Published in final edited form as:

Eur J Cancer. 2017 October ; 84: 325–334. doi:10.1016/j.ejca.2017.07.028.

Societal challenges of precision medicine: Bringing order to chaos

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Abstract

The increasing number of drugs targeting specific proteins implicated in tumourigenesis and the commercial promotion of relatively affordable genome-wide analyses has led to an increasing expectation among patients with cancer that they can now receive effective personalised treatment based on the often complex genomic signature of their tumour. For such approaches to work in routine practice, the development of correspondingly complex biomarker assays through an appropriate and rigorous regulatory framework will be required. It is becoming increasingly evident that a re-engineering of clinical research is necessary so that regulatory considerations and procedures facilitate the efficient translation of these required biomarker assays from the discovery setting through to clinical application. This article discusses the practical requirements and challenges of developing such new precision medicine strategies, based on leveraging complex genomic profiles, as discussed at the Innovation and Biomarkers in Cancer Drug Development meeting (8th—9th September 2016, Brussels, Belgium).

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Conflict of interest statement

None declared.

Keywords

Biomarkers; Drug development; Precision oncology; Preanalytical and analytical validation; Assay validation; Regulatory sciences

1. Introduction

The Council of the European Union (EU), while accepting that there is no commonly agreed definition of the term precision (personalised) medicine, has noted that this is generally understood to refer to a medical model which uses the characterisation of individuals' phenotypes and genotypes (e.g. molecular profiling, medical imaging and lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention [1]. For the cancer patient today, one of the precision medicine approaches in the clinic may be reflected in the selection of an appropriate targeted agent or treatment strategy based on a predictive biomarker assay, which measures a particular biological characteristic of the tumour.

As the number of drugs that target specific proteins implicated in the tumour phenotype increases, and as next-generation sequencing (NGS) and other technologies bring comprehensive genome-wide analyses to affordable levels, the perception that a much wider role for precision medicine in routine practice may be possible has now been conveyed to many patients with cancer. That such new analysis technologies will increase the efficiency of commercial drug development through the earlier integration of precision medicine approaches, is also a commonly held assumption. However, to realise such potential benefits, it may be necessary to develop complex biomarker assays through an appropriate and rigorous regulatory framework. This would be associated with tremendous challenges, on the one hand in relation to the problems inherent in the development of multiple assays in clinical trial settings and on the other hand, in relation to the regulatory approval processes necessary for implementation of the new assays into daily practice. In addition, there is currently no general regulatory framework for the approval of different, simultaneously developed, commercial biomarker systems measuring particular biological characteristics that may be relevant to a specific class of targeted drugs. Regulatory agencies cannot mandate this type of approach from independent companies, which may choose not to follow such a course for commercial and competitive reasons. However, having different biomarker systems and cut-offs for different approved drugs targeting a single protein potentially causes confusion in daily clinical practice. It may be that the establishment of developmental frameworks among industry, regulatory, governmental and academic stakeholders would facilitate comparisons of assay performance before regulatory approval, and that such frameworks would mitigate the somewhat chaotic current approach. These issues are ubiquitous throughout modern biomarker/drug development processes and are not specifically related to particular targets or pathways but rather are general considerations that impact on the regulatory sciences that are integral to the clinical development of modern oncology drugs.

The practical requirements and challenges of precision medicine strategies were discussed at the Innovation and Biomarkers in Cancer Drug Development (IBCD) meeting (8th—9th September 2016, Brussels, Belgium) organised jointly by representatives from the European Organisation for Research and Treatment of Cancer (EORTC), the United States (US) National Cancer Institute (NCI), the European Medicines Agency (EMA) and the American Association for Cancer Research. Different stakeholders from all parties gave particular consideration as to whether we are now able to deliver precision medicine, based on comprehensive tumour mutation profiles, in a sustainable and affordable manner. This meeting was prompted by findings and observations made during the establishment of the collaborative EORTC-led SPECTA (Screening Patients for Efficient Clinical Trial Access) and NCI-led MATCH (Molecular Analysis for Therapy Choice) molecular screening platforms, intended to facilitate clinical drug development [2,3]. We present a summary of the main issues discussed by the IBCD faculty, including consensus recommendations and key points for further consideration relating to the future development of precision medicine.

