Performance Considerations for Oncology NGS Panels under IVDR

AMDM 2022 Focus Meeting
Los Gatos, CA
October 20, 2022

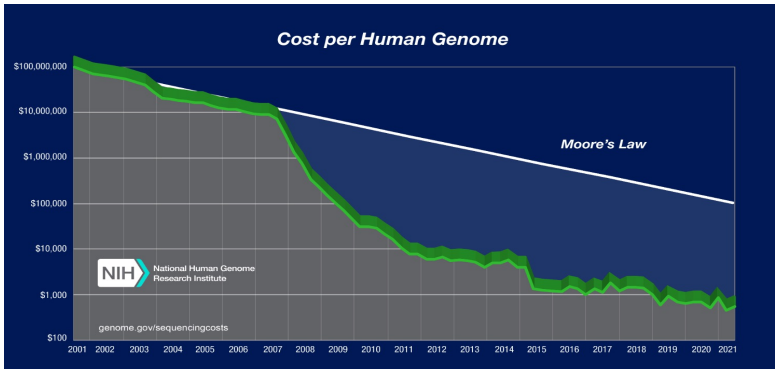
Eunice Lee, Ph.D.

Disclaimer

The views and opinions in this presentation are my own and do not represent those of Guardant Health, Inc.

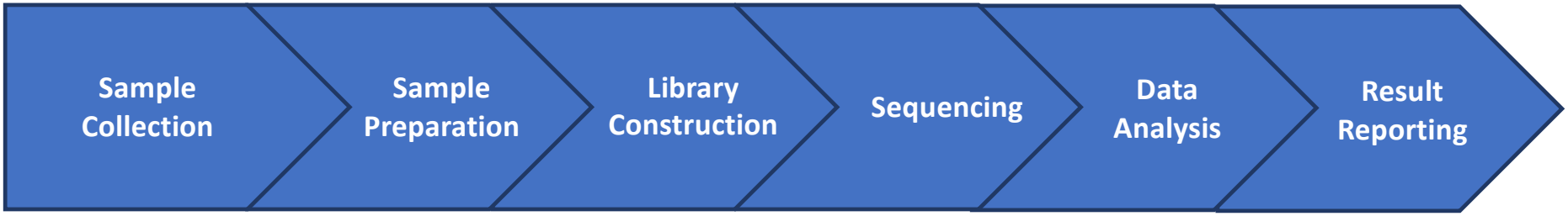
NGS is a powerful tool

- Next generation sequencing (NGS) is one of the most influential technologies in clinical science.
- NGS covers a wide range of applications—from single-gene testing to whole-genome sequencing and can be used across specimen types and indications.
- In oncology, advancements in precision medicine have been significant.
- Sequencing technology is becoming less expensive and more efficient and, as a result, NGS-based assays are increasingly employed in the clinical setting.



