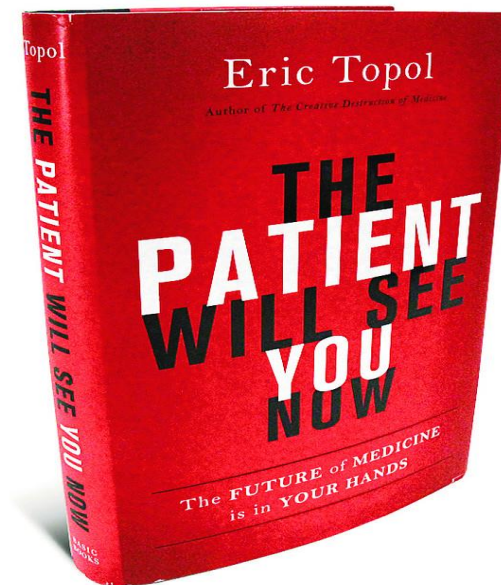
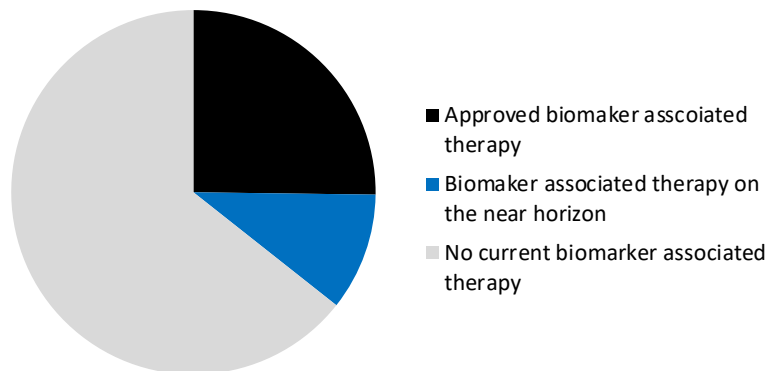


Workshop Report on the Critical role of Biomarkers in delivering drug development-related precision oncology



Mark Lawler (Co-Chair)

Professor of Digital Health, Queen's University Belfast; Board Member Cancer Drug Development Forum;

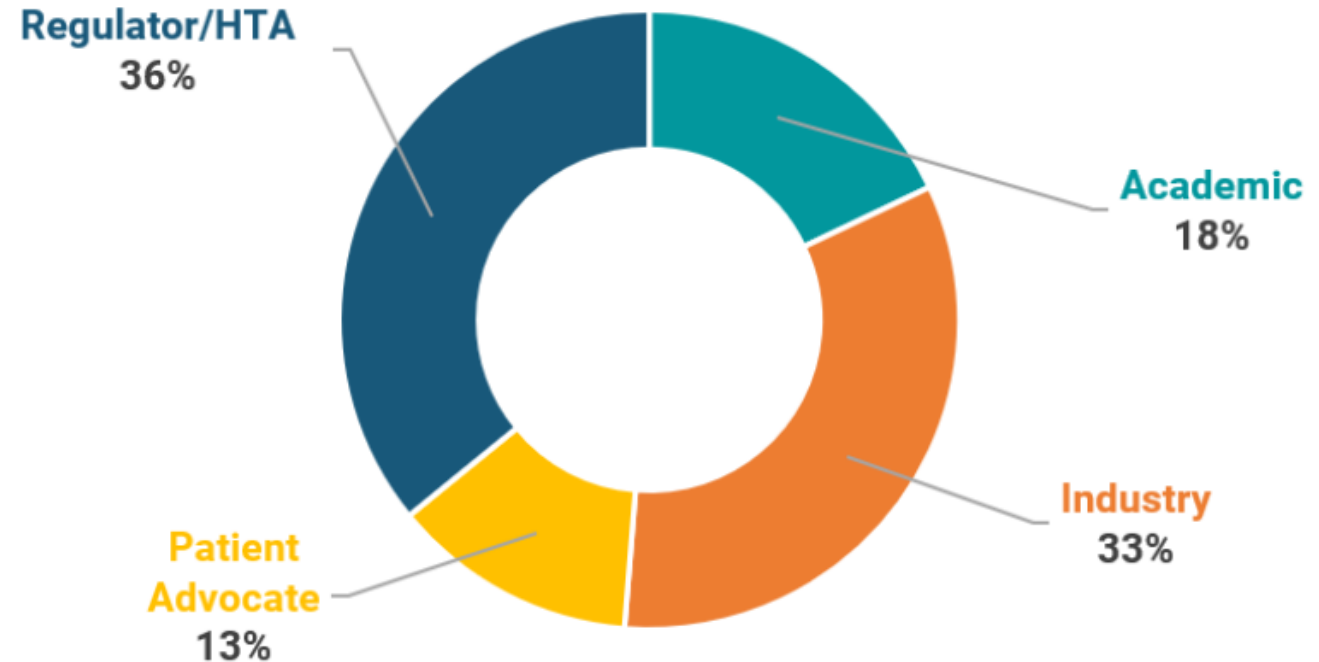
CDDF Annual Conference February 2024 Noordwijk aan Zee, Netherlands

