ESMO Roundtable:

EAPM seeks innovative solutions at ESMO for cancer patients

18th September 2020

European Alliance for Personalised Medicine

Introduction

Understanding of the potential of new approaches to cancer received a major boost among a broad audience of patients, professionals and policymakers in mid-September, when EAPM hosted an on-line satellite meeting at the ESMO Congress. The EAPM focus was on bringing innovation into healthcare systems through molecular diagnostics. Three sessions raised the quality of discussion on the paradigm shift driven by tumour agnostics, the new horizons opened up by advanced biomarkers, and the challenges of integrating real-world evidence into decision-making. The discussions helped to shape new definitions of the issues, and new consensus on avenues to move further ahead. The meeting demonstrated wide and enthusiastic support for TAx. 95% of participants and audience at the roundtable said in a survey that tumour-agnostic is a paradigm shift in cancer care. It embraced a strong consensus on the need for rapid and wide deployment and promotion of the use of biomarkers. And it provided a new level of agreement in the long series of successful EAPM high-level roundtables on the implementation of Real-World Evidence in healthcare in Europe, delivering sharpened recommendations on how to proceed, and demonstrations of growing willingness to go into the direction of Europe facilitating more public-private cooperation in maximising the use of RWE.

This was EAPM's 8th participation at ESMO, and prompted reflection on just how far science and healthcare have evolved over those years. ESMO's crucial and distinguished contribution to this progress is rightly acknowledged, with its annual congresses standing as landmark moments in advancing the discussion of cancer. In its own way, EAPM too can claim to have made a valuable contribution, with its particular achievement in multistakeholder coordination, that has enable it to consistently develop as a bridge from the scientific and medical world to policy makers.

The roundtable comes at a crucial time as Europe deploys new efforts to bring innovation into healthcare systems and to establish strategic cooperation. EAPM is actively engaged in discussions with stakeholders and with policymakers on the emerging Beating Cancer Plan and the Cancer Mission, the promised EU health Data Space, the review of research incentives in its orphan drug rules, the overarching Pharmaceutical Strategy scheduled to appear before the end of 2020, and the new determination – announced in mid-September - to go beyond the draft EU4Health programme and create a genuine European Health Union. MEP Dolors Montserrat, a former health minister of Spain, in her remarks to the roundtable, welcomed the growing calls for more EU competence for health, confirmed by Commission President Ursula von der Keyen in her recent State of the Union address, along with a strengthening of the EMA and ECDC. Montserrat declared herself a champion of the EU initiatives

on cancer, with their close links to personalised medicine, and urged closer cooperation on health among the 27 member states. integrating innovation will make health systems more efficient and sustainable, she said. She also highlighted the decision of the European Parliament to set up a new committee specifically on cancer: “We have a lot of tools. We have to improve it all together,” she concluded.

Much of the discussion reflected this EU context. There were acknowledgements of the role and potential of the European Reference Networks, and of the prospects for integrating the concept developed by EAPM of federated registries into the European health data space. Speakers also suggested that all stakeholders should pay attention to the quality of their messaging – in terms of definitions and priorities – in order to exert more effective influence on policy makers. And the roundtable demonstrated the appetite for closer cooperation among stakeholders in refining their thinking in the European context. “With this level of participation and level of experience in this in this area, we must continue to work together and support one another,” said one speaker. “Organizations like EAPM can bring a tremendous amount to this discussion and facilitate this dialogue across the multitude of oncology ecosystems at a European, international and national level,” said another. There was praise for “these roundtables where we try to facilitate multi-stakeholder co-creational approaches” and for “industry-academia consortia with open discussions on how to create benefit for all stakeholders.” And with an eye on the health plans of the European Commission and the Council, there was a welcome for “allowing us today to gather and get a real pan-European view of what’s going on.”

This latest EAPM roundtable was especially remarkable for its determinedly multistakeholder character. It was designed from the outset to offer bottom-up as well as top-down engagement, so alongside politicians, regulators, researchers and clinicians, there was prominent participation of patients and a wide range of healthcare professionals. It was able therefore to make links not just across stakeholder perspectives, but also across national- and EU- level perspectives. And it was on that basis that the EAPM roundtable was able to secure a new level of accord on many of the most contentious points at that intersection of the often-distinct perceptions of healthcare.

Denis Horgan
EAPM Executive Director

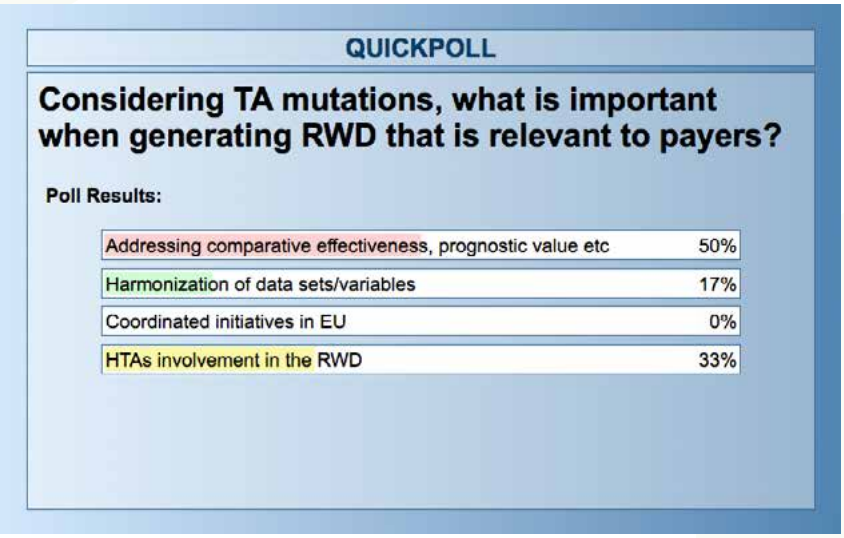
Executive summary

The potential of technologies in fighting cancer is under-exploited.
To highlight the barriers, EAPM organised exchanges on making more use of tumour agnostic medicines, molecular testing and diagnosis, and the wealth of real-world data that could speed new product development. The forum for these exchanges was a roundtable during ESMO, and it brought together experts from across the widest range of stakeholders – clinicians, academics, pathologists, policymakers, industry and patients.
The discussions resulted in sharper definition of the barriers and clearer understanding of distinct points of view on how to surmount them. Denis Horgan, Executive Director of EAPM, who moderated the roundtable, underlined the importance of bridges between the testing laboratory and lawmakers. The principal conclusion was that since good policy depends on good science, it is the responsibility of stakeholders – and particularly the scientific community and the patients it serves – to ensure that the issues are better understood by the policy community, and taken account of in policy formation.

