FEAM EUROPEAN BIOMEDICAL POLICY FORUM

FEAM
Federation of European Academies of Medicine

Companion diagnostics and precision medicine: regulatory and uptake barriers to patient access

Summary report of a round table discussion held on 27 September 2018

About FEAM, The Federation of European Academies of Medicine (www.feam.eu)

FEAM is the European Federation of National Academies of Medicine and Medical Sections of Academies of Sciences. It brings together under one umbrella 18 National Academies representing over 5,000 among the best scientists in Europe.

FEAM's mission is to promote cooperation between National Academies of Medicine and Medical Sections of Academies of Sciences in Europe; to provide a platform to formulate their collective voice on matters concerning human and animal medicine, biomedical research, education, and health with a European dimension; and to extend to the European authorities the advisory role that they exercise in their own countries on these matters.

About the FEAM European Biomedical Policy Forum

The FEAM European Biomedical Policy Forum provides a platform for discussion on key policy issues for the biomedical community.

The Forum is an initiative from the Federation of European Academies of Medicine (FEAM). It aims to bring together representatives from academia, research charities, industry, European and national trade associations and professional bodies, regulators, public health bodies, and patient and consumers groups. If you would like further information on the FEAM European Biomedical Policy Forum or becoming a partner, please contact silvia.bottaro@feam.eu

Disclaimer

Opinions expressed in this report do not necessarily represent the views of all participants at the event, the Federation of European Academies of Medicine (FEAM) and its Member Academies, or the FEAM European Biomedical Policy Forum partners.

All web references were accessed in October 2018.

Acknowledgments

FEAM warmly thanks Professor Peter Meier-Abt and Professor Stefan Constantinescu for chairing the round table. FEAM is very grateful to all the speakers for their contribution in preparing the event and this report.

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FEAM Federation of European Academies of Medicine

TABLE OF CONTENTS

Introduction

This report summarises the key points of the Federation of European Academies of Medicine (FEAM) European Biomedical Policy Forum round table discussion on "*Companion diagnostics and precision medicine: regulatory and uptake barriers to patient access",* which was held in Geneva (Switzerland) on 27 September 2018.

Background

Companion diagnostics (CDx) are critical tools for the implementation of precision medicine. However, there are many challenges (including regulatory) related to their implementation in daily practice.

One of these challenges is associated with the fact that regulatory pathways for medicines and associated companion diagnostics still remain separated in Europe.

Marketing authorization applications for medicines are submitted to the European Medicines Agency (EMA) while the certification of CDx for the obtainment of the CE mark is based on the assessment and approval from a Notified Body (an organisation designated by a EU country to assess the conformity of a medical device before being placed on the market), as regulated by the new EU Regulation on in vitro diagnostic medical devices (IVDR)[1]. As a result, certain aspects of medicines and CDx developments are often independently reviewed.

In view of the application of the new EU IVDR Regulation, in July 2017 the European Medicines Agency (EMA) published a concept paper on predictive biomarker-based assay development in the context of drug development and lifecycle[2]. The concept paper is intended to be developed into a guideline that will provide guidance relating to the interface between precision medicines and CDx.

Objectives of the meeting and expected outcomes

Objectives:

- Share information on existing initiatives aimed at improving the links between CDx and precision medicine;
- Discuss current regulatory and uptake barriers to patient access to CDx, and possible solutions, with the aim to inform any policy discussion and to identify recommendations for the biomedical community.

Expected outcomes:

- Enable an open and timely dialogue between stakeholders representing different biomedical sectors and with policy-makers;
- Enable the sharing of information and generate ideas for actionable suggestions and for possible follow-up actions by the relevant stakeholders/policy-makers.

[1] Regulation (EU) 2017/746

[2] https://www.ema.europa.eu/documents/scientific-guideline/concept-paper-predictive-biomarker-based-assay-development-context-drug-development-lifecycle_en.pdf

The agenda can be found at Annex I along with speakers' biographies (Annex II), the list of participants (Annex III) and a glossary (Annex IV).

The speakers' presentations are available on FEAM website, at the following link: https://www.feam.eu/events/feam-forum-round-table-on-companion-diagnostics-and-precision-medicine/

Summary

Companion diagnostics (CDx) are very important tools in precision medicine. They contribute to improve medicines' efficacy and safety, and for this reason their use is likely to increase in the future. Today CDx are mostly employed in the field of oncology, but tomorrow they might be more widely available across all indications. There are indeed important unmet medical needs in therapeutic areas such as respiratory, autoimmunity, cardiovascular, that would benefit from the use of CDx.

Although the value of CDx is recognised, there are some challenges concerning their development and implementation in clinical practice.

Participants at the round table discussed these challenges and possible solutions from a multi-stakeholder perspective. The round table brought together representatives from academia, industry, patients, healthcare professionals and regulators. Key topics approached during the debate included:

- **The importance of samples** – The biology of diseases is very complex, which means that the biology of diseases can change over time and develop resistance to treatments. Access to samples (and especially real time samples) is therefore crucial to develop and validate complex biomarkers and require cooperation among the academic and industry communities.
- **The need to identify biomarkers of efficacy in immunotherapy** – Today immunotherapy is based on a biomarker only in lung cancer. Immunotherapy works very well, but unfortunately only a minority of cancer patients respond to it. It is therefore important to identify biomarkers to avoid ineffective treatments to patients and to preserve the financial health of our systems.
- **Availability of infrastructures** – It is crucial to have infrastructures and laboratories that can perform testing on a broad scale and with very high-quality standards. However, not all countries might have the capacity to create the required infrastructures at national level. EU governments should collaborate more closely together and develop regional solutions that would allow resources to be pooled together in a cost-effective manner.
- **Investing in clinical utility studies** – There should be as many incentives to investigate clinical utility as there are for medicines' discovery. Indeed, sufficient evidence to justify modification of medical practice is available only for a minority of medicines.
- **Patients involvement in the full research lifecycle of CDx** – It is important to involve patients throughout the entire innovation chain (i.e. co-designed research, regulation development, HTA, pricing and reimbursement, evidence-collection, etc.) and to focus innovation on what matters most for the patients, listening to their needs and involving them in setting priorities.
- **Training of GPs** – General practitioners (GPs) have an important role as "mediators" between patients and specialist doctors. But to fulfill this role at best, GPs need to be trained to be able to provide the necessary explanations on CDx and other technologies available. They should also be trained in anxiety management as the predictive aspect of precision medicine might cause anxiety in patients.