https://www.genome.gov/about-genomics/fact-sheets/DNA-Sequencing-Costs-Data

NGS is a complex process

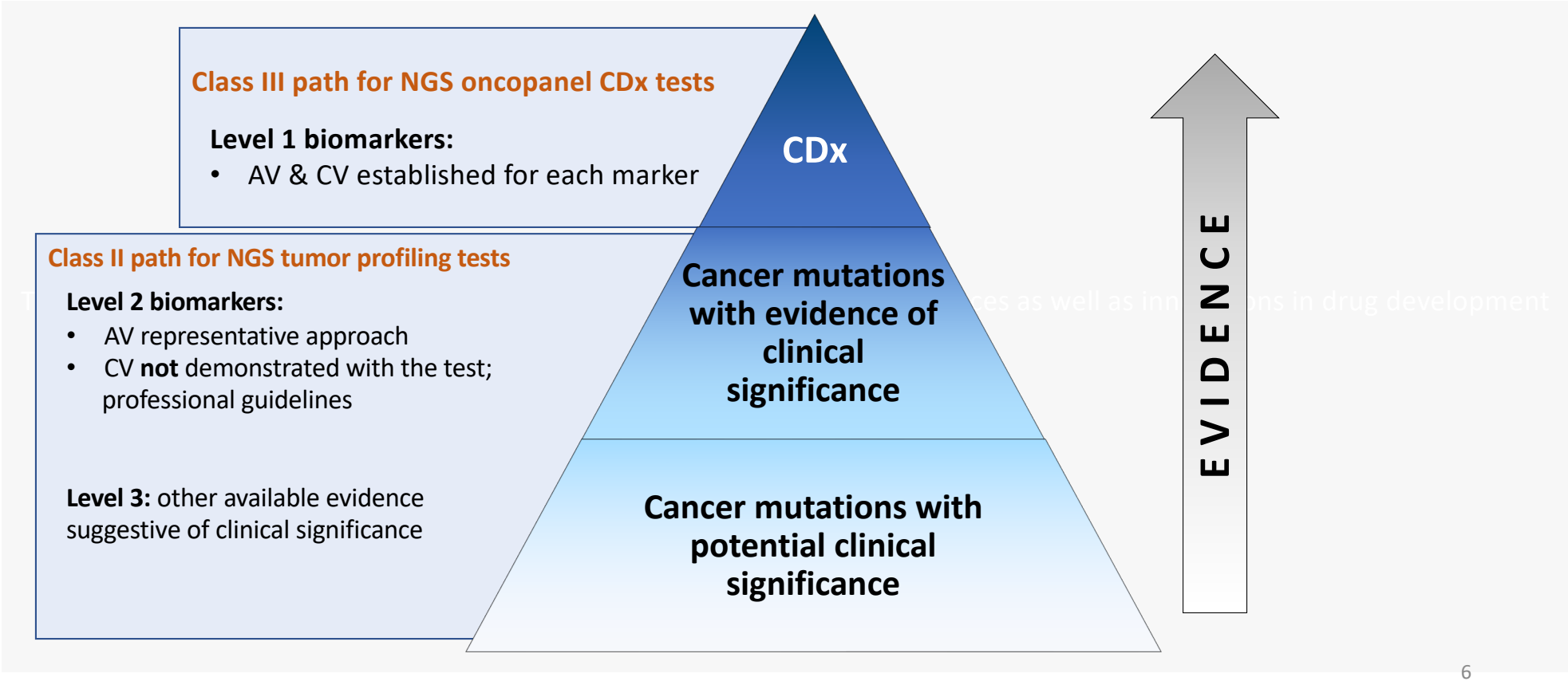


- Complex process with numerous variations in the workflow
- The entire process comprises the assay and will receive regulatory scrutiny
- Performance can differ based on variant type, genomic region, or other parameters
- Sources of error and bias can affect device performance