First session:
Tumour agnostics

Fittingly described by many speakers as a paradigm shift in cancer care, tumour agnostic therapies present a new promise of precision medicine – and accordingly, as was frequently argued during the discussion, they require a new way of thinking about cancer care. They offer new opportunities for patients with rare mutations, and the pipeline of potential tumour agnostic therapies/ indications is growing rapidly. According to Sushil Patel, Franchise Head of Lung, Agnostic, Skin & Rare Cancers, and VP of Global Product Strategy Oncology at F. Hoffmann-La Roche AG, "Tumor agnostic approvals to date are only the tip of the iceberg as further opportunities will arise from the pipeline." . At the same time, better and cheaper diagnostic technologies are opening the way to the use of more targeted therapies.

Because these are histology independent therapies, targeting specific genomic alterations in a tumour regardless of its anatomical location or histology, they are not evaluated with randomised clinical trials. Evidence is derived principally from small single arm trials and real world data, and as was repeatedly noted, this creates challenges, not least because of the lack of active comparators, and the use of biomarker-based or surrogate endpoints in small sample sizes of marked heterogeneity. Policy makers, payers and (to a lesser extent) regulators continue to require randomized controlled trials (RCTs) as primary evidence of drug efficacy. And because the use of TAx depends on sophisticated testing to select patients – notably next-generation sequencing (NGS) - deployment suffers from inadequacies in the diagnostic infrastructure.



Because they do not fit the customary patterns of care, or the assessment frameworks that are typically used by decision-makers, there is a need for developing stakeholder understanding and awareness so as to integrate them into clinical practice. This, it was argued, requires dialogue and collaboration across silos in an Inclusive strategy to develop therapeutic options. For Patel, the development of TAx offers more options for patients with rare mutations with high unmet need, and opportunities for multi- stakeholder collaboration to tackle barriers and consider solutions to advance precision medicine. It is a moment, he argued, to "agree on a road map for change."

There is also the need for government support in creating new pathways through HTA with acceptance of novel data sources, commitments from policymakers on reimbursement, funding and pricing, and expansion of testing infrastructure. Responding to these requirements should feature prominently in the EU's strategy for cancer and health, suggested speaker after speaker. A survey of participants showed that 86% favoured a combination of early regulatory and HTA dialogue, RWD collection and analysis, and adaptive regulatory and HTA pathways to integrate the perspectives of clinicians, regulators, payers, to ensure cancer patients can benefit from tumour-agnostic therapies.

Rosa Giuliani, Consultant in Medical Oncology at The Clatterbridge Cancer, was emphatic in her endorsement of the concept of a tumour agnostic approach to tackling cancer. In her view the paradigm shift it represents holds out the prospect of better treatment and streamlined drug development, if the right conditions are in place. "The paradigm shift is a rational shift," she said. "It is more rational to try to understand the driver of the tumor." She acknowledged the range of challenges to be overcome, including the uncertainty it engenders among patients, clinicians, regulators, HTA bodies and payers. But she was adamant that this was not an insuperable obstacle: "As a clinician I have had to deal with uncertainty and risk since forever," she said, adding that "Uncertainty can be managed

and contained pre- or post-approval."
She spoke of the need to get the message to policymakers to obtain government support, and saw the discussions at EU level on cancer, on orphan medicines and on a new pharmaceutical strategy as potentially helpful initiatives for advancing understanding and acceptance of the concept. "We need to supply a scientific message to the policy community," she said, suggesting that the novelty of TAx could make it a valuable pioneer for the process. A central part of the message must be for greater coordination among policymakers, she insisted, noting the political fragmentation that impedes health policy development. "During Covid we learned that it's very difficult to work in a fragmented system. It's critical to have a common approach."

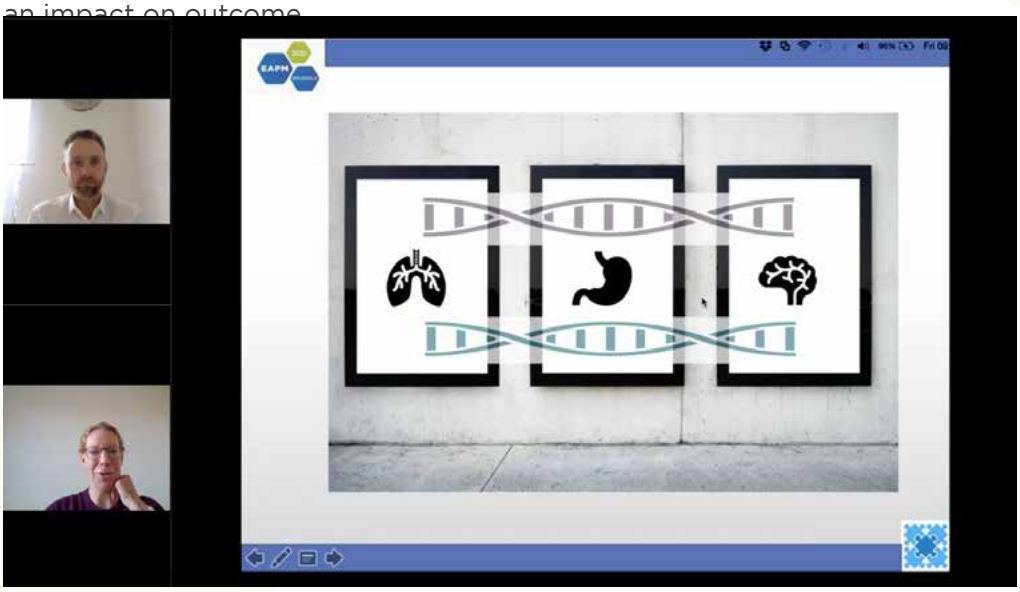
Fabrice Barlesi, Medical Director of Gustave Roussy, said that while he understood the demand for RCTs because they provide some control on the quality of data, the EU should address the issue of data quality from other sources: "RCTs are no longer the way to go," he said. He suggested that a way ahead could be EU support for trialling a new drug and delivering data to a centralised registry, which could give good consolidated data from across Europe.

Lotte Steuten, Vice President and Head of Consulting at the Office of Health Economics, addressed how to bridge the gap between pathways for regulatory and health technology assessment of histology independent cancer treatments, urging a search for new ways of securing evidence acceptance, greater use of conditional reimbursement, and more flexibility in relations between payers and companies.

Allan Hackshaw, Deputy Director of Cancer Research UK and the Cancer Trials Centre at University College London, took a more measured view of TAx. Research in this field is a priority, but is not "the priority", he said, noting some of the current obstacles: TAx drugs are currently expensive, and many patients have no access to NGS testing, or only at high cost. It remains equally important to seek effective new therapies and new combinations of existing therapies in unselected patients, and reduction in aggressive treatments. He highlighted the challenges of generating evidence that would persuade regulators – and still more, HTA agencies – of the merits of Tax.