- **Equity of access** – Huge disparities in access to medicines and related CDx exist not only among European countries, but also between regions in the same country. Innovative treatments tend to be costly, while governments are under pressure to cut costs.
  The biomedical community (academia, healthcare professionals, industry and patients) should work together to convince payers and governments that CDx can be cost-effective and develop new access models.
- **Ensure regulations include better links between precision medicine and CDx, from R&D to access** – Pragmatic regulatory systems as well as a supportive reimbursement environment are required to accelerate the development and uptake of approved targeted therapies and linked diagnostics.

Report of the event

Welcome and introduction

The meeting was opened by **Prof. George Griffin, President of the Federation of European Academies of Medicine (FEAM)** who welcomed the participants and thanked the Chairs for their work and contribution to the preparation of the meeting.

Prof. Griffin introduced the FEAM Forum, which provides a platform to discuss key EU biomedical policy issues among the FEAM member academies, the biomedical community and policy-makers.

Prof. Peter Meier-Abt, Vice-President of the Swiss Academy of Medical Sciences (SAMS), provided an introduction to the meeting. He underlined that companion diagnostics (CDx) are very important for targeted therapy and for precision medicine. For this reason, in the future we will see an increase in the use of CDx. Indeed, more than 90% of oncologists envision using multigene/multibiomarker diagnostic assays as the standard care in treatment decision making in the future[3]. This is due to the fact that CDx improve the efficacy and safety of medicines, and open up new treatment options.

Improving links between CDx and medicines - Regulatory barriers and possible solutions

Companion diagnostics in oncology

Prof. Christophe Le Tourneau, Head of the Department of Drug Development and Innovation at the Curie Institute (Paris) explained that the development of biomarkers emerged with the advent of targeted therapies, leading to impressive efficacy of new targeted treatments in oncology. Targeted therapies work only in the presence of a target that is usually specific to the tumour. These medicines are supposed to be less toxic than chemotherapy and are supposed to be used in conjunction with a companion diagnostic (CD).

However, there are three main challenges associated with the use and future development of targeted therapies in oncology and their related CDx:

1. **Identification of resistance biomarkers to targeted therapies/immunotherapy**

Targeted therapies significantly increase life expectancy for some cancer patients, proving to be very effective and for a very long time.

However, an important challenge for the cure of these patients is represented by the fact that the tumour sooner or later will develop a resistance to the treatment.

Possible solutions to advance research and care for these patients are represented by:

- Sequential analyses of tumour DNA – But this will require access to samples of the tumour during and after treatment.

[3] Jessica Lee, Ravi Patel. David Ruch - *InVentiv Health 2017*

- ctDNA analysis – These analyses are conducted on blood samples and would therefore avoid tumour biopsies, constituting a better solution for the patients.

2. **Identification of biomarkers of efficacy of immunotherapy**

Immunotherapy is the treatment of cancer by activation of the immune system. Immunotherapy is approved in many cancer types and the indications are growing every month.

Today immunotherapy is based on a biomarker only in lung cancer. In all other cases, immunotherapy is given to any patients, independent of any biomarker and in multiple tumour types, leading to very high prescription rates.

Immunotherapy works very well, but unfortunately only a minority of cancer patients respond to it. We need therefore to identify biomarkers to avoid ineffective treatments to patients and to preserve the financial health of our systems.

3. **Democratisation of high throughput technologies to identify targets**

Making high throughput technologies more widely available and easily accessible to analyse multiple biomarkers in a single assay will result in more effective use of time, money and tissue samples.

However, the quality of the data has to be ensured and the impact on CDx companies be considered.

Companion diagnostics in other therapeutic areas

Dr. Thorsten Gutjahr, VP, Global Head of Companion Diagnostics at AstraZeneca mentioned that the precision medicine approach is important not only in oncology but also in other therapeutic areas such as respiratory, inflammation, autoimmunity, cardiovascular and renal diseases.

There are huge unmet medical needs in therapeutic areas such as for example asthma and COPD (Chronic obstructive pulmonary disease), for which only few new medicines have been made available to patients in the last few years.

In contrast to oncology, the biology of these diseases is less well understood and shared efforts among industry and academic communities are needed in order to gain access to the right samples and cohorts available to validate biomarkers. To this end, AstraZeneca in collaboration with other partners initiated in April 2016 the *AstraZeneca and MedImmune Genomics Initiative,* a major project on genomics with the following aims:

- Understand more about the biology of health and disease
- Identify new targets for medicines
- Support selection of patients for clinical trials
- Allow patients to be matched with treatments more likely to benefit them

The project has the ambition to analyse up to 2 million genomes by 2026. This includes sequencing up to 500,000 genomic samples collected from AstraZeneca clinical trials.

Dr. Gutjahr noted that the following elements are needed to increase the success rate in precision medicine to benefit patients across all indications:

- Understand patients and physicians' needs

- Availability of suitable samples (not only in early clinical development but also in late clinical development)
- Continuous biomarker science and translation to the clinic
- Access to testing, 'finding' the patients and highly proficient testing labs
- Develop companion diagnostics and approval
- Diversity of testing methods
- Reimbursement of tests, to ensure all patients have access to them.

Dr. Gutjahr also noted the following critical success factors to drive precision medicine:

- Pragmatic regulatory systems enabling approval of emerging science of precision medicine
- Supportive reimbursement environment that accelerates the uptake of approved targeted therapies and linked diagnostics
- Continued investment in technology such as next-generation testing infrastructure (e.g., Next Generation Sequencing (NGS), ctDNA) to drive diagnostic innovation
- Coordinated health care delivery system that continuously educates health care practitioners and empowers patients
- Appropriate data sharing mechanisms that harness the power of population-level genomic and clinical databases.

