



# High Level Symposium: Health Policy & Personalised Medicine for Cancer – projecting the EU-China collaboration on the global arena

Main Outcomes & Key lessons



Integrating China into the International Consortium for Personalised Medicine (IC2PerMed) project aims to foster collaboration between the European Union (EU) and China in the field of Personalised Medicine (PM – also defined as precision medicine depending on the country/setting) research, innovations, and policies. The project is part of the ICPerMed initiative, which seeks to provide individuals with access to personalised, intelligent, and inclusive healthcare solutions in the near future. IC2PerMed, a Coordination and Support Action under the Horizon 2020 funding programme, strives to offer policymakers key solutions for harmonising the approach to PM for the benefit of global citizens.

The IC2PerMed project is reaching its final phase successfully, and a High-Level Symposium on Personalised Medicine was organised by the World Federation of Public Health Associations (WFPHA) in Geneva on May 26, 2023. The symposium focused on presenting the project's main outcomes, discussing its implementation at the national and international levels, and addressing the application of PM in cancer and beyond, with a particular emphasis on China and Europe. The symposium also explored the potential adoption of PM in other countries. IC2PerMed is part of a broader family of projects on the same subject, and its main deliverable is the Roadmap (Annex I).

Currently, cancer patients require access to more accurate and timely diagnostic testing and treatment. Digital health and artificial intelligence hold immense potential for improving the health of those people. While significant progress has been made in the field of PM over the past six years, only a small percentage of cancer patients receive individualised care. The healthcare system is under mounting pressure and needs optimisation to offer PM opportunities, along with new treatments and diagnostic tools.





"Putting together politicians, researchers, managers, patients, and citizens. We need to hear each other in order to implement a successful health program for personalized medicine" - Walter Ricciardi,

President of Mission Board for Cancer of European Commission

To bring innovation to healthcare systems, both the public and private health sectors play crucial roles. Healthcare workers are already making tremendous efforts, but the process is often slow due to political factors. The development of regulations and policies is a key aspect that influences innovation. Technological progress may be rapid, but the legislative process tends to be slow. The initial idea behind IC2PerMed was to facilitate coordination among various research agencies to avoid duplication. However, in the European Union, there is insufficient allocation of resources to support the implementation of PM, and politicians sometimes tend to exclude the private sector. This lack of support hinders innovation in healthcare systems. Europe is falling behind in this regard because it fails to involve the industry adequately. Although health technology is necessary, it requires a framework that promotes more extensive implementation at the EU level.

"The law should be written in a way to foster health developments" - Ricardo Baptista Leite, former member of Portuguese Parliament and CEO of I-DAIR

Nevertheless, the goal is to achieve the most effective treatments using the latest medical advances, ensuring equitable access for all populations worldwide and reducing inequalities between countries. Equity should be the primary consideration in offering PM, aiming to narrow the gap between rich and poor.

"We have to reduce the world's asymmetry by using new technologies" - Carlos Gadelha, Secretary of science, technology and innovation of the Brazilian Ministry of Health

Collaboration between the local governments and public health systems is key and the introduction of PM should be read in the context of prevention and as a means of saving money and lowering government and public health expenses. China recognises the challenges posed by industrialisation, urbanisation, an aging population, and new diseases and aims to address long-term health issues comprehensively. The National Health Commission (NHC) and the Ministry of Science and Technology (MOST) have led major PM projects at the national level. These initiatives focus on establishing a holistic and inclusive healthcare system, ranging from disease prevention to treatment and rehabilitation. The goal is to enhance health standards and equity across the country. Under the 13th Five-Year Plan, precision medicine was included as a strategic priority. The MOST launched a national research and development program with a significant investment of 600 billion yuan to support technological innovation and scientific advancements. The program encompasses five key areas: advancing clinical biomics technologies to analyse and apply genomics data effectively; creating large-scale population cohorts to study major diseases and develop personalised health risk assessments; establishing a comprehensive platform for big data in precision medicine to integrate, store, and utilise resources and knowledge; developing precise disease prevention and treatment plans and clinical





decision-making guidance; and building an integrated application demonstration system for precision medicine across regions and hospitals.

Within the field of medicine and oncology, there is significant waste of resources and inefficient organisation in many countries, as well as notable variations in the quality of care within the same region. The healthcare sector urgently needs to invest in personnel and workforce development. Several organisations in Europe are actively addressing these issues, with a focus on advancing precision medicine, such as through the implementation of new generation sequencing (NGS) and collaborative efforts in cancer research.

However, the availability of funds from European governments for PM is still subject to debate, with varying opinions among experts regarding the sustainability of PM. China experts believe that the investment would actually fund itself to make the savings to the healthcare system, with enough data to convince policymakers that more money should be spent on prevention through PM.

