Regions4PerMed

Interregional Coordination for a fast and deep uptake of Personalised Health

Regions4PerMed

Key Area 3: Personalising Health Industry

Report

HORIZON 2020

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 825812

DESCRIPTION

This report summarizes the content elaborated within the Technical Conference and the Interregional Workshops which took place online October 2020 and April – May 2021.

AUTHOR

Eva-Maria Stegemann (SMWK)

CONTRIBUTORS

Paola Bello (FRRB), Ana Cajaraville Leiro, Jose Maria Romero Fidalgo (ACIS), Claudia Mariut (TLS), Gianni D'Errico (TLS), Antoni Zwiefka (UMWD), Donata Kurpas, Dorota Stefanika Wojtas, Marta Duda Sikula (WMU), Advisory Board Members

AKNOWLEDGEMENT

We would like to give a special acknowledgement to the members of the Advisory Board and Interregional Committee of Regions4PerMed, who actively contributed to the Conference and Workshop with their precious experience and knowledge.
In addition, we would like to thank all speakers and chairs/rapporteurs for their active participation in the Conference and Workshop.

This report was closed in December 2021

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Abbreviations

ATMP	Advanced Therapy Medicinal Products
BMBF	Bundesministerium für Bildung und Forschung (Federal Ministry for Education and Science)
CAR-T cell	Chimeric Antigen Receptor T cell
CDx	Companion Diagnostic
CPG	Clinical Practice Guidelines
CSA	Coordination and Support Action
EMA	European Medicines Agency
EP PerMed	European Partnership PerMed
ERA-Net	European Research Area Network
EU	European Union
EUCOPE	European Confederation of Pharmaceutical Entrepreneurs
GGPO	German Guideline Program in Oncology
GCS	German Cancer Society (Deutsche Krebsgesellschaft)
HTA	Health Technology Assessment
ICPerMed	International Consortium for Personalised Medicine
LTD	Laboratory Developed Tests
MTB	Molecular Tumour Board
MGTO	Molecular Guided Treatment Options
MS	Member States
NFDI	Nationale Forschungsdatenstruktur (National Research Data Infrastructure)
NTRK	Neurotrophic-Tyrosine Kinase
PH	Personalised Health
PM	Personalised Medicine
PRO	Partnership Research Organisation
RCT	Randomised Controlled Trials
R&D	Research and Development
RWD	Real-World Data
SME	Small and Medium Enterprises
SRIA	Strategic Research and Innovation Agenda
WEF	World Economic Forum

1 Introduction to Key Area 3: Personalising Health Industry

An increasing availability of health-data and enhanced processing capabilities make the foundation of significantly improved health interventions in a progressively digitalizing health economy that will have a tremendous impact on citizen health while transforming health industry. This growing potential for an increasingly personalised medicine (PM) and healthcare (PH) represents a great development option for health industry while at the same time exposing it to new big challenges (Scheen 2015). Thus, the World Economic Forum sees an "urgency for stakeholders across the industry to transform their business models to remain relevant and financially viable in the long term" (World Economic Forum 2019). Ongoing medical innovation will include far-reaching business innovations when leading to a truly PM and PH. Market-entry of non-traditional competitors can be observed by established IT and tech companies, but also start-ups offering innovative personal health data tools and products (Perakslis/Coravos 2019). But though it may be comparatively straightforward to enter the personal health market with novel direct-to-consumer products and services, the introduction of personalisation in the regulated health system is far more complex. Thus, the uptake of PM in the public health systems of Europe has been perceived to be rather slow so far (Cattaneo 2018).

In this key thematic area on Personalising Health Industry, Regions4PerMed is taking a deeper look at what opportunities and challenges health industry is facing in Europe when aiming to embrace PM and PH, realising the vision of the International Consortium of Personalised Medicine (ICPerMed) of "integrating an individual's characteristics for early disease diagnosis, prognosis, optimal choice of treatment, accurate disease risk estimation, and targeted prevention" (ICPerMed 2020, 5). Implementation of PM and PH shall be the basis of a healthcare for Europe with improved and optimised health promotion, disease prevention and management accessible to all citizens (ICPerMed 2020).

For health industry this transition may present a true shift of paradigm – changing its value chain and traditional therapeutic

blockbuster-approaches. The ongoing medical and scientific innovation will entail novel research and development (R&D) approaches, product and production concepts, and consequently, also business strategies and models. These changes are not happening in isolation, as industry is always embedded in an ecosystem of other actors and stakeholders, closely interrelated and interacting at all stages of the value chain. This ecosystem also has an important geographical dimension that needs to be considered. *Whereas the global perspective may define the overall potential and innovation space of an industry, continental, national, regional and even local settings may be crucial for specific innovation opportunities and the success of individual industry participants and local or regional clusters.* In the context of healthcare, in Europe, the regional dimension warrants special consideration as healthcare here is not only regulated at the European and the national levels but, in many Members States (MS), to a significant degree also at the regional level, creating a complex market environment for health industry. Thus, innovation systems as well as health industry markets need to be considered in these regionally defined spatial (and also cultural) settings.

This regional perspective is the specific aim and objective of Regions4PerMed and sets the frame for this review and analysis of personalising health industry within this key thematic area.

2 Key Area 3 Technical Conference

2.1 Outline

In October 2020 the third technical conference of Regions4PerMed was organised by the Saxon State Ministry of Science, Culture and Tourism focusing on "Personalising Health Industry". Due to the Covid-19 pandemic, the conference was taken online.

The aim of the technical conference was to explore the third key thematic area of Regions4PerMed by investigating the value chain and ecosystem of health industry in the context of PM and PH. The individual sessions were thematically bundled around individual sections of the health industry value chain for PM and PH. The aim was to better understand the specific challenges faced by health industry and to look at novel approaches taken by industry to tackle PM and PH. As an additional important frame, the regional dimension with a special focus on the hosting region, and also the patient perspective were taken into account.

The 121 registrants to the conference were mostly representing regional and also national governmental entities involved in health policies coming not only from all project's partner's countries (Italy, Poland, Germany, and Spain), but from at least 16 countries, five continents, and including more than 15 regional representations. Participants were representatives of health policy governance, health industry, and industry organisations, health consultancies, public institutes, academia, research hospitals and also scientific experts. Conference participation is summarised figure 1.

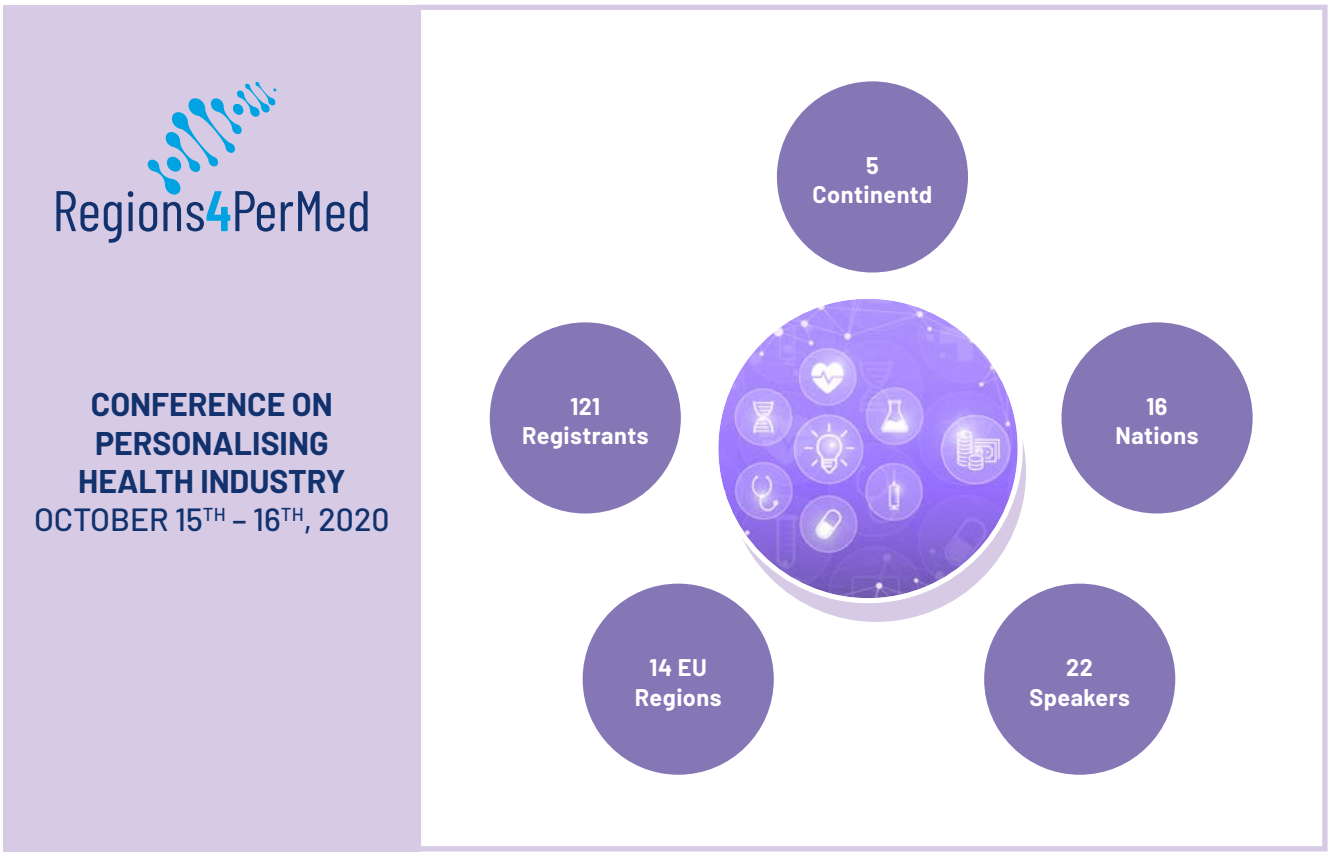


Figure 1: Conference Participation in a Nutshell

The conference was opened by the Saxon State Minister for Science, Culture and Tourism, **Sebastian Gemkow**, who emphasized the great relevance of PM for public health in light of the pandemic. He highlighted Saxony as an innovation hotbed building on its traditional strength and developing an increasing level of expertise in PM with its strong science base and application orientation. He emphasized the relevance of regional exchange, and highlighted Saxony's engagement in European Networks by participating in three ERA-Nets, one of them being ERA PerMed and also in Regions4PerMed, wishing for fruitful discussions. After a brief introduction to the concept and methodology of the Regions4PerMed project by coordinator **Gianni D'Errico** (Tuscany Life Sciences Foundation) the conference began.

2.2 Opening Session

The opening session outlined the regional health innovation ecosystem of Saxony and introduced the patient perspective in its keynote lecture. The session was opened by **Olaf Müller** (Healthy Saxony e.V., Germany) presenting a **Spotlight on Health Industry in Saxony**. He outlined the healthcare system in the Free State of Saxony with its well-established system of general practitioners (GP) who serve in large parts as a gateway to healthcare for the citizen - as in all of Germany. Due to an ageing population, Saxony is facing a significant challenge for succession in the field of GP especially in rural areas, where it is frequently difficult to replace retiring GPs.

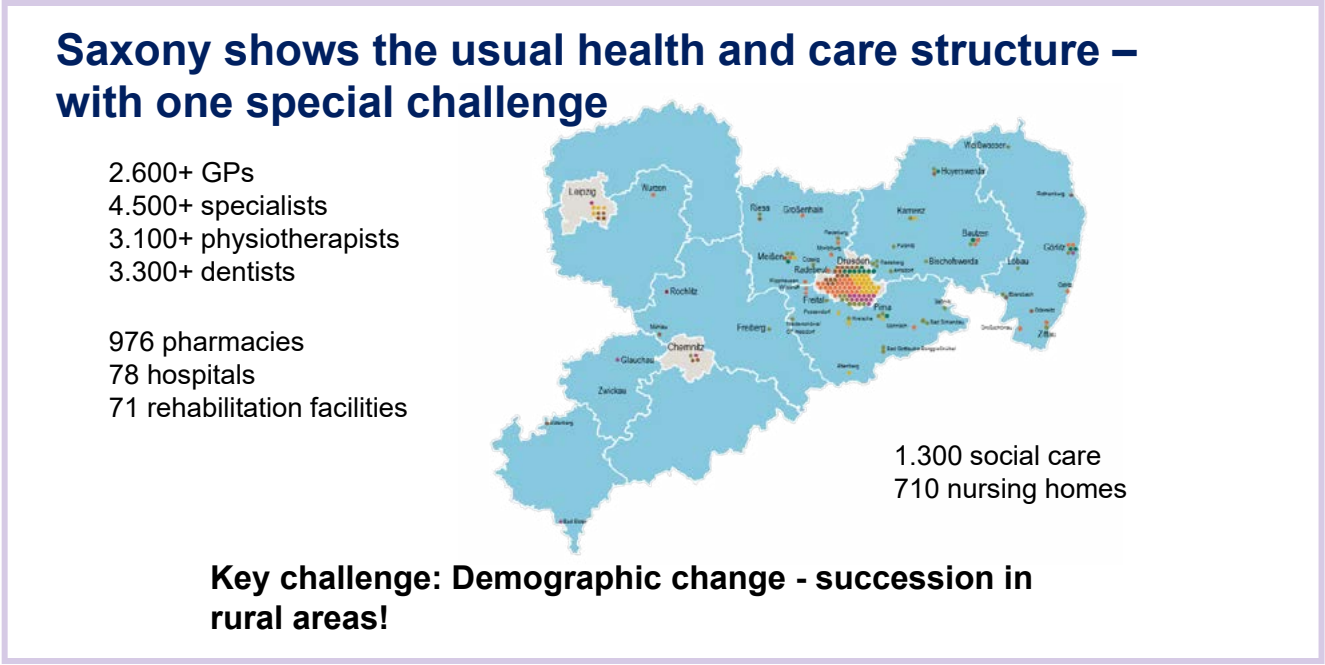


Figure 2: Health and Care Structures in Saxony (Healthy Saxony e.V.)

At the same time, Saxony is home to a thriving and complex R&D landscape in healthcare and related fields, encompassing academic & university institutes, as well as numerous facilities belonging to the large German research societies, Fraunhofer, Max-Planck, Helmholtz and Leibniz, with strong interlinkages. Numerous networking organizations exist, some with an industry specific focus such as Silicon Saxony that support a smooth and fast knowledge and innovation transfer, within industry as well as between industry and academia. Among these Healthy Saxony e.V. and biosaxony e.V. are the ones most relevant for health industry.

Healthy Saxony was founded in 2015 to **facilitate models transfer to and from health and care providers**, e.g. university

and regular hospitals, payer institutions, healthcare sickness funds, special service providers, e.g. nursing homes, and also small and medium sized enterprises (SMEs). It also *connects health and care stakeholders in Saxony* by functioning as a communication platform. By realizing and participating in regional and transnational model projects such as the Interreg Europe project TITTAN, knowledge transfer in the health and care sector is facilitated and improved. *Healthy Saxony participates in the European Innovation Partnership on Active and Healthy Ageing* and is part of the three-star reference site status in 2016 and 2019.

André Hofmann (biosaxony e.V., Germany) represented biosaxony e.V, a bioindustry networking organization **supporting innovation in the health industry in the Free State of Saxony.** Representing more than 130 members, and operating offices in Leipzig and Dresden, as well as an incubator in Leipzig, biosaxony is advancing health industry development as a fully integrated service provider, nurturing innovative projects from bench to bedside. A central aim of biosaxony is to help its partners, members and clients *reduce development timelines and thus time to the market.* It is also attracting foreign industry to develop regional activities within Saxony as well as advancing internationalization of Saxon biotech SMEs.

To that end, biosaxony has installed accelerator programmes, currently collaborating with the city of Leipzig to set up the *Medical Forge Leipzig.* This will be a translation supporting

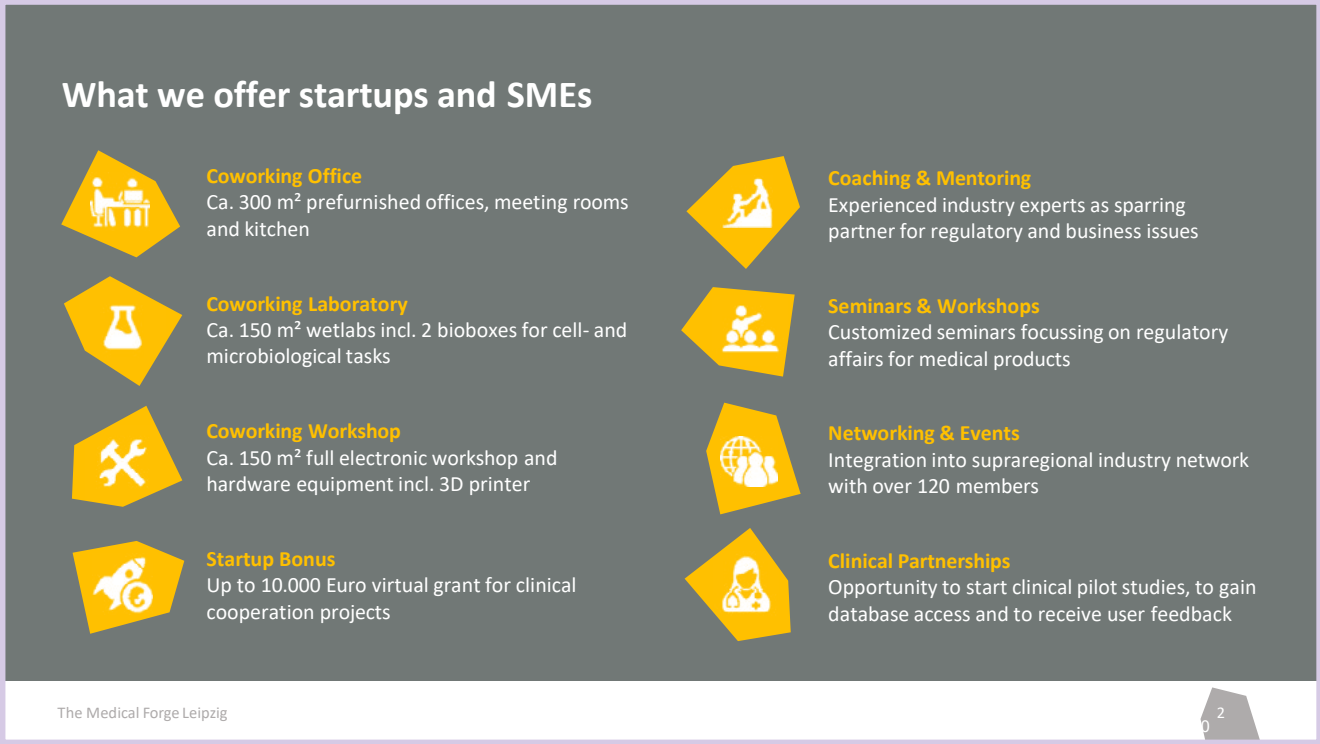


Figure 3: Medical Forge Leipzig – an Accelerator for MedTech (biosaxony e.V.)

programme aimed at *bridging the gap between start-ups and clinics* (www.medicalforge.de). For a period of twelve months, innovative startups in the medical field are supported in bringing their smart medical device and therapeutic products to the German healthcare market faster. The training part has a specific focus on *meeting the EU regulatory requirements* in that field, and other supporting aspects such as lab, office space, and travel reimbursement are included as outlined in figure 3.

In addition, biosaxony is currently preparing to set up a special digital platform in close cooperation with the city of Leipzig for digital projects in healthcare, that aims to improve development progress and timelines. As *specialised human resources for health industry are increasingly becoming a bottleneck regionally*, a programme was set up to *qualify GMP operators* that are needed for cell therapy production processes.

The keynote lecture was offered by **Joanne Hackett** (BIOS Health, United Kingdom) who spoke about **personalising health industry from an educated patient perspective**. She emphasized that PM and PH are highly dependent on the *combination and linkage of data*. The amount of data is growing exponentially across all areas relevant for healthcare, due to novel data collection means and tools (e.g. novel devices). Based on her long-time professional expertise, she advocated a federated approach for real-time, all sources combining data management to overcome the current separation in primary and secondary health data and to eliminate historically founded

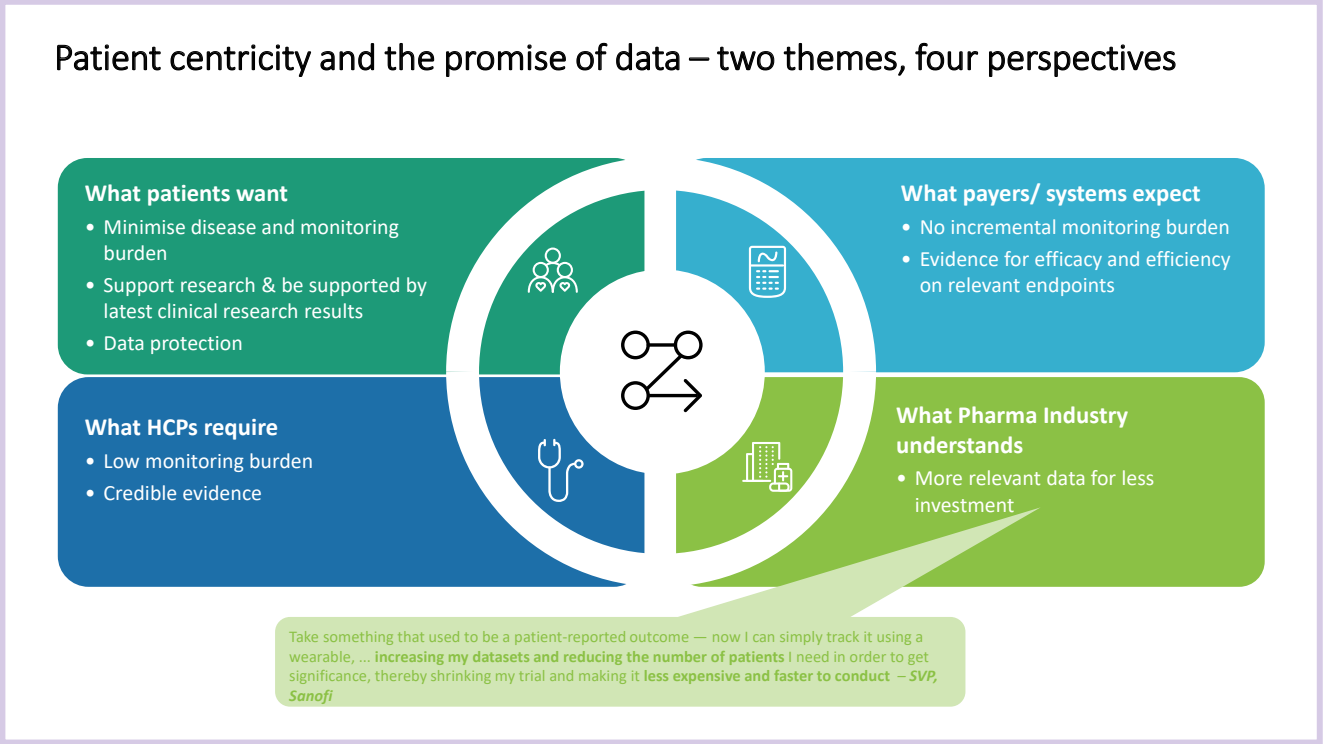


Figure 4: Patient Centricity and the Promise of Data (Joanne Hackett)

data-silos and fragmentation. Reflecting on the different needs of PH stakeholders, she pointed out that a *reduced monitoring burden of disease is a common denominator* for most, making this an important benefit of novel PH approaches on top of improving quality of care as shown in figure 4.

She described how added value can be generated for clinical research and patient care by novel approaches for longitudinal, individual patient monitoring and data collection, especially when combining and linking with other types of patient data (e.g. genomic data) and data of other patients. *Novel digital biomarkers* cold be generated to improve disease management. Novel *patient-centric endpoints* need to be implemented and *aggregation of data* is critical to capture its full value and generate patient benefits, including improved predicitive capabilities as summarized in figure 5.

With rapidly changing processes in R&D and patient care, realising these data-related developments will create new opportunities for personalising health industry, which will need to take a new view on stakeholder engagement, particularly with patients and caregivers. She closed with a reference to a new industry-sponsored expert network that has been formed to support healthcare system transformation (FutureProofing Healthcare Initiative, https://futureproofinghealthcare.com

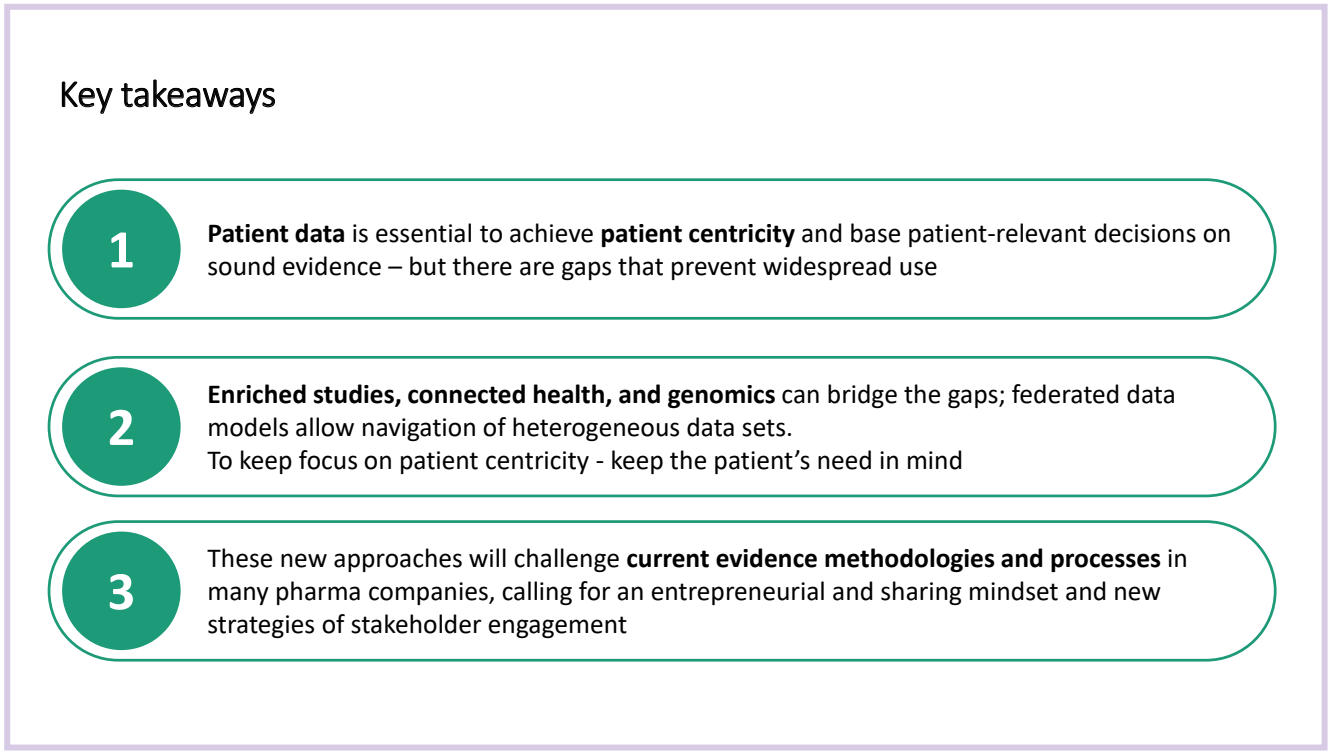


Figure 5: Key Takeaways for Patient Data in PM (Joanne Hackett)

2.3 Session I: Paving the Way: Infrastructures, R&D Approaches

Session I focused on infrastructures for R&D and novel R&D approaches for PM and PH. As R&D are the foundation of any innovation, they make up the first block of the value chain. As outlined in the key-note lecture, R&D for PM has particular requirements in terms of data and research approaches taken.

Michael Hummel (Charité Universitätsmedizin Berlin, Germany) presented biobanking activities at Charité Universitätsmedizin Berlin, which is part of the German Biobank Node, for which he is the speaker. He emphasized **the role and value of biobanks for PM** as they provide *long-term storage of data-annotated biomaterials*. Biobanking is a complex process, encompassing not only storage of many different kinds of biosamples, but also standardised sample collection processes, preparation, classification, and annotation (data linking) along defined interfaces between biobanks and their sources (e.g. clinic). These need to be performed and maintained by trained and specialised staff. An important aspect of biobanking is ensuring *long-term sample safety, documentation,* and provision of *sample access*, making **biobanks trustees for long-term use of biosamples,** and also qualified hosts for

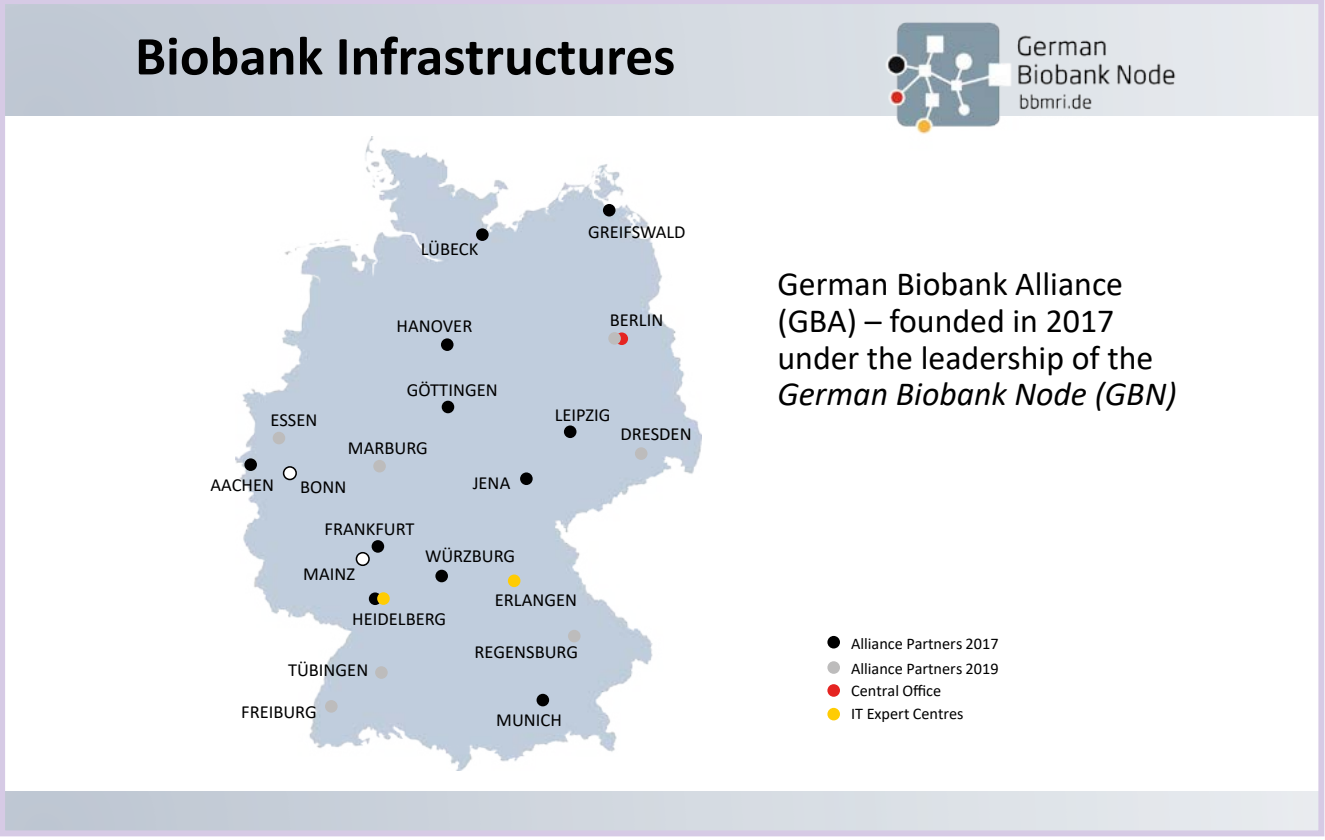


Figure 6: The German Biobank Node

sample and data storage of temporary research projects after funding has ended. To illustrate the value of biobanking for advancing research, Prof. Hummel presented the efforts of the Central Biobank of Charité/Berlin Institute of Health (ZEBANC), who have set up *a new biobank for long-term Covid-19 studies within just one week*, including standardized processes and documentation, thus laying the foundation for rapidly generating significant knowledge on this novel disease.

Michael Hummel pointed to the importance of a close cooperation between biobanks reflected in *network structures* like the German Biobank Node which has been set up in 2017 and has since almost doubled in size. The Node defined common quality standards, storing more than 22 M human biosamples and making these successively accessible through a web-based sample locator. Collaborating closely with other German research infrastructures, such as the German Medical Informatics Initiative (IMI), the German Centres for Health Research (DZG), the National Research Data Infrastructure (NFDI), and the Netzwerk Universitätsmedizin, it is contributing to important projects such as the National Pandemic Cohort Network (NAPKON). The German Biobank Node is also partner of the European Biobanking Infrastructure BBMRI-ERIC serving there as the central contact point for the German biobanking community. He concluded that *biobanking networks are essential* and generate value as accelerators for innovation in biomedical research.