Current regulatory framework and ongoing EMA initiatives

Dr. Falk Ehmann, Science and Innovation Support, European Medicines Agency (EMA), provided an overview of the current regulatory framework and European Union guidance in relation to CDx.

In 2017, the European Union adopted two new Regulations on medical devices (Regulation (EU) 2017/745) and in vitro diagnostic medical devices (Regulation (EU) 2017/746). These regulations introduced an increased pre- and post-market scrutiny especially of high-risk devices and new requirements for transparency and traceability.

The legislations also tackled challenges not previously addressed, such as CDx. For the first time, the Regulation on in vitro diagnostic medical devices provides a definition of CDx:

'Companion diagnostic' means a device which is essential for the safe and effective use of corresponding medicinal product to:

(a) Identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product, or

(b) identify, before and/or during treatment, patients likely to be at increased risk of serious adverse reactions as a result of treatment with the corresponding medicinal product[4].

[4] Article 2(7), EU Regulation on in vitro diagnostic medical devices (Regulation (EU) 2017/746)

This definition is aligned to the US definition, to facilitate global development of CDx, which is necessary given the difficulties in getting adequate population samples for studies.

The new Regulation on in vitro diagnostic medical devices also assigns a new consultative role to EMA concerning CDx's certification. Notified Bodies[5] will have to consult their national competent authorities or EMA regarding the suitability of the device in relation to the medicinal product concerned.

Dr. Ehmann also provided an update regarding the EMA Concept paper on "Predictive biomarker-based assay development in the context of drug development and lifecycle"[6], which was published in July 2017 and is intended to be developed into a guideline that will provide guidance relating to precision medicines and CDx.

In June 2018 the EMA held a multi-stakeholder workshop to inform the following aspects of the guidelines:

- Data requirements for CDx (analytical/clinical)
- Cross-labelling considerations for CDx and medicinal product
- Future interactions between EMA/NCA and Notified Bodies
- Post-authorisation and pharmacovigilance requirements for CDx
- Clinical trials including medicines and CDx
- Data requirements and review process/regulatory oversight for "follow-on" assays (CDx).

Dr. Ehmann concluded by encouraging stakeholders involved in the development of CDx to consult EMA at an early stage of development (ideally during Phase I or II of a medicine development). The EMA provides scientific advice to medicine developers, giving recommendations on the appropriate tests and studies required in the development of a medicine or on the quality of a medicine. However, out of around 600 scientific advices provided by EMA every year, only few include questions on CDx development. Given the increase of products developed and marketed with a CDx, this means medicine developers do not make sufficient use of the EMA scientific advice for CDx yet.

Physicians' perspective

Dr. Daniel Widmer, Vice-President, European Union of General Practitioners/Family Physicians (UEMO), presented the perspective of physicians, with a particular focus on the perspective of general practitioners (GPs).

The main objectives of UEMO are to study and promote the highest standard of training, practice and patient care within the field of general practice throughout Europe, to defend the role of general practitioners in the healthcare systems, to promote the ethical, scientific, professional, social and

[5] An organisation designated by an EU country to assess the conformity of a medical device before being placed on the market.

[6] https://www.ema.europa.eu/documents/scientific-guideline/concept-paper-predictive-biomarker-based-assay-development-context-drug-development-lifecycle_en.pdf

economic interests of European general practitioners, and to secure their freedom of practice in the interest of their patients.

UEMO also represents its members to the European authorities and international organisations. In this context, UEMO is involved in the healthcare professionals' group in the European Commission Health Technology Assessment (HTA) Network.

Healthcare professionals have an important role to play when it comes to the introduction of new health technologies, including CDx. They can appreciate the effects of treatments and contribute to real world evidence, qualitative research and to the continuous assessment of new medicines. But they also play a fundamental role in quaternary prevention, which is the prevention of overdiagnosis and overtreatment. Finally, healthcare professionals can help in topic selection: in partnership with industry and patients they can identify areas where technologies would bring added value.

From the GPs' perspective, the idea of companion diagnostics is good to lower side effects and reduce over-medicalisation. At the moment these tests are more available in the field of oncology, but tomorrow they could possibly be extended to other domains in general medicine, bringing positive impact in the daily practice of GPs. However, it will be important that these tests are supported by good evidence-based studies.

Finally, Dr. Widmer pointed out some elements that will need to be taken into account for the future development of precision medicine:

- The predictive aspect might increase anxiety in patients – GPs and other treating physicians need to be aware of this and be trained in anxiety management.
- The GP has an important role of "mediator" between the patient and the specialist doctor (e.g. cardiologist) – Therefore, GPs need to be properly trained for this role, to be able to provide the necessary explanations on CDx and other technologies available.
- There is the need to have legislation in place to provide the necessary framework to regulate the use of CDx.

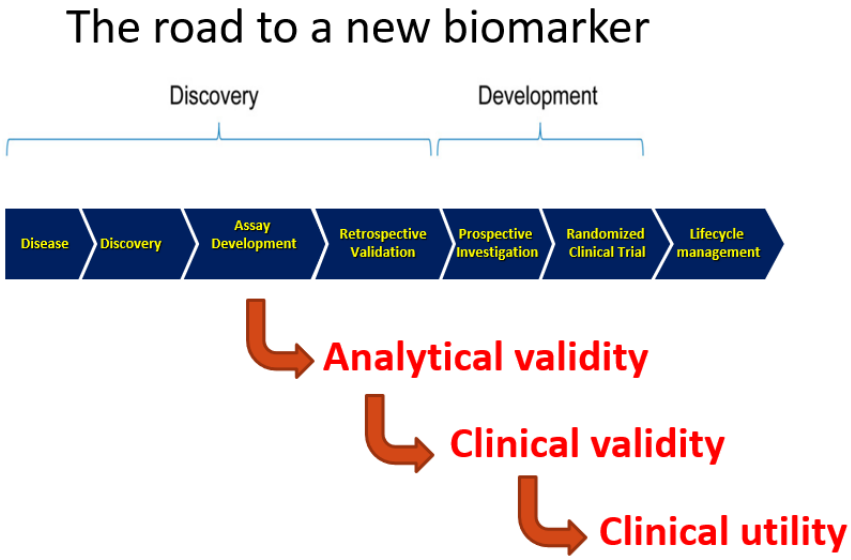
Genetic laboratories' perspective

Prof. Vincent Mooser, Head Clinical Chemistry at the Lausanne University Hospital (CHUV), explained how genetic association is worthwhile only when it is associated with clinical utility (i.e. improved clinical outcomes for the patient).