Giuseppe Curigliano, Associate Professor of Medical Oncology at the University of Milano and Head of the Division of Early Drug Development at the European Institute of Oncology, urged caution, particularly in the excessive use of NGS. "Universal testing cannot be sustainable," he said, urging that drug access according to the agnostic pathway should be justified by the level of evidence, the actionability of the targets and clinical

data. Highlighting the ESMO recommendations for NGS, he said medical needs should be defined in the disease setting identified where there will be an impact on outcome.



***Denis Horgan**, Executive Director, EAPM - **Lotte Steuten**, Vice President and Head of Consulting at the Office of Health Economics*

In his view there is a risk of disrupting public health in uncontrolled recourse to NGS. "Implementation of multigene sequencing in daily practice requires investments that have to be considered, especially regarding sequencing and bioinformatics workflows in order to deliver results to clinicians in a timely manner," he argued. "From a public health perspective it must also be considered that the results of NGS panels could lead to the recommendation of expensive drugs outside their approved indications." He concluded that there is "a need to regulate the volume of NGS procedures at the national level."

The challenges of persuading HTA agencies and payers of the merits of TAx was a recurrent theme in the discussions. Hackshaw remarked that acceptance of TAx remains problematical because of the different evidence base for them. Regulators may be more open to single-arm trials, but HTA agencies and payers are reluctant, he said. Payers used to a histology base do not want to pay for expensive drug that doesn't work for all patients; they will take time and require better efficacy and data to accept mutation-based treatments. And he had little optimism over early dialogue between HTA and regulators. ""They say they want to coordinate but the reality is different: they don't in practice, and some HTA agencies have been conspicuously resistant to evolve."

Curigliano pointed to the different endpoints between investigators and payers as a challenge to overcome, and Steuten highlighted the tensions between regulators and HTA agencies, observing that HTA bodies were not

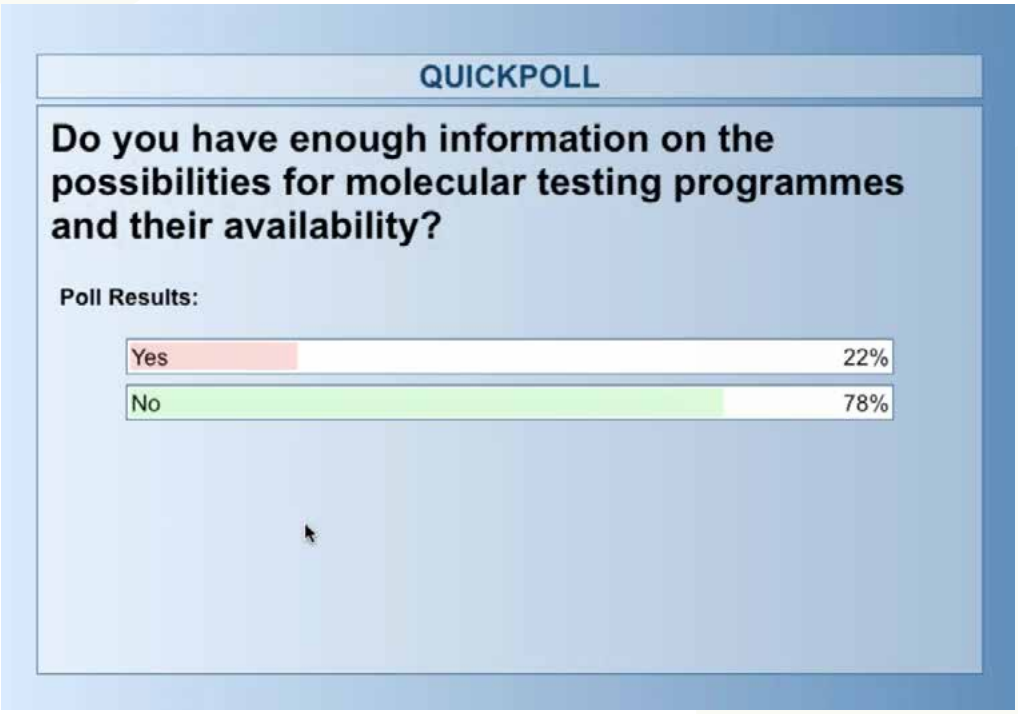
very rapid in adapting their perspectives and processes.
National divergences in approach were also an issue. Suschil spoke of varying HTA energy and expertise in Tax, and of HTA bodies' hesitancy In using available tools, and Barlesi was of the view that France remained rather conservative in HTA. Suschil insisted it was "essential to create alignment between regulators and HTA bodies".

Recommendations

- **Government support for regional/national patient registries for RWD**
- **Search for a common approach to assessment of TAx among HTA and regulators**
- **Alignment of data across countries**
- **More early dialogue, RWD collection and analysis**
- **Medical societies to give more guidance to policymakers**
- **Strengthen national cancer plans on screening and diagnostics through funding**
- **Invest in high quality testing including Next Generation Sequencing (NGS) capabilities and protocols**
- **Develop federated access to a pan- cancer registry built on harmonised data**

Second session:
Biomarkers and Molecular Diagnostics

Better and more equitable access to biomarkers and molecular diagnostics across Europe is a must for real progress, the roundtable agreed - but it remains a distant prospect. 100% of participants surveyed agreed that early detection programs (such as through biomarker testing and molecular testing) should be accessible across the EU. And 78% said that information on the possibilities for molecular testing programmes and their availability is currently inadequate. Keith Kerr, Consultant Pathologist at the Department of Pathology of Aberdeen University pointed to how new diagnostic technologies could give access to personalised medicine and help resolve inefficiencies, such as trial-and-error dosing, increased hospitalisation due to adverse drug reactions, and the problem of late diagnoses, and could also enhance the effectiveness of therapies through better tailored treatment administration. At the same time, it was argued, it would provide patients with the use of safer and more effective therapies, as well as increased confidence about treatment decisions. According to Ash Sharma, Head of Strategic Marketing and Market Access, Global Oncology and Diagnostics at AstraZeneca, the use of biomarker testing can help select appropriate treatments for tumors with multiple potential treatment modalities, and avoid wasteful use of drugs that would be less appropriate for a patient than other options. Reinhard Buettner, Director of Department of Pathology at the University Hospital in Cologne, noted how much progress testing on a molecular level had made possible to determine the individual optimal therapy since “really the Stone Age of personalized medicine in 2013”.



