Precision Medicine`s Journey to Transforming Healthcare

ICPerMed Workshop

Advancing Personalised Medicine through Technology Development

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Siena/, 15th November 2023

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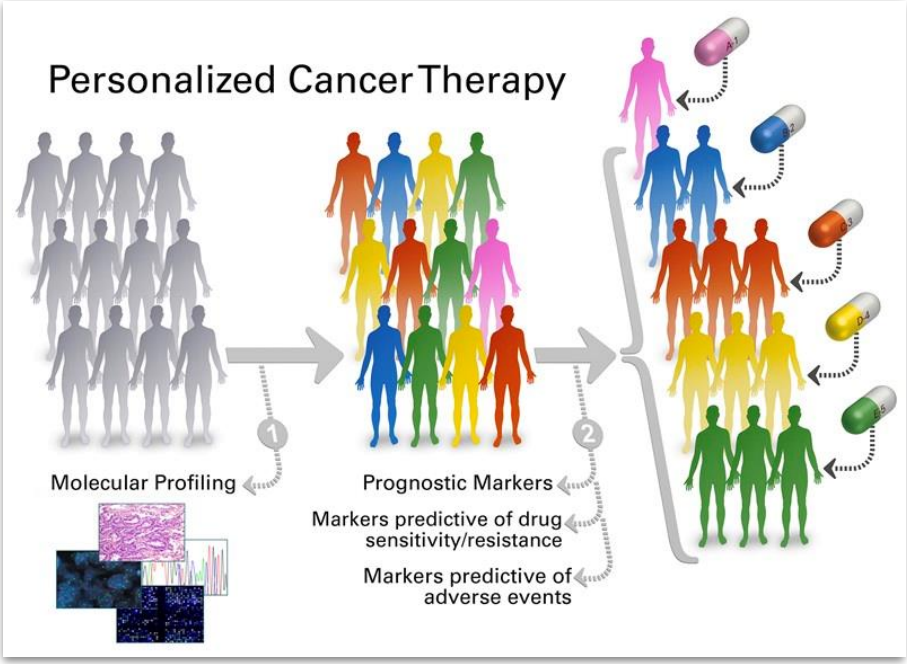
Delivering on the “concept” of Personalised Medicine



Dumbrava and Meric-Bernstam, 2018, doi: 10.1101/mcs.a001578

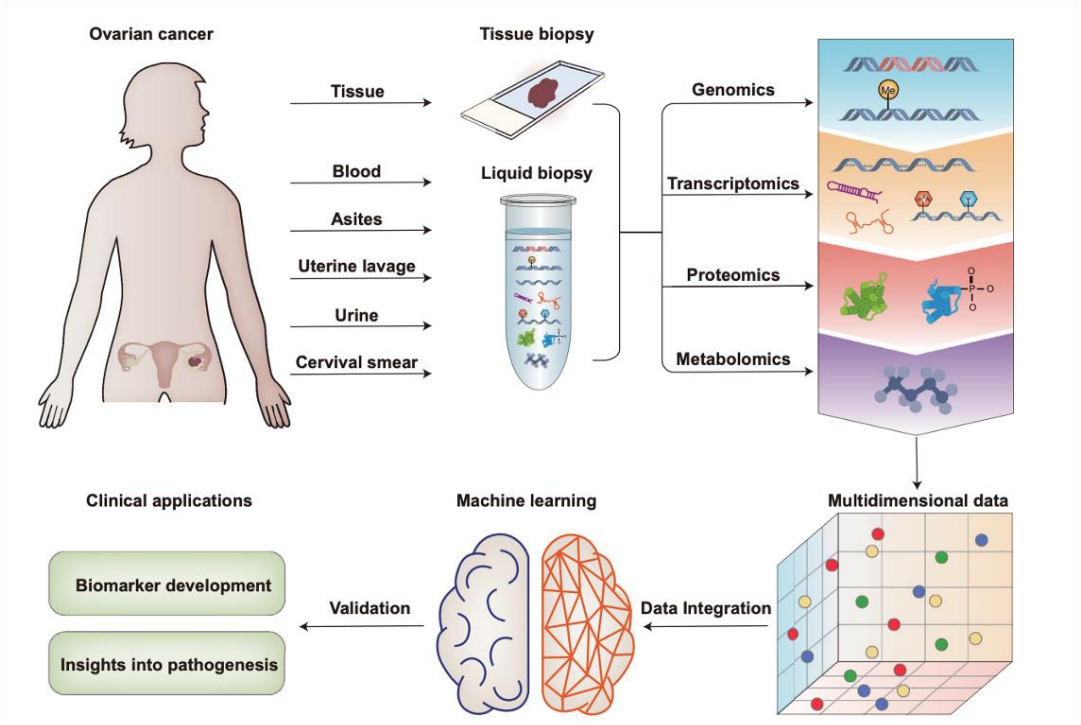
PERSPECTIVE | FOCUS
https://doi.org/10.1038/s41591-022-01717-2
nature medicine

