ICPerMed
INTERNATIONAL CONSORTIUM

Workshop Report

5th ICPerMed Workshop

Advancing Personalised Medicine through Technology Development

14-15 November 2023
Siena, Italy

Content table

I. Executive Summary

The International Consortium for Personalised Medicine (ICPerMed), initiated in 2016, brings together public and private 'not-for-profit' health research funding and policy organisations. The initiative comprises already more than 50 European and international partners from 32 countries representing ministries and funding agencies. The European Commission is participating as observer. ICPerMed serves as a flexible framework for cooperation among member organisations to drive the future of Personalised Medicine (PM).

With the support of the ICPerMed Secretariat (Work Package 2 "Stimulating cooperation and transfer of knowledge"), funded by the European Union, ICPerMed organises events, as workshops or conferences, in order to establish a forum to discuss needs and barriers for PM development, innovation and implementation, to develop research and strategic priorities and guidelines in the field of PM, to develop, share and disseminate standards and best practices.

The 5th ICPerMed Workshop, entitled **"Advancing Personalised Medicine through Technology Development"**, took place in Siena, Italy, on November 14-15, 2023.

The workshop was organised by ICPerMed and was financially supported by the European Union (through the ICPerMed Secretariat, grant agreement No 964197) and the Tuscany Regional Government (ICPerMed Executive Committee member organisation) with the support of Toscana Life Sciences (TLS).

The workshop was held in a hybrid format to ensure the participation of all interested and invited parties. The workshop assembled almost 90 international experts of diverse areas of PM in physical presence and about 10 experts virtually, including researchers, clinicians, representatives of biotech companies, pharmaceutical industry and of European infrastructures as well as ICPerMed members, representatives from ministries and funding organisations, and the European Commission (EC).

This pivotal workshop took an in-depth look at the technological innovations shaping PM today. Keynote lectures from international high-level speakers introduced the participants to the latest developments in a wide range of emerging technologies. During panel discussions and interactive sessions, speakers and workshop participants discussed how these can be used in personalised medicine approaches. The workshop facilitated the discussion and the exchange of experiences, ideas, perspectives between international and regional high-level experts in the field. It was organised around three panel sessions focused on three key areas in PM: Technologies in PM; Research and regulatory perspective for technology development; and Collaboration of research and healthcare providers to foster innovations. Four keynote lectures related to innovation, clinical, European National regional and international perspectives. In addition, there was one plenary session dedicated to the ICPerMed 'Best Practice in Personalised Medicine' Recognition 2022-2023.

This workshop report shortly summarises the discussions. Presentations, video statements of speakers, a workshop video as well as the workshop agenda and a document presenting the speakers are available on the ICPerMed website.

II. Workshop Agenda

The workshop was structured in the following plenary sessions, divided in two days:

Tuesday 14th November:

- Opening session.
- Keynote Lecture: Innovation perspective – A look to the future of PM, current innovations in the field and the role of technology in driving innovation into the healthcare sector.
- Keynote Lecture: Clinical perspective – A clinical perspective on PM technologies.
- Keynote Lecture: European Regional perspective - Presentation of activities concerning PM development and implementation.
- Keynote Lecture: International perspective – Current practices, advantages and needs as well as challenges for PM technology development and implementation in healthcare and clinical practice.
- Session: Technologies in PM including a panel discussion.
- The ICPerMed 'Best Practice in Personalised Medicine' Recognition 2022-2023

Wednesday 15th November:

- Session: Research and regulatory perspective for technology development including a panel discussion.
- Session: Collaboration of research and healthcare providers to foster innovations including a panel discussion.
- Closing remarks

III. Welcome & Introduction

The following speakers participated to this session:

- **Nicoletta Fabio**, the Mayor of Siena
- **Elisa Nannicini**, Director of health investments at the Regional Ministry of Health, Tuscany Region
- **Fabrizio Land**i, President of Toscana Life Science (TLS) Foundation
- **Indridi Benediktsson**, Policy Officer on Health Research, DG Research & Innovation, European Commission
- **Ejner Moltzen**, Innovation Fund Denmark, and Chair of ICPerMed

The speakers gave welcoming speeches and thanked the organising team of the workshop and the City of Siena for this event. Furthermore, the ICPerMed consortium was introduced to all the on-site and online attendees.

Monika Frenzel, International Coordinator in the Biology and Health department of the French National Research Agency, introduced as moderator of the event the overall topic of the workshop, the focus of the keynote lectures and sessions that represent together key aspects essential for technology development in PM and the later implementation of technologies in healthcare systems, e.g. through the keynote topics related to innovation, clinical, European National regional and international perspectives in PM but also the session topics.

She encouraged the active participation of the attendees to actively contribute to discussions and share their expertise, their knowledge and new perspectives and insights in order to contribute to PM advancement through technology development.

Nicoletta Fabio

Nicoletta Fabio started her opening speech with welcoming all the attendees for coming to the city of Siena.

Main points of the talk:

- Artificial Intelligence (AI) provides crucial support to healthcare.
- PM introduces new approaches in medical care, which makes treatments less invasive and more effective.
- The association of AI and PM represents a revolution in modern medicine.

She thanked the TLS foundation, one of the organisations of excellence of the city, as she indicated, for the significant contributions in scientific research and innovation they provided to the region for past years. She reaffirmed the importance of the event and that its contribution to significant advancements and wished good work to all the participants.

Elisa Nannicini

Elisa Nannicini expressed her great pleasure to initiate the workshop.

Main points of the talk:

- The EC and several initiatives that involved European National Regions hold a major role in the implementation of PM and translation of the success of clinical research.
- The Toscana region and the directorate encourage the investment in Research and innovation (R&I) as well as creation of solid structures and technology transfer activities to accelerate the market of innovative solutions, with the aim of facilitating the modernisation of regional health system.

- The organisational model for the valorisation of biomedical and pharmaceutical research with the TLS Foundation, office for the enhancement of research - UVaR, which aims to provide and integrate support to scientific research and to healthcare systems through the protection of intellectual property, to the management and exploitation of research results, as well as the support for industrialisation and clinical development.

- UVaR conducts its activities with regional stakeholders such as: universities, universal hospitals, public research organisations, etc. It has assisted 2027 inventions, 69 patent applications, developed and implemented 127 technology transfer agreement between 2009 and 2022.

- Precision Medicine project leads to the creation of PerMed, the regional centre for precision medicine, designed to set up and integrate a public and private open access precision medicine platform which allows companies and research organisations to strengthen their projects by sharing competences, facilities and resources, through the regional healthcare system.

- Setting up of a European international permanent network for health and social affairs, as well as the regional life science technology which has foster interactions and synergies between industries, universities and regional healthcare system.

- Between 2015 and 2023, the Toscana Region funded regional, national and international projects, and in total 193 projects with an investment of 99M Euros. It also developed and updated the regional Smart Specialisation Strategy, where PM is an investment priority and a PM definition in line with the ones adopted by EC.

- The internal collaboration strategy is to multiply the impact of activities already put in place as well as to fund all regional competences that are essential to prepare an environment supportive for research and tackling health challenges.

- The Toscana region has participated actively in ICPerMed and has invested through the ERA PerMed network a total of 918K Euros for different regional projects in PM, conducted by research groups from Tuscany for a total value of 3.9M Euros, which allowed investigators to engage with international research groups.

- The Toscana region contributed to improve the quality of R&I through cooperation with policy makers and research funders in other regions.

- The commitment in PM is going to continue: As member of the European Partnership for Personalised Medicine, EP PerMed, the Tuscany region committed to a financial investment of 2.1M Euros for transnational research projects in PM.

Elisa Nannicini concluded by thanking TLS, the EC, the Mayor of Siena, as well as all the attendees for their work and attendance.

Fabrizio Landi

Fabrizio Landi started his welcoming by introducing the history of Siena, and the vaccine tradition in the region, due to the overpopulation and the infectious diseases at that time, which made a basic history in Siena for focussing on Life Sciences. He cited as definition of PM: "the right treatment at the right time for the right patient".

