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Workshop Report

3rd ICPerMed Workshop

Personalised Medicine: How to Ensure Value-based Implementation

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Imprint

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List of abbreviations:

BC: Breast cancer

CBA: Cost-benefit analysis

CCA: Cost-consequences analysis

CEA: Cost-effectiveness analysis

CUA: Cost-utility analysis

QALY: Quality adjusted life-years

PERSPECTIVE I&I: Personalised Risk Assessment for the Prevention and Early Detection of Breast Cancer: Integration & Implementation

PM: Personalised medicine

Content

I- Executive Summary

The International Consortium for Personalised Medicine (ICPerMed) is a platform of over 30 European and international partners representing ministries, funding agencies, and the European Commission (EC). The central aim of ICPerMed is to align and encourage joint efforts in personalised medicine (PM) research and implementation.

This is the report of the 3rd ICPerMed Workshop, entitled "Personalised Medicine: How to Ensure Value-based Implementation", which took place in Brussels on June 21-22, 2022.

The Workshop was held in a hybrid format to overcome the Covid 19 pandemic limitations and ensure participation of all interested parties. More than 50 participants joined the hybrid workshop with 30 in physical presence.

The workshop was developed within the objective of the ICPerMed Secretariat Work Package 2 with the support of all members of the Secretariat. The scope and content of the workshop was developed by the ICPerMed Work Group 5 on Health Economics. In addition, the ICPerMed Executive Committee, EC representatives, invited international experts, partners of topic-related European, national and regional projects as well as ICPerMed Advisory Board members contributed to an important and lively discussion. With this workshop, ICPerMed intended to exchange and find agreements on the mechanisms and key aspects of value-based aspects to guide an appropriate implementation of PM for the benefits of patients and citizens.

The workshop facilitated the exchange of experiences and ideas between ICPerMed members and high-level international experts in the field of PM and enabling knowledge-transfer to specific targeted groups. It was organised in two plenary sessions and two parallel working groups sessions, one online and one on site

The working groups discussed key topics in relation to PM implementation with the aim of providing recommendations to appropriately guide introduction of PM approaches in healthcare systems with specific focus on value perspectives.

We are moving towards the "generation genome" and are seeing an increasing accessibility and interoperability of health data from a plethora of sources. Aspects into what this will mean for the evaluation and valuation of PM approaches for the healthcare system and public health approaches more generally were discussed. As a result of the discussions there was agreement on a high necessity to increase efforts in the following areas:

1. Develop improved health-economic models to estimate the value of PM, incorporating the full value for patients and citizens, including for example both short- and long-term aspects, cost of diagnostics/testing, as well as non-health factors;

2. Develop new business and reimbursement models, based on public-private partnerships at a broad level, to create a sustainable healthcare system including a sustainable business environment for industry;

3. Further develop data infrastructures to allow generation, sharing and second use of biomedical and healthcare data. This includes addressing all critical aspects such as ethical, legal, and quality/formatting aspects;

4. Continued research into pharmacogenomics approaches which is certain to provide useful PM based treatments;

5. Develop personalised prevention as this holds the promise to provide the basis for an overall better health for society in the future.

The outcomes of the 3rd ICPerMed Workshop are published by ICPerMed and will be integrated into future recommendations, guidelines, and strategic publications.

II- Workshop Introduction

The 3rd ICPerMed Workshop entitled: "Personalised Medicine: How to Ensure Value-based Implementation" was held at the Marriott Brussels Grand Palace in Belgium on the 21st and 22nd of June 2022 with the financial support of the European Commission.

The workshop was structured in plenary sessions and thematic parallel sessions:

Open plenary session

- **Welcome & Introduction**

  Ejner Moltzen (ICPerMed Chair)
  Carmen Laplaza Santos (European Commission Representative)
  Gaetano Guglielmi (ICPerMed Secretariat, Italian Ministry of Health, Italy)

- **Five keynote lectures**

1. Katherine Payne, Professor, PhD, University of Manchester: *Overview of health economics in relation to personalised medicine, including both economic and societal aspects.*

2. Avi Israeli, Chief Scientist, Israel Ministry of Health: *Implementation of personalised medicine in Israel.*

3. Deborah Marshall, Professor, PhD, University of Calgary: *Non-health benefits of PM from an economic perspective and spillover effects.*

4. Jennifer Brooks, Associate Professor, PhD, University of Toronto: *Implementation of personalised medicine in Canada.*

5. Maureen Rutten-van Mölken, Professor, PhD, Erasmus University Rotterdam: *HEcoPerMed outcomes and conclusions.*

- **Panels of two Working Groups – online and on-site sessions.**

  "Evolution of personalised medicine implementation and the meaning of this evolution for society"
  Moderators: Stefano Benvenuti; Etienne Richer; Gianni D'Errico

- **Final report of Working Groups within the plenary session**

- **ICPerMed 'Best Practice in Personalised Medicine' Recognition 2021 Award ceremony**

III- Plenary Session: Welcome & Introduction

The Chair of ICPerMed, **Ejner Moltzen**, gave a welcoming speech to all the present and online attendants. He introduced the topics of the workshop and underlined that the more PM-based concepts are moving towards implementation in healthcare, the greater the importance of value-based aspects, such as health economic aspects, becomes. He also emphasised that although this is a very complex area, it is extremely important to discuss and resolve these issues to ensure the full implementation of PM.

Some main questions emerged, to which the Workshop aimed to seek answers: what is the value of PM? And for whom? Is there a balanced cost benefit ratio? Is it cost efficient? Is there a value for patients and citizens? Is there a value for health systems?

There are many challenges, and it is also very important to realise that when we find a solution it cannot be adapted to all situations. In addition, we must be aware that every time we choose a solution, it has consequences that must be considered carefully, because these consequences will influence society for many years to come.

