

CDDF MULTI - STAKEHOLDER WORKSHOP on Biomarkers and Patient Access to Personalised Oncology Drugs in Europe

24th and 25th September 2018

Meeting report



List of abbreviations	3
Programme	5
Background and objectives.....	6
Introduction.....	6
Heinz Zwierzina (CDDF / Medical University of Innsbruck, Austria)	6
Personalised Medicine- The Future of Drug Development	8
Academic perspective on enabling precision immuno-oncology	8
Zlatko Trajanoski (Medical University of Innsbruck, Austria)	8
Industry perspective: the challenges & opportunities of personalized/ stratified medicine from a development and patient access perspective	10
Michael Zaiac (Novartis, Switzerland).....	10
Biotech perspective	11
Kieran O’Kane (Biosesix, United States)	11
Role of in vitro diagnostics in the authorization of anticancer medicines	13
Harald Enzmann (BfArM, Germany)	13
Payer’s perspective.....	14
Anouk Waeytens (RIZIV / INAMI, Belgium).....	14
Patient advocate’s perspective	15
Francesco De Lorenzo (ECPC, Italy).....	15
Discussion	16
Challenges for Access to Biomarkers.....	18
In Vitro Diagnostics (IVD) - European regulatory perspective.....	18
Markus Paulmichl (European Medicines Agency, Austria)	18
Case stories	18
David Browning (Oxford Cancer Biomarkers, United Kingdom)	18
Kieran O’Kane (Biosesix, United States)	19
HTA perspective	20
Sonia Garcia Perez (AEMPS, Spain).....	20
Patient advocate’s perspective	22
Kathi Apostolidis (ECPC, Greece)	22
Regulatory point of view: Industry perspective	22
Claudia Dollins (Merck KGaA, Germany, representing the EBE EFPIA Personalised Medicine Working Group)	22
Personalised cancer care: translating promise into practice - with multi-stakeholder approach.....	24
Titta Rosvall-Puplett (Bristol-Myers Squibb, Belgium).....	24
Discussion	25
The Way Forwards.....	26
Fostering collaboration in the era of precision oncology: academic perspective.	26
Tatiana Prowell (John Hopkins Kimmel Comprehensive Cancer Center, United States)	26
Strategies to allow indication-based payment for biomarkers	27
Afschin Gandjour (Frankfurt school of Finance & Management, Germany)	27

Developing practical guidance for Member States on implementing precision genomics in medical care	28
Marc Van den Bulcke (Sciensano, Belgium)	28
Access to biomarkers: “Are we ready for value-based precision medicine?”	29
Patricia Carrigan (Bayer, Germany)	29
Payer’s perspective: sustainability of healthcare systems	30
Annie Pannelay (United Kingdom)	30
Potential of real-world evidence for access to biomarkers	31
Jesús María Hernández Rivas (HARMONY/ IBSAL, Spain)	31
Discussion	31
Next Steps.....	32
Introduction on the EUnetHTA actions	32
Sonia Garcia Perez (AEMPS, Spain)	32
The provider’s point of view	33
Santiago Valor (Labco, Spain)	33
Multi-stakeholder approaches for addressing barriers to precision medicine:	
Diagnostic Quality Assurance pilot	34
Lindee Goh (Tapestry, United States)	34
Discussion	35
Perspectives on next steps	36

List of abbreviations

AEMPS: Agencia Española de Medicamentos y Productos Sanitarios - The Spanish Agency for Medicines

ASCO: The American Society of Clinical Oncology

BfArM: Bundesinstitut für Arzneimittel und Medizinprodukte - The German Federal Institute for Drugs and Medical Devices

BJMO: Belgian Journal of Medical Oncology

CDDF: Cancer Drug Development Forum

CDx: Companion Diagnostic

CNV: copy variation number

CODE: collaboration for oncology data in Europe

DNA: Deoxyribonucleic acid

EAPM: European Alliance for Personalised Medicine

ECOG: Eastern Cooperative Oncology Group

ECPC: European Cancer Patient Coalition

EFPIA: The European Federation of Pharmaceutical Industries

EGFR: Epidermal Growth Factor Receptor

EGRF: Epidermal Growth Factor Receptor

EMA: European Medicines Agency

EMQN: Molecular Genetics Quality Network

EQA: External Quality Assessments

EU: European Union



EUnetHTA: European Network for Health Technology Assessment
FDA: Food and Drug Administration
G-BA: Gemeinsamer Bundesausschuss - the German Federal Joint Committee
GDPR: General Data Protection Regulation
GenQA: Genomics Quality Assessment
GEP: gene expression profiling
HTA: health technology assessment
IBSAL: Institute of Biomedical Research of Salamanca
ICD: International Classification of Diseases
ICT: Information and communications technologies
IHC: Immunohistochemistry
INAMI: the Belgian National Institute for Health and Disability - Institut national d'assurance maladie-invalidité
INCa: Institut National du Cancer ... The French National Cancer Institute
ISH: In Situ Hybridization
IVD: in vitro diagnostics
KOLs: Key Opinion leaders
MAAA: Multianalyte Assay with Algorithmic Analysis
MALDI-TOF: Matrix Assisted Laser Desorption Ionisation-Time of Flight
MCDA: multiple-criteria decision analysis
MHRA: The Medicines and Healthcare products Regulatory Agency
NGS: Next Generation Sequencing
NHS: National Health Service
NICE: The National Institute for Health and Care Excellence
NSCLC: Non Small Cell Lung Cancer
ORR: Objective Response Rates
PCR: Polymerase Chain Reaction
PD-1: Programmed Death - 1
PD-L1: Programmed Death - Ligand 1
RADAR
RCT: Randomised Controlled Trial
RIZIV: Rijksinstituut voor ziekte- en invaliditeitsverzekering - the Belgian National Institute for Health and Disability
RWE: Real World Evidence
SPOT/Dx: Sustainable Predictive Oncology Therapeutics and Diagnostics

Programme

Day 1 Monday 24th September 2018	
13:00	Introduction - Heinz Zwierzina (CDDF / Medical University of Innsbruck, Austria)
SESSION 1: PERSONALISED MEDICINE - THE FUTURE OF DRUG DEVELOPMENT	
Co-chairs: Sonia Garcia Perez & Heinz Zwierzina	
13:10	Academic perspective on enabling precision immuno-oncology - Zlatko Trajanoski (Medical University of Innsbruck, Austria)
13:30	Industry perspective: the challenges & opportunities of personalized/stratified medicine from a development and patient access perspective - Michael Zaiac (Novartis, Switzerland)
13:45	Biotech perspective - Kieran O'Kane (Biodesix, United States)
14:00	Role of in vitro diagnostics in the authorization of anticancer medicines - Harald Enzmann (BfArM, Germany)
14:15	Payer's perspective - Anouk Waeytens (RIZIV / INAMI, Belgium)
14:30	Patient advocate's perspective - Francesco De Lorenzo (ECPC, Italy)
14:45	Roundtable discussion
15:40	Coffee break
SESSION 2: CHALLENGES FOR ACCESS TO BIOMARKERS	
Co-chairs: Isabelle Huys & Michael Zaiac	
16:10	In Vitro Diagnostics (IVD) - European regulatory perspective - Markus Paulmichl (European Medicines Agency, Austria)
16:30	Case stories - David Browning (Oxford Cancer Biomarkers, United Kingdom) Kieran O'Kane (Biodesix, United States)
16:50	HTA perspective - Sonia Garcia Perez (AEMPS, Spain)
17:05	Patient advocate's perspective - Kathi Apostolidis (ECPC, Greece)
17:20	Regulatory point of view: Industry perspective - Claudia Dollins (Merck, Germany)
17:35	Personalised cancer care: translating promise into practice - with multi-stakeholder approach - Titta Rosvall-Puplett (Bristol-Myers Squibb, Belgium)
17:50	Roundtable discussion
Day 2 Tuesday 25 September 2018	
SESSION 3: THE WAY FORWARD	
Co-chairs: Claudia Dollins & Tatiana Prowell	
09:05	Fostering Collaboration in the Era of Precision Oncology: Academic Perspective Tatiana Prowell (Johns Hopkins Kimmel Comprehensive Cancer Center, United States)
09:20	Strategies to allow indication-based payment for biomarkers - Afschin Gandjour (Frankfurt school of Finance & Management, Germany)
09:35	Developing practical guidance for Member States on implementing precision genomics in medical care - Marc Van den Bulcke (Sciensano, Belgium)
09:50	Access to biomarkers: "Are we ready for value-based precision medicine?" - Patricia Carrigan (Bayer, Germany)
10:05	Payer's perspective: sustainability of healthcare systems - Annie Pannelay (United Kingdom)
10:20	Potential of real-world evidence for access to biomarkers - Jesús María Hernández Rivas (HARMONY/ IBSAL, Spain)
10:35	Roundtable discussion
11:05	Coffee break
SESSION 4: NEXT STEPS	
11:25	Introduction on the EUnetHTA actions - Sonia Garcia Perez (AEMPS, Spain)
11:45	The provider's point of view - Santiago Valor (Labco, Spain)
12:05	Multi-stakeholder approaches for addressing barriers to precision medicine: Diagnostic Quality Assurance pilot - Lindee Goh (Tapestry, United States)
12:15	All stakeholders' perspective on the next steps
12:35	Roundtable with the programme committee

Background and objectives

Within the next 5 years, cancer incidence will increase up to 15 million patients, with a continued upwards trend. This puts more emphasis on the need for cancer prevention, research and effective anticancer drugs, including rapid licensing and market access for patients.

The unmet need for minimally invasive tests to determine subgroups of patients with a high probability of response to therapy is critical to accelerate drug development, reduce costs, increase efficacy and bring new and effective agents to patients as quickly as possible.

Biomarkers can be objectively measured as indicators of pharmacologic response to therapeutic interventions, and as such hold great potential to predict clinical outcomes and define a personalised treatment strategy.

In many instances a single marker cannot offer the necessary sensitivity and specificity, therefore research is now focussed on the development of multiplexed assays that screen multiple genes and proteins at the same time.

Regulatory challenges, the hurdles to achieve reimbursement, and access to clinical data are all barriers that will need to be addressed to achieve widespread use of biomarkers in clinical practice in future.

The multi-stakeholder workshop on Biomarkers and Patients' Access to Personalized Oncology Drugs in Europe was organised by the Cancer Drug Development Forum (CDDF), in collaboration with the European Cancer Patient Coalition (ECPC). CDDF is a not-for-profit association, whose mission is to improve the efficiency of oncology drug development and delivery by providing a unique forum for discussion where all those involved in cancer drug development can meet to address hurdles and explore potential solutions together.

This workshop aimed to give an overview of the status quo, challenges and developments in this space, as well as facilitating a collaborative discussion between regulatory bodies, HTAs, healthcare providers, academics, patients and industry on the challenges of equal access to personalised therapy within and between European countries.

Introduction

Heinz Zwierzina (CDDF / Medical University of Innsbruck, Austria)

Dr Zwierzina introduced the focus of the meeting as the science of personalised medicine (PM) and biomarkers and discussed how to align stakeholders on the importance of bringing biomarkers to the European market, and addressing the numerous challenges, including the heterogeneity of the European market compared to the US where biomarkers are concerned.

For biomarker development there are two basic approaches, one is hyper individualised therapy including biomolecular phenotyping, the other is based on biomarker-defined subgroup analysis (where industry and academia have been very successful).

Looking at individualized therapy based on biomolecular phenotyping, the Oncotyrol project is a collaborative initiative in Austria between commercial, academic and clinical enterprises (financed by the hospital administration), which aims to bring research into biomarkers and commercial testing together [1]. Currently, patient biopsies are being sent to Arizona for phenotyping by Caris, with results informing treatment decisions. So far over 200 patients have been tested (each with solid tumours, ECOG status 0-2, and no "standard therapy" available). The aim is for patients to have repeated biopsies as the tumour changes subsequent to treatment, however so far "re-biopsies" are often not possible for reasons including metastases not being accessible, and patient refusal. Independent from the

Oncotyrol program, tests are routinely done for HER-2, EGFR mutation status, K-RAS, B-RAF, EML4-ALK, and MSI, depending on the histopathologically defined disease entity.

