IVDR-
Performance Studies

AMDM's 49th Annual IVD Regulatory Meeting

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Disclaimer

The views and opinions expressed in the following PowerPoint slides are those of my own and should not be attributed to Roche`s position.

I am a full time employee and shareholder of F. Hoffmann La Roche

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Agenda

- IVDR- context
- New requirements
- Clinical Trials & Performance Studies
- Experience Performance Studies
- Few examples
- Impact on clinical trials in Europe
- US-EU
- Summary

EU IVD regulations: IVDD and IVDR

In Vitro Diagnostic Directive (IVDD) [98/79/EC]	In Vitro Diagnostic Regulation (IVDR) [EU 2017/746]
*Member states responsible for implementation of local medical device regulations	*In effect: 26 May 2022* Applicable to all EU Member States (no implementation in local law required)
	
IVDD ≅ 40 Pages	IVDR ≅ 160 Pages

IVDR is a broad rewrite of EU regulation:

- First change in medical device/IVD regulation in 20 years
- Sets high standards of quality, safety and reliability to safeguard patients and enhance innovation- **what is highly welcomed**
- Introduces (among others) more stringent documentation requirements, stricter requirements for clinical evidence and more systematic clinical performance evaluation of devices/IVDs - which may include a performance study
- Applicable to all EU Member States

Role of the IVDR -interplay with the regulatory ecosystem?

Multiple considerations and components of integrated solutions*

...which need to plug into an ecosystem

+

Address multiple gaps in the patient journey

Prevention (early detection/intervention)
Screening
Diagnosis
Treatment
Monitoring

***Consists of at least two components**

Therapeutic
Diagnostics (IVD-CDx)
Technologies
Tool
Services

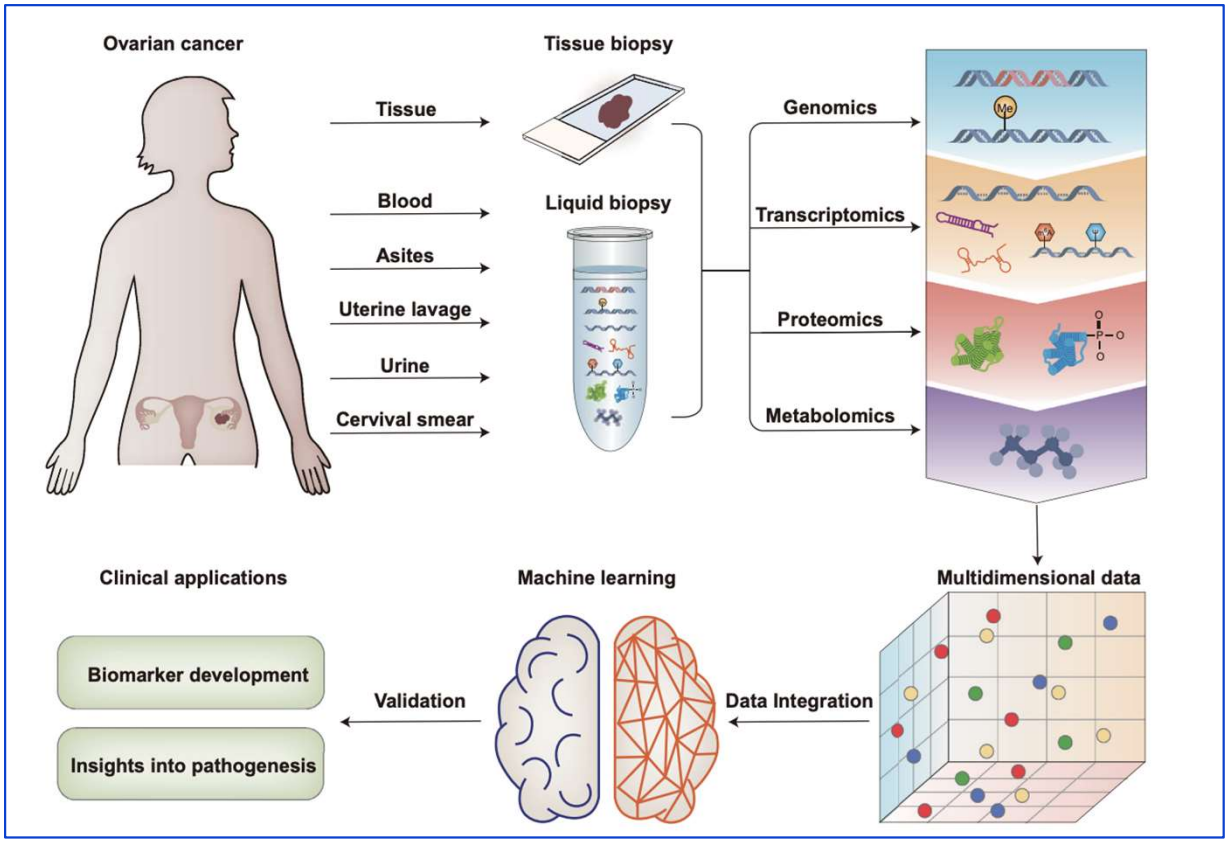
Successful implementation requires the right ecosystem