Main points of the talk:

- There is a strong cooperation between the healthcare system and the regional actors.

- A mix of public and private funders to support PM is essential.

- TLS promotes the role of healthcare technologies in research, and is involved in the management of investments and support stakeholders to invest in research and development (R&D), specifically for new technologies and processes.

Indridi Benediktsson

Indridi Benediktsson introduced the perspective of the EC on PM. He explained how the EC has been instrumental in the funding of research in the last decades and how they supported networks in this field, with ICPerMed and ERA PerMed as notable examples, as he said.

Main points of the talk:

- EC aims to push in the future the translation of results of research funding investments in the healthcare itself.
- Many events focusing on PM were organised by the EC in 2011 and 2015, before ICPerMed took over this activity and the animation of the PM community.
- It is time to put more promising research results in medical practice.
- There is an increased interest in PM on the political side, e.g. the intention of Germany to reimburse costs for genomic sequencing and analysis for cancer and rare diseases. Many regions (such as the Tuscany region) are working on introducing PM into healthcare system. Three European members states included PM in their agendas of the EU Presidency events: Sweden and Spain in 2023, Belgium in 2024.
- The EC will continue to promote the field of PM by funding research projects and networks. As example: A call for proposals on the topic "Personalised Prevention" with a budget of 50M Euros has recently been closed.
- EP PerMed has just starting with an initial funding of over 300M Euros, and will continue the work of ERA PerMed and supports ICPerMed, but will go beyond both initiatives by including new dimensions concerning innovation and the translation of research results in clinical practice.
- PM initial focused mainly on genomics, while it includes today all aspects in the profiling of patients to optimise prevention, treatment and care.

Indridi Benediktsson underlined that previous work has been fruitful and concluded with the need to and great potential of the translation of research results into clinical practice.

Ejner Moltzen

Ejner Moltzen underlined the importance of the workshop to provide inputs to the technology development in PM. He specified that the aim of the workshop is to focus on technology, R&D perspectives, regulatory perspectives and implementation perspectives.

Main points of the talk:

- Over the past years, research results turned into treatment for patients, and on the international level, PM is in the agenda for 3rd world countries for efficient and equitable access to healthcare.
- The implementation of PM in clinical practice and healthcare systems is still a challenge and solutions for PM are not easily adopted.
- The aim of the workshop is to invite health experts to provide and suggest solutions for technology development and its implementation, and to discuss how to overcome potential identified hurdles.
- Experts need to provide guidance to decision makers, key stakeholders, and to payers so they could take the right decision.

Mr. Moltzen concluded that the main objective of this workshop is to position ICPerMed and PM community in the right direction, to write a future with more effective healthcare system.

IV. Keynote Lectures

Moderator:

- **Monika Frenzel**, International Coordinator in the Biology and Health Department of the French National Research Agency, France

Speakers:

- **Kari Stefansson**, deCode genetics, Icelend
- **Matthias Schwab**, Department of Clinical Pharmacology, University Hospital Tuebingen, Germany
- **Francesco Dotta**, University of Siena, Italy
- **Simon Travers**, Hyrax Biosciences, Ireland

Kari Stefansson

Title of the talk: Contributions of genetics and environment to the foundations of precision medicine.

Overarching topic: Innovation perspective – A look to the future of personalised medicine, current innovations in the field and the role of technology in driving innovation into the healthcare sector.

Presentation's key messages:

- PM's definition: "Medicine practiced in the context of understanding of molecular nature of Human diversity".
- Human diversity is a result of 1) the diversity in ACGT (nucleotides) sequences and 2) the interplay between the environment and the genome. With increased age, there is a higher probability that the environment influences the genome.
- The further correlations were identified: 1) Diversity of proteins in plasma and the diversity in phenotype; 2) the proteins level and appearance of diseases; 3) the proteins level in blood depending on age or body mass index (BMI); hence, proteins are business molecules in our body
- Proteomics can be used 1) to find the causal gene; 2) to bridge the gap between the genome and clinical phenotype, 3) to provide biomarkers for disease progression and regression, or 4) age and organ's age prediction in mortality
- Gene-gene and gene-environment interactions begins with the study of variants.

Discussion's key messages:

- There is a need to develop a deep understanding of complex biological information and processes: proteomics, genomics, microbiome, etc. and of the deep complexity of the molecular diversity of human beings.
- Technological communities need to collaborate to create integrated molecular signatures.
- How will the PM community ensure the instauration of reproductible pathways? Challenge: Most results are irreproducible. A potential solution could be AI models helping to integrate the vast number of individuals' data.
- No correlation between polygenic risk scores and proteomic risk scores was found in a study conducted within a certain age range. The proteomic risk score changes with age. No correlation was found between proteomic risk scores and cardiovascular diseases.
- There is a need to look for new targets and biomarkers for treatment.
- How far is the translation of research results into clinical trials and practice? There is still a resistance (in Iceland) for using research data for clinical practice.

Overall key messages:

- PM is based to a large extend on genomic knowledge.
- AI solutions can be a great support for the future but cannot solve all currently existing challenges.

Matthias Schwab

Title of the talk: Pharmacogenomics and Personalised Medicine: Implication for Clinical Practice.

Overarching topic: Clinical perspective – A clinical perspective on personalised medicine technologies.

Presentation's key messages:

- PM's definition: "An emerging approach for disease treatment and prevention that considers individual variability in genes, environment and lifestyle for each person".
- PM is a delicate balance between benefit and risk.
- Major problems with clinical consequences are 1) the non-response of patients to drugs and 2) drugs that are not reaching the market as they are at the end non-effective (phase III and submission failure of 83 drugs from 2007-2010).
- Subdivision of patients in subgroups according to their genetic information: Genomic information from both, the patient and tumour, provides vital information to guide drug development and treatment decisions: prognostic, efficacy, toxicity and exposure predictors.
- For PM, genome, epigenome, lifestyle, nutrition, microbiome, age, gender, BMI and drugs taken should be considered.
- Pharmacogenomics (PGx) has shown the importance of genetic tests before treatment choice to avoid toxicity or death. Genotype-guided treatment reduces the incidence of adverse drug reactions. A study in 2022 has shown that 35% of drugs are cancer agents.
- Implementation of PGx into clinical practice at the Robert-Bosch-Hospital in Germany. PGx supported by AI to improve health, healthcare and health systems.

Discussion's key messages:

- Human and environmental variability could provide a geographical repartition of diseases.
- AI: there is a need of ethical regulations and equity in different countries.

How to bring PM to the patient and to clinical practice:

- Provide tools and information to clinical doctors.
- Introduce information systems in universities.
- Convince stakeholders, politicians, Ministry of Health and Research to invest in PM research, development and innovation.
- Convince people through the demonstration of benefits through PM.

Remaining challenges for bringing approaches in practice:

- Genetic studies are performed once in the whole life.
- Preference to start by sérobiotic study, then genetic information.

Overall key messages:

- The understanding of inter-individual variability to drug response is crucial for PM, comprising various levels of omics technologies.

- High evidence is currently given for the benefit of implementing PGx into clinical practice and recent data indicate a substantial decrease of adverse drug reactions considering preventive PGx testing.

- Major efforts needed to achieve reimbursement for PGx diagnostics by various stakeholders.

Francesco Dotta

Title of the talk: The Regional Centre for Personalised Medicine: A Precision Medicine approach to Type 1 diabetes mellitus.

Overarching topic: European Regional perspective - Presentation of activities concerning PM development and implementation.

Presentation's key messages:

- Sequencing costs per genome are decreasing, hence, molecular characterisation becomes affordable.

- PM requires the availability of large-scale databases and big data management tools that could be used as powerful "omics" patient characterisation tools.

- The challenge is the change of the medication approach from one-size-fits-all to a precision approach.

- Sharing experience from the Regional Centre for PM (a collaboration between the Università degli Studi di Siena, USIENA, the Azienda ospedaliero-universitaria Senese, AOUS, and TLS) a new precision medicine initiative to enable curing of diseases like cancer and diabetes and to give people access to personalised information with the overall goal to keep patients healthier. The intervention focused specifically on PM care for Type 1 diabetes (T1D) mellitus.