There are now a multitude of approved genomics guided therapies There was plenty of evidence that improvements are still needed. Technical barriers to biomarker testing are encountered in clinical practice where sample collection of a tissue biopsy is not feasible, where improper or insufficient specimens are collected, or where the specimen contains insufficient tumor content or high-levels of necrotic cells. There are also challenges in accurate staging or delays in tissue specimen processing. Standards have yet to be agreed and implemented on testing. Biomarker testing is also negatively impacted by low test sensitivity, prolonged testing turnaround times, test failures, lack of timely reporting to the treating physician, and difficulty in interpreting reports. And there can be challenges in ordering biomarker testing where it is not standardized or routine practice. More appropriate access and reimbursement to diagnostics and biomarkers is needed, with redefined healthcare budgeting processes. Payers remain to be convinced, with the result that clear reimbursement pathways are lacking and the use of molecular diagnostics across Europe is impeded. Kerr saw reimbursement as "one of the cornerstones of getting this system right, but it is so heterogeneous so variable and in some places. Paradigms that were developed 15 or 20 years ago have not caught up with the current situation." So despite the huge influence – as much as 60% - that diagnostics exert on clinical decision making, and although diagnostics account for less than 2% of total healthcare spending, most European patients remain effectively denied access.

Top row: ***Dolors Montserrat****, Member of the European Parliament -* ***Denis Horgan****, Executive Director, EAPM -* ***Reinhard Buettner****, Director of Department of Pathology, University Hospital Cologne*

Bottom row: ***Pierfranco Conte****, Full Professor of Oncology and Director of the Post Doctoral Fellowship Programme in Medical Oncology at the University of Padova -* ***Ash Sharma****, Head of Strategic Marketing and Market Access, Global Oncology Diagnostics, AstraZeneca -* ***Rodrigo Dienstmann****, Principal Investigator of the Oncology Data Science Group of the Vall d'Hebron Institute of Oncology (VHIO)*

According to Buettner, the minimal requirements today for an adequate testing scenario are full availability of histology, immunohistology, NGS DNAseq, NGS RNA seq, blood-based NGSseq, FiSH, and availability of genetic counseling, backed by interdisciplinarity between anatomical pathologists, molecular pathologists, bioinformaticians, and technicians, and with access to multidisciplinary tumor boards, all functioning with sufficient throughput to deliver diagnostics economically and with high-quality, with sufficient reimbursement throughout the healthcare system.

Pierfranco Conte, Full Professor of Oncology and Director of the Post Doctoral Fellowship Programme in Medical Oncology at the University of Padova, spoke of "an evolving landscape", in which widely available next generation sequencing will bring closer the identification of multiple potentially druggable alterations, with its prognostic/predictive role of molecular alterations on large cohorts of patients. But it will, he said, pose questions too, in the interpretation of results, and in integration of testing into diagnostic-therapeutic pathway. Pointing, like Curigliano, to the Esmo clinical practice guidelines on biomarker testing in breast cancer, he alluded to the possible promotion of off-label use and the implications this could have for health system sustainability. In his view, a vital role should be given to molecular tumor boards, to bring "order from chaos", delivering clinical recommendations that would make it possible to treat more, and treat better.

Benjamin Gannon, Vice President International Access, Policy and Advocacy at Myriad genetics, made the point that personalised medicines and genomics can offer a solution to healthcare in Europe, but they require clear frameworks to be delivered. In addition to the quality issues discussed above, he highlighted the need for a "balanced and efficient future-proof approach to evidentiary expectations and value assessment," and a "healthy European ecosystem for companion diagnostics (Dx)". Communicating the value of Dx is leading to significant improvements in patient care and value to healthcare systems, he said, instancing findings on greater impact or better cost-effectiveness in PARP inhibitor therapy, second generation breast prognostic testing, and multi-gene panel testing for hereditary cancers.

Discussing the pros and cons of liquid biopsy, Sharma characterised it as "a useful diagnostic tool for identifying tumor-specific genomic alterations," with particular advantages in rapid turnround time, and in patients where there are challenges in obtaining sufficient tumor tissue. He noted the ESMO guidelines recommending its use at diagnosis, along with ESMO's comment that the lack of sensitivity requires all patients with a negative blood test still to need tissue biopsy.

Top row: ***Denis Horgan****, Executive Director, EAPM -* ***Keith Kerr****, Consultant Pathology, Department of Pathology, Aberdeen University*

Bottom row: ***Benjamin Gannon,*** *Vice President International Access, Policy And Advocacy, Myriad genetics -* ***Frederique Penault-Llorca,*** *Director, Centre de Lutte Contre le Cancer de Clermont-Ferrand*

Frederique Penault-Llorca, Director of the Centre de Lutte Contre le Cancer at Clermont-Ferrand, considered the optimal resources to achieve best standard of care for biomarker testing ("assuming that we already have reimbursement") as quality on the basis of defined standards, an accredited lab infrastructure, early biomarker screening (first line) for the patient, and robust supporting data sets accompanying biomarker tests. In his view, each member state should create a centralised national system aligned with European standards to validate and set up tests, and Europe should move towards data centralisation, with structures to collect and share research data and real-world data and standardized registries of genomics and outcome data.

BIG Data is an umbrella term describing large data sets from any source

- Large scale or complex collection and analysis of data
- Massive production of digital footprints with devices (smartphones etc.)

Background to Big Data Initiative

Increased interest in (BIG) data source integration and potential use in health care ecosystems, from multiple stakeholders

General need for regulators to keep abreast of developments and plan for the future

Rodrigo Dienstmann, Principal Investigator of the Oncology Data Science Group of the Vall d'Hebron Institute of Oncology, gave examples of poor standards of quality and long delays in returning test results, which could be remedied in part by pathology education and even more basically, in surgery education for tissue acquisition and preservation. Kerr insisted results should accurate and consistent, with external quality assurance.

Sharma highlighted the implications for clinicians in the speed of development of testing. "There's just an immense amount of information to keep up with, so keeping track of which biomarkers to order and what methodology you can get that done by can in itself constitute barriers," he said. "How can we ensure that high quality testing can be delivered as testing needs increase in volume and complexity?"

Dienstmann agreed. "It's not like 10 years ago when we had just two or three biomarkers and a handful of drugs. Now it's just impossible to keep track of everything that is going on as we move from a single gene perspective to a multi gene perspective. Gannon shared the view: "The amount of new tests and technology is staggering. There is a real need for support for integration and harmonization of complex testing into clinical pathways." FPL wanted to see a scientific watch of upcoming biomarkers, with anticipation of the use of biomarkers/guidelines/education), and funding for experimental testing to bridge clinical research into standard clinical practice, with guidelines to improve patient outcomes.

Kerr considered it essential that test results are communicated to and discussed by a multidisciplinary patient care team with adequate facilities for communication and IT infrastructure, playing at the same time a role in knowledge-building and education. Dienstmann took a more pragmatic approach: "In the real world the minimum requirement is to have a hotline so that people can just call and say they don't understand the report, and can get a report in understandable language."