e.g. regulatory and healthcare infrastructure, development of new guidance and collaboration across all stakeholders

Advanced technology and Integrated solutions* strongly supports the patient journey

Advanced diagnostic technology - new opportunities

The scientific and technological environments are changing rapidly. Advanced diagnostic and biomarker technologies create novel opportunities for personalized medicine



Xiaa et al., The Lancet, VOLUME 79, 104001, MAY 2022

Biomarkers are widely used at every stage of drug discovery and development

Biomarker category	Description	Example
Diagnostic	A biomarker used to detect or confirm presence of a disease or condition of interest or to identify individuals with a subtype of the disease	Sweat chloride may be used as a diagnostic biomarker to confirm cystic fibrosis
Monitoring	A biomarker measured serially for assessing status of a disease or medical condition or for evidence of exposure to (or effect of) a medical product or an environmental agent	Monoclonal protein (M protein) level in blood may be used as a monitoring biomarker to evaluate whether individuals diagnosed with monoclonal gammopathy of undetermined significance (MGUS) are showing signs of progressing to other disorders, including some types of blood cancer which may require treatment[9]
Pharmacodynamic/ response	A biomarker used to show that a biological response has occurred in an individual who has been exposed to a medical product or an environmental agent	Serum LDL cholesterol may be used as a pharmacodynamic/response biomarker when evaluating patients with hypercholesterolemia, to assess response to a lipid-lowering agent or dietary changes
Predictive	A biomarker used to identify individuals who are more likely than similar individuals without the biomarker to experience a favourable or unfavourable effect from exposure to a medical product or an environmental agent	BReast CAncer genes 1 and 2 (BRCA 1,2) mutations may be used as predictive biomarkers when evaluating women with platinum-sensitive ovarian cancer, to identify patients likely to respond to poly (ADP-ribose) polymerase (PARP) inhibitors
Prognostic	A biomarker used to identify likelihood of a clinical event, disease recurrence or progression in patients who have the disease or medical condition of interest	BReast CAncer genes 1 and 2 (BRCA 1,2) mutations may be used as prognostic biomarkers when evaluating women with breast cancer, to assess the likelihood of a second breast cancer
Safety	A biomarker measured before or after an exposure to a medical product or an environmental agent to indicate the likelihood, presence, or extent of toxicity as an adverse effect	Serum creatinine may be used as a safety biomarker when evaluating patients on drugs that affect kidney function to monitor for nephrotoxicity
Susceptibility/risk	A biomarker that indicates the potential for developing a disease or medical condition in an individual who does not currently have clinically apparent disease or the medical condition	Apolipoprotein E (APOE) gene variations may be used as susceptibility/risk biomarkers to identify individuals with a predisposition to develop Alzheimer's disease

Gromova et al., Biomark Insights. 2020; 15: 1177271920974652.

