



Current Perspective

Empowering effective biomarker-driven precision oncology: A call to action^{*}

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ABSTRACT

Precision oncology has a significant role to play in delivering optimal patient care. Biomarkers are critical enablers for precision oncology across the continuum of cancer diagnosis, in defining patient prognosis, and in predicting the response to treatments and their potential toxicities, as well as delineating the risk of hereditary cancer syndromes. Biomarkers also potentiate cancer drug development, accelerating patient access to safe and effective therapies. However, despite an accurate and timely diagnosis being critical to patient survival, advances in genomic testing are not being fully exploited in daily clinical practice, leading to missed opportunities to deliver the most effective treatments for patients. Biomarker testing availability and implementation often lag behind approvals of respective biomarker-informed therapies, limiting prompt patient access to these life-saving drugs. Multiple factors currently impede the routine adoption of biomarker testing including, but not limited to, cost, lack of test reimbursement, limited access, regulatory hurdles, lack of knowledge, insufficient cooperation on assay development, and the urgent need to harmonize and validate testing assays, all leading to inefficient diagnostic pathways. Clinical guidelines increasingly include genomic profiling, and recent evidence suggests that precision oncology can be delivered in a cost-effective way for financially-challenged health systems.

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Therefore, precision genomic testing for cancer biomarkers must be embedded into the clinical practice of oncology care delivery going forward. We articulate a series of recommendations and a call to action to underpin the mainstreaming of a biomarker-informed precision oncology approach to enhance patient outcomes and deliver cost effective 21st century cancer care

1. Introduction

The last two decades have witnessed a paradigm shift in cancer treatment, from a ‘one-size-fits-all’ approach towards precision oncology. Although the goal is to tailor cancer treatment to molecularly-driven tumour subtypes, barriers to implementation persist. Critical to precision oncology mainstreaming is integration of biomarkers into drug development and clinical practice, crucially empowering individualized treatment.[1] (Table 1). While this paper focusses on solid tumours, blood cancers have been a paradigm for precision oncology,[2] informing practice-changing tyrosine kinase inhibitors (TKIs) in Chronic Myeloid Leukaemia (CML). Similar biomarker-driven approaches have been delivered for other haematological malignancies.[1] Mainstreaming biomarkers can enhance cancer diagnosis and treatment, enabling patients to be stratified response/non-response to specific therapies [1, 3].

2. Clinical relevance and potential applications of cancer biomarkers

2.1. Early diagnosis

Early diagnosis of cancer is critical to patient survival [4]. There is an unmet need for novel less invasive tools to identify cancer early across different tumor types. Liquid biopsies are a promising approach for early detection. Biomarkers can be identified in the blood (circulating tumor cells (CTC), cell-free DNA (cfDNA) including circulating tumor DNA) (ctDNA). In devising a cancer biomarker-based diagnostic test, key performance parameters include both sensitivity and specificity. [5].

Although ctDNA analysis has demonstrated potential, levels of

ctDNA in early stages of cancer are low. A number of blood-based cfDNA biomarkers are currently being explored for early cancer detection, the most encouraging of which are methylation signatures]. [6].

2.2. Prognosis

In early stages of cancer, many patients will be cured by surgery and local therapy; however some patients will have tumour cells undetectable by current imaging modalities. This persistence of cancer cells - molecular residual disease (MRD), is associated with high risk of disease recurrence. Numerous studies evaluating prognostic value of ctDNA testing [7,8], have clearly demonstrated that MRD detection is a key prognostic factor associated with recurrence risk. Thus, prompt identification of MRD could allow a more personalized adjuvant treatment approach, adopting a therapeutic strategy based on risk levels of individual patients rather than the one-size-fits-all approach, where some patients are over-treated, while others are under-treated.

Although MRD-negative patients have better outcomes, a small study in lung cancer indicated that a fraction of these patients will still experience disease recurrence [9]. The generalizability of this finding requires more detailed study in a wider range of tumour types. It is unclear whether this observed recurrence reflects limited sensitivity of the biomarker, or intrinsic biology of the tumour. Accordingly, MRD testing should follow key principles of assay development and clinical validation. Further research is required to demonstrate the clinical utility of ctDNA-based MRD detection for biomarker-guided adjuvant therapy.

Other biomarkers are also being investigated in the (neo)adjuvant setting, with ctDNA clearance after adjuvant chemotherapy a potential biomarker-of-response to early treatment [10]; providing a “window of opportunity” to either escalate or de-escalate adjuvant therapy based on ctDNA analysis.