The representative for the European Commission, **Carmen Laplaza Santos** (Head of Unit for Health Innovations & Ecosystems, European Commission), stated that the European Commission has been supporting PM in its multifaceted nature, and with the arrival of Horizon Europe the aim is to concretise the impact and translate the results into successful PM approaches that can be of benefit for patients, citizens, and healthcare professionals. This is the right time to develop this topic because Member States and regions are showing increasing interest in funding activities in this field and therefore the results of this workshop can be integrated with other activities and build a strategic research agenda that enables faster translation of the results.

Health economic analyses are gaining momentum for PM strategies, providing essential information to the decision makers towards sustainability of healthcare systems. In particular, as the introduction of a PM approach can radically change health systems, new tools need to be developed to ensure their financial and economic sustainability. And now is the time to act because the cost of doing nothing may be greater than the cost of doing.

The introduction of PM approaches is also important to improve a healthcare system in which the prescription of a drug is sometimes proven unnecessary, if not harmful to the patient, with a significant economic loss for the system. Personalised prevention should also be included in the cost-benefit assessment. A very complex topic, but one that would bring significant economic benefit.

Carmen Laplaza Santos concluded her introduction by mentioning one of the ongoing EC-funded activities on pharmacogenomics (**U-PGx** project). An activity that includes not only an understanding of the genetic profile in order to apply personalised treatment, but also the economic impact of this approach.

Gaetano Guglielmi (ICPerMed Secretariat, Italian Ministry of Health) introduced the Best Practice Recognition Award ceremony, part of the ICPerMed activities, that is essential to show the successful implementation of research evidence into practical healthcare and treatment.

Every year, and now in the fourth edition, ICPerMed launches a call to collect scientific papers, training programmes, and examples for interdisciplinary or intersectoral groups of collaboration, relevant to aspects related to PM.

The call was open worldwide. The applications were evaluated by a scientific expert panel and the three highest scoring applications were awarded.

The 2021 Recognition aimed to honour, encourage, promote, and disseminate the "implementation in personalised medicine research".

The objective of this recognition was to encourage and disseminate implementation in PM. With this vision, the successful applicants were invited to the ICPerMed Workshop and to present their results during the plenary session. In addition, the successful candidates received a 500€ non-cash dissemination support from ICPerMed for the dissemination of their implementation examples. This dissemination aims to provide the successful applicants with an opportunity to seek supplementary dissemination activities that will accelerate and maximise the potential impact of the research findings and learnings gained on implementation in PM. For more information, see the dedicated session.

A summary is available on the **ICPerMed website**

IV- Plenary Session: Keynote lectures

1. **Katherine Payne**, Professor, PhD, University of Manchester: *Overview of health economics in relation to personalised medicine, including both economic and societal aspects*

Katherine Payne's talk focused on her work on the application of Health Economics to PM, presenting examples of technologies available today and focusing on the usefulness and limitations of one and the other. She showed how important it is to respond to specific problems by using appropriate methods also from other disciplines or using them as a basis for developing new assessment methodologies.

Tackling economic costs in PM is a multi-level challenge. The use of a cost-effectiveness analysis method may not be sufficient to understand the multiple aspects of the challenge, because the outcome of an intervention is determined based on what is being evaluated.

The need to go beyond a cost-effectiveness analysis leads to assessing different methods of analysis, the inclusion of different points of view, e.g. welfarist versus extra-welfarist, including non-health aspects and sector preferences, not forgetting another aspect of the problem which is the role of behavioural economics.

PM is a complex multi-component intervention in which it must be considered how to implement health economics, as from the evaluation of this aspect a series of guiding information for decision makers arise.

Defining how to allocate resources to maximise patient benefits is part of the cost-effectiveness analysis process. The process starts with an assessment of unit costs, then evaluates the possible alternatives and the output in terms of clinical effectiveness, clinical response, or life-years gained (cost-effectiveness analysis: CEA); quality-adjusted life years [**QALY**] (cost-utility analysis: CUA); multiple outcomes (cost-consequences analysis: CCA); willingness-to-pay (cost-benefit analysis: CBA).

The analysis is made more complex by the assessment of what is to be monetised. Considering that there are several levels of evaluation starting from strictly considering the hospital level and extending to the public sector services to the more all-encompassing societal perspective.

The broader the scope of evaluation, the more factors, even those not strictly related to health, must be taken into account, and thus it is necessary to have evaluation systems that are also valid in parallel fields.

The evaluation of outputs also represents an important and significant parameter for the correct assessment of costs. Analysing the results from a welfarist and a non-welfarist point of view changes the decision-making approach. The welfarist system strives for a CBA by asking the question: how much the benefit exceeds the cost, analysing a contingent valuation and an individual point of view. The non-welfarist approach, which is more oriented towards cost-effectiveness analysis, on the other hand, focuses on setting a certain level of quality and thus defining how much one is willing to pay to achieve that level of quality.

The monetisation of health is another point that is difficult to resolve, because in the current system there are scales such as EQ5D, to calculate the utility score, which evaluates health according to a narrow range of defined parameters, and QALY (Quality Adjusted Life Year), which is used to analyse the utility score in terms of health impact.

A broader point of view, that also includes QALY, is "capability" defined as freedom to pursue health improvement perceived capability to function.

Capability has been suggested as a potential alternative for public health (and other) interventions, but it has not prescribed any particular domains

of functioning or capability and maximisation is not the objective but distribution and equity.

Capability is a useful parameter when health maximization is not enough for an effective intervention. In some cases it is also necessary to evaluate parameters and know what means to use for evaluation, which are not strictly health-related, such as the ability to make informed decisions for the patient.

It is also important to consider values not strictly related to health and to define how much people are willing to pay for them

In addition, the evaluation of costs also varies according to the point of view of the evaluator (patient or doctor, for example), since according to preference the choice of what one is willing to invest and what not changes.