IVDR- new requirements introduced

What is a Companion Diagnostic- New definition introduced

CDx: ‘companion diagnostic’ means a device which **is essential for the safe and effective use of a corresponding medicinal product** to:

- identify, before and/or during treatment, patients who are **most likely to benefit** from the corresponding medicinal product; or
- identify, before and/or during treatment, patients likely to be **at increased risk of serious adverse reactions** as a result of treatment with the corresponding medicinal product

IVDR covers more than “just” Companion Diagnostics

Scientific validity + Analytical performance + Clinical performance = Performance evaluation report

CE

IVDR Art. 2 (46)
“interventional clinical performance study” means a clinical performance study where the test results may influence patient management decisions and/or may be used to guide treatment. Prerequisite for a conformity assessment to obtain a CE mark,

This means that a Performance Evaluation Study Submission under the IVDR is needed for **all combined studies (drug + IVD)** with any medical decisions making in case
- a diagnostic test **has no CE marking**
- a diagnostic **test is used outside the approved intended use**.

And/ or the study data are part of IVD development to support a registration

Scientific validity, Analytical performance and Clinical performance data are prerequisite for CE approval.

Clinical Trials and Performance Studies

Implications on Clinical Trial Applications (CTA)

Examples clinical trials using CE marked- non CE marked IVDs for medical decision making

1. **CE marked IVD- used within Intended Use**

Used test for medical decision making is CE certified and the test is used within the intended use.
No further action needed for the usage of the test in the clinical drug trial

2. **CE marked IVD - used outside Intended Use***

Used test for medical decision making is CE certified and the test is used outside the intended use.
A performance study and Drug trial application (CTA clinical trial application) needs to be submitted for the test

3. **Used test for medical decision making is not CE certified.**

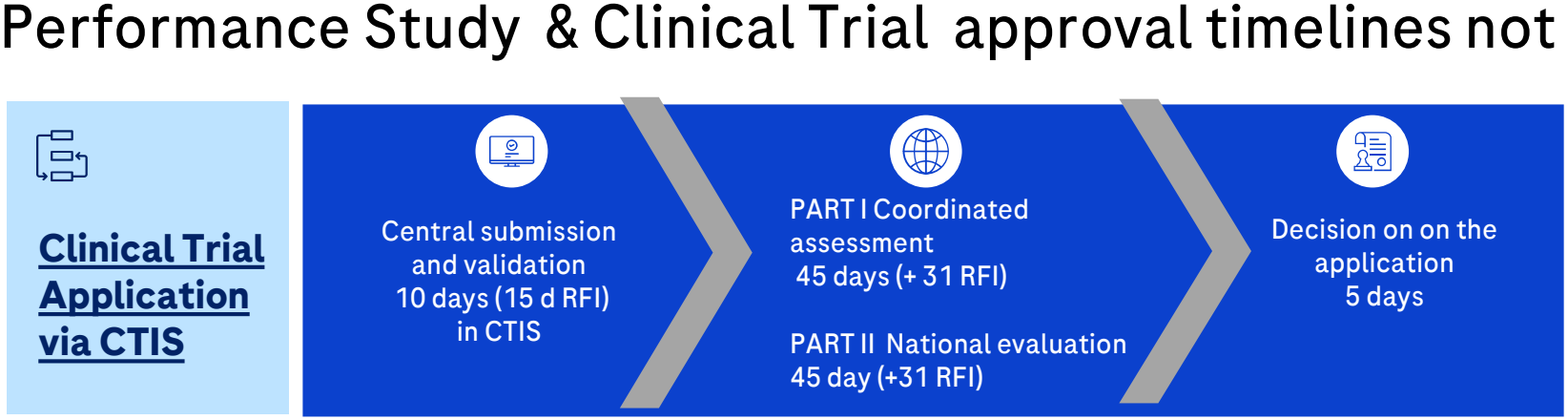
A performance study needs to be submitted for the test in parallel to the CTA of the drug.

2 & 3 :
More than **One trial** application

A **Drug Trial Application (CTA) AND** a **Device Trial Application** for the same study.