2.3. Treatment response in advanced cancer

Almost 30 % of patients with advanced cancer are eligible to receive a biomarker-informed therapy [1] (Fig. 1). To identify eligible patients, single gene-assays, companion diagnostics (CDx) or next-generation sequencing (NGS)-based tumor profiling technologies have been employed [11]. Several types of NGS panels are available, but which one (s) should be deployed in clinical practice remains unclear. ESMO recommends using small NGS panels (<50 genes) by tumor histotype, targeting only genes approved for clinical practice [11]; medium (50–100 genes) and large (>300 genes) panels are also available. The latter enable comprehensive genomic profiling (CGP) for all actionable mutations, but are more costly to perform, with more complex data interpretation. CGP is currently not routinely implemented in clinical practice in most EU countries.

For patients with advanced cancers, ESMO recommendations restrict liquid biopsy use for identification of predictive biomarkers when a tissue biopsy is not available, or upon treatment resistance [5]. There are currently missed opportunities to derive additional information from liquid biopsies in this setting. Dynamics of ctDNA in advanced cancer are a strong predictor of therapy response, [12]. Therefore, liquid biopsy approaches could be deployed to proactively monitor for molecular relapses. Similarly, molecular relapse could serve as an early/interim endpoint in clinical trials to identify treatment failure [13].

Table 1
Definitions.

Key terms	Description
Biomarker	A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions; molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers [1]
In vitro diagnostic (IVD) test	A system or tool with defined performance that is used to measure a biomarker status in the patient population [1]
Companion diagnostic (CDx) test	A type of IVD providing information that is essential for the safe and effective use of a corresponding therapeutic product [4]
Targeted drugs	Drugs that inhibit or interfere with defined molecular targets in cancer cells (such as kinases, receptors and other molecules) that are involved in intercellular or intracellular signaling pathways. They are primarily small molecule drugs, but also include shortpeptides and radioactive agents without an antibody moiety [5]
Targeted biologics	Biological products, including monoclonal antibodies, other antibody constructs and conjugates, cellular therapies, enzymes, fusion proteins and viral therapies. They typically recognize specific peptide sequences in proteins present on the surface of cancer cells and have high target specificity [5]
Cytotoxic drugs	Small-molecule drugs with the primary mode of action of inducing cellular toxicity, generally by interacting with DNA or components of the cell cycle. They affect rapidly dividing cells and are usually genotoxic[5]

IVD, in vitro diagnostic test

3. Perspectives on cancer biomarkers in drug development

3.1. Trends, successes and challenges

Precision oncology is critical to cancer drug development strategies, founded on three guiding principles: a strong biological rationale for the biomarker-driven treatment approach, clinical data demonstrating a large magnitude of effect, and a significant unmet clinical need. (Fig. 2).

Food and Drug Administration (FDA) approval trends (2000–2022) show that 573 oncology therapeutics were approved, including 206 distinct products. Targeted drugs and biologics comprised 91 % of approvals; cytotoxic drugs comprised only 9 % (Table 1), a clear shift to drugs designed with biological rationale. Furthermore, biomarker-defined populations accounted for 39 % of oncology approvals, with > 75 % of patient selection biomarker-informed [3]. Although the European Medicines Agency (EMA) has approved fewer targeted therapies [14], 70 cancer drugs with predictive biomarker tests were approved by end 2019 in the EU, increasing at a rate of 5–10 approvals per year.

Biomarker-based drug development has demonstrated several benefits to patient outcomes and therapy access. In lung cancer, accelerated approvals by FDA for indications in non-small cell lung cancer (NSCLC) have presaged a sharp decline in NSCLC-related population-level mortality, in contrast to small cell lung cancer where no actionable targets are available [15]. Drug development programmes enrolling biomarker-defined populations have a two-fold higher likelihood of approval [16]. Other opportunities include less risk of potential toxicity for biomarker-negative patients, and faster drug development with significantly less costs [17]. Current challenges include biomarker development, validation and clinical implementation.

3.2. Histology-independent trials

Another key challenge in conducting biomarker-driven trials relates to ‘histology-independent’ (EMA) or ‘tissue-agnostic’ (FDA) drug approvals. [3,18]. Such trials require screening large numbers of patients to identify a very small proportion eligible for, and ultimately enrolled in, histology-independent trials. In the histology-independent RAGNAR trial (erdafitinib in patients with locally-advanced or metastatic solid tumors and predefined fibroblast growth factor receptor (*FGFR*) 1–4 mutation or *FGFR* fusion), 11353 patients were screened by NGS centrally and 333 locally. Only 217 patients were enrolled in the study [18]. Therefore, establishing a biomarker-defined population is an important consideration for successful drug development; NGS is increasingly deployed in providing access to precision oncology therapies.