Behavioural economics must also be considered in this evaluation, quoting Hekker, who spoke of the fundamental role of social and behavioural sciences in 'precision health', 'targeting the genetic, biological, environmental, social and behavioural determinants of health'.

Regarding the transition current models used in health economics analysis with the inclusion of behavioural economics approaches, Katherine Payne explained that there are some preliminary works in this area, trying to expand the cost-effectiveness analysis to include individual preferences. Behavioural economics are a good starting point to ease the evolution of health economics assessments.

Finally, she spoke about the introduction of digital health technology. And the fact that they are generating big data not only on health but social activities and behaviour. And we can use this data to monitor or generate predictive algorithms, whether targeted or adaptive, to start targeting intervention.

In conclusion, Katherine Payne reiterated that there is a need for a science of implementation, which begins to address the seriousness of the health services currently provided, the degree to which the current services are being utilised, and whether things should be changed.

2. **Avi Israeli**, Chief Scientist, Israel Ministry of Health: *Implementation of personalised medicine in Israel*

Avi Israeli, member of the ICPerMed Working Group 5: 'Health economics', spoke about the Israeli National Health System, focusing on the National Health Insurance Law, explaining how it is structured and what evaluation criteria are used in the decision-making process.

In the NHIL there are 4 health funds (HF) and every resident is entitled to health insurance on the basis of an open enrolment with no risk selection behaviour.

There are three sources of funding: 1) the progressive health tax, levied by the National Insurance Institute, which divides the funds to each health fund according to a capitalisation formula; 2) co-payments; 3) additional funding from the annual state budget.

The HF receive the funds and are responsible for providing services to their members.

Each individual is free to move from one HF to another, and to them is guaranteed a wide range of services that is updated every year on the basis of clinical, economic and epidemiological evaluations.

Every year, the government allocates an additional amount of money dedicated to new technologies.

The overall assessment for the allocation of funds takes into account the following criteria:

- The magnitude of the problem, assessed through the use of prevalence and incidence indices of the disease state;
- The burden of the disease on the healthcare system in terms of mortality, morbidity, health service utilisation and/or functional disability;
- Existing alternatives to treat the disease, including prevention, diagnosis, treatment and rehabilitation;
- The cost of the disease according to the resources allocated to it and the costs of alternative treatments;
- The clinical and economic characteristics of the new treatment.

The expert panel for the evaluation consists of 18 members from different fields: physicians, health economists, HF representatives, public representatives, medical science, ethics, social science and welfare.

A technologies priority scale is elaborated from high priority to a low priority. The priority setting uses guiding criteria, of which the following are basic: accessibility and transparency, treatment of the 'silent population', comprehensive treatment for selected diseases and recommendations reached by consensus.

In this context, some critical aspects are considered: whether to opt to give a lot to a few or less to most of the population, what is meant by life-saving technology, what is the balance between solving and investing in urgent health needs and investing in future health.

For what concerns the right cost of technologies some input has been given as: price negotiations; defining specific patient groups who benefit the most from said technology; limitations, line of therapy, clinical characteristics; class effect; performance-based risk sharing schemes; capping agreements.

The Israelian system works through several steps of check and approval: the first is the Meeting of the National Health Council, then the approval by the Minister of Health, the Minister of Finance and the Government; then HF begin immediate provision of the technologies to insured members and at the end the official publication of the annual additions to the NLHS.

Israel has created a uniform nomenclature, definitions and methodology for HTA under governmental leadership. The mechanism is both feasible and practical for the needs of the Israeli healthcare system and involves all stakeholders. Due to the one-year cyclic nature of the Israeli process, rapid assessments are used. There is a direct link between HTA, decision-making and budget allocation. The process is highly accepted by the health system, judicial system, political system and the general public.

3. **Deborah Marshall**, Professor, PhD, University of Calgary: *Non-health benefits of PM from an economic perspective and spill over effects.*

In her speech Deborah Marshall presented the following topics:

- Measure Value in Health;
- Measure what matters (Engage Patients);
- Value frameworks for Personalised Medicine.

She emphasised that there are multiple aspects to be considered when assessing the value of

PM. It is not only an economic assessment (as e.g. seen from a payer's point of view). PM is not the equivalent of standard care. One must take into account that treatments have to be adapted to the individual characteristics, needs and preferences of the patient during all phases of treatment. Furthermore, it is necessary to consider patients, families and their communities from a societal perspective.

The hidden consequences of PM are enormous. There are not only the costs and quality of direct healthcare, which are only the tip of the iceberg. There is a large downstream mass, with significant consequences for patients, families, and communities. Thinking about the consequences of genetic testing for example, the productivity losses, the non-health benefits that patients and family members might have in terms of out-of-pocket expenses and personal disutility, the utility associated with specific treatments.

From this perspective, economic evaluation for decision-making in PM must also include personal preferences and utility, such as desirability: preferences for positive aspects (benefits) and acceptability: aversion to negative aspects (risks).

Aligning healthcare policy with patient preferences could improve the effectiveness of healthcare interventions by improving adoption of, satisfaction with, and adherence to clinical treatments.

Deborah Marshall presented the example of Calgary, where specific courses aim to involve patients and the community in research and decision-making, making them real partners at the table.

The value framework should, therefore, include not only the net cost but also other aspects related to patients' health and non-health benefits and should also consider the impact on families and carers such as labour productivity and employment and spillover effects such as time spent on care and their quality of life.

4. **Jennifer Brooks**, Associate Professor, PhD, University of Toronto: *Implementation of personalised medicine in Canada*

Jennifer Brooks spoke about Risk Stratified Breast Cancer Screening in Canada: The PERSPECTIVE I&I Study, (Personalised Risk Assessment for the Prevention and Early Detection of Breast Cancer: Integration & Implementation) as an example of PM in Canada.