Initially next generation sequencing (NGS) comprised only 30 targets, now over 200 targets are defined and supplemented by immunohistochemistry and RNA sequencing. The original aim was for the analysis to lead to highly individualised therapy, however the vast majority of patients return to chemotherapy. Additionally, the hope was to find druggable mutations in a variety of cancer types, but this has not happened yet.

Considering molecular phenotyping, many questions still remain.

- In theory there should always be a fresh biopsy before initiating targeted therapy, however in practice this is can be challenging. To address this, liquid biopsies should be a priority for the future.
- There is no curative therapy approach based on molecular phenotyping (with the exception of immunotherapy).
- Development of secondary resistance in all tumours is well known, however phase II and III trials may no longer be possible in these populations due to the small patient numbers (emphasising the need for new models of therapy development).
- In situations where patients have two or more mutations (each of which can be targeted by a drug that hasn't completed a phase II trial), combining these drugs in practice poses ethical challenges due to toxicity.

Based on these issues, the key question is whether a completely tailored approach will ever be possible. Currently individualized therapy defined by biomolecular phenotyping leads to chemotherapy in the vast majority of patients, partly because the majority of biomarkers are not suitable targets for a drug. Therefore, in the majority of cases, treatment is still defined by pathohistology. Dr Zwierzina's conclusion is that a completely tailored approach is achievable, however it will take time and alignment amongst stakeholders and processes.

Looking at the option for treatment of biomarker-defined subgroups (where molecularly defined subgroups are identified to minimise the risk of potentially effective drugs failing in phase III development), trastuzumab provides the best example, where the company developed a therapy for a biomarker defined breast cancer population, and only included HER2+ patients.

The identification of relevant biomarkers is very challenging, due to a high level of redundancies across biological networks. Additionally, biopsies pose further challenges due to the heterogeneity of samples based on their exact collection site (using a needle) in the tumour (with further evidence that tumours and metastases can also differ significantly).

To demonstrate the potential value of predictive biomarkers, Dr Zwierzina shared findings from the PROSE clinical trial [2]. Investigators assessed the predictive power of a test to stratify non-small cell lung cancer (NSCLC) patients according to their likely response to an EGFR tyrosine-kinase inhibitor. The study found that Matrix Assisted Laser Desorption Ionisation-Time of Flight (MALDI-TOF) based serum proteomics was predictive of differential benefit in overall survival for erlotinib vs. chemotherapy in second-line, and patients identified as likely to have a poor outcome with erlotinib performed better on chemotherapy than on erlotinib. Despite a large prospective randomised controlled trial (RCT) to support the predictive value of the test, the positive outcome still does not support access in Europe (highlighting a key challenge).

Looking to the future, biomarkers will increasingly be integrated into drug development, with serum blood markers overcoming some of the logistical challenges of taking repeated biopsies. For this, access to serum plasma banks will be crucial. From the healthcare system

perspective, access to biomarkers that define the patients that may or may not respond to therapy will also be crucial to improve treatment standards and efficiency of care.

To conclude, Dr Zwierzina emphasised that predictive biomarkers that define subgroups of patients as well as molecular phenotyping will change paradigms of drug development. 'Big data' analyses will be an important part of the process (as the number of clinical trials are predicted to reduce significantly). Overall, this presents a significant challenge and opportunity for multiple stakeholders (including academics, industry, regulatory authorities, HTA bodies and Payers), however alignment on the optimal approach to ensure development and access for biomarkers and companion diagnostics (CDx) in Europe will be key.

Personalised Medicine- The Future of Drug Development

Academic perspective on enabling precision immuno-oncology

Zlatko Trajanoski (Medical University of Innsbruck, Austria)

Dr. Trajanoski spoke regarding the promise of enabling precision immuno-oncology, and associated challenges from the academic perspective.

Considering the increasing number of clinical trials with immunotherapies (3042 trials in December 2017), and the number of new patients that need to be recruited for these trials, there will be insufficient patients available to carry out the research with meaningful outcomes.

In this context, there are some major issues regarding cancer immunotherapy.

- Identifying mechanisms of intrinsic resistance to checkpoint blockade, for instance predictive biomarkers for response [genetic, immunological, metabolic, microbiome], is important because whilst 20% of patients respond, 80% do not respond;
- Identifying mechanisms of acquired resistance to checkpoint blockade (e.g. what are the predictive markers for relapse?) is relevant because 30% of patients who respond to checkpoint blockage eventually relapse;
- Identifying combination therapies with synergistic potential, common combination are PD-1/PD-L1 drugs with other therapies.

To illustrate the challenges, Dr. Trajanoski presented two reviews [3, 4] summarising the evidence for candidate biomarkers of response to immune checkpoint inhibitors in melanoma. He explained that so far, none of the biomarkers reviewed has proved efficient, with cohort sizes small, and p values borderline. Further examples of studies with small cohort sizes and borderline p values are shown in **Table 1**.

Table 1: Predictive markers for immunotherapy with anti-PD-1 antibodies in melanoma

Publication	Marker(s)	Cohort size /p Value
Johnson DB et al., Cancer Immunol Res 2016, 4:959-967	Mutational load	n=32/33; p=0.003/0.002
Hugo et al., Cell 2016, 165:35-44	IPRES signature	n=28; p=0.04
Johnson DB et al., Nat Commun 2016, 7:10582	HLA-DR	n=30/23; p=0.055/0.046
Diem et al. Br J Cancer 2016, 114:256-261	LDH	n=29; p<0.001 (ANOVA)
Charoentong et al., Cell Rep	162 immune genes	n=28; p=0.025

2017, 18:248-262		
Ayers et al., J Clin Invest 2017, 127:2930-2939	28 immune genes	n=62; p=0.027

To better understand the challenges with identifying a biomarker for predictive response to checkpoint blockade, Dr. Trajanoski presented findings from a recent paper on the hallmarks of successful immunotherapy which addresses the problems that arise trying to identify these biomarkers [5].

Dr. Trajanoski discussed the findings from further studies [6-8] that explore the use of immune markers such as CD₃ and cytotoxic CD₈ to stratify patients. The type, density and location of infiltrating immune cells within the tumour sample were found to be a good predictor of either tumour recurrence or survival. Understanding the interaction with other components such as the tumour stroma, vascularisation and systemic factors such as circulating chemokines is also important.

Additional challenges include;

- Heterogeneities amongst patients (epigenetic, genetic and immunological), heterogeneities within a single tumour and changes within the tumour, hence the need for multi-region samples taken at multiple time points.
- Extrinsic factors such as metabolism also influence the efficacy of infiltrating the cells.
- Interactions between therapy types such as chemotherapy, radiotherapy and targeted therapies pose further challenges.

What we are missing are techniques to assay the entire complexity of the tumour micro-environment. RNA sequencing has limitations because of use of bulk tissue, and immunohistochemistry cannot be used for all markers. A solution combining RNA sequencing and immunohistochemistry was proposed two years prior to this talk. One takes the bulk of the tumour to perform RNA sequencing, and then using computational methods escalate the type of the tumour infiltrating lymphocytes, also use information from pathology looking at slides to count the number of cells that have infiltrated the tumour, and then this number can be used to upscale the densities of the tumour infiltrating lymphocytes.

Regarding the topic of identifying acquired resistance to checkpoint blockade, this is more complex, because once you start immunotherapy the system changes. There is a concept of immunoediting, so if the tumour is heterogenous and there is no T cell response, then the tumour remains heterogenous. If the tumour is heterogenous and there is some T cell response, then T cells are recognising tumour cells, but then the tumour becomes more homogenous which can be the source of checkpoint blockers. This is not easy to study in humans. A study published on four melanoma patients receiving checkpoint blockers looked at a number of mutations after relapse and calculated the heterogeneity of the tumours. In one patient tumour heterogeneity did not change, in one it increased but in one patient it decreased (which was also seen in the mouse model) [9].

If you have a heterogeneous tumour for which you use the maximum tolerable treatment dose, and you have a mixture of sensitive and resistant cells, then at the maximum tolerable dose you kill all sensitive cells and only the resistant cells will survive. Instead of the maximum tolerable dose, you could use an adaptive dose causing competition between sensitive and resistant cells, not eradicating the tumour but slowing growth. This approach was tried with two patients.

To address the challenges of identifying acquired resistance to checkpoint blockade, liquid biopsies will help. Also, radiomics is an emerging technology, and we may extract something

about heterogeneity just through tumour imaging. Finally, we have to measure the T Cell repertoire in the periphery.

Regarding identifying combination therapies with synergistic potential, Dr. Trajanoski referred to three hundred trials with drugs that have been approved including targeted drugs plus checkpoint blockers. In this context, there are several problems to address in order to select the best combination to treat a specific patient (thereby enabling precision immunology).

- Mutational and neoantigen landscapes are highly individual (extreme heterogeneity amongst antigens between patients).
- Oncogenic signalling is cell context-specific.
- Tumour evolution and immune responses are dynamic and interwoven systems (in general molecular data only from single time points is available).
- Mouse models are not suitable for testing precision immunology (patient-derived xenograft mouse models are immunocompromised; current humanized mouse models cannot mimic the entire complexity of the tumour microenvironment).

To make a prediction on the combination therapies with synergistic potential for a specific patient type, it is necessary to look at data from several time points. Instead of using a single measurement, there is a need to use multiple time points to resemble the complete genetic model of the patient. Hybrid avatars using in vitro and in silico models to run scenarios specific to individual patient types are now a growing area.

To conclude, Dr. Trajanoski stated that the identification of predictive biomarkers for response to immune checkpoint blockers is challenging and requires novel comprehensive assays or assay combinations to identify the best markers. There is also a need for identification of predictive markers for relapse, requiring non-invasive assays for tumour monitoring, along with greater use of avatars and perturbation data to enable precision immunology.

Industry perspective: the challenges & opportunities of personalized/stratified medicine from a development and patient access perspective

Michael Zaiac (Novartis, Switzerland)

Dr Zaiac opened the talk by clarifying some terminology. He stated that stratified medicine is prospectively identifying a group of patients who will benefit or not from treatment, or who will experience side effects or not. In order to facilitate 'precise treatment' of patients, a precise diagnosis is required, with genomics and proteomics.

The delivery of stratified medicine in practice requires the explicit definition of subgroups, robust measures of efficacy within the subgroups, and a clear difference in efficacy between the subgroups. However, questions remain as to how this can be achieved, for instance there could be several tests (with different sensitivity/specificity) for stratification, and there could be more than one treatment for each subgroup (potentially at different doses). Additionally, for all stratified medicines available in practice, the degree of certainty regarding the expected outcome for patients varies depending on the biology of the disease and the reliability of the marker and test.

In current clinical development, studies on stratified medicines either randomize all patients with the diagnostic test result specified in one or more arm(s) or have strata of patients with no expression to various degrees of expression of the target marker. This results in smaller sample sizes in trials which means less patients are at risk; however, the clinical effect of the drug remains unknown in a wild type or 'otherwise diagnostic not positive' group. There is also lack of clarity on adverse drug reactions in selected patients (there are many working groups in the EFPIA considering this). Finally, a very important question for the pharmaceutical company is 'who is developing the testing methodology'?

Moving to the future, it will be very important to move from sporadic testing of patients to 'real time oncology', using novel biopsy methods (such as liquid biopsy) to avoid challenges with repeat biopsies, and also leverage artificially supported intelligence. This should integrate continuous assessment of key genomic, epigenetic and proteomic analysis, describing the disease, the micro-environment and the interaction, along with measurement of real time impact for any modification in treatment. This should help understand sources of variability in a medicine's benefit/risk profile.

Dr Zaiac also identified regulatory challenges for development and access to biomarker tests, with differences between the European Medicines Agency (EMA) in Europe and the Food and Drug Administration (FDA) in the United States, resulting in lack of clarity in expectations. In particular, there is a question on how much the response to a medicine has to be enriched in the stratified group (if the trial includes a broad, non-stratified population) to justify approval in the stratified group only. Additionally, there is a need to enhance temporary approval to allow early access to stratified medicines, with real world evidence (RWE) to confirm efficacy/diagnostic protocols.