2. Biomarkers: clinical utility

Biological assays or biomarkers have an increasing impact on the clinical development of new drugs and, in some instances, on the eventual tailoring of treatment administration. At the early stages of clinical testing, pharmacodynamic biomarkers may be used to demonstrate that a drug is engaging meaningfully with the intended cellular target, when administered at tolerable dose levels. In addition, biological assays may be used to demonstrate that off-target effects of a drug on normal cell populations are unlikely to be clinically detrimental [4]. Biomarker assays may also provide prognostic information, indicating perhaps how aggressive a tumour is likely to be, and may thereby support decisions on whether an immediate intensive treatment approach is most appropriate. By contrast, positive or negative predictive biomarker assays may be used to define subsets of patients with tumours that are likely to respond particularly well, or are unlikely to respond, to an individual drug or combination regimen. The biomarker-based exclusion of patients unlikely to benefit from a specific treatment approach not only means that patients are spared from unnecessary toxicity, it also facilitates the earlier selection of alternative more appropriate treatment options and improves overall cost-effectiveness. The discovery, refinement and validation of predictive biomarker assays may only be feasible when large numbers of patients have been treated with an agent, their tumours have been typed with the assay, and outcomes are known; for example, after analysis of phase III clinical trial data. If a certain biomarker status is a prerequisite for receiving a specific drug, the biomarker assay is defined as a companion diagnostic. Biomarker assays providing non-prescriptive information for patient management can find use as complementary diagnostics. The key steps in the development of a predictive biomarker include discovery, pre-analytical/analytical validation, clinical validation and the demonstration of clinical utility, i.e. confirmation that the test can guide an intervention that can change outcomes and thereby affect patient management [5].

To integrate these processes efficiently into daily practice, it has become evident that a re-engineering of clinical research is necessary so that regulatory considerations and procedures facilitate the efficient translation of new biomarker assays. Such re-engineered

research would use novel study designs and efficacy endpoints, whether in formal trials or in real-world studies. It would also account for the heterogeneous and evolving status of biomarkers and their interactions within patients over the course of treatment. Understanding these features may lead to highly individualised treatment opportunities for patients.

3. Quality assurance and control

There are significant technical challenges associated with biomarker assay development, and the integration of such assays into clinical practice, including how issues of quality assurance and quality control impact on this process. The lifecycle of a biomarker progresses from initial discovery in a research laboratory through a research assay to a clinical test that provides actionable information for diagnosis, prognosis or treatment prediction. A test procedure must be analytically and clinically valid to reassure the medical community and patients that the information is accurate and reliable. Analytical validation includes determining the limit of detection (also called analytical sensitivity), precision and reproducibility. Clinical validation includes determining the true positive (sensitivity) and true negative (specificity) rates for the condition of interest, as well as the positive and negative predictive values, with test accuracy critical to the overall cost-effectiveness of precision medicine approaches [6]. Finally, with these requirements met, a test must have clinical utility; that is, the test should provide information to the physician and patient who directly inform treatment decisions. Two types of tests exist, those that are manufactured, validated and distributed by commercial organisations to third-party laboratories (called *in vitro* diagnostic devices) and those that are established, validated and performed by a single laboratory (laboratory developed tests). In the US, the former are regulated by the Food and Drug Administration (FDA), the latter by the Center for Medicare and Medicaid Services and individual states such as New York. In the EU, the requirements for companion diagnostics are evolving following the recent publication of the new *in vitro* diagnostic medical devices regulation [7]. Independent of the mechanism of regulatory oversight, approval for a new test to be offered depends on the test having been shown to (a) measure what it claims to measure for the condition and patient population it was designated to (intended use); (b) be analytically and clinically valid and (c) have clinical utility. If these conditions are met, a test for a new biomarker can be offered to the general patient population.

The potential utility of comprehensive genomic profiles (CGPs) has grown as more targeted therapies have become available to physicians, with the expectation that such profiles might provide information that could dramatically transform patient care. CGPs have the potential to address challenges associated with the selection of appropriate targeted therapies by identifying different tumour-associated alterations across a large panel of cancer relevant genes, including base substitutions, insertion-deletions, gene copy number alterations and preselected chromosomal rearrangements [8,9]. In addition, genomic signatures such as microsatellite instability and tumour mutation burden may also be informative in this context [10]. However, designing, developing and reproducibly running an NGS assay or other high-throughput technology based on deriving CGPs or even using relatively simple immunohistochemistry-based biomarker assays in daily clinical practice, has been shown to be extraordinarily challenging, often eliciting confusion in the field. The move from a

research and development platform to clinical use requires comprehensive validation in a clinical laboratory setting, as well as ongoing quality control and quality assurance monitoring.