- The T1D disorder in an autoimmune disease. There is a high heterogeneity, hence different forms of diabetes due to interaction of genetics and environment. T1D heterogeneity has implications for disease prediction, prevention, diagnosis and treatment: Clinical, genetic, immunological, metabolic and pathological heterogeneity. Main objectives of a study in this field of the Regional Centre for PM are the identification of predisposed persons to be treated and the identification of a treatment strategy.

- The FDA approved the use of the first immunomodulatory drug for the prevention of T1D in 'at-risk' individuals.

- The remaining challenge is the identification of 1) specific endotypes of T1D subjects on the basis of the expression profiles of circulation biomarkers, 2) of circulating microRNA/small RNAs and of 3) rapid and slow progressors.

- An example of a partnership in the field of T1D is the INNODIA Biomarkers Research Study.

Discussion's key messages:

- Could the molecular characterisation of a panel of genes be extended to other autoimmune genes to predict other autoimmune diseases? Some RNA pattern could be associated to other diseases. Still ongoing studies have shown that a single microRNA can target several genes.

- The translation of one experience to another region, from one context to another, can be achieved through training ("Train people to do the right things."). Overall, multidisciplinary approaches should be used.

- How to move to other regions considering the ethical part to collect data? The INNODIA foundation is open to all clinical centres who want to participate to this clinical trial to be approved

from ethical committees. Furthermore, alignment of legislation for the collection of data is essential.

- Was a patients' platform developed to share data on national and international level? Electronical data record will be approved and shared, and will be a source of important information in T1D.

Overall key messages:

- Environmental trigger initiates selective autoimmune destruction of the pancreatic beta cells in genetically predisposed individuals.
- Two-seq platforms profiling reveals two distinct T1D subjects' groups.
- Therapeutic interventions allow B-cell preservation.

Simon Travers

Title of the talk: Bringing scientific innovation from academia to business: our journey, lessons learned and other stories.

Overarching topic: International perspective – Current practices, advantages and needs as well as challenges for personalised medicine technology development and implementation in healthcare and clinical practice.

Presentation's key messages:

- It is essential to bring scientific innovation from academia to business.
- There is inequity in receiving treatments for HIV+ (human immunodeficiency virus positive) patients between countries.
- More than 20% of individuals may be resistant to one or more first line drugs. Drug resistance can be detected using DNA sequencing. Drug resistance testing reduces treatment failure.
- Example for the transition from academia to business: Development of "Exatype", a disease agnostic software platform. Development of unique plugs for specific applications.
- Challenges are 1) Lack of knowledge for business model creation; 2) Lack of funding; and 3) Lack of understanding or not adapted regulatory.

Discussion's key messages:

- For moving from academia to business, 1) there is a need to make a difference with the proposed approach, and 2) this is a long process transition with many difficulties.
- There is a need for people to be consulted with expertise in business model creation. One option could be to work closely with the technology transfer offices in universities or medical research council. Another option could be to integrate in teams a person with industry expertise.
- For the business development it is important to understand the demand for the product/platform so that scaling of e.g. new plugs is less problematic.
- Productivity doesn't depend on the number of persons in the team.
- Next steps in business growing strategy: 1) Working with big players, 2) having a value in topics with a high medical need and healthcare burden like infectious diseases, 3) having a potential growing to the oncology perspective, 4) study the partners' needs.

Overall key messages:

- Remove barriers from DNA sequence analysis to enable anyone to transform raw sequence data into actionable results. Thereby, it is essential to enable global access by sharing and develop-

ing expertise, provide computational resources, consider price (of product or service) sensitivity (availability of product or service for different healthcare systems in low, middle- and high-income countries) and reduce complexity for the implementation of the service/product.

- Consider the translatability of approaches from one medical/disease field to another, e.g. problems solved for HIV are applicable to a wide-variety of applications. The system developed by Hyrax Biosciences has a value in infectious diseases, but could be applicable to a wide-variety of applications and diseases.

- To move from academia to industry, there is the need of 1) having a business model in place, 2) leverage/attract the necessary funding, 3) understand and follow the current regulations, and 4) have the required expertise.

V. Session: Technologies in Personalised Medicine

Moderator:

- **Ejner Moltzen**, Chair of ICPerMed, Innovation Fund Denmark

Panellists:

- **Frédéric Dayan**, ExactCure, France
- **Carlotta Masciocchi**, Gemelli, Italy
- **Silvio Weber**, Miltenyi Biotec, Germany

Aim of the session:

Provide an overview about different technologies implemented in the field of or supporting PM and how those (can) contribute to personalised care, e.g. facilitating the prescription of specific therapeutics that are best suited for an individual for example based on pharmacogenetic and pharmacogenomic information, or supporting the decision making by considering different sets of health information. Furthermore, the session will present existing tools enabling cell and gene therapy.

Frédéric Dayan

Title of the talk: A Digital Twin for a proper use of medications.

Presentation's key messages:

- Around 36% of patients do not receive the correct medication. Personalisation will avoid cases with inappropriate medication. "ExactCure" is an example of a digital health technology, focussing on the proper use of medication: The right drug to the right dose, to the right patient and the right time, no standard patients.
- Digital Twin: Prediction of the PM from individuals (from the drug intake, the period of drug efficacy, and the cases of overdoses and under-dosing).
- The know-how behind the medical device: information of pharmacological publications is integrated into mathematically models. The models are evaluated with external cohorts of patients.
- Multidrug interactions: toxicity situations – focus on the pharmacokinetic and pharmacodynamic simulations

Discussion's key messages:

- The Digital Twin technology can reproduce the systematic bias found in the literature and reflects the state of the art. The technology is still in preliminary phase. The integration of this technology into the healthcare system, the analysis of its practicability and acceptability is still ongoing.
- Important steps: Testing the accuracy of the simulations, the impact in terms of clinical application and understand as well as communicate the benefits for patients.
- The target of the Digitial Twin technology: the healthcare system throughout the entire value chain and environment.

Overall key messages:

- Digital twins' technology can help to avoid inappropriate medication: The proper use of the medication is essential.
- Digital Twins should be used not only to design new drugs, but also as companions of real-life patients, and to understand each personalised response to medications.
- ExactCure's main challenges: acceptance from healthcare professionals and hospitals of the benefit of their software. These challenges are related to an access to data and validation of data, but also to trust and responsibility issues in relation with the use of AI.

- Despite these challenges, the ExactCure system has been implemented at some hospitals and hopefully these implementations can be used to promote the system further – and in due time to reach the personal avatar vision of the company.

Carlotta Masciocchi

Title of the talk: The Gemelli Generator concept: the development, implementation, and future perspective.

Presentation's key messages:

- Gemelli Generator: Generator Real World Data's (RWD) mission and the know-how of their mathematicians, physicists and engineers that together with the clinical team, support data-driven health research by determining early diagnoses and making tangible tailor-made and patient centred therapies.

- Its mission is the support of clinical research to develop personalised/precision medicine leveraging real world evidence and data sciences methods, through scientific research, industrial cooperation, deployment in clinical practice and field-specific education. They aim to maximise the use of data, that clinicians daily integrate in the electronic health record in order to perform scientific research and industrial cooperation.

- Keywords are predictive, participatory, preventive and personalised.

- Development of real-world evidence solutions in order to get a multi-centric training of predictive models.

- A digitally-enabled models of care project, which guarantee to patients a continuity of care within the hospital: data coming from the hospital is connected to the data coming from outside the hospital (integration inpatient/outpatient pathways).

- Primary research asset: retrospective observational cohort of patients characterised by a diagnosis or group of diagnoses with data from standard of care.

- Personalised care patterns: automatics alerts in order to communicate with the clinician some complex situations for patients.

- Mobile app for patients allows self-reporting, communication and self-care.

- Clinical dashboard for clinical staff for monitoring, advise to patients, prevention and defining intervention.

- Integrated care protocol following guidelines, standard operating procedures, technical instructions and support.