He illustrated this via two examples: one where genetic association was linked to clinical utility, and the other where such a link was missing. The first example concerned a medicine used for the treatment of HIV. Studies found and confirmed a genetic association between a marker called HLA-B*5701 and a hypersensitivity reaction causing important side effects to patients. These studies resulted in the US Federal Drug Administration approving in 2008 a change in the labelling of the medicine and requiring that a genetic test was performed before administering it.

The second example concerned statins. There have been a lot of studies investigating the reasons why in some people statins are very effective while in others they cause adverse reactions such as myopathy (a disease of the muscle in which the muscle fibers do not function properly). Although for statins the association between a genetic polymorphism and myopathy has been well established, its clinical utility is still missing. More evidence on cardiovascular and safety outcomes is indeed needed for all statins to demonstrate the benefits of pharmacogenomic testing in clinical practice.

Prof. Mooser explained that, similarly to medicine, new genetic tests have to go through discovery and development. This road to a new biomarker starts with a disease, and then continue to the following phases: discovery, assay development, retrospective validation, prospective investigation, randomised clinical trial, and lifecycle management (see picture 1). And there is the need to demonstrate the analytical validity, the clinical validity and the clinical utility.



Picture 1: The Road to a new biomarker, from Prof. Vincent Mooser's presentation.

Prof. Mooser reported on the work of *The Clinical Pharmacogenetics Implementation Consortium (CPIC)* which addresses the barrier of clinical implementation of pharmacogenetic tests by looking at gene/drug pairs and the level of confidence that is required for these pairs to change prescribing decisions. To this end, the Consortium publishes detailed gene/drug clinical practice guidelines that are freely available, peer-reviewed, evidence-based and updated as the evidence changes.

Prof. Mooser concluded by stating that there should be as many incentives to investigate clinical utility as there are for medicines' discovery. Indeed, sufficient evidence to justify modification of medical practice is today available only for a minority of medicines. He also mentioned that an evolution towards pre-emptive pharmacogenetic testing (which aims to optimize medication use by having genetic information at the point of prescribing) is the only way towards cost-effectiveness.

Patients' perspective

Dr. Stanimir Hasardzhiev, General Secretary of the Patient Access Partnership and Board Member of the European Patients' Forum highlighted the fact that precision medicine gives hope to patients and hope is part of the patient-centred healthcare.

Precision medicine should go hand-in-hand with CDx. However, the reality is different.
Huge disparities in access to medicines and the related CDx exist not only among European countries, but also between regions in the same country. Innovative treatments tend to be costly, while government are under pressure to cut costs. Access and equity are therefore an important concern to patients but there are currently no solutions at EU-wide level.

The Patient Access Partnership (PACT) provided a framework to holistically define what access means. According to PACT, access is composed of the following five elements:

- **Availability:** Whether services are available in the first place
- **Adequacy:** Whether there is an adequate and continued supply of available services
- **Accessibility:** Whether the services are effectively available for utilisation
- **Affordability:** A system for financing health services so people do not suffer financial hardship when using them
- **Appropriateness:** Services available must be relevant and should meet the needs of different population groups.

CDx bring new challenges such as quality assurance and verification, pricing and reimbursement and availability after the marketing authorisation of the medicine.

Patients should be part of the solutions to these challenges. It is indeed important to involve patients throughout the entire innovation chain (i.e. co-designed research, regulation development, HTA, pricing and reimbursement, evidence-collection, etc.) and to focus innovation on what matters most for the patients, listening to their needs and involving them in setting priorities.

It is also important to re-think future policies, by:

- Reconsidering HTA and pricing and reimbursement to tailor prices in line with expected outcomes, affordability and value
- Ensuring regulations include better links between precision medicine and CDx, from R&D to access
- Making the necessary regulatory changes to enable the implementation of new needed access models.

Dr. Hasardzhiev concluded by saying that patients should be involved in the entire lifecycle of precision medicine and CDx pricing, and that they should pay for CDx according to their real value for individuals and society.

Discussion

Development phase

The importance of samples

With a better understanding of the disease biology, it is possible to identify the biomarkers to be validated. The challenge is that the biology of the diseases is very complex and currently it is not possible to have access to real time samples to monitor changes in the biomarkers' expression. That is why cohort samples are very important together with the ability to analyse them.

It was also underlined that having the entire genome sequence of all patients in a clinical trial would be a very cost-effective manner to easily identify the causes of adverse reactions to medication.
Having the entire genome sequence of patients would also be cost-effective in routine care. Pharmacogenetics testing could be used by the pharmacists and treating physicians to avoid side effects and to identify the most effective treatments for the patient. It was noted that some countries like The Netherlands are now implementing such solutions and that this constitutes an interesting example that other countries might consider following in the future.

Speeding up medicines' development

It was noted that precision medicine is accelerating the development of medicines. By identifying biomarkers, companies can take faster decisions on the indications that are more effective.

Implementation phase

Accessibility of tests' interpretation

It was stressed that not only availability of tests, but also accessibility of interpretation is important. Artificial intelligence could potentially help interpreting tests' results but the physicians' role remains crucial in explaining those results to patients.

Data ownership and confidentiality

It was mentioned that patients are in general happy with their data being used for research as long as their data will not be used against them. There should be appropriate mechanisms and regulatory frameworks in place to provide patients the autonomy to decide to whom the data should be given and for which purposes.