The Canadian healthcare system recommends breast cancer (BC) screening every two to three years for women aged 50 to 74 years. But many screening programs do screen outside of these guidelines. The healthcare system in Canada is administered provincially through the provinces and territories, and so each province has slightly different programs. The screening is based on age rather than risk, despite the evidence that may result in over-screening women at lower risk and underscreening women at higher risk. Therefore, the Ontario high Risk Screening program started about 15 years ago. It screens women starting at age 30 from age 30 to 69 annually with paired MRI and mammogram and women must meet one of four high-risk criteria: BRACA mutation carrier; relative of unknown carrier; personal history of chest radiation or treatment of a prior cancer; have a family and an estimate risk.

Canada is performing the PERSPECTIVE I&I Study with the aim to improve personalised risk assessment to offer cost-effective risk-based screening and prevention of breast cancer to individuals most likely to benefit and to determine the optimal implementation approaches within the Canadian healthcare system.

The patients are provided with a booklet (paper or computer) that explains how the risk is estimated and what measures can be taken to reduce it. This includes the action plan for screening. High-risk individuals are contacted by a counsellor or research nurse (depending on whether in Ontario or Quebec).

5. **Maureen Rutten-van Mölken**, Professor, PhD, Erasmus University Rotterdam: *HEcoPerMed outcomes and conclusions*

Maureen Rutten-van Mölken started her speech focusing on the value of health economic assessment, and how cost-effectiveness assessments help to quantify the costs of a health intervention to improve the decision-making process.

Doing a cost effectiveness analysis often requires designing a healthy economic model, but currently there are no economic models validated for PM, because this is a highly complicated and multi-headed system. PM entails dealing with several different treatment pathways for differently stratified subgroups creating highly increased need for extensive testing. This creates more uncertainty, as we are dealing with smaller subgroups and fewer patients. Therefore, we may have less comparative effectiveness data since we may not have the necessary clinical data for all subgroups.

The HEcoPerMed consortium published an article entitled "**Guidance for the Harmonisation and Improvement of Economic Evaluations of Personalised Medicine**" with the goal to develop guidance contributing to improved consistency and quality in economic evaluations of PM, given current ambiguity about how to measure the value of PM as well as considerable variation in the methodology and reporting in economic evaluations of PM.

Another paper published by the consortium was "**The Net Benefit of Personalised Medicine: A Systematic Literature Review and Regression Analysis**". A main result is that PM intervention provides more health gains than non-personalised intervention. But these health gains for individuals do not automatically translate into substantial added value for society, because the costs for the interventions must be taken into account as well. The consequences in terms of costs, which are often higher than previously expected, have also been examined to the fact that sometimes quite a lot of people have to be tested to identify the few that may benefit from the personalised treatment. Thus, the testing infrastructure must be created to get the data to personalise the treatment. Very often the lifetime health gains, and the cost savings are factored into the price of the personalised treatment.

Maureen Rutten-van Mölken also presented several examples on how genetic testing could result in more financial gain as well as health gain for patients that receive PM-based treatments, both through higher efficacy and less side effects.

A good way to improve the analysis is to look not to a static efficiency, that only addresses the question whether PM currently provides the best value for money for a cohort of patients, but to look at a dynamic efficiency, considering the future innovation that may emerge from actual activities. An example is to reward innovation now with higher prices, which would reduce the excess of patients to current treatments, in exchange for faster access to future innovations.

Another aspect to consider is that the value assessment does not consider the fact that drug prices fall over time, especially after patent expiry.

The attention then moved on the element of value that should add to the economic evaluation, as cost of informal care, value of hope, etc.

Equity issues associated with PM are often large and unaddressed. It is obvious that compared to a one-size-fits-all approach, PM by definition increases some forms of inequality, but the undesirable effects of inequality on equity have to be avoided. Vulnerable groups may be underrepresented in databases that are used to personalise the intervention. There might be a correlation between certain biomarkers that is

used for personalising interventions and equity relevant variables such as ethnicity or socioeconomic status. There might be delays in regulatory and reimbursement decision making because of the greater uncertainty on effectiveness of PM in small group.

There is a high need for implementation strategies that stimulate the adoption of proven, cost effective, PM interventions and that requires a behavioural change among professional care providers, patients, and payers. One way to stimulate that behavioural change is by incorporating economic evidence into clinical guidelines and clinical decision support tools to stimulate the adoption of proven cost-effective PM, which can be called value-based healthcare.

V- Working Group Panels

During the online and on-site session, two panels discussed the evolution of PM implementation and the consequences of this evolution for society.

ONLINE SESSION:

Several themes were discussed during the session starting from the input given by the lecturers.

The topics encompassed economics, ethics, legal, healthcare system and people perspectives involved in the health economic assessment and the barriers that need to be overcome to implement PM approaches.

1. Finances:

The issue of the use of financial means was addressed, from which several critical issues emerged: fragmentation of the healthcare system (for example in the UK where Wales, Scotland and England make their own decisions. This means that the budget and decision-making is not centralised but regulated at the national level and therefore it is more difficult to move money to where it is most needed). A similar trend is seen in many European countries and regions. Moving money from the healthcare system to other activities albeit deemed valuable is complicated, and one must also take into consideration how and by whom the spending on tests and treatments is incurred. Various key aspects were highlighted:

I. Transparency regarding how money is moved in the healthcare system is needed. Trying to understand more about the commissioning process, i.e. who pays for things will be important. If that cannot be worked out, it will be hard to tackle the implementation projects.

II. Another important aspect of implementation is to get to the political level. There is a high need to translate the evidence into political language to facilitate the political buy-in and thereby ensuring that the right decisions are taken.

Another key element, that emerged regarding finances became clear during the Covid pandemic. People might be willing to pay and invest in PM, but the economic evaluation output will be negative, because from the patients' and people's perspective other issues take precedence, e.g. handling of a pandemic, considering the fact that spending money to improve PM, means taking money away from other fields of intervention.