To address the challenges associated with bringing NGS CGPs into the clinical environment, several organisations have generated written guidance and have provided guidelines for best practice. Among others, these include the Next-generation Sequencing: Standardization of Clinical Testing (Nex-StoCT) workgroup [11], New York State, the College of American Pathologists and Clinical Test Evaluation Process Analytical and Clinical Validity. Many of the standards, guidelines and recommendations overlap among these and other sources and should be used by clinical laboratories as a starting point in developing quality systems that will support reproducible and accurate CGP results. Part of assay development and validation should be focussed on applying the requirements and guidance in a way that is technically meaningful for that specific assay. Meeting these requirements should never be a ‘box checking’ exercise but rather should address the underlying risk that the requirement is intended to address [12]. Furthermore, software development and validation is just as critical to the quality of an NGS CGP assay and should be managed with the same level of rigour as work completed in the laboratory.

Integrating complex new methods and changes into clinical decision-making can be challenging and, if not managed appropriately, may introduce the risk of misclassification of patients to particular treatments [13,14]. Examples of such changes might include the addition of content to an existing assay, or the introduction of a new method such as a cell-free DNA assay or RNA sequencing. New types of assays would likely have unique technical challenges that would need to be addressed through design, development and validation activities. Risks can be mitigated by planning early and involving a cross-functional team during design, validation and transfer of a new process or product. As well, a robust-change control process based on risk facilitates a smoother transition of changes and will reduce unintended consequences. Part of introducing any change or new assay should always include installation qualification, operational qualification, performance qualification and process performance qualification of equipment, facility and processes, followed by final validation performed under production conditions and monitoring of key process and performance metrics [15,16].

It is arguable as to whether genomics precision medicine approaches have so far failed and not yet truly delivered, added value to patients in daily practice [17–21]. The Cancer Genome Atlas project has shown that only 50–60% of mutated genes are transcribed and only 30–60% of mRNAs are translated. To understand the complexity of cancer, the proteome has consequently been shifted back into the research focus, mostly due to a higher awareness of the importance of quality assurance measures to enhance the reproducibility of results [22]. In particular, understanding the link between genetics and phenotype is seen by many as essential for further progress. Therefore, network science (also called systems biology) approaches may be necessary to integrate all information obtained from the patient’s tumour at the DNA, RNA and protein level. It may be argued that our increasing understanding of the cancer genome has outpaced our ability to usefully implement those findings in the clinic, explaining partly the apparent discordance between the amount of

genomic information generated and the apparent lack of use in daily practice. It is important to note in this context that gene and protein expression and DNA quality may be significantly affected by surgical procedures and postsurgical processing of tissue samples [23–26]. Within minutes of cold ischaemia time, phosphorylation of signalling molecules, as well as expression levels of cancer-relevant receptors such as epidermal growth factor receptor may change, making it more difficult to understand complex cancer biology when tissues are not collected in a uniform way and, most importantly, as soon as possible after completion of surgical resection. At least an exact documentation of intra and postsurgical processing time should accompany every tissue block to mitigate potential variation in analytical data. The lack of such standardised tissue collection processes for target validation and drug development may be one of the contributory factors explaining why not all of academic landmark studies in this area can be reproduced [27].

When it comes to the future of precision medicine, with its goal of identifying optimal treatments by understanding individual tumour biology, it will be critical for certain types of predictive biomarker assays to include the assurance of tissue quality in the diagnostic process. Otherwise, the failure rate of targeted therapies that rely on such predictive tests is likely to remain too high, and healthcare providers would be well advised not to reimburse such approaches. In this context, it will be important to develop an appropriate clinical and pathology infrastructure that allows collection of tissues and clinical data under identical protocols in a global clinical network. A key effort will be to ensure that tumour tissues are always collected rapidly in the surgical suite and that samples are processed under identical protocols. The development of appropriate standard protocols that control pre-analytical variables is therefore imperative, whether this is in academic, industry or industry-supported settings. Implementing such tissue-quality control procedures in cancer care might make the difference between the failure and success of a new drug or biomarker, thereby reducing development costs and leading to more drugs with better tests.