The Critical role of Biomarkers in delivering drug development-related precision oncology

- **Multi-stakeholder CDDF Workshop**
- 13-14 November 2023 Amsterdam, Netherlands
- **12 Speakers/ 8 Chairs**
- **Attendees = 176**
- **Breakdown of Attendees**



Onsite Participants & Speakers



The above graph illustrates the distribution of online and onsite speakers/chairpersons/panelists alongside onsite attendees.

134

ONLINE
ATTENDEES

42

IN-PERSON
ATTENDEES

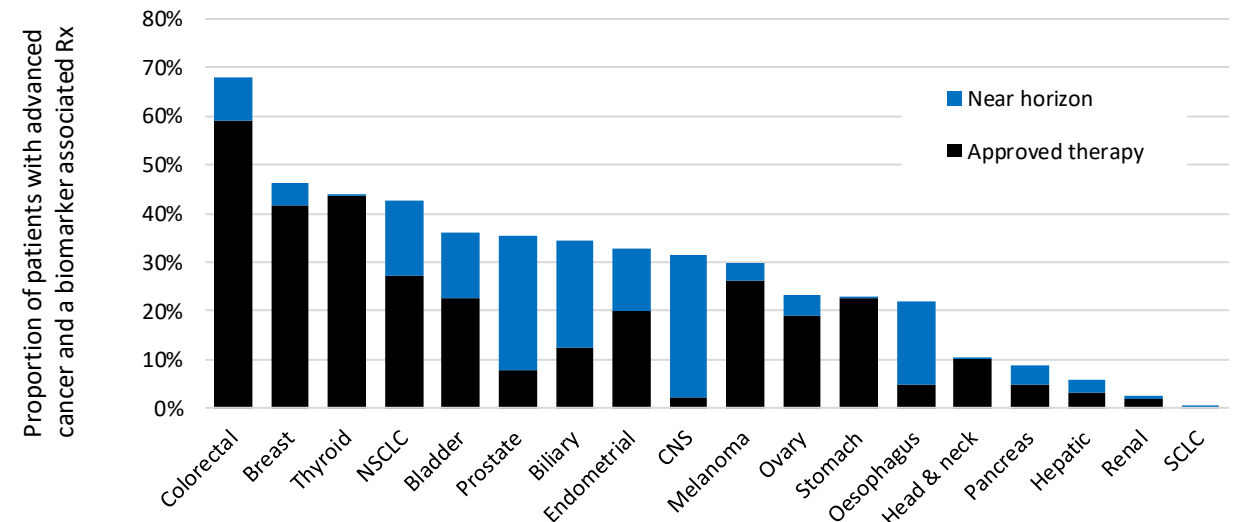
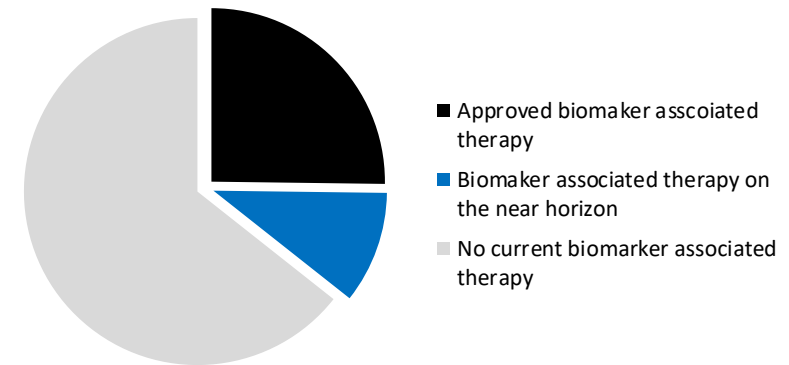
Precision Genomic Testing: the key to unlocking the potential of Precision Oncology