- Case heart failure programme with a retrospective heart failure data mark that is daily updated, in which all the relevant information about heart failure and different clinical questions are included in order to accelerate the answer to the clinicians.

- Creation of a dashboard in order to provide the general view of the patient to clinicians.

- Electronical record: Heart Failure Datamart with daily updated procedures, in order to create data visualisation dashboards and predictive modelling. The workflow is as followed: Step 1: Cohort definition and clinical data extraction, with structured data (e.g. demographics, laboratory values, echocardiograms, observations) and unstructured data (functional scores, comorbidities, treatment); Step 2: Data transformation through formula based calculated variables; Step 3: Data Quality Assurance.

- Example: Azimuth, a digital project, a care model that enables to build a better self-management of patients, with periodic visits to hospital and remote

monitoring in order to prevent some acute events. It is connecting information coming from retrospective approach by including all the information coming from outside the hospital (environmental data, pharmacological prescription).

Discussion's key messages:

- The digital solution is currently focused on heart failure. Patients enrolled have just one hospitalisation into the hospital.

- To be able to work in an overarching approach by integrating all information around one specific disease and by respecting the legal frameworks, each patient must fill a consent form. A close collaboration with clinicians and the API (application programming interface) of the project is essential.

- Applicability or extrapolation of the approach to other hospitals, i.e. the export of this technology to other hospitals is challenging and an ongoing task. It requires an exchange with the data warehouse in the respective hospitals in order to understand how data are organised and how to integrate them. Validation procedures are needed to extract knowledge from reports written by clinicians. Before the technology and infrastructure developed by the Gemelli Generator Real World Data facility are exported, it is necessary to standardise the procedures.

Overall key messages:

- It is necessary to collect all patient's information and to maximise the use of data.

- The current system is very localised, including patients directly linked to the hospital, and has already shown good results in terms of better treatment for the patients, including preventive actions.

- The Gemelli project is very successful, but there are data challenges concerning the increase of the geographical scope. However, the Gemelli concept and the solutions it has developed have the potential to be exported to other hospitals for local applications.

Silvio Weber

Title of the talk: The technology provider´s dilemma – When new developments put great biotechnology platforms at risk.

Presentation's key messages:

- More than 10.000 patients have been treated so far with the CAR-T therapy. The main obstacles for the implementation of this therapy are the low accessibility and the high costs for the patients. There is a need to change the traditional treatment paradigm to build-up a personalised medicine environment, that integrates bioanalysis, bio-monitoring and bio-engineering, from the very beginning of the disease.

- The goal should be to get from treatment to cure.

- Miltenyi Biotec is a biotech company focusing on cell therapies. More than 6.000 patients have been treated with cell products using these technologies.

- MACS (flow cytometry) Technology is based on three methodological steps to obtain the maximum purity and highest yield of viable cells: Magnetic labelling, magnetic separation and elution of labelled.

- The MACSima technology is one example of the devices and an automated imaging system which enables users to visualise in one experiment more than 100 proteins in one sample (for example in a solid tumour tissue). It provides the possibility to draw a schematic picture of a tumour micro-envi-

ronment, which is essential for the success of the treatment

- The CliniMACS Prodigy is a bioengineering device, for late-scale clinical and commercial industrial scale manufacturing. It integrates a formulation unit that enables automated and sterile sampling as well as final formulation and filling of the cell product.

- Integrated in the CliniMACS Prodigy workflow, the CliniMACS Electroporator enables flexibility in large-scale transfection of various cell types.

- The different technologies allow a decentralised manufacturing at point-of-care, hence the establishment of multiple point-of-care manufacturing centres with an easy technology and assay transfer of processes and analytics. The technology has a high degree of automation and standardisation and allows a more patient specific approach.

- Biomonitoring is the next step which will allow the analysis of high-throughput drug release in living cells and in vivo structures for later application.

- The bio-digitalisation strategy aims to integrate the different workflows and connect the different products.

Discussion's key messages:

- For patients the time between the sample collection, the sample processing and the communication of results back to the patient is crucial. Typical critical cases are late-stage cancer patients as they might not have the time to wait around six (6) months to start a genetic therapy. Therefore, an accurate data flow is key.

- The understanding on how to reduce the costs of new experimental techniques could be gained through new innovations.

Overall key messages:

- Gene therapy is a key strategy in personalised treatment, however it is very expensive.

- Developments of cell and gene therapies are still at an experimental stage and major investments are needed to fully develop the opportunities in this field.

- Validation of these therapies can be challenging. In some cases, they are considered as medical devices and here the new requirements of the In-vitro Diagnostics Regulation (IVDR) for clinical validation can become a major problem due to the small patient populations within relevant indications.

Panel Discussion of the session Technologies in Personalised Medicine:

- Today, there are already advancements in early clinical translation. To bring PM to the citizens and the patients research outputs have to be translated into practice. To achieve a successful translation, the product development should be directly relayed to research. Health economic research should be considered, e.g. in order to compare prevention and treatments efficiency and the benefit for the healthcare systems. The incremental cost-effectiveness ratio analysis can support the comparison of new products or interventions, healthcare system assessment and application for new products (that might be more efficient and even less expensive than already existing and approved drugs). It is essential to connect the legacy of drugs development and healthcare execution and to bring drug development phases (1, 2, 3) and the connected technologies together.

- The translation of PM research results into clinical practice also requires acceptance by regulatory authorities and society, patients and citizens. The overall concept of personalised medicine needs to be accepted (to apply health technology assess-

ment overall to precision medicine). Patients as well as end users or other stakeholders should be involved in the research, innovation and implementation processes from the very beginning (not only at the end), e.g. to well identify the right target of research or innovation, to enable equal accessibility to avoid social imbalances and overall to support that innovations are responsible, equitable and affordable. Also considered should be the efficiency of new digital devices for the elder population.

- It is essential to reflect on: "Do we apply research to gather more insights and understand biology better?" and "Do we want to provide a solution that is truly transformative and change outcome of patients?". The private sector is in a position to bring new solutions to the market. It should be always carefully reflected on taking off healthcare solutions that might not be state of the art anymore vs. implementing constantly new technologies, hence healthcare systems might be overwhelmed by the high number of new technologies. Overall, healthcare systems should show transparency and new technologies implemented evidence for the benefit of the patient.

Perspectives for the future: The most important next step towards implementation of PM are:

- Business models, the market need/access and technology development must be considered together and interconnected.

- It is essential to share results and the evidence from real-world data, including adverse events in order to understand how a specific drug or specific models work/s in a real-world setting.

- Demonstration of drug safety and drug effectiveness.

- AI that could integrate all information in the field of PM from research, literature and clinical trials.

Conclusions of the session Technologies in Personalised Medicine:

- Technology development in PM have the high potential to reduce costs for diagnostic tests for patients.

- New technologies will continue to be a key driver in the further development and implementation of PM. There is therefore still a high need for major investments in all PM-related technology field at a broad level.

- Issues relating to data is a general theme for all PM areas. These issues concern technical aspects (curation, standardisation), access to data (legal frameworks, consent) and use of data in an ethical manner (general acceptance of use of data among patients and citizens).

- Reluctance to accept new technologies is an issue, both among healthcare professionals (HCPs), patients, and citizens. Such reluctance is to some extent due to the lack of resources in the healthcare system to take on board new technologies, but is also due to conservatism on the side of the HCPs and fear on the patients or citizens side. There is thus a high need for more information, communication, and education to overcome these barriers and convince all stakeholders about the benefits and opportunities the new technology solutions offer.

- Use of new technologies, e.g., cell and gene therapies, are seen as being expensive from an isolated perspective. Thus, there is a need to rethink how healthcare systems are funded. The traditional funding and reimbursement systems cannot accommodate a set of new upcoming solutions and there is a high need to identify new health economic models.

- Regulatory requirements can become an increasing hurdle. For example, some of the new technologies are considered as medical devices and for those the new IVDR regulation with its increased focus on clinical validation can become a major problem.

VI. Session: Research and regulatory perspective for technology development

Moderator:

- **Hemma Bauer**, Head of Unit for Life Sciences at the Australian Ministry of Education, Science and Research.