This means that if we want to move forward, we do not only need a micro evaluation in the PM field, but also a macro-evaluation of the entire health system. For that purpose the assistance of implementation scientists, anthropologists, and behavioural scientists is needed to define a useful method taking all aspects into account.

Moreover, new cost-effectiveness evaluation methods need to include non-economic aspects, which are a key point of the implementation. There is a high need to invest further in this area to move forward.

2. Data:

Another aspect that needs to be tackled concerns data: data collection and data access policies for primary and secondary use, as well as data quality and standards.

A specific example on how data quality can affect the health evaluation was given: In England, recently an Evaluation of the Diagnostic Accuracy of a Panel of Variants in DPYD and a Single Variant in ENOSF1 for Predicting Common Capecitabine Related Toxicities was published. The study analyses an extended panel of 18-21 DPYD gene variants. The authors show that inclusion of rare DPYD variants in the prediction panel identified in patients with DPD deficiency and with supporting evidence of a functional impact on DPD activity does not compromise prediction of 5-FU related toxicity and provides improvements in the sensitivity to predict risk of haematological toxicities. Such an extended panel would be especially

helpful to capture variants prevalent in ethnically mixed populations.

A major problem is to get enough data, a situation which is made difficult due to interoperability issues, and due to the varying quality of uploaded data. Getting enough data will ensure capturing the diversity and the knowledge needed to make the right decision for all types of populations.

In this field it is very important to consider the diversity of the population. It is critical to identify who is not getting the appropriate care due to the lack of diversity, and to be aware that this will impact the validity of health economic evaluations. There is a need to include those elements, but this is not easy, because a good representation of specific subpopulations within a study is very rarely given. This represents a major issue why it is still a long way to personalise therapy for some subgroups. In addition, we also have a long way to understand the pathophysiology of many diseases. As an example the importance to distinguish between healthy and sick individuals was discussed, as little is known for healthy individuals the added value is limited and it is problematic to demonstrate from a health economic perspective. The situation is much better for patients where more evidence is abundant.

Another aspect to consider is the one of co-morbidities. It is necessary to take a life cycle approach as there can be variability along the life cycle and unexpected new effects. A major benefit would be to be able to use all data from the full life cycle of a patient for any given disease incident at any time for the patient. This is not possible today.

Current approaches of pharmacogenomics at a drug-by-drug treatment of diseases, are harder to implement in an older population than in younger populations. The impact of genetic modifications might change over time. This is another implementation challenge. Currently, there are no data to show that there is a difference, but it is known that the metabolism changes over time and instead of running studies in young and healthy populations only, they should also be done in older populations to capture the effects for change in metabolism.

The proper definition of the subpopulations of relevance and the comparators is crucial; are we sure that we are capturing all relevant subpopulations? Often studies are generalised to subsectors of the population, which are not relevant for the particular study. That leads to outcomes of for example economic modelling not addressing the correct situations, which in turn leads to wrong decisions regarding which studies are relevant to the specific research questions or to society.

In order to improve bringing the research to the people that matter, there is a need to invest in translating evidence and making an impact. That is seen as an important role for ICPerMed.

3. Personalised Prevention versus Personalised Treatment

There is a need to act at the level of public health campaigns, and currently the value of personalised prevention is being discussed and whether this is the road forward. It is very hard to get people to act on a probability, hard to know how many people will adhere and collaborate, with huge ethical issues that need to be assessed.

Personalised prevention would be helpful by identifying genetic or individual risks for specific diseases and specific risks for side effects from drug treatments. This could be done through direct monitoring, but the public perception is very important. Society must be convinced of the benefits of this approach and decision makers must be convinced that it is a good idea.

People often do not want to know what predispositions for disease they have or what they are susceptible to. However, in some areas, like breast cancer, prevention can be very important.

In other fields, like prostate cancer, it is harder to have good early diagnosis. It all comes down to being able to demonstrate the value and to translate this evidence.

4. Patient perspective:
Participants suggested several aspects concerning the patients' perspective:

The personal preferences of the population in the selection of accessible services should be done by default. People vote for a government that will fund healthcare services and make decisions. However, it is clearly different in reality. Getting the patient/citizen perspective is not possible at the individual level as it is impossible to please everyone. Thus, doing consultations of subgroups would not be fully informative.

Including patients has proven to be successful to push research that addresses real patients/citizen needs. The more patients are involved in the research projects, the more they are likely to adhere to the PM approaches as they are implemented.

The question of the perception of the value comes back to the definition of PM. If parts of it is based on genomics, it might cause scepticism and a lack of trust. Some populations are strongly opposed to genomic testing as they are afraid of the stigma; it raises a lot of questions, and this affects the perception of the value.

Another hurdle is that there are people that would like to be involved but cannot due to systemic barriers. An example is the lingual barrier: for example a letter sent for mammogram in the UK that is in English only, with a notice in the back that it can be requested in another language;

Inclusivity is so important, especially when moving towards personalised screening; this has to be tackled in order not to increase health inequities.

5. Building evidence:
Build strong evidence aims to foster the PM implementation:

While research and innovation on PM and health innovation in general, is relentless, healthcare systems are struggling with current organisational hurdles (i.e. long waiting lists, access inequality etc), that request investment and human workforce. In order to facilitate decision making when it comes to investing in PM stronger evidence of the benefits that PM approaches would bring to the system needs to be demonstrated, with a view to future value for generations to come. Lay communication and general dissemination could ease future investment in PM at regional and national level as well.

There is a need to build evidence and to share the impacts. If evidence supports the implementation of a PM approach and that services are rolled out, we need to continue to collect long-term data and to create links with electronic health records and registries to demonstrate the real-world impact and value of these approaches.

6. Private sector:
The topic centred on the assumption that the private sector can decide to invest or not based on economic advantage, in an independent manner from its technical ability. A different aspect is that in Europe start-up companies do not have such a supportive environment as in other parts of the world. Due to the fragmented system in Europe, it is difficult to obtain funding in order to get to the market or to develop a company around a novel technology or drug. It is possible to be successful but it is difficult and often slow and there is a high risk that the company might be taken over by large international players. This might possibly result in the relocation of the production to another country outside of Europe.