Physicians and patients' role

Patients should be empowered and granted full autonomy for their health (disease and life style) data, but also physicians should be ready for this empowerment. It was recognised that the mentality is changing and that physicians should look at patients as real partners in care.

Companion vs complementary diagnostics

It was noted that there exists a difference between companion diagnostics and complementary diagnostics: the first are tests that are essential for the effective and safe use of a treatment, and that they are linked to a specific medicine; the second are tests that may inform the treating physician about how to improve the benefit/risk ratio without restricting medicine access.

A test is not always developed as a complementary diagnostic. Sometimes a test is developed as a companion and then the regulator proposes it as a complementary diagnostic.
It was mentioned that complementary diagnostic is a good concept and can be especially important to improve patient management and to give guidance on the therapies available.

Role of stakeholders and policy-makers

Update of clinical guidelines and clinicians' training

Participants outlined that clinical guidelines should be updated more frequently to reflect the latest solutions available. The development of new solutions and treatments evolves very rapidly: the guidelines need to incorporate these developments at a faster pace.

It is also important to train clinicians on the new CDx available. Sometime, a test might be available but not used because of a lack of awareness.

Work together to guarantee patient access

The fact that a treatment is included in the guidelines does not guarantee patients' access. To solve this problem, patients, academia, industry, healthcare professionals should all work together to convince governments and payers that CDx can be cost-effective and develop new access models.

European cooperation on infrastructure development

Participants agreed that it is crucial to have infrastructures and laboratories that can perform testing on a broad scale and with very high-quality standards. France adopted an interesting solution by centralising national laboratories. However, not all countries might have the capacity to create the required infrastructures at national level. EU governments should therefore collaborate more closely together and develop regional solutions that would allow resources to be pooled together in a cost-effective manner.

Concluding remarks

Prof. Peter Meier-Abt, Vice-President of the Swiss Academy of Medical Sciences (SAMS), concluded the meeting by inviting all participants to continue the debate on this topic among their respective networks. In publishing this report, FEAM intends to provide a tool to continuously engage the biomedical community and foster future discussions in this area. Prof. Meier-Abt also thanked all the speakers and participants for their contribution and for their commitment in supporting the FEAM European Biomedical Policy Forum's activities.

Annex I - Agenda

27 September 2018 (15:00-18:30)
Hotel Mon Repos - 131 rue de Lausanne, Geneva, Switzerland

15:00-15:30	**Registration**
15:30-15:40	**Welcome of participants** Prof. George Griffin, President, Federation of European Academies of Medicine (FEAM)
15:40-15:50	**Introduction** Prof. Peter Meier-Abt, Vice-President, Swiss Academy of Medical Sciences (SAMS) – Meeting Chair
15:50-16:10	**Improving links between CDx and medicines - Regulatory barriers and possible solutions. <u>Impulse presentations</u>:** **CDx in oncology** Prof. Christophe Le Tourneau, Head, Department of Drug Development and Innovation, Curie Institute, Paris
16:10-16:30	**CDx in other therapeutic areas** Dr. Thorsten Gutjahr, VP, Global Head of Companion Diagnostics, AstraZeneca
16:30-16:50	**Current regulatory framework and ongoing EMA initiatives** Dr. Falk Ehmann, Science and Innovation Support, European Medicines Agency (EMA)
16:50-17:05	**Coffee break**
17:05-17:20	**Physicians' perspective** Dr. Daniel Widmer, Vice-President, European Union of General Practitioners/Family Physicians (UEMO)
17:20-17:35	**Genetic laboratories' perspective** Prof. Vincent Mooser, Head Clinical Chemistry, CHUV - Lausanne University Hospital
17:35-17:50	**Patients' perspective** Dr. Stanimir Hasardzhiev**,** General Secretary, Patient Access Partnership and Board Member, European Patients' Forum
17:50-18:20	**<u>Discussion with all participants:</u>** **Moderators:** - Prof. Peter Meier-Abt, Vice-President, Swiss Academy of Medical Sciences - Prof. Stefan Constantinescu, Vice-President, Federation of European Academies of Medicine (FEAM) *Proposed questions for discussion:* • Development phase: how can we generate evidence during the development of medicines that support the validation of CDx? And also move beyond oncology, e.g. into cardiovascular or respiratory diseases? • Post-approval phase: How can we monitor, evaluate and maximise relevant uptake as well as ensure quality measures of CDx testing in clinical practice? • Companion vs complementary diagnostics: what are the regulatory challenges? • What could be the role of the European Medicine Agency, Notified Bodies, National Competent Authorities and other stakeholders (clinicians, patients, etc.)?
18:20-18:30	**Concluding remarks and perspectives** Prof. Peter Meier-Abt, Vice President, Swiss Academy of Medical Sciences (SAMS)

Annex II - Speakers' biographies

Chair

Peter Meier-Abt

Vice-President, Swiss Academy of Medical Sciences (SAMS)

Professor PJ Meier-Abt received his MD from the University of Basel in 1974. After training in Internal Medicine and Clinical Pharmacology at the University Hospitals of Basel and Zurich, he completed a two year research fellowship in hepatology at Yale University School of Medicine, New Haven Ct USA. In 1984 he became chief of the Division of Clinical Pharmacology and Toxicology at the University Hospital Zurich. In 1992 he was promoted to full professor for Clinical Pharmacology and Toxicology. He served also as medical director of the Swiss Toxicological Information Center, Zurich (1989-2003) and as first director of the Center of Clinical Research of the Medical Faculty Zurich (2001-2004). His research interests focus around the molecular physiology of bile formation, hepatobiliary bile acid and drug transport, pathophysiology of cholestatic liver disease, drug and toxin induced liver damage, pharmakogenetics/-genomics of adverse drug reactions and individualisation of drug therapy and drug safety. His research resulted in >250 publications and many honours and research awards. Prof. Meier-Abt served at numerous boards of national and international associations and research organisations including the Swiss National Science Foundation (SNSF; 1993-2004), the Swiss Academy of Medical Sciences (SAMS; 2004-now) and the Swiss Clinical Trial Organisation (SCTO; 2009-2012). He coordinated the national MD-PhD Programme (1998-2008) and is especially committed to the further development of translational/clinical research and personalized medicine in Switzerland. Between 2005 and 2011 Prof. Meier-Abt was vicerector for research & talent promotion at the University of Basel, and between 2011 and 2016 he acted as president of the SAMS. Since 2017 he serves the SAMS council as vicepresident and chairs the National Steering Board of the Swiss Personalized Health Network, a SAMS led initiative to foster Personalized/Precision Health in Switzerland.