- *The Primacy of Precision Genomic Testing in Precision Oncology*
- **Empower** the selection of which patients will respond to a more **personalised treatment** while sparing non-responders the therapy-related toxicity
- Precision Genomic Testing must be **embedded into the real world of oncology delivery**
- Testing must be **implemented across Europe**, with the intended aim of narrowing, not widening the inequity gap for patients.
- **Cancer patients** must be placed unambiguously at the **centre of a cancer biomarker informed precision oncology care agenda**

Normanno N, Apostolides K, de Lorenzo F, Beer PA, Henderson R, Sullivan R, Biankin AV, Horgan D, Lawler M. [Cancer Biomarkers in the era of precision oncology: Addressing the needs of patients and health systems.](#) *Semin Cancer Biol.* 2021 10:S1044-579X(21)00214-5.

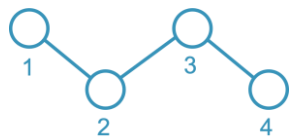
Cancer Biomarkers and Precision Genomic Testing go mainstream

- At the end of 2019, there were **70 approved cancer drugs which required or recommended predictive biomarker tests**, with this number increasing at a rate of 5-10 new approvals per year.
- At present, nearly a **third of patients** with advanced cancer will have a specific malignant subtype that is **eligible for a biomarker-informed systemic therapy**



Navigating the complex diagnostic and treatment pathway can lead to inefficiencies and hinder unlocking the full potential of Precision Medicine

Although precision oncology is promising, currently, patient access to better treatments is still **significantly impeded** because of **ill-prepared diagnostic and clinical ecosystems**



4.5 years

is the average delay of a diagnostic assay to be available and adopted¹



>20%

of cancer patients have inferior response due to failure of receiving a treatment matched to their genomic profile^{3,4}



Complexity

in clinical care pathways involving multiple steps and requiring optimal interaction and awareness among different stakeholders



High variability

in the levels of biomarker testing and appropriate treatment decisions across different practice settings, tumor types and biomarkers

Sources

1. Diaceutics PM readiness report 2019
2. Diaceutics analysis
3. <https://pubmed.ncbi.nlm.nih.gov/33009371/>
4. <https://pubmed.ncbi.nlm.nih.gov/31888672/>

Regulatory Challenges

- **Regulatory issues** may also limit Europe-wide implementation of PGT
- In the EU, cancer biomarkers and PGT were regulated under the **In Vitro Diagnostics Directive (IVDD)**.
- However, this is being superseded by the **In Vitro Diagnostics Regulation (IVDR)**, which may have significant implications for cancer biomarkers, particularly in their validation.
- A potentially contentious issue is the position of **Laboratory Designed Tests (LDTs)** which complement the commercially manufactured **Diagnostic Test kits, (CDx)**.
- Under IVDD, LDTs were approved, but their status is less clear under the new regulation.
- **Could lead to significant shortages of cancer biomarkers** that comply with the regulation,
- Unintended consequences of **inhibiting diagnostic innovation** and adversely impacting on the care of the cancer patient.
- IVDR will come into full effect **shortly**, so there is a **need to act quickly and decisively**.