Delivering precision oncology to patients with cancer

Joaquin Mateo[1,18], Lotte Steuten[2,3,18], Philippe Aftimos[4], Fabrice André[5], Mark Davies[6], Elena Garralda[1], Jan Geissler[7], Don Husereau[8], Iciar Martinez-Lopez[9], Nicola Normanno[10], Jorge S. Reis-Filho[11], Stephen Stefani[12], David M. Thomas[13], C. Benedikt Westphalen[14,15,19] and Emile Voest[16,17,19]

“...the delivery of its full potential and impact on clinical practice depends greatly on ensuring ***wide and equal patient access to diagnostic technologies and therapeutics***, beyond a few academic centers in privileged countries…”

Advanced diagnostic 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

IVDR covers more than just Companion Diagnostics

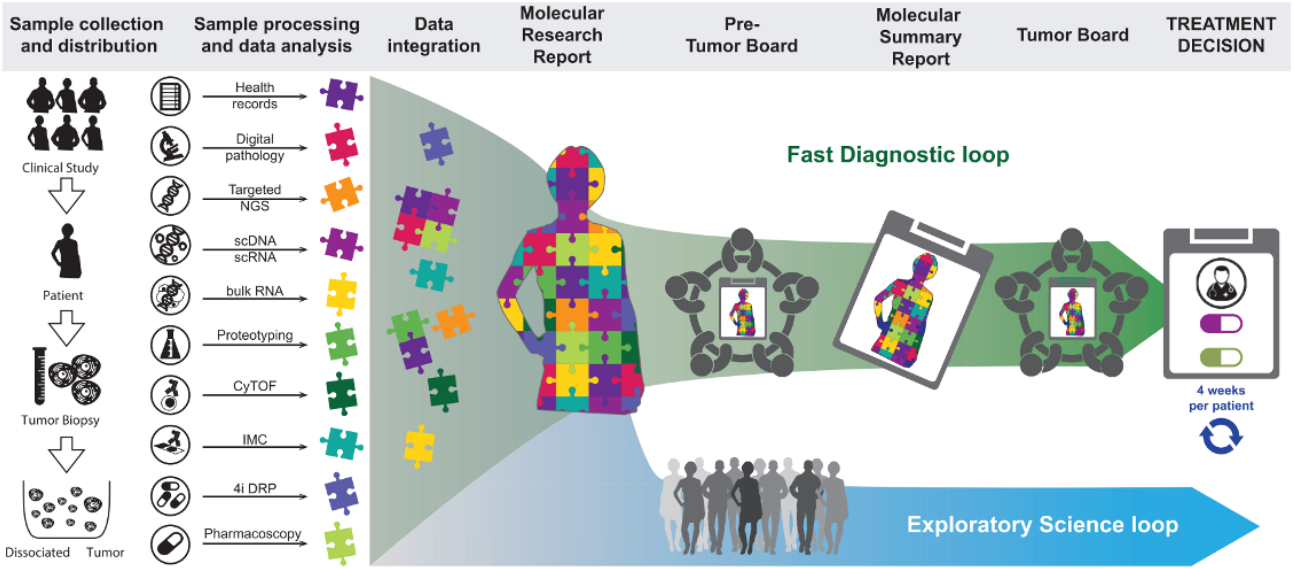
Scientific validity + **Analytical performance** + **Clinical performance** = **Clinical evidence Performance evaluation report** CE

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**

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.

The Tumor Profiler Study - use of RUO tests

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.