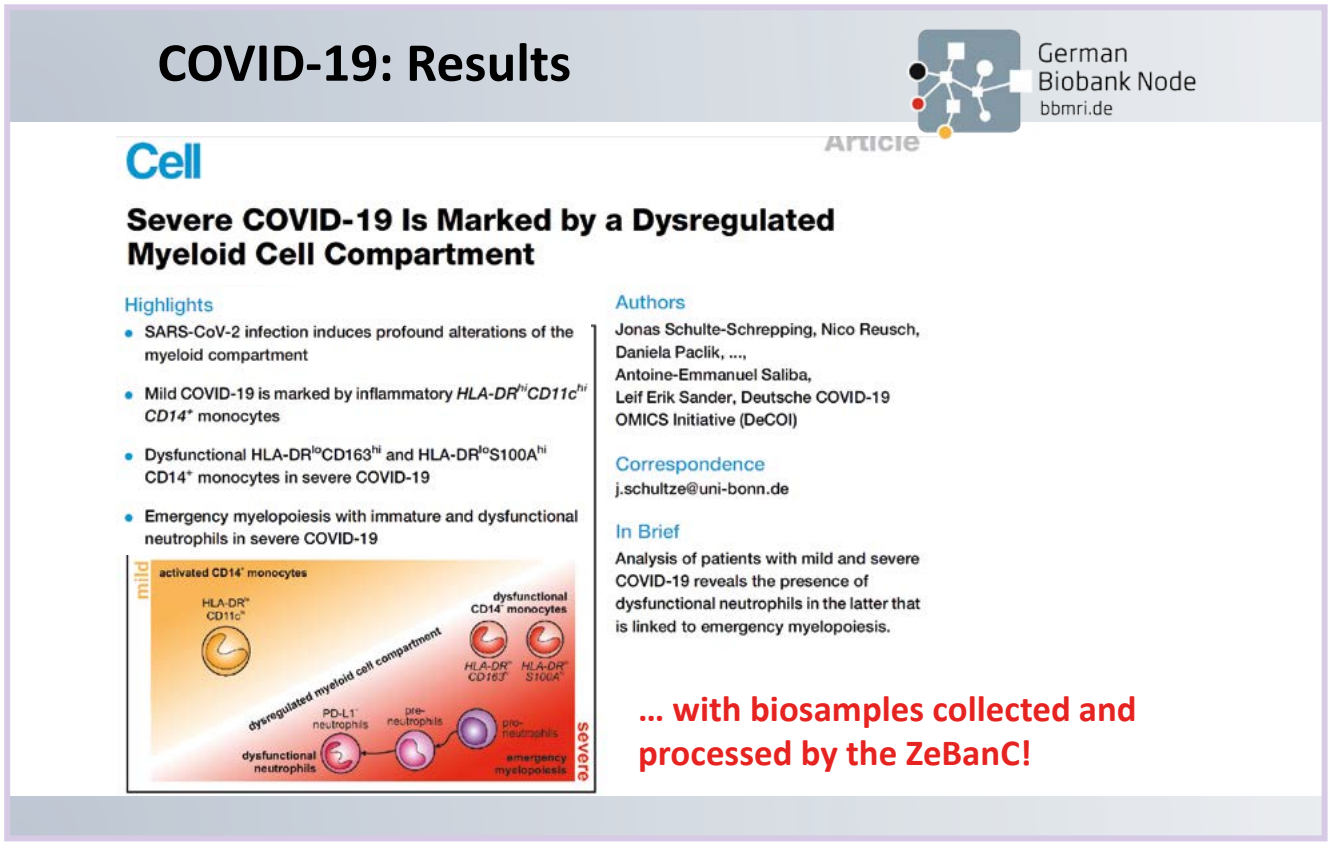


Figure 7: Research Results based on a novel Covid-19 Biobank (Michael Hummel)

Mario Braga (Agenzia Regionale Sanità, Italy) presented the value of the **integration of real-world data (RWD) in healthcare** by providing examples of Tuscany Region. As the regional public health agency, Agenzia Regionale Sanità (ARS) is responsible for monitoring and evaluating regional healthcare policies, epidemiological surveillance, health service research and statistical indicator systems within Tuscany. Having access to an extensive data warehouse, ARS is well positioned to successfully analyse and use RWD, also to ensure equitable access to healthcare for vulnerable groups.

Mario Braga pointed out that RWD can be derived from many different sources (e.g. electronic medical records, patient registries, healthcare applications) and showed how *data collection has substantially expanded in Tuscany region over the past 20 years* to now include more than 20 different (administrative data) sources. In regionally organized health systems like in Italy, there is a high degree of institutional availability of large administrative data archives.

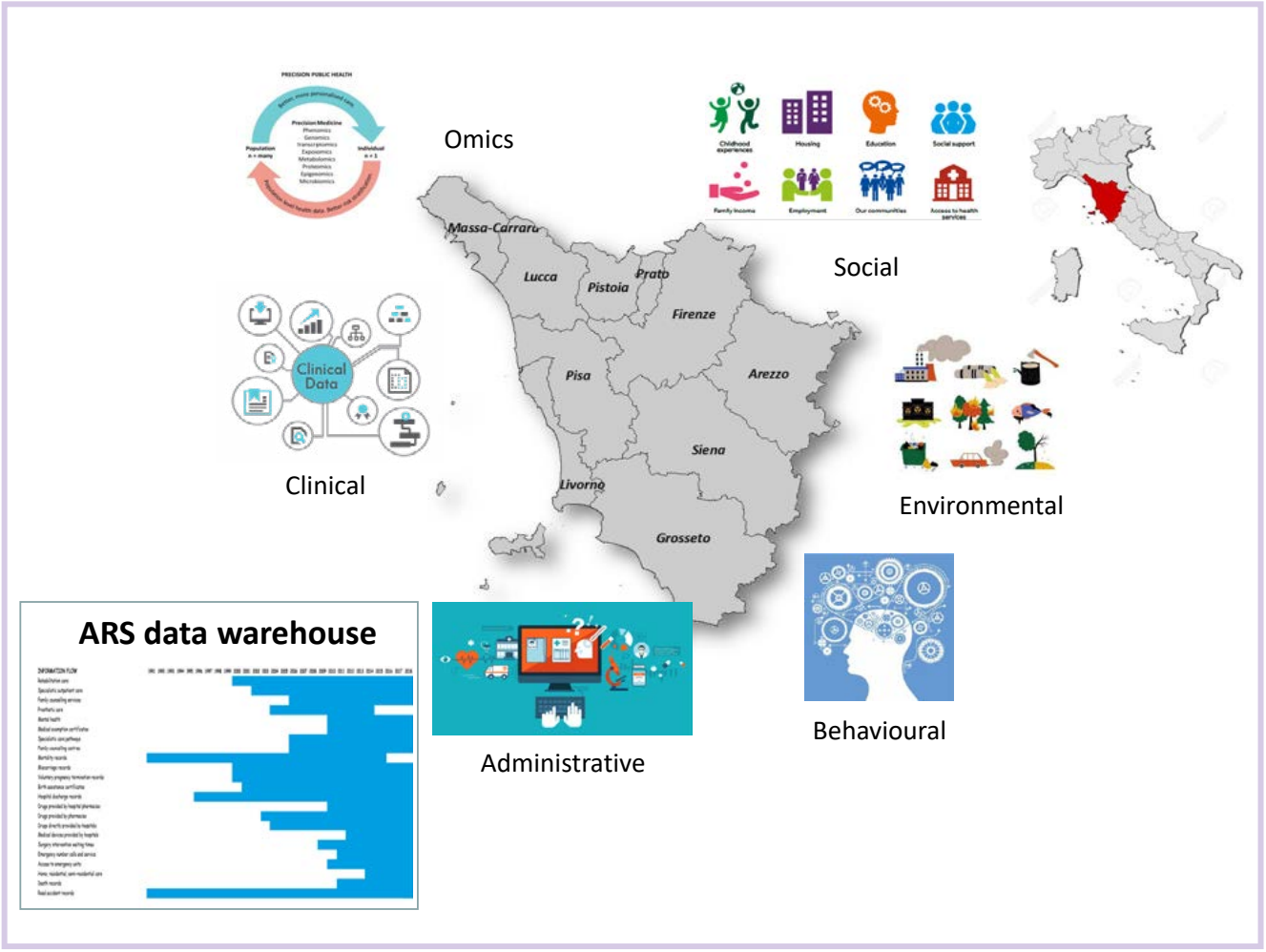


Figure 8: Real World Data used by Agenzia Regionale Sanità (Mario Braga; two slides combined)

RWD is of high value for the assessment of medical treatment options pre- and post-marketing. In the first case, RWD can be used to better understand disease populations, support the recruitment of patients for clinical trials, facilitate drug positioning and help assess the economic impact of novel treatment options. In post marketing, RWD can be used for benefit-risk profile assessment, post-authorization safety studies and healthcare pathways analysis.

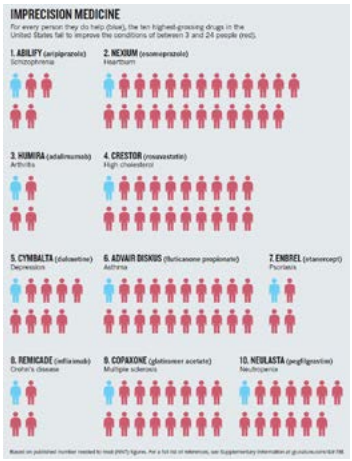
Mario Braga presented two retrospective RWD studies based on administrative datasets from Tuscany region for drug usage analysis, the first focusing on the adherence to lipid-lowering-therapies in cardiovascular disease, the second on the use of triptans in migraine treatment. In both cases valuable knowledge on how the respective drugs are used in real life could be gained, demonstrating the value of RWD analysis on the regional level. He sees a *significant potential for public-private collaboration on the regional level.*

Nicholas J. Schork (TGEN, USA) discussed the **concept of N-of-1 clinical trials as a source of deep insight for personalized interventions** in healthcare. He explained the rationale for N-of-1 trials in which (personalised) medical interventions are assessed in a single patient, thus deviating from the classical concept of large-scale clinical trials generally used in evidence-based medicine. The latter require large numbers of patients to be screened in a double-blind setting in order to judge treatment efficacy by referring to previously defined clinical endpoints, frequently without assessing whether individual patients are unequivocal responders. *It is well established that this statistically validated assessment of medical interventions does not allow conclusions on the medical benefit for the individual patient.* While a fraction of patients may respond well, others may remain unaffected by a treatment – which is one of the major arguments for PM and for improving patient stratification.

As Nicholas Schork pointed out, *a focus on the individual patient and his/her wellbeing is needed,* in order to *treat individual patients instead of populations.* With the advent of truly individualised therapies, an N-of-1-approach may be increasingly needed to validate the effectiveness of such therapies.

Nicholas Schork presented some examples N-of-1 trial-designs for different applications, demonstrating how such approaches may lead to deeper insights by generating rich individual patient data, especially if aggregated across a group of patients. He highlighted the high value of novel (connected) devices as these enable continuous monitoring. Additional data can now be easily collected that had previously been hard to obtain. The combination of rich data from different sources,

Motivation for N-of-1 Clinical Trials: Not Everyone Responds to Interventions!



USA FDA Organized Meeting, ASCPT 2012

- A greater focus on the ***science of response*** should **guide** clinical trials (e.g., identify unique individual pathobiologies)
- Most large phase III trials don't generate enough data on any one person to determine if they are **unequivocal responders/non-responders** to an intervention (see also: Senn, Nature (2018); PMID: 30482931)
- Focus: objectively assess ***patient's condition/well being,*** not necessarily the intervention…

Figure 9: N-of-1 Clinical Trials for Understanding Treatment Response (Nicolas J. Schork)

including continuous monitoring of patient-reported-outcomes and biomarkers, allows for *a comprehensive understanding of patient response and well-being.* He emphasized the new opportunities of genomic medicine for N-of-1 settings. He shared insights on how variations in the set-up of such trials may influence their validity, pointing out the *historic use of single patient analysis mostly in proof-of-concept studies.*

However, one of the biggest remaining hurdles in medical science lies in understanding *the intermediate physiology for the individual patient.* With novel monitoring and data capturing technologies, N-of-1-trials may become an increasingly important tool to gain deeper insights in individual pathophysiological processes and lead to a better in-depth understanding of medical interventions. A number of resources on the topic were recommended for further reference (e.g. https://quantifiedself.com and https://www.nof1sced.org).

Hans-Georg Eichler (European Medicines Agency, The Netherlands) presented his personal expert views on whether it is needed to **rethink evidence generation for personalised medicine.** He highlighted the *changing profiles of newly authorized active substances* for medical use within the EU in terms of compound class, e.g. biologicals and complex advanced therapy medicinial products (ATMP), and fields of application. There is an increasing trend to target indications

fulfilling the criteria of rare diseases, thus addressing only small patient populations. At the same time, understanding of heterogeneity in drug functionality is also increasing. Traditional (uniform) chemical compound drugs address the same target in a patient population. However, some diseases contain a high degree of target variability[1], leading to differing target-compound interactions. Also, novel ATMP can be designed in a more patient specific (individualised) way, similarly leading to differing drug-target interactions that vary between patients. Consequently, the physiologic mode-of-action for a given product (class) may differ between patients leading to heterogeneity in the effect-size of a treatment for different patients.

In addition, in the future, personalised unique treatment-lay-outs may become possible, such as combinations of individualised oligonucleotides specifically designed for a single patient. Also, novel ATMP may be continuously adapted while already on the market. The *definition of what a drug is, will therefore become more fluid*. The extreme will be N-of-1-drugs for which no adequately powered randomised controlled trials (RCT) are possible, as for these target and patient populations may be identical and other forms of clinical evaluation need to be found.

Thus, evidence generation for therapeutic interventions is likely to change for some scenarios. In many instances a combination of classic RCTs with novel approaches, such as N-of-1 trials may be mandated leading to a matrix of evidence generation. For differing applications, unique combinations of differing depth and breadth of information, and context could be generated. This might lead to complete sets of information in some cases, whereas in others information would have to remain incomplete. This could have further implications for health technology assessment (HTA) and reimbursement decisions.

[1] *As an example Prof. Eichler refered to cystic fibrosis that may be caused by up to 2000 mutations.*

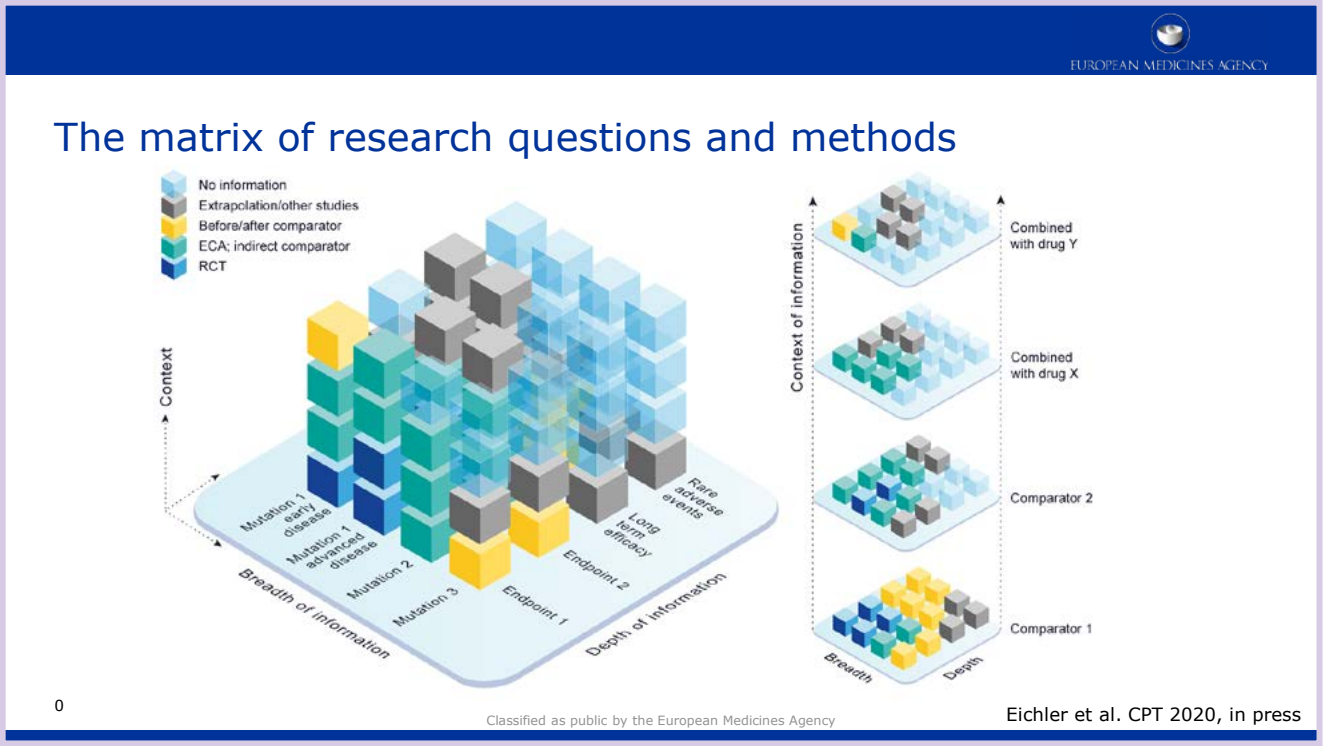


Figure 10: *The Matrix of Evidence Generation (Hans-Georg Eichler)*

Evidence generation may be further complicated in case of small effect sizes in small target populations, which may, despite being small, still be *relevant from a patient perspective*. For a *full implementation of PM*, Hans-Georg Eichler envisions a future in which *combinations of randomised and non-randomised methods will be used*, drawing on a variety of data sources, with data being prospectively and/or retrospectively collected. For the latter, *patients will need to be followed up for prolonged periods of time, including post-authorisation*. He points out that unavoidable (unresolvable) *uncertainty needs to be accepted in the context of PM*; this requires transparent communications on all levels including *communication of what is not known*. Novel methods of data integration will be needed to combine data from different sources, especially non-RCT and RCT data, and in the interest of payers, a framework is needed that allows *frequent reimbursement-assessments* as knowledge accumulates over time.

Conclusions of Session I

For PM, biobanking is a powerful data generation tool that also serves as a trustee for long-term use and storage of biosamples and data. It requires highly trained staff, standardized and quality-controlled procedures, an elaborate data management system and an adequate infrastructure, which may be regionally limited. Regions need to invest to tackle these needs and build capacities.

RWD, on the other hand, is also fuelling important PM health research, providing valuable evidence on health benefits of therapeutic interventions that will be increasingly needed for developing PM. RWD can be derived from many different data sources, which are already being maintained within regional and national health systems, thus enabling more complete post-authorisation studies of medical interventions. Under the precondition that data quality is sufficient, this knowledge could and should feed into reimbursement systems in a timely manner, enabling a system of regular reviews of state-of-the-art mecial interventions.

N-of-1-trials can provide in-depth clinical information on therapeutic interventions. They lend themselves to the assessment of individualised therapies and rare diseases and can be particularly valuable to elucidate individual physiological processes related to therapeutic interventions.

Clinical evidence for increasingly individualised therapies will have to rely on all the sources outlined above, plus additional ones (e.g. -omics data). For an integration of these different data resources, and to realize their full potential, their data need to be interoperable. This will require increasing standardization of terminologies, scales, and harmonized operationalisation of data in all relevant areas and on all levels, e.g. across regions, national borders and eventually also across disciplines as outlined in the keynote lecture. Despite this increasing availability of data, though, it will become even more important to understand limitations in current knowledge acquisition. These limitations will need to be handled in a transparent fashion. True personalisation will always entail some degree of unavoidable uncertainty.

2.4 Session II: Setting the Scene: Aspects of Commercialisation, Product Strategies and Business Models

Session II focused on aspects of commercialisation, product strategies and business models. To gain a deeper understanding, speakers from three different types of companies were invited: an internationally operating leader in comprehensive diagnostics development, a regionally embedded SME, as well as a representative of a large globally operating pharmaceutical company. In addition a representative of a German pharmaceutical industry association was invited.

Jonathan Arnold (Qiagen, USA) began his talk on **the benefits and challenges of personalised diagnostics** by characterising the market for precision medicine and genomics from the perspective of Qiagen, a world leading diagnostic solution's provider. Precision medicine is highly dependent on scientific progress in genomics, biologics, computational tools, and data analytics enabling complex genomic biomarker algorithms for clinical decision making. By analysing genomic drivers of diseases, patient stratification and treatment efficacy can be improved. As some innovative and expensive therapeutic interventions suffer from a high rate of non-responders (up to 75% for some indications) these could be better identified pre-treatment. Therefore (complex) biomarkers are increasingly used in clinical trials. This is supported by a trend towards liquid instead of tissue biopsies to obtain the necessary material for novel analysis tools. At the same time new regulation (e.g. EU IVD-Regulation) and more sophisticated demands of payers (e.g. health insurances) are also *changing market dynamics.*

Qiagen has been (and is) supporting more than 30 pharmaceutical partners with companion diagnostic (CDx) development services. There is an ongoing shift towards next genome sequencing (NGS), and to more complex products that can deliver comprehensive diagnostic information on multiple indications and markers with a single test, thus streamlining the diagnostic process.

Qiagen has identified *three critical success factors for CDx* development:

1. technology breadth allowing to choose the best technological approach
2. the ability to overcome the translational gap & regulatory hurdles by turning novel medical knowledge into a marketable device, and
3. ensuring patient access to therapy through CDx testing.

It takes years from marker discovery, subsequent development of a CDx to eventually achieve a high level of market penetration. As *patient access is frequently lagging far behind market approval* of new CDx. To overcome this, Qiagen has developed a worldwide *Day-One Lab Network* with leading molecular labs that implement novel CDx workflow before product approval and are therefore prepared for uptake of commercial testing upon time of drug and test launch.

Jonathan Arnold described *Qiagen's engagement in the World Economic Forum's (WEF) Global Precision Medicine Council.* As one of six thematic councils whose topics are shaping the ongoing *forth industrial revolution* as perceived by the WEF, the council for precision medicine developed a vision paper outlining *five governance gaps* in need of action to release the full potential of precision medicine for a transformed healthcare.

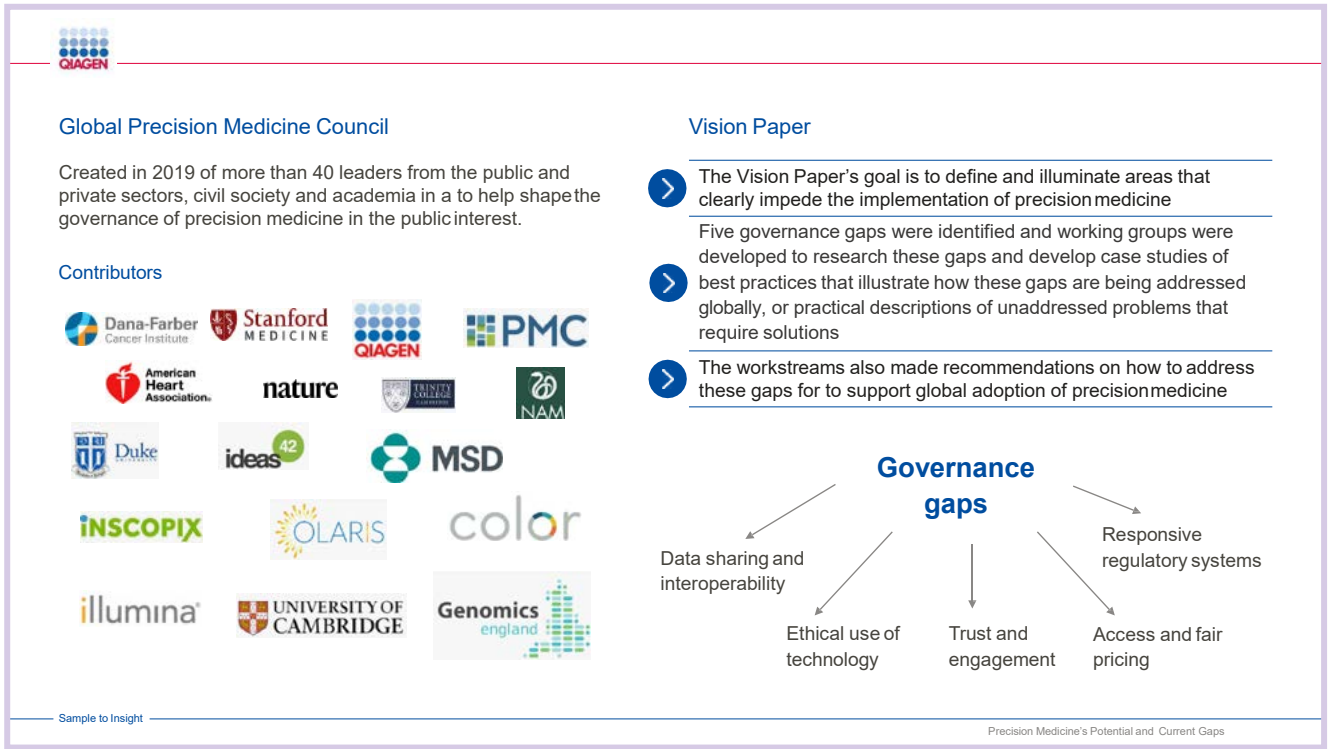


Figure 11: The World Economic Forum (WEF) Global Precision Medicine Council

The identified governance gaps relate to

1. Data sharing and interoperability
2. Ethical use of technology
3. Trust and engagement
4. Access and Fair pricing
5. Responsive regulatory systems.

Jonathan Arnold closed with a brief summary and discussion of some of its recommendations as outlined in figures 11 and 12. The Precision Medicine Vision Statement of the WEF is accessible at https://www3.weforum.org/docs/WEF_Global_Precision_Medicine_Council_Vision_Statement_2020.pdf.

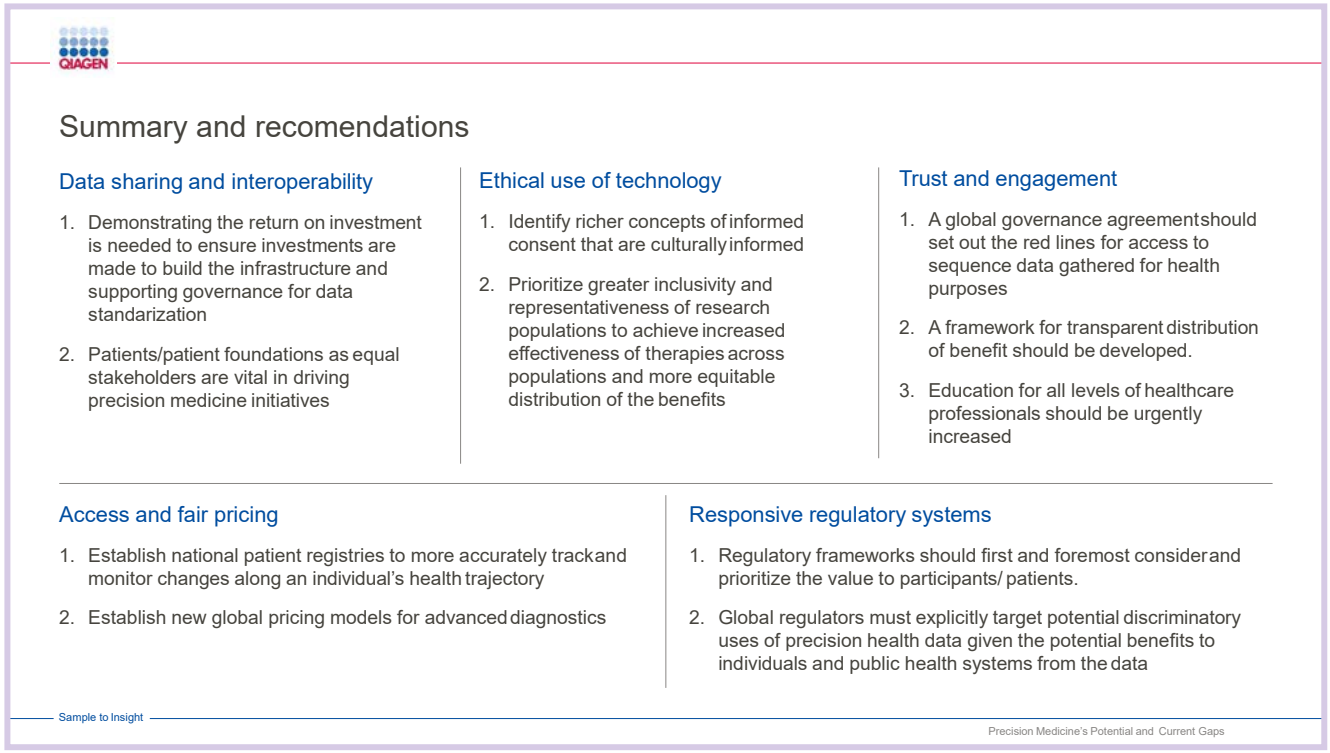


Figure 12: Recommendations from the WEF Vision Statement

Dr. Norman Gerstner (Molecular Diagnostics Group, Germany) presented the perspective of an SME on **personalised diagnostics as a driver for personalised health showing the benefits of a synergistic business model.** Dresden based Molecular Diagnostics group has a unique profile being comprised of three independent businesses operating in the fields of molecular diagnostics (Biotype GmbH), software and data management (Qualitype GmbH), as well as molecular imaging and radiotherapy (Rotop GmbH). The synergistic business model of Molecular Diagnostics Group is generated by combining and integrating the specific expertise of its three businesses, while each is also offering its own unique portfolio. The overall innovation and commercialisation processes are overseen and integrated by Molecular Diagnostics Group, allowing for synergies and cross-fertilization of ideas.

After showing data on the poor patient response rates on many high-cost drugs, Norman Gerstner described the challenges of moving from a disease- to a patient-centred approach. Diagnostic information on a given patient usually relies on different diagnostic modalities that are rarely well integrated. This results in incomplete and insufficient diagnostic information for medical practitioners. *A novel approach to store and combine patient centred information is needed, integrating all diagnostic information, also encompassing data on the healthy patient as baseline information*. There will be a conceptual advancement from PM to PH using personalised

Some ideas to improve personalised health in Europe

- Improve the communication to people about the benefits of personalised health
  - Healthy living: e.g. strengthening your immune system
  - Health Apps: recommendations and guidelines
  - Broadcast health-related information
- Promote innovation more strongly in Europe (pro-active, pro-risk)
  - Innovation fund for Startups and SMEs (€300 million per year, € 1 million per company once, no strings attached, prototype development)
- Create the legal framework to lower the market entry barriers for novel, innovative products
  - Simplifying beta-testing and pilot studies (bring customer, industry, health insurance, regulatory bodies together)
- Find a balance between data protection and data usability
  - Personal health data is key: IT security and data management (acquisition, handling, analysis, transfer, interpretation)
- Use the momentum of the COVID-19 pandemic for pushing innovation in diagnostics
  - Imagine it would be easy to do a COVID-19 test each morning at home and share that data safely...

Figure 13: Improving Personalised Health in Europe (Norman Gerstner).

diagnostics not only for better informed treatment decisions but rather to guide personalised preventive interventions that will lead to improved public health. He made suggestions how to improve the conditions for PM and PH in Europe that are summarized and shown in figure 13.

He concluded taking up some of the thoughts of the keynote lecture, emphasizing how important it is to better manage health data across Europe while at the same time ensuring that data ownership will remain at the level of the individual citizen/ patient.

Giovanni Giuliani (Roche, Italy) presented **challenges and barriers for PM and PH from the perspective of a big pharmaceutical company.** He pointed out how the Covid-19 pandemic has demonstrated a need for a stronger focus on PM and improved patient pathways. To support patients optimally in a personalised manner, *patient pathways need to be adapted,* be based on solid data analysis, guided by a *supportive regulatory framework,* allowing for integrated solutions offered by multidisciplinary teams. A big hurdle is the traditional silo-style approach that is *also nourished by the way physicians have been trained,* frequently putting a strong focus on specific fields of expertise, leading to a narrowing of perspective. Optimally *physicians would become orchestrators* that support patients within their specific pathways.

The added benefits of integrated solutions that improve patient monitoring and communication need to be supported by *remuneration/reimbursement schemes that encourage their application.* He pointed out the *dual role of data analysis* not only for early research but also to *evaluate treatment outcomes for further improvements*, emphasizing the value of RWD. He outlined developments in oncology, demonstrating the improvements that PM approaches offer when implementing molecular tumour boards (MTB) and using comprehensive genomic profiling (e.g. NGS) that enable molecularly guided treatment option (MGTO) decisions. In Italy this pathway is accessible to patients without other valid treatment options, representing a special use case. In such cases, treatments may be prescribed that lack EMA approval for the indication-at-hand *(off-label use).* In Italy, for the patient, novel, not yet standard treatments can become accessible through early access frameworks, by participating in clinical trials or through specific molecular guided treatment option (MGTO) funds. He also outlined results of the NEXT project demonstrating cost-effectiveness of NGS versus standard approaches on top of improved patient outcomes. To implement such approaches, it is essential to introduce *viable reimbursement rules and budgets for MGTO approaches.* He pointed out how different levels of governance apply to different topics of relevance for PM, so that on all levels policy action may be needed.