4. Biomarker-based regulation, registration and reimbursement

4.1. Food and drug administration

The biomarker landscape has evolved significantly over the last decade, with a shifting regulatory paradigm for CDx [1] (Fig. 3), posing multiple challenges. The sudden increase in FDA approvals of biomarker-driven therapeutics alongside their respective CDx, with the drug label stipulating the ‘partner’ CDx test name, led to availability of multiple drugs with identical indications, including the same target mutation, detected using different CDxs. For example, in detecting epidermal growth factor receptor (*EGFR*) alterations for targeted NSCLC treatment, multiple tyrosine kinase inhibitors (TKIs) were approved alongside their respective CDx (to determine patients’ *EGFR* mutation status) – erlotinib with cobas® test, afatinib with thescreeen®, gefitinib with Oncomine™. These CDx-related specificity issues led to the FDA publishing the Group Labelling guidance [19]. This enables US-based oncologists to employ one test to determine which TKI drug to prescribe for *EGFR*-mutated NSCLC patients.

In specific circumstances where FDA may decide to approve a therapeutic without authorizing a corresponding CDx, tests offered as Laboratory Developed Tests (LDTs), are deployed for treatment decisions. This led to the FDA publishing the Oncology Diagnostics Pilot guidance [20], a voluntary pilot programme, increasing transparency regarding required performance characteristics, supporting better, more consistent LDT performance.

4.2. European medicines agency and in vitro diagnostics regulation (IVDR)

The evolving EU regulatory framework raises issues which could potentially limit precision genomic testing implementation in real-world clinical practice. IVDs, including those for biomarker detection and measurement, were previously regulated under the In Vitro Diagnostics Directive (IVDD), but the In Vitro Diagnostics Regulation (IVDR) became applicable from May 2022 [21]. In the EU, two separate legislative frameworks underpin authorization of medicinal products and IVD certification: (1) EMA and European Commission are responsible for medicinal products approvals, (2) Notified Bodies are responsible for granting CE marking for defined IVDs.

Although IVDR is a step forward in ensuring test quality and safe use, feedback from industry, academia and clinical laboratories has characterized IVDR implementation as challenging (Table 2). A survey performed by the European Federation of Pharmaceutical Industries and Associations (EFPIA) found that > 42,000 patients are envisaged to be negatively-impacted by clinical trial delays due to IVDR [22]. IVDR implementation particularly impacts development and approval of

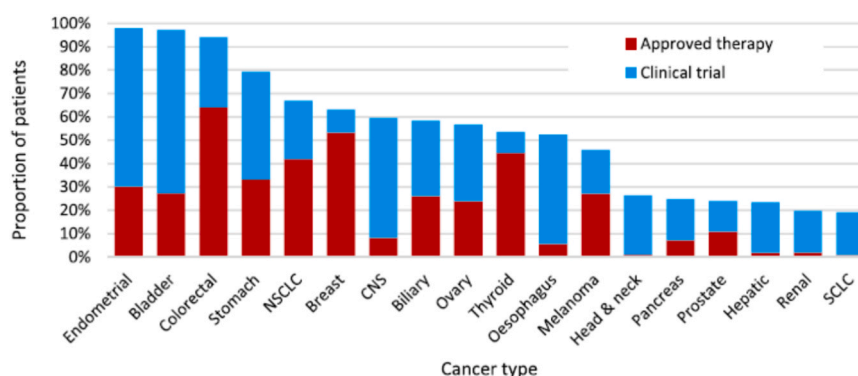


Fig. 1. Biomarker-driven therapy eligibility of different advanced stage cancers A multitude of novel cancer biomarker-driven systemic therapies are either approved or in late-stage clinical development in the advanced/metastatic setting, with around a third of patients potentially eligible to receive these as available biomarker-associated therapy or biomarker-driven clinical trial. NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

Fig. from Casolino R et al. [11], adapted and updated from Normanno N et al. [3].