ONSITE SESSION:

Topics addressed in the onsite session included the evaluation of system costs in the future perspective and relationships between public and private companies by advancing hypotheses on possible fields of intervention.

1. Setting the economic value of health:

The economic process works by defining a cost for each service, including health. That means there is a need to apply a price tag to show the benefit of a PM treatment, starting with industry negotiation and setting a maximum price for treatment.

Research is funded by national/regional funders but that is not taken into pricing. Industry does not calculate these early steps when trying to show a business case; thus a paradigm shift is needed. It means a lot for the people in industry to do something for the patients. SMEs are important for innovation, they survive because of venture funding by industry or private investors. The public sector is not equipped to collaborate with industry and improved settings for public-private partnership are needed. Patents prevent products from being cheaper (monopoly of the company). Universities file patents but do not do drug development, so industry pays back to the university to develop the drug.

Costs for drug developments are not only due to genomics but also due to technically challenging areas such as Advanced Therapy Medicinal Products (ATMPs) like cell therapy or gene therapy. Societal aspects should also be included in the consideration. As most costs incur due to drug failure/side effects not for the drug itself or genetic testing, there is a need to understand how to include economic evaluation of drug failure/side effects.

The healthcare system is not efficient in stopping inefficient therapies; e.g. to avoid overtreatment or wrong treatments.

For the patients a change from a "Health Insurance" to a "Health Insurance Fund" would be necessary, to guarantee access to the healthcare system.

2. Implementation of pharmacogenomic diagnosis in healthcare systems

The Ubiquitous Pharmacogenomics (U-PGx) Education Programme is a pilot project how to implement pharmacogenomic diagnosis in healthcare systems. The key learning from the project was the importance of education of clinical doctors. Another important outcome was that side effects were 1/3 less in the genetic tested groups, thus showing the benefit of the approach. The question now is how to convince the healthcare systems and the politics behind it to implement such an approach. Implementation in the public field would be needed. However, the infrastructure to put it in practice is missing. Reality is that in most countries health data are not linked to genetic data knowledge has to be shared and IT infrastructures need to be harmonised.

3. Cost Evolution in Healthcare System

Healthcare costs are skyrocketing and the health systems' "status quo" is not something people are willing to give up. Therefore, other ways to ensure sustainability need to be explored:

The costs of in vitro diagnosis are projected to increase even more in Europe with the adoption of the medicinal device regulation (Regulation (EU) 2017/745). That is a difference to for example Canada, where test panels can be changed or added without big problems as the method itself was tested. In Europe there is always the need for clinical evidence if adaptions of test panels are needed. The difficulties are just due to the implementation of the new regulation not to the regulation itself.

Health economic assessment also need to be standardised across countries, as there are many country related factors that can determine different outcomes. The societal and quality of life

aspects need to be factored into the assessments. For example, in countries with low wages the cost-effectiveness analysis would look different from a country with high wages, since the gain in productivity balance the costs differently. This is a problem of most of the Eastern European Countries.

The main pain point is the price paid by national and regional authorities. The productivity gain and the costs are factored in by the pharma companies that charge mark-ups that make therapies unaffordable.

The new In-vitro-Diagnostic device (IVD) regulation may affect the developing costs of screening technologies and worsen the financial burden of the healthcare systems.

What to do?

One way would be to pursue personalised prevention approaches including e.g. polygenic risk studies.

With polygenic risk scores for prevention strategies multiple polygenic risk scores will be needed in order to stratify the individuals for which indication they have to take most care (e.g. breast cancer or cardiovascular disease, etc.);

A strong economic case of pharmacogenomic approaches could convince the policy-makers to make it a standard procedure in healthcare.

Cost efficiency in the roll-out phase is often a contradiction. Evaluation has to be performed on the long run.

Relying on the approach followed in the HEcoPerMed project, it was stressed that infrastructures for generating health economic data are necessary and still represent a bottleneck to obtain more accurate measurements. The cost-effectiveness methodology that HecoPerMed applied on specific test cases showed the importance of considering testing costs as well as treating costs when evaluating the value of PM approaches.

Another test case evaluated within HEcoPerMed showed how personalised intervention could actually reduce the costs for a therapy by reducing unnecessary tests and treatments.

4. Barriers to overcome

A bottleneck to tackle is training of medical doctors. Often genetically based personalised treatments are not pursued by the medical doctors, simply due to lack of knowledge and information. Thus, very often the standard treatments are widely used although better options are available. The cost of training is a barrier that needs to be tackled to promote the use of new approaches in PM.

5. The Cost of the Data

The cost of generating data is very often underestimated. It has been shown in the HEcoPermed project that including cost to collect diagnostic data can actually turn the cost-benefit into a negative outcome. It is thus important to have the optimal strategy for data collection. This is both a policy as well as a health economic problem, that needs to be solved in order to get the full benefit of PM in a sustainable way.