Recommendations

- **Government support for NGS testing infrastructure**
- **Government support to achieve best standard of care for biomarker testing.**
- **Government support for regional/national patient registries for RWD**
- **Government support for multidisciplinary tumour boards**
- **Governments to promote reimbursement of testing**

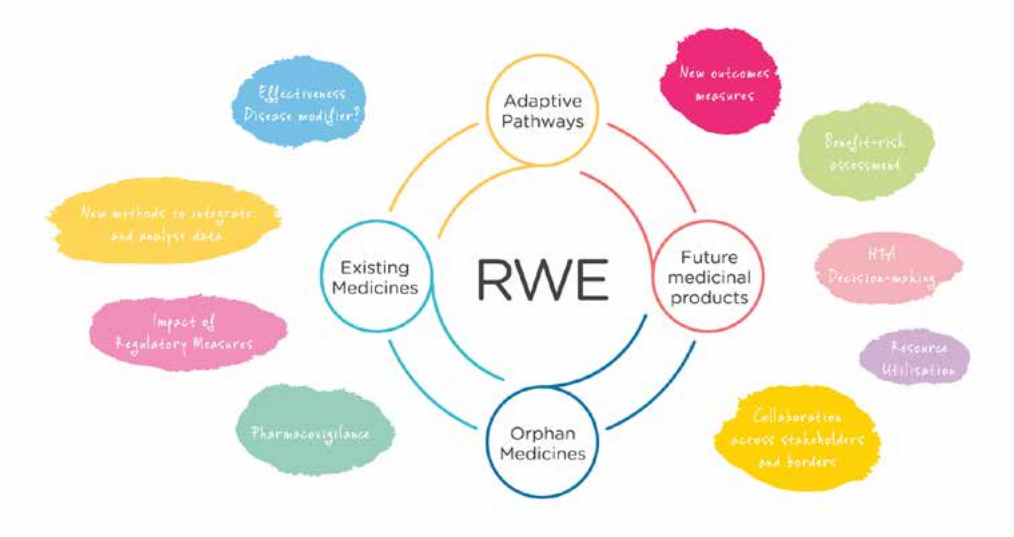
- **Develop a pan European HTA with objective processes for testing**
- **Test results need to be promptly available for therapeutic decisions**
- **Ensure adequate logistics and communication between labs and clinicians, with hotlines, Establish experienced multidisciplinary test centers able to counsel patients and translate molecular findings into an optimal therapy plan for the patient**
- **Assess the performance of lab tests against clear agreed standards**
- **Cooperation on information and education among developers of biomarkers, PAGs, HCPs medical societies.**
- **Cooperation on pan-cancer studies among drug and diagnostic developers, clinicians, biologists, biostatisticians and digital technology groups**
- **Greater centralization of diagnostics and decision making in personalized medicine in Europe**

Third session:
Real-World Evidence

The discussion made clear that the simplicity of the concept of using RWE in healthcare belies the many complexities underlying its exploitation. Harnessing health data from many sources in real time should help faster and better medical decision-making. But it will not happen automatically, as the roundtable made clear.

Healthcare data that are not collected in conventional randomised controlled trials – such as patient data, or data from clinicians, hospitals, payers and social surveys - is an invaluable complement to the implementation of adaptive clinical trials. Iterative phases of evidence gathering – to use the terminology of EMA's MAPPs project – will ideally utilise RWE to more accurately detect patient responses to new therapies in real time. But barriers include the lack of the necessary data infrastructures in Europe, insufficient harmonisation of data collection systems, and advances in health information technology that constantly outpace regulation and the capacity of regulatory authorities. Two thirds of respondents to the roundtable survey said their country's (including France and Germany) health system does not accept real-world data with regard to drug approvals or funding decisions. EU data protection legislation may also compromise the use of Real World Evidence in clinical development. The regulatory challenges will grow, as the next generation of healthcare exploitation of Real World Evidence will be increasingly multisectoral and multidisciplinary.

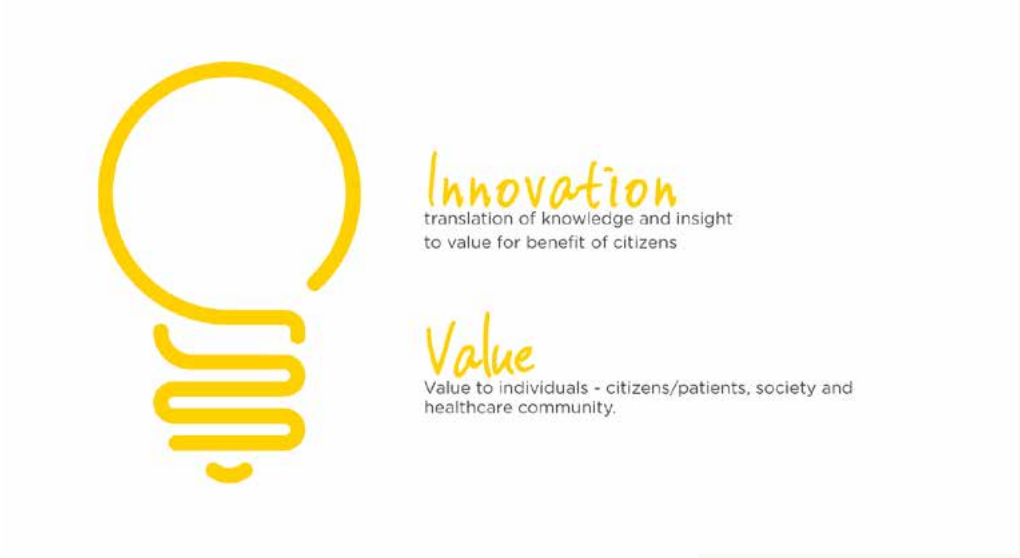
RWE is crucial to the implementation of adaptive clinical trials. The roundtable highlighted some of the regulatory needs for its implementation: health information technology implementation with wide scope for eHealth and mHealth applications, support for projects that investigate its use in approval and reimbursement of new therapies at the member state level, and incorporation of the opinions of patients with conditions for which there are currently limited treatment options.



In a provocative introduction to the session, Benedikt Westphalen, Koordinator Molekulare Onkologie at the Comprehensive Cancer Centre of the University of Munich, described the concept of real world data as "pretty simple". He said "we work as doctors and we generate data all the time we collect this data, we analyze it, and from this data that is generated in the real world's study we create insights that then inform practice. So far so good: this concept is easy to follow." But, he went on, "just because we have a concept doesn't mean that we actually have data that we can work with in the oncology space."