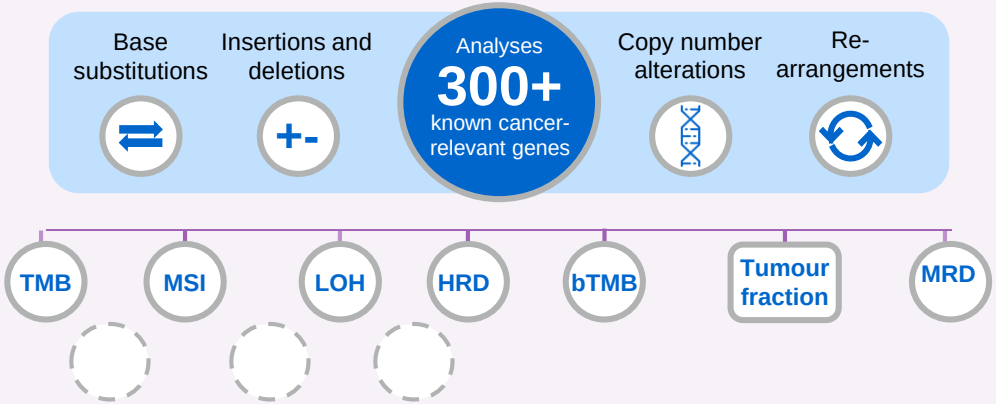


Irmisch et al., Cancer Cell 39, March 8, 2021

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**

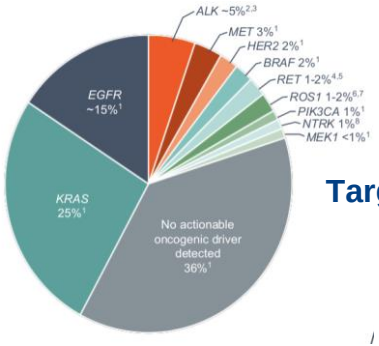
Comprehensive genomic profiling has revolutionised oncology



CGP is a next-generation sequencing approach, that detects novel and known variants of the four main classes of genomic alterations and genomic signatures[1–3]

Tumour genomic profiling can

- refine **cancer subtype** classification,
- identify which patients are most likely to **benefit from systemic therapies**
- screen for **germline variants** that influence heritable cancer risk.



Targetable mutations in lung cancer

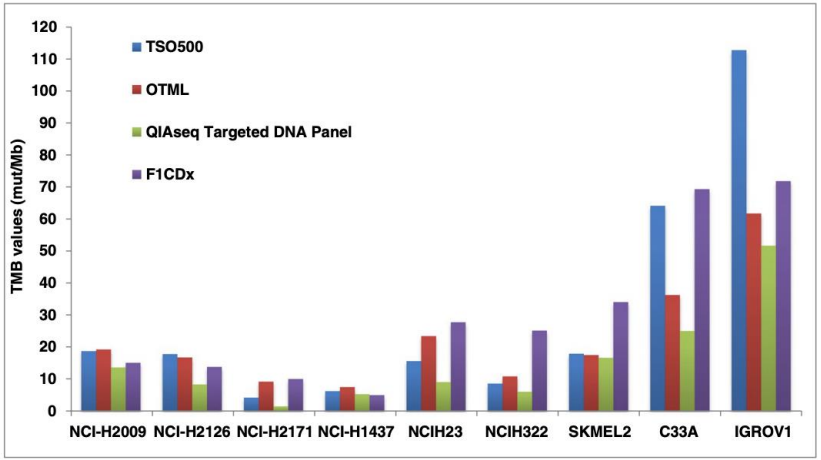
bTMB, blood tumour mutational burden; CGP, comprehensive genomic profiling; cfDNA, cell-free DNA; LOH, loss of heterozygosity; MSI, microsatellite instability; TMB, tumour mutational burden, MRD, minimal residual disease

1. Foundation Medicine. FoundationOne CDx. Technical specifications. Link. (Accessed 9 June 2020); 2. Woodhouse R *et al. J Clin Oncol* 2020;38:e13685-e13685; 3. Foundation Medicine. FoundationOne Liquid CDx Technical specifications: Link. (Accessed 16 Sep 2020); 4. Choudhury AD *et al. JCI insight* 2018;3:e122109.