4. Assay development

The optimal approach for biomarker discovery and validation may well be to have the development of such assays integrated into oncology clinical trials and thereby intrinsically linked to the wider drug development process. In this context, there are particular considerations that are relevant to assay design for early (phase 0/I) trials seeking evidence of agent-target engagement. For example, when establishing a new pharmacodynamic biomarker, it is first necessary to validate the assay itself, which will require preliminary testing on specimens as similar as possible to those that will be collected during the proposed trial. In addition, calibrators are essential in defining a new assay, both in relation to the amount of clinical material present in each assay and the amount of drug signal that may be generated. In particular, it is critical to define the baseline sample variability to understand the required dynamic range and sensitivity of the assay in relation to detecting a real drug-associated effect. A further consideration is that experience has shown the limitations of xenograft model systems in relation to the prediction of both the pharmacodynamic behaviour and the efficacy of drugs in humans. Also bearing in mind the possibly confounding effects of tumour heterogeneity, the most effective approach for pharmacodynamic biomarker development, especially for first-in-human trials, is therefore

likely to be a multiplex testing strategy, including, for example, assays measuring agent-target interaction alongside others reporting on downstream pathway effects. A further advantage of using such a multiplex approach in early-phase trials is that the insights gained may be informative in relation to designing candidate-predictive biomarkers for testing in later stage phase II or III trials.

Immunohistochemical tests in particular may currently and in the future be used to guide clinical decisions. In a prognostic test the result is associated with a clinical outcome, but the read-out is generally qualitative, with expression status often assigned as positive or negative. However, a predictive immunohistochemical test that will guide therapy may be quantitative, having been appropriately calibrated using specimens from cases with known treatment and outcomes. Such tests can be very challenging to develop. Several specific recommendations can be made: although this might be a reasonable starting point, do not automatically assume that the drug target is the best predictive biomarker, with other markers in the same or unrelated pathways potentially being equal or more informative; do not apply an existing test to a new intended use without considering the possibility that it might have to be re-engineered for the new purpose; do not expect the same scoring system to be equally predictive across different tumour types or settings and consider that a technical improvement in a biomarker assay, such as the development of an antibody with higher sensitivity, might not necessarily lead to improved clinical performance.

Turning to the capabilities afforded by molecular imaging, it is now apparent that the use of radio-labelled compounds can accelerate all phases of drug development. In early-phase trials, this approach can be used to confirm that the drug target is expressed and accessible, to assess the pharmacokinetics and biodistribution of an agent and by looking at off-target effects, to anticipate some toxicities [28]. Imaging can also be used to optimise dose and scheduling. It should be noted that the radiochemistry used to label drugs for such studies must be acceptable to both pharmaceutical manufacturers and regulatory authorities. In particular, the radio-labelling should not affect the properties of the drug, such that no additional toxicology studies are needed. The labelled compound should additionally be produced in compliance with Good Manufacturing Practice, in a cost-effective manner, and the labelling process should not delay the initiation of clinical trials. On the imaging side, standardised and quantitative procedures are required.

When considering the particular challenges of biomarker development in immunotherapy trials, it is becoming clear that response hypotheses for immunotherapy agents carry more uncertainty than those for other types of targeted agents because the effects are indirect. Preclinical models in mice have been useful for investigating mechanisms, but they do not fully represent the human tumour and have not accurately predicted which indications will respond clinically. Overall, a better baseline understanding of the immunophenotype is needed, taking into account the tumour micro-environment and peripheral pharmacodynamic biomarkers including cytokines and circulating immune-cell populations.