"The health care system should be designed in such a way that we can use the full potential of the Personalised Medicine" - Ejner Moltzen, ICPerMed coordinator

The overall problem of health economics and equity is far more complex that deciding where to invest. PM does not fit the current health system model. We need to create a sustainable health system to accommodate PM, and also provide the industry with the right setting to offer PM treatments. We have all the research-based opportunities, but not all countries or regions are able to present them to the general public. PM must be tailored to specific requirements of the nations and the individual so it can be accessible to as many people as possible. PM should be shaped as a top-down initiative from our decision-makers and an essential component of our future health care systems.

"Implementing Personalised Medicine becomes overly complicated, despite the fact that it should be straightforward" - Denis Horgan, Director, European Alliance for Personalized Medicine

Data collection management and privacy remain another key issue. The International Agency for Research on Cancer/World Health Organization (IARC/WHO) has been working closely with China, consistently using high volumes of data to inform the general global cancer overview. When it comes to implementation questions, we frequently encounter resistance because new technology takes too long to integrate into the regular operations of the health care systems. There are not enough incentives to make it possible to apply those innovations to health care practices. Technology is fine, and data is not a problem; it is more about framing the solution new technologies offer so that the implementation runs smoothly. A significant achievement in data security regulations for healthcare institutions has been achieved. In China, the Measures for the Administration of Cybersecurity of Healthcare Institutions and the Data Exit Security Assessment Measures ensure the secure management and transfer of personal information and data. Beijing Friendship Hospital's collaboration with the





University of Amsterdam Medical Center became the first approved case for data exit security assessment, promoting compliant cross-border data exchange and utilisation. However, many challenges, including data sharing and utilisation, regulatory pathways for personalised genetic testing, ethical considerations, training, and innovative payment systems for high-value drugs, remain to be addressed. To overcome these challenges, it is of utmost importance to increase the supply of health insurance, fostering international scientific and technological cooperation, and supporting the establishment of scientific research funds and scientist exchange programs. Overall, China is committed to advancing precision medicine to significantly improve public health, reducing ineffective and excessive treatments, mitigating harmful healthcare practices, and curbing rising healthcare costs.

In the private and research sectors, innovation and speed are crucial factors. The prevalence of non-communicable diseases (NCDs) worldwide, especially in low-income countries (LIC), poses a significant challenge. While a substantial amount of money is allocated to treating NCDs, governments often neglect investing in screening and prevention programs. The global population is aging, while unhealthy lifestyles are on the rise. Unfortunately, there is currently limited focus on innovative approaches for NCD prevention. In this global context, there is room for improving PM, particularly through the utilisation of pharmacogenomics and polygenic risk scores which assess the likelihood of developing a disease based on an individual's genetic makeup.

"When properly implemented, personalised medicine can be a powerful tool" - Kirsten Tief-Kuery, Vice President Commercial EMEA, Genetic Analyses Solutions, Thermo Fisher Scientific

Although the IC2PerMed roadmap for PM implementation remains very relevant, it still presents challenges. Indeed, to achieve effective implementation, we must consider the "users." Patient-centered care differs from PM, but both approaches share the same underlying principles that could be considered as precision medicine. Our world is primarily driven by economic factors, raising the question of what can be done to address this issue. The determination of medical needs is often overshadowed by financial considerations. When examining public health perspectives, PM is not prominently mentioned in the WHO's papers listing the top 16 barriers in public health and prevention.

Public and patient's education is crucial. Clinics require PM, but they also need clinicians who have been educated outside of academic environments, as healthcare professionals (HCPs) often lack the necessary training, particularly in the emerging field of PM. The training of healthcare professionals will be essential to make precision medicine a routine practice. The world is experiencing a shortage of healthcare providers, particularly nurses. Adequate staffing is fundamental to enable healthcare professionals to engage in focused conversations with patients, understanding their needs and developing personalised plans that incorporate PM. The HCPs role is vital in coordinating and integrating care, as well as in building trust.





"Education of the general public and clinicians can help foster the implementation of Personalised Medicine" - Jens K. Habermann, Director General BBMRI-ERIC (The European Infrastructure for Biobanking and Biomolecular Resources in health and life sciences)

Within healthcare systems, there is resistance to paying for innovation, leading to delays in adopting new technologies, techniques, and instruments until they become more affordable for a larger patient population. Similar challenges exist in other fields, such as infectious diseases, where payers question the strength of evidence, or the high prices associated with certain treatments. Physicians and other health professionals face the consequence of insufficient resources or technology, hindering their ability to treat patients. The international code of medical ethics already require physicians to apply medical standards and to utilise a precision medicine approach in cancer treatments. The ethical foundations are in place; what is lacking is adequate investment and resources.