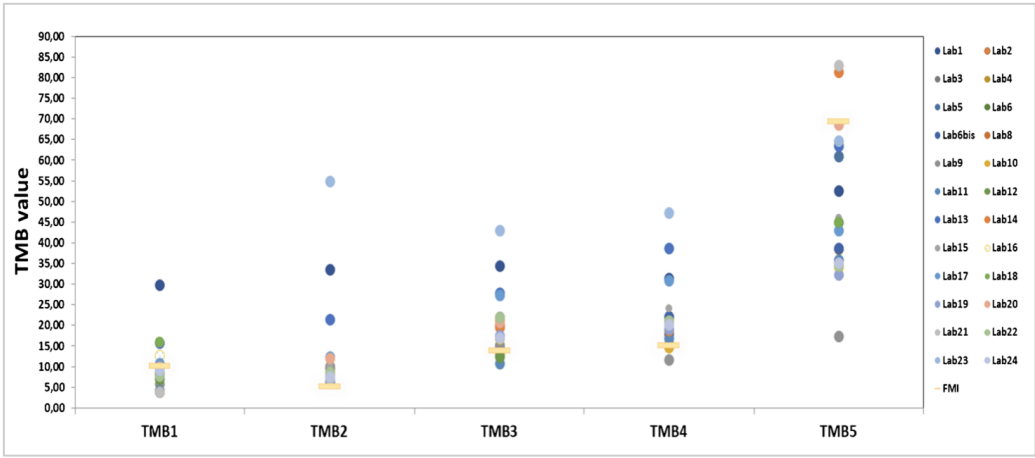
High inter-laboratory variability in *Tumor Mutational Burden* (TMB) testing as compared with the F1CDx assay

International Quality Network of Pathology (IQN Path) organised a pilot for TMB testing with the collaboration of different academic partners (AIOM, Gen&Tiss, ESP, GenQA, EMQN, cIQc, RCPA Quality Assurance Programs). The main aim of this pilot was the validation of the materials and the procedures for the EQA of this complex biomarker.

Results of the internal validation phase on 9 cell lines.



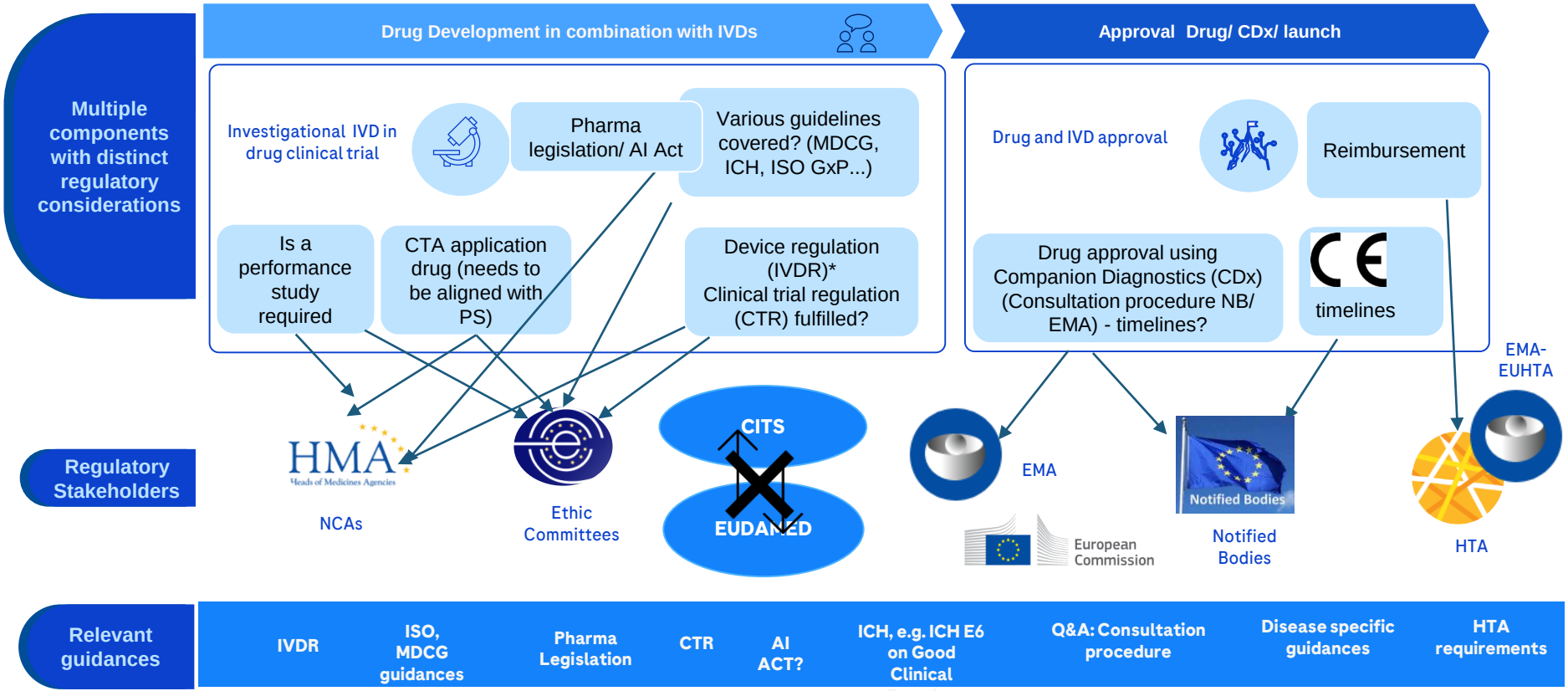
Summary of results for TMB test submitted by different laboratories