Co-chair

Stefan Constantinescu

Vice-President, Federation of European Academies of Medicine (FEAM)

Stefan N. Constantinescu is Professor of Cell and Molecular Biology at Université catholique de Louvain. He coordinates the Cell Signaling and Molecular Hematology Pole of de Duve Institute at UCL and is a Member of Ludwig Institute for Cancer Research, at the Brussels Branch. Trained as an MD at the Carol Davila University of Medicine and Pharmacy in Bucharest, he uncovered in 1989 a major pediatric AIDS outbreak in Romania that has changed blood transfusion practices and impacted the pediatric AIDS field. His PhD thesis concerned mechanisms of signaling by type I interferons. He undertook postdoctoral work with Prof. Harvey F. Lodish at Whitehead Institute at Massachusetts Institute of Technology (1995-2000) on oncogenesis via erythropoietin receptor and is an independent group leader since 2000.
His research focuses on molecular bases of blood formation and cancer, and on fundamental aspects of cytokine receptor and transmembrane protein structure

and function. His laboratory at de Duve Institute (UCL) and Ludwig Cancer Research has contributed to the identification and study of the driver mutations in human myeloproliferative neoplasms Polycythemia Vera, Essential Thrombocythemia and Myelofibrosis (JAK2 V617F, W515 mutants of Tpo receptor, mechanism of oncogenesis by calreticulin mutants). He was elected to both the Royal Academy of Medicine in Belgium, and the Romanian Academy of Medical Sciences, and is Vice-President of FEAM since 2016.

George Griffin

President, Federation of European Academies of Medicine (FEAM)

Prof. George Griffin gained BSc in Pharmacology and Molecular Biology at King's College London Sciences, where he was awarded the Delegacy Prize for Excellence in Preclinical Science. He was awarded PhD in Cell Biology/Biochemistry, University of Hull, and returned to clinical studies at St George, University of London, where he was awarded the MBBS. Professor Griffin's postgraduate training paralleled basic and clinical science. During this time, he was awarded a Harkness Fellowship of the Commonwealth Fund of New York at Harvard Medical School. On return to the UK, he continued clinical training at Royal Postgraduate Medical School where he was tutor in Medicine, and the National Hospital for Nervous Diseases. He then returned to St George's as lecturer and was awarded a Wellcome Trust Senior Lectureship and became consultant physician on the Clinical Infection Unit where he was instrumental in developing an internationally renowned research unit twinned to the Clinical Unit. He held prestigious research fellowships in the University of Michigan and National Institutes of Health.

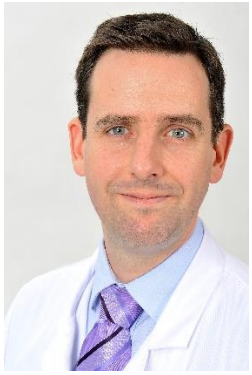
He has chaired scientific advisory boards in major pharmaceutical industry in the USA and UK. He has been chair and member of major Wellcome, Medical Research Council and Gates Foundation committees. He was censor at the Royal College of Physicians and was made a member of the Academy of Medical Sciences in which he has been elected to become foreign secretary and council member. He was appointed to the board of Public Health England where he will help shape strategy for research and clinical development. Professor Griffin was awarded the distinction of CBE in 2018 (Commander of the British Empire) for his research and its contribution to Public Health.

His research has focussed on the host response to infection at cell, molecular and whole body level. Such work involves immune and metabolic responses in vivo in humans. Furthermore cell and molecular studies include culture of human mucosal explants and definition of macrophage activation in vitro by microbial agents. A macrophage is a cell which ingests particles (microorganisms or host cells) for destruction and immune presentation. It is important in intracellular infection and also produces cytokines (a category of signaling molecules) as part of the immune response.

Professor Griffin's principal clinical contributions to knowledge have been in the characterisation of intestinal disease in HIV infection, mechanism of weight loss in HIV and definition of loss of mucosal immune response in advanced HIV infection. The dominant cell and molecular achievements have been the characterisation of NF-kb, a crucial factor maintaining macrophage differentiation and the role this transcription factor plays during tuberculosis infection of the macrophage and the mechanism of enhanced HIV transcription in such cells. More recently he has characterised the role of co-infection of HIV infected cells with herpes virus in enhanced HIV transcription in the genital epithelium.

Christophe Le Tourneau

Head, Department of Drug Development and Innovation, Curie Institute, Paris



Christophe Le Tourneau is senior Medical Oncologist at the Institut Curie and Professor of Medicine at the Versailles-Saint-Quentin-en-Yvelines University. He is heading the Department of Drug Development and Innovation as well as the Head and Neck Clinic. Christophe Le Tourneau was certified in Medical Oncology in 2005 and got his PhD in Clinical Epidemiology in 2007. He did a 2-year Clinical Research Fellowship at Princess Margaret Hospital in Toronto, Canada, in the Drug Development Program. His main interests are precision medicine, phase I clinical trials with a special attention at the methodology to conduct these trials, as well as Head and Neck oncology. Christophe Le Tourneau is the principal investigator of numerous phase I and II trials, as well as of clinical trials in Head and Neck oncology. He ran the first randomized precision medicine trial (SHIVA01) that compared the efficacy of matched targeted therapy versus conventional chemotherapy in patients with advances cancer. He has published 120+ peer-reviewed papers in international journals.