Panellists:

- **Johannes Haubold**, University of Duisburg-Essen, Germany
- **Marlene Thomas**, Roche, Switzerland
- **Saheli Datta Burton**, University College London-STS, United Kingdom

Aim of the session:

The main aim of the session was to discuss the frameworks needed for PM technology development and innovation and what should be considered when it comes to implementation of innovations in healthcare.

It was an opportunity to shed light on the existing regulatory framework and to present along concrete examples of technology development in PM positive and negative experiences of manoeuvring the innovation process through the regulatory requirements and demonstrating clinical evidence. Furthermore, it was the aim to bring also a science policy perspective into the discussion and to reflect what is needed in order to support and facilitate innovation processes in PM.

Presentation of case studies or examples of HTA assessments of personalised medicine technologies and interventions, and support of personalised medicine technology developments through adequate regulatory and legal frameworks.

Johannes Haubold

Title of the talk: Clinical AI-Integration.

Presentation's key messages:

- Show-case of the development of a new AI application with the focus on non-invasive image-based tumour decoding and virtual sequencing that is used in-house at the university hospital Essen. A particular aspect of his presentation was on the validation processes of the AI applications.
- The main obstacle is the data integration of AI applications into clinical routine. Every hospital has different clinical data for each patient. There is a lack of connection between different data sets.
- A solution could be the creation of Smart Hospital Information Platform including for the "application" question a system of innovation, a platform that enables the differentiation of data and for new data a system of record.
- The Fast-Healthcare-Interoperability-Resources (FHIR) system connects more than 4000 subsystems and allows to check 1,3 billion data points in the smart hospital info subsystems.
- It is important to root the right data point to the right algorithm.
- There is the possibility to integrate data manually in "DICOM-Metadaten" but manual data integration generates an uncertainty.
- Using algorithm segmentation of the body in different compartments in a single platform allows combining of Body and Organ Analysis (BOA). Thereby, 93% of the entire body is automatically segmented by the algorithm. The integration of analysis in a DICOM note and examination performed is automatically analysed.

Discussion's key messages:

- No discussion (the speaker sent a video presentation)

Overall key messages:

- Quantitative parameters, especially the body composition parameters, has clinical benefits (example studied: the positive influence in the survival of non-metastatic patients).

- AI applications should be integrated into clinical routine.

Marlene Thomas

Title of the talk: Precision Medicine's Journey to Transforming Healthcare.

Presentation's key messages:

- The concept of PM is to envision a wide and equal patient access to diagnostic technologies and therapeutics beyond a narrow circle of academic centres in privileged countries.

- There is an evolution of biomarker testing: Biomarkers are widely used at every stage of drug discovery and development (diagnostic, monitoring, pharmacodynamic, predictive, prognostic, safety, risk).

- Commercialised medical devices or in vitro diagnostics that are used in clinical settings for patient management decision or to guide treatments fall under the IVDR (In Vitro Diagnostic Regulation) or MDR (Medical Devices Regulation), respectively, and need to demonstrate scientific validity, analytical performance and, importantly, since 26 May 2021 when the MDR has become applicable, clinical performance.

- A performance Evaluation Study Submission under the IVDR is needed for all combined studies (drug + IVD) with any medical decisions making.

- Cancer example: Tumour Profiler Study (RUO tests), a combination of 10 individual test results to improve the biological understanding of the disease and to predict optimal treatment path. The tumour genomic profiling has revolutionised the oncology field through the refinement of cancer subtype classification, the identification of patients who most likely benefit from systemic therapies, or the screening for germline variants that influence heritable cancer risk.

- Neurodegenerative disease example: Wearable sensors applied to the human body for neurodegenerative diseases (NDDs) diagnosis. Syde, formerly known as "Actimyo" is a wearable device for the Duchenne Muscular Dystrophy (DMD) and a qualified endpoint designed to monitor ambulation in DMD during normal daily living in clinical trials.

- Addressing practice gaps and building sustainable care infrastructures are critical to deliver on the promise of precision medicine. For example, 64% of potentially eligible patients with advanced non-small-cell lung cancers (NSCLC) are not benefiting from precision oncology therapies.

- There is a need of multi-stakeholder collaboration to accelerate the implementation of innovation in routine care, to align quality standards and patient centricity, and to ensure that care infrastructures are in place to facilitate fast access and reimbursement to healthcare innovations.

Discussion's key messages:

- Current situation: A complex regulatory framework is in place with various regulatory stakeholders (HMA, Ethics Committees, Notified Bodies, CITS/EUDAMED, EMA, HTA) to be involved in order to bring a PM approach to the market.

- Concerning PM, it is even more complex as diagnostic and treatment approaches are often combined and data intense so that not only one

legislation applies but two or more that have to be adhered to. Finally, even if a PM approach has reached market access, gaps in clinical practice might hinder the roll out on equally high standards. Therefore, in order to roll out PM innovations in routine care quality standards and patient centricity need to be better aligned, sandbox mechanisms need to be created for future healthcare and regulatory solutions, and care infrastructures need to be in place to facilitate fast access and reimbursement to healthcare innovations.

- There is the need for conformity of medical devices to the IVDR.

- There is the need to establish and work in a PM favouring environment.

- There is a need of algorithms to use secondary tests and combine data.

Overall key messages:

- In order to roll out PM innovations in routine care, quality standards and patient centricity need to be better aligned, sandbox mechanisms need to be created for future healthcare and regulatory solutions, and care infrastructures need to be in place to facilitate fast access and reimbursement to healthcare innovations.

- There is the need to make clinical validation (on national level) simpler and to standardise procedures of validation.

Saheli Datta Burton

Title of the talk: Responsible Personalised Medicine: It all starts here.

Presentation's key messages:

- Responsible Research and Innovation (RRI) is an interactive process by which societal actors and innovators become mutually responsive to each other with a view to the (ethical) acceptability, sustainability and societal desirability of the innovation process and its marketable products.

- Responsible 'Development' is the move from the governance of risk to the governance of innovation itself.

- An incentive could be a risk-based governance, including environmental risks, risks to privacy, ethical-moral risks focused on managing the relationship between science and the public.

- Most of research results do not get transferred to the market and wider society due to the lack of professionalised technology transfer project managers at universities, research centres, and related organisations.

- An incentive is the instalment of a Competence Centre on Technology Transfer (CCTT) that provides training and knowledge to create a support system for the commercialisation of research results, and provides knowledge, methods and tools for the identification, evaluation and protection of technologies, management of intellectual property rights, business development, and negotiation of commercial deals.

- There is the need to provide regulatory knowledge exchange specific to health and medicine.

- The successful clinical translation of computational models developed by small and medium developers or public research institutions need to build robust investor or public funder's confidence in the commercial viability of their innovation to attract the substantial capital resources and regulatory expertise necessary to fund and drive the clinical evidence generation, evaluation, verification, and validation processes needed to reach the market.

- Use existing regulatory knowledge to expand and strengthen capacity, e.g., collaboration with established technology transfer offices (TTOs) at large research universities.

Discussion's key messages:

- Responsible research and innovation is seen as a transparent, interactive process between innovators and societal actors in order to face the societal needs and to make innovations more impactful. There is still a lack of capacity to initiate this dialogue, e.g. between researchers and regulators. The instalment of regulatory departments on institutional level can be a solution to share knowledge also with smaller institutions with no capacity.

- Responsible innovation goes hand in hand with a change from a governance of risk to a governance of innovation.

- The engagement and partnership between public institutions and patients can improve the translation and implementation so that R&I align with the society need.

Overall key messages:

- Currently, research and innovation is funded with a high risk to fail. With a change towards a governance of innovation in which the research community and the regulatory stakeholders conduct regular exchanges, it is expected that innovation processes will be more successful.

- The existing governance framework of RRI provides an excellent policy lever for advancing the implementation of PM.

- The encouraging uptake of the RRI framework within various technology governance areas of the European Commission presents a foundation ready for extending its current focus on "risk-based governance to the governance of innovation itself".