VI- Plenary Session: Final report of the Working Groups

Stefano Benvenuti summarised the outcomes of the discussions in the parallel session:

1. Value: how to incorporate the value for patients in health economics models?

a) According to the "mainstream" value for patients is already included as "gain in health". Any additional element of value may lead to a budget reallocation from other interventions in favour of PM approaches. If we put this into a broader context, are we sure that citizens want to trade off health gains due to non-PM intervention to ensure additional value to some of the patients?

b) The value of diagnosis is not easy to capture within the current models when little or no intervention is available. We need to invest in proper tools to estimate the value of diagnosis per se, including the collection of systematic data on patient journey towards diagnosis, to estimate the use of healthcare resources to get the diagnosis with the standard approaches versus PM approaches. See as reference for example the **PhD thesis** by Martin Eden (2016)

2. Enablers of PM deployment and related costs:

a) Data exchange is key for PM (better data, better infrastructures, better decisions) but problems and barriers are still very relevant:

- The adoption of PM approaches requires investments in infrastructures for data collection and sharing and this represents an additional cost for PM implementation whenever such infrastructures will not be created in the absence of PM approaches. An example: infrastructures for electronic health records may often be considered as non-linked with PM while infrastructures for storage, analysis and exchange of genomic data are PM driven.
- The current legal framework, especially in Europe, is a major obstacle to data sharing and use of data. There is a need for a friendlier legal framework and less proprietary data (more openness in sharing data). The novel legislation on European Health Data Space should be of help.
- Data quality is also a problem, especially when dealing with real-world evidence or retrospective data that often does not have the correct consent to be shared. There is a strong need to train clinicians both in data collection and in the use of data.

b) Organisational barriers exist and are very relevant for the full deployment of PM approaches; to remove such barriers has a cost that economic modelling cannot solve.

3. Prevention: healthy individuals may not "trust" the system when it comes to genetic data + they may prefer not to know. There are fields and applications where personalised prevention may be interesting but the translation to the clinical practice is not obvious.

4. Pharmacogenomics: is a clear area with high potential for the implementation of PM. However, it also suffers from the above-mentioned lack of infrastructures and organisational barriers. Moreover, to fully implement it, we need to better understand non-genetic factors affecting the metabolism of drugs. All in all, pharmacogenomics could be the pilot application that builds "genetic paths" within the healthcare systems. This could translate genomics in clinical routine paving the way for further applications.

5. Innovative treatments: when calculating the benefit we may consider spillovers effects on the overall economy related with a highly innovative field. HTA is not the only key for market uptake,

price and reimbursement mechanism and R&D financing options are also very relevant. Start-up companies (biotech) do not find a supportive environment in Europe due to market fragmentation both on the capital side and on the commercialisation of therapies in 27 different markets. The European Commission should act as for the COVID vaccine to reduce market fragmentation.

VII- Plenary Session: ICPerMed 'Best Practice in Personalised Medicine' Recognition 2021

Two out of three winners have been able to participate in the Workshop and to present their work, Dr. Jorge Simón, and Dr Juan Josè Beloqui both from Spain.

Below is a brief sketch of the winners and a summary of their works.

Dr Jorge Simón obtained a PhD in Biomedicine, specialising in hepatology, in 2020 and an MBA in Pharma Industry in 2021. He holds a postdoctoral position in the Liver Disease Laboratory (CIC bioGUNE) funded by CIBERehd, appearing as a co-author in 17 publications in Q1 journals and first author in 3 Q1 and 2 D1 journals. Dr Simón has a strong translational profile, and, from this, he is a co-author of 2 patents and has participated in a collaboration agreement between the Liver Disease Laboratory and the biotech company Silence Therapeutics GmbH. He also led a project in CRAASH Barcelona 2020 and is a member of the EASL, SEBBM and EIT Health Alumni. He is also co-supervising a doctoral thesis expected to be read in 2024. His current research is focused on reaching a Phase I with a siRNA compound generated by Silence Therapeutics and elucidating the role of magnesium modulation by Cyclin M4 in other liver pathologies such as cholestasis or liver cancer.

Jorge Simón presented his work on "Alterations in serum glutamate levels are presented as a new risk factor in Metabolic associated fatty liver Disease".

Current lifestyle and nutritional habits have an impact over global health, spreading the development of obesity worldwide. In this context, the liver is the main organ responsible for the maintenance of energetic and metabolic homeostasis. Added to the appearance of cardiovascular diseases, liver pathologies are also spreading worldwide. Metabolic-associated fatty liver disease (MAFLD) is estimated to affect around a 25% of global population, where the chronicity of the disease may lead to more severe hepatic disorders. MAFLD is characterized by an abnormal lipid deposition in the liver that can promote the appearance of hepatic fibrosis, and derived cirrhosis, and even liver cancer.

When lipids are accumulated, hepatocytes attempt to increase their consumption to restore the balance. However, the effort is normally not sufficient so that a pro-inflammatory stage is developed. Such inflammation is one of the main responsible for the progression of the disease to the aforementioned severe stages. The enhanced lipid consumption is accompanied by an increased mitochondrial activity, with the subsequent stimulation of the central metabolic pathway known as Krebs cycle. The interconnection existing among the different metabolic pathways links such Krebs cycle overactivity with an increased glutamine degradation to fuel it.

This is why MAFLD patients, especially the ones that develop steatohepatitis, show higher glutamate levels by an increased expression of the hepatic glutaminase 1 (GLS1) enzyme. In Dr. Simón's work that was led by Dr. Cardoso Delgado and Dr. Martínez-Chantar, the Liver Disease Laboratory (CIC bioGUNE & CIBERehd) has discovered that a siRNA-based therapy is able to diminish the Krebs cycle overactivity, decreasing the inflammation and rewiring the metabolic flux. Under the downregulation of GLS1, hepatocytes are able to synthesize phospholipids that are essential for lipid clearance in form of lipoproteins. The work sets the basis of a better understanding of the metabolic abnormalities that occur during liver pathologies, and the role of the enzyme GLS1, which had been previously related with severe hepatopathies but not with MAFLD.

Dr Juan Josè Beloqui graduated from pharmacy school and is educated as a Hospital Pharmacist, serving in several senior positions in public hospitals in Spain. He became a Board Certified Pharmacist in Pharmacology in 2016. He had the opportunity to get involved in the development of the NAGEN-1000 project, designing the first pharmacogenetic panel and learning the great possibilities of the NGS techniques. He combines his work as a clinical pharmacist at the University Hospital of Navarra with the work as head of pharmacogenetics at the Genomic Medicine Unit at Navarrabiomed.

Juan Josè Beloqui talked about his project "PHARMANAGEN", an interesting training programme and example of interdisciplinary groups of collaboration.