Approval for **both drug and device trials** is required for study start and use of data in filings

Performance Study & Clinical Trial approval timelines not aligned



IVDR performance study applications be submitted through EUDAMED (European Database on Medical Devices)

- EUDAMED **will not be available** in the near future, **no link to CTIS**
- Current guidance – submit applications via respective national procedures to each participating member state until EUDAMED goes live
- Without EUDAMED, there is no common timeline for EC and CA review, it will vary from state to state
- Guidance continuing to evolve for specific application processes to individual member states

No alignment of Clinical trial and Performance Study approval timelines- adapt project planning

A drug CTA and a device trial application will be required for combined studies (drug + IVD) when IVDR applies

Drug Trial Application

- Investigational Medicinal Product(s)
- Drug protocol
- Drug IB
- Drug safety data collection & reporting
- Patient consent to participate in drug study
- Clinical trial sites & monitoring

+

Device Trial Application (Annex XIV)

- Investigational Device (e.g. IVD)
- Device protocol = Clinical Performance Study Plan (CPSP)*
- Device IB*
- Device safety data collection & reporting
- Patient consent to participate in device study
- Device testing sites & monitoring

*For each device in the study; there can be multiple devices in a study

Device trial application (IVDR application) Process

General Procedure:

1. Submit an IVDR application to Competent Authority (CA) for a study application number[1]
2. Submit to the Ethics Committees (EC) in all participating member states for an opinion on the applicability of country-specific IVD laws[2]
3. If the EC opinion is favorable, then application is submitted to the CA for their approval/authorization

Collaboration is needed: Pharma /Device Partner co-drafting Clinical Performance Study Plan and device IB

Estimated EC and CA review varies, up to 9 months

Review timelines varies depending on country

Single application to EUDAMED (European database on medical device) is planned to be in place Q2 in 2024?

[1]You can email a health authority in advance of the first submission and ask them for an EU study application number.
[2]Only a few member states require EC approval in advance of CA approval. Many have parallel submissions.

Experiences Performance studies

Experience Performance studies

Preparation of Performance Studies

National Competent Authorities:

- Not all Member States have defined process yet for “preparation”/ submission of PSA in that Member State
- Variable documentation requirements across Member States
  Countries generally use IVDR Annex XIII-XIV* as basis for a PS- applications, but there is high variability in the local documents required and accepted:
  - individual member state application form (not the MDCG template)
  - country-specific or site-specific Ethics Committee application form (sometimes in local language)
  - different requirements related to the CPSP
- In some countries questions related to PS-submission are responded very slowly

Member State specific requirements of Ethic Committees:

- Various country-specific or site-specific Ethics Committee application form (sometimes in local language)

*updated requirements by MDCG in Dec

Experience Performance studies

Submission of performance studies

National Competent Authorities:

- Problems with submission portals: non-functional portals or even non existing portals
- Member State specific requirements that delay submission of the PSA:
  - hard copy/wet ink signature requirements, application has to be mailed in
  - Paper copy/wet ink signature requirements and certified translations
  - List of submitted documents has to be a word file, pdf is not accepted
  - Requires detailed personal information of company representatives
  - PMPF plan as part of a study submission

Member State specific requirements of Ethic Committees:

- In some countries Clinical Trial Application (CTA) and Performance Study Application (PSA) for combined studies must be submitted simultaneously on the same day
- Some countries require submission of individual applications to the local ECs for each site
- In some counties the PI has to submit the application to the local EC instead of the Sponsor
- In some countries the PI has to submit application to EC via a dedicated portal; the sponsor is not permitted to complete this task by proxy to expedite the submission.

Experience Performance Studies

Review of Performance Studies

National Competent Authorities:

- Some Member States respond to questions slowly/ long review timelines
- Process for review of PSA not in place in some Member States
- Volume of questions varies and some countries a lack of clarity on combined study can be observed
- Variable documentation requirements across Member States
  Countries generally use IVDR Annex XIII-XIV as basis for a PS- applications, but there is high variability in the local documents requested for review.

Review by Ethics Committees (EC)

- No clear review timelines for EC approval
- EC structure under national law not optimized to enable IVDR reviews

Experience Performance studies

Additional challenges for Pharmaceutical industry- Device manufacturer combined studies

Assessment- Is a Performance Study application required?

- Lack of alignment between scientific and legal aspects lead to confusion about when a Performance Study application should be required.
  Open discussions and clear guidance would be desired for the following cases
  - Investigating combination therapies: In cases where one drug is mentioned in the IVD intended use label and the second investigational drug is not.
  - Investigating monotherapies: If the drug is used within the analytical claim of a CE marked IVD, but the investigational drug is not mentioned within the IVD CE label.

  In both scenarios IVD would be used according to its analytical claim, within the same indication and with the same validated analytical method and the same indication-specific cut-off.