Putting the patient at the Centre of Personalised Medicine

Personalised Medicine: A Guide for Patients



AN INITIATIVE OF THE EUROPEAN CANCER PATIENT COALITION



**QUEEN'S
UNIVERSITY
BELFAST**



European Cancer
Patient Coalition

Keeping the Patient at the Centre of Personalised Medicine

- **Personalised Medicine – A Guide for Patients**
 - An Initiative of the European Cancer Patient Coalition
- A **Resource** that **specifically addresses** the **needs of patients**
- Important that the cancer patient is **well informed** as to the **opportunities and challenges** that personalised medicine and immunotherapies present
- **Empower** patients to make the **best and most informed decisions** about their personal care

<https://ecpc.org/wp-content/uploads/2020/12/ECPC-personalised-medicine-booklet-V.pdf>



European Cancer
Patient Coalition

Cancer Biomarkers and Precision Genomic Testing: Cost and Value¹

- Cost effectiveness of **Precision Genomic Testing**
- **Comprehensive health economic analysis** undertaken in colorectal and lung cancer
- **Colorectal:** Health economic assessment **supported use of PGT** in certain scenarios ²
- **Lung:** PDT guided therapy versus “Therapy-for-All” approach – **PGT was cost effective in 100% of scenarios**³
- Both studies emphasised the **need for more robust health economic evaluation** approaches, **underpinning value-based care** and enhanced outcomes for cancer patients.

¹Lawler M, French D, Henderson R, Aggarwal A, Sullivan R. [Shooting for the Moon or Flying Too Near the Sun? Crossing the Value Rubicon in Precision Cancer Care](#). *Public Health Genomics*. 2016;

²Henderson R, French D, Sullivan R, Maughan T, Clarke M, Lawler M. [Molecular biomarkers and precision medicine in colorectal cancer: a systematic review of health economic analyses](#). *Oncotarget*. 2019

³Henderson R, Keeling P, French D, Smart D, Sullivan R, Lawler M. [Cost-effectiveness of precision diagnostic testing for precision medicine approaches against non-small-cell lung cancer: A systematic review](#). *Mol Oncol*. 2021

Cancer Biomarkers and Precision Genomic Testing: Cost and Value

- When considering biomarkers and genomic testing in Europe, there is an absolute need to **ensure that PGT is available and is reimbursed appropriately**, and not just in the elite countries of western Europe, but to all of Europe.
- A systematic review and meta-analyses found that there are **socio-economic inequalities** in predictive biomarker tests and biological and precision therapy utilization.
- Issues such as the **cost** (personal, clinical, financial) of “**not testing**” are of paramount importance, but are currently not well defined or understood.

Norris RP, Dew R, Sharp L, Greystoke A, Rice S, Johnell K, Todd A [Are there socio-economic inequalities in utilization of predictive biomarker tests and biological and precision therapies for cancer? A systematic review and meta-analysis.](#) *BMC Med.* 2020 18:282.

Revisiting the economics of Precision Medicine

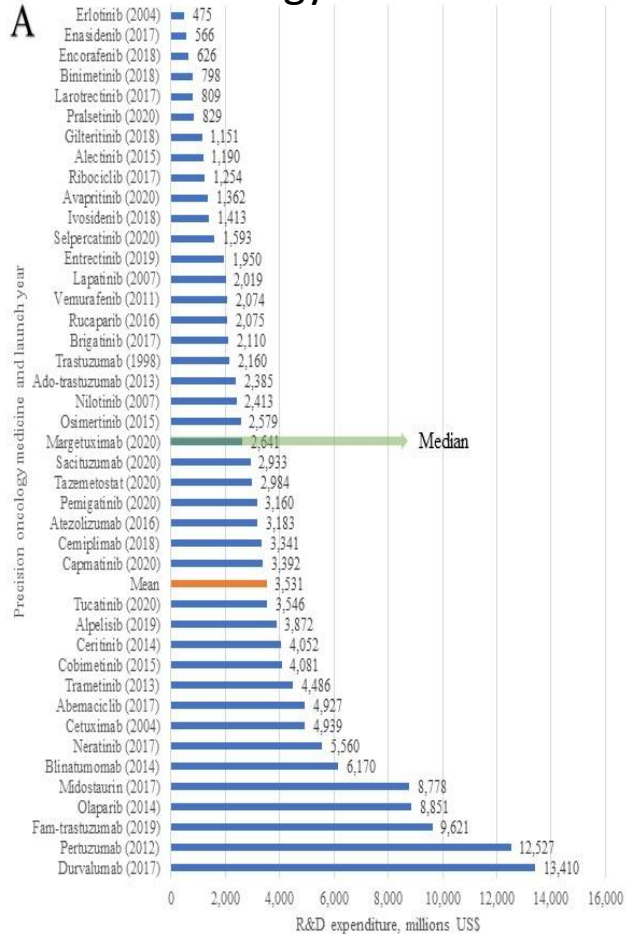
- Financial comparison of **R&D costs and Revenue** of 133 oncology therapies (1990 to 2020 - 30 years of data).
- **CDx versus non CDx**
- **Detailed side by side analysis** of 71 drugs (42 with CDx / 29 without CDx)
- Previously published papers on Pharma's ROI have **NOT evaluated precision oncology vs non precision oncology**.
- Currently NO external ROI reference around precision medicine