PHARMANAGEN is a strategic project developed with the aim of going deeper into genetics through exome sequencing, generating first level evidence to support it and creating the tools for its correct implementation in routine clinical practice. Part of this objective is to generate a new dimension of safety and efficacy within the Navarra Health Service-Osasunbidea (SNS-O), adding it to other disciplines, such as pharmacokinetic monitoring, which form part of PM.

To carry out these objectives, a consortium of institutions has been created, formed by Navarrabiomed, which is the biomedical research centre of the Government of Navarra; the Navarra Health Service through the Navarra University Hospital (HUN), involving professionals from different fields: Pharmacy Service, Gastrointestinal Service and Haematology Service of the HUN, the Evaluation and Planning Section, the Pharmacy Sub-Directorate and other clinical resources. This diverse composition has made it possible to bring together different experiences and expertise, ranging from knowledge of routine clinical practice, knowledge of drugs and their pharmacogenetics to knowledge of top-level evaluation and evidence generation tools. It should be noted that the project has managed to break down one of the existing barriers to the implementation of pharmacogenetics at the clinical level. It has managed to generate first level evidence for the systematic review of thiopurinic drugs in Inflammatory Bowel Disease and has also created a compilation of revised pharmacogenetic recommendations adapted to our local situation. The final table of pharmacogenetic recommendations includes recommendations for a total of 52 drugs. Thirteen different genes have been chosen, encompassing 43 different genotypes. The final number of recommendations is 114. The drugs involved cover almost all anatomical groups, with those related to anti-infectives and the nervous system standing out for their number.

These tools, together with the pharmacogenetic prescription aid system implemented within the electronic Clinical Decision Support System in Navarra, are the first piece that will allow access to pharmacogenetic data throughout the Navarra Health Service, regardless of the level of care. This entails a paradigm shift that brings a discipline of extremely high scientific-technical complexity closer from the limited field of specialised care to the general field, which will enable a much more rapid development of this discipline in the coming years.

The sequencing of the complete exome of 274 patients with Inflammatory Bowel Disease or candidates for Haematological Transplantation has been achieved. 2,192 variants have been found in these patients that can mark their response or toxicity to drugs commonly used in clinical practice. All patients had at least 1 gene with a phenotype different from normal, with an average of 8 altered genes per patient, and all patients had a unique pharmacogenetic profile that distinguished them from other patients.

In conclusion, the PHARMANAGEN project has opened the way for the direct implementation of pharmacogenetic data in the SNS-O, acquiring and generating the necessary knowledge and tools so that not only the patients included in the project, but all those patients, past and future, for whom the study of the human genome or exome is a clinical option, can benefit from personalised prescription.

Ludmilla Thomé Domingos Chinen is a Senior Researcher of A.C.Camargo Cancer Center and has a line of research (Circulating Tumour Cells). She graduated in Biochemistry/Pharmacy at the Federal University of Goiás (1998), did her MSc in Tropical Medicine (Immunology) at the Federal University of Goiás (2001) and her PhD in Microbiology and Immunology (2005) at Federal University of São Paulo. She was manager of a Pharmaceutical Company (2005-2006) and Biochemistry/Pharmacology professor at a private university (2005-2006). Her present research focuses on Circulating Tumour Cells (CTCs), their role in tumour metastasis and their clinical significance. Recently, she received the commendation of pharmaceutical merit. It is an award from the Regional Pharmacy Council aimed to professionals with recognised excellence in teaching, assistance or research. In the end of 2018, she was invited to participate on the project: Diagnosis and treatment in cancers with high mortality in Chile (REDES nº 180064.CONICYT).

In her project: "Higher platelet-to-lymphocyte ratio is prevalent in the presence of circulating tumour microemboli and is a potential prognostic factor for non-metastatic colon cancer" (Translational Oncology 14 (2021) 10093(https://doi.org/10.1016/j.tranon.2020.100932) she worked with Circulating Tumour Cells (CTCs) in metastatic colon disease for a long time and was able to show that CTCs counts, and kinetics are prognostic factors in this scenario (OncoTargets and Therapy 2016:9 7503–7513; Diagnostics 2021, 11, 502).

In the case of patients treated with target therapies, when the primary tumour is not available for KRAS analysis, she showed that CTCs can be used as surrogates (Cancer Biology & Therapy 16:9, 1289-1295; 2015). In metastatic disease her group also showed that protein analysis of genes related to resistance to chemotherapy (TYMS and MRP-1) can be evaluated in CTCs and that their expression in these cells directly correlated with disease progression. Their expression in primary tumour and metastasis did not correlate with disease progression (Int. J. Cancer: 137, 1397–1405; 2015; Int. J. Cancer: 139, 890–898; 2016).

In the paper with which she applied for the ICPerMed Recognition (Translational Oncology 14 (2021), Ludmilla Thomé Domingos Chinen decided to work with early-stage disease and showed that stages I-III colon disease releases CTCs (median number of 69 patients=2.5 CTCs/mL), which was surprising, and that the levels were related to tobacco use.

The circulating tumour microemboli (CTM) presence was related to platelet-lymphocyte ratio (PLR). It was very interesting to observe that of 18 stage I patients, 33.3% had CTM and of 51 stages II or III patients, 13.7% had CTM ($p = 0.08$).

They are following all patients to better understand the role of CTM in this disease. Patients with a high PLR (> 124) were mostly (75.6%) diagnosed with high-risk stages II/III cancer (stages I/low-risk II, 24.4%; $p = 0.014$). All 8 patients that had disease recurrence during follow-up had a high PLR ($p = 0.02$).

The findings of this paper show that not only CTCs and CTM, but also PLR (an easy and old tool) may be clinically relevant for management and risk stratification of patients with early-stage diseases, that is when any therapeutic or diagnostic intervention can be really useful to help patients and avoid tumour evolution.