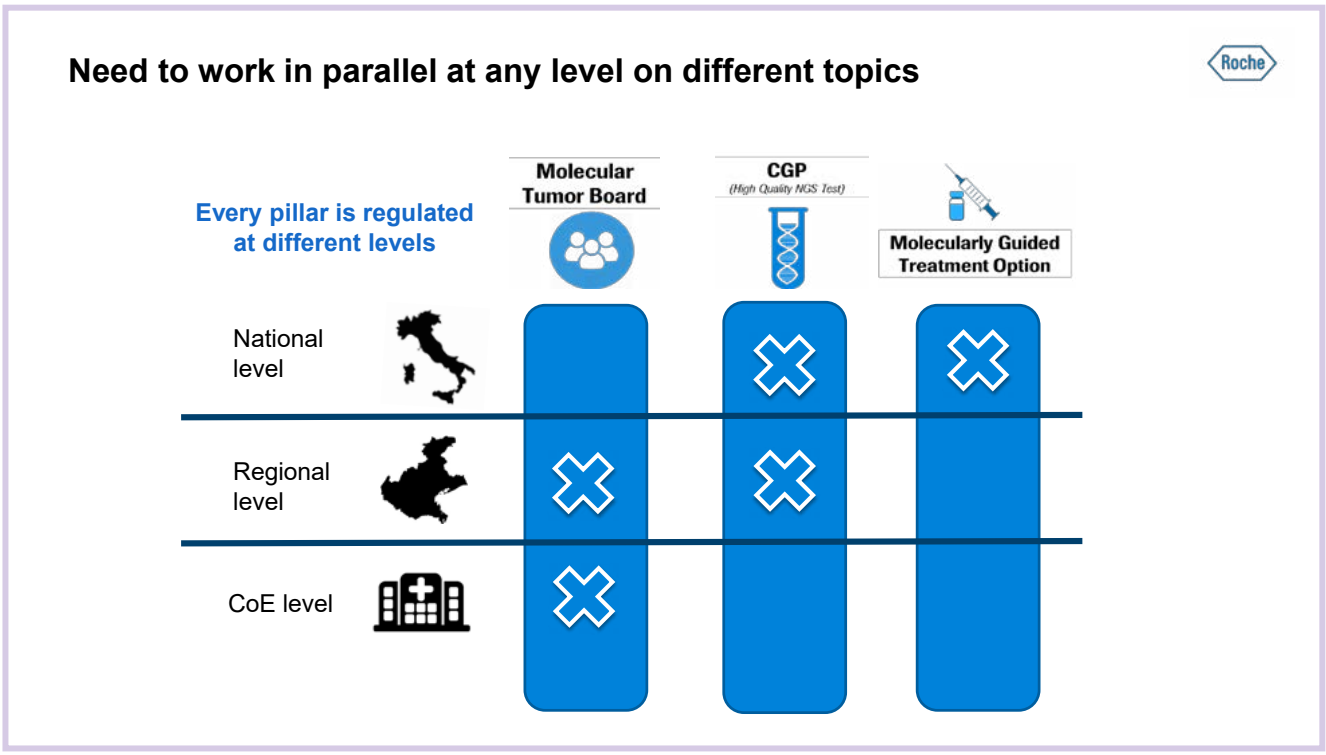


Figure 14: Levels of Governance for PM (Roche)

Thorsten Ruppert (vfa, Germany) presented **the current status and outlook of PM from the view of the pharmaceutical industry in Germany.** He described the advantages of PM for patients and doctors, who can make better informed choices to improve efficacy, safety and dose finding of therapeutics leading to an *improved quality of life* for the patient. There is an increasing trend to use biomarkers in clinical trials, e.g. in more than half of all oncologic trials. These are mostly used to better identify/monitor therapy response, also as inclusion criteria (patient stratification), to monitor treatment safety, or to obtain a prognosis of therapy response and have been shown to increase success rates of clinical trials significantly. The approval rate for CDx guided therapeutic substances has risen significantly in the EU to more than a quarter of total approvals. In Germany, there are 79 medicines on the market that require or recommend the use of a CDx.

PM and CDx development is challenging as both depend on differing sets of expertise and technical capabilities and also gain market access by separate processes. He raised the issue of quality and reproducibility of laboratory developed tests (LTD), currently not requiring an external accreditation process but widely used to save costs compared to industrial standardized tests. With the novel CE-IVD regulation (2017/746) LTD use will be more constrained, requiring additional validation. However, legal requirements for CDx used in early clinical trials need to be clarified to facilitate their use. Frequently, tests are not fully developed when early clinical

trials take place so that they are not yet certified. This may create problems and should be addressed.

Torsten Ruppert described how reimbursement for diagnostic tests is organized in Germany in a hospital setting (in-care), where CDx are included in case-based reimbursement tariffs, which do not reflect their added value. To obtain full refund of cost, patients are frequently switched between in- and outpatient-care changing reimbursement modes. CDx test rates are comparatively low in Germany, even in indications where defined as mandatory, leading to inefficient therapeutic approaches and lost life years (e.g. EGFR mutations with a test rate of 52%). There is a need for higher testing rates and related to this a need to adjust the reimbursement system to better support CDx use. It is necessary to better educate doctors about all available testing options. He highlighted the added value and potential of NGS over sequential and incomplete testing approaches, as NGS allows for faster and more complete identification of relevant known markers of a given disease.

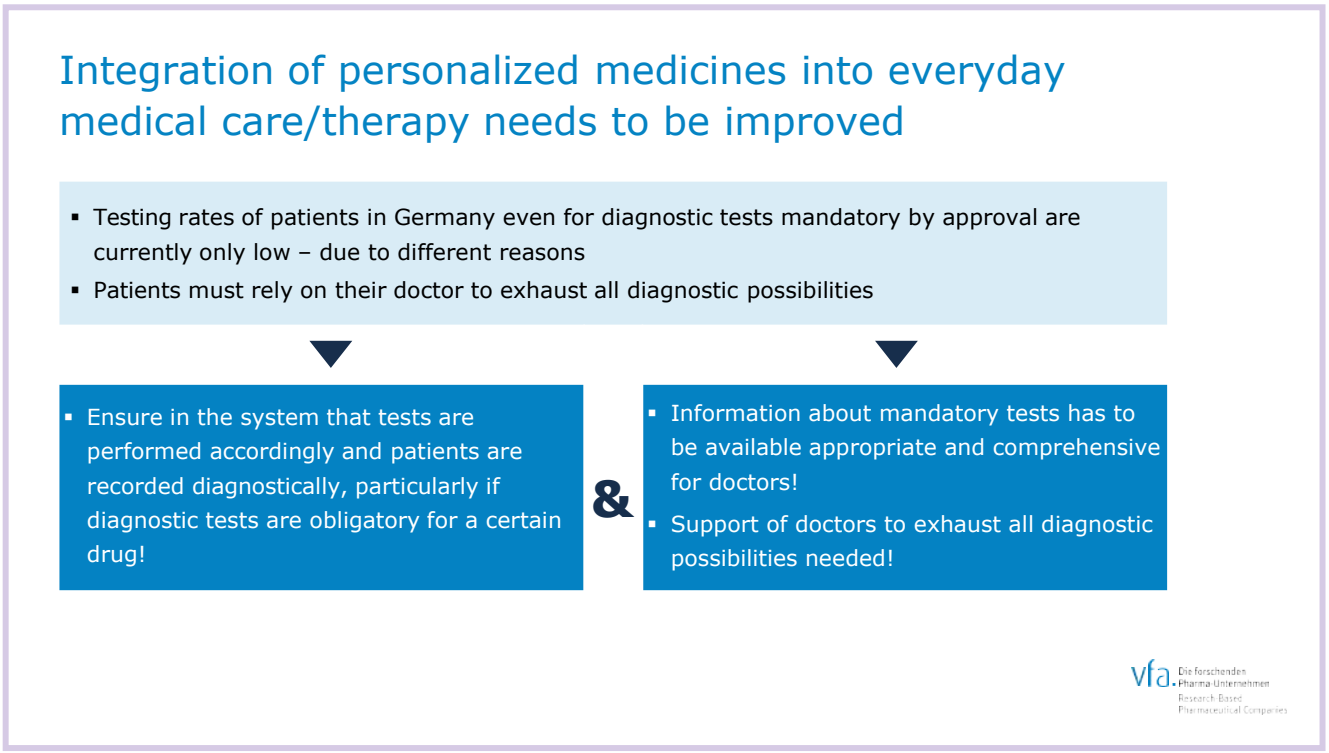


Figure 15: Recommendations for CDx Integration in Germany (vfa)

Conclusions of Session II

The development and full-value chain integration of comprehensive innovative diagnostics is an essential prerequisite to achieve personalisation of therapeutic interventions. PM can only realize its therapeutic potential if corresponding CDx are not only developed, but also marketed and applied in clinical routine. Currently, therapeutic potential is lost due to insufficient use of already existing testing options. Regulatory fragmentation poses an important bottleneck, as well. Market access regulation as well as reimbursement policies should be adjusted to better fit to these requirements and set incentives in a more supportive manner, allowing for faster market approval and market uptake.

Incentives should not only cover up-front diagnostics but also the integration of improved (continuous) monitoring that not only serves to guide therapy adjustments and control therapy success, but also supports further therapy development, e.g. by providing comprehensive outcome data that could feedback into later therapy adjustments. However, to allow for such improvements to more easily reach the patient, regulatory hurdles need to be analysed and possibly lowered to facilitate post-hoc modification of prior market authorisations.

Medical practitioners as well as patients need to gain more awareness of personalised diagnostic options. It needs to be ensured that (specialised) medical practitioners have a thorough understanding of all potential patient pathways to optimise individual treatment. This calls for further education of medical practicioners and could and should be accompanied by more interdisciplinary-interlinked patient guidance structures. In addition, the digital availability and accessibility of comprehensive and complete individual patient health information, in the form of electronic health records, would support doctors and patients, when navigating complex health issues. This is not yet a standard in many European regions. Further regulatory and structural changes as well as increasing patient education may be required to support this change and increase patient and health practitioner engagement.

2.5 Session III: Making it real: Intellectual Property, Funding and Institutional Support

Session III focused on the supportive environment for industry, including IP, market, financing, and the role of clusters.

Challenges of intellectual property protection in PM were discussed by **Anne Lauber-Rönsberg/Sven Hetmank** (Technische Universität Dresden, Germany). As PM requires significant investments in technology and product development (including algorithms) the question of intellectual property (IP) protection to secure the economic benefits of these inventions is of paramount importance. Providing a brief overview of different IP rights (patent, copyright, database rights, trademarks etc.), the speakers described how certain traits of PM products and procedures may reduce their patentability. For example the use of naturally occurring correlations, such as biomarkers to identify a disease, may not be considered an invention. Also AI and algorithms may be problematic to protect due to abstractness and incomplete discloseability. Medical treatments may not be patented in the EU, when they are performed on the living body (Art 53(c) EPC), however new dosage regimens of an existing substance are patentable (Art 54 (4) (5) EPC), which may be relevant

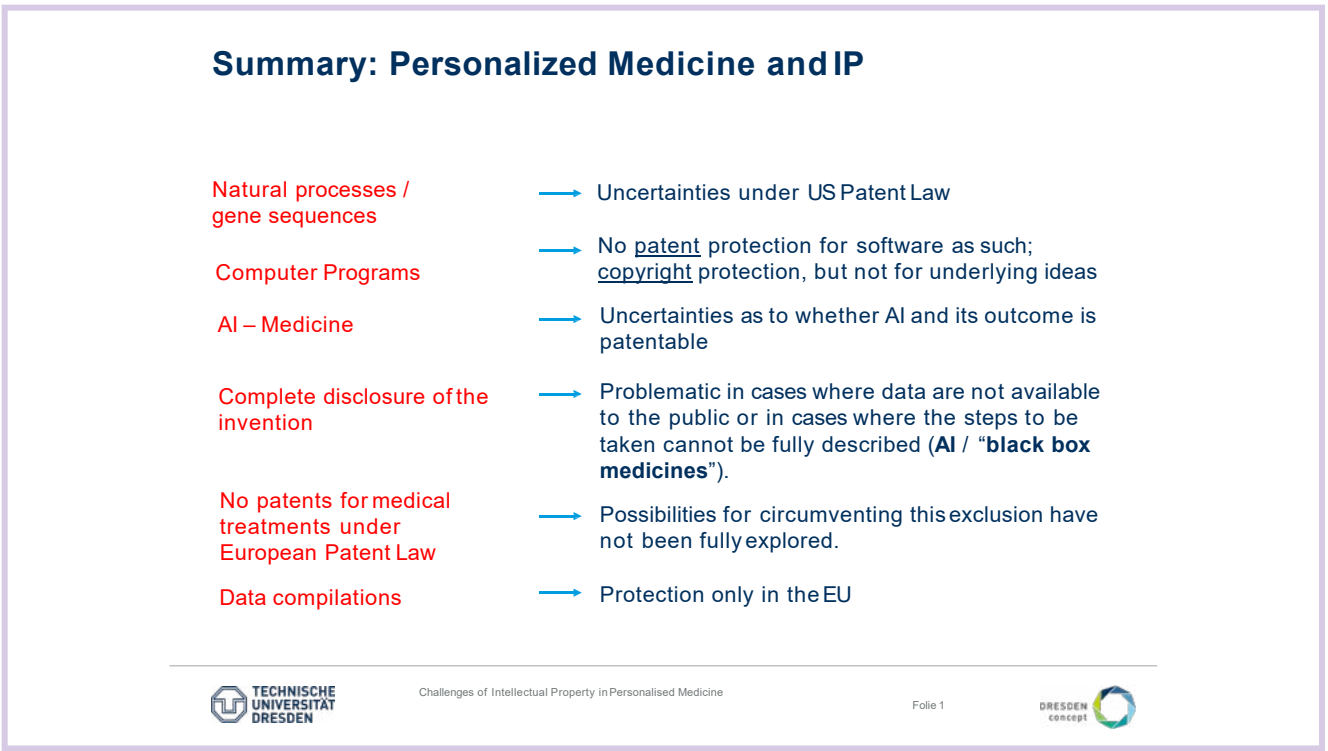


Figure 16: Limits in IP protection for PM (Anne Lauber-Rönsberg/Sven Hetmank)

for *repurposing of drugs*. In the US, the patentability of certain inventions that are based on natural phenomena are dependent on the proof that the claim as a whole amounts to "significantly more" than the natural phenomenon. The vague definition causes legal uncertainty, which is generally reducing the likelihood of commercial investments in a given technological field.

Differences in US and European patent law may lead to differing decisions on patentability in both jurisdictions. As patent law leaves gaps, specifically for data compilations and software, copyright protection may apply to some degree, for instance if a computer programme is the author´s own intellectual creation; however, the scope of protection is limited, functional aspects are not covered. Also, databases are not fully protected. In the EU sui generis database right gives some protection that does not exist in other jurisdictions. However, the re-use of data by competitors is not protected, so that protection is limited. In sum, a number of IP issues are not supportive for PM development, because PM development is not always easily integrable into the existing legal system and is therefore associated with unforeseeable legal risks. This may reduce investor willingness to support R&D investments in this field.

Siegfried Bialojan (EY, Germany) shared insights on **good translational practices for a supportive environment of innovative life sciences companies**. He outlined general

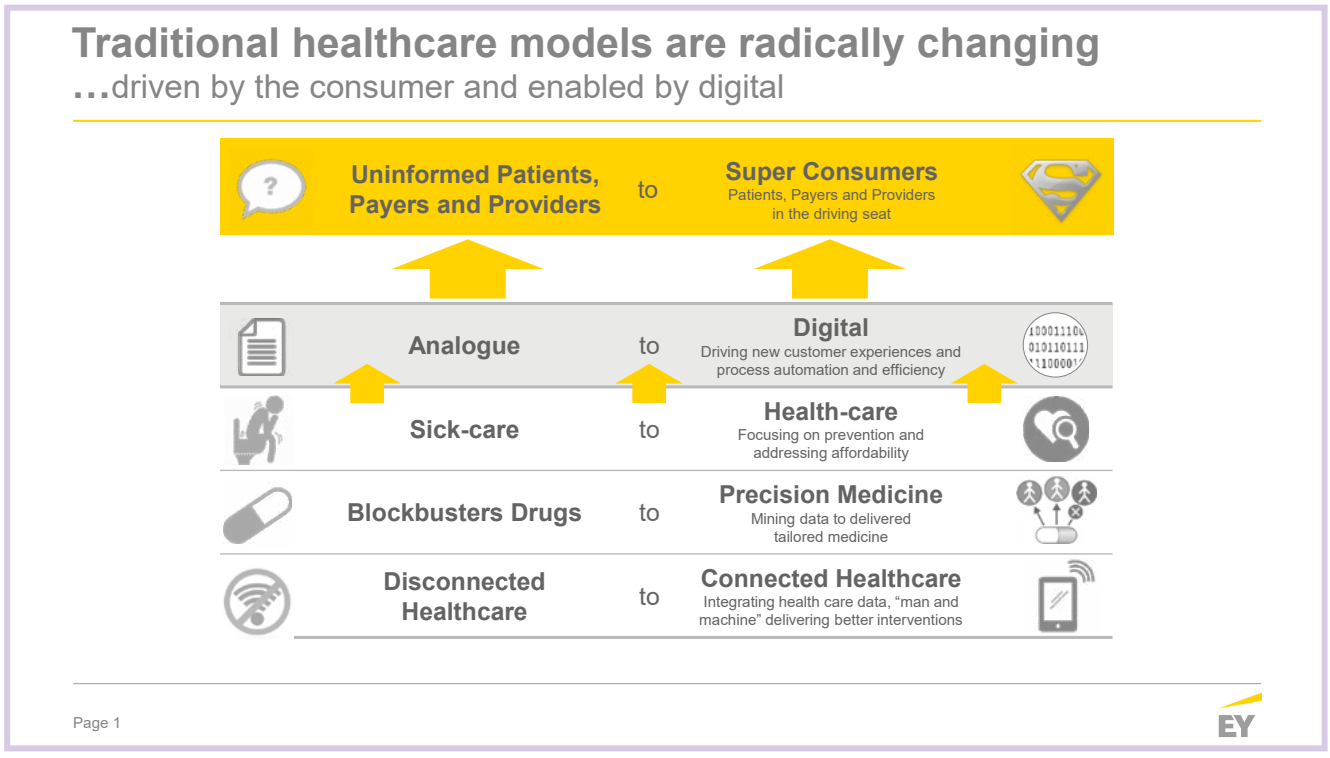


Figure 17: Current and Future Healthcare (EY)

trends impacting the life sciences industry, such as socio-economic developments, e.g. an aging population, and a growing share of healthcare cost of national gross domestic products (GDP), technology forces such as digitization, personalisation, changing customer demands of patients, practitioners, payers, and investment requirements (e.g. capital efficiency of R&D investments). Therefore, the business model of health industry is rapidly changing (see figure 17).

Terming the new industrial landscape Life Sciences 4.0., EY characterises it by increasingly educated and demanding *super consumers* and a high speed of largely IT driven technology advancement. This notwithstanding, regulatory hurdles, patent issues, and reimbursement pressures characteristic for life sciences industry in the past persist. These developments are leading to a stronger focus on patient outcome, giving more power to payers and patients. The ecosystem for health science companies is becoming increasingly dynamic, with disruptive innovation being introduced mostly by IT technologies. Personalisation will likely develop beyond using biomarkers to include also behavioural and social aspects. *Added value may be created by building a stronger customer engagement, creating high information relationships with patients, doctors, and payers* from which all stakeholders may benefit. Added value is generated by combining, connecting

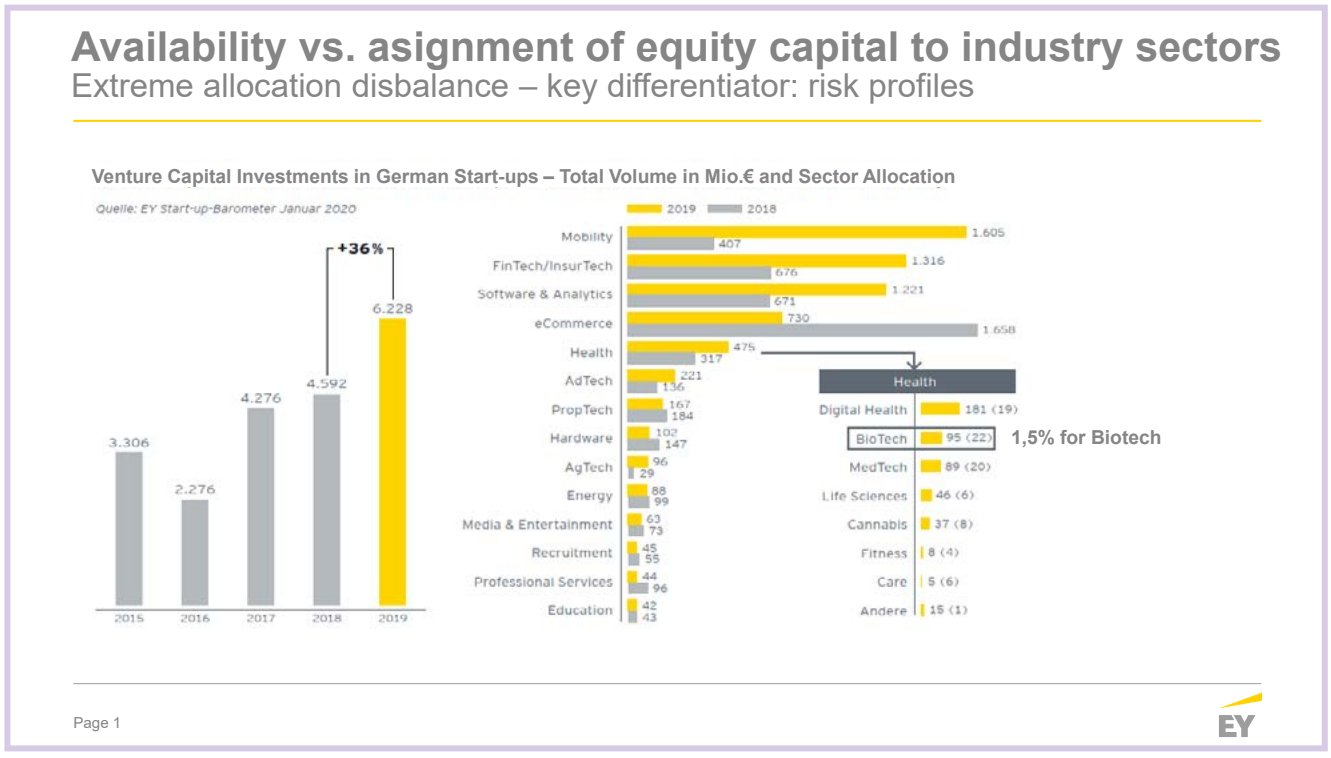


Figure 18: *Allocation of Equity Capital in Germany (EY)*

and sharing novel (patient) data made usable by novel analysis tools. However, looking at the highly innovative biotech sector in Germany, it shows that results from the excellent academic science base are *not easily translated into commercially viable businesses.* A number of cultural (risk aversion, underdeveloped entrepreneurial culture) and systemic (lacking access to sufficient equity capital) factors are responsible for this. *In Germany only 1.5% of available equity capital are allocated to biotech companies.*

As these factors are not easily changed in short term, another approach to support life sciences start-ups could be to increase their chances for success by reducing risk. *Supportive structures that address the translation phase could serve as risk reducing catalysers.* LabCentral/BioLabs is a well-established, highly successful model for this. The incubator in Boston (USA) offers fully equipped lab and office space, general-use equipment, support services, but also networking support, and has leveraged almost six billion US dollars of investments over the past eight years. Also, in Germany a number of support infrastructures/ initiatives exist that reduce translational risks. But most of these approaches address only an early phase of translation, with support in place mostly before company formation. *More initiatives addressing later translational phases are needed.* Relevant stakeholders, investors, and policy makers should further support industry development in the life sciences.

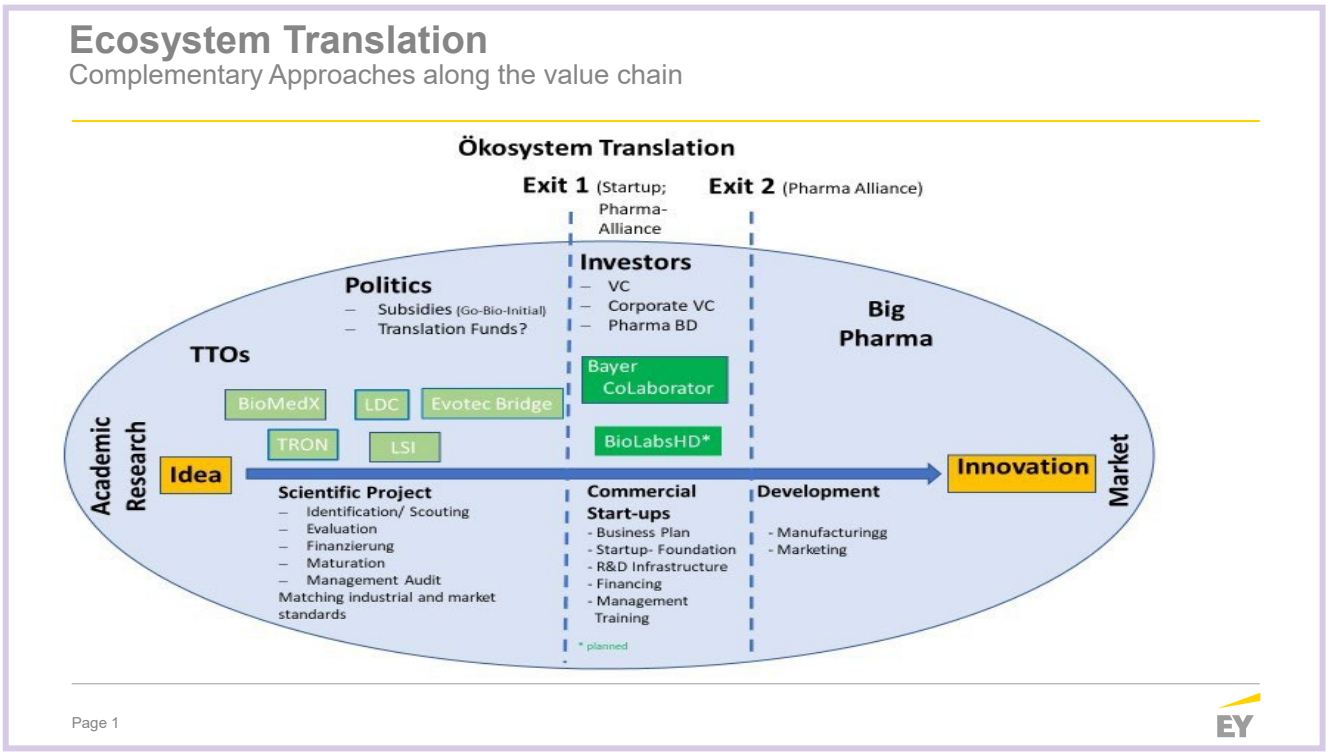


Figure 19: A Translation Ecosystem (EY)

Anaïs Le Corvec (CEBR, Belgium) discussed **European biotech clusters as supporters of translation.** The Brussels-based Council of European BioRegions (CEBR) represents 40 European Biotech Clusters from 15 EU countries, serving as a networking link between different health and life sciences ecosystems across Europe. CEBR supports regional exchange through different working groups (e.g. on digitalisation, international markets), by sharing best practices, offering dedicated support schemes for SME, enabling skills exchange between clusters, and connecting to other ecosystem stakeholders. In the beginning of the Covid-19 pandemic CEBR helped its members to collaborate on solutions for regional needs, e.g. to obtain and find new production means for protective equipment. CEBR reports *a significant lack of funding for SMEs across Europe.* In numerous MS, there is a lack in pre-seed and R&D funding. Better alignment of public funding policies and general strategy among different policy levels is needed. Sometimes public funding schemes and regulations are contradictory, especially if provided by different levels of governance, so that regional funding cannot be combined with multi-regional/national funding. Recommendations for further policy development within the EU to better support life sciences clusters and SMEs were published in a white paper (see figure 20). Suggesting how funding support for life sciences SME could be improved, CEBR reported good experiences with *voucher schemes and considers public procurement and pre-procurement of innovation an attractive* option, though it might imply bureaucratic hurdles for SMEs. The value of health-related cluster organizations was demonstrated in countering the ongoing Covid-19-crisis, their experience should also be used in support of EU recovery funds as clusters are harbours of local and regional knowledge.

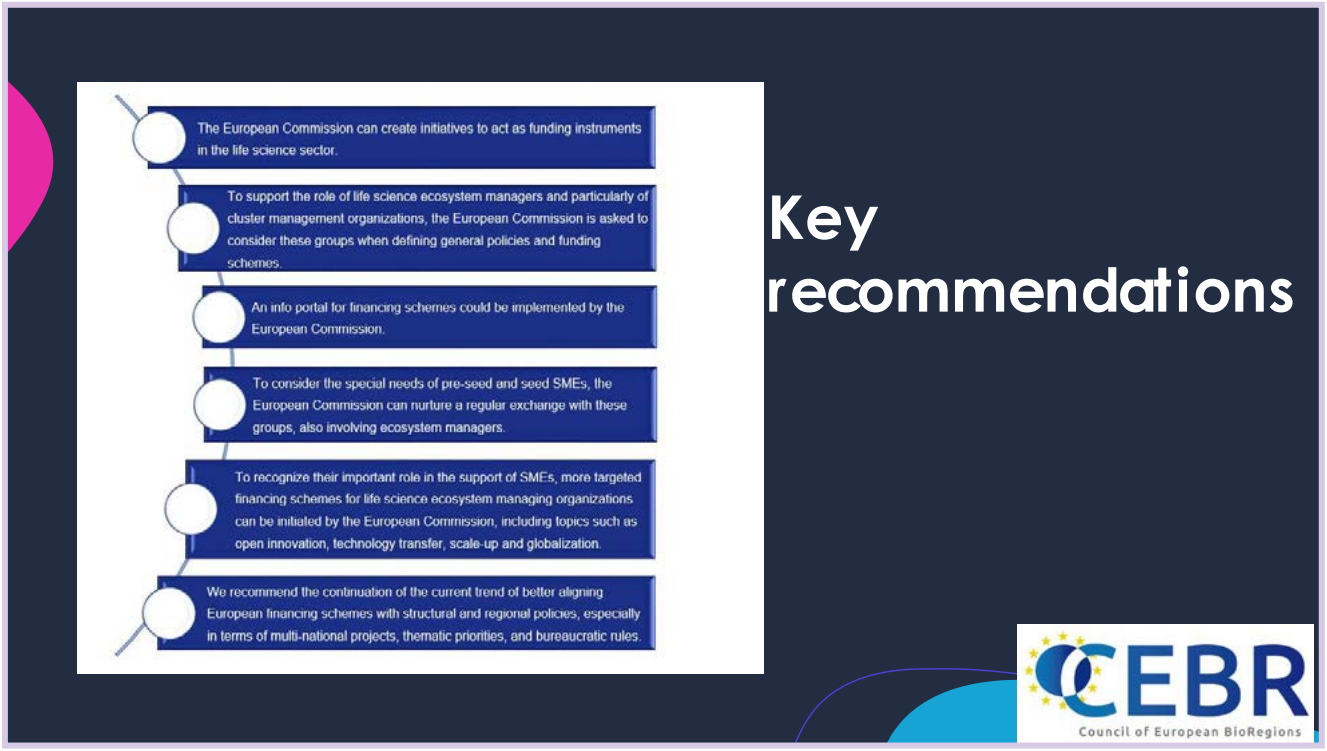


Figure 20: Policy Recommendations for Life Sciences Clusters (CEBR)

Conclusions of Session III

The development of PM products poses significant challenges that already begin with appropriate IP strategy. In many technologies underpinning PM, IP protection is limited and complex in use (e.g. in the case of algorithms and artifical intelligence, as well as databases) thus failing to convey proper protection where needed. In some parts this uncertainty derives from too vague definitions, and also a lack of international consistency. Thus, IP rights for PM products may differ significantly in important markets.

However, a clear IP protection is fundamental to channel R&D investments and support entrepreneurship. PM would benefit from a more adequate IP regulation and training programmes, especially in relation to data and data processing systems (tools and collection).

The translational environment for PM entrepreneurship is also characterized by other deficiencies. In Europe, funding opportunities for biotech and life sciences startups such as availability of risk capital are still far less developed than in the US, with relevant differences also within the EU. The lack of access to finance leads to diminished market opportunities. And even though need may spur creativity to some degree, frequently the outcome is a loss in growth potential for start-up companies. Even worse, it may also cause relocations of high-potential start-ups to more favorable locations in their quest to obtain better access to finance and thus imply a loss of potential for regional, national and EU ecosystems. On top of direct economic effects this sends discouraging signals to potential novel entreupreneurs.

A resolution of this setting is clearly beyond the scope of regions. More initiatives to create and establish a flourishing European-style capital market with the potential to also service PM might be needed. Nevertheless, a reduction of translational risk by means of comprehensive support structures is a possible and viable instrument to ease the situation. This approach is directly accessible to regions and also lends itself to further develop interregional collaboration and knowledge transfer. Existing clusters may be useful structures to initiate and realize such approaches and could be further developed to advance PM.

2.6 Session IV: Reaching the patient: Regulatory Aspects, Valorisation, Medical Societies, Patient Trust

Session IV focused on aspects of reaching and involving the patient providing broad insights into the role of patient registries; valorisation of novel PM therapies, the role of medical societies and medical guidelines and approaches to support building patient trust.