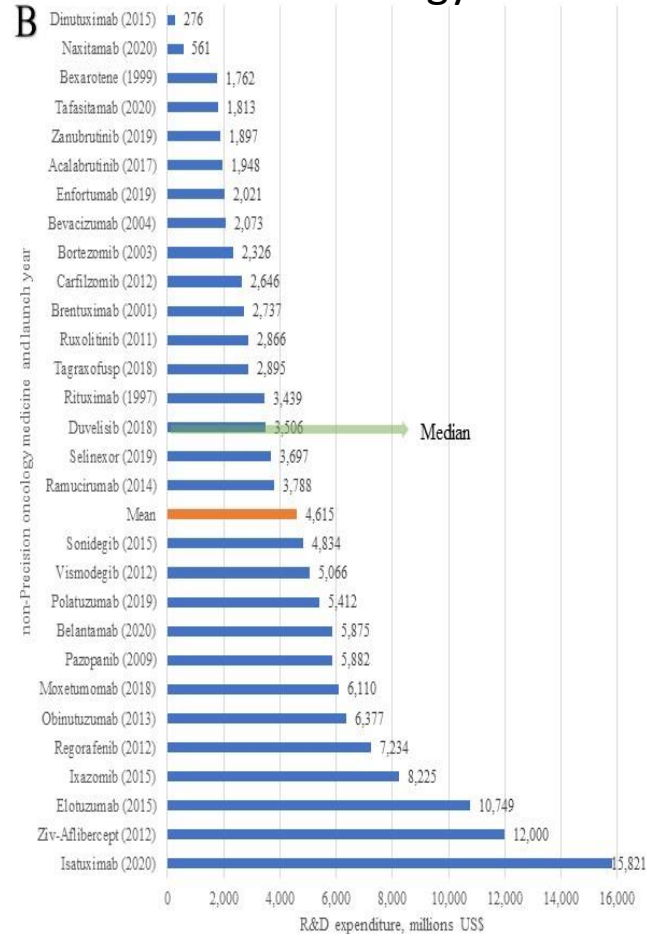
Latest research:
Published by Journal of
Clinical Oncology, Delivering
the Precision Oncology
Paradigm

Deploying data to deliver the precision oncology paradigm

Precision Oncology Medicines



Non Precision Oncology Medicines



- R&D spend for **42 precision oncology medicines**, (\$475M to \$13,410M) v **29 non-precision oncology medicines** (\$276M to \$15,821M).
- **Probability of Success (POS)** for precision v non-precision oncology medicines: **\$1,486.6M** v **\$2,077.9M**, a difference of **\$591.3M**.
- **Increased POS** associated with a **CDx** in clinical trials - employment of a **CDx approach increases POS** v non CDx approach **by a factor of 2.5**

Henderson RH, French D, Stewart E, Smart D, Idica A, Redmond S, Eckstein M, Clark J, Sullivan R, Keeling P, Lawler M. [Delivering the precision oncology paradigm: reduced R&D costs and greater return on investment through a companion diagnostic informed precision oncology medicines approach.](#)

J Pharm Policy Pract. 2023

Landmark study demonstrates economic benefit of precision medicine in treating cancer

Approach

- **Most comprehensive study** of precision oncology medicines in the marketplace
- Examined **economic impact of precision oncology medicines** compared to traditional oncology medicines.