NGS validation considerations

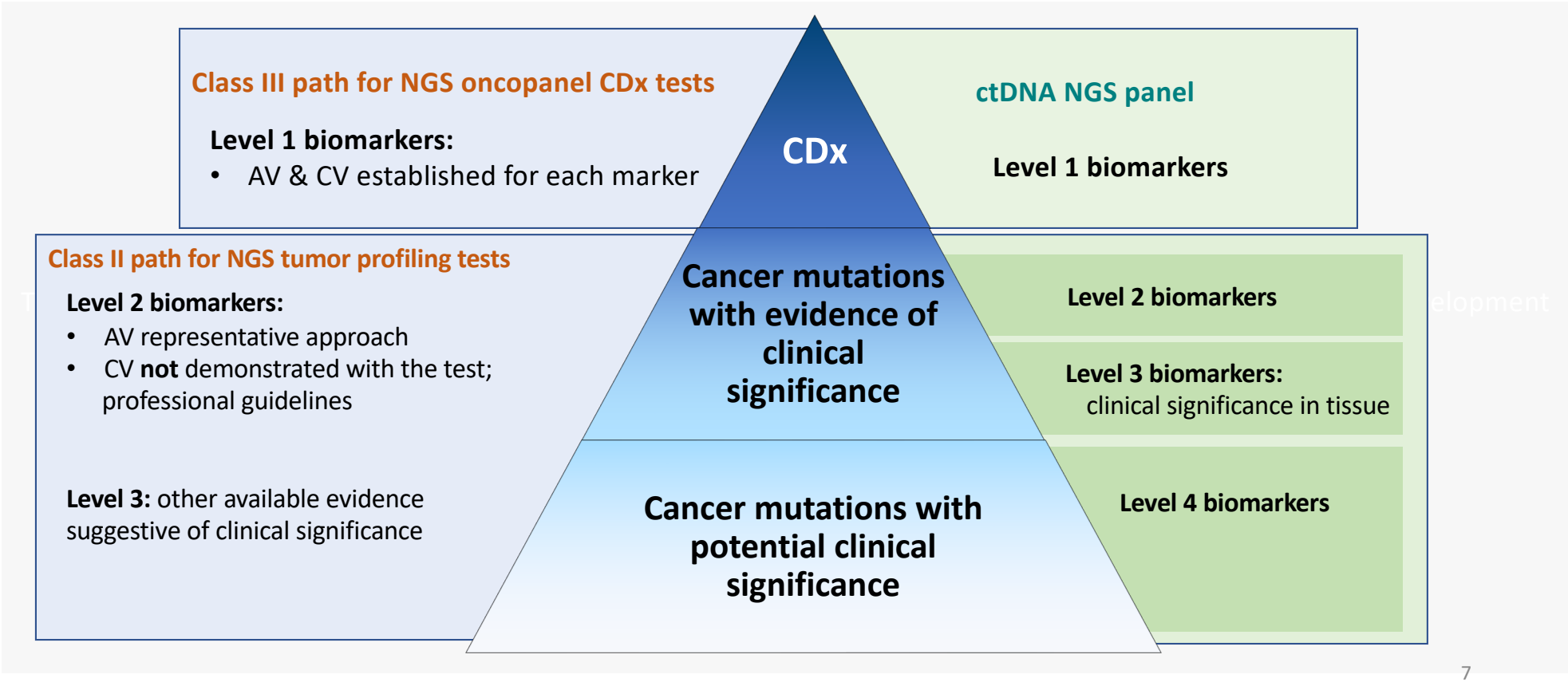
- Validation studies should be designed to support the performance characteristics and intended use of the device
- High complexity of NGS systems and the magnitude of results generate challenges
- Validation challenges:
  - Not feasible to validate all possible alterations in the reportable range
  - Clinical specimens may be limiting
  - Not feasible to assess every possible tumor type for broad indications
  - Lack of reference methods and standards

US FDA regulatory paradigm for NGS panels



Adapted from FDA Fact Sheet: CDRH's Approach to Tumor Profiling Next Generation Sequencing Tests (2017)

US FDA regulatory paradigm for NGS panels



Adapted from FDA Fact Sheet: CDRH's Approach to Tumor Profiling Next Generation Sequencing Tests

