirements
-No option to submit a single application for a coordinated assessment **(by May 2029)**
-Time needed for the IVD performance evaluation study approval must be calculated into the schedule of the clinical trial

Courtesy of Deborah Lo Giacco

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The VHIO molecular prescreening program

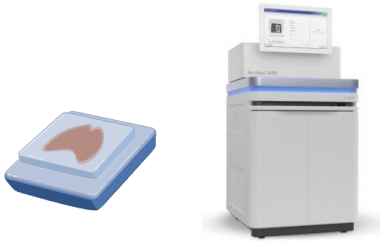
VHIO-300 (Tissue based hybrid capture panel):

- Chemistry: Region-specific capture and NGS (Illumina)
- >430 genes involved in cancer:
- mutations & indels
- copy number alterations
- TMB
-Loss-of-heterozygosity (LOH)- HRD

IVDR (EU) 2017/746 requirements:

-In House IVD only used at VHIO
-Addressing special needs of population
-Accredited with EN-ISO 15189
-Fulfills GSPRs and QMS

UNE-EN-ISO:15189:2023
Accreditation Nº 1052/LE2022



<5% failure rate in FFPE

Min. Tumor area 20-50%
TAT: <3 weeks

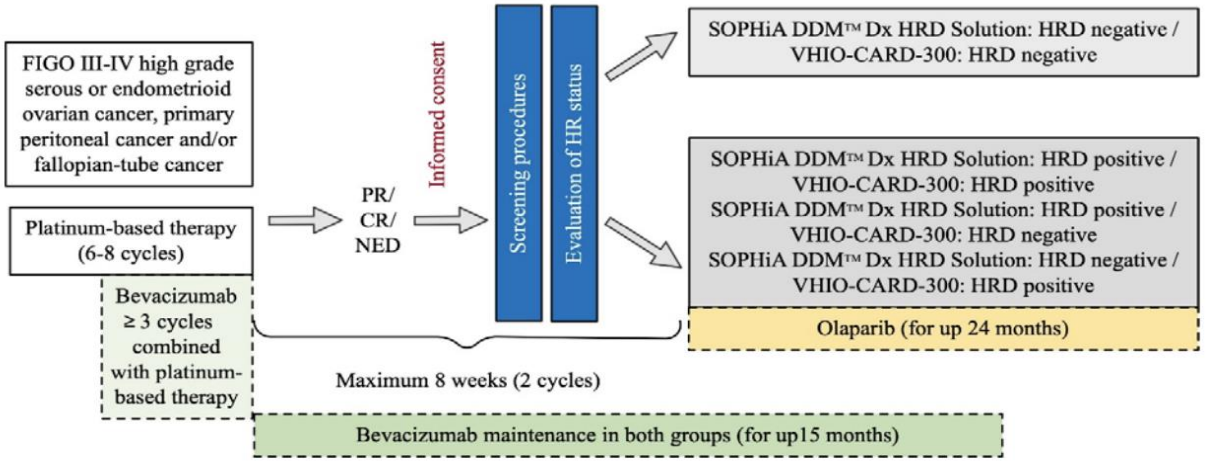
Jan 2021
Flexible accreditation

Pi: Ana Vivancos
Quality Dep. Lead:Deborah Lo Giacco

Real-world case : Investigator initiated trial with biomarker selection

Non-Randomized, Open-Label, Prospective Phase II Trial to Better Characterize the Status of HRD leading to a Benefit from Olaparib in Combination with Bevacizumab in Patients with Advanced FIGO Stage III-IV High Grade Serous or Endometrioid Ovarian, Fallopian Tube, or Peritoneal Cancer After Standard First-Line Treatment

Figure 1 Study design



HRD: homologous recombination deficient; PR: partial response; CR: complete response; NED: no evidence of disease

PI: Ana Oaknin
Sponsor: VHIO

Real-world case : Investigator initiated trial with biomarker selection

-Academic CRO (VHIO)
-Support from
1-Quality Unit VHIO
2-External consultancy agency

Ana Oaknin
Ana Vivancos
Susana Muñoz

Take home messages

- **The EU IVDR regulation impacts clinical laboratories and investigator initiated trials.**
- **Partial Exemption for In-House Devices:** Under Article 5(5), healthcare institutions can develop and use in-house IVDs, but must ensure compliance with GSPRs and maintain an appropriate QMS.
- **Potential variability in interpretation:** National competent authorities may enforce Article 5(5) differently across Member States
- **ISO 15189 Limitations:** ISO 15189 alone does not satisfy IVDR manufacturing requirements. A QMS that includes post-market surveillance (PMS) and performance monitoring is needed for in-house IVDs.
- **Clinical Trials Complexity:** Non-CE-marked IVDs in clinical trials may follow two compliance routes: as in-house devices or performance evaluation studies. Combined clinical trials involving IVDs and medicinal products face extended approval timelines and complex regulatory hurdles.

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- Study Coordinators

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Our patients!

Email: albertohernando@vhio.net

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