Differences in TMB testing could result in a misclassification of the samples in high vs low TMB.

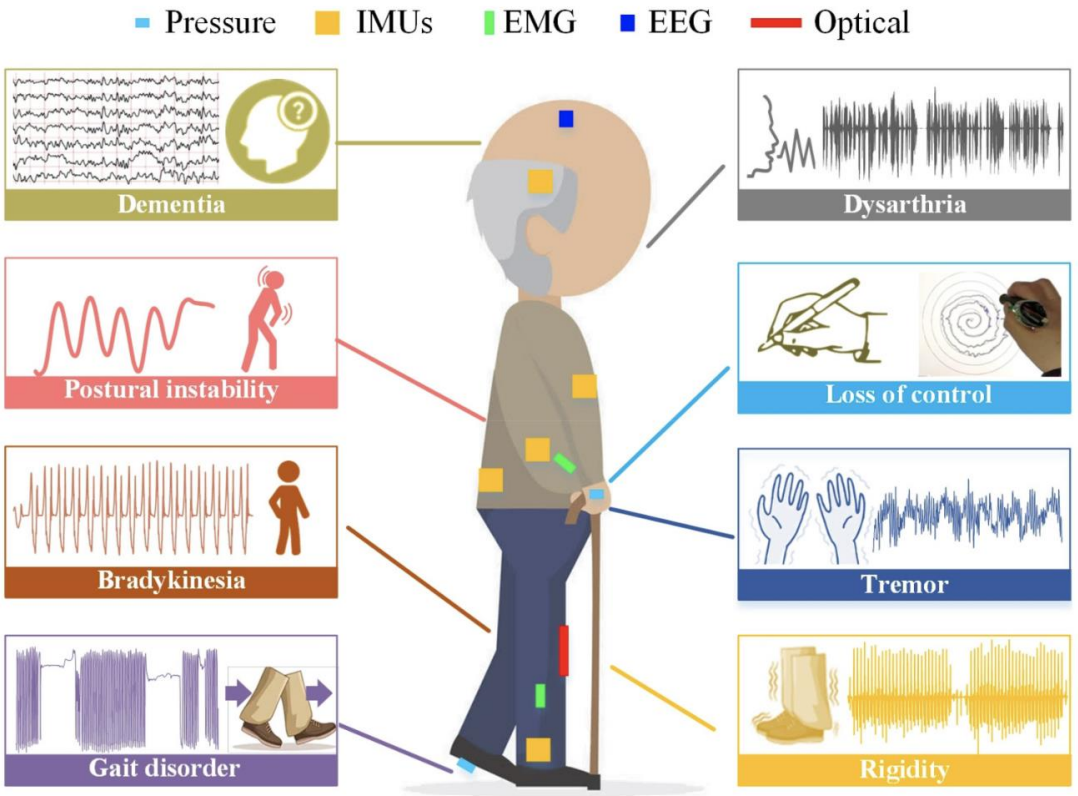
Riziero et al., Virchows Archiv (2023) 482:347–355

Regulatory challenges IVDs



CTA = Clinical Trial application; AI = Artificial Intelligence; PS= Performance study; EC= Ethic Committees; EMA= European Medicines Agency; HTA= Health Technology Assessment Body; NCA= National Competent Authority

Wearable sensors applied to the human body for neurodegenerative diseases (NDDs) diagnosis



https://journals.sagepub.com/doi/full/10.1177/20552076231173569

Syde: a wearable device in Duchenne Muscular Dystrophy and a qualified endpoint

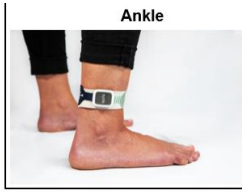
- Syde, formerly known as «Actimyo» is a **wearable device designed to monitor ambulation in DMD during normal daily living** in clinical trials
- **EMA qualification of SV95C**, a **measure of ambulation in DMD patients for use as a secondary endpoint**
- **Capture of movement in real-world**, enabling **continuous measurement of functional ability**