In the lively discussion that ensued, the merits and demerits, potential and limitations, and possible ways of exploiting RWE were energetically discussed among Christophe Le Tourneau, senior Medical Oncologist at the Institut Curie and Full Professor of Medicine at Paris-Saclay University, Lars G. Hemkens, Deputy Director of the Basel Institute for Clinical Epidemiology and Biostatistics and Senior Scientist, Department of CliniCal Research, University Hospital Basel, Inaki Gutierrez Ibarluzea, Director of Organisational and Managerial Innovation of the Basque Foundation for Health Innovation and Research, Frederik Buijs, Global Medical Director, Real World Evidence at Roche, Stefan Gijssels, Executive Director of Digestive Cancers Europe, and Ralf Herold, Scientific Officer, Oncology, Haematology & Diagnostics, Scientific & Regulatory Management Department at the European Medicines Agency.

Pursuing his iconoclastic approach, Westphalen demanded to know why real world evidence should be needed to support clinical decision making or even as a substitute for clinical trials. There is uncertainty over who set standards for real world data, who is responsible for its quality control, who is responsible for data collection, and who owns it, he pointed out. "When I see a patient in my clinic, I make notes in my electronic system but this is by no means data that can be used as a substitute for data from patients enrolled in a clinical trial, or even in registries with some control over inputs."



Le Tourneau was less confident that trial data is always so reliable. “They are also very filtered - it depends on how you use these data,” while and in the clinic “some data is quite accurate - perhaps even more accurate, as there’s not always much empirical data in a trial on the comparison of the data quality from registries.” With the exception of approval trials, “I’m not so sure if they are definitely better than routinely collected data.”

The discussion turned on how to build and utilize real world evidence and data and to bring it into health care in a more structured manner, benefiting from the opportunities that may arise under the European health data space and the beating cancer plan. Of particular concern was the issue of collecting and using data from different registries - complicated not only by data privacy considerations but also because different countries and different regions have different methodologies in their healthcare systems. If a system built on trust is to emerge, cooperation between these different stakeholders in regulatory and governance frameworks must be developed and facilitated, it was argued. Buijs suggested that bias in different data sources can be mitigated through choice of data sources depending on the research question, and taking bias into account. “We need to look for solutions and I think that data does offer opportunities in that area.”

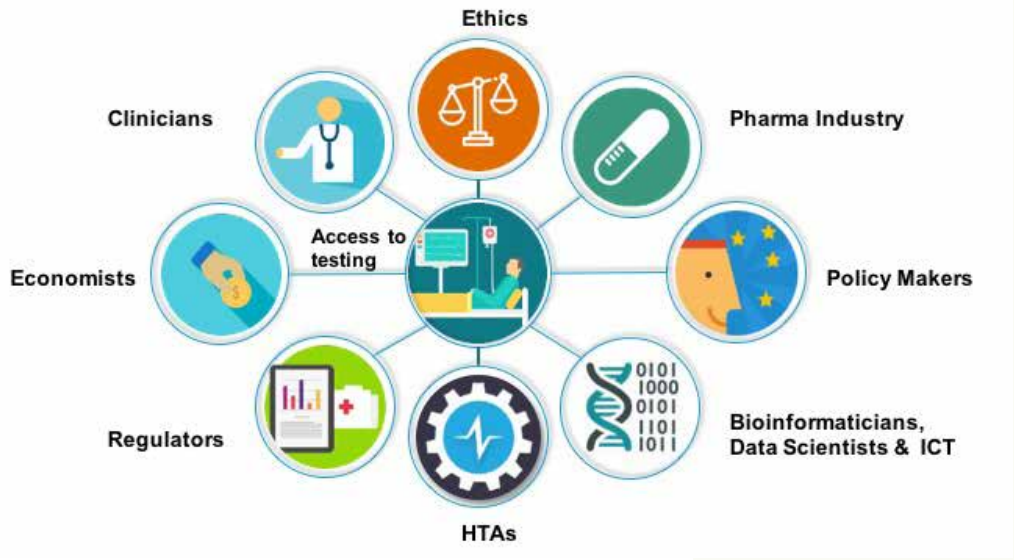
Le Tourneau saw RWE as capable of generating science, but principally as a contributor to drug development. “We haven’t been able to date to use real data to speed up drug development,” he admitted, noting some reticence in France over such directions. “We need very high-quality standardized data that has been accurately recorded and checked.” It will not be enough just to transfer data from hospitals’ electronic systems into the database: “We need a way to input standardized data that is of as high quality as in a clinical trial.” And for that, he said, academia may require assistance in a collaborative approach with industry. “I really think this is the way to go with registries,” he said.

Hemkens favoured exploring hybrid designs “where you link registries with approval studies under highly controlled situations,” which he saw as “a

great opportunity to use that data to work with traditional clinical research." He praised the speed and effect of the RECOVERY trial which had led – on the day of the roundtable – to the EMA recommendation on the use of dexamethasone for COVID-19 patients on oxygen or mechanical ventilation. And he questioned the presumption of automatic superiority and completeness of trial data, citing studies that found 35 out of 100 FDA approvals of novel anti-cancer drugs from 2000 to 2016 were based on evidence from a single pivotal trial without any further supporting evidence on beneficial effects. Routinely collected data can help RCTs in patient recruitment and increasing the number of RCTs. And through assessment of outcomes such as length of hospital stay, adverse events, complications, mortality in survival, it can deliver more patient relevant results.

Buijs noted that generating evidence supporting clinical-decision making is becoming increasingly challenging, as cancer classifications shift from tumour type and histology towards specific genomic alterations and biomarkers. "An integrated evidence generation approach is needed," he said. Reliance solely on RCTs risks delaying patient access to therapy, while an integrated approach combining interventional clinical trials and RWE, can optimize evidence generation so we can get more patients on the right treatment faster. We need to leverage the opportunity that RWE offers us to learn from the real life setting to ultimately expedite patient access and optimize healthcare delivery.

He emphasized that a multi-stakeholder (patients, academia, payers, health authorities and industry) collaboration and co-creation is needed to achieve the full potential of RWD for a sustainable evidence generation approach to improving patient outcomes faster..