- RRI is an incentive to increase acceptability and research translation and to reduce e.g. lack of trust between clinicians and developers is one cause for low entrance to the market.

- Support for regulatory knowledge exchange could be provisioned as part of the ongoing RRI Awareness initiatives for researchers in health and medicine generally, and PM particularly.

- Technology "non-adoption and abandonment" is the typical result of an unclear technology proposition in terms of a clear benefit for patients and an affordable real-world service model.

- Dialogical engagement and knowledge exchange between research(ers) and regulators remain key for successful research utilisation in health and medicine, and will speed up innovation. The lack of knowledge of the current regulations is a barrier to clinical translation.

Panel Discussion of the session Research and regulatory perspective for technology development:

- The intensive dialogue with regulators (e.g. EMA) is a classic procedure for start-ups bringing innovation to the market with limited resources and knowledge. The constant dialogue and engagement with EMA help start-ups to navigate in the regulatory space.

- There is a need to focus on extending already existing risk based RRI frameworks and initiatives for the provision of regulatory knowledge exchange specific to health and medicine (beyond the current focus on IP), and to use existing regulatory knowledge capacity to expand, strengthen, (and democratise) capacity, e.g., collaboration with established technology transfer offices (TTOs) at large research universities.

- Pathways for supporting regulatory knowledge exchange could be via provisioning knowledge exchange as part of ongoing Responsible Research and Innovation (RRI) Awareness initiatives for research(ers) in health and medicine generally, and Personalised Medicine particularly, and/or by integrating regulatory knowledge exchange in research funding calls for applied (downstream) P technologies, e.g., as part of policy impact or research exploitation.

- Industry or the private sector has knowledge about regulations that does not exist in this form for researchers and academia. Funding organisations should better support innovation, and public money should not be used for publications only.

- Regulatory education should be available for researchers.

- A shift in the mindset of regulatory authorities is needed to see the need to revise processes. Also, regulators need to actively support innovation. Engagement, recognition and acknowledgement for the need of exchange and conversation, is needed at all levels (management and execution).

- Ethic committees should be involved and the need of companies considered.

- Incentives and mechanisms are needed to accelerate implementation efficiently.

- PM-technologies need to demonstrate clinical evidence.

- Technology-dominated PM-approaches have to become widely accessible in healthcare and require respective clinical infrastructures in order to be delivered to patients in a standardised and quality-controlled way.

Conclusions of the session Research and regulatory perspective for technology development:

Knowledge and expertise on the legal requirements are key for a successful development and implementation of PM approaches, in particular when technology-dominated or combined approaches such as companion diagnostics, AI or wearables are involved. Ways to overcome these gaps are:

- to raise the awareness on responsible innovation among all stakeholders involved in research and innovation: researchers, funders, regulators, etc.

- apart from knowledge on IP, to build up regulatory expertise in tech transfer offices of universities and research organisations.

- to foster collaborations among universities to share this knowledge.

- to enhance education and training also on regulatory aspects apart from scientific skills.

- to exchange with regulators on regular basis over the development and innovation process.

- to build up public-private partnerships since industry has a long-standing experience on regulatory issues and a strong network with the regulatory stakeholders.

VII. Sessions: Collaboration of research and healthcare providers to foster innovations

Moderator:

- **Gianni D'Errico**, Head of Project Management Office at Toscana Life Sciences (TLS)

Panellists:

- **Jean-François Mangin**, NeuroSpin, CEA, France
- **Hermann Nabi**, Université Laval, Canada
- **Robert Doczi**, Genomate Health, Hungary

Aim of the session:

Innovation is not a linear process from research to clinical application but also requires a feedback loop back to research after implementation of a technology in clinical practice. The Strategic Research and Innovation Agenda for Personalised Medicine (SRIA for PM, 2023) promotes that overall, the system must be considered as a "System of Health" where results from one element feed into the next steps, but also feedback to previous steps in the value chain, forming a cycle of knowledge and insights that flows in both directions.

This panel included and showcased collaborative efforts in research, industry, and healthcare, addressing key aspects such as stakeholder involvement, long-term collaboration, translation of basic research into innovation and clinical development, technology development and healthcare uptake, stressing the difficulties faced in Europe compared to the international level.

Jean-François Mangin

Title of the talk: A large instrument for population neuroimaging.

Presentation's key messages:

- A challenge in the neuroimaging field is that the analysis of the same brain in different PET (positron emission tomography) scanners yields in different results. A solution is the standardisation for multicentre imaging by comparing brain scans allowing to find similar results.
- The MEMENTO cohort is an example for a multicentre study aiming to harmonise and standardise data from different Magnetic Resonance Imaging (MRI) machines between study centres. The study was built in the context of a cohort dedicated to the natural history of Alzheimer's Disease, to make multicentre neuroimaging affordable.
- CATI is a French initiative launched in 2010 to handle the neuroimaging of MEMENTO. It is support by more than 40 French, European and International centres clinical studies, and is integrating data acquisition and analysis as well as quality controls. To be compatible, the established database is being harmonised with other datasets via algorithmic approaches, e.g. with the UK biobank.
- A typical project supported by CATI is "ENSEMBLE" that aims to predicting outcome in infants at risk for Cerebral Palsy. Machine learning approaches are used to integrate scans from different clinical sites.

Discussion's key messages:

- (Neuro)Imaging standardisation's procedures are essential to establish (sufficiently) large datasets for each type of scanner so that neuroimaging, as deep phenotyping approach, can support doctors as decision support tool. Medical consultation requires high data quality.
- Standardisation's procedures can support the integration of (brain) scans from different projects and that patterns are decrypted by algorithms.
- To obtain harmonisation and standardisation of processes and procedures, a permanent monitoring is needed to use the instrument reliably in routine care.

Overall key messages:

- Standardisation of data acquisition is mandatory for precision medicine.

- Lessons learnt and recommendations for multi-centre imaging are: 1) AI does not improve (data) acquisition quality at the moment; 2) standardisation processes and permanent monitoring are required to obtain high data quality, data harmonisation and compatibility of data sets; 3) GDPR needs to be respected, including a federated organisation in order to be in line with the GDPR; 4) business models should be considered for new tools/technology created, including support for spin-offs, to move towards the implement into healthcare systems; 5) push acquisition standards into routine care and create a feedback loop to the research to enable correction of bias.

Hermann Nabi

Title of the talk: Optimising the integration of innovations from personalised medicine into healthcare: we need different stakeholders working together in COLLABORATION.

Presentation's key messages:

- PM's is the right drug, with the right dose, for the right patient, at the right time.

- Achievements so far are tremendous insights into mechanisms and models of diseases, genes and biomarkers discovery.

- The challenge remaining is the "lost in translation" of PM from guideline to health practice and from practice to health impact. Delivering PM is a complex task, particularly for already established healthcare systems, due to multiple steps to be taken for implementation and application. One example is breast cancer (BRCA) testing access (technology and logistical part) but also access for genetic counselling (human resources, knowledge/education, service implementation).

- Solutions could be 1) funding for earlier research, 2) alternative genetic analysis delivery model and 3) a collaborative approach and partnership between stakeholders, researchers, industry, patients, prescribers, regulators etc., leading to an increase in genetic counselling.

- Examples are 1) MONGENE, a "Collaborative Model to Implement Flexible, Accessible and Efficient Oncogenetic Services for Hereditary Breast and Ovarian Cancer" focussing on personalised risk assessment/risk-stratified screenings; 2) SciLifeLab, a Swedish national centre for molecular biosciences, including clinical genomics.

- A future perspective could be risk-stratified breast cancer screening that requires four steps: 1) Identification and understanding of the biology that leads to risk, 2) stratification of risk groups, 3) development of an implementation approach, including 4) economic analysis. To take those steps, it requires a big team with diverse expertise including regulators and law, to maximise advantages and minimise effects of over-screening.

Discussion's key messages:

- Address clinical endpoints that regulators are interested in, e.g. mortality level/numbers. Consider and work in collaborative approaches and integrate also early endpoints. Convince regulators that survival is not the only endpoint. This can be achieved via collaboration between stakeholders that will be speaking with one voice and therewith better reach out to FDA, EMA and other regulators instead of having fragmented communication.