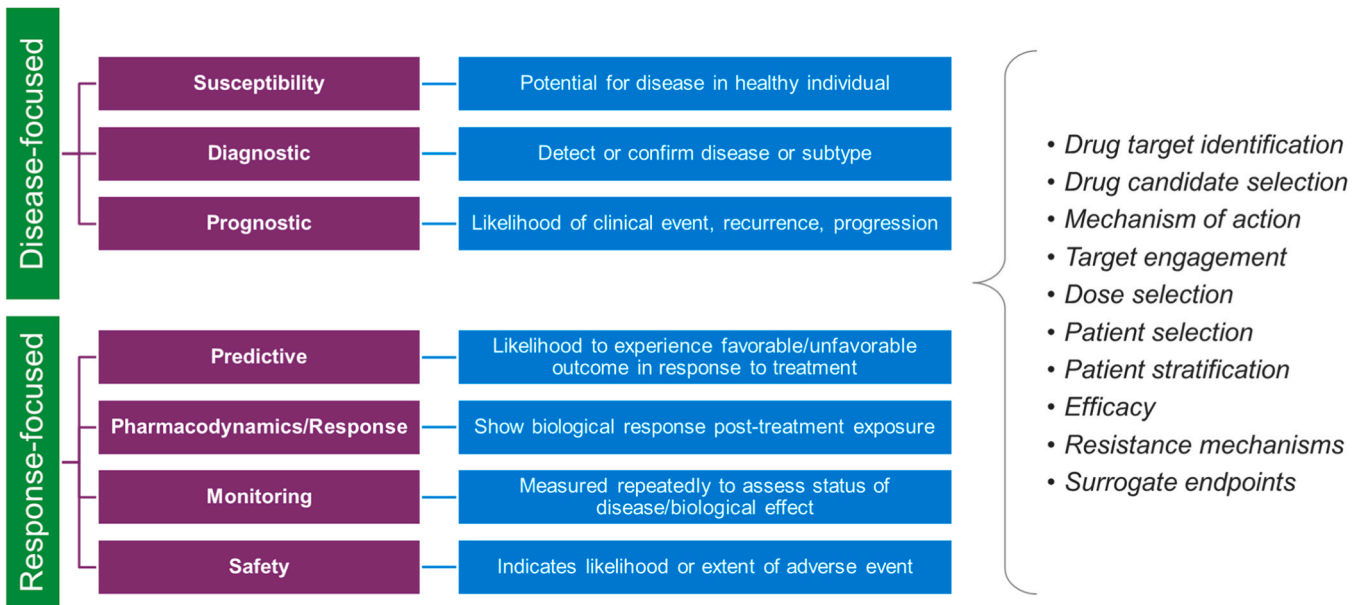


Fig. 2. Biomarkers in cancer drug development Biomarkers in cancer drug development can be used to characterize disease-related aspects or can be focused on treatment response.

Adapted from FDA-NIH Biomarker Working Group (2016), BEST (Biomarkers, EndpointS, and other Tools) Resource [1].

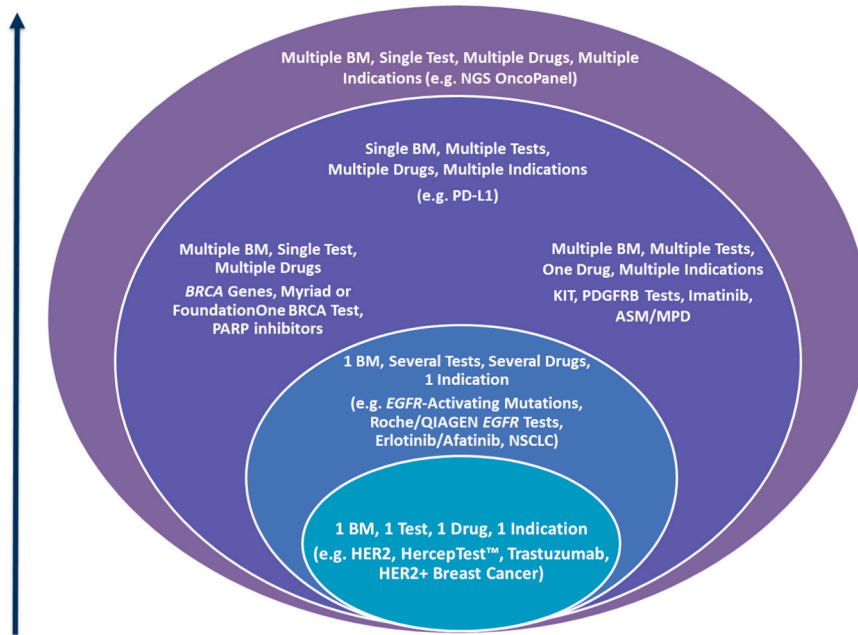


Fig. 3. The shifting regulatory paradigm for CDx The approval of biomarker-associated oncology drugs initially started with the format of ‘one analyte/biomarker–one test–one drug–one indication’ (e.g. HER2 receptor expression–HerceptTest™ –trastuzumab (Herceptin)–HER2 + breast cancer). This equation then shifted to ‘one biomarker –multiple tests– multiple drugs–one indication’ (e.g. EGFR activating mutations–Roche or QIAGEN EGFR tests–erlotinib or afatinib–NSCLC), and then expanded to where we are today with ‘one or multiple biomarkers –one or multiple tests–one or multiple drugs–multiple indications’. Today we also have ‘multiple biomarkers–a single NGS test panel–multiple drugs–multiple indications’ underpinned by the advent of NGS where available. ASM, aggressive systemic mastocytosis; BM, biomarker; BRCA, BReast CAncer gene; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; KIT, c-Kit receptor tyrosine kinase; MPD, myeloproliferative disorder; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; PARP, Poly (ADP-ribose) polymerase; PDGFRB, platelet derived growth factor receptor beta; PD-L1, programmed death-ligand 1.

novel cancer therapies. If a new biomarker is deployed in a clinical trial for medical decision-making, two separate submissions are required – a clinical trial application for the medicinal product, and a performance study application for the IVD.