Experience Performance studies

Additional challenges for Pharmaceutical industry- Device manufacturer combined studies

Assessment- Is a Performance study application required?

- Stratification: Q&A IVDR-CTR guidance (MDCG) is unclear.
  Divergent feedback from HAs. Depending on the study design stratification could have an impact on patient management/ treatment decisions and a performance study submission could be required.
  However in case a stratification performed to achieve a balanced distribution in the study arms would not require a submission of a performance study.

Feedback of Health Authorities varies and the lack of guidance has led to a spectrum of interpretations across diagnostic providers and pharmaceutical companies and Health Authorities/ Ethic Committees .

Experience Performance studies

Additional challenges for Pharmaceutical industry- Device manufacturer combined studies

EU Representative:
If the clinical trial and the performance study is conducted in the EU and the Sponsor or the legal manufacturer is not located in the EU an EU representative of the Sponsor and the legal manufacturer needs to be established in the EU.

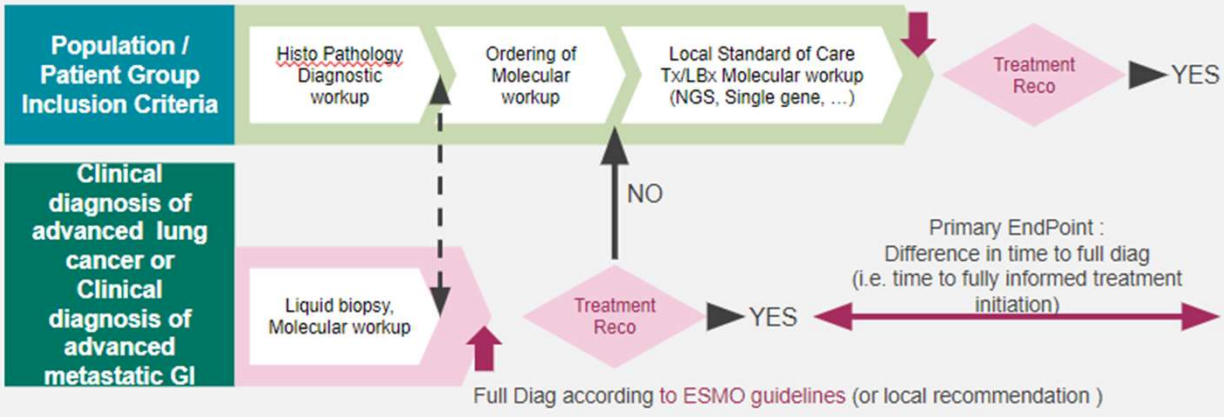
Collaboration Pharma- Device Partner:
Close collaboration between Pharma Partner and Device Partner needed: Agreed responsibilities

Invasive sample taking:
Blood draw is considered as invasive

Few examples

Liquid First Study

The primary objective for this study is to assess the impact of concomitant early use of liquid biopsy within the diagnostic pathway compared with the standard of care diagnostic pathway in participants with basic workup at enrolment (tissue biopsy not yet performed).