- Support the feasibility of the implementation of a new technology/approach, e.g. via a simulation study that is not a complete replacement of a current practice, but a first step to implementing PM approaches.

Overall key message:

- Implementation of PM in healthcare requires collaboration between stakeholders.

Robert Doczi

Title of the talk: Computer-Assisted Treatment Decision in Precision Oncology.

Presentation's key messages:

- Genomate Health is a European Tech Spin-out in the US, that started from a foundation of a precision oncology company in Hungary in 2003. They provide services and innovation in precision oncology and support computer-assisted treatment decisions.

- The goal of PM in oncology is the identification of targeted drugs. This requires the identification of suitable biomarkers to be associated with a specific therapy approach.

- Remaining challenges are 1) the complexity of tumour profiles that are often underestimated; 2) the potential impact and contra-indication of simultaneously detected alterations are usually not considered; 3) Molecular tumour board decisions are often highly discordant with a low overall agreement between tumour boards, this prevents scalability broader than remote-hospitals; and 4) difficulty in drug assignment, as on a molecular level there are different drivers, targets and drugs that interplay in each tumour.

- A solution is to move from single associations to computable networks of evidence associations for each individual molecular profile (not a deep-learning approach). Development of an AI-based prediction tool for precision oncology based on experiences of 10.000+ cases.

- Transition of the ONCOMPASS Medicine company to the spin-off Genomate to clinically validate the invented drug assignment system. Clinical validation of the tool took place in the SHIVA01 trial, a prospective, randomised PM trial software, predictive in terms of clinical outcome. The success of the company was rewarded by opening the floor to new cooperation, like with the Mayo clinics that opened up access to big data sets to furthermore improve the tool.

Discussion's key messages:

- A method to encrypt sensitive data without including the patient's identity is to only use in algorithms molecular profiles.

- An incentive in the implementation is to achieve acceptance of and the wish to use new technologies by clinicians, e.g. by having reports generated automatically that provide guidelines (decision support) for clinicians. This can be developed in a step-vice process by 1) getting in touch with clinicians from tumour boards during tool development (e.g. ENCOMPASS), and 2) moving on to other physicians as soon as the tool allows automatic reports.

- Great opportunity comes from the off-label use of existing efficient drug. Already approved drugs could be administrated based on the molecular profile analysis, hence each tumour can be treated as an individual disease. This still requires the establishment of off-label drugs regulation processes. Today, for some countries, off-label drug use is not allowed.

- Remaining challenge is to convince clinicians for the validation of a tool or outcome if only small sample sizes are available. This can be solved through the use and integration of additional real-world data sets. For example, pre-clinical data for validation are produced in Hungary and transnational consortia. Another option could be the organisation of clinical trials for individual tumours.

- Another challenge is the differences between healthcare system and the acceptance of new tools (adapted versions have to be developed).

Overall key messages:

- To avoid discordant treatment recommendations by Molecular Tumour Boards due to the data's complexity, a proposed approach could be to move from single associations to an evidence network, i.e. a computable networks of evidence associations for each individual molecular profile. Those computational solutions might be helpful to address the complexity of tumour profiles.

- Acceptance of new technologies and tools by clinicians has to be achieved.

- Need to speed up regulatory adapted frameworks.

- Steps and hurdles to be still taken are 1) clinical validation, 2) analysis of the potential impact and contra-indications, 3) development of regulation to deal with off-label drugs, and 4) handle efficiently the diversity of healthcare systems in Europe.

Panel Discussion of the session Collaboration of research and healthcare providers to foster innovations:

- There is still a lack so a need to increase the acceptance of new technologies.

- There is a need to combine research and clinical data in one platform to be available for both.

- Work in partnerships and achieve a collaborative approach particularly in complex projects: 1) Start with the identification of experts to be involved in the project; 2) Identify issues to be addressed, e.g. in translation, by involving in all steps the different concerned stakeholders and value their respective expertise; 3) Cooperation with industry or private partnerships are drivers of innovation; 4) Involve clinicians and invite them to use new tools, this can also result in additional clinical datasets to be used/integrated.

- A large number of patients do not respond to therapy, hence there is an increasing importance of molecular testing. Progress in applying PM was made in the cancer field. Thanks to advanced diagnostics and stratification, with molecular and genetic characterisations (evaluation of the change of molecular printing), single tumours are more and more defined as single diseases. Treatments can change the molecular subtyping of the tumour, i.e. an evaluation of the change of genetic printing, hence adapted monitoring, is required (changes during disease progression). This is bringing up the challenge of equity as in many countries there is due to high costs related to the analysis no possibility to do molecular characterisation. To convince healthcare systems of new approaches to be implemented in care, business models but also funding mechanisms for innovation development are needed.

- For many researchers, clinicians and innovators, there is still a lack of knowledge about but also low flexibility of regulations what slows down PM implementation. It is a challenge for regulators to get effective regulations that respect both, an open research field by protecting sensitive clinical data.

- The General Data Protection Regulation (GDPR) provides high flexibility but leads also to different interpretation of GDPR application. This lack of harmonisation slows down collaboration efforts for a lot of processes and led to a disruption of European research outputs.

- For clinicals there is the need of curation data. Research data are less sensitive as they are pseudonymised/anonymised.

Conclusion of the session Collaboration of research and healthcare providers to foster innovations:

- Regulatory frameworks are needed for both, clinical development of PM solutions (diagnostics and therapeutics) and for data access and data exploitation.

- Set in place Technology Transfer Strategies and models at the basis of public-private partnerships to ensure economic sustainability and market uptake of new innovations.

- Supportive for PM development and implementation are multidisciplinary and multinational collaboration models.

VIII. Session: ICPerMed 'Best Practice in Personalised Medicine' Recognition 2022-2023

The aim of the 5th ICPerMed Recognition was to honour outstanding clinical research projects related to data sharing in PM. This represents the sixth Best Practice Recognition (BPR) supported by ICPerMed and open for applications worldwide.

Overall, the ICPerMed BPR aims to spread knowledge and awareness in the PM field. The annual calls aimed to collect scientific papers, training programmes, and examples for interdisciplinary or intersectoral collaboration relevant to PM.

The topic of the sixth ICPerMed BPR was "Fostering PM implementation through research". In a timeframe of two months, from February to April 2023, 21 applications were received from all around the world, presenting proposals published or developed between January 1st, 2021 and December 31st, 2022, consisting of one or more of the following:

- Scientific paper focused on novel approaches for the implementation of PM
- Training programmes for personal health, increasing the level of awareness on PM's potential
- Examples of interdisciplinary or inter-sectoral groups of collaboration (governmental and non-governmental organisations, academic management, medical research and healthcare and industry for the implementation of PM, including Ethical, Legal and Social Issues (ELSI) activities).

A panel of experts reviewed the proposals giving a score for 5 criteria such as:

- Knowledge Production
- Research capacity - building and targeting
- Informing policy and practice
- Population health and health sector benefits
- Economic impacts

Awardees had the chance to present their work during this plenary session of the workshop "Advancing Personalised Medicine through Technology Development" for further dissemination. Furthermore, the three winners will receive a €500 worth non-cash contribution for further dissemination of their best practice examples.

Moderator:

- **Chiara Ciccarelli**, ICPerMed Secretariat, Italian Ministry of Health

Award winners:

- **Mireia Seuma**: Institute for Bioengineering of Catalonia, Spain
- **Nurulamin Noor**: University of Cambridge, United Kingdom
- **Laura Valinotto**: Centre for Research in Genodermatosis and Epidermolysis Bullosa (CEDIGEA) Argentina

Chiara Ciccarelli introduced the award ceremony for the ICPerMed "Best Practice in Personalised Medicine" Recognition 2023.

Mireia Seuma

Title of the talk: "Using genomics to map amyloid nucleation in Alzheimer's disease".