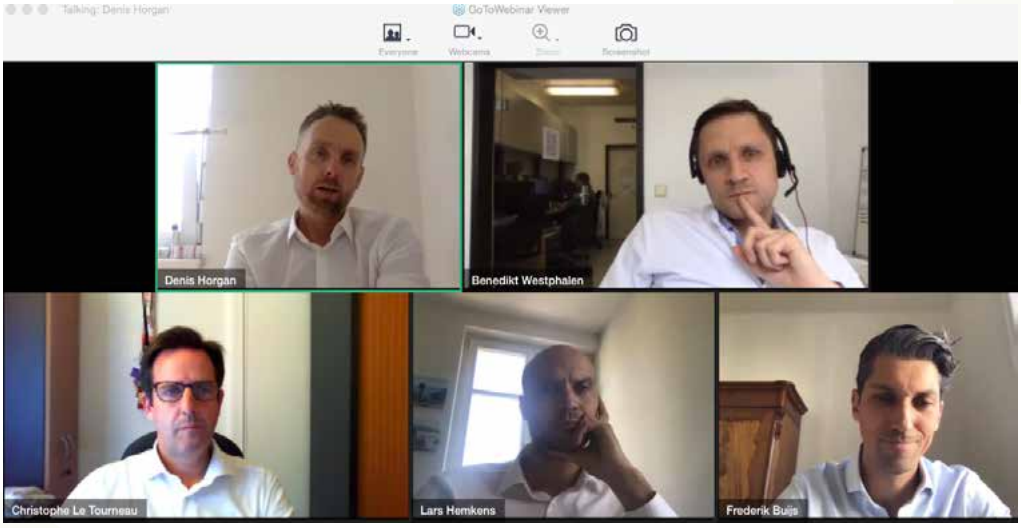
The many sources of RWD - disease and product registries, diagnostics / omics databases, health surveys, PROs and electronic / medical health record - can be retrospectively leveraged or prospectively implemented to answer specific questions. But to harness the power of RWE, certain challenges need to be addressed: existing datasets are often unfit, and data should be of high quality, complete, and shared.

Buijs proposed a learning model in the form of a global pan-cancer registry, collecting data involving patients diagnosed with solid tumours and profiled using next-generation sequencing while following their diagnosis, treatment decision and outcomes. The registry is supported and co-created by a multi-stakeholder committee and data and insights will be shared cross border so healthcare stakeholders can leverage the data most important to them. As such, the registry would support a collaborative community where stakeholders across all domains discuss RWE, share learnings, data and insights while generating evidence on how to improve healthcare and outcomes for patients

It is a point of view that received support for from the earlier sessions of the day. Hackshaw said "RWD is here to stay and we must get used to it."

Gutierrez Ibarluzea instanced the EU's EHDEN project as a possible approach to interoperability across different cohorts, but recognised the challenge in persistent reluctance among many hospitals and health care systems to share their data. "We need to share much more data than we're doing right now and also to create infrastructures and something that that is interoperable around Europe," he said.

Stefaan Gijssels, Executive Director of Digestive Cancers Europe, Ken Matris, Board Member, European Cancer Patient Coalition and Fabrizia Galli, Vice-President of ABRCAdaBRA, presented patient perspectives. Gijssels pointed out that the inputs of 1.5TR a year on EU healthcare were directed into what were mostly known factors – hospitals, medicines, staff, devices… – but "of the patient, in contrast, hardly anything is known." In his view, the way forward was to invest in outcomes data in line with the investment and costs. Cancer registries should capture all RWE in a harmonised way (patient, treatment, performer, …); or every organisation that receives tax-payers' money should be obliged to track and trace the outcomes in minute detail and send the results to registries; or Patient Data Donation Programmes should be created with added non-clinical data (social, financial, professional, …) organised and managed by patient organisations; or a true multi-stakeholder approach should be created with real-time, complete, transparent and accessible data.



Tow row: ***Denis Horgan****, Executive Director, EAPM -* ***Benedikt Westphalen****, Koordinator Molekulare Onkologie, Comprehensive Cancer Centre, University of Munich*

Bottom row: ***Christophe Le Tourneau****, senior Medical Oncologist at the Institut Curie and Full Professor of Medicine at Paris-Saclay University -* ***Lars G. Hemkens****, Deputy Director of the Basel Institute for Clinical Epidemiology and Biostatistics, University Hospital Basel -* ***Frederik Buijs****, Global Medical Director, Real World Evidence, Roche*

Herold emphasised in his presentation that there is a need for a "learning health care system" comprising medicines development, agents, processes, and infrastructures. The aim, he explained, was for science, informatics, incentives, and culture to be "aligned for continuous improvement and innovation, with best practices seamlessly embedded in the delivery process and new knowledge captured as an integral by-product of the delivery experience. [... Such systems ...] explicitly use technical and social approaches to learn and improve with every patient who is treated."

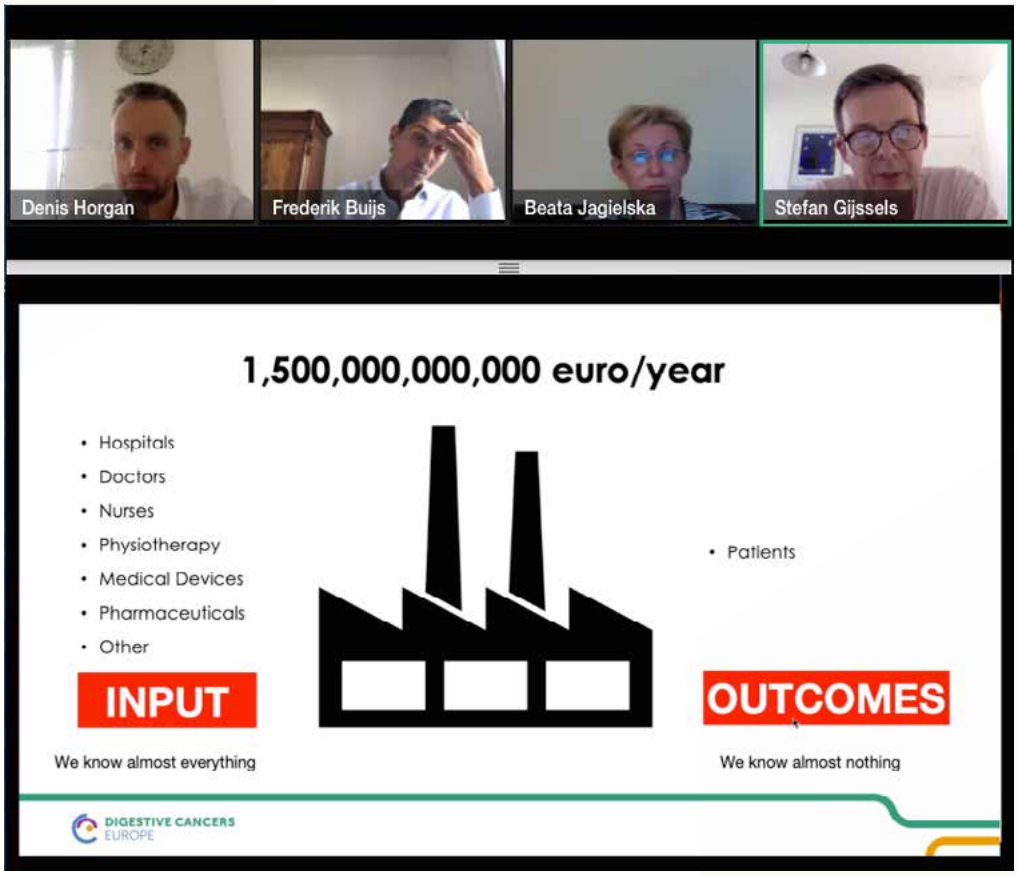
Work within EMA on registries of molecular and genetic features of cancer had focused on governance, data elements and quality assurance, and a registries guideline is now scheduled for publication.