Key results

- **Over \$1 billion less in R&D** spend to develop a medicine guided through clinical trials in a precision oncology approach, compared to a “one size fits all” approach
- **CDx-guided approach** can deliver **health benefits at a potentially affordable cost, lowering expensive clinical trial attrition rates** and **sparing patients from ineffective treatments** with significant side effects.
- Treating patients based on their **genomic make-up** is the **direction of travel that we should be pursuing**, this study highlights how it can be achieved in an efficient and cost-effective way.

Take Home Messages

- **Precision medicine** can be a **cheaper, more efficient way** to treat cancer
- **If we don't deploy a CDx-guided approach** we are **missing a huge opportunity** to deliver the best, most affordable care to our patients.



European Cancer Organisation Community 365 Round Table on Genomic Tumour Testing

- Convened by the **European Cancer Organisation (E.C.O.)**
- Chaired by Prof Matti Aapro (Immediate Past President E.C.O) and Prof Mark Lawler (Board Member E.C.O.)
- Convened interested and experienced **patient, research, clinical, policy, political and industry stakeholders** to address the **key opportunities and barriers for genomic tumour testing in Europe**
- Series of Meetings and a High Level Workshop (2nd December 2021), culminating in an Action Report
- ***Put to the Test: Empowering Genomics to Improve Cancer Care and Patients lives***

Lawler M, Aapro M, Schirmacher P, Möslein G (2022). Put to the Test: Empowering Genomics to Improve Cancer Care and Patient Lives. European Cancer Organisation; Brussels



Put to the Test: Empowering Genomics to Improve Cancer Care and Patients lives

- Key Overarching Message:

““Put to the Test” aims to provide helpful guidance and information to interested stakeholders and policy-makers in order to embed genomic tumour testing as standard of care for European cancer patients.”



ARE WE REALLY SOLVING THE ISSUES THE COMMUNITY AND OUR PATIENTS ARE FACING?

Comment

How current assay approval policies are leading to unintended imprecision medicine

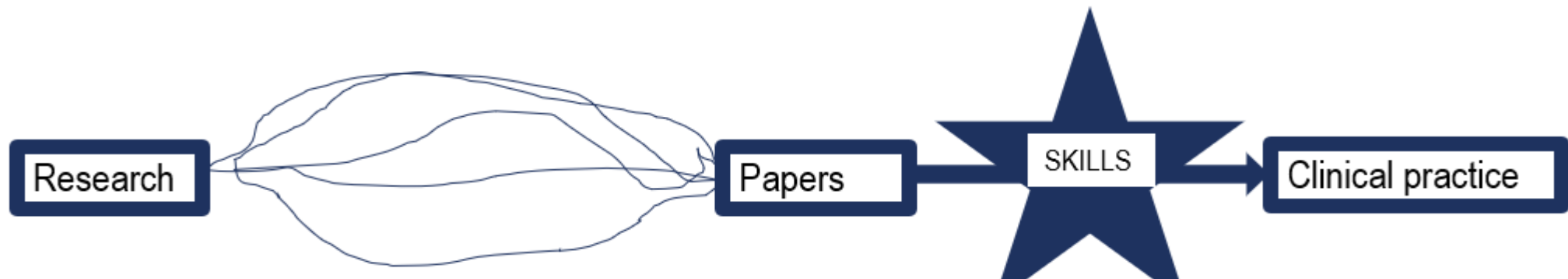


Panel: Solutions to improve the current assay approval pathway

- Industry should be mandated to do concordance studies with other similar assays or standardised controls before a drug is approved
- Industry should support, in concert with all stakeholders, relabelling or revising approved companion diagnostics if evidence exists that the labelling might lead to uncertainty in the identification of patients for treatments
- Industry should support, in concert with all stakeholders, relabelling or revising of the companion diagnostics if equivalent clinical validity has been shown with other biomarkers or standards, providing access to clinical trial tissues to validate other assays
- Industry, when considering the incorporation of assays in their trials, should communicate and share assay information when using an assay that identifies the same molecule (eg, epitope, antigen, DNA, RNA) as in other competitive trials—eg, method information related to the binding sites of the antibodies used in the companion diagnostic assay should be made public, even if this information is commercially sensitive
- Pathways for regulatory acceptance of other assays that are equivalent, but less expensive and easier to implement in daily practice, should be developed by governments and regulatory agencies, ideally before a drug is labelled together with a companion diagnostic
- Early engagement by all stakeholders in external quality control schemes to allow rapid development of guidelines and quality standards is essential, preferably before an assay is approved by the regulatory agencies
- Clinical practice guidelines developed by professional organisations like the American Society of Clinical Oncology and the European Society for Medical Oncology should endorse not just a companion diagnostic assay used in the trial, but any rigorously and technically validated equivalent laboratory assays that can define essentially the same population as the companion diagnostic
- Regulators should require data confirmation of the analytical validity of the companion diagnostic in the distributed setting in which it would be applied, at a level of rigor similar to that required to show efficacy of the drug in question