At the payer level, stratified medicine is desirable due to identification of patients who may benefit from treatment, saving resources, and bringing more certainty on outcomes. However, as stratified medicines may receive regulatory approval with less outcomes data, greater flexibility is needed to support interim funding to ensure patient access while further RWE is collected.

Implementation of diagnostic testing can be difficult for the healthcare system, particularly if the number of tests needed is high. The cost of testing can result in use of lower cost 'home brew' tests, the accuracy of which is variable compared to commercially developed tests. In this case, variability in tests for the same marker may result in different populations receiving the medicine in the real world than in the clinical trial, with implications for real-world efficacy (and cost-effectiveness). Conversely, challenges can also occur when a test may be so specific that it can only be performed in limited centres (e.g. for CCR5 testing that was only performed in one global centre), inhibiting patient access.

Biotech perspective

Kieran O'Kane (Biodesix, United States)

Mr. O'Kane highlighted the benefits of co-developing therapies and CDx. Benefits include improved cost-effectiveness, increasing probability of success in drug development, decreasing trial size and time to approval. This is supported by the growing number of CDx included in regulatory approvals, with 27 FDA drug labels now containing a CDx requirement. Currently, most approved CDx tests are single analyte assays (1 drug, 1 target), however next generation sequencing (NGS) is emerging as a solution in malignancies with multiple CDx targets (e.g. Lung). Challenges from a market access & reimbursement perspective remain a concern.

Considering the increasing costs of drug development (with 10 immune checkpoint inhibitors targeting the programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) pathway in development all following the same biomarker strategy, each with development costs of ~\$2.5 billion) and global costs of oncology therapies increasing faster than economic growth (expected to be 6%–9% growth per year through 2021, when global costs are expected to exceed \$147 billion), the importance of CDx in accelerating access/lowering development costs and increasing the efficacy/efficiency of treatment is clear. This is supported by the significantly lower costs of cancer diagnostics compared to cancer drugs, e.g. in 2016 global

spend of cancer drugs was \$89.6 billion compared to global spend on cancer diagnostics of \$3.5 billion¹.

Delivery of testing will evolve, with implications for the willingness of diagnostics manufacturers to invest, however presenting challenges for reimbursement in European healthcare systems.

- **Single analyte testing:** At present, the majority of companion diagnostic testing is done with single analyte tests (e.g. IHC, ISH, PCR), at low costs, with decentralised testing and high tissue consumption if multiple tests are performed. This form of testing is vulnerable to lab developed tests/home brew testing, which can reduce the return on investment for diagnostics companies.
- **Multi-analyte testing:** This is emerging as a solution where multiple targets exist, using NGS, multiplex PCR and IHC. Testing allows identification of multiple targets with a single assay, however requires more expensive capital investment, has a higher per sample cost (depending on sample batching), and can have slower turn around times (e.g. for NGS). Although this results in more protection from commoditisation and higher return on investment for diagnostics companies, there are widespread challenges for reimbursement across European healthcare systems.
- **Multianalyte Assay with Algorithmic Analysis (MAAA):** This is a novel solution for interrogating complex biology, using gene expression profiling (GEP) (PCR, NGS, optical barcoding) and Quantitative Proteomics (Mass Spec). Currently this is most commonly used in prognostics testing (e.g. OncotypeDx), however companion diagnostics are in development. For MAAA, the complex workflow drives the need for (semi-) centralised laboratories, high development costs (and per sample costs), and the requirement for advanced logistics to keep turn around times low. Therefore, although MAAA tests have good protection from commoditisation, higher return on investment for diagnostics companies, and will drive future advancement in stratified medicine, reimbursement is likely to be a key challenge for adoption in Europe.

Going forward, Mr. O’Kane predicted that the ‘1 drug, 1 test’ paradigm cannot continue, with multiple targets in each tumour type requiring multiplex testing, and continuing advances in immuno-oncology requiring more complex testing methods. To address this, MAAA CDx are on the horizon, however reimbursement in Europe is challenging. The UK is the only market with a single integrated pharmaceutical-CDx assessment process at The National Institute for Health and Care Excellence (NICE) (although this is built around the pharmaceutical assessment). In comparison, CDx assessment is not coordinated with pharmaceutical assessment in Germany (although proposed legislation aims to amend this), in France (except where the national cancer institute, INCa, tries to secure simultaneous access), and in Italy and Spain.

In summary, Mr. O’Kane highlighted key challenges for the European CDx market, covering challenges with reimbursement for advanced testing methods (due to fragmented markets with lack of a consistent approach to health technology assessment (HTA) for CDx, and resistance to value-based pricing); local reference/pathology laboratories dominating the market (that typically only want to add commodity products to their services), and a preference for pharmaceutical companies to have CDx that are widely available with minimal risks (driving reluctance to adopt novel testing). Furthermore, although multi-variate tests address complex clinical dilemmas, they are mechanistically more complex, meaning challenges explaining the concept/value to regulatory authorities and payers, and advanced

¹ Combined (and calculated) data from Seo 2018 and Quintiles Global Oncology Trends (2017)

logistics if there is a centralized approach. Machine learning approaches can also add to the difficulty with regulatory and payer submissions.

Despite these challenges, progress is being made. There are defined paths to reimbursement for CDx in the UK, and Germany and France are making progress. There are also fewer regulatory hurdles for companion diagnostics than in the US (although this is changing with the new In Vitro Diagnostic Regulation), and favourable access to samples (e.g. through collaborations with academia), to support research and development for diagnostics companies.

Role of in vitro diagnostics in the authorization of anticancer medicines

Harald Enzmann (BfArM, Germany)

Dr. Enzmann set the context for his presentation in stating that half a century ago, cancer treatment remained highly unspecific, with targets for anticancer agents in many cases unknown. Today, with defined molecular targets for clearly defined patient groups, new challenges exist, and the efficacy of the medicine depends on the precision of the diagnosis.

Regarding the regulatory assessment for pharmaceuticals and CDx, Europe has traditionally used two different regulatory processes. Pharmaceuticals follow the authorisation procedure with the EMA, however in vitro diagnostics (IVD) can be assessed by several notified bodies across the European Union (EU) who consider analytical validity and can award a CE mark. This process is expected to change with the In Vitro Diagnostics Regulation (fully in force after a transition period ending 2022), which will include a mandatory consultation between the EMA and the notified body if the CDx under assessment has a key role in determining the efficacy and safety for a medicine under assessment the by EMA. The EMA will provide an opinion to the notified body that will at least need to be considered.

Importantly, any data protection that applies to a medicine does not apply to the CDx; therefore within weeks or months of the marketing authorisation for a medicine, there may be a number of competing similar diagnostics available. This creates potential for divergence in the analytical performance, e.g. sensitivity and specificity of tests, resulting in differences in clinical validity, e.g. the risk of poorer (or better) clinical outcome. It is therefore important to understand how a new CDx launching for an existing stratified medicine compares with the reference CDx on which the regulatory decision was taken. The simplest approach would be a head to head non-inferiority study, however there is currently no general consensus on the margin for non-inferiority and the number of samples that would be required for assessment. In this situation, the best outcome for the new CDx would be 'as good as, but not better than the reference test'. However, this misses the potential for a new test to be an improvement over the reference test, the question is how this improvement should be measured. This will require the notified body assessing the CDx to determine the acceptability of any differences vs. the reference test, involving consideration of the medicine's benefit risk profile as assessed by the EMA. For instance, if you have a stratified medicine with high efficacy and benign toxicity, then a new CDx with higher sensitivity and reduced specificity is likely to be acceptable. Vice versa, lower specificity and higher sensitivity may be considered problematic for a medicine with frequent and severe adverse effects, which are not clearly and by far outweighed by the medicine's benefit. Further consideration is needed on how to define acceptable differences between competing diagnostics, with arguments on patient benefits the most important.

Going forward, it will be important for manufacturers to notify regulatory authorities with the type of information to support decision making between competing CDx. If there is a marketing authorisation application containing a crucial biomarker test, it will be helpful to include in the initial application for Marketing authorization submitted to EMA detailed information on the test, such as:

- Analytical performance (including specificity, sensitivity, reproducibility, accuracy, precision).
- Clinical validity (including positive/negative predictive values and number needed to treat).
- Complementary information (e.g. inter-laboratory comparison, extrapolation to other subgroups [e.g. children, poly-morbid patients] and effect of inadequate handling of samples).

Such information will be used by the EMA in their assessment and subsequently allow notified bodies to make an informed decision regarding the CDx, and any future CDx for the relevant target. Failure to provide this information on the test may result in additional questions during the EMA's assessment procedure, and may delay the overall decision-making process.

Implications for home brew tests will depend on political decisions at member state level. The primary role of the EMA will be to make the performance data of the CDx used in the pivotal study transparent, it will then be up to policy makers and payers in member state healthcare systems to determine the status for home brew alternatives.

Payer's perspective

Anouk Waeytens (RIZIV / INAMI, Belgium)

Dr. Waeytens identified the key opportunities for stratified medicine from the payer perspective (including improved health outcomes, avoiding unnecessary treatment costs/toxicities, avoiding loss of treatment time and a clearer benefit/risk profile in target patients), as well as the value for industry (including smaller, shorter clinical studies, improved/clearer cost-effectiveness and high market shares within selected patient groups).

27 stratified medicines have been reimbursed in Belgium since 2002. The most important reason behind the slow development and reimbursement of stratified medicines is development of relevant biomarkers, that prove analytical and clinical validity, and also utility. However, the clinical utility of a biomarker is not always evident. For example, with cancer immunotherapy, objective response rates (ORR) differ depending on the percentage of expression of PD-L1 and patient characteristics. This provides an indication of 'possibility of response', however payers prefer markers of 'absence of response' to reduce uncertainty. For this we probably need more complex biomarkers, and to handle this complexity we need standardisation and exact quantification to reduce variation and bias. This can be supported with centralization of expertise, automation, and digitalization of the testing process.

Dr. Waeytens emphasised the importance of considering response rates to therapies that are already available. For example, with trastuzumab, the ORR is ~70%, however as a payer there is a need for a biomarker to predict who the ~30% of non-responders will be to optimise resource use. Other targets for further development include personalised dosing and identifying which patients could perform well with de-escalation of therapy (which has little commercial value for manufacturers, but could significantly benefit patient QoL and payer budgets).

To realise the potential value from biomarkers, early dialogue between industry, regulators and payers is very important. Last year the EMA and EUnetHTA launched a parallel procedure for early dialogue to support the decision-making process. Additionally, the new In Vitro Diagnostics Regulation will come in to force in 2022, including a new risk classification system, clinical evidence requirements (including an EU-wide coordinated procedure for authorisation of multi-centre clinical investigations), and specific rules for CDx, and laboratory developed tests. In the opinion of Dr. Waeytens, proof of clinical utility for a CDx can be demonstrated retrospectively or without co-development when evidence is of sufficient methodological quality. This was the case for the K-RAS biomarker that came from post-hoc analyses.

Additionally, competitor CDx can be assessed in the same way as a biosimilar (vs. an originator medicine).

In terms of the payer value for CDx, cost-effectiveness is important to ensure budget allocation in an efficient, equitable manner. Dr. Waeytens illustrated through a tornado diagram that the specificity of the CDx has the single greatest impact on cost-effectiveness for a new therapy (greater than the cost of therapy, sensitivity and cost of the CDx). This emphasises the need for quality of diagnostic testing from a payer perspective, informing initiatives in Belgium for diagnostic laboratories to undergo external quality validation, to drive consistent standards for testing across the country. Additionally, as efficacy in trials does not always translate into effectiveness in practice, the accuracy of testing to ensure selection of true responders is important to ensure efficient budget management.