5. Access and regulatory hurdles

The EORTC SPECTA platform was developed to improve the collaborative efforts of academia and industry partners by providing access to molecular testing to patients not participating in clinical therapeutic trials and to provide a unique European longitudinally developed common infrastructure for translational research projects and bio-banking of samples. The use of such collaborative platforms should increasingly facilitate patient access to precision medicine trials. Some of the challenges that have been noted on the NCI precision medicine trial initiatives include the quality of archival tissue used for genomic analysis, the actual mutation prevalence rates compared with those expected and patients' inability to participate in trials despite being eligible (rapid progression of their disease, worsened performance status, start of another therapy or death) have been noted. Furthermore, two trials focussing on lung cancer, i.e. Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trials (ALCHEMIST) and Lung Cancer Master Protocol (Lung-MAP) needed to undergo major amendments when nivolumab was approved by the FDA, based on a demonstrated survival advantage over docetaxel in the second-line setting. In the Lung-MAP trial, the control arm of docetaxel was deemed to no longer be ethically sound and the design was modified to single-arm phase II studies, whereas an arm studying nivolumab in the adjuvant setting was added to the ALCHEMIST trial.

The identification of multiple, potentially, clinically relevant biomarkers in common cancers such as lung cancer has led to the subdivision of existing classifications into multiple, smaller, molecularly defined subtypes. This has in turn led to novel clinical trial designs like master/basket/umbrella protocols with adaptive designs and surrogate and intermediate end-points. The ideal cut-off points for tests based on the expression level of potential biomarkers such as PD-L1 remain controversial [29]. However, analytical and clinical validation of new biomarkers and new technologies is essential for the safe and effective use of therapeutic targeted drugs. In addition, the clear labelling of indications and the limitations of such biomarkers and tests is essential. The FDA has published several guidance documents and held workshops to help develop personalised therapies as rapidly as possible [30]. The Japanese Pharmaceuticals and Medical Devices Agency has also recently published evolving Japanese regulations on companion diagnostics [31] and is currently discussing how to regulate NGS-based diagnostic systems and evaluate equivalency between plasma samples and tissue samples. In the EU, the EMA has published a number of pharmacogenomics guidelines, including guidance on the co-development of pharmacogenomic biomarkers and assays in the context of drug development [32].

We must also consider the challenges faced by patients, especially in relation to understanding the terminologies used for precision therapies and a lack of understanding that targeted agents may not be the best treatment option for everyone or even perhaps for all patients with a particular tumour driver mutation. Improved dialogue between physicians and patients was identified as the key to addressing such concerns. In particular, the potential benefits and toxicities of particular precision medicine approaches need to be explained by the physician, while not discouraging participation in clinical trials. It was noted that cancer patients in general are more willing to accept a higher level of treatment-related risk than it might be expected because of the risk of death that they face. From the pharmaceutical

company's perspective, choosing the best biomarkers in the arena of multiple possibilities and picking the right drug amongst many available remains challenging, along with the burden of not only getting the drug but also the appropriate companion diagnostic approved through the regulatory agencies, which may differ globally.

It is clear that with biomarker assays and related technologies constantly evolving, analytical and clinical challenges will increasingly impact on clinical decisions and regulatory acceptability. Pre- and post-marketing balance with the increased role played by real-world evidence requires regulatory adaptability. It needs to be emphasised that there is a social benefit to clinical science, as related to the better integration of research and care. To facilitate this, more open dialogue is needed across stakeholders for new solutions embracing patient preferences, revisiting clinical research methodology, ensuring appropriate data interpretation and delivering optimal and affordable access to robustly developed treatment. Statisticians have also indicated the risks inherent in the level of uncertainty we are facing in relation to the interpretation of the significance of molecular alterations within tumours. The appropriate limits for risk tolerance therefore need to be re-assessed by all stakeholders, taking into account this potentially higher level of uncertainty; this represents a major regulatory challenge. The need to control uncertainty fed back into the earlier discussions for pre-analytical and analytical quality which sustain data generation and interpretation, highlighting the continuum of the process through drug development and the need to have a suitable chain of actions between stakeholders. While many parameters are evolving, regulatory systems may be stretched in the future from considering one drug/one assay to considering one or multiple drugs/genomic panels. However, demonstrating clinical utility remains the ultimate goal and this can only be achieved through robust clinical trials.