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

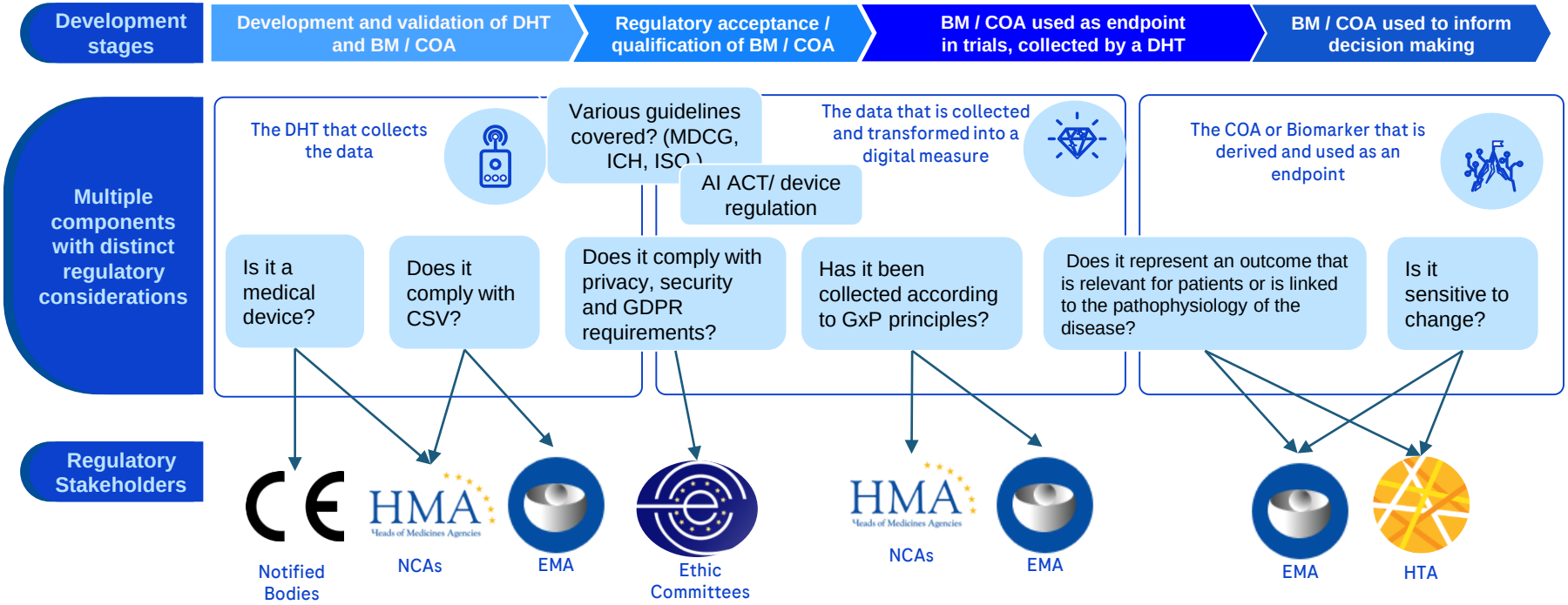
26 April 2019
EMA/CHMP/SAWP/178058/2019
Committee for Medicinal Products for Human Use (CHMP)

Qualification opinion on stride velocity 95th centile as a secondary endpoint in Duchenne Muscular Dystrophy measured by a valid and suitable wearable device*

Dimensions	Apple Watch 5	ActiMyo v4.0
Weight (g)	36.0	13.5
Dimension (mm)	38 x 44	31 x 36
Thickness (mm)	10,8	9.0