Anna Ambrosini (Fondazione Telethon, Italy) talked about **facilitating patient-led initiative with industry – patient registry data access.** She introduced Fondazione Telethon, a non-profit fund supporting research on rare genetic diseases that was founded by the Muscular Dystrophy Association in Italy three decades ago. Telethon has set up a patient registry for neuromuscular diseases and founded a dedicated legal entity for the registries' stewardship. Explaining the invaluable role of registries in driving medical research and for more efficient planning of medical trials, Anna Ambrosini, who is a member of the executive board of the European Neuromuscular Centre (ENMC), discussed the potential role of patient organisations as partners in a co-creation processes for driving the research agenda, referring to a whitepaper of the ENMC on the role of patient organisations (https://www.enmc.org/wp-content/uploads/2020/02/WhitePaper-FINAL-26-2-2020-2.pdf).

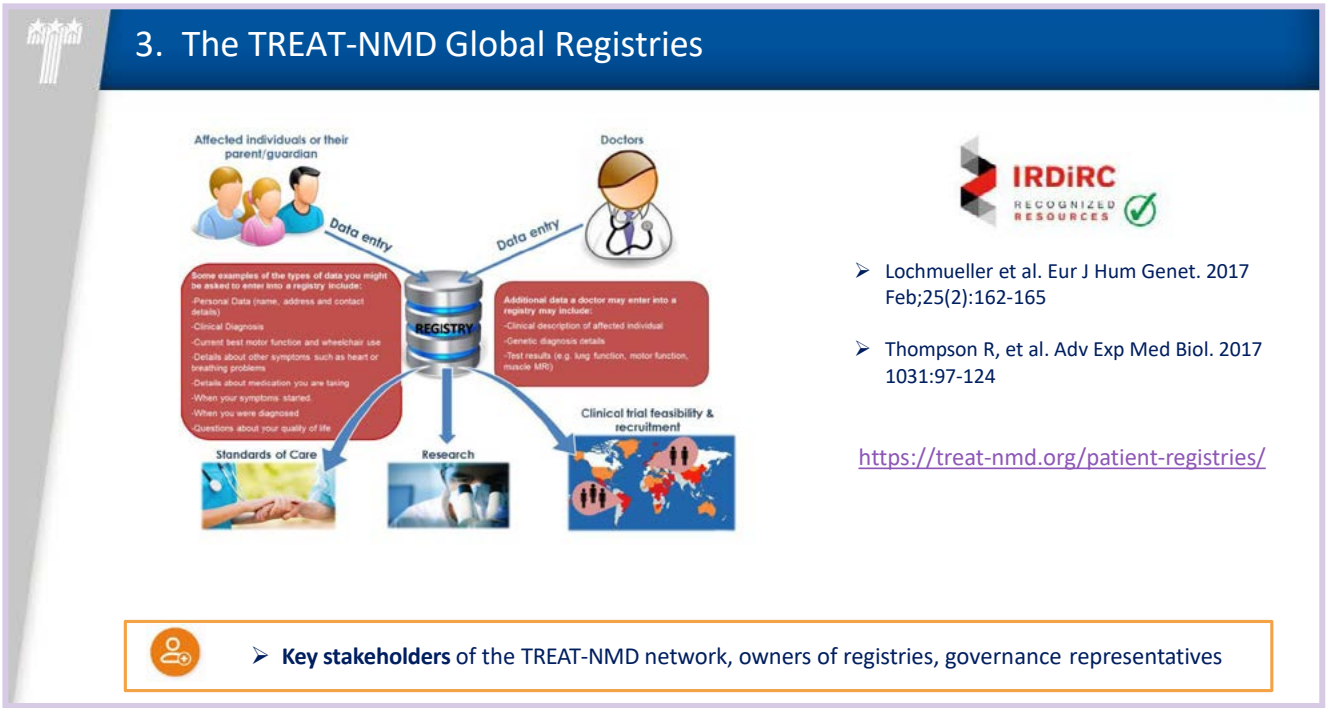


Figure 21: The TREAT-NMD Global Registries (Fondazione Telethon)

She presented three examples demonstrating the value of registries:

- the *Italian neuromuscular patient registry platform* serves as a web-based virtual place, allowing patients and clinicians to collaborate, ensuring that disease registries are managed according to a transparent governance, collecting data of longitudinal study protocols, promoting good clinical practices (GCP) and FAIR data sharing
- the *Duchenne muscular dystrophy natural history registry* was set up with support of patient groups; due to the unique nature of the disease, simple statistics are not applicable, so a novel sophisticated analysis tool was developed that helped stratify patients according to the disease progression and has already been used to improve and advance clinical study design
- the *TREAT-NMD Global Registry network* is a service to industry for trial feasibility and patients' recruitment; it helps harmonize the clinic in neuromuscular diseases on an international scale. It involves about 70 registries worldwide, so that *data across registries is handled in a standardized manner,* and therefore can be pooled anonymously for analytical purposes to feed clinical research and support recruitment of external partners, e.g. industry. She highlighted the high degree of patient involvement in the set up and management of the registries involved.

There are many benefits of patient registries for disease research, e.g. promote early clinical & genetic diagnosis and treatments, better inform the definition of standards of care and patients' follow up, improve trial readiness and clinical networking. Ultimately, they may contribute to facilitate patients' access to international trials, provide relevant information to regulatory authorities, and serve in the collection of post-marketing-data of efficacy. Anna Ambrosini emphasized the high value of patient organisations in steering these activities and their contribution in registry development.

Apostolos Tsiachristas (HEcoPerMed, Oxford University, United Kingdom) presented aspects of **valorising PM and therapeutics**, analysed within the Coordination and Support Action **HECOPerMed** that aims to stimulate the adoption of PM in the EU by providing guidance on how to conduct modelling in PM and proposing novel payment/reimbursement models. He first discussed benefits of PM on different levels ranging from the individual to eventually the world economy by achieving productivity gains. Due to current misalignments between the financing of R&D and payments (reimbursement) for PM, the interest of investors in the field is rather low. To overcome the limitations of current reimbursement models, *a trend to trying new outcome-oriented reimbursement*

approaches could be observed, entailing more risk-sharing between payers and providers, such as *managed entry agreements*. However, only few practical examples exist so far. The incorporation of value in reimbursement models is difficult. There are different elements of perceived value for PM that can be distinguished and are discussed in the literature. The isolated use of quality adjusted life years (QALYs) and net costs is put into question as being insufficient to capture the full value of PM.

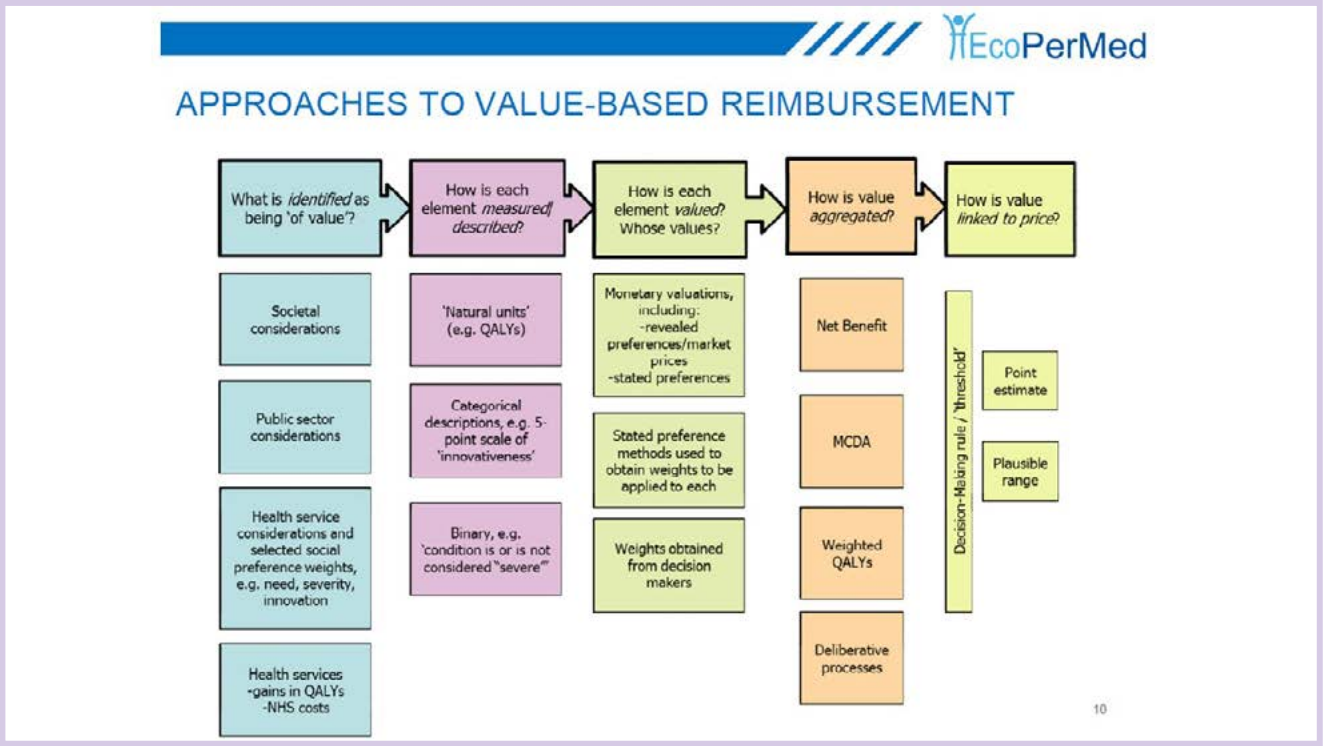


Figure 22: Approaches to Value-Based Reimbursement (HEcoPerMed)

Apostolos Tsiachristas outlined approaches for value-based reimbursement, e.g. net benefit, multi-criteria decision analysis (MCDA), and weighted QALYs in a quality analysis framework, pointing out advantages and disadvantages. Their operationalisation into value-based contracting is difficult. The inclusion of additional value elements for PM is also criticised, as they refer to unclear means of measuring and monetising, risk of double counting, a biased focus (on positive elements), or reduce comparability to other therapeutic approaches. Other questions relate to the *timing of evaluation, volatility in cost calculations due to high speed of innovation, lack of robust data* in cases when RCTs are lacking. A guidance with 21 recommendations was developed by HEcoPerMed to improve consistency and quality across different health economic models in PM.

For the future *a more dynamic framework for PM may be needed* in which regulators and payers collaborate on assessing relative safety and efficacy before market approval to align expectations and allow for *faster market access and reimbursement decisions*. This might improve their willingness to achieve *risk sharing agreements*. Value

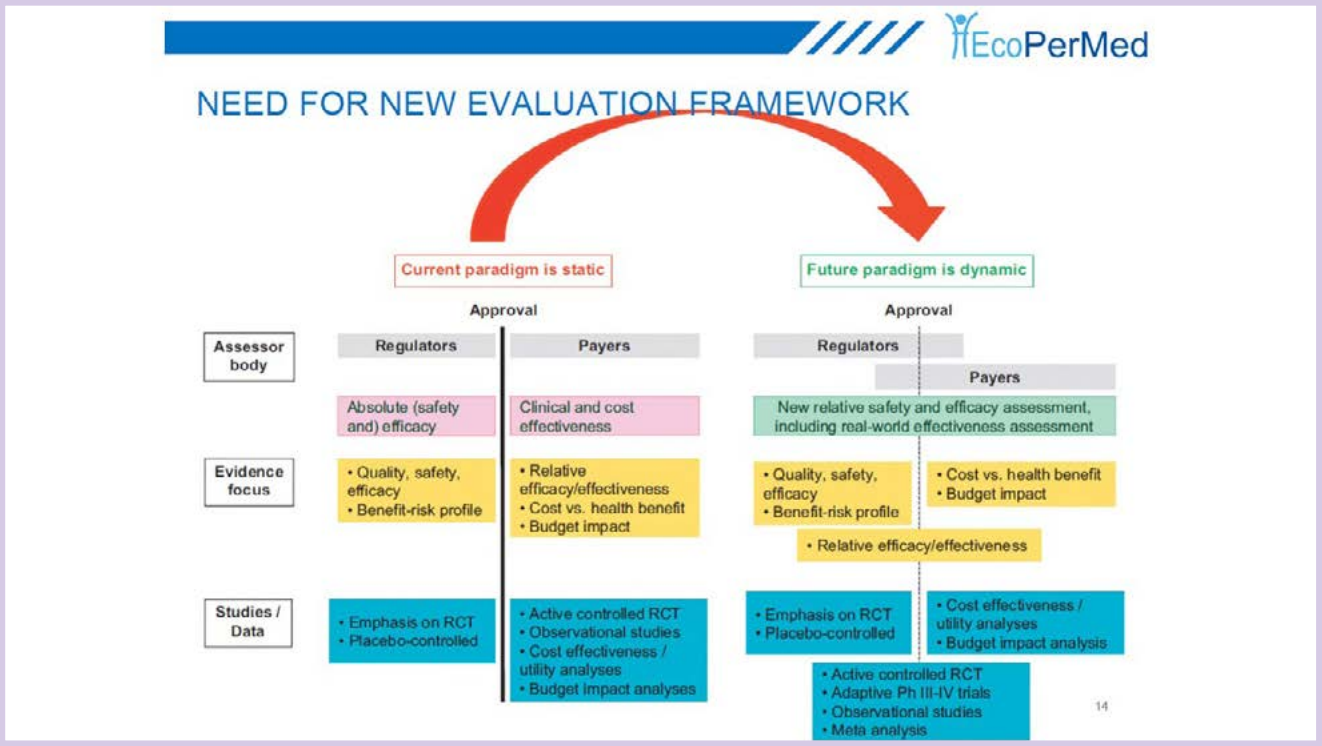


Figure 23: Need for a New Evaluation Framework (HEcoPerMed)

based reimbursement remains challenging, value elements and modelling instruments need to be agreed on. *Performance based reimbursement seems to be a realistic and achievable alternative,* e.g. by setting up annuity type contracts with milestone-assessments and performance-dependent payments. However, this may only be feasible for (relatively rare) high profile treatments. Real world data in adaptive phase III/IV trials could be used to generate evidence for outcome-based risk-sharing agreements speeding up market access of innovations.

Markus Follmann (Deutsche Krebsgesellschaft e.V., Germany) addressed aspects of **integrating personalised approaches into guidelines in the field of oncology.** He described the German Guideline Program in Oncology (GGPO), which was started in 2008 based on the German Cancer Plan (Nationaler Krebsplan) as a cooperation between the German Cancer Society, the German Cancer Aid and the Association of the Scientific Societies in Germany. Their aim was to improve quality development in cancer care, knowledge transfer and networking. The programme's objective is to support clinical practice guidelines (CPG) development by scientific medical societies, providing independent funding for CPG development, and improving methodological quality, the implementation of patient guidelines (lay versions), performance measures, and guideline access. He provided an overview of guideline developments in the last decade, pointing out regular updates, making some living documents, and increasing digital accessibility. He described a cooperation of GGPO with the Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

(IQWIG; engl. Institute for Quality and Efficiency in Health Care) on integrating German regulatory (AMNOG[2]) processes in the guidelines, as well as linking up with the Gemeinsamen Bundesausschuss (G-BA; engl. Federal Joint Committee). Guidelines are made available in English, and cooperation with cancer registries and the GCS certification system and student training are installed.

Markus Follmann presented a study on the uptake of personalised medicine in published guidelines of the GGPO, based on keyword search. Presence of these keywords in the background text of the documents had them classified as "concept present"; the appearance of keywords found within recommendations was counted separately to obtain a total count of recommendations per guideline. Results are shown in figures 24 and 25. 10% of guidelines used the term "personalised medicine", almost 90% included genetic-testing related terms, and half referred to "mutations". On the level of recommendations, 35% of guidelines had some for or against genetic testing; a third of the guidelines referred to specific mutations in the context of treatment. He demonstrated examples on melanoma, lung cancer, and breast cancer summarizing that guidelines are able to address personalised medicine, nevertheless the way and the amount remain a point of discussion. Integration of PM in guidelines can and should take place taking into account that guidelines are based on available and accessible evidence. He pointed out that *guidelines remain the most important tool to date to transfer current knowledge to doctors (and patients) and optimise health care.*

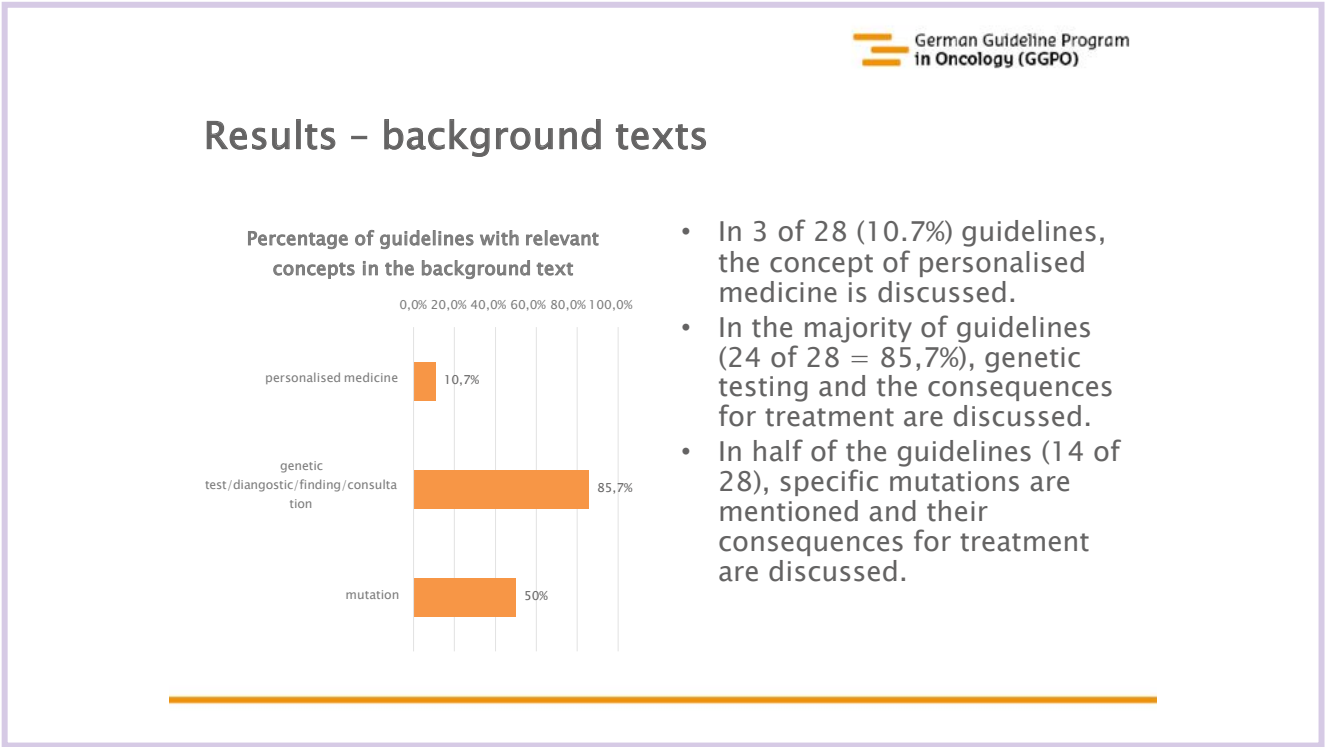


Figure 24: References to PM in Background Texts of Clinical Practice Guidelines (German Cancer Society)

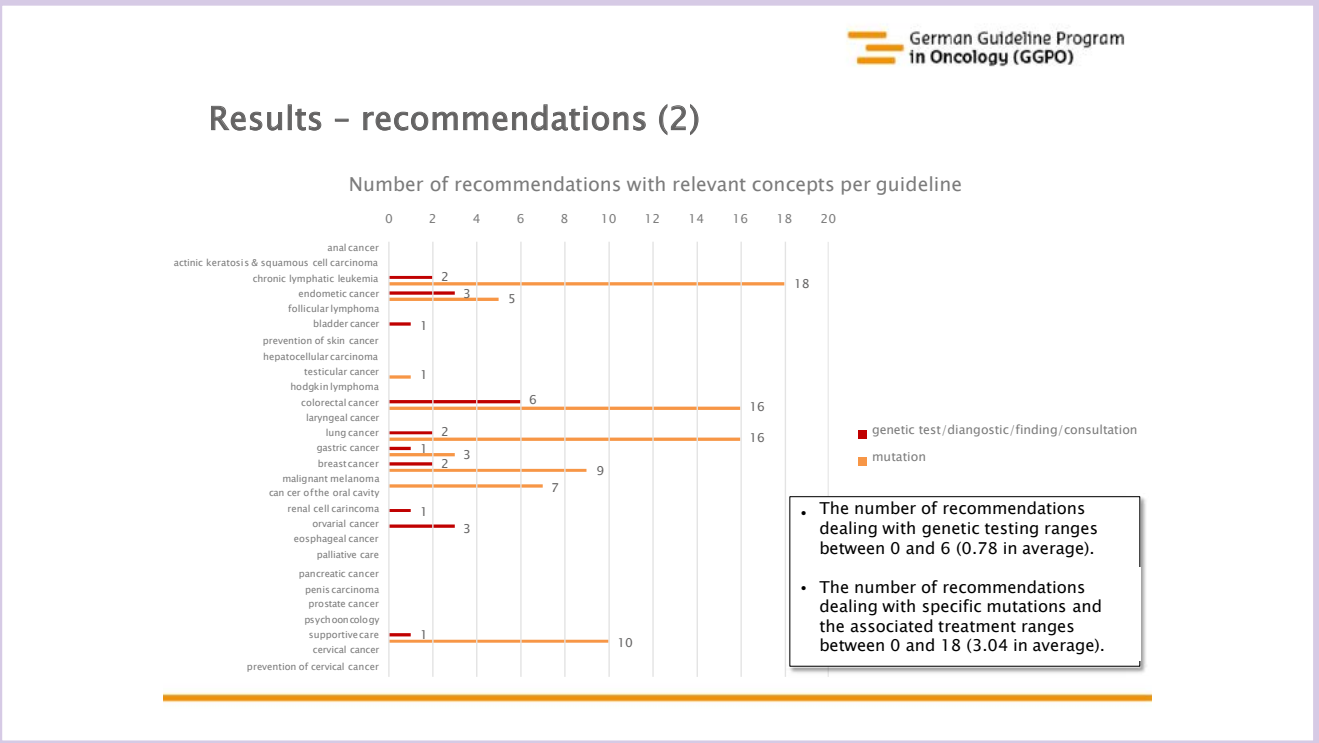


Figure 25: References to PM in Recommendations of Clinical Practice Guidelines (German Cancer Society)

Ralf Porzig (Sächsische Krebsgesellschaft e.V., Germany) presented the Onkolotse[3] reflecting on **patient education and trust: guidance and support in an increasingly complex setting.** Onkolotse is a support scheme for cancer patients. Cancer patients are confronted with an increasingly complex therapeutic setting while facing the physiologic and psychologic burden of a cancer diagnosis. The objective of Onkolotse was to improve personal support of patients and their relatives along the patient's treatment path and across all medical sectors, inpatient and outpatient care, by specifically trained aides called "Onkolotsen". An important aspect of the training is to improve patient education and therapy adherence (compliance). Lack of adherence (non-compliance) could amount to 7.5-10 B € additional annual healthcare cost in Germany.

The development of the concept for Onkolotse started in 2009, with the first training and implementation being supported with a grant of the Saxon State Ministry of Social Affairs and Cohesion supported with EU funding. Today, Onkolotsen are not only providing patient support in Saxony, but in many parts of Germany and have since 2019 been included in nursing care

[2] *Arzneimittelmarktneuordnungsgesetz; engl. Pharmaceutical Market Restructuring Act*
[3] *The term "Onkolotse" is a combination of two words: "Onko" meaning "Cancer" and "Lotse" meaning "guide" or "navigator", a term which is frequently used in shipping or in aviation. A direct translation could be "oncoguide".*

insurance remuneration schemes. However, reimbursement is not fully available for hospitals or practices yet. Studies to demonstrate cost effectiveness are ongoing, partially in collaboration with statutory sick funds. He described the benefits of the approach for patients, who need orientation and whose therapy adherence is improved, which is critical for therapy success. It is important to allocate sufficient time to support and pass on knowledge to the patient, which is essential for patient participation, but which would overburden doctors. He outlined factors that reduce therapy adherence and described how Onkolotsen can ameliorate their effects in practice, giving examples from pharmacies, and doctor practices.

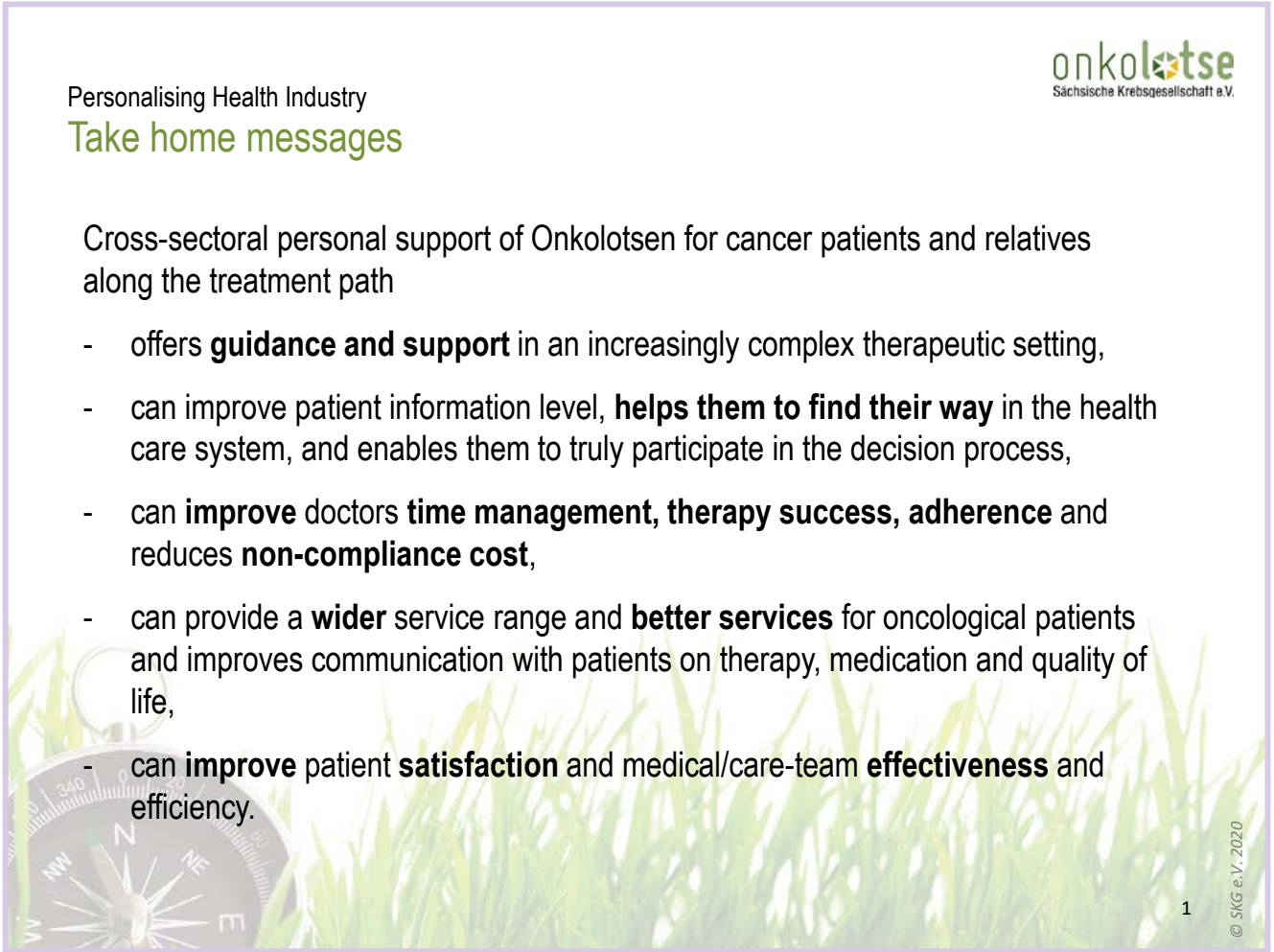


Figure 26: Benefits of the Onkolotsen Approach (Sächsische Krebsgesellschaft e.V.)

Conclusions of Session IV

Session IV covered a diverse set of topics, some relating to prior sessions, so that some cross reference is integrated here.

Disease registries are an important tool for collecting and combining patient and disease data in a standardized fashion, making these available and usable for PM supportive research, patient recruitment for clinical studies, and improving personalised patient care. By integrating patient perspectives through patient involvement in their set-up, it is ensured that they serve patient needs best. For the development of PM, they may be particularly useful, as they have the potential of collecting and combining in-depth information on patient variations. However, it is important that they fullfill quality standards.

As most registries typically target rare forms of disease with the aim of bringing together regionally disperse information, registries may not be a first aim of regions per se, but they need to be hosted in the context of medical specialisation. This may well be supported by regions, however, it could and should also be supported and coordinated on higher levels of governance.

The economic assessment of PM is not trivial. It is yet undecided whether entirely novel models are needed and prove useful in practice. However, it seems almost certain, that in the longer run, a more dynamic framework for PM may be needed in which regulators and payers collaborate on assessing relative safety and efficacy early on before market approval to align expectations and allow for faster market access and reimbursement decisions. This is very much in-line with the assessment of Hans-Georg Eichler (Session I) about a more fluid understanding of what a drug is, also including a need for repeated reimbursement assessments.

The use of guidelines as information tools for the medical community (and also patients) was highlighted. Their frequent adaption is particularly important when medical treatment options evolve more rapidly. It became evident that PM cannot yet be seen as a standard approach in oncology guidelines.

The concept of Onkolotsen was shown to be a valuable tool for patient support in an increasingly complex therapeutic environment. Patient guides could become a valuable and well transferable approach to support PM introduction as one of their aims is patient education. Though in the long-term perspective needing integration in general reimbursement plans, with regional support this approach could be useful for advancing PM introduction.

2.7 Main Outcomes of the Conference

Scientifically, PM is developing with increasing velocity. It is fundamentally relying on leveraging data, by assembling, connecting, and properly analyzing it and thus making use of ever-increasing amounts of patient and disease related data. By aiming to gain a deeper understanding and knowledge of disease, improved therapeutic interventions tailored to the individual patient are being developed. To enable this, handling of data needs to be developed along the lines already outlined in KA1 (see report). Next to interoperability, further standardization and development of shared meaning and definitions will be essential. This can be achieved to some degree by grass-root activities and scientific interaction. However, high level supportive policy and coordinative action to support and guide such processes will be needed including and engaging stakeholders from all areas.

Regions are well suited to develop and incentivize more relevant data development (e.g. particularly in terms of biobanking, and supporting disease registries) which is also still needed. Beyond this, they should ensure that existing (health) data within its boundaries, is de-siloed, thus making it accessible and fruitful for further research. For this, additional dedicated resources will be needed. Regions need to ensure that these processes do not happen in isolation, but in relation to outside structures and developments (e.g. novel standards and scientific communities). External linking should be incentivized. Regions that intend to support the development of PM should advance the integration of real-world-health data (RWD) in research and support further the development of novel research concepts to gain deeper medical knowledge, such as N-of-1 trials.

The implementation of PM in practice is, at least for the foreseeable future, very much dependent on the development and use of corresponding companion diagnostics (CDx), which can provide great benefits in terms of patient stratification, and also improve clinical trial success rates. Though the co-development of these products faces hurdles of its own, the time until they are broadly introduced into medical practice is too long, so that their potential frequently remains underused. Reimbursements schemes need to be adjusted to encourage their use, but also the medical community may need additional education on novel diagnostic tools. This could be regionally flanked by supportive educational programmes for medical practitioners. Development of PM should be complemented by installing patient guides that support patient health education and orientation within changing health systems and expanded treatment options in the context of PM that bears a risk of becoming enigmatic for the average patient.

IP is a critical pre-requisite for commercial development of PM interventions and products, especially for start-ups requiring funding. IP rights show loopholes in areas highly relevant for PM. The lack of adequate IP protection likely represents a stronger hurdle for start-ups and SMEs than for large incumbents (multinational pharmaceutical companies), which can fund development projects on their own. To adjust IP regulation to PM needs, high level coordinated policy action is needed.

Also, availability of funding needs to be addressed further and on all levels as it is highly relevant for high risk company-formation and growth: pre-seed, seed, start-up and growth-capital needs to become better accessible. Access to equity capital is too limited which is a significant blocking point for the entire industry; also restricting the development of a supportive financial ecosystem that could fertilize industry development. High level cooperative policy adjustments are needed on EU and MS levels to ensure sustainable and balanced approaches of sufficient momentum. Regions that are offering or contemplating supportive PM funding schemes should ensure their alignment to other instruments. Translational PM supportive structures that reduce risk could be a viable approach for regions; however, to become effective these need sufficient scale. Supportive policy development on this level may prove useful. A long-term perspective is important for both. Interregional exchange and cooperation between supporting entities should be encouraged to ensure and facilitate interregional knowledge transfer for mutual benefit. Regional availability of adequately trained human resources needs to be secured. Regions should develop supportive schemes to ensure availability of highly qualified HR in specialized fields.