Concerns with these new regulatory changes pertain largely to lack of a harmonized processes, with significant delays to obtain IVD

regulatory approval (Table 2). Real-world impact is that patients may be denied or delayed participation in clinical trials using innovative biomarkers, or that a targeted cancer therapy receives approval without its respective CE-marked CDx, thereby significantly delaying treatment access. Another potential issue is LDTs, broadly deployed under IVDD, but less clear under IVDR. There is an urgent need for quick and decisive

Table 2
EU's IVDR – Definitions and new challenges.

Definitions per IVDR	
In vitro diagnostic medical device	Any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information on one or more of the following: (a) concerning a physiological or pathological process or state; (b) concerning congenital physical or mental impairments; (c) concerning the predisposition to a medical condition or a disease; (d) to determine the safety and compatibility with potential recipients; (e) to predict treatment response or reactions; (f) to define or monitor therapeutic measures. Specimen receptacles shall also be deemed to be in vitro diagnostic medical devices. (Article 2(2) IVDR[32])
Companion diagnostic	A device which is essential for the safe and effective use of corresponding medicinal product to: (a) identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product, or (b) 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. (Article 2(7) IVDR[32])
Key challenges associated with the new regulation and potential issues	
New risk-based classification system for IVDs	Is the submission of a performance study required for a given clinical trial? How is a performance study classified? E.g. stratification vs randomization. How to provide the intended use of a CDx (a CE-marked device) when the respective drug is still in development?
Lack of harmonized approval process for performance studies across the EU	Currently no system in place for industry to submit performance studies to all EU member states in parallel, resulting in 27 different application procedures, dealing with individual NCAs and national Ethics Committees each with their different requirements, and thus no harmonized approval timelines either. EUDAMED which could be a helpful tool in this context is significantly delayed (estimated to be operational by 2028/2029).
New consultation procedure between EMA and Notified Bodies on new CDx products	Uncertainties regarding the new EMA–Notified Bodies consultation procedure on the suitability of the CDx when submitting an application for a new CDx-associated drug approval.
Longer approval timelines to obtain CE marking for CDx	This new step of the EMA–Notified Bodies consultation procedure (per above) likely to result in longer timelines to receive the ‘CE mark’ approving new CDx products, due to Notified Bodies currently being overloaded as only a small number of them are able to certify in accordance with IVDR. The real-world impact of these delays to patients may be that a targeted cancer therapy will receive regulatory approval without its respective CDx, whose approval is lagging significantly behind.
Lack of scientific consultation	No possibility for scientific discussions between EMA and Notified Bodies which could be beneficial to all stakeholders.

Table 2 (continued)

Status of LDTs under new IVDR	Much uncertainty regarding the required evidence to justify the use of an LDT.
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CDx, companion diagnostics; EMA, European Medicines Agency; EUDAMED, European Database on Medical Devices; IVD, in vitro diagnostic; IVDR, In Vitro Diagnostics Regulation; LDT, laboratory developed test; NCA, National Competent Authority

action to reduce the complexity of existing EU regulatory frameworks and improve their connectivity. (Table 3).

4.3. Payer’s perspective – the Dutch model for reimbursement and patient access

In the Netherlands, the Treatmeds Foundation receives funding from payers to provide financial support for biomarker implementation [23]. The DRUG-Access Platform enables patient access to promising drugs through a ‘personalized reimbursement’ scheme, whilst generating evidence for clinical effectiveness [24].

The Drug Rediscovery Protocol (DRUP) is an ongoing adaptive platform trial, initiated in the Netherlands to facilitate access to

Table 3
Key factors for payers to consider to reimburse biomarker testing.

Key Factors	Description
Biological rationale for a precision oncology treatment	A ‘targeted’ therapy must have solid evidence for its comparative efficacy and cost-effectiveness
Clinical and analytical validation of CDx and its cost-effectiveness	A validated assay that meets the local and regional regulation should be used Centralized testing may improve cost-effectiveness
Different tumor types and disease stages	When to test in the early stage of cancer (e.g. screening NSCLC patients for neo-adjuvant or adjuvant treatments)? When to test in later stages, when there are no satisfactory treatment options available (histology-independent indications)? Can screening for clinical trials be reimbursed?
Complex biomarkers	Does the use of different assays lead to different outcomes (e.g. PD-L1 expression)? Complex biomarkers (e.g. continuous or incremental biomarkers) may need further harmonization
Equal access	Is a list of essential biomarkers to be tested per tumor type available? Are these lists being regularly updated? Is there a national monitoring approach to ensure the efficacy of molecular testing? Is there equal access to a Molecular Tumor Board for the interpretation of complex genomic outcomes?
Creating a learning healthcare system	Can we establish an infrastructure to learn from genomic data and identify new biomarkers for response?
Cost of biomarker testing	Depends on different factors such as: prevalence of the biomarker, testing strategy, the point at which the test is required in the treatment pathway (i.e. frontline or later lines), whether the cost can be shared across multiple technologies (e.g. for lung cancer, the cost is reduced by screening for multiple biomarkers at the same time)
Cost-effectiveness of biomarker testing	Whether it is appropriate to reimburse the biomarker test for tumors with an extremely low mutation frequency, given the resource utilization (e.g. test, workforce, interpreting results) and the cost per the few patient who might actually benefit

CDx, companion diagnostic; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1

approved targeted oncology drugs beyond their labels for patients with rare cancer subtypes, based on the tumour's molecular profile [25] (Fig. 4). At time of writing, > 30 compounds are available on DRUP, with 18 countries interested in rolling-out this protocol.