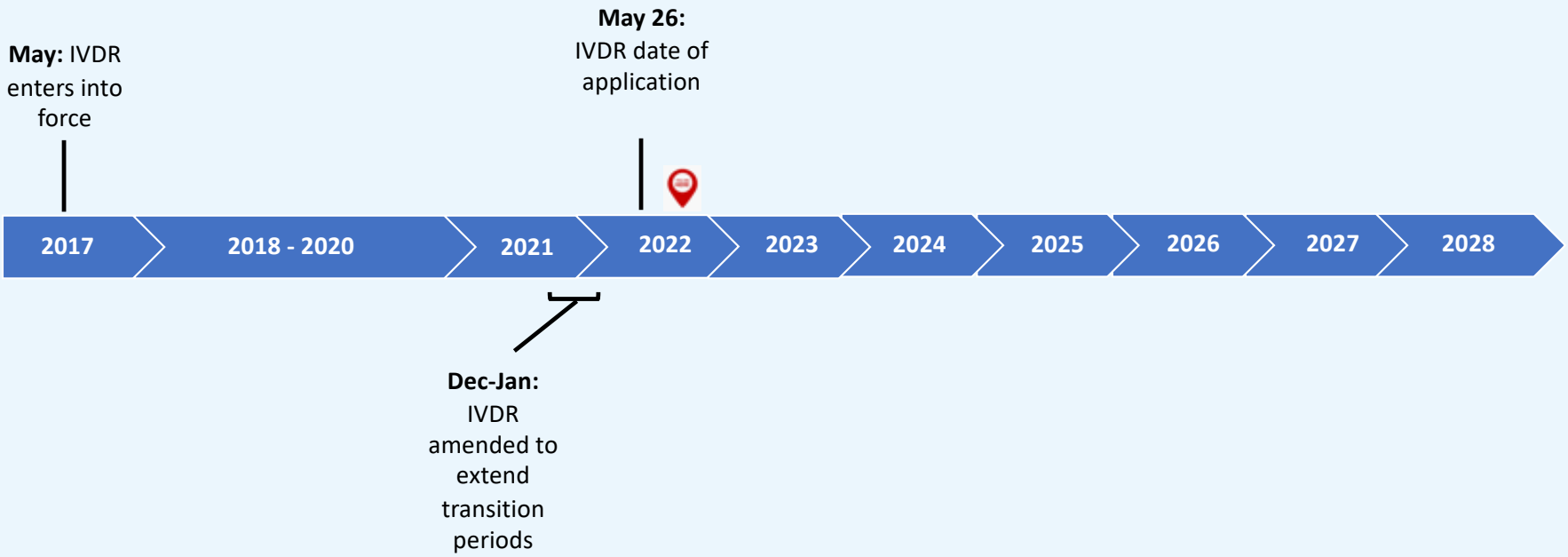
What is IVDR?

- IVDR is the new regulatory framework for IVDs that replaced the IVD Directive (IVDD). Regulation (EU) 2017/746 is law in every member state.
- It is intended to create a robust, transparent, and sustainable regulatory framework, that improves clinical safety and creates fair market access for manufacturers.[1]
- It is estimated that at least 70% of IVDs will require a conformity assessment by a Notified Body.[2]
- This has posed increased responsibility and resource needs for IVD manufacturers to comply with all applicable IVDR requirements, including:
  - more technical documentation to demonstrate safety and performance,
  - updated clinical evidence requirements,
  - a new post-market system requiring continuous evaluation during a product's life cycle,
  - EUDAMED requirements…
- Some devices CE marked under IVDD are eligible for transition period under IVDR.

1 https://health.ec.europa.eu/sites/default/files/md_newregulations/docs/ivd_manufacturers_factsheet_en.pdf
2 https://www.medtecheurope.org/news-and-events/press/medtech-europe-welcomes-the-in-vitro-diagnostic-medical-devices-regulation-and-urges-continued-work-to-deploy-the-new-regulatory-system/

Transition from IVDD to IVDR

Regulation (EU) 2017/746 is law in every member state



IVDR device classification for oncology NGS

Article 47

Devices are divided into classes A, B C, and D, taking into account the intended purpose and inherent risks.