Taking all such issues into account, a debate was held during the meeting on the following topic: can cancer precision medicine be delivered in a sustainable and affordable manner? Cancer precision medicine was first defined as the concept of delivering personalised multiagent therapies that are customised based on the unique and often complex genomic signatures of tumours and the genomic background of patients. This concept includes the notion that combinations of targeted agents will be prescribed on the basis of complex analyses of complex data, with all the caveats about data quality and data processing but without extensive rigourous clinical experience regarding efficacy and safety to guide physician recommendation and patient counselling. Any such debate should not now be about whether or not cancer diagnosis and treatment should be based on individual characteristics that affect outcomes such as histology and stage; and increasingly, on molecular characteristics. Also, the proposition that increasing refinements will be made in targeted therapies and associated molecular diagnoses should not be in dispute. However, we must consider at what point does precision cancer medicine become therapeutic anarchy, where individualised treatment plans could be based on many different diagnostic platforms and treatment recommendation algorithms that could vary among practitioners? There is now a clear consensus that we are close to the point of anarchy, where patients and oncologists are abandoning standard therapy to use unproven precision medicine regimens, as represented by off-label drug use based on non-clinically validated genomic biomarkers. There are initiatives underway to gather data on these practices, such as the American

Society of Clinical Oncology's CancerLinQ and TAPUR (Targeted Agent and Profiling Utilization Registry) initiatives.

A further consideration is whether the research focus on precision medicine will likely benefit only high-income individuals in resource-rich countries, where sophisticated diagnostics and a wide range of therapeutic agents are available, whereas low-income individuals and resource-poor countries would benefit from the opposite approach, focussed on delivering standard therapies with proven benefit that could be used in broad unselected populations. In short, will the research focus on precision cancer medicine only benefit the privileged population of the first world? There was consensus on this item also. While it is possible that knowledge gleaned from precision medicine, patient experience could ultimately be applied to less developed countries, largely the focus on cancer precision medicine diverts resources from other approaches that could help more people.

Another key question is whether the rush to commercialise diagnostic testing is pushing precision medicine too quickly into the clinic? There was a consensus among participants that this is indeed the case. It has been estimated that the precision medicine market in 2022 will be worth $88 billion [33] and that between 100 million and as many as 2 billion human genomes could be sequenced by 2025 [34]. Diagnostic technology companies' and medical institutions' commercial interests have converged in a rush to establish themselves in the market and to sell the concept of precision medicine long before clinically validated diagnostics tests, sufficient genetic target coverage with active drugs and strategies to evaluate cancer precision medicine effectiveness have been developed.

Therefore, there was general agreement on the overall state of integration of cancer precision medicine into clinical practice. Despite the agreement on the specific questions, there was disagreement over the ultimate outcome. It might be argued that the sustainability and affordability of precision medicine can be considered as an overall process, one which requires scientific discipline but which will ultimately lead to advances in cancer care. By contrast, it cannot be ignored that there is still a widely held belief that the roll-out of cancer precision medicine largely constitutes a trend that has received a lot of hype but one that will not at the current time lead to widespread changes in clinical practice.

6. Conclusions and recommendations

In the narrowest sense, the answer to the question as to whether precision medicine can now be delivered in a sustainable and affordable manner to patients with cancer is arguably yes it can, in so far as certain clinically validated molecular biomarkers may be used to select patients for particular targeted therapies, with clear patient benefits. Where such biomarkers allow the restriction of administration to the fraction of the overall patient population most likely to derive a significant benefit, they can improve the cost-effectiveness of a given treatment while sparing patients who are unlikely to benefit from the risk of unnecessary toxicity. The focus of the IBCD meeting, which involved stakeholders from industry, regulatory agencies, academia and government, was to explore the practical issues relating to how biomarker assay development could be more effectively integrated into the drug development and regulatory approval processes to drive further progress in cancer-related

precision medicine, all this benefiting society within a healthcare context. This is of particular importance given the emergence of commercial entities offering for-profit tumour DNA sequencing services directly to cancer patients or through the hospital-setting, which may in turn create patient demand for non-evidence-based, off-label, targeted therapies. Taking into consideration the presentations and discussions that took place during the meeting, we have therefore developed a series of critical points and consensus recommendations relating to the forward development of precision medicine approaches in oncology.