A challenge for health systems is the high number of patients requiring molecular screening. Cost of testing can vary among tumour types [26] (Table 3); however it is unhelpful if a precision medicine is reimbursed, but test cost is not. Therefore, HTA bodies should incorporate the test-treatment combination within cost-effectiveness analyses (Table 3). In the Netherlands, a national tripartite consultation committee, comprising healthcare professionals, health insurance companies and patient advocates, is responsible for approving biomarkers for screening, to promote equal access to the necessary testing.

5. Hurdles to implementing cancer biomarker testing

5.1. Need for harmonization and validation of assays

With advanced diagnostic technologies (e.g. NGS) and histology-independent oncology trials more widespread, demand for reliable, accurate testing prompts an urgent need to harmonize/validate 'in-house' LDTs. Stringent testing criteria should be implemented, with rigorous systems for accreditation and quality assessment. Participation in External Quality Assurance (EQA) programmes, currently only voluntary, should be mandated for overall consistency across Europe [1].

5.2. Inadequate infrastructure for biomarker testing in current EU health systems

Recent surveys show that access to precision oncology drugs and high-quality biomarker tests is widely inconsistent across the EU, with inadequate permeation of genomic testing into clinical practice (Fig. 5). Lack of diagnostic laboratory infrastructure, inefficient organization and/or insufficient public reimbursement narrow access to biomarker tests in many EU countries. Access to advanced biomolecular technologies (e.g. large NGS panels/ CGP) is highly heterogeneous. Main barriers to NGS implementation include financial constraints, lack of NGS testing capabilities, and failure to include NGS testing in treatment guidelines [27,28]. But bottom-up approaches such as Genome

Medicine Sweden, uniting key stakeholders from academia, healthcare, industry and patient organisations, have provided a national infrastructure for implementing precision medicine across the country, with regionally-distributed genomic services, empowered by a national informatics infrastructure for data analysis and sharing.[29].

Although DRUP is a success story in the Netherlands, there are challenges in other EU countries. A lack of commitment by health systems to reimburse test and/or drug de-incentivises participation in DRUP-like trials. From a payer's perspective, if drug is made available for off-label use outside DRUP-like trials, the necessary effectiveness data will not be gathered. Ultimately, DRUP-like trials can pave a smooth path from experimental treatment to reimbursement stage, thereby ensuring enhanced patient access.

5.3. Lack of patient education

From the patient's perspective, awareness and understanding of biomarker testing availability, benefits and timely access is lacking. These situations represent missed opportunities for patients to make informed decisions about their care, based on personal circumstances/preferences. Addressing this gap requires more active contribution (through educational initiatives) to this crucial part of the patient's journey. Patient advocacy organizations are also crucial, providing accessible and understandable information, promoting access to biomarker testing in routine care and participating in initiatives that foster patient awareness.

6. The cost of not implementing biomarker testing in precision oncology

6.1. Clinical cost to patients – missed opportunities

The Italian Register of Actionable Mutations (RATIONAL), a national programme of NGS-based genomic profiling of patients with advanced solid tumors, found that only 12 % of patients received targeted therapy based on genomic testing, versus 46 % with identified actionable genomic alterations, highlighting a wide treatment gap and important missed opportunity [10]. This study also confirmed that, deployment of large NGS panels for CGP was extremely limited, more frequently used