Annex VIII, Rule 3

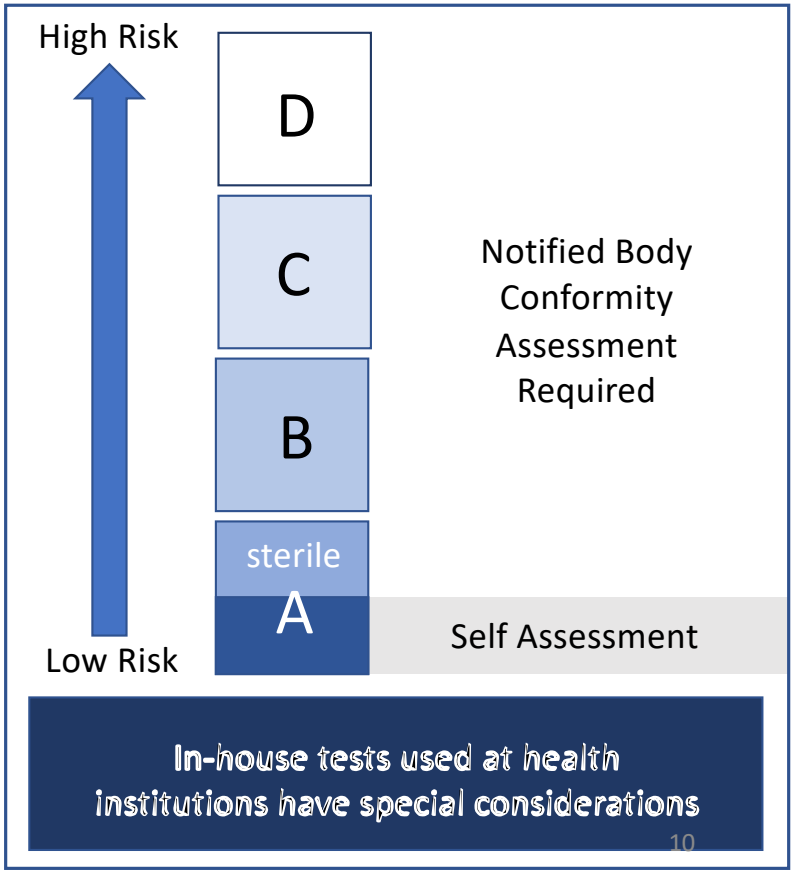
Devices are classified as **class C** if intended:

(f) to be used as companion diagnostics;

(h) to be used in screening, diagnosis, or staging of cancer;