In Belgium, additional initiatives are in place to support access to diagnostic testing and uptake of stratified medicines. For example, fees are being revised for tests that have been on the market for several years. Furthermore, in future CDx will follow the short assessment process for medicines, resulting in reimbursement for both the medicine and the CDx at the same time (at present reimbursement of medicines takes 6 months plus possible suspensions, and reimbursement for diagnostics can take 18 months or longer). After the short HTA, tests will be reimbursed according to three new generic nomenclature codes reflecting levels of complexity.

For more complex testing such as NGS, authorities in Belgium are starting to implement these in routine analysis. This will create reimbursement for NGS, whilst ensuring uniform high-quality analysis through NGS expert platforms, with monitoring and validation of quality and results.

In future, collection of RWE through registries will be increasingly important to support payer decisions for stratified medicines, particularly in the context of adaptive pathways for early market access.

Patient advocate's perspective

Francesco De Lorenzo (ECPC, Italy)

Dr. De Lorenzo emphasised that biomarkers are critical for the delivery for personalised medicine, and the debate is no longer if personalised medicine will impact cancer care, but rather whether Europe is capable of delivering the complex infrastructure needed for universal coverage and equitable access to health care.

To realise the benefits of personalised medicine, testing is as important as the treatment. However, currently biomarker testing, molecular testing, and whole genomic sequencing are overlooked.

From a patient organisation perspective, key challenges for biomarker testing in Europe are:

- Accessibility of biomarker testing varies from country to country, but also within cities and regions. Biomarker diagnostics are often performed at larger hospitals only, access to which may add additional barriers to timely diagnosis.
- Administrative barriers lead to delays and longer waiting periods for biomarker test results which vary from a few days to a month in some countries. There is no established organization between hospitals to perform a test and share the results of these tests effectively.
- Reimbursement of biomarker testing varies by country. For example, the RAS Biomarker testing is reimbursed at varying rates in 21 of the 28 EU Member States.

To address this, Dr De Lorenzo identified solutions required at the European and Member State levels. At a European level, there is a need to promote research and development in

biomarkers, adapt regulatory frameworks to the specificities of new health technologies, and harmonise HTA across Member States. At the national level, there is a need for healthcare expenditures in cancer to match the burden of disease, to train patient advocates and healthcare professionals on the importance of biomarker testing (with inclusion in guidelines, including possibilities and limitations of diagnostic procedures), and to adapt reimbursement frameworks to the specificities of new health technologies.

Additionally, there is a need for close collaboration between the European Cancer Patient Coalition (ECPC) and the Cancer Drug Development Forum (CDDF), to raise awareness and educate patients/policy makers regarding biomarkers and personalised medicine. In particular, the ECPC is calling for:

- Increased access to biomarker testing (with communication focused on how access to testing can aid in patient care and provide an important opportunity to engage patients in managing their health as active partners).
- Increased awareness of biomarker testing (and the value for facilitating faster diagnosis, a targeted personalised treatment plan, and avoid wasting resources on ineffective treatments).
- A harmonization framework for biomarker testing across Europe (with regulatory and reimbursement processes adapted to the specificities of new technologies).

Discussion

A question was asked to Dr. Enzmann (BfArM, Germany) regarding the potential advantages and disadvantages of maintaining separate regulatory approval pathways between medicines (EMA) and diagnostics (notified bodies) in Europe.

Dr. Enzmann stated that although there are some advantages with the US FDA approach of having a tight link between diagnostic and medicine (e.g. protecting against the risk of lower quality home brews, and decreasing the real-world efficacy of medicines), the price is less opportunities for alternative, possibly competing tests, which limits the opportunity to promote innovation and improvement in diagnostic quality. If you link a medicine to a specific branded test and put that into label, the drug can only be used with that specific test. Then if a better test becomes available, it is up to the marketing authorisation holder to ask for the label to be changed (potentially delaying access to the improved diagnostic). The European approach allows quicker access to innovation, and this is worth the greater uncertainty.

A question was asked to Dr. Waeytens (RIZIV / INAMI, Belgium) regarding further details on the new process in Belgium for parallel HTA for stratified medicines and companion diagnostics.

Dr. Waeytens stated that there is a need to find budget for new innovative interventions, requiring close collaboration with all relevant stakeholders to implement new complex testing strategies. The objective of the programme in Belgium is to set high quality testing criteria using a standardised approach in diagnostics laboratories so that patients tested in Antwerp will not get different treatment to those in Brussels because of testing process. It is also important that not all laboratories perform NGS, to optimise investment allocation and ensure acceptable test turnaround times.

A question was asked to Mr. O’Kane (Biodesix, United States) on the value of having simultaneous assessment of stratified medicines and CDx (from an industry perspective)

Mr O’Kane stated that in the US there is a synchronised process with the FDA, which takes a lot of collaboration between pharmaceutical companies, diagnostic companies, regulators and payers. This parallel assessment drives earlier dialogue amongst stakeholders, ensuring alignment between the pharmaceutical and diagnostic manufacturers on submission

requirements, and the products are on the payer RADAR (so they can discuss any potential need for further data analysis).

Dr. Enzmann (BfArM, Germany) added that even though there is no parallel diagnostic assessment with the EMA, regulators would like to see clear, scientific description of the performance of the CDx making it clear what different parameters were tested. This opens the door for future competitors and potential improved treatment standards.

A question was asked on the potential for EMA approval of tumour agnostic indications for new medicines (as done by the FDA), and required levels of evidence to achieve this.

Dr. Enzmann (BfArM, Germany) stated that tumour agnostic indications would not be excluded by European regulators, but the burden of proof will be on the marketing authorisation applicant. If there is sufficient evidence that for each histological subtype the new therapy has a positive benefit/risk profile, then this is something the EMA will consider.

Dr. Waeytens (RIZIV / INAMI, Belgium) added that for immune-oncology therapy, there is an agreement in Belgium, where whenever the EMA approves a new indication for a reimbursed immuno-oncology therapy, there is no new dossier required in Belgium, and reimbursement is immediate.

A question was asked on the possibility for Member State agencies to propose solutions to align decision-making at the European level to support faster access to biomarkers to improve treatment outcomes.

Dr. Enzmann (BfArM, Germany) stated that EMA decisions for medicines cover the whole EU, however it has been a political decision to leave the assessment of IVD and medical devices with the Notified Bodies at Member State level. As this is not going to change in the foreseeable future, the best course of action is to make sure there is sharing of information between those who assess diagnostics and those who assess the medicine (where the new In Vitro Diagnostic Regulation will be a step forward). Another step forward will be the case for aligning HTA at a European level (due to very heterogeneous decision making currently for biomarkers).

Dr. Waeytens (RIZIV / INAMI, Belgium) added that there are on-going projects in Europe to combine capabilities for HTA, for example the BeneluxA initiative (between Belgium, Netherlands, Luxembourg and Austria). Additionally, there are many discussions on-going with EUnetHTA regarding how expertise/resources can be shared across European HTA bodies.

A question was asked regarding potential for use of RWE and value-based reimbursement for stratified medicines, in light of possible 'financial toxicities' with high cost combination therapies.

Dr. Enzmann (BfArM, Germany) stated his preference for well controlled RCTs over RWE, however complexities with stratified medicine will not be solved with traditional data generation giving RWE a place despite 'pitfalls' associated with it. Medium term, better means of analysing large volumes of RWE will be required, starting with the best available RWE from healthcare systems (e.g. from social insurance/hospitals).

Dr. Waeytens (RIZIV / INAMI, Belgium) added that there is a lot of pressure on reimbursing new therapies with early market access, often based on phase II/single phase III trials. Then once the product is on the market, collection of RWE is often challenging due to lack of commercial interest. In this instance, Belgian payers provide temporary reimbursement through a managed entry agreement, and ask the company to collect RWE on Belgian patients. Performance based agreements are possible, whereby rebates are offered if specified outcomes are not met in practice. Additionally, there is an important role for RWE informing

the optimal treatment sequence when multiple therapies are available for the same target (e.g. EGFR mutation + NSCLC).

Challenges for Access to Biomarkers

In Vitro Diagnostics (IVD) - European regulatory perspective

Markus Paulmichl (European Medicines Agency, Austria)

Dr Paulmichl introduced the regulatory context for new guidelines on biomarker analytics and activities concerning new regulation on IVD. He stated that guidelines need to apply to all Member States in the European union (recognising that drug development is a global issue, with variation still existing between the US, Europe and Japan).

The EMA guidelines developed in 2012 regarding 'Use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products' evolved further and an addendum to this guideline was published in 2017 (to provide clear definitions of terms used for PGx phenotyping, and propose concepts regarding the translation of genotypes into the predicted metabolic phenotype).

A key guideline effective from 1st September 2018 is entitled 'Good pharmacogenomic practice' and focuses on the quality of assays. Importantly, molecular diagnostics based on the use of a primer or the use of NGS can seem very straightforward, however very few stakeholders know the difference between minimum coverage and mean coverage, and this should be standardised. Additionally, for NGS there are some key limitations where you have very similar genes, in these cases NGS is not a good methodology. Also, allele specificity is not considered in many laboratories, however this should not be the case, and allele drop out can 'falsify' the test results and dramatically change the predicted phenotype. This guideline helps to identify potential problems and describes requirements related to the choice of appropriate genomic methodologies during the development and life cycle of a drug (including principles for a robust clinical genomic dataset). The document also highlights the key scientific and technological aspects for the determination and interpretation of the genomic biomarker data and translation into clinical practice.

Going forward, there is a need for further guidance on the quality of how testing is done. This is evidenced by a proficiency study that was run with 24 countries regarding CYP2D6 copy variation number (CNV), where only one laboratory picked up a hybrid gene. Also, from a regulatory perspective, the approval procedure for CDx is currently a complex, lengthy procedure involving the EMA for pharmaceuticals and notified bodies for CDx. The proposed consultation between EMA and notified bodies in the assessment of stratified medicines and CDx as part of the new In Vitro Diagnostics Regulation is a step forward, however there is a need for closer alignment to ensure linking between the specific technical and clinical data package.

Case stories

David Browning (Oxford Cancer Biomarkers, United Kingdom)

Mr Browning highlighted the challenges ensuring access to new biomarkers for healthcare systems and patients, and in realising the opportunity for improving testing standards and screening capabilities.

Mr Browning shared some of the experiences of his company in colon cancer, an area where earlier diagnosis can lead to significantly improved outcomes. For instance, current survival rates for early stage colon cancer are excellent (94% 10-year survival for stage I patients at diagnosis), however 110,000 lives and £4 billion could be saved in Europe through earlier identification of bowel cancer risk. Additionally, it is currently not possible to identify Stage II patients at risk of relapse leading to unnecessary overtreatment with chemotherapy.

Oxford Cancer Biomarkers has developed a range of products for colorectal cancer, including Colopredict to identify the risk of developing disease, Coloprolog to identify the risk of recurrence, and Toxnav to identify the risk of a toxic response to pharmaceutical therapy.

Mr Browning related some key challenges encountered as part of the development and access for diagnostic and prognostic tests:

- Firstly, it is difficult to obtain access to validated clinical samples with outcomes, due to heterogeneity in population genomics and the need for RWE for validation.
- Secondly, regulatory approval and reimbursement are complex. For example, in the UK there are multiple stakeholders (e.g. NHS, NICE, MHRA), with uncertainty as to who the key decision maker is and what evidence they need.
- Thirdly, there is the need for balance between the value of intellectual property and getting publications to drive the science forward.

Additionally, in relation to screening programmes, the most significant challenge is RWE (which payers typically need to see before they will reimburse). In some cases where the relevant clinical outcomes take many years to realise, this poses a barrier to the development and access for a new technology. There is also a need for more 'joined up thinking' between oncologists, pathologists, and payers, to inform the long-term health economic benefits of diagnostic/screening approaches, to drive the case for access and uptake.