KEYWORDS:

#federated health data
#biobanks
#patient registries
#N-of-1-trials
#IP protection
#CDx
#companion diagnostics
reimbursement
#market access
market penetration
#equity funding
#translational support
#risk reduction
#guidelines
#patient guides

3 Key Area 3 Interregional Workshops

3.1 Outline

Following the outcomes of the conference in October 2020, and due to pandemic-related delays in KA2, it was decided to organize two virtual workshops in April and May 2021, putting a focus on specific aspects that were extracted from the conference.

The hosting partner was again the Saxon State Ministry of Science, Culture and Tourism (SMWK), who organised virtual workshops on April 25th and May 19th, 2021.

The programme of the workshops was derived from the outcomes of the conference. For the workshops the analytical concept of value chain was complemented by the concept of regional innovation ecosystems thus introducing a shift in perspective. Along these lines the workshops enabled a more regionally focused discussion about the barriers and needs of a personalising health industry. European stakeholders and regional authorities with an interest in PM were invited to reflect viable approaches in terms of investments and policy.

Therefore, the workshops served to elaborate priority actions to be communicated and disseminated to European regions and policy makers. With this goal in mind, all speakers had been selected according to their expertise and their ability to trigger a debate.

Both workshops have been organised with the purpose of leaving sufficient time for the discussion. As the focus was on the overall topic of personalising health industry, again, industry representatives (SME, large company, industry association) were invited to open each workshop with an industry-focus session which was then followed by a session on regional best practices.

The two workshops have been planned as follows:

- **Workshop I** (April 28th, 2021) focused on the Saxon PM R&D innovation ecosystem with a special focus on advanced therapy medicinal products (ATMPs), among which are the most personalised therapeutic health products on the market to-date. The first session was dedicated to industry contributions with a focus on ATMP, while in the second session best practices from the Saxon PM R&D ecosystem were presented, broadening the focus beyond ATMP to provide a comprehensive insight. This was followed by a poll and plenary discussion.
- **Workshop II** (May 19th, 2021) was dedicated to translational ecosystems for PM. Again, the workshop was opened with a dedicated industry session, followed by a session providing best practices on translation from all over Europe. Again, this was followed by a poll and a plenary discussion.

The workshops were moderated by a regional expert (cluster representative of Healthy Saxony e.V. and biosaxony e.V.) and a representative of SMWK.

Speakers were prepared by teleconferences ahead of the events to elaborate on the topic and to identify challenging questions, aimed at triggering the debate among participants.

There were overall 134 attendants in both workshops coming from 17 different countries. 18 regions were represented by 78 regional participants. The largest group of the audience were representatives of regional/national organisations and authorities in relation to policy development.

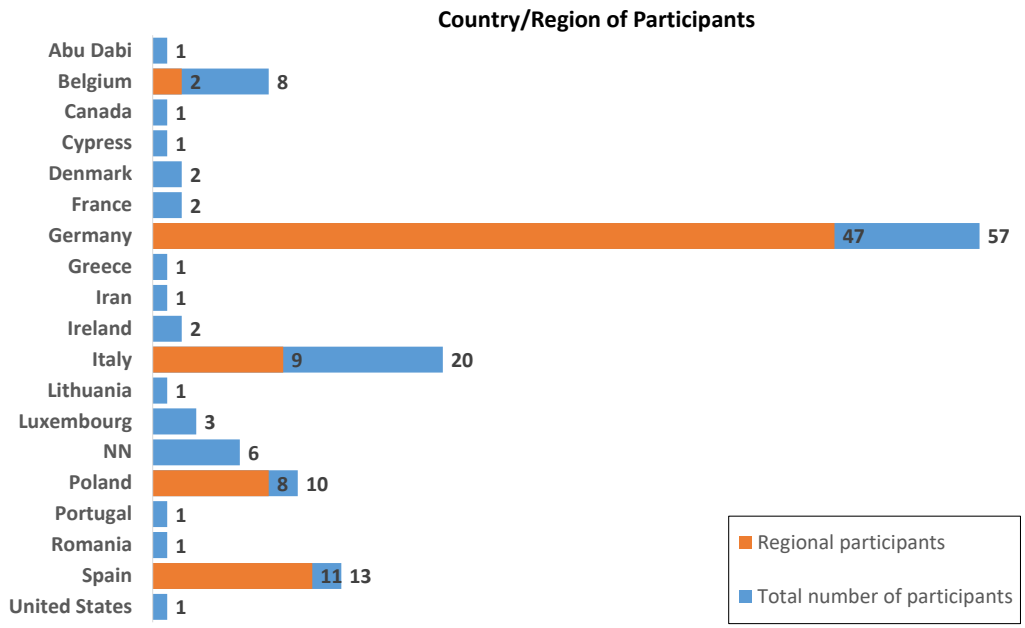


Figure 27: Participation in the Workshops by origin

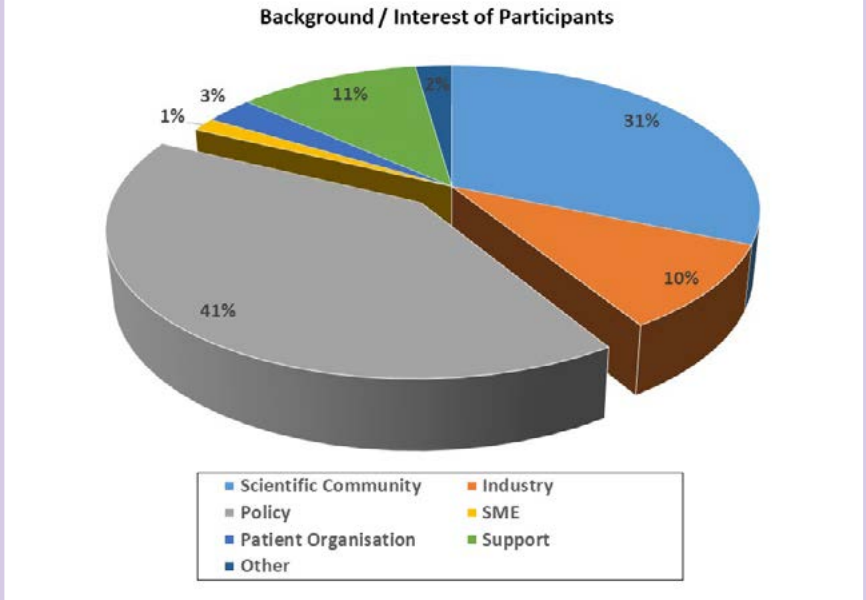


Figure 28: Affiliation of Workshop Participants

3.2 - Workshop I: A Regional R&D Ecosystem for Personalising Health Industry – Spotlight on the Free State of Saxony

3.2.1 Opening

The workshop was opened by **the state minister of the Saxon State Ministry of Science, Culture, and Tourism, Sebastian Gemkow,** who highlighted Saxony as an innovative region engaged in PM, pointing to recent developments in Saxony such as the creation of SaxoCell and SaxoChiLD as well as the recently founded Else-Kröner-Fresenius Center for Digital Health. This was followed by an introduction to the Regions4PerMed project by **Gianni D'Errico, Tuscany Life Sciences Foundation**, who coordinates the consortium.

3.2.2 Session I: Health Industry Perspective on Regional Ecosystems for Personalised Medicine and Health

Thorsten Ruppert (vfa, Germany) presented **advanced therapy medicinal products (ATMP) with a focus on regional aspects in R&D ecosystems to consider.** ATMPs include gene and cell therapeutics as well as bioengineered tissue products. These are gaining increasing attention in the medical community due to their high therapeutic potential. After the first EU approval of gene therapy in 2012, 12 ATMPs have been centrally authorized in the EU so far (9 gene therapies, 1 cell therapy, and 2 tissue therapies). Six additional products are in the EU approval process. Worldwide there are more than 1000 clinical trials ongoing in the field of ATMP, 75% of which are cell-based and non-cell-based gene therapies and approximately 20% are cell-based therapies, with the majority of projects in *clinical phase II*. Diverse indications are addressed, mostly from oncology, but also in tissue regeneration and for the treatment of cardiovascular disease and a variety of rare diseases. In Germany a steady increase in gene-therapy trials could be observed over the past decade. However, in international comparison, *Germany* lags behind the leading US (ca. half of trials) and China (ca. 40%), as it counts for *only 4.4% of all trials worldwide*. According to vfa, this is due to a *lack of readiness for funding private business activities in this field (in particular lack of venture capital),* which is *problematic particularly for SMEs.* vfa also points out that translation takes longer in Germany, e.g. to prepare a clinical trial and prepare the necessary contracting. Innovation friendliness is limited. There are too few functioning ATMP networks and a lack of ATMP production facilities. Showing data for CAR-T-trials, a similar picture emerges as in the case of gene therapies in general (see figure 29).

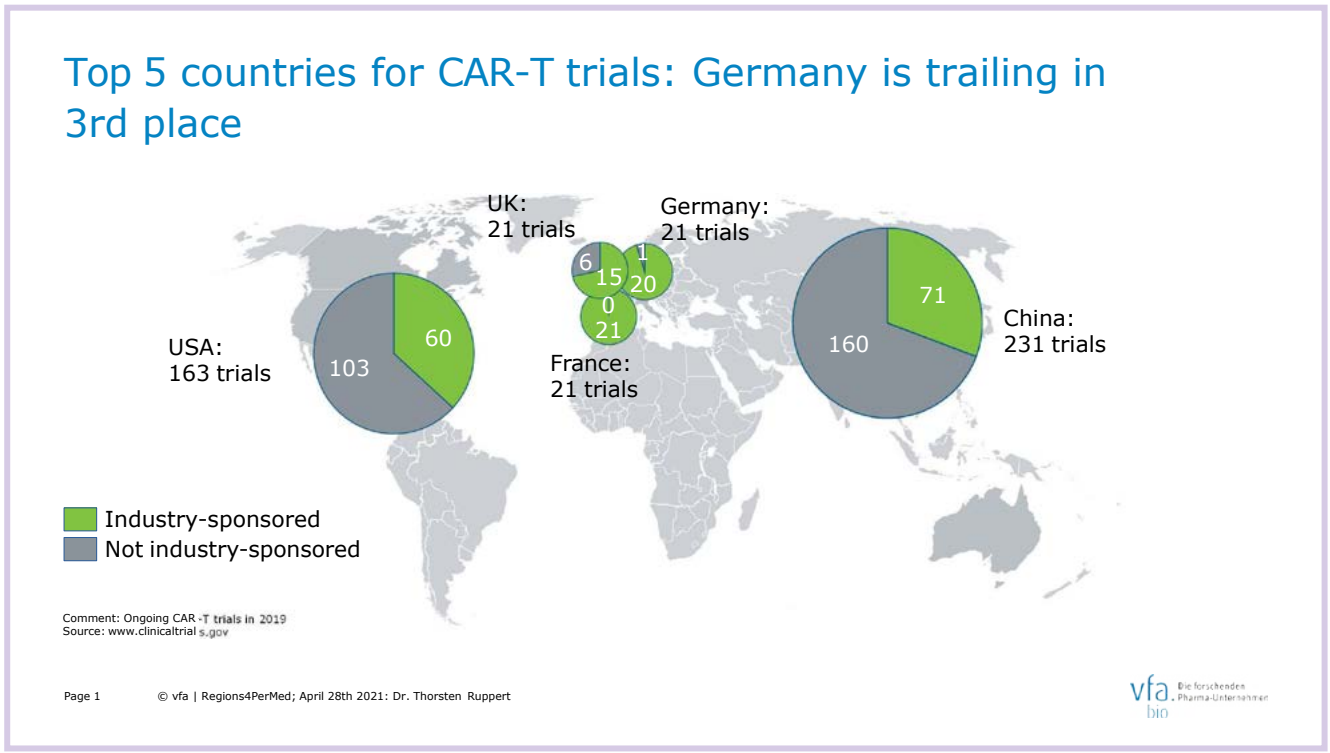


Figure 29: CAR-T Cell Clinical Trials Worldwide in 2019 (vfa)

There is a need to take action on the national level to create a more innovation supportive ecosystem for ATMP development. In the context of ATMP, vfa suggests to:

- *establish a German centre of health research for ATMP,*
- set up an *ATMP task force to harmonize the requirements for clinical trials* within Germany which would benefit from regional harmonisation,
- provide *better staffing at relevant regulatory institutions* to speed up processes and provide more regulatory guidance to SME, and also
- *support education and training personnel* to expand capacity, and lastly
- *close the funding gap for hospitals, as reimbursement for ATMP therapies* is difficult in practice, making these hard to access for patients.

Oliver Stenzel (Novartis Deutschland GmbH, Germany) discussed **what makes a region attractive for an established large player with an interest in PH and ATMP.** He set out with the recognition that *regional exchange is important.* Novartis is an international corporation focusing on the development of new ground-breaking innovation for healthcare. In 2019 Novartis launched five medicines worldwide based on novel

therapeutic approaches, including a gene therapy to treat rare diseases. Operating 10 sites in Germany with more than 7.000 employees, Novartis is involved in many innovation supporting activities, including the German "Dekade gegen Krebs" (Engl. Decade Against Cancer) and has invested more than 25 B € in R&D in Germany over the past 10 years. Partnerships with scientific institutions are of central importance for the R&D activities of Novartis.

Regional clusters are highly relevant for investment decisions by large companies. The potential pool of skilled labour and the connection to the scientific ecosystem are decisive. Due to existing well-established collaborations, Novartis is the pharmaceutical company conducting the most clinical studies in Germany (169 studies in 2020, 44 in early phase) and highly appreciates Germany's good scientific structures and science base. However, as a research location Germany risks falling behind as it is losing ground in terms of clinical studies, being now in fifth place compared to formerly second. Therefore, Germany 's clusters and science regions should work together to promote it as a research location. Generally, regions need to engage more actively in politics to remain attractive. This is true for *science regions that are researching advanced therapies* and that *are dependent on good framework conditions in the long term*. As these *research conditions are increasingly formulated in Brussels*, regions need a *commitment to Europe as a research location*.

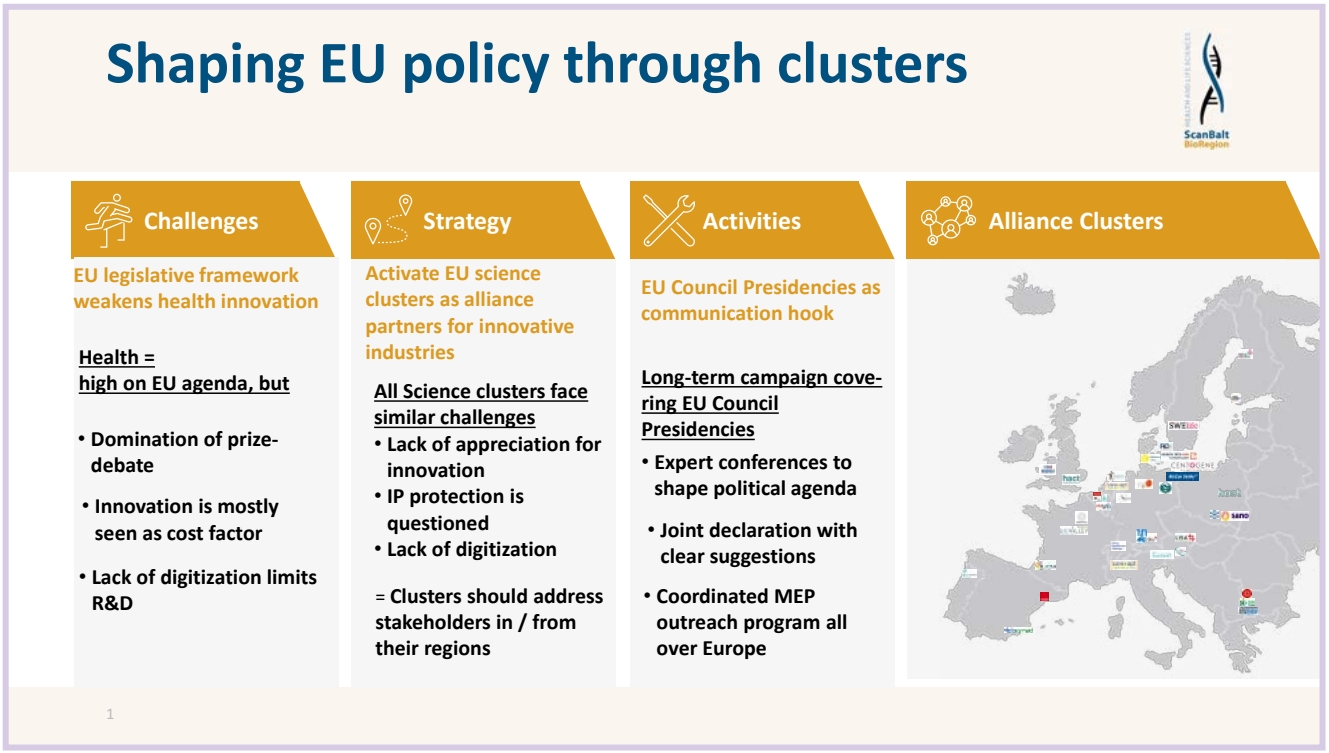


Figure 30: Scanbalt – Interregional Cluster Cooperation and Coordination (Scanbalt)

He described the engagement of Novartis within Scanbalt, a multiregional cluster organisation; founded in 2001, containing a large and wide range of partners from European regions, located around the Baltic Sea that *collaborate in the field of life sciences representing their regional health ecosystems.* Scanbalt wants to support upcoming EU projects, e.g. the creation of the European Data Space for R&D from the perspective of science regions. Oliver Stenzel pointed out that *EU legislative framework weakens health innovation as* the debate frequently centres on cost and price, especially in context of ATMP, while at the same time *lack of digitization is hindering R&D and market access.* In this context clusters face similar challenges such as a lack of appreciation for innovation, *problematic IP protection, lack of digitization* and can join to raise the word for R&D in Europe. He voiced *a need for regions to be directly engaged in Brussels*, including participation in consultations of the European Commission, dialogue with members of parliament, regionally, nationally and at the European level.

Wolfgang Knirsch (vita34, Germany) presented an **entrepreneurship perspective** on the **PH ecosystem in Saxony**. Vita34 AG is a private stem cell bank founded in 1997 in Leipzig and has been listed in 2007 on the Frankfurt Stock Exchange. The company has followed a steady growth strategy, including market expansion by acquisition of other stem cell banks to expand internationally, with its main market being Germany. With two central labs, in Leipzig and Rostock, the company is operating one of the biggest (private) stem cell banks in Europe, storing more than 250 thousand sample-units[4]. Whereas public cord blood banks store donated samples for free for public use (mostly for hematopoietic applications), the *business model of vita34 is based on a fee-for-service concept* for long-term storage of umbilical cord blood and tissue for private use (with public donation possible). The use of the stored material is restricted to the contractor of the given sample who can use the cells as a repository for a personal(ised) therapy later in life, if needed. There is a quality advantage of cell storage early in life. With contractor consent, public donation is feasible using a pre-defined process. Such HLA-characterized samples are listed in a publicly accessible database.

[4] *This number and all other information here is based on vita34 AG alone, it dates back to before the merger with polish biobank Polski Bank Komórek Macierzystych S.A. came into effect, which has been initiated in July 2021.*

Regions4PerMed

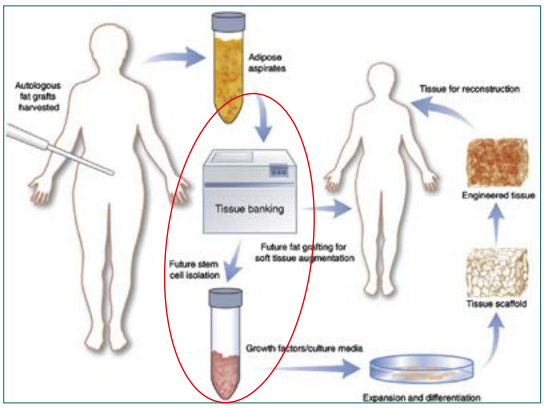
ViTA34

2) GMP process for cryopreservation of **adipose tissue** for autologous fat transplantation

3) GMP process for the isolation of **stem cells from frozen (cryopreserved) adipose tissue**

Our Goal:

- Patient empowerment ("I can preserve my own body's potential today – to get the perfectly fitting therapy tomorrow!")
- Preserve stem cells for aesthetic applications (e.g. improve texture and consistency of connective tissue)
- Preserve stem cells for use in regenerative therapies (e.g. apply fat tissue-based stem cells to improve wound healing in wound healing disorders)
- Preserve stem cell potential for future therapies which "might grow from basic research tomorrow"



Shu et al., 2015. "Update on Cryopreservation of Adipose Tissue and Adipose-derived Stem Cells." *Clinics in Plastic Surgery*

Figure 31: *vita34 – Potential Uses of Stem Cells From Adipose Tissues*

So far, vita34 reported 48 applications of stored samples, mostly for restorative therapy, with demand increasing in the last years. This use is in-line with reports from the US, where larger data sets are already available. For the future vita34 expects more interest in cell-based personal(ised) therapeutics. A service-expansion including more cell-types is thus part of its corporate strategy, e.g. adipose tissue, immune cells (e.g. for CAR-T cell therapy), and stromal vascular fraction.

The regional ecosystem in Saxony was and is important for vita34's corporate development: logistics (truck, train, and plane) are favourable in Leipzig, which is a DHL hub, the existence of a well-equipped biotech-incubator providing lab and office facilities, and the proximity to technologically fitting specialised academic/institutional collaboration partners like Fraunhofer Institute for Cell Therapies and Immunology, and University Clinic Leipzig. Early-stage financial support and availability of well-educated employees were important for company growth, though this could become a bottleneck in future, as demand of qualified staff is growing in the region. Reliable timelines for regional approval processes are very critical, as delays can lead to missed business opportunities.

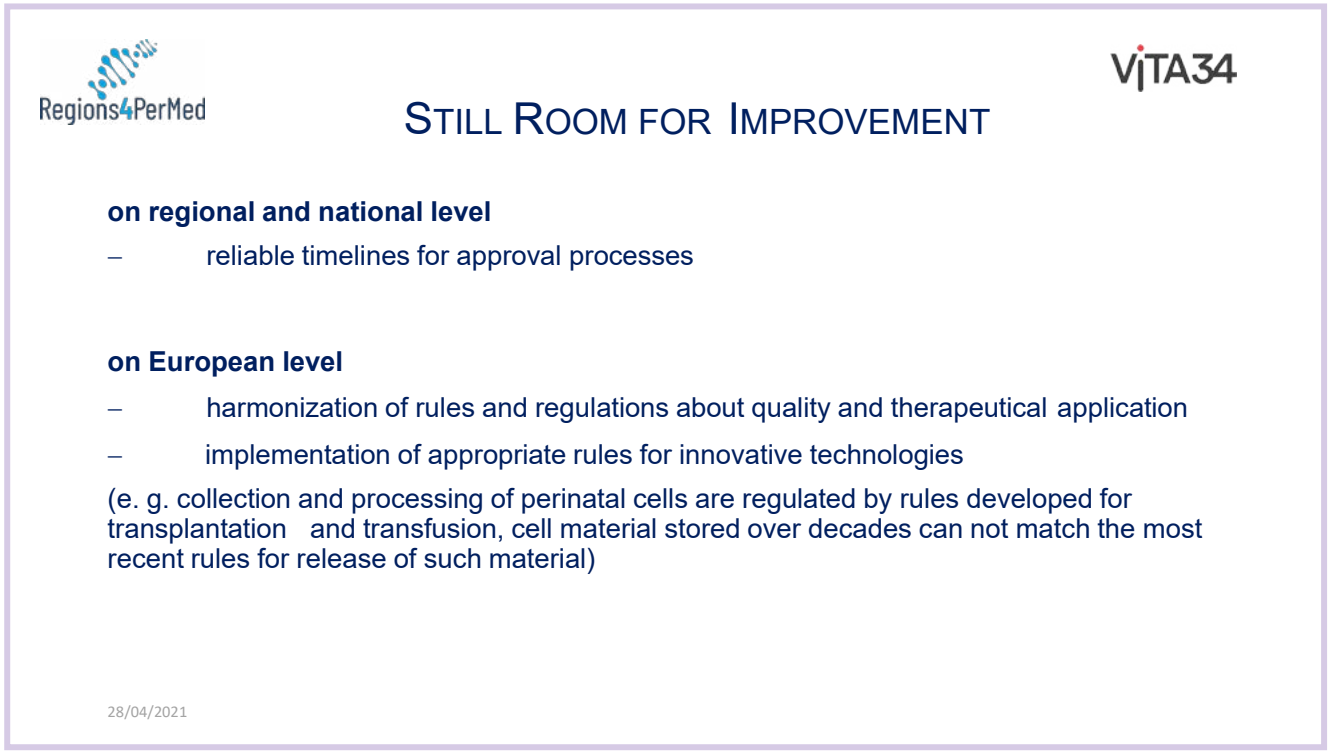


Figure 32: Room for Policy Improvements (vita34 AG)

On the European level Wolfgang Knirsch identified *a need for further regulatory harmonisation of quality and therapeutic applications* and especially a need for adaption of existing rules to better fit novel innovative technologies. This adaption process is currently taking too long, so that existing regulation increasingly becomes a hurdle.

Conclusions of Session I

For personalising health industry, the quality and set up of the respective regional innovation ecosystem in which industry participants operate is of central importance.

A major part of EU economy is based on regionally embedded SMEs. To facilitate growth of the latter, and also to attract internationally operating corporations, access to excellent science, qualified personnel and well organised logistic settings of a region are pivotal.

Especially for SMEs and start-ups other factors, such as pre-existing well-equipped facilities (e.g. bio incubators), early funding support and access to growth-capital may be equally relevant. Frequently, the access to (debt) funding to set up new facilities is scarce. Lack of funding (including risk capital) may be the most critical bottle-neck in otherwise well-furbished ecosystems.

At the same time, for the successful regional development of an innovative industry, a supportive and reliable regulatory setting is paramount. Much of this regulation is beyond the scope of regions, as it is determined either on national or on EU-level. However, ethics committees authorizing clinical studies, for instance, are regionally embedded. For Germany, vfa and others explicitly named the need for a German Research Centre of health research for ATMP to progress the field, and equally important to create an ATMP task force to harmonize clinical trial regulation in Germany.

A need to adapt regulation on EU level has been repeatedly voiced, as well. To support their health research ecosystems, regions could function as ambassadors and supporters for their industries, collaborating to improve the regulatory settings on national and European level.

3.2.3 Session II: Elements of the R&D Innovation Ecosystem for Personalised Medicine and Health in the Free State of Saxony

Ulrike Köhl (Fraunhofer Institute for Cell Therapy and Immunology, Germany) presented **SaxoCell – expanding and developing regional strengths in the field of ATMP through collaboration.** SaxoCell is a newly formed cluster for early transfer in which Saxon research institutes and academic groups (38 in total), and many industry partners in and out of Saxony, participate. It received a three-year funding of up to 15 M € from the Federal Ministry of Education and Science (BMBF) in the **Clusters4Future Programme.** The project aims to bring novel ATMP products more speedily to the patient. It may receive up to 45 M € for a total of 9 years to develop novel gene- and cell therapeutics.

There will be a paradigmatic change for future medicines: today, most medicines consist of chemical compounds that need to be continuously taken based on a symptom-guided diagnosis. Future precision medicines will consist of immunotherapies and also genome-editing and gene therapies. There will be one-time treatments generating a (life-)long-lasting healing impact. This paradigmatic change will be applicable for many indications, especially monogenetic diseases, cancer, cardiovascular- neurological, and also infectious diseases. First examples are the successful treatment of chronic granulomatosis patients with gene-therapy, and the application of CAR-T cells which show high success rates in leukaemia and lymphoma. In Saxony, UniCAR-T-cells were developed for the treatment of acute myeloid leukaemia. However, many challenges remain: the area of use for patients is still restricted to a few indications; long-term product safety needs to be proven; production processes are still costly and time-consuming. The translational gap needs to be closed: only a fraction of all global clinical trials take place in Europe in these fields (less than 10%), while most activity locates in the U.S.A. and Asia. SaxoCell envisions to change this by becoming Europe's Hub for ATMPs (see figure 33).

The SaxoCell network presents strong skills:

- **innovation,** having access to novel ground-breaking ATMP technologies,
- **GMP manufacturing** (+21 cleanrooms), being the largest academic GMP facility in Europe that is providing CAR-T cell production services for large pharma (Novartis) which is covered by a comprehensive proprietary patent portfolio,
- **broad clinical network for ATMP development** that are already conducting studies and are able to bring a product from the lab to the patient in five years.

This set up was possible, as Saxony was successfully developed as an innovation region since 1990[5] offering excellently trained staff (scientists, doctors, specialists), a well-developed networking-culture, brought forward by a cooperative mentality that is allowing for comprehensive synergies, a business-friendly environment, characterized by comparatively low cost and supported by a favourable logistics infrastructure. In this ecosystem, SaxoCell plans to accelerate the development of ATMP for the benefit of society.

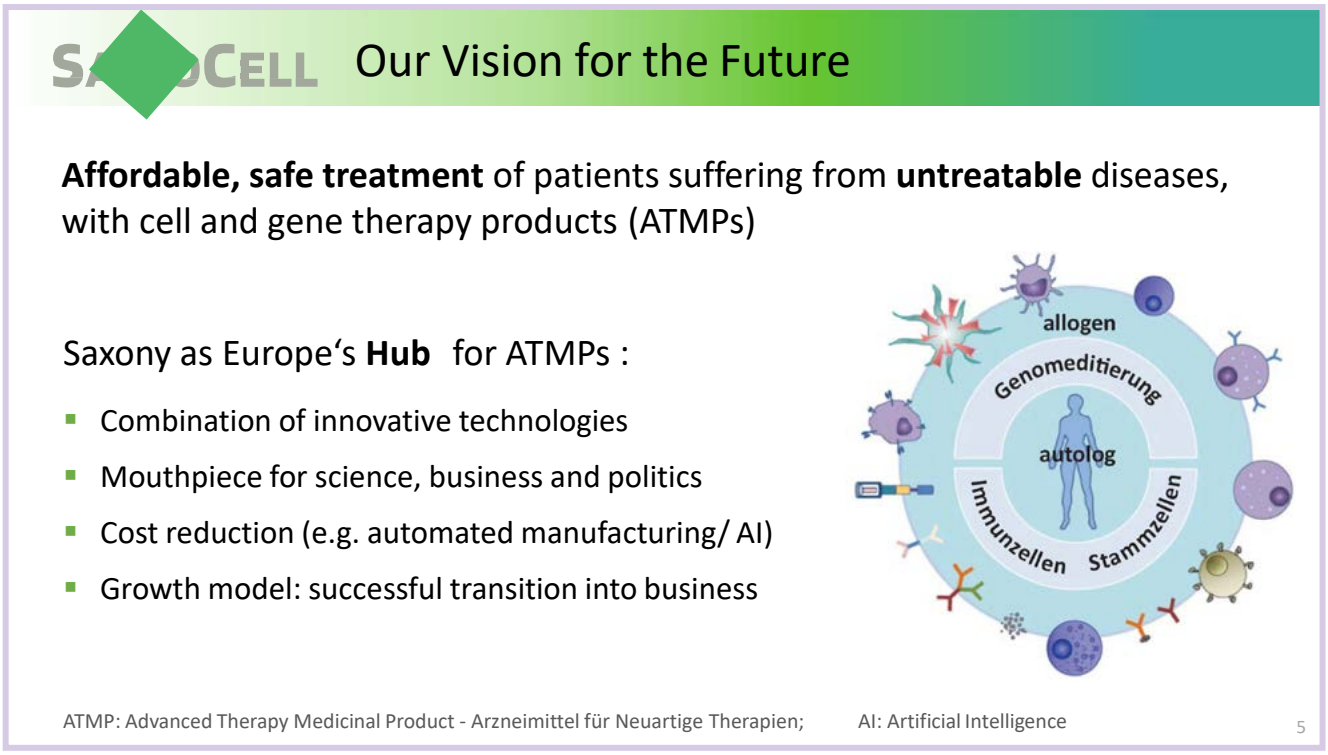


Figure 33: SaxoCell - a Hub for ATMPs in Europe (SaxoCell)

The consortium is focusing on twelve projects ranging from development to the clinic, most with oncologic focus, e.g. one project centres around a clinical platform comprising automated manufacturing of allogeneic bi-specific CAR NK cells (CAR NK 4.0) for myelodysplastic syndrome (MDS). An innovative infrastructure was developed encompassing biomarker-based patient stratification (SaxoCellOmics), integrated automated manufacturing processes (SaxoCellSystem), a clinician network (SaxoCellClinics) which are supported by a pipeline accelerator programme (PAP) for project management, an innovation culture programme (ICP)

[5] *Year of German re-unification. Saxony is part of former German democratic republic, that had followed a communist concept and was economically in a problematic situation, when it ended peacefully in 1989.*

and a cluster matching program (PCP) which aid business transfer. The consortium is following a long-term vision making ATMP affordable and thus accessible to broad patient groups with many different indications and the aim to heal disease instead of ameliorating symptoms. The consortium envisions regional economic benefit through the creation of new jobs, spinouts, novel academic training programmes, and in the long-term establishing SaxoCell as a leading cell and gene therapy location in Europe, becoming a future industry-base in the field.