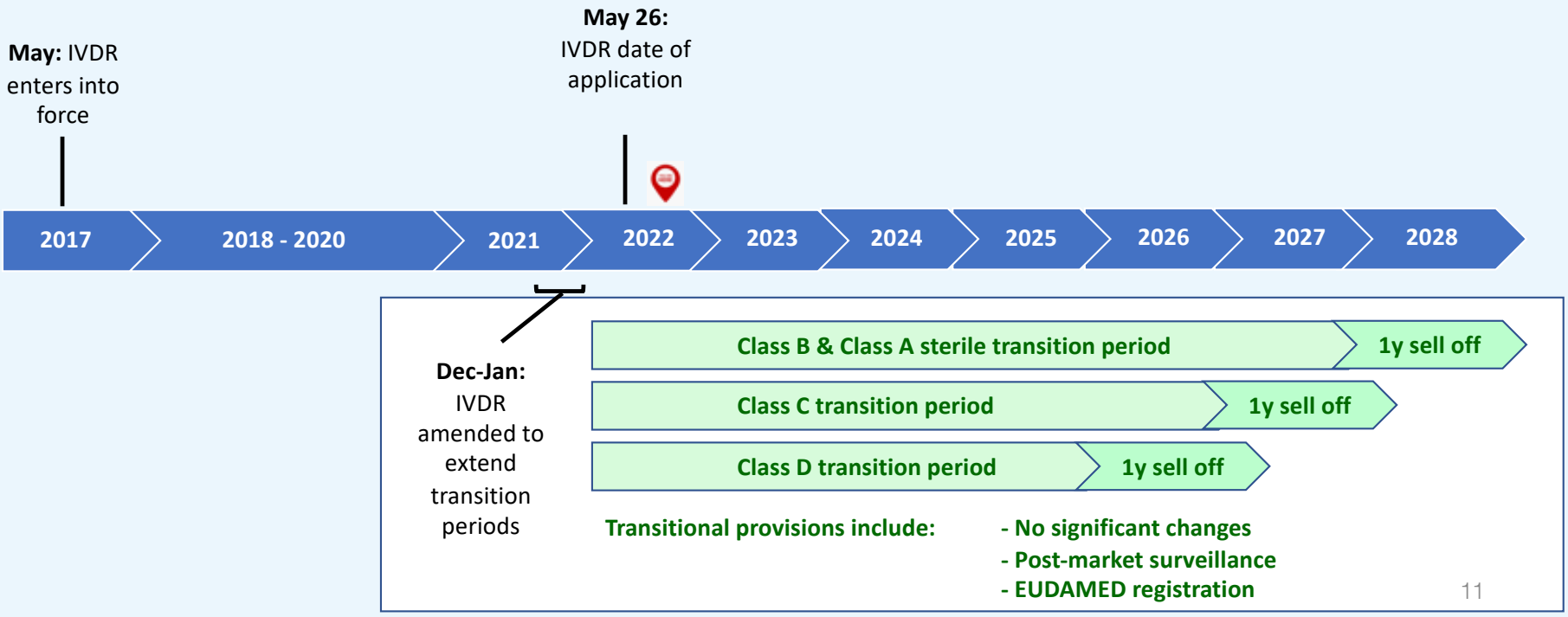
(i) for human genetic testing

Subject to conformity assessment based on a quality management system and assessment of technical documentation (*Annex IX*)



Transition from IVDD to IVDR

Regulation (EU) 2017/746 is law in every member state



IVDR technical documentation

There is increased complexity to capture validation data and building extensive dossiers; Technical Documentation should follow Annexes II and III

Annex II – Technical Documentation

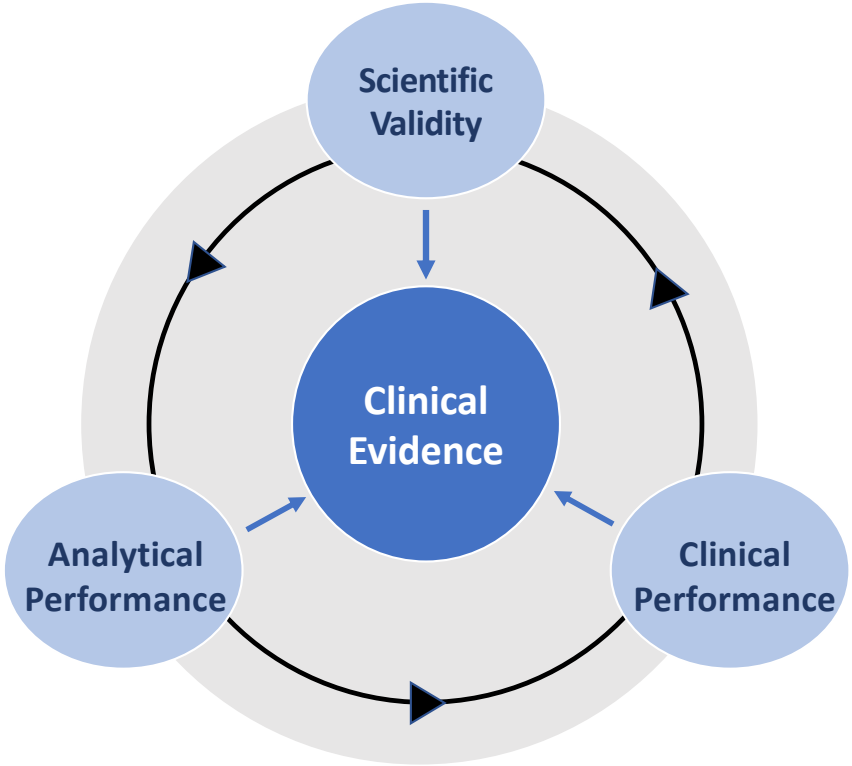
- Device description and specification
- Information supplied, such as labeling and packaging, as applicable
- Design and Manufacturing information
- General Safety and Performance Requirements
- Benefit-Risk Analysis and risk management
- Product Verification and Validation – **Performance Evaluation**
- Summary of Safety and Performance (for class C and D)