A range of analytic methodologies applied to clinical development have been proposed or refined, including borrowing external control group data, construction of an external control group, indirect comparisons for relative efficacy or safety, reweighting of RCT results to reflect real life, predictive approaches to heterogeneous treatment effects, extrapolation of inferences to an unstudied population, and predictive approaches to heterogeneous treatment effects – even extending as far as replacing RCTs by RWD analyses.

But beyond analytic methodologies there are open questions. The different nature of outcomes in RWE data needs to be understood for clinical reasoning (e.g. relapse is derived as probability based on pre-defined sets

of utilised resources). The purpose should be identified that is driving a RWE approach (e.g., how do costs and value compare to experiment / trial? Whenever an RCT is feasible and necessary, why should it not be conducted?). There are questions over quality management and good RWE practices (e.g., how could RWE be inspected?). And the possible pitfalls of RWE approaches merit consideration, notably for oncology (i.e., confounding by indication, handling of intercurrent events and selection bias in complex setting; assessment bias with interim endpoints; guaranteed-time bias).

So although analytic methodologies are promising, they are unlikely to deliver robust results in all scenarios, and are not fully validated and accepted. New data sources without new accepted analysis methods (statistical, epidemiological) and clear purpose will not move the needle. So to overcome "methodology aversion", there is a need to evaluate a new methodology like a new drug: prospectively, well controlled and according to a pre-agreed plan. What is required is a 'methodology qualification procedure' to support acceptance by regulators and other decision-makers. The values for clinical evidence generation apply also to RWE.



***Denis Horgan**, Executive Director, EAPM - **Frederik Buijs**, Global Medical Director, Real World Evidence, Roche - **Beata Jagielska**, Head of the Oncological diagnostics, Cardiological Oncology and Palliative Medicine Clinic, National Institute of Oncology Maria Skłodowska-Curie - **Stefan Gijssels**, Executive Director, Digestive Cancers Europe*

There must be transparency establishing the identifiability of the RWE exercise, enhancing public verifiability, sharing accountability, and informing future use. Reproducibility of exercise will be needed, supporting the use of RWE by protocols, standards, and auditing. Replicability of results will also be needed, Implemented through principles and methods, as a fundamental expectation in medicine regulation.

Beata Jagielska, Head of the Oncological diagnostics, Cardiological Oncology and Palliative Medicine Clinic at the National Institute of Oncology Maria Sk odowska-Curie, urged the use of digital health solutions as effective, economical and safe for research work, development of professional literature and knowledge, research. A digital health strategy can bring greater patient satisfaction, competitive advantage, reduced numbers of clinical errors, and validations and monitoring, she said.

Recommendations

- **Government support for regional/national patient registries for RWD**
- **EU regulators should support the use of real world data for approval and reimbursement of new therapies at the member state level**
- **The opinions of patients with conditions for which there are currently limited treatment options must be incorporated when considering alternative evidence bases such as realworld data**
- **EU data protection legislation should be reconsidered with regards to healthcare to prevent disadvantage for the use of real world data**
- **Wide regulatory scope for eHealth and mHealth applications**
- **Interoperable data infrastructures in Europe with harmonisation of data collection systems**
- **Data should be of high quality, complete, and shared, to integrate it into health care in a structured manner,**
- **Closer cooperation between stakeholders in regulatory and governance frameworks**
- **Academia and industry collaboration on inputting standardized data to registries**
- **Invest in outcomes data, with focus on patient experience.**

Conclusion

This EAPM roundtable demonstrated a high level of engagement from senior figures across the wide range of stakeholders in cancer. The exchanges, though often featuring robust defences of strongly-held positions, led in many cases to new understanding among distinct points of view, and a new degree of consensus on some of the most contentious issues. The recommendations from the three sessions overlap slightly, since the subject matter of the three sessions inevitably overlapped somewhat. In many cases, they could become elements of discussion in the EU's developing initiatives on health and medicines. The principal action points for further consideration, distilled from the recommendations, appear below. But perhaps the most impressive conclusions from the roundtable are the vitality of the discussions and the clear support for continued dialogue among the widest range of stakeholders to advance new approaches to tackling cancer. perceptions of healthcare.

Action points for discussions in the context of the EU's Beating Cancer Plan, Cancer Mission, EU Health Data Space, the review of research incentives in its orphan drug rules, the Pharmaceutical Strategy, the draft EU4Health programme and the promised European Health Union.

Towards policymakers:

- Promote investment in high quality testing (via Cancer Mission, & Coordination of funding lines between member states)
- Promote common approach to assessment of new technologies among HTA and regulators
- Promote support among regulators for the use of real-world data for approval and reimbursement of new therapies
- Promote support for regional/national patient registries for RWD
- Promote support for adequate laboratory and data infrastructure in Europe
- Promote interpretations of GDPR that permit data use for research
- Promote investment in outcomes data, with focus on patient experience.

Towards stakeholders

- Ensure patient opinion is incorporated into discussions of evidence bases
- Ensure continued cooperation among stakeholders on pan-cancer studies
- Ensure rapid delivery of high-quality and clear test results for therapeutic decision-making
- Collaborate in clear messaging to policymakers on areas of agreement

About EAPM

The European Alliance for Personalised Medicine was launched in March 2012, with the aim of improving patient care by speeding development, delivery and uptake of personalised medicine and earlier diagnostics, through consensus.

EAPM began as a response to the need for a wider understanding of priorities in personalised medicine and a more integrated approach among stakeholders. It continues to ful l that role, often via regular major events and media interaction.

Our stakeholders focus not just on the delivery of the right treatment for the right patient at the right time, but also on the right preventative measures to ensure reliable and sustainable healthcare.

The mix of EAPM members and its broader outreach, provides extensive scienti c, clinical, caring and training expertise in personalised medicine and diagnostics, across patient groups, academia, health professionals and industry.

Relevant departments of the European Commission have observer status, as does the EMA, and our engagement with MEPs and Member State health ministries in key policy areas is a crucial part of our ongoing work.

Contact:

Denis Horgan
EAPM Executive Director

Avenue de l'Armee/Legerlaan 10, 1040 Brussels

+ 386 30 607 281
denishorgan@euapm.eu
www.euapm.eu

Next EAPM events

12 October, 2020:
German Presidency Conference: "Building a decentralised, data-rich biomarker space to speed better care and quality of life for citizens and patients"

November 2020:
2nd EAPM Global Conference: "Providing a global forum to ensure Public Trust in empowering Digital Data for health Science in a Covid and Post Covid World"