Uwe Platzbecker (University Hospital Leipzig, Germany) spoke about **coordinating research in the field of myelodysplastic syndromes (MDS) - EMSCO and D-MDS**. MDS is one of the most common haematological disorders, but still a rare disease with incidences of 4-5/100.000 in the population but rising with age (30/100.000 in patients >70 yrs.). In an ageing population, the general prevalence of the disease is thus rising, expanding the need for new and better therapies. The disease is diverse, clinically characterised by cytopenia of different blood-cells, and is considered a pre-leukemic condition. 30% of patients develop leukaemia, which is hard to treat, especially in elderly patients. He outlined treatment options for patients, showing that there are many novel therapeutics under investigation. It is increasingly possible and necessary to better stratify patients using biomarkers. However, as the disease is diverse and showing a complex pathophysiology, defined markers (e.g. genetic mutations) corresponding to specific symptoms may be extremely rare, so that patient-subgroups are very small. A coordinated research approach across larger populations is needed to enable recruitment of sufficient patients in clinical studies for developing therapies for such complex diseases, requiring national and international collaboration.

International collaboration encompasses additional challenges, such as language barriers (increased risk for misunderstandings), regulatory differences, and diverging requirements of authorities, different budget requirements, and also more complex logistics. To address these challenges and to foster clinical trials in MDS within the EU, Uwe Platzbecker together with Pierre Fenaux (Paris, France) founded an international European platform for clinical research in MDS, called **European Myeolodysplastic Syndromes Cooperative Group, EMSCO**, with initial support of the European Leukaemia Network. EMSCO has steadily grown and now includes partners from several countries that are joining efforts for new research projects and acquiring funding. *Funding of investigator-initiated-clinical research* has greatly improved in this setting in comparison to projects initiated by a single researcher, as *large pharmaceutical companies prefer collaborating with networks* instead of stand-alone university

hospitals. The *consortium is self-sustained* (no external long-term funding; studies funded by industry collaboration or public grants) with five completed and three ongoing clinical studies, and four in preparation. EMSCO hosts regular meetings and conferences, has developed an MDS App and is involved in guideline development. Also, a national study group (D-MDS) was set up in Germany to enhance collaboration between MDS centres, which organises scientific exchange (bi-annual meetings) and has installed a MDS registry and a biobank (again, without dedicated external funding).

Looking to the future, Uwe Platzbecker depicts *a comprehensive system of patient stratification*, including clinical data, patient reported outcomes, and multi-omics data integrated by complex data analysis and modelling tools (machine learning, prediction models) to better target patient subgroups. An ongoing research project to better model the disease aims to set up a *virtual tumour board* offering AI-based risk stratification and suggestions for personalised treatment, including also information on ongoing clinical trials as this information is particularly hard to obtain, even for specialists. He also noted that bureaucratic hurdles for clinical research have increased and become significantly more complex over the last five-ten years.

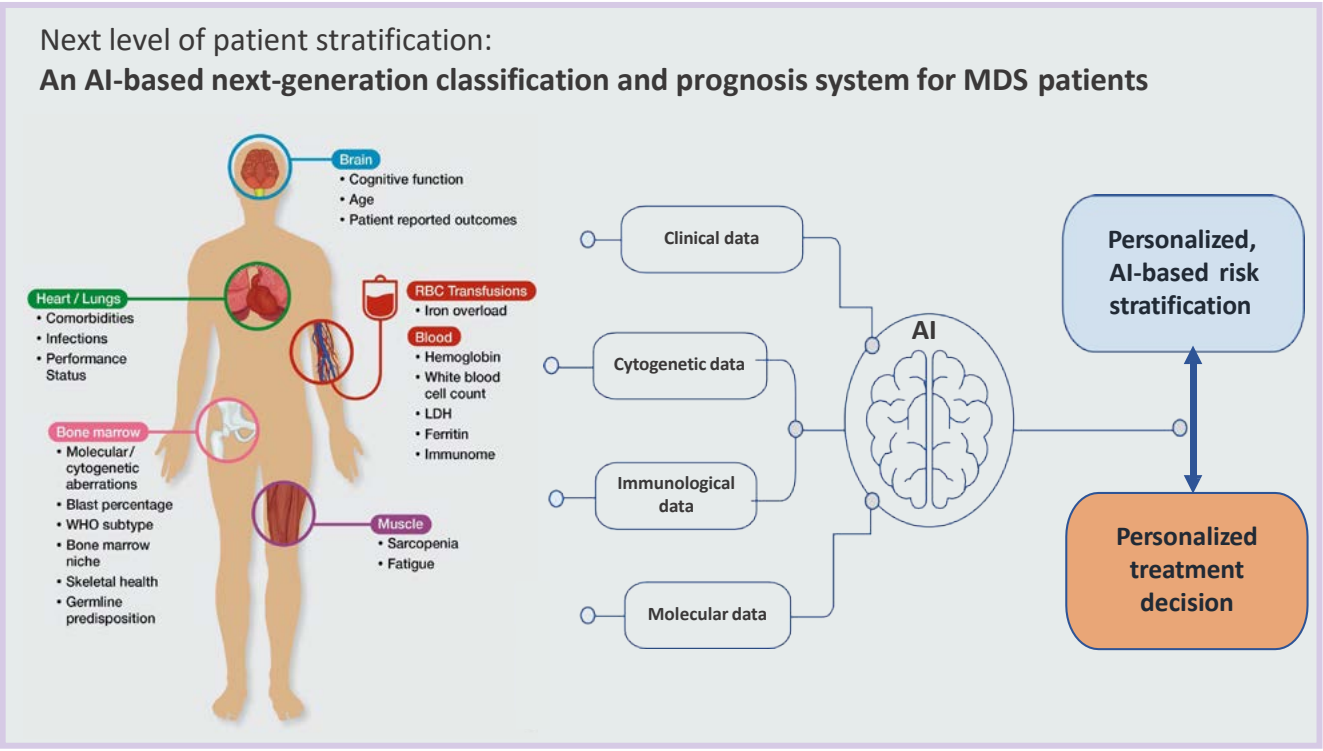


Figure 34: Next level of Patient Stratification in MDS for Personalised Treatment (Uwe Platzbecker)

Jacques Rohayem (GWT-TUD GmbH, Germany) presented the GWT-TUD GmbH[6], which is a fully owned daughter of the TUDAG, a holding society of Technische Universität Dresden that markets innovation generated within the university. GWT-TUD was founded 25 years ago with the aim to support *science and knowledge transfer from the university to the market*. The company has a strong focus on medicine, and industry solutions, and operates three subsidiaries in Dresden, Berlin, and Rossendorf. The company has a turnover of 24 M € p.a., 200-250 employees, and serves as a CRO, having run 300 clinical trials and studies, more than 550 R&D projects, numerous scientific studies, and also organises scientific meetings for customers from more than 30 countries. Having developed a broad expertise in clinical trials, the company supports eleven ongoing clinical studies and has *sponsored 35 investigator-initiated trials since 2005.* GWT-TUD is also operating an epidemiologic centre that is managing registry trials with the aim of improving personalised treatment plans and hosts an early clinical trial network for phase I/IIa studies, providing hands-on support for customers. Indications the supported are in oncology, haematology, dermatology, vascular diseases, and diabetes/metabolic diseases. Across Europe, the company has eleven cooperation partners for conducting clinical trials in different set-ups (see figure 35). Several examples were presented.

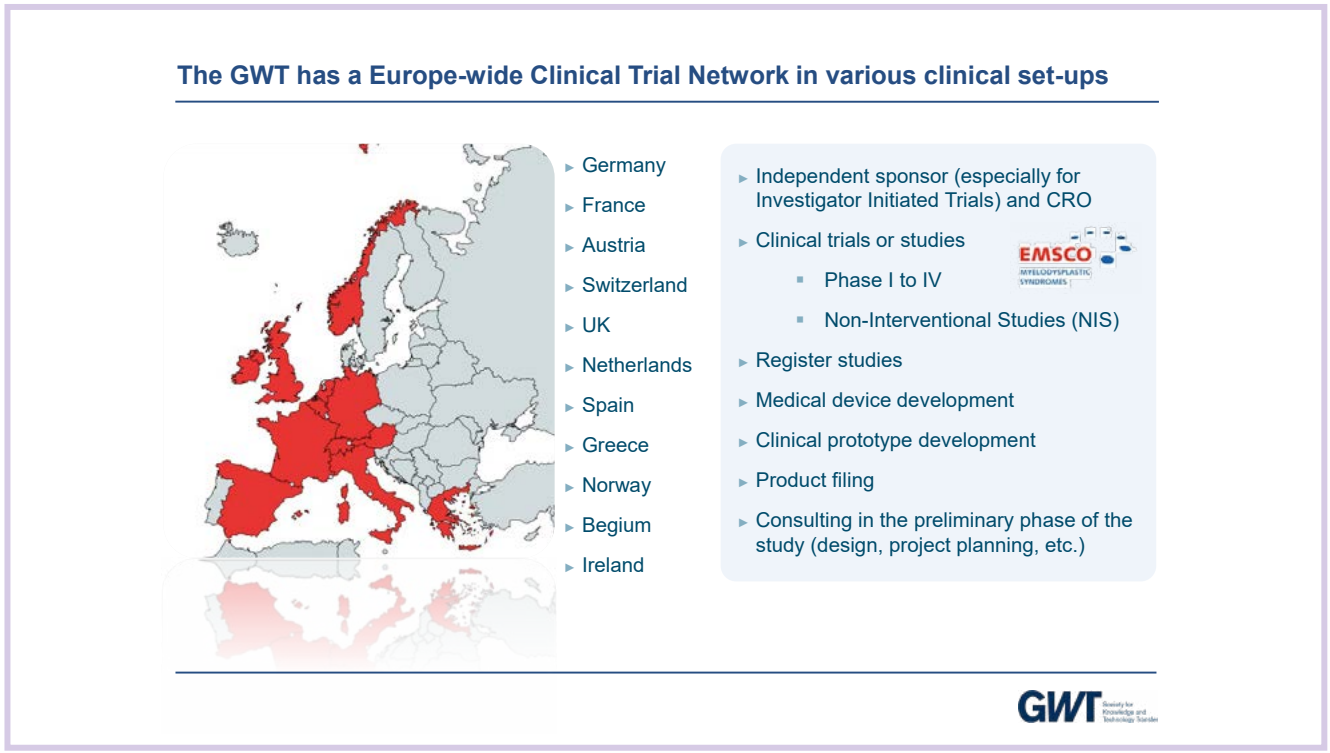


Figure 35: Geographical Network of GWT in Europe for CRO Services

[6] *GWT is an abbreviation for "Gesellschaft für Wissenschaft und Technologietransfer" which translates to "Society for Science and Technology Transfer". TUD is an abbreviation for Technische Universität Dresden.*

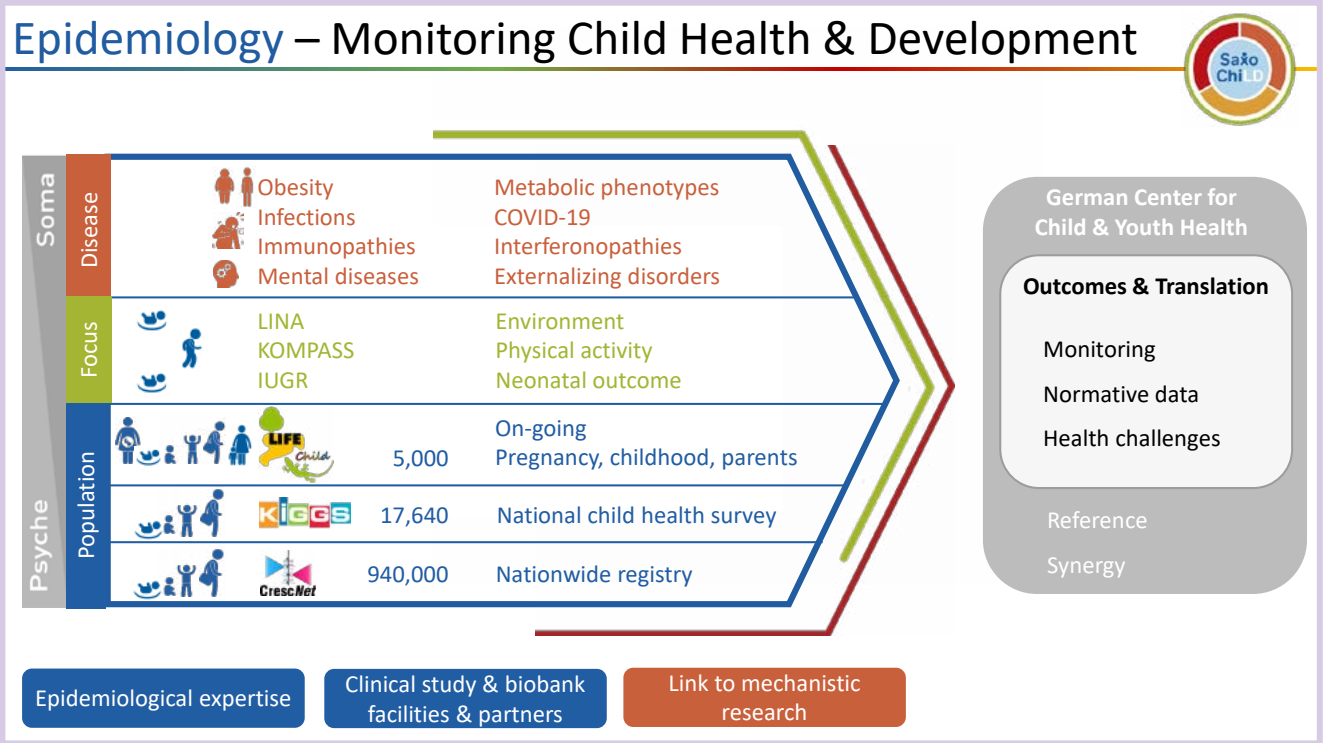


Figure 36: Epidemiologic Research Base of SaxoChiLD

Just recently, GWT-TUD has set up a Life Sciences Hub to support start-ups in the field of innovative medicines funded by the Saxon State Ministry of Economic Affairs, Labour, and Transportation. The Life Sciences Hub offers laboratory space and hands-on business development support to advance the process from the bench to the market by providing its translational expertise in medical research and development through a coaching programme.

Antje Körner (Leipzig University, Germany) presented **SaxoChiLD – Saxonion Child health innovation Leipzig-Dresden**, a new German health research centre funded by the Federal Ministry of Research and Education (BMBF). SaxoChiLD is set up as a network of regional research institutes headed by the universities of Leipzig and Dresden (co-chair: Reinhard Berner), joined by Robert-Koch Institute. Established collaborations are used, while drawing on the specialisations of the partners in the fields of epidemiology, metabolic and neurologic diseases, and oncology. SaxoChiLD's focuses on environmentally induced health risks that trigger chronic disorders originating in childhood, like obesity, immunopathy, and mental disorders. Using comprehensive cohort-based surveillance of child health and development within an environmental context, and considering predisposition, as well as psyche- and soma-interactions, risk and resilience factors

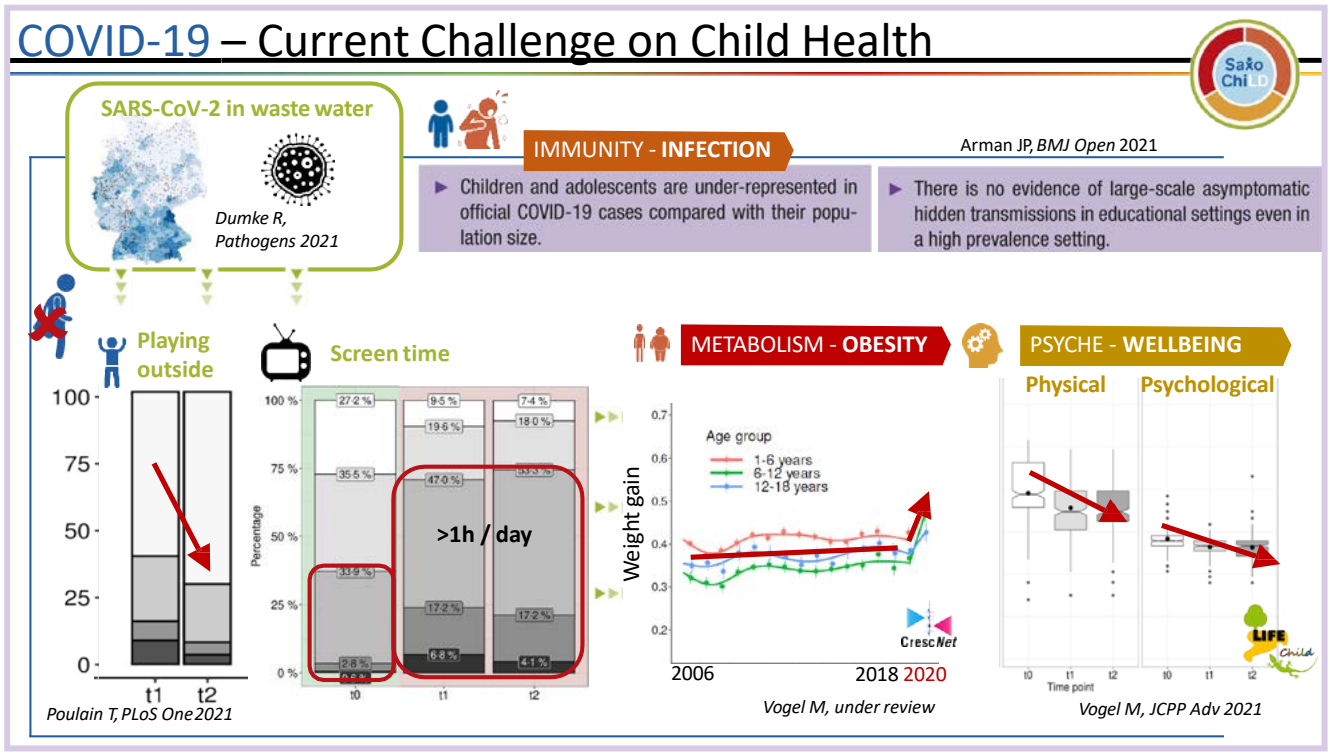


Figure 37: Research Results on Effects of Covid-19 Pandemic on Child-Wellbeing (SaxoChiLD).

are identified. This is complemented by biologic research on disease mechanism. SaxoChiLD covers the full translational chain from epidemiological studies to basic and clinical research aiming to develop novel and more precise detection, prevention, and therapy tools. The consortium keeps a unique collection of complementary active and longitudinal cohorts consisting of local and nation-wide data, covering all developmental phases and the full spectrum of clinical manifestations including environmental factors.

Using analytic platforms and innovative monitoring tools, SaxoChiLD characterises environmental drivers for health risks to make predictions and understand mechanisms, as exemplified in obesity. Vulnerable phases during development could be identified by tracking of obesity from early childhood into adulthood and risk factors and mechanisms leading to obesity and associated mental and somatic comorbidities were investigated. Environmental hazards and pollutants during perinatal period were shown to affect adipose tissue accumulation; inflammation in this tissue is a key driver for metabolic co-morbidities. Numerous psychological effects could be singled-out, e.g. stigmatization, self-esteem disorders; and opportunities for intervention were determined. Based on this, concepts for prediction, prevention and individual therapy were developed. This framework can serve as a blueprint for other lifestyle diseases.

Results from recent *Covid-19 research* showed that children were underrepresented in official statistics, compared to overall population. In Saxony there was no evidence for large-scale hidden transmission in educational settings. However, other health-effects of the pandemic on children especially during lockdowns were seen. For instance, their outside-time was strongly reduced, whereas screen-time had risen. Correlated was a steep rise of obesity and a measurable reduction of psychic and physical well-being.

The ultimate aim of SaxoChiLD is to ensure healthy development of children. How is their health supported and threatened by the environment - as seen in the Covid crisis. Re-thinking child-health and disease to not only prevailing but also new arising health challenges is needed.

Cristina Nieto (National Health Institute Carlos III, Spain) presented **ERA PerMed - coordinating research in personalised medicine and health across borders**. ERA PerMed is the biggest EU-co-funded Era-Net in health, funding research in the field of PM. It belongs to the family of activities related to the International Consortium of Personalised Medicine, a European coordination and support action advancing the uptake of PM in the EU.

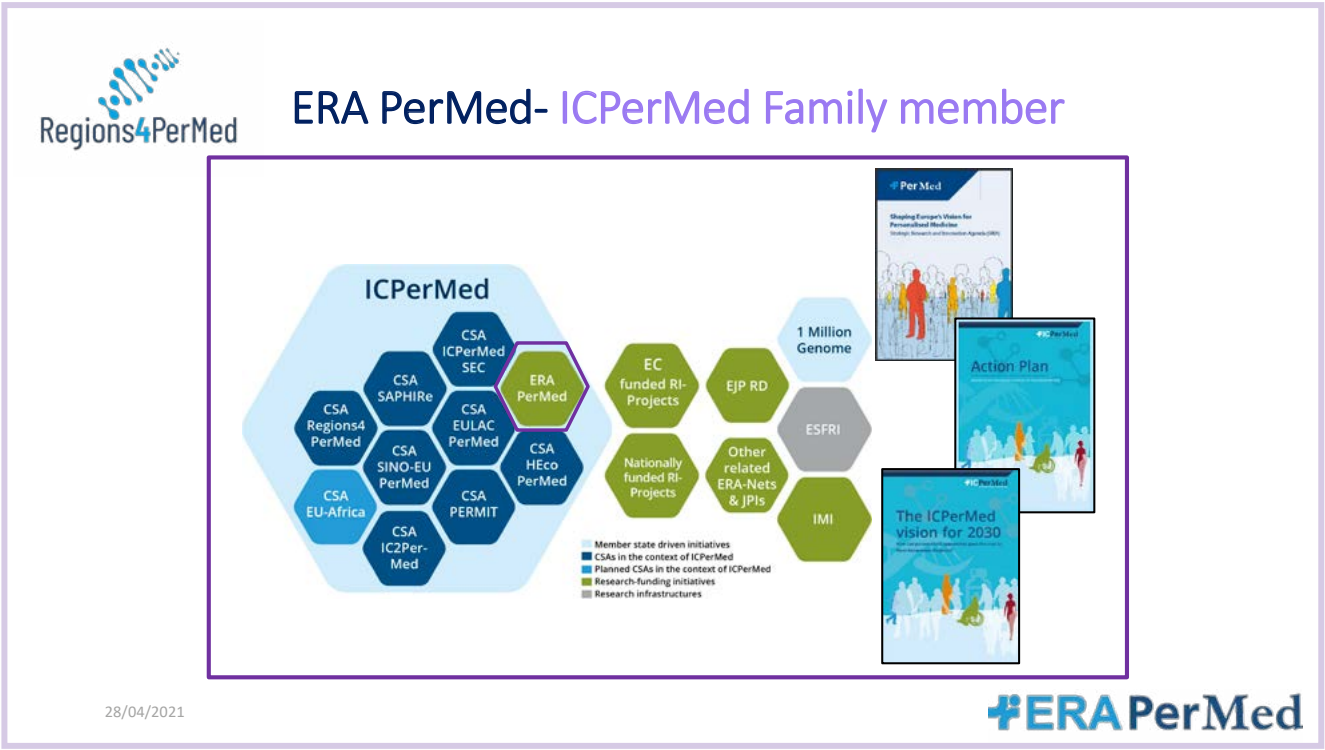


Figure 38: ICPerMed Family (ERA PerMed)

The ERA PerMed consortium includes 32 partners from 23 countries, including five regions. It has been set up for 5 years and was extended to 6 years due to the pandemic. The consortium publishes annual joint transnational calls (JTC) on PM topics that have been outlined in the EU strategic research and innovation agenda (SRIA) on PM. Participation in the JTC is also open to funding organizations from (NonEU) third countries, such as Egypt, Panama, Brazil and Chile, who joined in the fourth JTC 2021. The calls were so far well received in the scientific community, making them very competitive with an overall funding rate of around 10% of applications. At the time of the workshop, 65 projects had been funded in the first three JTC, amounting to 76 M €. The proportionate regional participation in the calls is high, generating a strong visibility for the regions involved. As competition on funds tends to be lower on the regional than on the national level, regional participants have a preferred access to the international PM community.

ERA PerMed calls are open to all indications and though disease areas like oncology, neurology, immunology and cardiovascular dominate, many other areas are represented. Funding organizations benefit from participating. They

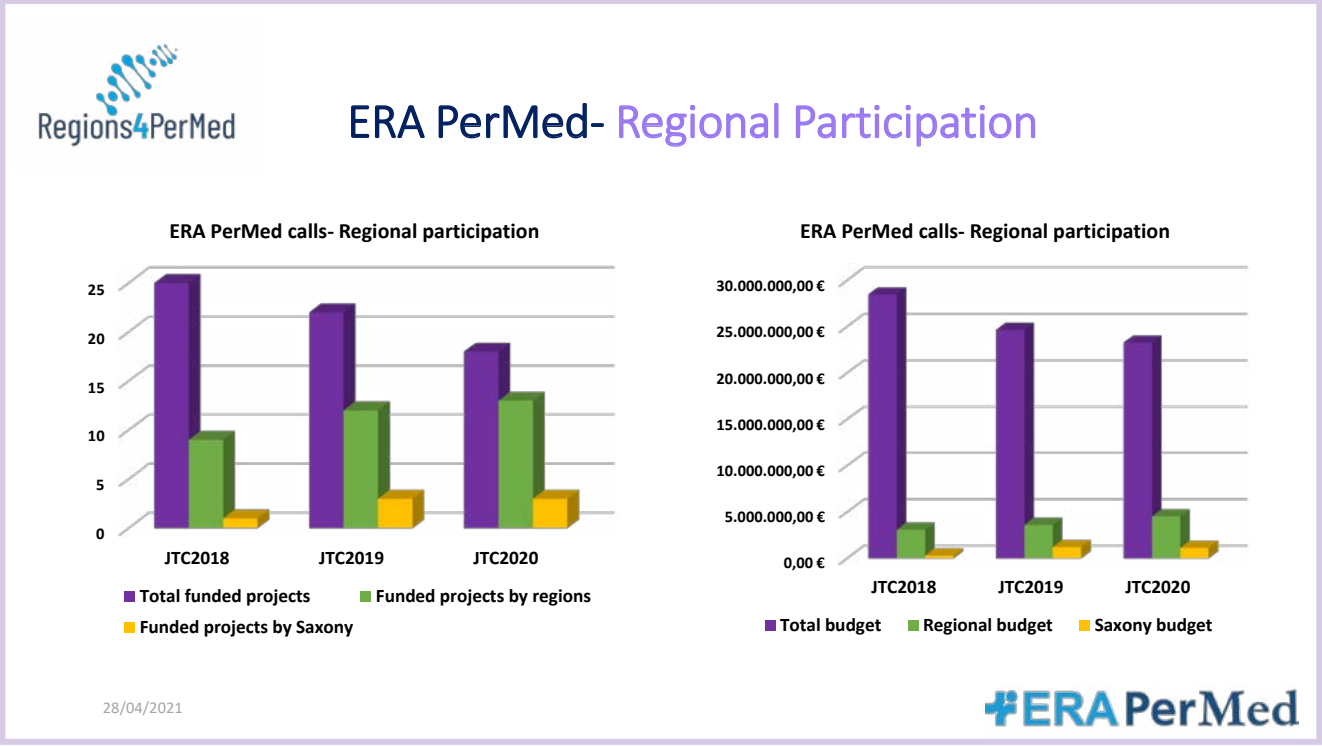


Figure 39: Regional Participation in ERA PerMed Joint Transnational Calls (ERA PerMed)

strengthen their international position in the field, enhance networking and quality of research teams, when supporting interdisciplinary consortia combining complementary expertise from the public and private sector. At the same time they are leveraging their own health R&D spending by aligning expenses with external funding organisations. In the long term, positive socio-economic impacts such as better health service and new employment opportunities may result. Participating researchers gain novel sets of expertise, networking opportunities and may be encouraged to participate in technology transfer, potentially being motivated to become entrepreneurs.

For the future, it will be likely that ERA PerMed's activities will integrate into the foreseen European co-funded partnership on PM (EP PerMed) that is scheduled to start towards the end of 2023. The partnership will further integrate all PM activities across MS and regions. Even though the partnership is prepared on the level of the European Commission and EU-MS, the integration of regions will be important, as in many MS, the health system has a regional dimension in terms of policy, governance, and implementation. The aim of the partnership is to enable PM for the citizen by putting Europe at the forefront of research and innovation in PM, harmonize implementation of PM in healthcare systems across Europe, facilitate uptake of PM innovation by health systems and develop a common language and understanding on PM for citizen, patients and health professionals. This shall be achieved by four pillars of activity, which consist of joint funding, strategic alignment, improved education, and policy development that will be coordinated by a higher-level structure.

Conclusions of Session II

The regional PM innovation ecosystem in Saxony is a demonstration of how regionally embedded inner- and interregional collaborative R&D structures are highly supportive for PM and can have a positive impact on a regional scientific, industrial and economic development. These structures are generating knowledge and advancing R&D in a synergistic fashion, increasing national and international visibility; they build momentum and align resources and research strategies within the research community.

In Saxony, several of such structures exist. Irrespective of source of funding (which in the case of SaxoChiLD and SaxoCell is provided federally by BMBF), such collaborative structures can shape regional development and open up new opportunities. As shown by EMSCO, industry engagement is strongly facilitated when researchers join forces also across regions. In terms of PM health research this is following an intrinsic logic, as increasing patient stratification will lead to better defined, but smaller patient-subgroups, necessitating the enlargement of the research base. Other inward effects of such cooperative approaches, such as better development of novel concepts and ideas due to enhanced scientific exchange and a creative and stimulating research environment are also highly relevant. The development of (researcher initiated) focused R&D collaborative structures for PM should be supported by additional funding to facilitate their creation and maintenance.

Collaborative R&D structures are attractive for large pharma (Session I, Oliver Stenzel) which actively engage in such initiatives and participation in such regional structures may thus be a helpful vehicle for regional start-ups of academic origin and SME to better position themselves in the R&D market for industry-collaborations. Regional collaborative structures may also induce and facilitate development of further supportive activities, e.g. training programmes for specialised staff; thus creating a virtuous circle for regional development.

The creation and support of thematically specialised collaborative R&D structures is a highly useful and valuable tool that is accessible to regions and should be leveraged. It increases scientific momentum and thus also visibility of a region within the scientific community, making the region more attractive for novel talent. It is important to recognize that the generation and development of such structures is to some degree dependent on the ability of the individual actors to collaborate well, and such soft factors have been described in the discussions.

The regulatory environment in Europe is not perceived as optimal for transnational clinical research. Regulatory requirements and processes are not yet harmonized across Europe. The execution of international, multi-centric studies is therefore more difficult, requiring specialised knowledge and increased efforts, leading to delays and causing higher cost. For (academic) investigator initiated international studies, such regulatory hurdles may be particularly problematic, as these have limited resources. The same is true for start-up companies of academic origin. Further harmonization is thus an important aim to facilitate interregional collaboration, which is essential for advancing PM. Ongoing initiatives for harmonisation should be accelerated. Regions should be supportive of such processes.

The upcoming EP PerMed will be an important high-level instrument to advance and align PM related R&D activities and also the regulatory and institutional environment across Europe. Regions participating in this effort will gain a privileged access to the international PM R&D community and may be able to shape the development of PM in Europe. Also, EP PerMed could be designed to further advance collaboration between regionally and nationally embedded collaborative structures.

3.3 Workshop II: Regional Translational Ecosystems supportive of Personalising Health Industry

3.3.1 Opening

The second Workshop day was opened by **Jean-Luc Sanne** (European Commission, Belgium), who explained that the Covid-19 pandemic has shown that for Europe collaboration is critical as value chains are complex. Therefore, a synergy between programmes, availability of open infrastructures, cross-fertilisation among innovation actors like universities, research centres, biotech companies and larger health industry companies are necessary, as well as cooperation though partnerships with stakeholders of the public sector and society. This is why policy stakeholders are gaining an increasing interest in ecosystems. Horizon EUROPE has put a focus on developing innovation ecosystems. The aim of the EU is to create a more connected and efficient ecosystem to support the scaling of companies and to encourage innovation and stimulate cooperation between regional and national and regional and local innovation actors. As it is holistic, PM is particularly well suited for the creation and the development of innovation ecosystems.

3.3.2 Session I: Health Industry Perspective on Regional R&D Ecosystem Support

Alexander Natz (European Confederation of Pharmaceutical Entrepreneurs - EUCOPE, Belgium) outlined ongoing and expected EU level policy changes with relation to PM from EUCOPE's perspective. In the next years several policy adjustments are expected, like the proposal to harmonize health technology assessment (HTA) across the EU. EUCOPE sees a real need for this, as a more uniform HTA across Europe would facilitate market access for companies in a timelier manner. Currently, companies are facing differing requirements in all member states, e.g. AMNOG process in Germany or NICE submission in the UK. This is tedious, time consuming, and costly, slowing down the time to market for innovative products. For relatively rare diseases or personalised treatments, a uniform approach would be particularly beneficial as it would also further support data bundling across different legislations, leading to a more robust data base and a uniform value assessment.