Annex III – Technical Documentation on Post-Market Surveillance

- Post-market Surveillance plan
- Post-market Surveillance report
- Periodic Safety Update report (PSUR) (for class C and D) – updated at least annually

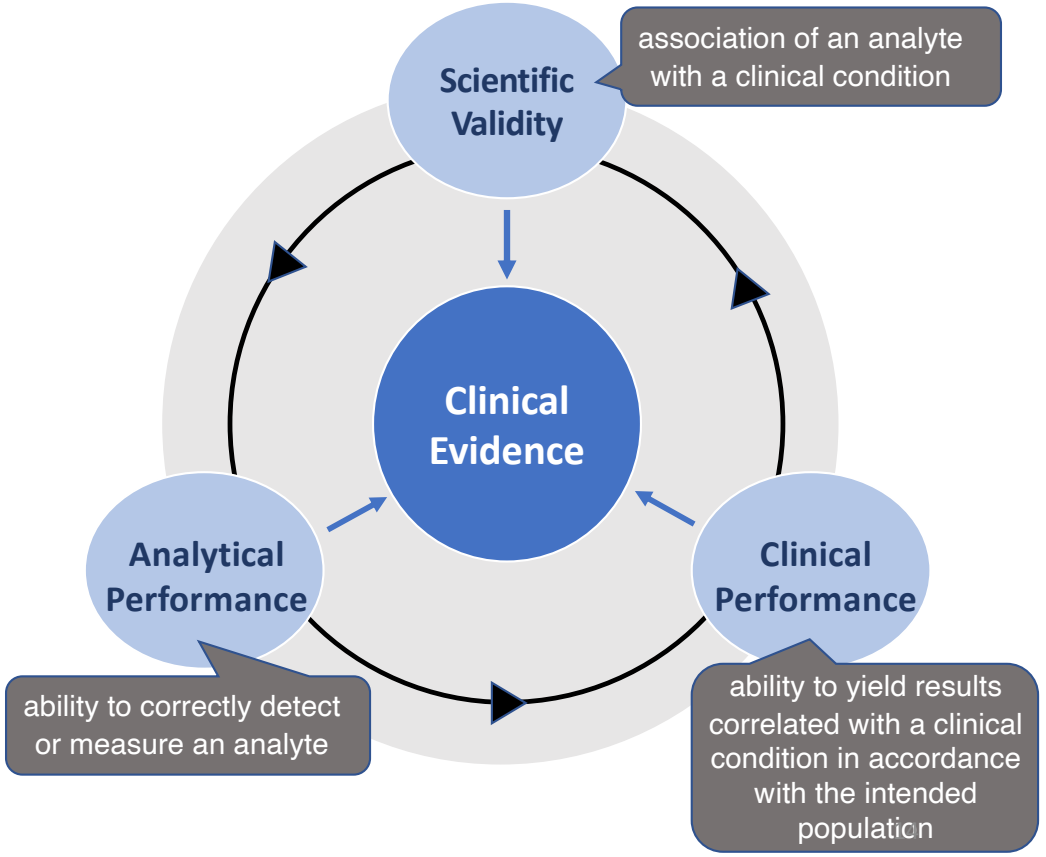
Performance evaluation

- Continuous process to generate and maintain clinical evidence to support the product's intended purpose.
- Clinical evidence is based on data on scientific validity, analytical performance, and clinical performance.