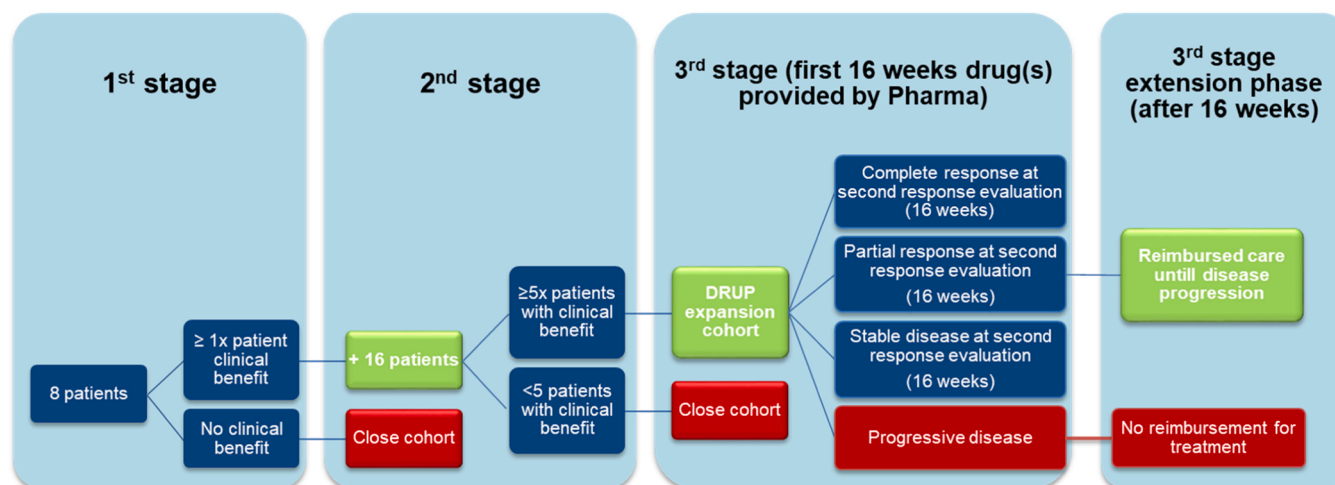


Fig. 4. Drug Rediscovery Protocol trial and personalized reimbursement scheme. DRUP is an ongoing adaptive platform trial facilitating access to approved targeted oncology drugs beyond their labels for patients with rare subgroups of cancer, based on the molecular profile of the tumor. Once a patient exhibits sufficient clinical benefit after 16 weeks with a given therapy during Stages 1–2, demonstrating drug effectiveness in an individual patient, they can move to the DRUP expansion cohort in Stage 3 with a performance-based, personalized reimbursement scheme in which commercial medication will be reimbursed by payers. This step, however, is subject to the approval of the Dutch Health Care Institute which eventually also analyzes the evidence generated by repurposing an existing therapy in a rare indication. As a result of the DRUP trial, nivolumab is now available in the Netherlands for patients with high microsatellite instability and deficient DNA mismatch repair, regardless of histology (similar to the pembrolizumab indication as approved by the FDA) (van der Velden et al., 2019). DRUP, Drug Rediscovery Protocol. Fig. adapted from van Waalwijk van Doorn-Khosrovani et al. [39]

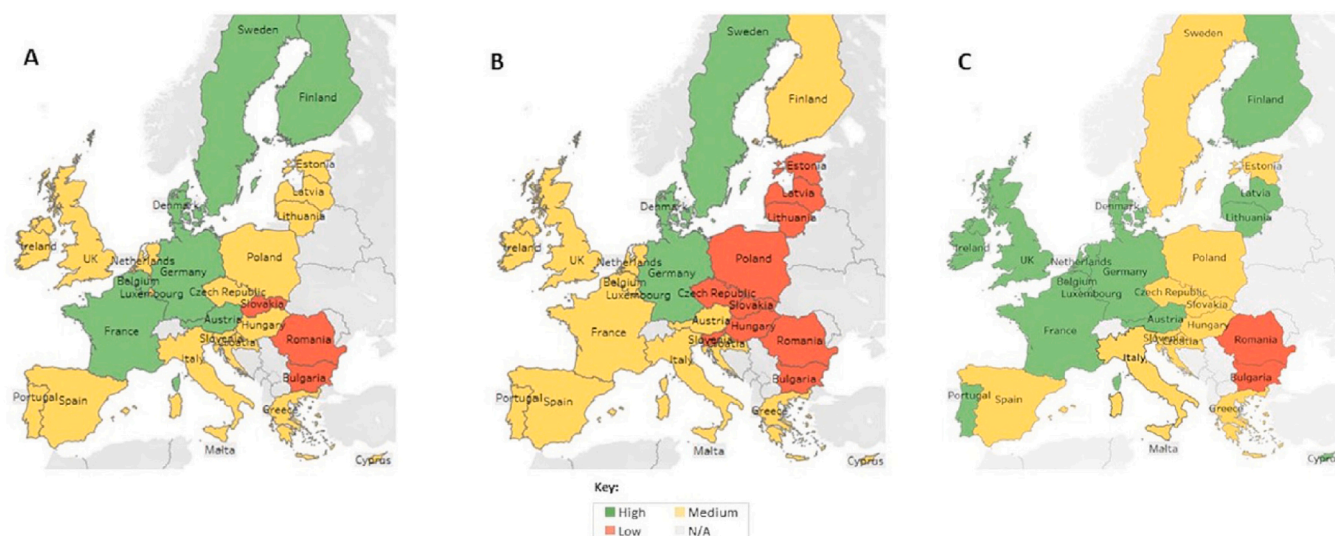


Fig. 5. The current status on quality and access to biomarker testing in Europe. The access to and quality of current biomarker testing practices in solid tumors were evaluated across Europe by the International Quality Network for Pathology, the European Cancer Patient Coalition, and the European Federation of Pharmaceutical Industries and Associations. (A) Single biomarker test access; (B) Multi-biomarker test access; (C) Biomarker test quality. Figure courtesy of Normanno et al. Eur J Cancer [42].

in heavily pre-treated patients with poor clinical outcomes, treatment resistance, with little chance of benefit. CGP needs to be implemented more routinely and earlier in clinical practice.