- Assays and technologies are entering daily clinical practice much too early, without proper analytical validation [15,16], including the determination of false positive and false negative rates, with false positive tests in particular leading to the administration of expensive drugs to patients unlikely to benefit, which in turn places an unjustifiable financial burden onto healthcare systems. This premature roll-out is mainly driven by commercial interests and aggressive marketing strategies by diagnostic technology companies and academia. This pushes laboratories, patients and clinicians to adopt assay practices and treatments long before clinically validated diagnostic tests, sufficient genetic target coverage with active drugs, and strategies to evaluate cancer precision medicine effectiveness have been developed and more importantly evaluated. Consequently, the added value to society of precision medicine approaches is, at present, debatable and currently (too) expensive for healthcare authorities, impeding sustainability; more scientific discipline is required.
- Improved dialogue between genomic medicine-informed physicians and patients is crucial in providing to patients' accurate assessments of potential benefits, limits, uncertainties and toxicities of precision medicine approaches, while not discouraging participation in clinical trials, thus avoiding the current treatment anarchy of patients and clinicians sometimes abandoning standard therapy to use unproven targeted drugs. This necessitates educational frameworks for clinicians, laboratories and patients.
- Assay validation for use in clinical trials requires preliminary testing on specimens as similar as possible to those that will be collected on the proposed trial, to ensure that the assay has the necessary analytical sensitivity and dynamic range and to assess the baseline variability in assay results. Confounding effects of tumour heterogeneity can be mitigated by using multiplex testing strategies to capture agent-target interaction alongside other tests reporting on downstream pathway effects.
- Any assay and corresponding software development and validation should be focussed on achieving fitness for the specific purpose that the assay is intended to address.
- Lack of standardised tissue-collection processes for target validation and biomarker development, with unknown pre-analytical parameters, necessitates a framework for investments in appropriate clinical and pathology infrastructure

that allows collection of tissues and clinical data under identical protocols in a global clinical network.

- Before an assay can appropriately be offered to the general patient population within a healthcare setting, any new test should at the end of the validation cycle be shown to have clinical utility. It is imperative that a framework is developed through close collaboration between industry, regulatory agencies, government, patient representatives and academia, early in the development and validation process, including an assessment of level of risk tolerance for the uncertainty of interpretation of the significance of all genomic alterations found and an assessment of the necessity for real-world confirmation of clinical trial results. This would avoid a too-rapid implementation of commercially developed assays and technologies in clinical practice.
- Among the many different possibilities for biomarkers and drugs, the following principles may help in choosing the most appropriate combinations for companion diagnostic development: (1) Bear in mind that the drug target might not be the best predictive biomarker, with other markers in the same or unrelated pathways potentially being equally or more informative; (2) Consider the possibility that an existing test might have to be re-engineered before it is applied to a new intended use; (3) Be aware that the same scoring system/cut-offs might not be equally predictive across different tumour types or settings and (4) Consider that a technical improvement in a biomarker assay, such as the development of an antibody with higher sensitivity, might not necessarily lead to improved clinical performance.
- As exemplified by biomarker development in the context of immunotherapy, no general regulatory framework exists for the approval of different, simultaneously developed, commercial biomarker systems measuring particular biological characteristics and defining cut-offs that may be relevant to a specific class of targeted drug. As there are no formal barriers to companies and other agencies collaborating within the existing system to resolve such issues, a common-sense approach to improve the current situation would be to establish developmental frameworks among all stakeholders including industry, regulatory, government, patient representatives and academia to facilitate comparisons of the performance of the assays before regulatory approval and harmonising the approval process subsequently across regulatory agencies in different continents.
- Finally, precision medicine approaches should be able to benefit not only high-income individuals in resource-rich countries but also low-income individuals in both resource-rich and resource-poor countries.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Medical writing assistance was provided by Jim Heighway PhD, Cancer Communications and Consultancy Ltd, Knutsford, UK and was funded by the EORTC. IBCD conference was made possible due to the generous support from Amgen (Europe) GmbH; AstraZeneca LP; Boehringer Ingelheim Pharma GmbH & Co. KG; Bristol-Myers Squibb; Celgene International II Sàrl; Région de Bruxelles-Capitale (Innoviris); Janssen Research & Development; LLC, KEOSYS Medical Imaging, Lilly USA, LLC; Pfizer Pharma GmbH; F. Hoffmann-La Roche Ltd; Millennium Pharmaceuticals, Inc. and Transgene SA. Roberto Salgado was supported by the Breast Cancer Research Foundation (BCRF) (BCRF-16–182).

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