Thorsten Gutjahr

VP, Global Head of Companion Diagnostics, AstraZeneca

Thorsten Gutjahr is a recognized precision medicine scientist and distinguished leader in the area of Precision Medicine, Biomarkers and Companion Diagnostics.

Over the past 16 years, Thorsten developed and implemented precision medicine approaches with a focus in Oncology. In 2014 he joined AstraZeneca (AZ) as VP and Global Head of Companion Diagnostics in AZ's Precision Medicine and Genomics (PMG) function.

Thorsten leads the Oncology Companion Diagnostics team which delivered, since 2014, 23 new Diagnostics tests across 3 key regions (US, EU, Japan) linked to AZ/MedImmune's Oncology portfolio. These include essential diagnostic tests for olaparib (Lynparza), osimertinib (Tagrisso), durvalumab (Imfinzi) and gefitinib (Iressa). In addition, Thorsten plays a critical scientific leadership role in setting the Precision Medicine strategy for the organisation including Diagnostic development of novel multigene panels and innovative ctDNA approaches. Prior to this role, Thorsten was at Roche for more than 12 years, both in the Pharmaceutical and the Diagnostic Divisions. During this tenure, he led the global personalised healthcare R&D and commercial teams for trastuzumab (Herceptin), and erlotinib (Tarceva), delivered >30 novel biomarkers for Diagnostics development and was responsible for coordinating the PHC/Companion Diagnostic cooperation between the 2 Divisions including Chugai in Japan.

Thorsten gained his PhD in molecular biology at the University of Stuttgart, Germany, and was a post-doc in the Haematology/Oncology School of Medicine at University of California San Diego. He studied biological sciences at the Universities of Stuttgart-Hohenheim and Tuebingen (both Germany) and at the University of Sussex (UK).

Falk Ehmann

Science and Innovation Support, European Medicines Agency (EMA)

Falk Ehmann is currently working at the European Medicines Agency (EMA) in the Division Science and Innovation Support Office. His main responsibilities include managing the Innovation Task Force promoting Innovation and novel methodologies in drug development with focus in the areas of Pharmacogenomics (Clinical Pharmacology), Nanomedicines, Borderline and Combined Medicinal Products, and other -omics especially in connection with Personalized Medicine.

Further areas of expertise include policy development of Similar Biological Medicinal Products (Biosimilars) with focus on monoclonal antibodies and Vaccines.

He held various positions and responsibilities at the EMA since 2004, including Scientific Advice during product development and working as Product Team Leader in the Oncology and Anti-Invectives therapeutic areas of the EMA Unit for Human Medicines Development and Evaluation.

As part of engagement in Pharmacoeconomics, Health Care Market Place and Early Drug Development with King's College Falk created a cost-benefit decision model, designed protocols for First in Man clinical studies and proposed a definition for Innovation in Health Care in order to value it, which has been shared with the National Institute for Health and Care Excellence (NICE) and the UK ministry of Health.

Prior to joining the EMA Dr Ehmann studied European and International law at the University Berlin, worked as Public Health Researcher at the Robert Koch Institute, at the Representation of the European Commission in Berlin and as Medical Intern at different University Hospitals. He attended his military service in the German Air Force.

Falk Ehmann wrote his PhD thesis on *Molecular Intra Cellular Cell Signalling* at the Institute of Biochemistry and Molecular Biology at the University Hospital Hamburg-Eppendorf. His Master Thesis discusses coping mechanisms and responses of European Health Care Systems to the 2009 H1N1v Influenza Pandemic.

Daniel Widmer

Vice-President, European Union of General Practitioners/Family Physicians (UEMO)

Date of birth. Sept. 6, 1952
Nationality: Switzerland
Doctor in medicine, University of Lausanne, 1982.
Chargé de cours, University of Lausanne, 2009. Institute of Family Medicine. Member of research Unit.

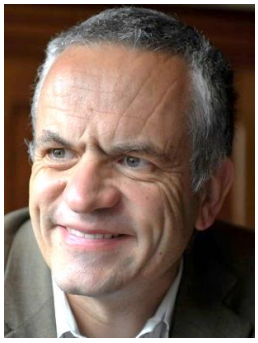
1977: Federal diploma of physician – University of Lausanne.
1985: Title of specialist in general medicine. Today general internal medicine.
1985: Opening of a group practice in Lausanne, today with 3 doctors.
2000: Certificate FMH psychosomatics and psychosocial medicine.
2012: Training in qualitative research – institute of general practice Antwerpen.

Political, associative and professional activities: - 1994-2000: Member and secretary of the committee of general practitioners (canton de Vaud).
1998-today. Member of the board of the CAS (Certificate of Advanced Studies, University of Lausanne and Geneva) in psychosomatic and psychosocial medicine.

2000- today. Redactor of Primary and Hospital Care, journal of swiss general internists.
2001 – today. Head of swiss delegation UEMO
2015: Vice president of UEMO, European Union of Family Doctors. Member of Health Care Professionals group at the EC- HTA Network (European Commission Health Technologies Assessment)

Vincent Mooser

Head Clinical Chemistry, CHUV - Lausanne University Hospital



Vincent Mooser MD combines a broad academic and industry experience in internal medicine, laboratory medicine, pharmaceutical sciences and genomic / precision medicine.
After an extensive training in clinical, experimental and molecular genetics research in Switzerland, Australia and Dallas TX, he was granted a six-year research professorship to study genetic contributors to lipid disorders and coronary artery disease.
In 2002, Vincent Mooser joined GSK R&D in Philadelphia to lead the effort in genetics of cardiovascular diseases. In this position, he co-designed and co-run the CoLaus cohort. He subsequently run roles of increasing responsibility (head of applied genetics and head of genetics for rare diseases) in GSK before returning to academia in Lausanne in 2011.
In CHUV Lausanne, he run for 6 years the Laboratory Department. In this role, he designed and implemented the foundation for genomic medicine at CHUV/UNIL, with the creation of the Lausanne Institutional Biobank. His present activity focuses on clinical chemistry and biomarker development, which complement genomic medicine.
Vincent Mooser is a Board member of the Swiss Academy for Medical Sciences, a member of the Executive Committee of the Swiss Personalized Health Network, and a board member of the Swiss Biobanking Platform.
He contributed to 200+ peer-reviewed publications.