Among advanced-stage patients who underwent CGP as part of RATIONAL, cancer of unknown primary (CUP) was among the most frequent histological type (11 %); actionable genomic alterations were detected in 53 % of CUP patients [10]. Patients with CUP have inferior overall survival than those with a metastatic cancer of a known primary site [30]. Accordingly, there is a strong case for implementation of routine CGP for patients with CUP, as already implemented in several European countries (e.g. the Netherlands, UK). [30].

6.2. The health economics of precision oncology

A common concern for national health systems is the cost of biomarker testing; however we must also address “the cost of not testing”, negatively impacting patients’ quality-of-life, productivity and placing unnecessary pressures on health systems, particularly through missing early diagnosis or treatment and having to manage more advanced disease, with concomitant escalating costs and less chance of successful outcomes.

A more comprehensive appreciation of the health economic landscape of precision oncology is needed. Systematic reviews [31,32] have emphasized the value that CDx-precision oncology drug approaches can bring to health systems and patients [3].

Evidence from health economics analyses was crucial in Bowel Cancer UK’s recent success in achieving a cancer policy change in England, thereby permitting treatment breaks for colorectal cancer patients receiving biomarker-informed cetuximab therapy [33]. In addition to improved quality-of-life, this work also projected savings of £ 1.2 billion for the NHS. A recent landmark paper, looking at precision oncology medicines on the market for the last 30 years highlighted how precision oncology (as compared to one-size-fits-all) can deliver considerable value, saving \$1.1 billion in R&D costs and significantly reducing time intervals for drugs to reach the market [17]. These data support a shift in the narrative from focusing on the cost of testing, to the consequent missed opportunities and costs of not testing, and on the economic value of delivering better outcomes for cancer patients.

7. Conclusions

Biomarkers play an integral role across the oncology drug development spectrum, with targeted therapies and biomarker-selected populations increasingly becoming the norm, and biomarker-driven research potentially leading to faster, more effective and cost-efficient drug development. However, new logistical/regulatory challenges have emerged; there remain real-world hurdles in implementation of precision genomic testing in clinical practice, with missed opportunities for patients and inequities exposed across Europe. We provide a series of robust recommendations to address these challenges and an urgent call to action (Panel). Mainstreaming biomarker sequencing panels, responsible collaboration between all stakeholders (academics, industry, regulatory agencies, payers and patient advocacy organizations), and sharing of data is required to enhance access to biomarker-informed precision oncology and improve patient outcomes for all.

Panel: Recommendations and Call to Action

1. Place patients at the center 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 policy stakeholders to recognize the primacy of cancer biomarkers in precision oncology, and consider the real-world setting for biomarker-informed treatment.
- Implement testing consistently across Europe, with the aim of narrowing not widening the inequity gaps for patients.
- Increase access to broad biomarker sequencing panels and repeat testing (when appropriate, be it liquid or tissue biopsy) to help address the spatial and temporal heterogeneity across tumors.

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

- Better integrate the diagnostic and treatment delivery pathways so that diagnosis and treatment are not implemented in silos, with biomarker testing firmly embedded in the diagnostic pathway.
- Reduce the current complexities with the In Vitro Diagnostic Regulation, including better connected regulatory frameworks and coordinated approval procedures in the EU.
- Develop strategies that stimulate building evidence to develop pragmatic payment models, with health systems taking the costs of both the drug and biomarker testing into consideration.

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

- Empower better collaboration between academics and industry to standardize local biomarker testing for enhanced patient access to treatment and clinical trial enrolment.
- Ensure laboratory-developed tests have strict regulatory oversight to empower their harmonization and validation through mandatory participation in External Quality Assessment schemes and accreditation, to ensure confidence in local biomarker testing.

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

- Systematically assess the cost of not testing.
- Ensure greater transparency to understand the economic gap holding back better testing, to underpin incentivisation of biomarker testing for all stakeholders.
- Improve the cost-effectiveness of biomarker testing in enabling early treatment, monitoring response to treatment, and identifying families with hereditary cancer syndromes.

5. Provide education for patients, healthcare professionals and policy makers.

- Promote patient awareness and understanding on the importance of precision oncology and its impact on their care through focused educational initiatives.
- Ensure collaboration between academics, industry and regulatory agencies to generate the data required to support implementation of biomarker-driven precision care.

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