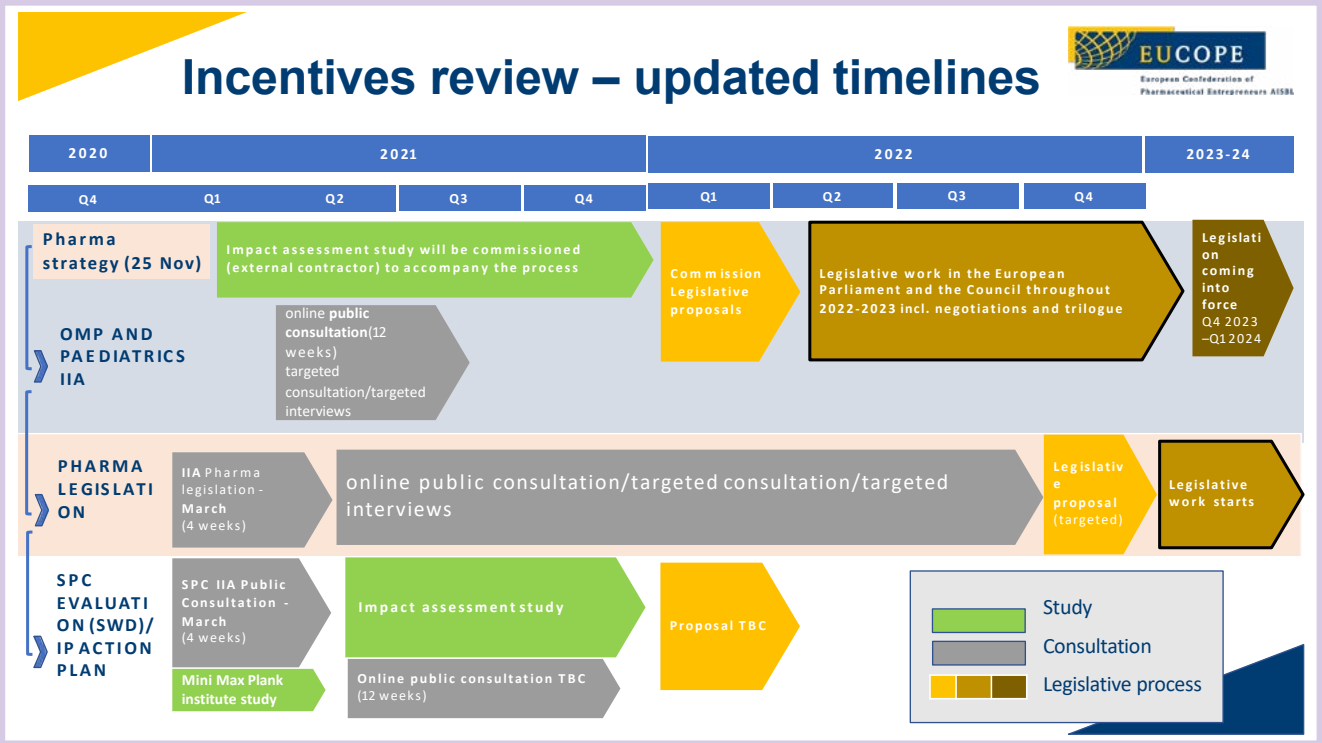


Figure 40: Timelines of Incentives Review (EUCOPE)

Touching on the ongoing incentive review, he pointed out the importance of a set-up supporting market introduction of innovative therapies, such as the (ten year) market exclusivity for orphan medical products (OMP) which led to their increased development, with more than 180 drugs being in the EU market today. As predictability is critical for industry, current approaches should be maintained to tackle those 95% of rare conditions for which still no treatments exist. Often the market for these products is very small. The pharmaceutical strategy of Europe, which is currently revised by the commission, shows potential to tackle large topics, such as anti-microbial resistance, unmet medical need, access and affordability of medicines, regulatory efficiencies. Alexander Natz gives a very positive assessment of the European Medicines Agency (EMA), which in face of the pandemic has brought four vaccines into the market in short time, and has successful been allowing speedy market entry of innovative medicines in the past 20 years and developed new tools like PRIME[7] which is very helpful for SMEs. He also referred to the European health data space as an important development to promote better exchange and access of health data. Data held by regulatory authorities or HTA institutions should be shared with other

[7] *PRIME is a scheme launched by the European Medicines Agency (EMA) to enhance support for the development of medicines that target an unmet medical need.*

authorities to facilitate processes. He discussed the cross-border healthcare directive which is under review regulating access to medical treatment (and reimbursement) of EU citizens in the EU c outside of their home countries. EUCOPE sees shortcomings in respect to rare diseases and ATMPs and also a lack of harmonization across member states, noting that S2 regulations are still in use. He highlights Europe's Beating Cancer Plan which puts a focus on early detection and prevention and also on certain cancer areas, such as paediatric cancer, that still suffer from a high unmet medical need.

Florian Pühler (Bayer AG, Germany) presented the **pharmaceutical industry perspective on personalised medicine**. He pointed out benefits of individually customized therapy for patients, physicians, regulatory authorities and payers. Bayer is developing a biomarker strategy with the aim to better identify patients who are most likely to benefit from a new therapeutic approach in clinical trials (patient stratification) for every active substance in Bayer's development pipeline. For most oncology projects this has already been implemented and is underway in other areas, e.g. cardiovascular and cell & gene therapy research projects. Precision oncology, based on genomic information and including immunotherapy is characterized by a better prognosis and quality of life then "traditional" chemotherapy, radiation and surgery-based approaches. In the past twenty years numerous technological developments have led to increasingly personalised approaches. He exemplified a rare

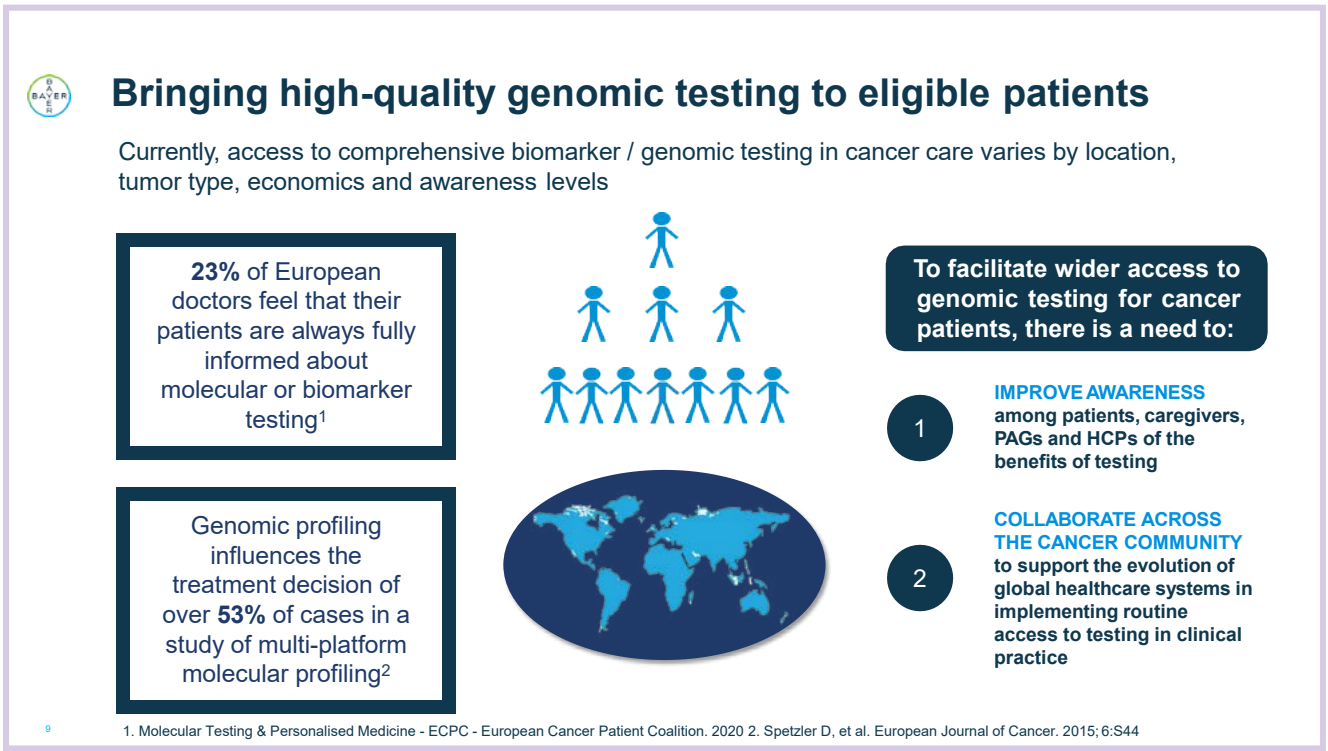


Figure 41: Patient access to Genomic Testing (Bayer AG)

subgroup of cancers which are driven by genomic alterations leading to tumour formation anywhere in the body, affecting potentially all cell types, and which can only be identified by genomic testing. Today these can be much better targeted by novel therapeutics (e.g. NTRK-fusion proteins). More than 50 precision medicine cancer therapies have been approved by FDA. By identifying cancer biomarker panels, treatment susceptible patients can be identified. High quality testing should be available to all oncology patients. This potential is not used yet and many patients are not aware of it, as a study of the European Cancer Coalition has shown (see figure 41). With a web-based campaign (www.testedeinentumor.de / www.testyourcancer.com) Bayer is supporting patient education.

There are still many challenges ahead for precision oncology: Regulatory authorities so far have failed to recognize genomically driven cancers that are independent of tumour type; unpredictable Health Technology Assessments exist for histology-independent treatments; the diagnostic infrastructure is not up-to date with medical developments and a coherent Europe-wide precision oncology strategy is missing (see figures 41 and 42). Even though the evolution towards PM is accelerating, there is a high *need for more awareness among patients and the medical community* on the benefit of comprehensive biomarkers and genomic testing. More education is needed; also *more collaboration across disease communities* would be beneficial.

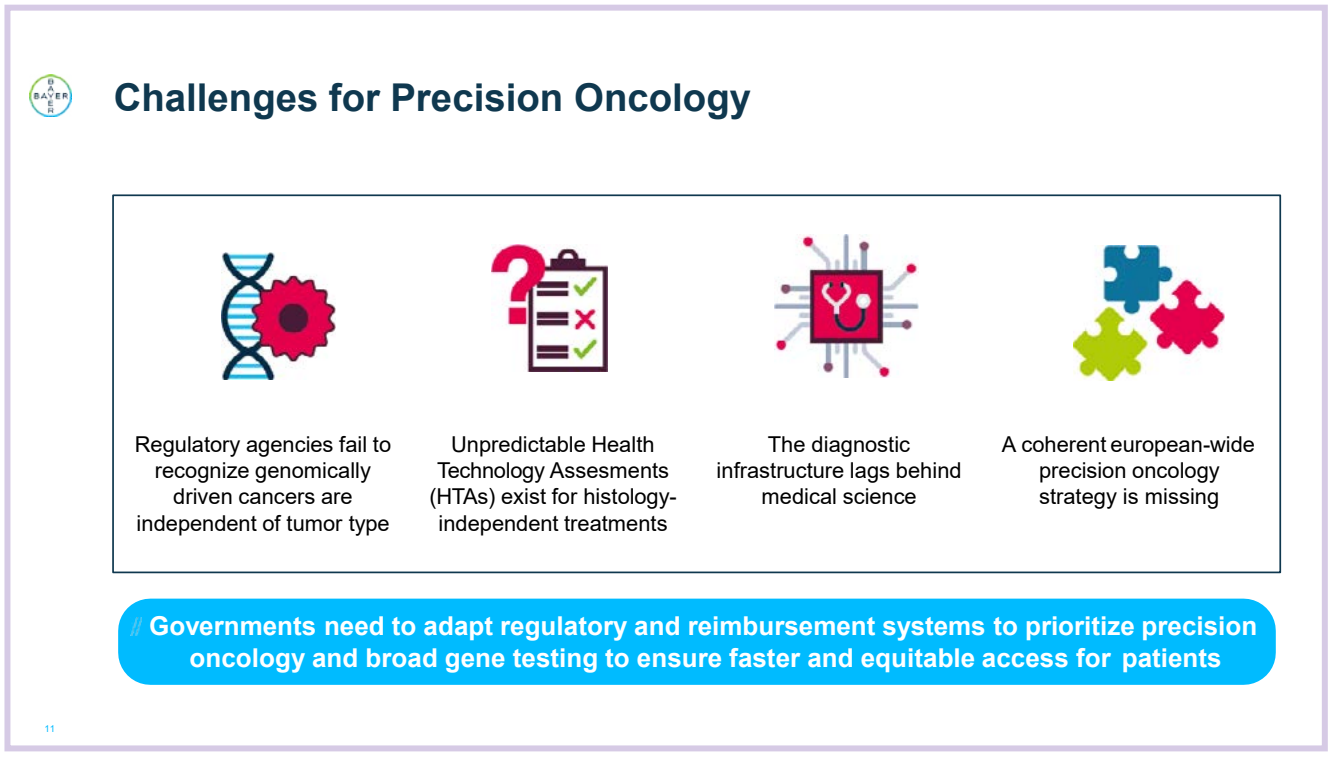


Figure 42: Challenges for Precision Oncology (Bayer AG)

Sophie Raynal (Metabrain Research SA, France) presented the **entrepreneurial perspective on translation in practice – developing and bringing a PM product to the market**. She outlined the inception of Metabrain Research in 2009 by two French scientists (Valerie Autier and Micheline Kergoat). The Paris-based R&D company has 20 employees. It develops innovative therapeutics to restore muscle function. The company follows a partnership-based approach for R&D and terms itself a partnership research organization (PRO), having built a supportive community of stakeholders and commercial partners and customers around its integrated research approach and has three defined areas of action: *Metabrain lab* is the discovery platform of the company; *Metabrain engine* focuses on muscle and physical activity science, and Metabrain tech on start-up creation in the field of biotech, foodtech and e-health (see figure 42).

Metabrain described its participation in Codex4MEs (described in more detail later in this document) for a CDx development R&D project related to the kynurenine metabolic pathway for muscle pathology. Access to human cohorts was needed for the development of a standardized biomarker to enable clinical trials. Codex4SMEs is an Interreg project supporting PM development by offering translation support to SMEs. Through Codex4SMEs a collaboration with the Integrated

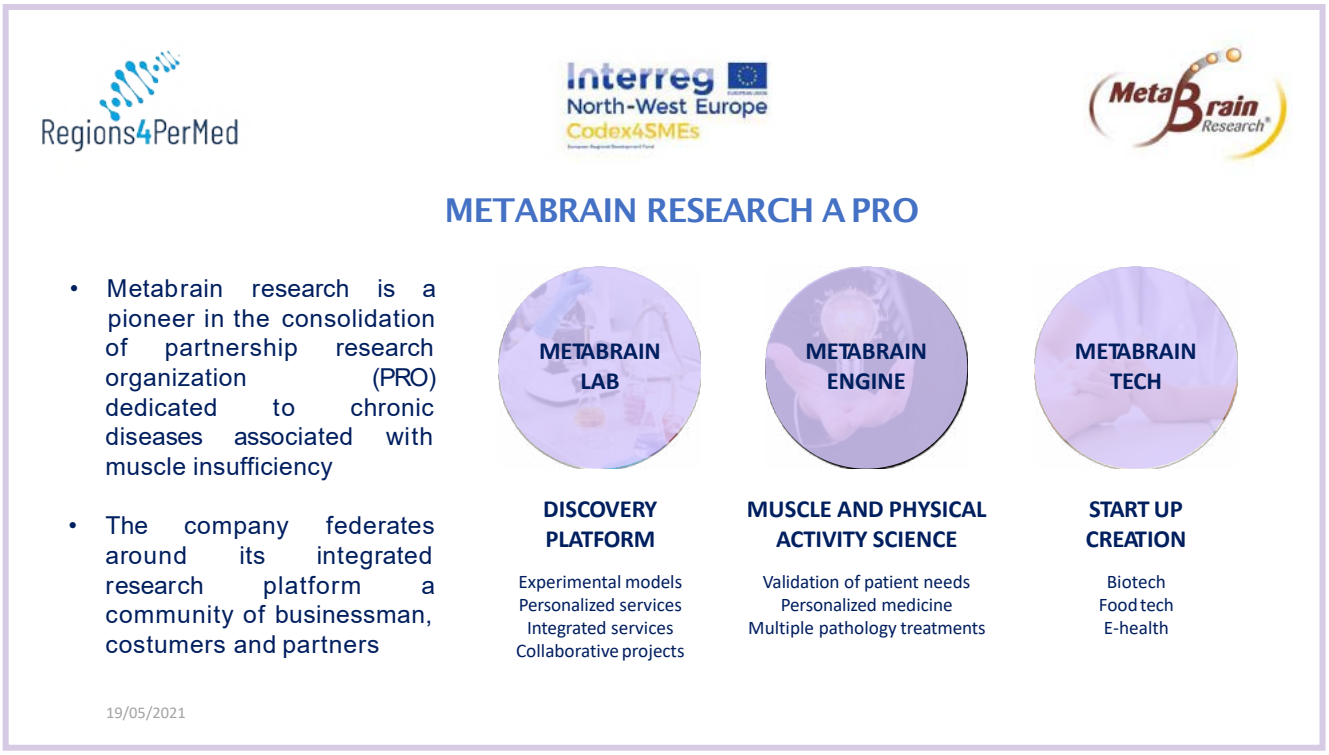


Figure 43: Metabrain Research, a Partnership Research Organisation (Metabrain SA).

Biobank of Luxemburg (IBBL) was set up that helped Metabrain Research to develop high level quality procedures, support the development of validated SOPs and also the validation of its biomarker in human samples. IBB is a biomedical research institute of the Luxembourg Institute of Health (LIH) that provides biospecimen-related services and a biobanking infrastructure for applied medical research. The collaboration proved to be of high quality, allowing procedure optimisation and a transfer from lab to the clinic in an international setting, also including procurement support in terms of material-cost information. Metabrain Research could save time, cost while validating its testing approach for CDx development (the savings amounted to at least 6 months FTE and 40 T€ in cost of goods). The company intends to develop further therapeutics in conjunction with CDx and can build on the knowledge gained in Codex4SMEs for these projects for which it intends to set up new collaborative R&D partnerships following its PRO approach.

SMEs need sufficient funding to cover R&D cost for developing PM. CDx development and clinical trials are costly. In PM there is a strong focus on oncology, leaving other areas potentially underserved. Personal data protection is critical and not fully resolved, making *investors shy to invest in SMEs that are follow a PM approach*, particularly if it is not in the field of oncology. They are still waiting to see the *evolution of the market, the development of an adequate legal framework and the position of payers in respect to reimbursement of PM technologies and therapies.*

Conclusions of Session I

There are many regulatory issues impacting the development and implementation of PM. Incentives and regulatory frameworks need to be set in a way that is supportive for PM industry. As PM relies on data, the handling of data and its regulation are critical on many levels. Also, the regulation of clinical trials can be very burdensome for industry, causing delays and high administrative cost. While large pharma can mitigate this to some degree due to availability of adequate resources and existing structures, this may be a real bottle-neck for SME and even more so for individual researchers from academia and university-associated clinicians.

To advance PM, investigator-initiated studies, which serve as an independent external validation of novel PM, may be particularly important as PM depends on accumulation of stratified clinical information. Further harmonization and simplification across Europe should support regionally based interconnected research approaches. For PM, also HTA processes are critical. There is a need for further harmonisation across Europe and data sharing between involved authorities should be facilitated.

Looking to the market introduction of PM solutions, even in the fast-advancing PM field of oncology, adoption of comprehensive testing lags behind (at least partly due to reimbursement issues as was discussed in the conference). To advance this and open this market, a direct route to patient is taken by large pharma, sensitizing customers (patients) to increase demand. Such an approach is not possible for SMEs that very often lack financial resources.

A lack of funding and the corresponding loss of business development opportunities also reduce growth opportunities for such entities in Europe. Despite some valuable ongoing initiatives and novel dedicated funding tools, start-up and growth support, further action is needed. Competition in the field is global and US-based start-ups ups can obtain significantly easier access to capital. Initiatives supporting translation for SMEs can fill a funding gap to some degree, especially for early-stage development, by providing access to high-level external resources, as shown by the SME case example. However, especially lack of high-risk growth funding needs to be overcome to mitigate the danger of a cheap-sell out of European start-ups.

Most relevant regulation for PM is defined on the European or MS level. However, regions are involved in its implementation and some regulation and its execution is organised regionally. To facilitate PM industry development, it should be aim to further harmonise regionally governed regulation across Europe. This will require a time-consuming process that could be supported by EU action.

3.3.3 Session II: Translational Ecosystems for Personalised Medicine and Health

Felipe Prosper (Universidad de Navarra, Spain) introduced **Navarra as a European Entrepreneurial Region with a focus on personalised medicine**. Navarra is one of 17 autonomous regions of Spain, located in the south of the Pyrenees, with around 650 thousand inhabitants. For Navarra health is a prominent business sector. With two universities, five biomedical research centres with +2.400 professionals, the region hosts more than 30 dedicated biomedical companies and more than 40 in related fields and is seat of one of Spain's largest pharma companies. Navarra has a long track record in cancer research within EU networks with a particular focus in immune-oncology and personalized medicine. In its smart specialisation strategy, it has put a focus on PM and intends to position itself as a national leader. In support of this, the Instituto de Investigacion Sanitaria de Navarra (IdiSNA) was founded serving as an umbrella to bundle existing structures. A dedicated PM programme was developed and NASERTIC, a national hub for genomics and supercomputing Networks was formed, that supports the integration of genomics and clinical data. Public funding is allocated to PM in a coordinated manner for strategic projects, supporting technological centres and industrial partners, investing more than 60 Mio € in the past three years. Dedicated projects in the field of genomics and ATMP are supported. A special challenge are rare diseases, which can be addressed by whole genome sequencing (WGS). NAGEN1000, having been formed to put the technology into clinical practice, was awarded the best practice award of ICPerMed in 2018. Related projects have been started, such as NAGENCOLX, pharmaNAGEN, and NAGENpediatrics.

Several projects advance the use of genomics and cell therapies in cancer, e.g. DIANA, DESCARTHeS, and AGATA. Within these projects, novel technological approaches were validated using NGS panels and leading to novel diagnostic tools for both haematological malignancies such as AML and MDS as well as solid tumours. New drug targets for epigenetic inhibitors could be identified and validated. The development of new diagnostic technologies aiming to replace solid tumour biopsies by liquid biopsies is advanced. Single-cell technologies addressing tumour heterogeneity are developed. In the field of immunotherapy, the development of chimeric receptor CAR-T cells is being advanced as there are still many limitations of the technology, such as therapy failure, antigen modulation by the tumour cells, CAR-related toxicities and a limited accessibility of solid tumours. Novel approaches for CAR-T-cell optimisation are being assessed.

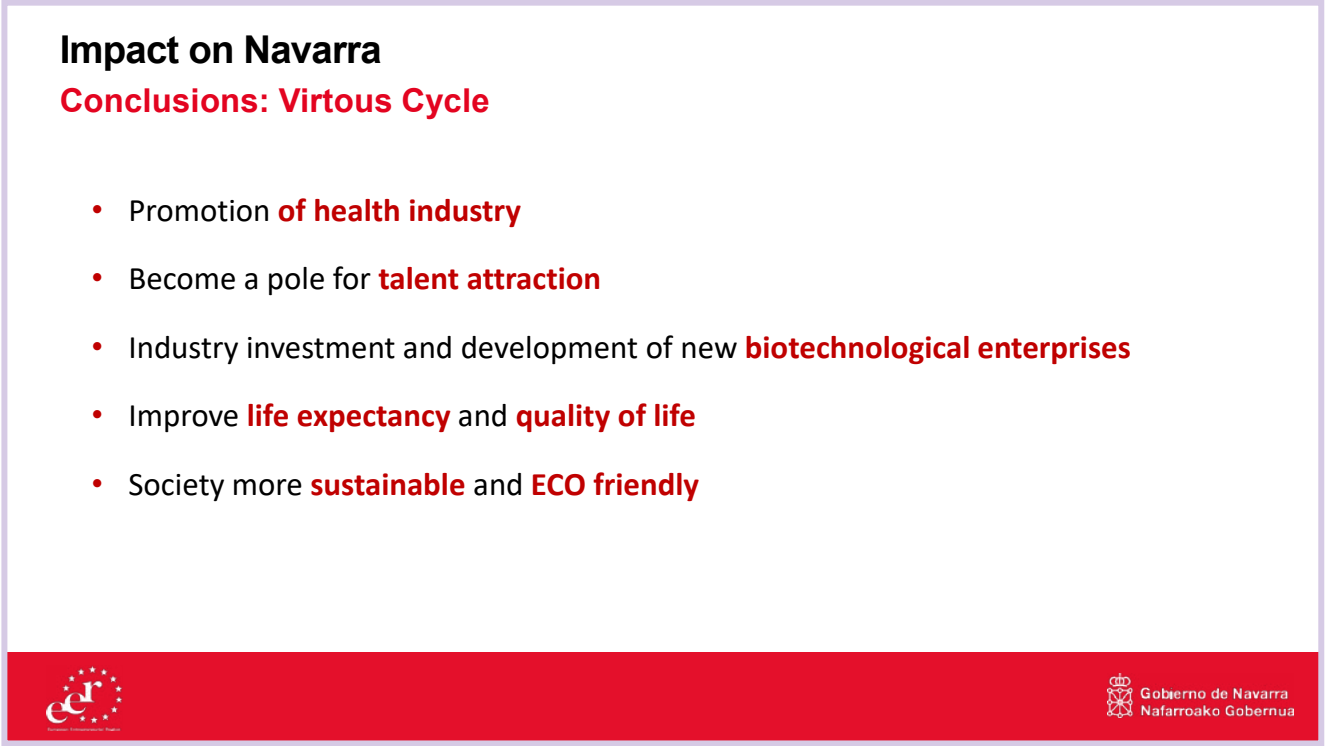


Figure 44: A Virtuous Cycle of and for PM (Felipe Prosper)

The overall vision for cancer therapy is that the disease should be understood as a truly individual disease, different in each patient. With the help of biomarkers, advanced therapies and strategies based on genomic knowledge the deathrate of cancer in the EU could and needs to be significantly reduced. Implementation of these PM tools will positively impact patients in Navarra. Public-private partnerships and involvement of biotech companies will further drive economic growth. A virtuous cycle of positive economic and healthcare development can be initiated that will benefit the region of Navarra on all levels described.

Andrée Rothermel (TRON - Translationale Onkologie an der Universitätsmedizin der Johannes Gutenberg-Universität Mainz gGmbH, Germany) spoke about **bridging the translation gap for personalised medicine in oncology**. Bridging for translation begins already with understanding and overcoming the different ways of thinking in industry and academia, making the development of a common language to achieve mutual understanding a basic translational task. TRON supports this by educating and training staff in translational research. Founded in 2010 by Ugur Sahin, Özlem Türeci and Christoph Huber as a non-profit research institute, TRON operates as a *transdisciplinary R&D hub*, collaborating with academia and industry on the mission to combat cancer and other diseases of high unmet medical need. Shareholders are the state of Rhineland-Palatine, Johannes Gutenberg-Universität Mainz,

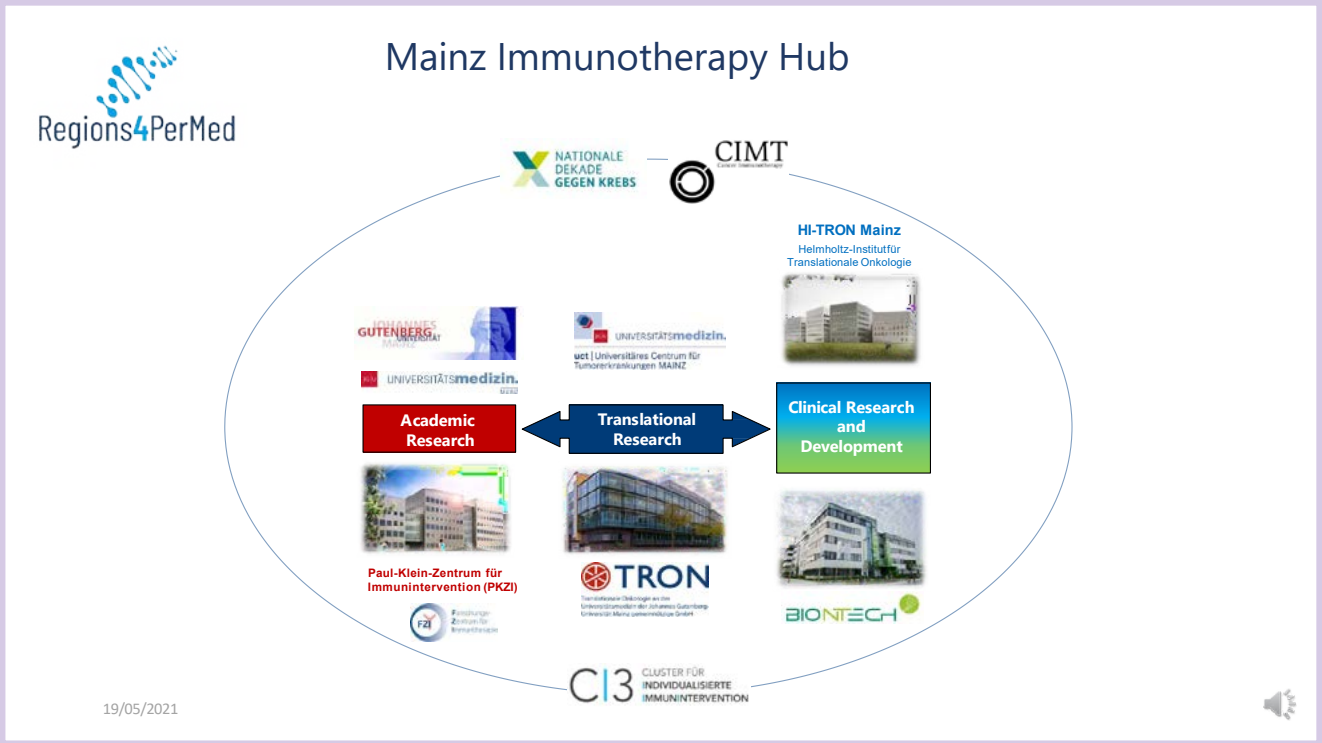


Figure 45: Mainz Immunotherapy Hub (TRON)

Universitätsmedizin Mainz, and Ugur Sahin. Early support of the state with substantial funding (~15 M €) allowed TRON to install an outstanding R&D infrastructure with cutting edge technology. At the start, TRON covered almost half of its cost through industry-generated revenues. With steadily growing licensing revenues state funding is no longer needed.

TRON nourishes a collaborative corporate culture characterized by a creative, curiosity-driven and pro-active mind-set. With the Mainz Immunotherapy Hub and the Cluster for Individualised Immune Intervention (CI3), TRON is embedded in a supportive environment, with a strong academic and institutional research base, with the latter having recently been supplemented by the Helmholtz Institute for Translational Oncology (HI-TRON). A preferred on-site industrial partner is BioNTech. The local Network has strong ties to national and international networks, especially the Nationale Dekade gegen Krebs[8] and to the Association for Cancer Immunotherapy (CIMT) which are providing access to a large number of international SMEs, pharma companies, and research institutes. To facilitate knowledge exchange, framework agreements have been set up with preferred partners.

TRON's business addresses the translational gap (valley of death) in drug development. The R&D phase that TRON bridges

[8] *The Cluster for Individualized Immune Intervention (Ci3) e.V. is a non-profit organization and is partner in the "Dekade gegen den Krebs" which is a German nationally funded ten-year programme to combat cancer.*

is particularly risky, as it is associated with high cost while characterized by low success rates. Support is given in two directions: Academia is aided, by supporting translation of new concepts, value generation from patents, and access to HT technologies. Clinical research and development is advanced by providing access and integration into an excellent academic environment, and facilitating access to matured innovation and research platforms.