Stanimir Hasardzhiev

General Secretary, Patient Access Partnership and Board Member, European Patients' Forum

Dr. Stanimir Hasardzhiev is one of the founders and current Chairperson of the Bulgarian National Patients' Organization (NPO) – the biggest patients' umbrella organization in Bulgaria which accounts to around 80 disease-specific member organizations representing patients with different socially significant diseases in all 28 regions in Bulgaria.
Dr. Hasardzhiev has devoted himself to the work in the patients' advocacy sector and in defense of patients' rights. In 2011 and 2015-2016, he represented the Bulgarian patients in the Supervisory Board of the National Health Insurance Fund.
As of May 2013, Dr. Hasardzhiev has been a board member of the European Patients' Forum as well as a member of several regional and international organizations and networks, e.g. World Hepatitis Alliance, European Community Advisory Board, International Capacity Building Alliance and others.
In addition, he is one of the initiators and founders of the joint initiative of the European Patients' Forum and the Bulgarian National Patients' Organization – the Patient Access Partnership (PACT) –, where Stanimir takes the position of a Secretary-General.
Dr. Hasardzhiev serves as a Secretary of the initiative "Health Partnership" which was officially launched in March 2015 as a permanent consultative body

to the Council of Ministers. The platform incorporates representatives of the patient organizations, governmental institutions, unions of medical practitioners, hospitals, industry and providers of health care services, appliances and facilities.

Stanimir is also a Secretary-General of a newly established organization named CEE4Health. It is a Think Tank group on patient access focusing on the CEE region which brings together patient representatives, health professionals, pharmacoeconomists and all other kind of experts in the field of healthcare (but not only) who work together to identify regional challenges in healthcare and propose sustainable solutions to national governments.

Stanimir Hasardzhiev has many Bulgarian and international awards, such as the Best Media Award for the World Hepatitis Day campaign in 2008 “Am I number 12”.

Annex III - Participants' list

Last Name	First name	Position	Organisation
Antoine-Poirel	Hélène	Physician expert	Belgian Cancer Registry
Artiges	Agnès	Perpetual Secretary	French Academy of Pharmacy
Bottaro	Silvia	FEAM Forum Policy Officer	Federation of European Academies of Medicine (FEAM)
Carrigan	Patricia	Head Oncology RA companion diagnostics	Bayer
Charpentier	Bernard	Vice-President	FEAM – French Academy of Medicine
Constantinescu	Stefan	Vice President	FEAM – Belgian & Romanian Academies of Medicine
Čulig	Josip	Fellow	FEAM - Croatian Academy of Medical Sciences
Do Ceu Machado	Maria	Vice-President	FEAM – Portuguese Academy of Medicine
Ehmann	Falk	Science and Innovation Support	European Medicines Agency (EMA)
Fleckenstein	Bernhard	Fellow	German National Academy of Sciences 'Leopoldina'
Foidart	Jean-Michel	Perpetual secretary	Belgian Royal Academy of Medicine (ARMB)
Griffin	George	President	FEAM – UK Academy of Medical Sciences
Gutjahr	Thorsten	VP, Global Head of Companion Diagnostics	AstraZeneca
Hasardzhiev	Stanimir	General Secretary Board Member	Patient Access Partnership European Patients' Forum
Kučinskas	Vaidutis	Professor, Faculty of Medicine, Vilnius University	FEAM - Lithuanian Academy of Sciences
Le Tourneau	Christophe	Head of Department	Department of Drug Development and Innovation, Curie Institute, France
Legros	Laurence	Executive Director	Federation of European Academies of Medicine (FEAM)
Meier-Abt	Peter	Vice-President	FEAM - Swiss Academy of Medical Sciences (SAMS)
Mooser	Vincent	Head Clinical Chemistry	CHUV | Lausanne University Hospital
Parier	Jean-Loup	President	French Academy of Pharmacy
Pirmohamed	Munir	Director	MRC Centre for Drug Safety Science and Wolfson Centre for Personalised Medicine
Quinn	Rachel	Director of Medical Science Policy	UK Academy of Medical Sciences
Sandström	Anna	Science Policy and Relations Director Europe	AstraZeneca
van der Meer	Jos	Fellow	Royal Netherlands Academy of Arts and Sciences

Last Name	First name	Position	Organisation
Widmer	Daniel	Vice-President	European Union of General Practitioners/Family Physicians (UEMO)
Zoellner	Petra	Regulatory Affairs Senior Manager	Medtech Europe

Annex IV - Glossary

Analytic validity: the ability of a genetic to test accurately and reliably for the genetic variants of interest in the clinical laboratory in specimens that are representative of the population of interest. (Teutsch et al., 2009)

CDx: Companion diagnostics

As defined by article 2(7) of the in vitro diagnostic medical devices Regulation (Regulation (EU) 2017/746) *'Companion diagnostic' means a device which is essential for the safe and effective use of corresponding medicinal product to:*

(a) Identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product, or

(b) identify, before and/or during treatment, patients likely to be at increased risk of serious adverse reactions as a result of treatment with the corresponding medicinal product.

Clinical utility: the evidence that the genetic test improves clinical outcomes measurably and that it adds value for patient management decision making compared with current management without genetic testing (Teutsch et al., 2009)

Clinical validity: the ability of a genetic test to identify or predict accurately and reliably the clinically defined disorder or phenotype of interest. (Teutsch et al., 2009)

EMA: European Medicines Agency

Genetic association: Evidence that a particular gene is responsible, or partly responsible, for a disease (Medical Dictionary - The Free Dictionary)

GP: General practitioners

HTA: Health Technology Assessment

Rue d'Egmont, 13
1000 Brussels | Belgium
+32 (0)2 793 02 50
E-mail: info@feam.eu
Twitter: @FedEuroAcadMed

www.feam.eu