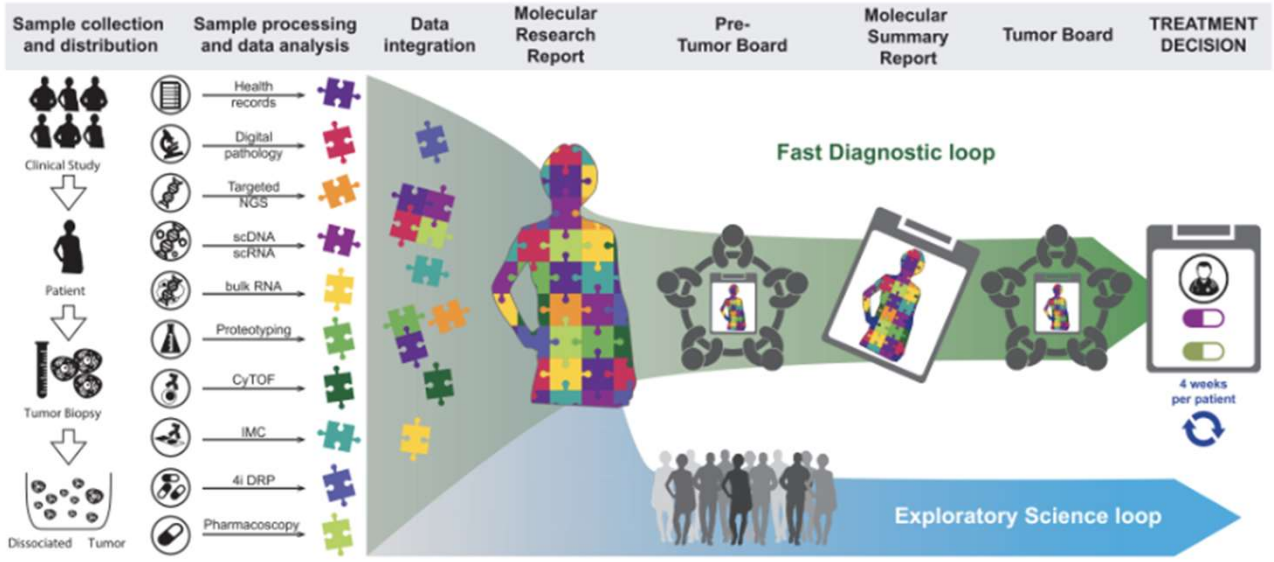
Liquid biopsy test is CE marked. The use will be within the intended use of the assay and no registrational claim will be made based on this study. No medical product is investigated.

Challenges:

- Could be seen as interventional clinical performance study, Art. 2 No. 46 IVDR., in which the test results have an impact on decisions on patient management and/or are used to guide treatment
- Classification complex, diverse feedback form EC & HA

The Tumor Profiler Study

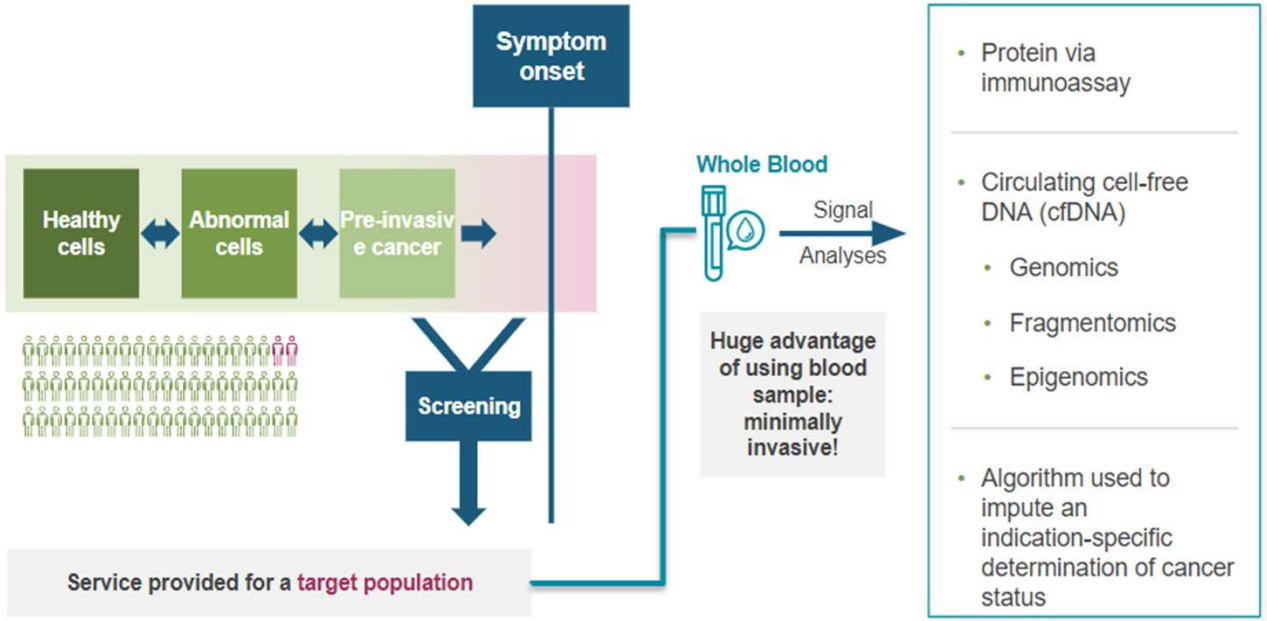
An academic observational trial combining a prospective diagnostic approach to assess the relevance of in-depth tumor profiling to support clinical decision-making with an exploratory approach to improve the biological understanding of the disease.