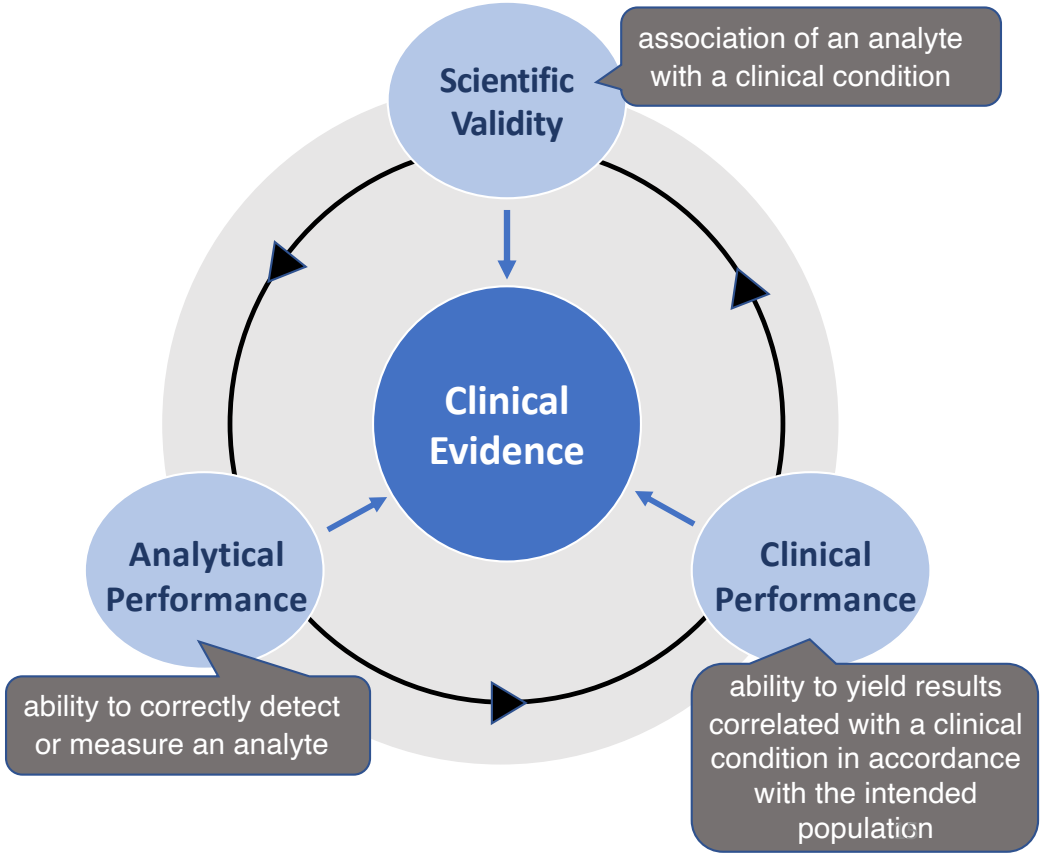
Performance evaluation

- Continuous process to generate and maintain clinical evidence to support the product's intended purpose.
- Clinical evidence is based on data on scientific validity, analytical performance, and clinical performance.



Performance evaluation

- Continuous process to generate and maintain clinical evidence to support the product's intended purpose.
- Clinical evidence is based on data on scientific validity, analytical performance, and clinical performance.
- Demonstration of compliance with the general safety and performance requirements should be based on clinical evidence.



IVDR performance characteristics

Annex I, Chapter II

Analytical Performance

Analytical sensitivity
Analytical specificity
Trueness (bias)
Precision (repeatability and reproducibility)
Accuracy
Limits of detection and quantitation
Measuring range
Linearity
Cut-off
Specimen Collection and handling
Endogenous and exogenous interference
Cross-reactions

Clinical Performance

Diagnostic sensitivity
Diagnostic specificity
Positive predictive value
Negative predictive value
Likelihood ratio
Expected values in normal and affected populations

Annex II

Stability

Final thoughts

- Regulation of clinical NGS tests is relatively immature in the EU.
- There are no defined requirements for performance studies; though justification is needed to account for the intended use and performance requirements of the device.
- Under IVDR, Notified Bodies are playing an important role to assess and monitor whether devices comply with the safety and performance requirements.
- There is uncertainty about performance expectations for NGS panels in oncology. Regulatory experience is needed to understand the regulatory principles and expectations. This is key to develop efficient strategies moving forward.

THANK YOU