Due to its excellent R&D facilities and expertise, TRON is a sought-after partner for R&D collaborations, especially from industry. It is operating in two main departments: biomarker diagnostics and immunotherapy development, consisting of around 30 functional units that can handle more than 100 ongoing projects in total. The company implemented a dynamic quality management system early on that was an important market facilitator for industrial standard R&D cooperation. TRON is following an active publishing policy and has filed more than 140 patents over the past 10 years. One example for this is mRNA-based individualized immunotherapy in oncology (tumour vaccination) that was developed by TRON and another one is its contribution to the development of the Covid-19 vaccine (Comirnaty). Though situated in a particularly favourable environment, TRON has provided proof

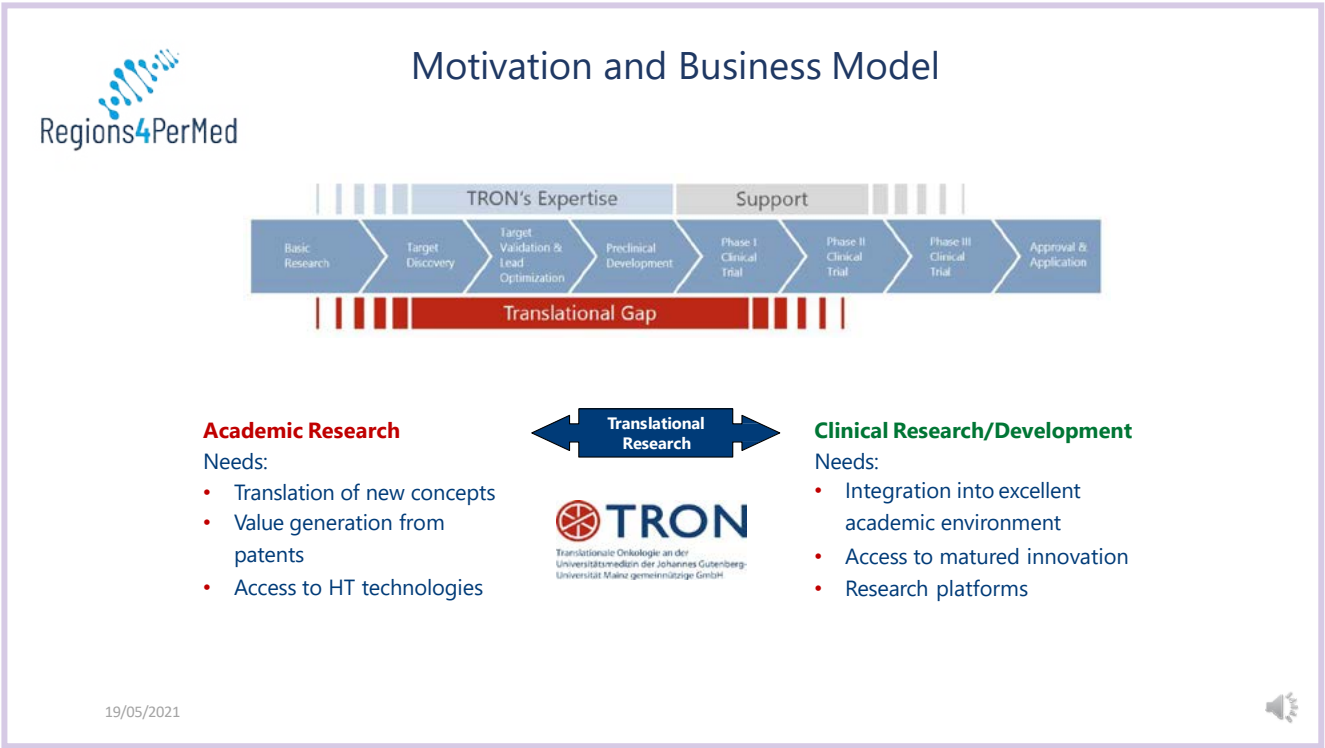


Figure 46: Motivation and Business Model of TRON (TRON)

that translational concepts in the field of life sciences can be successful. There is more room for translational institutions in Germany and Europe. To install these, trustful investor support is needed, as well as highly qualified staff, functional structures and an inspiring scientific environment.

Sabine Marschollek (Else Kröner Fresenius Center for Digital Health Dresden, Germany) presented the **Else Kröner Fresenius Center for Digital Health Dresden as a platform and nucleus for networking in the field of digital health**. Located next to Dresden University Hospital, the centre has been set up on a competitive grant of 40 M € for a period of 10 years from the Else Kröner-Fresenius Foundation to fast-forward digital health development. Aiming to connect medicine and high-tech in a new way, the centre is integrating many different fields, such as smart materials, digitization, AI, new tools and devices, robotics, sensors & implants, and regulatory affairs. Despite its huge potential, the benefits of digitization are neither fully developed for nor yet implemented in patient care. This is leading to a lack of integrated information and information loss. In med-tech R&D a valley of death exists, that is blocking the translation of innovations from the lab/bed to the market (patient) (see figure 46). To address these shortcomings, the EKFZ is following three approaches: innovative project

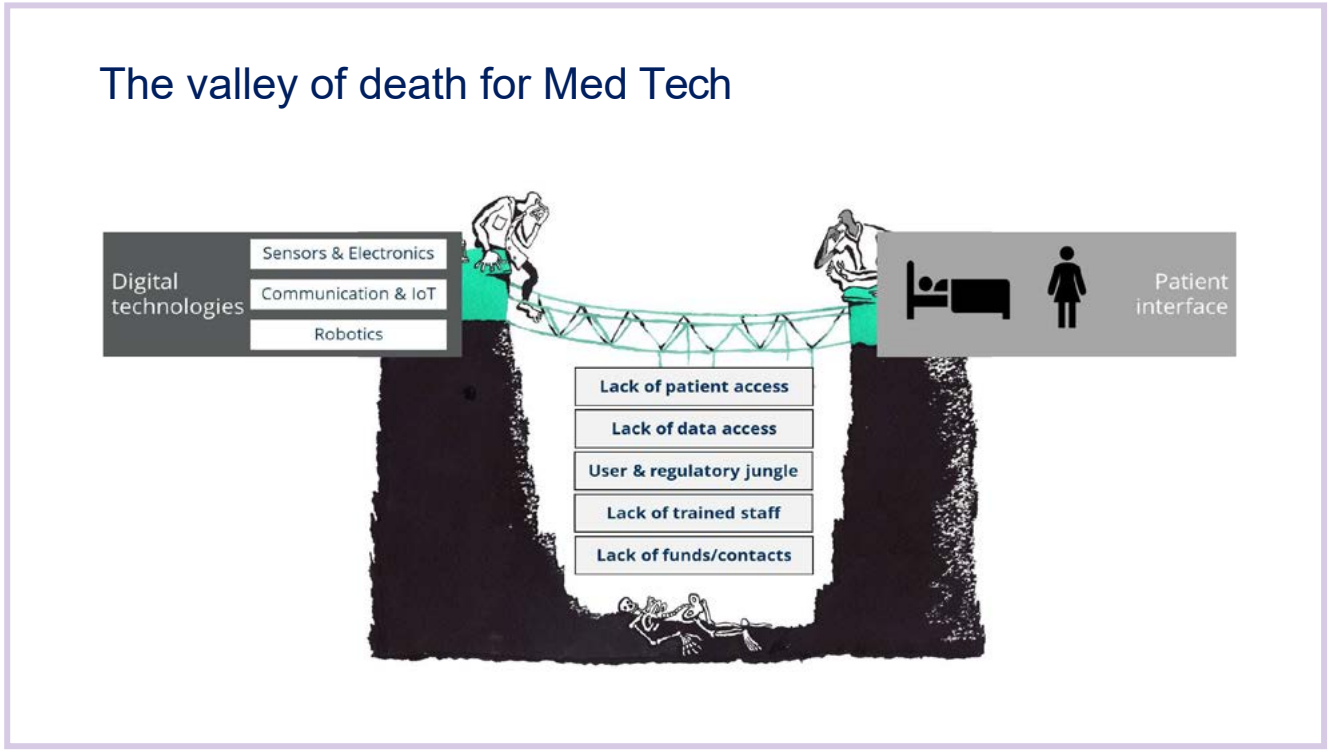


Figure 47: The Valley of Death for MedTech[9] (EKFZ for Digital Health)

[9] *Figure adapted from Butler, D. Translational research: Crossing the valley of death. Nature 453, 840-842 (2008). https://doi.org/10.1038/453840a*

funding, developing talents and professionals, and building a strong on-campus and outward industry network.

The flexible funding format (see figure 47) supports proof-of-principle projects on campus for up to 2 years (and to 400 T € per project) with short decision timelines. Projects need to address a real medical need, integrate "new" talents, clinical and tech specialists, and an experienced clinician as mentor, and contain technical expertise beyond state-of-the-art. Integration into specific medical context is essential. Projects need to be truly interdisciplinary; topics are not restricted except for an integration of digital-health concepts. Ongoing projects are characterized by steep learning curves allowing for a broad and deep knowledge transfer between participants from the clinic and the tech-side. This is flanked by regulatory training, e.g. through workshops. Current projects belong to the fields of new tools for physicians, improved intensive care and emergency medicine, and personalised medicine.

"Finding the right people" focuses on building a local community of gifted and motivated talents. Interested students can join early during their academic training by participating in an interactive spring school, "Clinicum digitale". Scholarships for doctoral students participating in funded projects have been set up, and a so-called "Talentschmiede"[10]

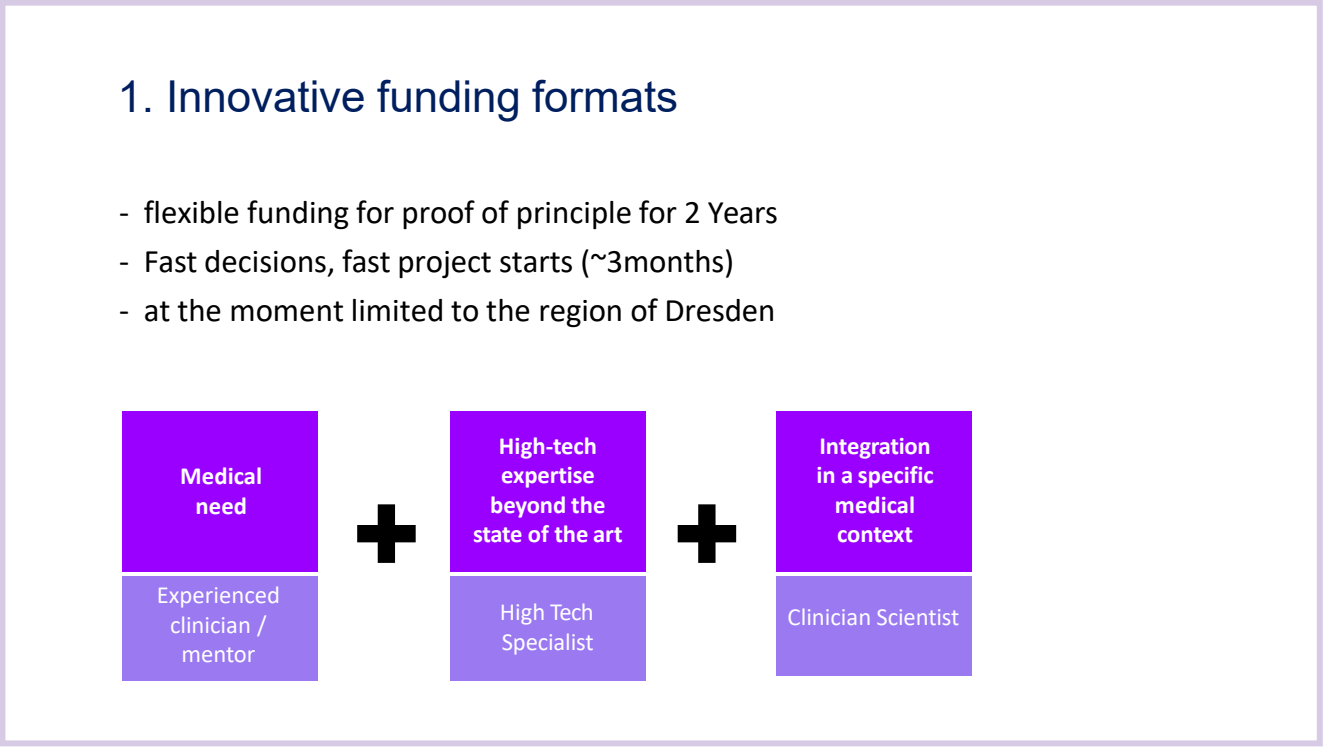


Figure 48: Overview of Innovative Project Funding (EKFZ for Digital Health)

[10] *Translates into "talent academy".*

was installed, in which (doctoral) students and young clinicians train each other by presenting their specific expert knowledge. In addition, novel academic facilities are being created to form *a nucleus of leaders for digital health. Five novel professorships* have been created, focusing on *regulatory research, implementation research, bioelectronics, clinical artificial intelligence and medical software engineering*. Up to now, there has been no professorship for medical device regulatory science at a medical faculty in Germany. A regulatory affairs office was set up in addition at EKFZ to support innovation teams from the beginning to think about the regulatory frameworks and challenges.

The third focus lies on building a strong scientific and industry network for digital health in Dresden and beyond. Many ties to regional SMEs and international players have been set up and collaborative structures are being formed. To further advance this, the EKFZ is also partnering in the SEMECO concept for the ongoing Clusters for Future Competition of the BMBF.

Margot Jehle (BioRegio SterN, Germany) presented **Codex4SMEs-interregional collaboration for companion diagnostics**. BioRegio SterN is a regional life sciences industry cluster organisation supporting industry development. It is acting as coordinator in the Interreg North-West Europe project Codex4SMEs. Running for 51 months, the project aims to improve healthcare by enhanced adoption of PM in North-West-Europe and beyond by providing a supportive network for SMEs along the value chain of CDx development. It includes 9 partners from Austria, France, Ireland, Luxemburg, The Netherlands and UK, partly cluster and partly research organisations. The European Infrastructure for Translational Medicine (EATRIS) is involved as an associated partner. The projects offer SMEs access to the respective ecosystems of its partners; interested supportive stakeholders can register in a public database. The project offered participants a toolbox covering the whole CDx development pathway allowing to support individual projects tailored to their specific needs (see figure 49). Among them have been market-analysis support, sample access programmes, and knowledge transfer for pre-clinical and clinical research, as well as market-entry support, e.g. by business model development and organising roadshows to attract Venture Capital, including a pitch learning programme.

The support addressed three phases along the value chain. In the first phase a gap-analysis has been performed to identify areas of need for the SME and a supportive network has being set up. The “acceleration phase” centred around providing R&D access for SMEs. The “growth” phase focused on market

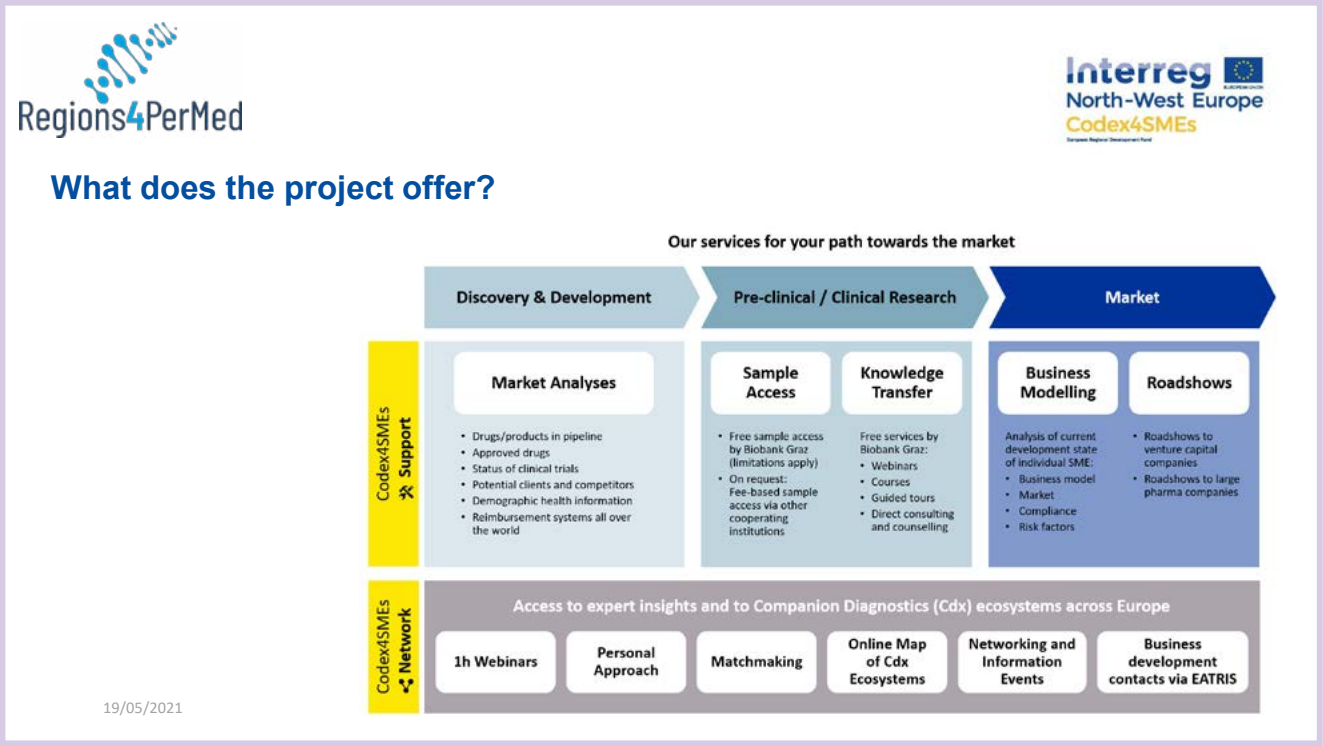


Figure 49: Service Spectrum of Codex4SMEs

access support. A number of success stories were shown[11] for each project phase, demonstrating the benefits of this tailored support for SMEs. More than 250 SMEs have so far participated in the project, of these 15 have received sample access and biomarker validation support (from the Biobanks of Graz and Luxembourg) and 16 have profited from dedicated knowledge transfer services (by the Biobank of Graz). 17 SMEs have benefitted from pitching events. Collaborations with synergistic projects, e.g. BiC, Boost4Health, and CELIS were established.

Putting Codex4SMEs into perspective, Margot Jehle explains the high relevance of CDx for PM. As *their development is complex and costly, networks are essential to overcome these hurdles for start-up companies of academic origin.* Most supportive networks, such as regional cluster organisations, operate in a national context and setting. However, the markets for CDx are global, and regulations for these products and their reimbursement differ across jurisdictions, also in the EU MS. To advance implementation of PM in Europe for an improved healthcare, engaged stakeholders need (to be able) to join forces. Interregional and transnational collaborations (in Europe) are particularly important, but establishment

11 One of them is Metabrain Research which is presented in Session I of 2nd Workshop. The others were life& soft, mediagnost, Holywood Mecial, ParmaCytics.

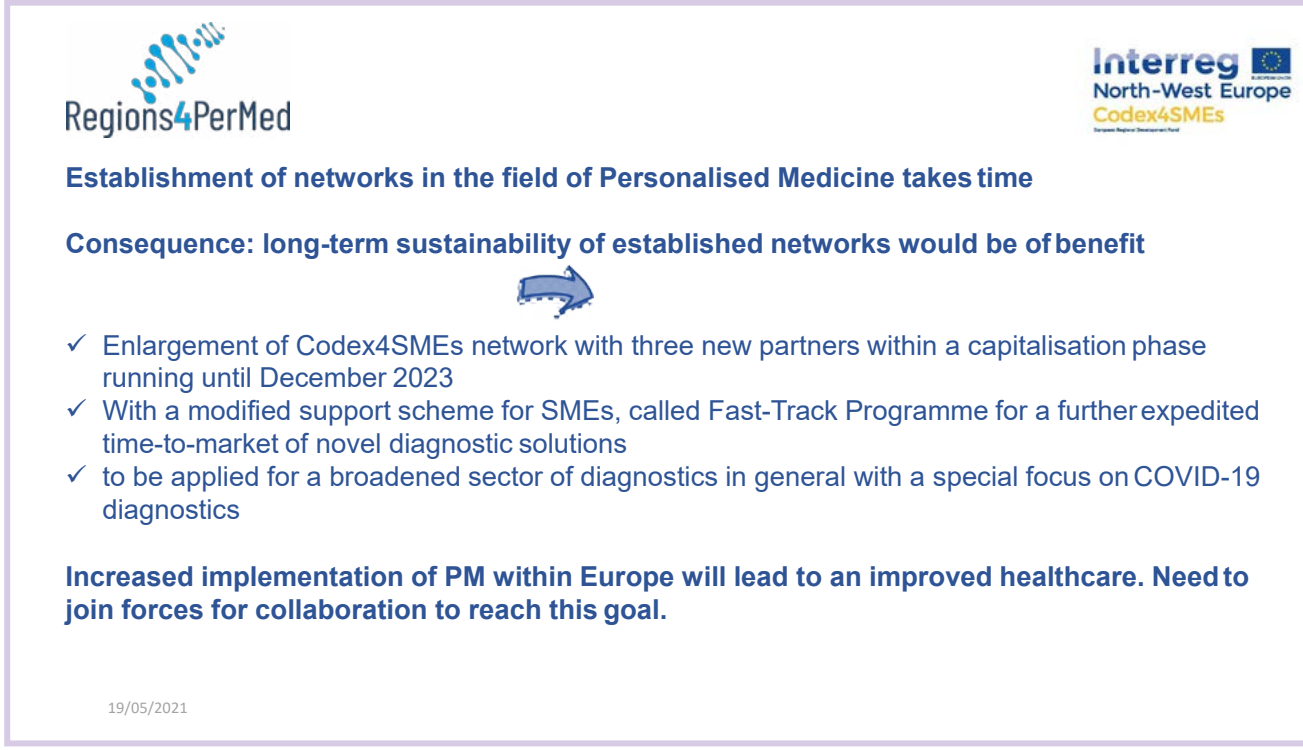


Figure 50: Networks in the Field of PM (Codex4SMEs)

of international networks is time consuming. To ensure the long-term benefit of such networks, a long-term perspective to sustain their success is critical (see figure 56). Therefore, the Codex4SMEs partners are pleased to have secured the opportunity to proceed with further activities until end of 2023 as the project received approval for a "Capitalisation phase" beginning in March 2021. As a part of this, Codex4SMEs is enlarging its established network by the involvement of 3 new partners. The original support scheme for SMEs will be modified into a new Fast-Track Programme to further expedite the time-to-market of novel diagnostic solutions and to be applied for a broadened sector of diagnostics in general with a special focus on COVID-19 diagnostics.

Katharina Ladewig (EIT Health Germany) presented **EIT Health** as an enabler of **pan-European collaboration, acceleration and co-investment** for PM. EIT Health is a pan European community of more than 150 organisations collaborating across borders, funded under Horizon 2020 and Horizon Europe frameworks. It was set up in 2005 as a European-wide research & translation powerhouse inspired by the Massachusetts Institute of Technology (MIT). Collaboration is highly important for success, particularly in a complex field as PM. EIT Health

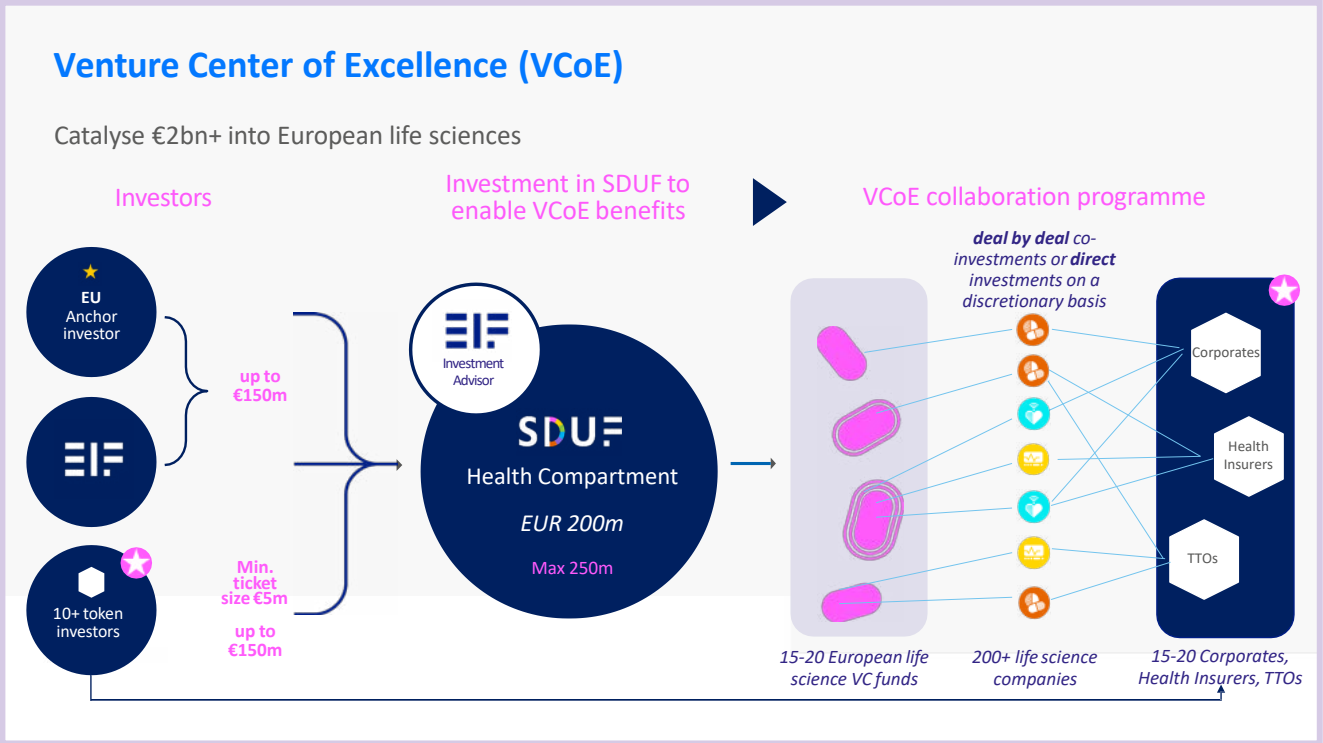


Figure 51: The Venture Center of Excellence (VCoE)

is supporting collaboration across Europe, operating in six regional innovation hubs. Additionally, EIT Health InnoStars is spanning several geographic regions (Hungary, Italy, Poland, and Portugal) and a regional innovation scheme (RIS) including 13 additional regions and it also operates nodes to external ecosystems in USA and Israel. Partners come from industry, universities, healthcare providers, research organizations, payers, incubators/clusters and some cities and regions.

Through guided access to its networks, EIT Health supports innovators and entrepreneurs by providing programmes in which they can gain patient and market insights, data access, regulatory affairs support, product testing and validation, business plan validation and pitch training, dedicated funding (within Horizon Europe) and education opportunities. Its activities are grouped in three main pillars: acceleration, education, and innovation. The accelerator is a catalyst to business growth to deliver transformative products and services. So far this has supported more than 740 start-ups and helped raise investments valuing around 248 M € until 2019. There are different level programmes, such as bootcamps, mentoring and coaching networks for MedTech, biotech and digital health, digital Sandbox & RABBIT (providing access to public biobanks), start-up meets pharma (a challenge-based acceleration programme) and a bridgehead programme to support internationalisation. Access to finance is supported by providing access to an investor network, operating

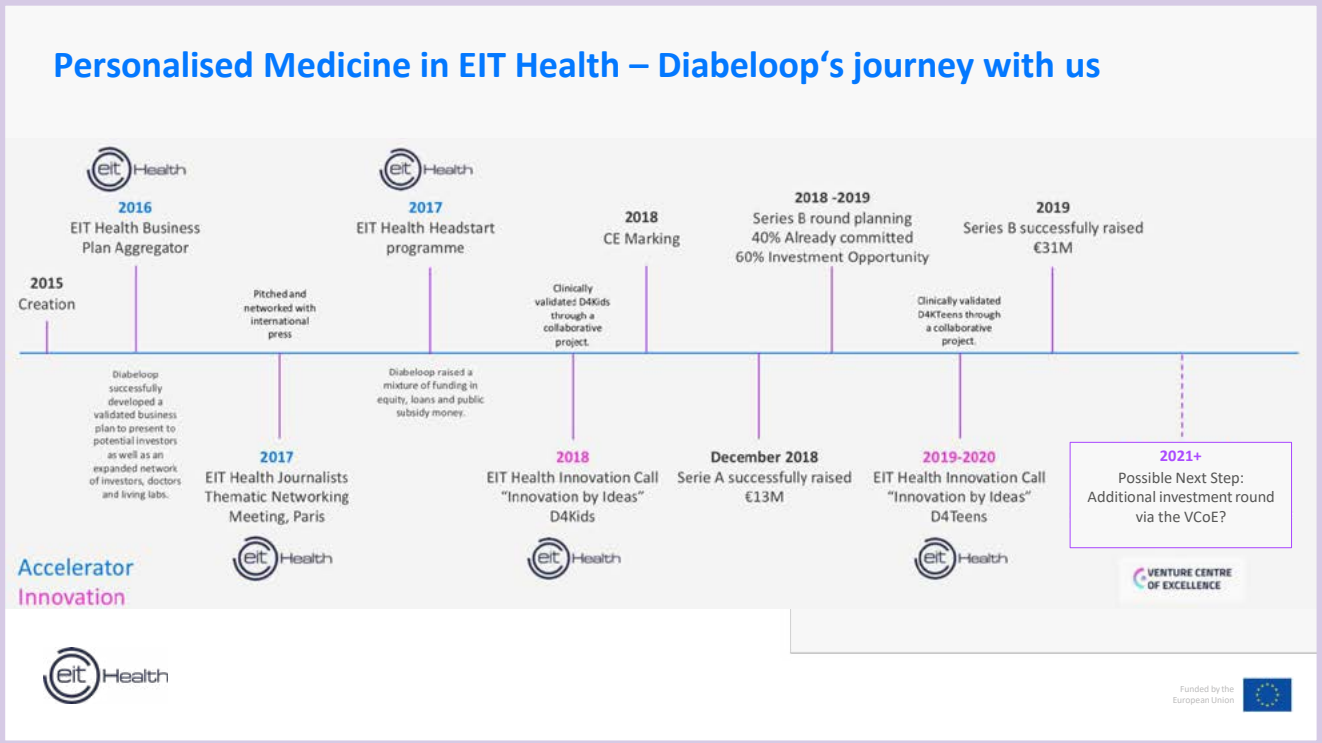


Figure 52: Diabeloop's Development Journey with EIT Health

a crowdfunding platform, and recently the Venture Centre of Excellence (VCOE) was launched as a collaboration with the European Investment Fund with a 150 M € anchor investment of the EU for high potential scale-ups (late stage B or series C investments) shown in figure 51.

Diabeloop is a successful example of the accelerator in action (see figure 52). Diabeloop was founded in 2015, around the invention of the first automated insulin delivery device. After winning the business plan aggregator in 2016, the team gained access to the large EIT network. It won the EIT Health Headstart programme in 2017 with D4Kids enabling a first round of financing. Succeeded in the EIT Health innovation call in 2018, it received a CE Marking for its lead product in 2018 and was able to secure an investment of eventually more than 44 M €. In 2019/20 it succeeded in another EIT Health Innovation Call with D4Teens.

The education efforts of EIT Health are directed at bridging the gap between academia and enterprise to upskill professionals on new innovative techniques and providing practical knowledge and inspiration. Innovation support is achieved by annual calls for proposals to turn ideas into viable products or services.

Conclusions of Session II

Regional specialisation focusing on PM can set in motion a virtuous circle of regional economic and citizen health benefits as PM draws on many diverse fields of scientific expertise that can synergistically improve healthcare.

Thus, economic effects may well be created beyond further developing health and biotech industry, but also radiate to advance related fields. Such a specialisation will attract human talents and create high quality regional employment opportunities.

To successfully realise such a strategy, public regional investments need to be aligned and investments need to be well-balanced and distributed in a synergy-promoting way.

To support the realisation of regional economic benefits of PM-related R&D, translation supporting structures should be installed as these are effective tools to overcome existing translational challenges related to PM development. The lay-out of such structures cannot be pre-defined but needs to fit respective regional needs. This requires a careful regional analysis involving all relevant regional stakeholders.

Successful translation supporting structures share a number of characteristics, such as a broad and deep access to high quality regional, national and international scientific networks; access to high quality R&D resources; and the development and implementation and use of industry standard processes (defined standard operating procedures). They support talent education and development in a coordinated and fitting approach and in the best case create also a scientifically stimulatory environment.

Apart from such direct translational support, such approaches are serving their communities through increasing excellence and professionalisation. This implies a certain size and duration to build relevant capacities and networks. The translation supporting structures presented in this workshop (including SaxoCell of workshop day I, session II) have in common that they include some degree of R&D and market-directed specialisation, which is a critical pre-condition for generating excellence.
To create sufficient momentum, it is important that regional investment is sufficiently dimensioned and allows for a longer-term perspective.

4. Key Messages to European Regions

The conference and the interregional workshops have outlined the role that local and regional authorities can play in implementing PM and PH and supporting personalising health industry. A regionally aligned strategy for implementation of PM and PH can initiate a virtuous circle with the potential to become self-enhancing. Economic benefits and improved citizen health may result in the medium and long term. In the short term, highly visible reputation gains in terms of scientific excellence may be generated, attracting foreign investment and qualified and skilled labour.

Local and regional authorities have a deeper knowledge of their communities and can leverage different sources to drive investments in infrastructures, enabling technologies and supportive structures. They can use this to expand regional specialisation supportive of PM and PH. In doing this, they need to ensure that regional instruments are in line with higher level policies so that they act complementary.

Regions, as the administrative entities closer to the needs of a territory, should involve all relevant actors to shape industry supportive policies, bearing in mind the purpose of their strategy. Alignment of approaches across different areas of policy implementation along a defined and agreed-upon common strategy is critical to achieve high impact results. Collaboration is key also on the level of policy development and their implementation through public investments and programmes.

Political and administrative policies taken at regional level normally require a shorter time before they can be implemented, with a more effective impact. This is particularly true when it comes to the health sector. Regional pilot studies can be an important tool to support implementation, but alignment to the overall regional strategy is fundamental.

Also, regions can create new interregional and cross-border links, aimed at creating collaboration among areas that demonstrate many similarities. A valuable tool for this is participation in European Partnerships. In the field of PM the upcoming EP PerMed is an especially important tool as it will bundle all PM related activities within the EU and build linkages to other related EU-wide initiatives, as well. Participating regions will profit from an increased visibility, preferred access to the international R&D community, and the opportunity to participate in policy guiding activities within Europe.

Regions also have a strong interest in supporting economic growth inspiring activities. PM and PH offer such an opportunity. They also offer additional benefits in terms of improved healthcare for citizens, supporting equitable access, promoting prediction and prevention of disease. Population health benefits are to be expected that increase quality of life within regions.

Research and investment in the field of precision and personalized medicine will significantly improve quality of life in modern society but need to be integrated with economic and industrial development. It is also necessary to raise public awareness so that these advances will be able to really impact society at all levels, keeping in mind the need for an equitable access for all citizens.

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