Going forward, a more collaborative attitude towards innovation as seen in the US will be essential to leverage insights from academia and realise the value of biomarkers in clinical practice. Oxford Cancer Biomarkers has established partnerships with Key Opinion Leaders (KOLs) in the US, who are happy to provide clinical samples and facilitate local studies. There is also a trend for leading university hospitals to come forward where they have annotated samples and are looking to leverage those with industry. The US regulatory pathway for fast track innovation is also beneficial, with research-use-only ahead of FDA approval enabling validation by expert laboratories. Additionally, education forums are growing, spreading information on scientific developments through online interaction. Finally, it will be very important for the diagnostics industry to act as the translator between academia and clinicians (where ideas are developed) and large industry players (to drive product development and reimbursement).

Kieran O'Kane (Biodesix, United States)

Mr O'Kane provided a case study on the access and reimbursement of a MAAA diagnostic (Multianalyte Assay with Algorithmic Analysis) in the EU.

Genomic Health launched Oncotype Dx in the US in 2004 and established an EU commercial presence in 2009. This received positive NICE guidance in 2013, and some regional reimbursement throughout Europe supported by guidelines. Despite significant investment from Genomic Health, they achieved <10% global sales, failing to penetrate the European market because they did not fully understand the hurdles of access in Europe.

With hindsight, the following barriers to success can be identified:

- **Delays in test turnaround time** limited clinical utility (as all testing was undertaken at a centralized lab in California, time to results was reported at ~4 weeks)
- **High perceived cost was a barrier to entry** (with early reluctance from Genomic Health to compromise on price delaying adoption, and late implantation of undisclosed discount schemes)
- **Competitive pressure** from similar technologies

- **MammaPrint (Agendia, Amsterdam)** launched in 2004, however because the sample is limited to fresh-frozen tissue, this increases logistical challenges and hinders broad adoption. Additionally, European testing is conducted in a centralized laboratory, and the product is perceived as lagging behind Oncotype Dx in evidence generation while similarly priced. Formalin-fixed, paraffin-embedded (FFPE) testing was available in 2012, but this had limited impact due the Oncotype Dx foothold.
- **EndoPredict (Sividon, Cologne)** launched in 2011. This had an aggressive pricing strategy to drive local adoption in Germany and highly price-sensitive tender based markets such as Spain. The company was acquired by Myriad in 2016, and plans to seek FDA clearance and decentralize testing in EU.
- **Prosigna (NanoString, Seattle)** launched in 2013. This provides a decentralized option for local laboratories. Adoption was initially hindered by the up-front cost of instrument acquisition, but test 'naturalization' is very attractive for European payers. In practice, the kit based model and local testing reducing turnaround time, is driving adoption throughout Europe

Looking at the current situation, up to 2018 there was still limited adoption of prognostic breast cancer testing in the EU, despite high demand and Guideline inclusion, with the market still representing 10% of the US. The only national reimbursement remains in the UK (following positive NICE appraisal), with the German Federal Joint Committee (G-BA) delaying a decision pending further data, regional/tender based access in France and Spain, very limited access in Italy, and favourable adoption in certain regions e.g. Nordics, Portugal.

Expectations on the level of evidence required for diagnostic tests (with diagnostics companies having limited resources to undertake drug-like multi-centre prospective studies, with a high risk of never receiving a return on investment) are unrealistic, and the lack of consistent HTA processes across Europe (requiring significant investment from diagnostics companies to navigate the payer landscape, and a reluctance to reward innovation with value-based pricing) all create a barrier to entry for diagnostics.

Going forward, there are several MAAA companion diagnostics in development that will face access challenges in Europe unless EU-wide solutions to the above issues are found. Currently, pharmaceutical companies continue to be cautious about CDx opportunities with MAAAs (often sacrificing a better test for a tried and trusted approach with a single analyte). Furthermore, logistical solutions are essential for centralised laboratories to maintain acceptable turnaround times for CDx testing, and value-based pricing needs to become standard for novel diagnostics that bring value and utility to the clinic.

HTA perspective

Sonia Garcia Perez (AEMPS, Spain)

Ms Garcia Perez highlighted the challenges with providing access to biomarkers, with over 60,000 genetic tests available for more than 4,000 disorders, but with few molecular diagnostics embedded in clinical practice in Europe, and unequal access across and within countries.

Oncotype Dx provides an example of the challenges with HTA of biomarkers. Recently, IQWiG (Germany) concluded that Oncotype Dx has sufficient evidence to guide breast cancer adjuvant chemotherapy decisions based on the TAILORx study results. However, when the same assessment was performed in 2016, the evidence was 'inadequate to assess the benefit of such tests'. It has therefore taken a phase III study following over 10,000 women with follow up for an average of 9 years to inform the positive HTA for this product.

Ms Garcia Perez introduced a draft reflection paper from EUnetHTA titled 'Personalised medicine and co-dependent technologies, with a special focus on issues of study design'. The main conclusion is that no special assessment is needed for personalised medicines compared to other types of technologies. The document provides the different types of study designs that can be developed for personalised medicines, with associated advantages and disadvantages.

The options for clinical study designs covered in the EUnetHTA reflection paper are as follows:

- **The randomize all design:** With patients stratified according to the result of the biomarker test, according to whether they are biomarker positive or biomarker negative. Then both groups are randomised to receive the intervention and the control.
 - The key advantage is that only this design can assess the individual components of a test-treatment strategy and their interaction. This provides answers to questions on whether the treatment is effective, whether the biomarker is sufficiently predictive, and the prognostic value of the biomarker.
- **The enrichment design:** Where only patients that are biomarker positive are included in the study. These patients are randomized to receive the intervention or control.
 - This approach can address questions on the efficacy of the treatment in the biomarker positive population, however does not provide information on the prognostic and the predictive value of the biomarker.
 - This type of study can be used when sufficient evidence is available on the specific biomarker and there is sufficient knowledge on it as a prognostic factor.

In practice, many companies propose studies in which only biomarker positive patients are included, with all patients receiving the intervention, without an active control. Their proposal is usually to compare results from this study with a historical control arm. In this case, none of the priority questions on treatment efficacy, predictive value of the biomarker and prognostic value of the biomarker can be addressed.

This situation creates some important questions/concerns from an HTA perspective:

- **Lack of evidence on the prognostic value of the biomarker:** This means uncertainty on whether the pharmaceutical could be offered to a broader population, with potentially beneficial effects for biomarker negative patients. For example, some therapies effective in a biomarker positive population may also be effective to a lesser extent in a biomarker negative population (but still more effective than chemotherapy). The biomarker could also be a strategy from the manufacturer to maximise price in a niche population, before expanding the population once available in clinical practice.
- **Ensuring testing in clinical practice reflects testing in the pivotal clinical study:** As cost-effectiveness of treatment will depend on available CE-marked diagnostic test(s), that may not have been available during drug development, it is important to ensure the population identified by the test is the same population to be targeted with the treatment (relating to standardisation of the quality/processes for diagnostic testing).
- **Selecting appropriate historical controls:** Finding matched patients in historical sources is difficult, with issues around lack of diagnostic test availability where a biomarker was not previously recognised as a prognostic/predictive factor. There is

also likely to be heterogeneity between populations in the clinical trial vs. historical source.

To conclude, Ms Garcia Perez identified some factors that can be improved on the HTA side to support the assessment and access for biomarkers. Previously, unclear or non-existent reimbursement pathways, together with the lack of clear evidence requirements, have led to significant delays in the assessment of molecular diagnostic technologies in certain countries.

Therefore, clear evidence requirements are essential- to ensure manufacturers know what needs to be submitted for a positive assessment. Alternative strategies for access should also be considered, such as temporary/conditional reimbursement with use of RWE to inform validity/prognostic value of the biomarker. Finally, increased alignment among relevant stakeholders is needed, to realise the broader value of diagnostic test adoption and reduce delays in commissioning.

Patient advocate's perspective

Kathi Apostolidis (ECPC, Greece)

Ms Apostolidis emphasised the challenges for patients in securing access to biomarker testing and personalised medicine. The key challenges can be grouped as follows:

- **Patients encounter difficulties finding information** (relying on their doctors, requiring good health literacy in the absence of peer to peer information).
- **Lack of printed lay information from physicians** (patients likely to forget 60% of what they hear during a medical appointment).
- **Patients cannot decide on treatment at their first appointment** (requiring a second appointment to discuss the results of biomarker testing, and needing time to digest new information).

The implications of this situation are shown in a European Cancer Patient Coalition (ECPC)-European Alliance for Personalised Medicine (EAPM) survey (2016) on patient awareness of biomarkers across Europe. Only 70% of respondents were aware of the existence of biomarkers, 60% had not been proposed biomarker testing by their oncologist, and 70% said the importance of biomarkers was not adequately explained.

Additionally, there are healthcare system level challenges with access to biomarker testing and innovative personalised medicines across Europe. Results for biomarker tests can take between 7-30 days across Member States, representing a significant barrier to clinical decision-making. There is also variability in reimbursement for testing across Member States, shown through the ECPC-EAPM survey. Aside from diagnostic testing, there is also variability in access to personalised medicines, with significant variation in average cancer expenditures per citizen across Member States, for instance lbrance is not yet reimbursed in Greece (although this is available through special administrative procedures).

Ms Apostolidis concluded that more progress is needed towards building a harmonised and more efficient regulatory framework for biomarkers. It will be important to increase access and decrease waiting times for high-quality biomarker testing to make personalised healthcare a reality.

Regulatory point of view: Industry perspective

Claudia Dollins (Merck KGaA, Germany, representing the EBE EFPIA Personalised Medicine Working Group)

Dr Dollins stated that although there are clear benefits from personalised medicine (such as better patient outcomes, optimised regimens, savings, effective resource use for healthcare systems), there are currently different adoption models with varying degrees of access to personalised medicine in the EU.

Dr. Dollins emphasised the disparate landscape of regulatory requirements for early phase personalised medicine clinical trials, with CE marking required for early phase development (not just commercialisation of the final test). This is a significant hurdle to clinical development in the EU. To address this, Dr Dollins proposed a risk-based approach for biomarker assay development in clinical trials as an alternative to CE marking. To achieve this, validation of an assay in early drug development should follow the concept of 'fit for purpose' (i.e. the marker must be reliable generating reproducible and accurate data and be fit for purpose). This would allow continuous and evolving validation of biomarker assays in the course of drug development. Then, where assays deployed in early clinical trials pose a low risk, a technical validation based on a 'fit for purpose' approach would be sufficient (following international/harmonised standards, with results of the validation well documented).

Regarding the new EU In Vitro Diagnostics Regulation, Dr Dollins identified considerable uncertainty on what this will mean for development and access for biomarker tests. The key challenges impact every aspect of assay developing, covering:

- **Performance evaluation** including required performance evaluation for different patient risk categories (e.g. observational screening vs. patient selection) and requirements for investigational use (where Dr. Dollins states CE marking should not be required for early co-development programmes).
- **Regulatory procedures** including delineation of responsibilities and procedural guidance for interaction between EMA, national competent authorities and notified bodies, and the timing of various assessments (including joint advice during development, involvement of HTA bodies, process for information sharing, conditional/accelerated approval scenarios, possibility of approval of a therapeutic product without approval of a CE marked CDx).
- **Specific uncertainties** regarding harmonised terminology in the new process, labelling requirements, and implications for use of novel technologies such as NGS.

In future comprehensive genomic profiling NGS will be used as a CDx to determine treatment. Associated regulatory challenges will include setting performance goals (where uniformity is not appropriate), differentiation between somatic vs. germline mutation testing, lack of standardisation, transparency in labelling, rapidly changing hardware/software, and uncertain evidence requirements for investigational settings.

To address these regulatory challenges, Dr Dollins made the following recommendations:

- Performance metrics should be consistent with the context of use
- Common performance goals should not be established
- Need for global reference materials with known performance characteristics
- Need for labelling with transparency on limitations and performance characteristics
- Development of best practices for change management
- Clear regulatory guidance on appropriate validation requirements

Additionally, regarding data protection and data storage, there is a need for coding schemes to protect privacy, informed consent, transparency in the communication of NGS results, and storage of/access to NGS data and samples.