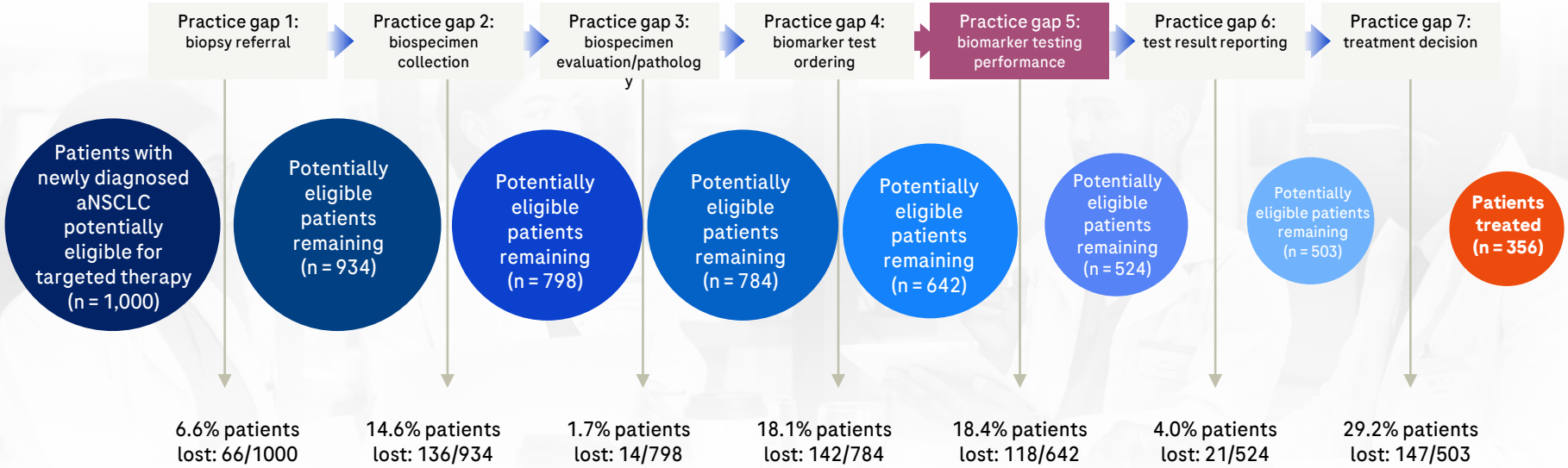


Regulatory challenges digital endpoints



BM= Biomarker COA = Clinical Outcome Assessment; CoI = Concept of Interest; CoU = Context of Use; CSV= Computer System Validation; IU = Intent of Use, DHT = Digital Health Technology; EC= Ethic Committees; EMA= European Medicines Agency; HTA= Health Technology Assessment Body; NCA= National Competent Authority;

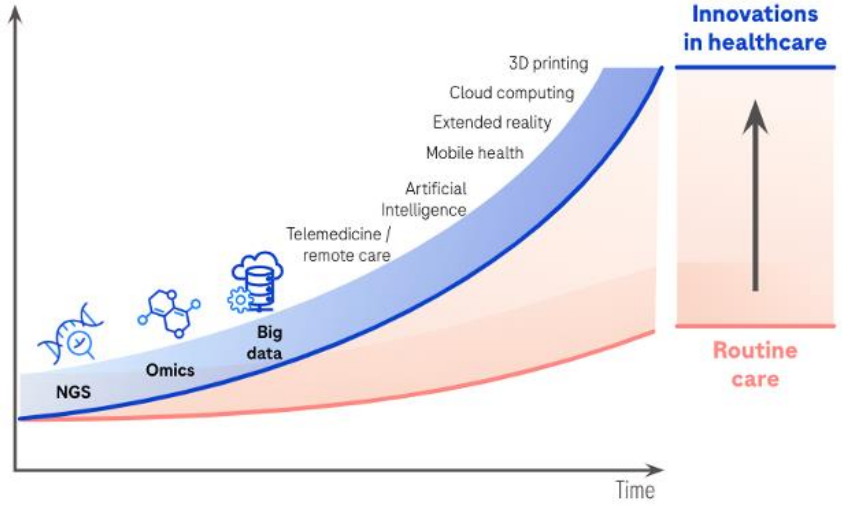
Impact of clinical practice gaps on the delivery of precision oncology for advanced NSCLC



64% of potentially eligible patients with advanced NSCLC are not benefiting from precision oncology therapies. Addressing practice gaps and building sustainable care infrastructures are critical to deliver on the promise of precision medicine.

Sadik et al., JCO 2022

Get the foundational elements right to accelerate implementation of innovation in routine care



Partial diffusion of innovative practices
vs.
broad access and scale

Multi-stakeholder collaboration to

align on **quality standards** and **patient centricity**

create a sandbox mechanism for future **novel healthcare and regulatory solutions.**

to ensure **care infrastructures** are in place to **facilitate fast access and reimbursement** to healthcare innovations.

Doing now what patients need next