Key Message

- We are **too good** in producing academic output
- We are **not so good** in changing clinical practice
- **Good at Breakthrough - Poor at Follow through**
- A **worldwide** community effort, including patients and industry should drive interactions with regulators, and that should determine clinical practice.



Conclusion

- Need to move to a situation where **Precision Genomic Testing/CDx is embedded** within health systems and **really delivers for our patients**
- Upgrading infrastructure and ongoing expenditures need to be carefully assessed against rigorous benchmarks to **deliver affordable care**.
- The **IVDR issue** must be addressed
- The **Economic Argument** must be articulated more **clearly** and **robustly**
- **Education** is required, for patients, for health care professionals and for policy makers/health care providers,
- We must **avoid a multi-speed Europe** that leaves many patients behind
- An **equality agenda** must be pursued to ensure that **Precision Genomic Testing narrows rather than widens cancer disparities** across Europe
- We have a huge opportunity within our grasp. **LET'S TAKE IT!**

Draft Recommendations (1)

1. Place patients at the centre of the precision oncology care agenda, with timely comprehensive genomic testing embedded within health systems to ensure equal access to biomarker-driven cancer treatment for all patients.

- Call to regulators and payers to **recognise the primacy of cancer biomarkers in precision oncology**, and consider the **real-world setting for biomarker-informed treatment**.
- Testing must be **implemented consistently** across the EU, with the aim of **narrowing not widening the inequity gaps for patients**.
- Increasing access to broad biomarker sequencing panels and repeat testing can help address the spatial and temporal heterogeneity across tumours.

Draft Recommendations (2)

Develop a multi-pronged strategy to deliver precision oncology to patients, including mechanisms to streamline biomarker testing delivery, approval, access and reimbursement.

- Closer interaction between diagnostic and treatment delivery pathways are urgently required, with **better integration of biomarker testing** in the diagnostic pathway.
- The **current complexities** with the **In Vitro Diagnostic Regulation** **must be reduced**, including better connected regulatory frameworks and coordinated approval procedures across Europe.
- The **regulatory environment** must **keep pace with the speed of scientific innovation** to facilitate broad access to biomarker testing.
- Strategies must be developed that stimulate **building evidence to develop pragmatic payment models**, with health systems taking the costs of both the drug and biomarker testing into consideration.

Draft Recommendations (3)

3. Ensure that In Vitro Diagnostics are constantly refined to generate high-quality biomarker tests.

- **Better collaboration** is needed between academics and industry **to standardise local biomarker testing** for enhanced patient access to treatment and clinical trial enrolment.
- **Laboratory-developed tests** should have **strict regulatory oversight** to ensure their harmonisation and validation through mandatory participation in External Quality Assessment schemes and accreditation, **to ensure confidence in local biomarker testing**.

Draft Recommendations (4)

4. Articulate the economic argument for the benefits of biomarker testing more clearly and robustly.

- Greater and urgent transparency is needed to **understand the economic gaps holding back better testing**. Only then can we incentivise biomarker testing for all stakeholders
- Systematic assessment of the **cost of not testing** is urgently required.
- The **cost-effectiveness of biomarker testing** in preventing (advanced stage) cancer, enabling early treatment, monitoring response to treatment, and identifying families with hereditary cancer syndromes is required.

Draft Recommendations (5)

5. Provide Education for patients, healthcare professionals, policy makers and healthcare providers.

- Patient education on the importance of precision oncology and its impact on patient care must be promoted .
- Collaboration between academics, industry and regulatory agencies to generate the data required to support implementation of biomarker-driven precision care must be encouraged.

Thank you for Your Attention