Personalised cancer care: translating promise into practice - with multi-stakeholder approach

Titta Rosvall-Puplett (Bristol-Myers Squibb, Belgium)

Ms. Rosvall-Puplett stated that realising the potential of precision medicine for all patients will require close collaboration between all relevant stakeholder groups. Put simply, it is clear what can be achieved through collaboration. If we can share experiences and learn from each other, we could improve efficiency of cancer care by ensuring provision of the right drug to the right patient, accomplishing our collective mission of precision medicine.

At Bristol-Myers Squibb, we define digital health as an intersection, or convergence of technology with healthcare, living, and society that can enhance the productivity and efficiency of healthcare delivery, and drive greater personalisation and precision. Yet we rely on high-quality, high-validity, accessible data.

An example of what can be achieved in this field is CODE (the collaboration for oncology data in Europe - <https://www.code-cancer.com/>). This initiative aims to expand knowledge of anti-cancer medicines use through a dedicated Oncology Data Network, to aggregate data for all forms of cancer, in all patients at Europe's cancer treatment centres, in near real-time, to understand drug use by patient within the treatment paradigm. The target is to collaborate with 200 cancer treatment centres in seven European countries over three years, to enable the oncology community to derive greater value from anti-cancer medicines for patients.

In addition to biomarkers, it will be important to redefine outcomes based on what matters most to patients, as 'inefficiency is any aspect of cancer care that is not focused on what matters to patients. This will also help improve efficiency and sustainability of cancer care in an environment of ever-increasing cost pressures. Such is the intent of an international multi-stakeholder initiative All.Can (<http://www.all-can.org/>) that is already working in 8 countries and to draw recommendations from concrete practise of care [10].

Additionally, industry perspectives from the EFPIA to translate the promise of precision medicine into clinical practice should be followed. This includes the following key recommendations to improve equitable access to personalised medicines in the EU:

- National policies to ensure prioritisation of personalised medicine should work hand in hand with existing health strategic plans (e.g. national cancer plans).
- Continued emphasis is needed on better management of care, consolidating expertise and resources to ensure adequate 'personalisation of care'.
- National governments should continue investing and co-operating in next-generation testing infrastructure (such as molecular genetic laboratories) as well as developing dedicated funding pathways to ensure access to diagnostics.
- Collecting data to track access to diagnostics (making this public) and putting greater emphasis on External Quality Assessments (EQA) of laboratories to ensure consistent testing quality throughout Europe and allow comparison between approaches.
- Tackling delays to reimbursement of new treatments and guideline inclusion to ensure more systematic and equitable access.

Finally, according to a recent CDDF position paper, 'taking RWE into account in regulatory and HTA in a thoughtful and balanced fashion will enrich and justify sound decision making'[11]. As we build a more robust evidence case for new treatments using RWE, we can improve access and build a stronger value proposition to support effective reimbursement strategies. This is crucial to ensuring the efficiency and sustainability of cancer care for future generations, and to expand/ expedite the reach of innovative medicines for patients.

Discussion

A question was asked to Mr. O’Kane (Biodesix, United States) on whether the costs of testing with MAAA diagnostics is likely to fall in future (and the implications for access to diagnostic testing).

Mr. O’Kane stated that although current NGS platforms will become cheaper over time, current platforms will be surpassed by other innovative higher cost technologies (e.g. with quicker turnaround time), therefore it cannot be assumed that the overall cost of innovative high value diagnostic technologies will reduce. The onus is on the diagnostics companies to demonstrate the value of technologies to the healthcare system, and justification for a value-based price.

Titta Rosvall-Puplett (Bristol-Myers Squibb) added that the cost of testing and treatments should be evaluated according to their value to patients and society over time, to ensure decisions are made based on what matters most to patients. Paying attention to the patient perspective also results in better use of resources, a goal that should appeal to all stakeholders [12].

A question was asked on the future EMA regulations/guidelines on the use of RWE, and possible consequences for the collection and interpretation of RWE for new diagnostic technologies.

Mr. Browning (Oxford Cancer Biomarkers, United Kingdom) stated that the emphasis needs to be put on obtaining good quality, well annotated samples (and getting this message out to researchers). Ethnicity will also be an important consideration, to ensure information is specific to smaller populations.

Dr Dollins (Merck, Germany) added that the more you segment patients according to biomarker status, the more difficult it becomes to have meaningful clinical developments. Therefore, biomarker quality is a very important issue to support innovation.

Ms Rosvall-Puplett (Bristol-Myers Squibb, Belgium) added that to facilitate data generation in smaller populations, other options for data generation should be considered (e.g. single arm trials in a biomarker population).

A question was asked regarding the feasibility of quality assurance for diagnostic laboratories that are conducting biomarker testing.

Mr. Browning (Oxford Cancer Biomarkers, United Kingdom) responded that there are national and international schemes for quality assurance for diagnostic testing, where samples are distributed to laboratories for analysis. Oxford Cancer Biomarkers is also looking at the possibility for electronic quality control. Overall, there is a need for better access to quality control mechanisms for new diagnostic tests.

A question was asked on the feasibility of using liquid biopsies to address growing testing requirements and limited availability of tissue from biopsies.

Mr. O’Kane (Biodesix, United States) replied that liquid biopsies have been a development target for a number of years (e.g. in lung cancer where there’s a growing panel of markers to be tested). There is also a growing trend to test for mutations with a liquid biopsy upfront before using tissue, then save the tissue for informing other options (e.g. if liquid biopsy is negative, or later stage testing). A number of institutions have tried to look at PD-L1 in liquid biopsies, but have not been successful.

Mr. Zaiac (Novartis, Switzerland) added that a liquid biopsy is conceptually the only way to have true personalised medicine, to see what is changing in response to the medicine.

A question was asked on why best practice guidelines for diagnostic testing/treatment are not always followed across European markets.

Mr. O’Kane (Biodesix, United States) replied that the issue may be education, with many clinicians not sitting in academic institutions, and may not be aware of the latest developments. Industry therefore has a role in educating and disseminating information. There may also be socioeconomic factors, i.e. if a physician doesn’t have access to the drug, they won’t test for the biomarker.

The Way Forwards

Fostering collaboration in the era of precision oncology: academic perspective

Tatiana Prowell (John Hopkins Kimmel Comprehensive Cancer Center, United States)

Dr. Prowell provided an overview of what happens in the absence of collaboration in precision medicine. As of September 2018, there are still only 26 package inserts in the US that contain a CDx, and most are for 1 drug with 1 target. This creates a challenge for clinical practice, as well as drug development (with questions around how to prioritise use of biopsy specimens). There is also a lot of duplication, with many companies developing similar tests. As the number of immune-oncology agents in development increases (from January to September 2017, there were 469 new combination IO studies with target enrolment of 52,539), the proliferation of diagnostic tests increases in parallel, leading to possible redundancies due to the similarity in the tests, and ‘every resource (patients, research dollars, etc.) invested to address a redundant scientific question is a resource diverted from novel research’.

There are key clinical challenges surrounding cancer diagnostic testing in practice. Firstly, reporting of test results is often confusing, due to fears of overstating clinical utility leading to ‘phonebook-style’ test reports, and there is no uniform approach for how best to display on-label recommendations, off-label use of approved agents, ‘high priority’ clinical trials etc. Secondly, pockets of scientific/clinical expertise lead to result curation at tertiary care centres, with second opinion appointments required due to often limited understanding of biomarkers from physicians (which can pose geographic challenges), and genomics tumour boards often involved with decision making.

The development model for diagnostics is also ‘less forgiving’ than for pharmaceuticals. Tests are typically sold at a single time point (unlike pharmaceuticals), with low barriers for competition, and a reliance on a pharmaceutical manufacturer for collaboration. There is also the ongoing issue of reimbursement, with most US carriers still denying claims for unapproved test content, and greater challenges across Europe. Furthermore, there are intellectual property questions around ownership of data (for example, recent ethical challenges around a private company accessing a large set of tissue samples at Memorial Sloan Kettering). There is a need for practical solutions to allow access to this valuable data.

Looking specifically at NGS coverage in the US by the Centres for Medicare and Medicaid services in 2018, NGS is only covered for patients with recurrent, relapsed, refractory, advanced or metastatic cancer; no prior testing of the primary tumour with the same NGS; plans to pursue additional treatment; under treatment of the physician ordering the test. Additionally, the test must be performed in a CLIA (Clinical Laboratory Improvement Amendments) laboratory; have FDA approval as a companion IVD; have an FDA-approved indication for use in the specific cancer type and have results provided to the treating physician using a report template that specifies treatment options. Importantly, these instructions for use may prioritize company deal-making over the best therapeutic recommendation, as clinical claims tie back to business relationships between pharmaceutical

and diagnostic partners. Therefore, simplified reporting will be critical to limit industry deal-making for 'preferred' placement.

Draft FDA guidance on NGS is intended to decrease development costs and timelines, foster competition, streamline the regulatory review and encourage data sharing. The implications are that universal CDx platforms are increasingly likely, and collaboration with academic and community oncologists, patient advocacy organisations, and pharmaceutical companies will be essential to access rare specimens and make clinical claims.

To deliver this, open science initiatives will be essential to drive the science forward. Whereas the closed model involves limited access to global academia, limited access to funding, and slower paced accumulation of knowledge, the open model involves knowledge accumulation that is less repetitive and fast, with unlimited access to global academics, larger pooled funds, and quicker adoption. An example of open science in action is The Metastatic Breast Cancer (MBC) Project, set up by Dr. Nikhil Wagle of Harvard Dana Farber Cancer Institute in collaboration with 28 cancer patient advocacy organizations, with 4,800 women and men with metastatic breast cancer having joined since launch less than 3 years ago. This is a very successful initiative, collecting highly valuable data across multiple cohorts considering epidemiology, clinical behaviour, and real-world practice patterns.

Dr Prowell also provided the example of the TAPUR study (sponsored by ASCO). This has the objective of describing anti-tumour activity and toxicity of commercially available, targeted anti-cancer drugs prescribed for the treatment of tumours with a genomic variant known to be a drug target, or to predict sensitivity to a drug. This trial involves a patient's treating physician ordering a genomic profile of the tumour, then a Molecular Tumour board meet via WebEx to propose treatment options, then a participating pharmaceutical company provides the study drug at no cost to the patient. Data is collected on standard efficacy and toxicity outcomes, before results are studied to determine whether a treatment is promising for a particular cancer and genomic variant. ASCO then publishes findings in peer reviewed journals. This has significant benefits for patients (who access study drugs matched to genomic profiles), physicians (who receive assistance interpreting genomic results and identifying treatments), the cancer community (identifying new uses for targeted anti-cancer drugs for patients with no standard options), manufacturers (gaining insight on new uses for existing drugs), and regulators (who learn about side effects and outcomes for approved drugs in other cancers). As of March 2018, 750 patients had initiated treatment. This represents a highly promising approach to research in precision oncology.

Strategies to allow indication-based payment for biomarkers

Afschin Gandjour (Frankfurt school of Finance & Management, Germany)

Dr. Gandjour provided an overview of the concept of indication-based pricing, namely that one product may have different prices for different indications. This should align drug prices with clinical value, with higher value yielding a higher price, and vice versa. Indication-based pricing fully extracts consumer surplus, which is the willingness to pay for a drug minus the actual price. This aligns prices with willingness to pay for each patient group/indication.

The key advantages of this approach are to increase revenues for manufacturers and avoid the typical price decline associated with indication expansion (unless there were high prices in low-value indications before), it also sends positive signals for R&D investment and improves access to treatment (by enabling payers to have a low price for a low-value indication).

To achieve indication-based pricing in practice, there are a number of approaches:

- Different brand names according to the indication (however this may create confusion and is not usually considered an option for manufacturers).

- One brand name with separate discounts per indication, based on treatment failures in the various indications, by tracking actual outcomes on a per-patient basis (for example risk-share schemes used in Italy).
- One brand name with a single weighted-average price, where implicit prices in different indications are weighted according to the estimated population size (as in France and Germany).

Tracking real-world utilisation requires either a change in data protection regulation (so indications for drug use are reported on prescription labels or communicated to the pharmacist); or that data are collected through an information system/registry that tracks patient characteristics, diagnostic criteria, prior lines of therapy, and concomitant medications, etc.