Challenges:

- In house developed research tests (RUO)
- Combination of 10 individual test results to predict optimal treatment path
- Academia usually does not invest in IVD development
- Limits use in prospective interventional studies

Blood based early cancer screening – preparing for the future



Blood-based cancer screening can lead to major shifts in the diagnostic and therapeutic landscape of cancer, including patient benefits due to earlier detection.

https://www.who.int/europe/news-room/fact-sheets/item/cancer-screening-and-early-detection-of-cancer

Challenges:

- Blood draw is seen as an invasive procedure- performance study submission required?
- No therapy assignment however results can help to define treatment recommendations- how should the test be classified?
- CDx development for each cancer type impossible
- How can this approach be aligned with IVDR requirements without stopping innovation?

Huge impact of IVDR on clinical trials in Europe

IVDR- impact on biomarker development and innovation

The IVDR sets high standards of quality, safety and reliability to safeguard patients and enhance innovation, which is highly welcomed.

Critical challenges for clinical trials following IVDR

Complexity in Performance Study Application process leads to:

- Delayed clinical study initiation and delayed clinical trial launch (6-12 months)
- Reduction in access to clinical trials for European patients
- Delayed access to novel therapies for European citizens

Adverse impact on other initiatives e.g. Europe's Beating Cancer Plan, Accelerating Clinical Trials in the EU (ACT EU)

Expected impact of the IVDR on clinical trials in Europe

EFPIA survey published in March 2023

82-160*	Trials currently delayed
238-420*	Trials potentially delayed over the next 3 years
6-12 months*	Most frequently reported length of delay
33`815- 24`200*	Patient impacted (patients enrolled not patients screened)
16`812- 27`400*	Cancer patients impacted
228-410*	Trial that may enroll fewer EU patients

* Range of numerical responses provided by respondents

EFPIA surveyed Members anonymously to gather data on the impact of IVDR on clinical trials and delayed patient access to those trials

- More than 2/3 of EFPIA large member companies responded
- Results represent a *conservative estimate of impact*

New European legislation designed to protect patients is delaying clinical trials for thousands of people with cancer and rare diseases (efpia.eu)

US-EU

US-EU

Differences in IVD regulatory regimes

USA:

- Unified regulatory authority under the FDA -> CDER (Rx) and CDRH (IVDs); clear IVD regulatory framework
- Co-development does not require simultaneous development of CDx and drug from beginning to end
- Biomarker discovery and test development can occur at any point during the drug development process
- Validation of CDx within clinical trials as an integrated part of drug development (FDA)
- Difference in definition of CDx: Monitor response to treatment with the therapeutic product for the purpose of adjusting treatment (e.g., schedule, dose, discontinuation) to achieve improved safety or effectiveness

US-EU

Differences in IVD regulatory regimes

Europe

- Fragmented regulatory authority (EU + EEA + UK + Switzerland)
- Investigational device trial applications are reviewed by the National Competent Authorities and Ethic Committees of each country
- Clinical trial applications follow CTR and are submitted centrally via CTIS
- CTIS not connected with EUDAMED
- Biomarker development needs to be done in accordance with IVDR (PS required if Biomarker test is used for medical decision making)
- IVD market authorization review by Notified Bodies and European Medical Agency (EMA is consulted for CDx review only)
- UK and Switzerland have their own regulations and national authorities

Summary

Summary

- The IVDR is quite a complex regulation which is overlapping with pharma regulation: **More guidance at EU level** is urgently needed.
- IVDR is representing a **new time limiting step** and developers need to consider the IVDR in the project planning accordingly.
- **Risk-Classification uncertainties & complex process** of performance evaluation applications: **More alignment needed**.
- Delays of initiation of clinical trials within the European Union for products requiring an investigational diagnostic **need to be avoided under any circumstances**.
- Recommendation: **Start early** with biomarker strategy and plan well in advance for performance studies. **Invest time in trainings and set up of the right infrastructure**.

Doing now what patients need next