Presentation's key messages:

- Deep Mutational Scanning (DMS) is a powerful technique to preventively measure the impact of all variants in a protein sequence on a phenotype of interest.
- Specific topic presented: Development of a DMS strategy that reports on Amyloid formation.
- The enrichment scores arising from the assay

accurately capture all familial Alzheimer's disease (AD) mutations (outperforming previous datasets and predictors).

- Insertion-deletions (indels) occur in the population and they can cause genetic disease.
- AD is a nucleation disease.
- Mutations out of the structured amyloid core are of concern but so far there is no tools to understand them.

Discussion's key messages:

- Current disease models are quantitatively validated by Human Genetics.
- There are several steps required to be able to employ functional assays such as DMS in the clinic for diagnosis/prognosis and personalised treatment.
- Still to be elaborated are actions for case of variants that are not actionable, e.g. breast cancer risk vs. AD risk.

Overall key messages:

- Not only to be developed is precision medicine but also pro-active medicine.
- There is a potential to know in advance what a mutation in a patient or healthy individual will do.
- There is a need to develop scalable selection assays to quantify "all" variant effects.
- Need to study variants beyond single insertion or deletion of bases in the genome.

Nurulamin Noor

Title of the talk: "Predicting Outcomes for Crohn's disease using a molecular biomarker".

Presentation's key messages:

- Inflammatory Bowel Disease (IBD) is a chronic, progressive condition increasing in both incidence and prevalence around the world, with a major impact on quality of life for patients but highly heterogenous outcomes between patients.
- Multiple new therapeutics and multiple potential personalised medicine tools and biomarkers currently under investigation.
- A blood-based prognostic biomarker has previously been developed and independently validated in a multi-centre prospective observational cohort study.
- To date, no biomarkers in IBD have been formally assessed in a Randomised Controlled Trial (RCT) setting.
- PROFILE: the first-ever biomarker-stratified RCT in the field of IBD, where the above-described blood-based prognostic biomarker has been assessed for clinical utility, to determine whether a biomarker-stratified approach would lead to better outcomes for patients.

Discussion's key messages:

- Need for mechanistic work and biomarker discovery to be incorporated into early-phase clinical trials.
- Next step is the biomarker validation to be routinely incorporated into late-phase clinical trials ideally using pragmatic designs.
- Validated biomarkers can be assessed in real-world, pragmatic settings and need to be easy to

implemented and interpret in order to be widely used.

Overall key messages:

- Translation of research findings to clinical practice takes a long time. It is important to speed up this translational process.
- To be assessed if personalised care approach in IBD leads to better outcomes for patients.

Laura Valinotto

Title of the talk: "Center for Research in Genodermatosis and Epidermolysis Bullosa, finding answers to rare skin diseases".

Presentation's key messages:

- CEDIGEA, the Centre for Research in Genodermatoses and Epidermolysis Bullosa, at the University of Buenos Aires, Argentina, has as primary focus hereditary skin diseases with very low prevalence (1:100,000 or less), studying the challenges in diagnosing and treating conditions lacking a cure.
- Foundation and early challenges: The establishment of CEDIGEA was driven by the urgent need for molecular diagnosis in Epidermolysis Bullosa (EB) patients from low-income families. Initial challenges in sequencing and prioritising variants led to unique insights into the molecular basis of EB in a population with an unexplored genetic background, such as native South American peoples.
- Impact and Expansion: The centre expanded its scope to cover other genodermatoses, securing funding through research projects. Cost-effective diagnostic algorithms were developed, and novel variants were identified, contributing to a comprehensive database. A second branch was established for adult patient's follow-up.
- Adoption of High-Throughput Sequencing Technology: In 2016, the centre adopted high-throughput sequencing technology, expanding the range of diagnosable diseases and developed analytic strategies for complex genes through long read nanopore sequencing.
- Education and Outreach: Challenges were addressed through education, training, healthcare professional networks, and virtual conferences. By time, there was a transition from local annual meetings to virtual global events connected experts worldwide.

Discussion's key messages:

- Possibility of treating genodermatoses: Patient and family education, as treatment, is mostly preventive and symptomatic, with no possibility of a cure for the majority of genodermatoses. Gene therapy has been approved, facilitating wound healing for a type of epidermolysis bullosa. Testing and use of biological drugs based on monoclonal antibodies for the treatment of other genodermatoses are becoming more common.
- In practice, two patients with the same pathogenic variants do not respond in the same way to the same biological treatment.
- There is a need to continue the research to determine the factors that predict the success in these therapies.

Overall key messages:

- The project seamlessly integrates scientific research, healthcare training, and interdisciplinary collaboration. This intersection contributes to the implementation of Precision Medicine, addressing the complex nature of genodermatoses.
- Regional insights that contribution to novel phenotype-genotype associations: Having a centre specialised in genodermatoses permits uncover-

ing unique genetic backgrounds in the Southern Hemisphere for genodermatoses and building a comprehensive database with clinical, epidemiological, and mutational profiles.

- Raising awareness of rare diseases among the medical community had a significant impact on the early detection of genodermatoses, even in remote areas of the country.

- Sustainable growth and future collaboration: The team is open for international scientific collaboration to ensure the continuity of the project despite economic challenges in the country.

- Implementation of PM can be achieved even in economically unfavourable situations, e.g. driven by the desire to reduce inequality and provide equal attention to all patients, regardless of their socioeconomic level. Healthcare professionals wish to implement PM but may believe it is an impossible goal in low-resource countries. Examples like CEDIGEA can be shared as good practices to demonstrate that implementation of PM is possible also in countries with low resources.

IX. Conclusion

Technology developments within genetic science gave birth to PM almost two decades ago. Development of technologies made it possible to study links between genetic defects and related diseases. Disease treatment could be then being performed on a much more personalised basis, using genetic information.

Advanced technologies support PM and thereby contribute to more personalised care facilitate the prescription of specific therapeutics for an individual, for example based on pharmacogenetic and pharmacogenomic information, or support the clinical decision making by considering different sets of health information.

New technologies will continue to be a key driver in the further development and implementation of PM. Therefore, there is still a high need for major investments in all PM-related technology field at a broad level.

Current issues related to data concern both technical aspects (curation or standardisation), access to data (legal frameworks, consent) and the use of data in an ethical manner (general acceptance among patients and citizens for the use of data). These issues have been known for a long time, but it is getting more and more critical to resolve them: "Active participation of decision-makers and politicians are needed more than ever", said Mr Moltzen, the ICPerMed Chair.

Reluctance in accepting new technologies is another issue, both among healthcare professionals as well as patients and citizens. Such reluctance is due to the lack of resources in the healthcare systems to take on board new technologies but is also connected to conservatism of healthcare professionals and fear of patients and citizens. Thus, there is a need to rethink how healthcare systems can better support information sharing, communication, and education to overcome these barriers and convince all stakeholders of the benefits and opportunities new technology solutions do offer.

Development of PM approaches might comprise the application of a set of different therapeutics, companion diagnostics, other diagnostic tools, AI, etc. Therefore, regulatory requirements represent an increasing hurdle. For example, some new technologies are considered as medical devices and new IVDR regulation with its increased focus on clinical validation can become a major problem. On the other hand, drugs, medicinal products, diagnostics and medical devices that are applied to patients have to be safe and effective. In order to guarantee that, development processes of healthcare innovations have to adhere to an extensive regulatory framework. The situation for researchers, clinicians and innovators is increasingly complex as various different legislations (Clinical Trials Regulation, IVDR, Pharma legislation, AI Act, etc.) and guidelines (ISO, GxP, ICH, MDCG, etc.) have to be respected.

There is a need that research and development investment in PM focus on the clinical validation phase and new public-private partnership models should be explored for it. Training on IPR and technology transfer for researchers are pivotal to secure intellectual property and ensure clinical uptake of the results. The depth of molecular diagnostic tests is rapidly increasing, just as the number of approved and experimental targeted therapies. It is highly challenging and complex to keep up with this pace of progress, particularly when this requires the constant amendment of guidelines.

The amount of data and level of complexity in PM requires investments in computational solutions, and international and multidisciplinary teams to carry out basic, translational and clinical research on PM to improve quality of research and ease the uptake into the healthcare sector.

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