There are a number of obstacles to deliver indication-based pricing. Who pays for data collection systems (where payers have no incentive to invest if this will result in higher prices), and the costs of incentives to physicians for data entry. The need for informed patient consent for personal information to be used for billing. Misclassification through ICD coding, and likely to be delays between data collection and reimbursement.

With regard to precision medicine, it is unlikely that indication-based pricing will result in healthcare system savings under a value-based pricing scheme. This holds because manufacturers price up to the limit of what healthcare systems are willing to pay. Indication-based pricing usually increases revenues for manufacturers, which may stimulate more clinical trials/product development, but may also lead to wasteful 'excessive innovation'. More importantly, indication-based pricing does not address the fundamental question of how to set the cost-effectiveness threshold for reimbursement of new healthcare technologies.

Developing practical guidance for Member States on implementing precision genomics in medical care

Marc Van den Bulcke (Sciensano, Belgium)

Dr. Van den Bulcke explained that the Belgian Healthcare Knowledge Centre was tasked to undertake a study on the feasibility of bringing 'omics' into the Belgian healthcare system. This has involved assessment of the feasibility; development of an intervention plan, and now the pilot phase (2018-2020). The next phase will be structural integration (2021-2023), then ongoing monitoring and surveillance.

The roadbook for the implementation of NGS in clinical practice in oncology and haematology includes 10 key actions. Examples include:

- **Action 1:** Establish a commission for Personalised Medicine (to be consulted and provide advice to the reimbursement agency on platform CDx)
- **Action 2:** Development of national guidelines for NGS use in oncology (which will be available through Belgian Journal of Medical Oncology (BJMO) practice guidelines 57). This will include standards for test levels to inform the rationale for biomarker use in practice, and test algorithms to inform the cascade of molecular testing to be performed for a particular cancer (to ensure stakeholders follow the 'rules of testing', although the document does not specify exactly which test should be performed).
- **Action 6:** Implement NGS registration, storage and data management. This is because NGS generates large amounts of data, which adds value when analysed to look at quality, outcome analysis and reimbursement allocation (as well as clinical and public health research). The goal is for a central molecular registry with the results of all molecular tests to improve access to data for clinical research, and facilitate evaluation of decision making for policy makers.

- **Action 8:** Apply genome information in health care. This will require developing practical guidance for organizing the societal debate on ethical, legal and privacy issues on the use of genome information in healthcare.

Regarding action 8 covering the societal debate, this is very important as making genomics a success will need support from citizens (e.g. informed consent). Therefore, citizen research has been undertaken to inform balanced policy recommendations. This has involved a focus group study, including patients in the implementation of genomics in the clinic, with the objective of drafting informed consent guidelines. There has also been a citizen's forum, to gain citizen's perspectives on ethical, legal and privacy issues regarding genomics.

Access to biomarkers: "Are we ready for value-based precision medicine?"

Patricia Carrigan (Bayer, Germany)

Dr. Carrigan highlighted the paradigm shift ongoing in cancer care, from treatments based on the tumour-site in the body to treatments targeting oncogenic drivers. Histology-independent drug development is a new paradigm in precision medicine and represents a new way of defining and treating cancer based on the genetic makeup of cancer cells rather than the tissue of origin. This approach is addressing the question: Does the cancer cell have a specific gene mutation or gene re-arrangement which is the cause of cancer and/or makes it responsive to a specific treatment?

The value of genomic testing underscores the value of precision medicine, including benefits for patients (improved efficacy, reduced adverse events), healthcare systems, society (early treatment of disease, improved resource allocation efficiency), and innovation (more effective clinical trials, reduced R&D costs, and more ethical trials).

Dr. Carrigan shared a case study highlighting the value of precision medicine, where a 2-year-old girl with infantile fibrosarcoma (a large rare tumour behind the knee), underwent 2 cycles of chemotherapy, and was left with amputation of the leg as the only treatment. However, after three months of histology-independent therapy in a clinical trial, significant reduction in tumour size occurred and the tumour could be removed in surgery, with no amputation needed.

NGS testing is becoming more widely available and recent evidence shows that NGS testing can be cost-effective. Furthermore, although pairing of drugs with well-established CDx platforms has been the key to success, novel platforms will play a central role in diagnostic testing in future. However, country investment in advanced infrastructure to take advantage of NGS varies across Europe, ranging from 70% of laboratories performing biomarker testing having NGS infrastructure available in Sweden, Switzerland and France, to a large reliance on IHC/other relevant methods and poor NGS infrastructure in Ireland, Italy and Spain. Additionally, regardless of NGS infrastructure, lack of adequate funding for diagnostics in Europe can lead to eligible patients not being tested even when infrastructure exists.

However, even if countries invest in advanced testing infrastructure, there are other important components that facilitate access to precision medicine. France and the UK for example make significant investments in the testing environment but have limited access to innovative precision treatment. The key point is that the test may be right, but you need to also pay for the innovation. The main components to facilitate access to precision medicine are mechanisms of value assessments; use of RWE, speed of reimbursement and speed of updating guidelines.

Dr. Carrigan concluded with recommendations on developments to support implementation of value-based precision medicine. Firstly, for patients, doctors and healthcare systems, high-quality and broad genomic testing, such as NGS, should become part of routine clinical practice. This can be improved by; better reimbursement of testing, including genomic testing

in clinical guidelines, and increasing the number of certified laboratories with capacity. Secondly, tackling delays to reimbursement of new precision medicines will ensure more systematic and equitable access for patients. This can be improved by: better alignment of data requirements between regulators and HTA bodies; a more flexible approach to clinical/economic evidence to allow reimbursement of new treatments including combinations/triplets; allowing more flexibility when assessing evidence for precision medicines (e.g. RWE); allowing performance-based reimbursement agreements and introducing interim/early access programmes that favour precision medicines (taking into account unmet needs and provide funding for early reimbursement).

Payer's perspective: sustainability of healthcare systems

Annie Pannelay (United Kingdom)

Dr. Pannelay set the context on the sustainability of healthcare systems by describing how healthcare budget growth (and pharmaceutical sales growth) is outpacing economic growth across France, Germany, Italy, Russia, Sweden and UK. One driver for this is the aging population (with the global population aged >65 years representing 7% in 2015 predicted to reach 15.6% by 2050) however there are other important factors that must be considered.

Across Europe, inpatient care represents the largest contributor to health spending. In a sample across European countries, expected growth for spending on medicines was over 5% from 2017-2020. To address this, payers/HTA bodies are trying to allocate resources as efficiently as possible, to get the maximum health benefit for the resources available.

Looking at biomarkers, research has increased dramatically in recent years (2.5 fold increase from 2005 to 2017), however adoption of biomarkers in healthcare systems remains low. This is due to a number of reasons, such as no separate framework for qualification of novel technologies unless this is a pharmaceutical-CDx combination; pharmacoeconomics requires a whole pathway approach; and there are no value-based pricing guidelines for innovative diagnostics in any EU Member States.

Considering the HTA perspective, this is also a barrier to adoption of biomarkers. Typically, there is a discrepancy between where evidence is generated (global) and where the reimbursement decision is made (pharmaceuticals at the national level, diagnostics at the regional/local level) and this is especially relevant to biomarkers as most of them fall with diagnostics for coverage and procurement aspects. Many companies, particularly SMEs with constrained resources which constitute a significant share of biomarkers developers and suppliers, struggle to produce the evidence needed to demonstrate the value of their technologies to each stakeholder involved. Payers are also anxious regarding the costs associated with testing, and lack of supporting clinical evidence. For instance, testing large at-risk populations who may benefit from a diagnostic test can be highly costly, with uncertainty on the clinical benefit due to lack of data at the time of diagnostic launch. Supporting this, a study in Germany [13] found that of 11 diagnostics available on the self-pay market, only 1 was studied in an RCT that looked at patient relevant outcomes. This demonstrates that evidence expectations for HTA are far removed from what the biomarker industry is developing.

To support the development of HTA processes suited to biomarkers, Dr. Pannelay put forward a number of recommendations. Firstly, there should be early HTA to inform the potential value of new products in development. Methods could include economic modelling (avoiding Markov modelling that is not always suited to the complexity of biomarker implementation), MCDA, headroom analysis. Secondly, the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) Test Evaluation Working Group (TE-GW) conceptual framework of the test evaluation cycle (driven by the clinical pathway) should be considered as part of the HTA process. This involves the following:

- **Step 1:** Identifying the unmet need for the biomarker (considering the clinical management problem and desired outcomes);
- **Step 2:** Verifying the unmet need for the biomarker (considering if there is an existing solution and whether the proposed solution could be effective/cost-effective, and any barriers);
- **Step 3:** Validating the intended use of the biomarker (looking at how the biomarker will contribute to the solution/improve current practice compared to the desired outcomes identified in step 1);
- **Step 4:** Assessing feasibility of the biomarker in practice (considering commercial, economic, technical and organisation feasibility, and any other barriers).

Potential of real-world evidence for access to biomarkers

Jesús María Hernández Rivas (HARMONY/ IBSAL, Spain)

Dr. Hernández Rivas introduced the many biomarker categories that exist, covering clinical efficacy across multiple therapy areas, and safety factors across multiple different organ/system toxicities. Additionally, biomarkers for clinical efficacy can be used across a wide range of contexts, including selection of dosing for phase III studies, proof of concept, utilization in study (i.e. as a criterion for enrolling patients), PK-PD, monitoring disease progression, treatment response, and as a surrogate endpoint.

Billions of biomarkers exist, there are already published data on mutation profiles of over 100,000 tumours. But importantly these require clinical validation.

NGS studies are leading to new cancer classification, where trying to manage the tumour according to the tumour type, not the classification of the disease is the key challenge. NGS on rearrangements also represents the most accurate method for determining minimal residual disease, with sensitivity of 0.001-0.0001% (compared to RT-qPCR or RT-ddPCR on fusion-genes, with sensitivity of 0.01-0.001%, and cytogenetics and FISH with sensitivity of 1-0.1%).

There is significant potential for big-data to support biomarker development and validation. In recent years, the HARMONY project has been building a high-quality big data platform to analyse haematological malignancies. The objective is to increase the application of 'omics' data in clinical practice and speed up drug development. The project includes 53 organisations from 11 European countries, covering all relevant stakeholder groups (including ethics, pharmaceutical industry, policy makers, bioinformaticians, data scientists and ICT, HTA bodies, regulators, economists and haematologists). The first datasets are currently being incorporated in the platform, and the analysis phase of pilot studies will commence. One key learning to highlight is the need for compliance with recently introduced General Data Protection Regulation (GDPR) requirements, therefore involving anonymisation of all patient data.

To summarise, Dr. Hernández Rivas highlighted the need for ongoing data integration, data validation, data harmonization and outcomes definition to support development and access for biomarkers. Big data will be an important tool to help this process, however humans must drive the challenge.

Discussion

A question was asked on whether it is time to take a different methodological approach to HTA, considering the holistic, long term value of a new technology throughout the value chain (not just focusing on the pharmaceutical budget and the diagnostic budget).

Dr. Pannelay (United Kingdom) responded that these considerations are taking place in HTA bodies, but there still needs to be practical consideration of the impact on budgets. There are however discussions taking place at the EU level about harmonising processes for pharmaceutical and diagnostic assessment.

Dr. Gandjour (Frankfurt school of Finance & Management, Germany) added that there should be caution considering the holistic realisation of saving across multiple areas of the healthcare system, as rational commercial manufacturers will price to the highest possible level considering the economic value (including cost-offsets) to the healthcare system.

A question was asked on the challenges with approval, access and uptake for a diagnostic test, compared to the process for a pharmaceutical.

Dr. Pannelay (United Kingdom) responded that the issue is not related to the number of samples/tests used to validate a diagnostic, it is about the need to link the use of the diagnostic to patient relevant outcomes (e.g. mortality/morbidity). These are the data that drive reimbursement, and by design diagnostics performance rarely include patient relevant outcomes, which inhibits this data generation at the moment.

Dr. Dollins (Merck, Germany) added that there is a disconnect with the data generated for a diagnostic in development, and what is actually seen in clinical practice (in terms of the demonstration of clinical value).

A question was asked on what type of support is provided by the pharmaceutical industry to cover the cost of biomarker testing for relevant patients.

Dr. Dollins (Merck, Germany) stated that in many countries pharmaceutical companies with products that require a CDx do pay for testing. However, in future, the sustainable solution will be reimbursement for the diagnostic testing.

Next Steps

Introduction on the EUnetHTA actions

Sonia Garcia Perez (AEMPS, Spain)

Ms. Garcia Perez introduced the objective for EUnetHTA, to build a sustainable model for the scientific and technical cooperation on HTA in Europe. This has so far been delivered across three Joint Action plans (2010-2012; 2012-2015, and currently 2016-2020). The collaboration involves 80+ organisations from 30 countries.

Work package 4 involves 'joint production', namely the production of joint assessments within the network. This can include 'Rapid Relative Effectiveness Assessments' (REA) and 'Full Assessments', with the aim to produce reports in parallel with the CHMP assessment to ensure Member States have the reports in time to inform national decision making. Currently, the key challenge is that the process is led by the applicant, and EUnetHTA are not receiving voluntary assessments. This process is now changing, with EUnetHTA engaged in horizon scanning to identify products for assessment, and selected products will be requested to submit a dossier.

Work package 5 includes the objective to provide support for evidence generation along the lifecycle of a technology. This involves an opportunity for early dialogue with manufacturers (for advice in the early stages of clinical development) and parallel consultations for manufacturers with EMA and EUnetHTA. Additionally, work package 5 includes a focus on post-launch evidence generation, with the first pilot of a European registry in parallel with the EMA.

Work package 7 involves the national implementation of EUnetHTA activities, with the objective to support the development of a sustainable mechanism of cooperation amongst HTA bodies in Europe. This drive for cooperation is based on the shared aim to ensure timely

access of health technologies to patients considering limited resources, along with similar methodologies for assessments (and comparator products) across the EU. This also aligns with the current move towards mandatory joint assessment, as covered in the proposed Directive (2018/0018) which outlines activities required for a European HTA. Discussion in the council is ongoing on whether assessments should be mandatory or optional.

The provider's point of view

Santiago Valor (Labco, Spain)

Dr. Valor provided an overview of the challenges diagnostic laboratories face with regard to the delivery of personalised oncology medicine. The primary issue is the need to assess the quality/value of many new technologies (that typically claim to replace existing products, and result in cost savings). A lot of time and effort is spent differentiating the value of tests to produce the required outcomes, with a large amount of pressure coming from patients for empowerment with greater information on their conditions.

Looking at the economics of testing, laboratory services are not usually reimbursed on a volume-based model. Funding is usually provided on a fixed budget model, at the request of regional administrations (in Spain), or due to customers (namely treatment centres) using this method to manage demand. Therefore, the most common economic issue for providers is not available reimbursement per test but managing the available budget to meet the overall costs/demands for testing. Additionally, a new challenge is that testing methods are evolving into multivariate panels, so the traditional cost cycle of a diagnostic test no longer applies. Previously, after a new test was launched, the price would come down, however this does not apply to new products such as MammaPrint and OncotypeDx.

It's also worth noting that 15% of health spending is paid out of pocket by patients, and since 2009 direct out of pocket spending has grown more rapidly than public spending across EU countries. We are therefore working in a complex, strained environment where economics is key. This presents an important barrier to uptake of new biomarkers in pathology services.

Dr. Valor identified two different types of pathology services. Those assigned directly to hospitals (working for 'captive customers'), and commercial laboratories that compete for business from multiple customers. In the former, the value of diagnostic testing is under recognised. In commercial laboratories, there is an understanding that unless a high-quality service is provided supporting good clinical outcomes, then the lab will no longer receive test prescriptions. This requires addressing the challenges of commoditization (reducing cost and improving the service, dealing with volume growth and less budget), providing clinical value, and empowering patients/clinical decisions.

Regarding the need for high quality service, this requires time and effort identifying the best in class products, considering an often-limited evidence base. Dr. Valor also stated this his laboratory has decided to move away from home brews to increase the standardisation and quality of testing. Quality is also ensured through association with bodies such as The European Molecular Genetics Quality Network (EMQN), and Genomics Quality Assessment (GenQA).

Regarding the need for improving knowledge in the laboratory, oncology is now transforming practice. This has enabled an environment for the appropriate use of biomarkers, with all pathology disciplines integrated, and knowledge circulation amongst stakeholders. There is also a focus on process improvement, where instead of just being 'suppliers', laboratories are becoming 'partners'. This means working together with providers to address requests for services that are more difficult to manage, such as multi-site sampling in breast cancer. There is also a need for further empowerment, with pressure from patients to provide early access to new technologies.

Data is an area of improvement that could help significantly with service improvement. The amount of data that could be shared by pathology services to support research/validation of biomarkers is extensive, and time and opportunities are being lost to collect data that could be helpful to support the introduction of biomarker testing and improve oncology services.

Dr. Valor concluded by stating that overall laboratory/pathology services represent around 5% of hospital costs. The introduction of biomarkers into clinical practice is currently being slowed down due to funding issues, impacting less than 1% of the overall budget. Reimbursement is therefore key to transform services and improve adoption of innovation. This should involve:

- Payments per test performed (instead of global budgets)
- Bundling payments for the diagnostic testing with payment for pharmaceuticals
- Allowing interim approval (and reimbursement) to generate data
- Providing a voice to laboratories/pathology services as a corporate stakeholder (e.g. being able to discuss the prescribed tests for a given patient)

Multi-stakeholder approaches for addressing barriers to precision medicine: Diagnostic Quality Assurance pilot

Lindee Goh (Tapestry, United States)

Dr Goh started with posing the question of who regulates the quality regarding diagnostic testing. To address the ongoing uncertainty about diagnostic regulation in the United States, the Quality Pilot emerged in 2013 out of the multi-stakeholder Sustainable Predictive Oncology Therapeutics and Diagnostics (SPOT/Dx) working group, with a focus on improving patient outcomes by equipping healthcare leaders with tools to advance clinical decision-making for the diagnosis and treatment of cancer and required regulatory and reimbursement infrastructure.

The Diagnostic Quality Assurance Pilot launched in 2015 [14], with the objective to equip molecular pathology laboratories with traceable reference samples to assess whether participating laboratories' appropriately validated tests can achieve diagnostic performance comparable to a CDx for targeted cancer therapy. Accuracy of genotyping is determined regardless of whether laboratories use the FDA approved CDx or laboratory developed tests (the objective is not to specify any one test that should be used, but to give the option for laboratories to use any tests as long as they can show equivalence).

The pilot is currently running, and due for completion in early-mid 2019. This uses a candidate CDx comprised of a two-gene, multiple variant NGS panel volunteered by Amgen and CDx partner Illumina. Performance specifications are set by the Illumina CDx for a targeted colorectal cancer therapy, and a CDx that was under FDA review for a new indication (pre-market, that was subsequently approved in June 2017). The College of American Pathologists has selected a vendor for production of reference samples, and managed distribution of samples to four laboratories and coordinated data collection and analysis for an initial proof of concept phase that aims to ensure the reference samples work as intended. Following the proof of concept phase, 20 pilot laboratories will then have an opportunity to demonstrate their ability to accurately analyse reference samples for a variety of DNA variants, and report findings of clinical decision points for the targeted therapy.

The reference samples included a so-called 'wet challenge' and a 'dry challenge'. The 'wet challenge' includes blended genomic DNA samples with pre-defined variant profiles. The 'dry challenge' includes pre-defined variant profiles introduced by a computerised process into the participating laboratories' own BAM and/or FASTQ files (from either amplification-based or capture-based assay designs, run on either Torrent-based or Illumina-based platforms).

A key learning from the process so far has been ensuring the interests of all stakeholder groups are aligned. Within the pilot, each sector's concerns constructively informed the work of other groups, providing greater transparency about priorities and processes.

This approach within the pilot, if proven successful, could be scaled-up to include patient samples, more laboratories, and/or focus on a different CDx for a different disease. Regarding the implications for the precision medicine community, some stakeholders have shared early ideas that the process could be institutionalized via a 'gold seal of approval' for laboratories that demonstrate equivalent performance of their laboratory developed tests to the CDx. The standards generated could also be used by laboratories globally, and the pilot approach could be integrated into pre-clinical development programs and/or adapted for areas beyond molecular diagnostic panels. The long-term implications, however, will be further discussed once the pilot is completed in 2019. Importantly, the pilot has also helped informed a recently launched effort by the FDA and medical device community looking into the gaps for somatic reference samples (see <http://mdic.org/clinicaldx/somatic-reference-samples/>).

More information on the pilot can be found at: <https://www.tapestrynetworks.com/our-work/healthcare/diagnostic-quality-assurance-pilot>

Discussion

A question was asked regarding potential for new technologies such as blockchain to be integrated into diagnostic testing.

Dr. Goh (Tapestry, United States) responded that it is too early to say what the implications of new technologies such as blockchain will be. There was a consideration from the Sustainable Predictive Oncology Therapeutics and Diagnostics (SPOT/Dx) working group on how big data can be integrated into clinical practice, and blockchain and artificial intelligence technology were discussed. The FDA is also moving rapidly regarding such technology tools from a regulatory perspective (e.g. regarding personal access to medical information), so this area should be monitored for future developments.

A member of the audience added that the primary value from blockchain technology is security of data. For some areas of diagnostic research/testing this will be useful, however 'there is currently a lot of hype and lack of understanding around how this can be used'.

A question was asked regarding the quality controls that should be followed by companies developing companion diagnostics, to ensure the product is accepted as a valid/high quality.

Dr. Valor (Labco, Spain) responded that this is not an easy issue to address. The laboratory would request the same level of validation that is used for one of its own laboratory-developed tests. However, this will evolve. In future, laboratories will request a completely independent validation of test quality from regulatory agencies. Inter laboratory testing will not be enough.

A question was asked regarding the implications/future developments for EUnetHTA's plan to directly approach companies regarding centralised joint HTA.

Ms. Garcia Perez (AEMPS, Spain) stated that this development is in the very early stages, so far only the horizon scanning has been completed and the target companies/products for joint assessment have not yet been approached.

Going forward to the proposed mandatory joint assessment, this could be implemented in a number of ways. The joint assessment could be adopted as the complete HTA (to inform reimbursement and pricing negotiations at Member State level) or could simply be used as a reference or bibliography to inform HTA at the Member State level. Successful collaboration

will require trust amongst HTA bodies across different Member States (to inform a model similar to the CHMP, where the assessment for centralised decisions is often carried out by bodies at Member State level), however this is currently not the case.

An audience member from Novartis added that the company previously partnered with EUnetHTA to work on a pilot joint assessment. In this case, the assessment report was used as a reference only at the national level, and did not complement the national HTA process. However, it is hoped in future that Member States will avoid this duplication and adopt joint assessments done at the European level to inform their decision making.

Perspectives on next steps

The following key points were identified for further exploration in future meetings:

- Innovative methodologies for designing clinical trials including biomarkers, to demonstrate clinically relevant value for patients and healthcare systems (considering the need to bring new biomarkers to market, whilst recognising the constraints of standard pharmaceutical development programmes).
- The role of HTA in assessing the holistic incremental clinical, economic and humanistic value of biomarkers, to inform timely reimbursement decisions and optimise treatment decisions.
- Innovative access strategies to support rapid reimbursement and adoption of biomarkers in clinical practice (including balancing the requirements for clinical data to inform payer assessments, with the need for accelerated access and experience in clinical practice).
- A multistakeholder approach to ensure the attractiveness of Europe as a market for the development and launch of oncology biomarker tests.
- The importance and regulations surrounding keeping, protecting and sharing patient data for the purposes of researching the identification of new biomarkers and their associated companion diagnostics.
- The harmonisation and validation processes that need to be considered in the context of developing companion diagnostics to ensure their quality and the consistent reproducibility of tests.

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