"Healthcare is often viewed as a cost rather than an investment. Unless this perspective changes, progress in innovation will continue to be hindered" - Otmar Kloiber, Secretary General, World Medical Association

Innovation is undoubtedly crucial, but we must acknowledge the diverse realities experienced by different countries. There are significant disparities between the global North and South. For many people, access to basic healthcare remains a challenge, making the question of PM irrelevant. While introducing technology is beneficial, it is insufficient without an effective healthcare system in place. When making decisions that impact a significant portion of the population, but are not adequately supported by the system, caution must be exercised. For instance, in low-income countries, access to opioids for managing cancer patients' pain in their final weeks of life is often limited. In this context, it raises questions about the direction that technology is actually taking us and whether we are bridging the care gap for global cancer treatment. While we desire innovation, we must also address equity issues worldwide. It is essential to consider the cost of delivering and maintaining technological advancements in lowand middle-income countries when focusing on advancing precision medicine. Companies developing new medicines often do not consider from the outset how to provide them in an affordable manner to LICs. As a community, we must tackle the question of how we can uplift LICs to the level of higher-income countries in terms of healthcare. Can we expect the WHO to include precision / personalised medicine on its list of recommendations in the next 5-10 years, considering affordability?

"These are challenging and exciting times, where progress is being made in privileged areas, but unfortunately, many parts of the world still lack access to these advancements" - Cary Adams, CEO, Union for International Cancer Control

From a hospital perspective, precision medicine is just one of many innovations with great potential. It has the capacity to drive a shift towards a value-based healthcare delivery system, where hospitals strive to maintain long-term patient health to reduce healthcare costs, as opposed to a volume-based system that rewards treating as many





patients as possible. Precision medicine has the potential to transform the hospital sector and prioritise public health.

"My hope is that Personalised Medicine will transfer the industry, specifically the hospital industry, toward a value-based system approach" - Ronal Lavater, CEO, International Hospital Federation

In Chinese hospitals, initiatives like Neuro-oncology tumor boards, and molecular tumor boards are implemented to support clinical treatments. Patient information is collected through Next Generation Sequencing for tumor cancer, and personalised treatment plans are discussed in Molecular Tumor Board. If the initial treatment fails, innovative therapies are explored.

"China is actively integrating personalized medicine into treatment approaches - WenYa Wang, Tsinghua University

The perspective of public health professionals is complex, as we work in various settings, ranging from low- to high-income countries. Furthermore, significant disparities exist even within the same country, where wealthier communities often receive better healthcare. Affordability encompasses more than just the price of drugs; access to treatment is another crucial factor. In consortiums like IC2PerMed, the representation of LICs is lacking, hindering our understanding of their specific obstacles and needs. For precision medicine to be approached fairly, representatives from the global South should be included in discussions from the outset. For decades, we have observed a vertical approach to health systems, with significant donors from wealthier countries investing in specific diseases. However, it is essential to prioritise investing in strong health systems first before introducing innovation. Many LICs rely heavily on external donors, which is not a sustainable way for a country to develop. True decolonisation of healthcare requires meaningful participation and representation of individuals from LICs.







# **Speakers & Chairs**

- Bettina Borisch, WFPHA CEO
   <u>Carlos Gadelha</u>, Secretary of science, technology and innovation of the Brazilian
   Ministry of Health
- Cary Adams, CEO Union for International Cancer Control
- Denis Horgan, Director, European Alliance for Personalised Medicine
- Einer Moltzen, ICPerMed coordinator
- Howard Catton, CEO, International Council of Nurses
- Jens K. Habermann, Director General BBMRI-ERIC (Biobanking and BioMolecular Resources Infrastructure-European Research Infrastructure Consortium)
- <u>Kirsten Tief-Kuery</u>, Vice President Commercial EMEA, Genetic Analyses Solutions, Thermo Fisher Scientific
- <u>Li Ning</u>, Vice President for BGI Group
- Marta Lomazzi, WFPHA Executive Manager
- Matti Aappro, President, Sharing Progress in Cancer Care and UICC board member
- Otmar Kloiber, Secretary General, World Medical Association
- Ricardo Baptista Leite, former member of Portuguese Parliament and CEO of I-DAIR
- Ronal Lavater CEO, International Hospital Federation
- Stefania Boccia, Professor of Hygiene, Preventive Medicine and Public Health & PI IC2PerMed
  - <u>Walter Ricciardi</u>, WFPHA Immediate Past President & President of Mission Board for Cancer of European Commission
- WenYa Wang, Tsinghua University
- Zisis Kozlakidis, Head Laboratory Support, Biobanking, and Services, IARC

# **Funding**

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 874694

This project has received funding from the Chinese MOST Intergovernmental Project of National Key R&D programme under grant N#2021YFE0192400





# **Annex I - The Roadmap**



### **IC2PerMed Working Groups**



### Working Group 1

# Shaping sustainable

This WG's activities focus on awareness and empowerment of citizens and patients, education and curricula of healthcare professionals, and healthcare sustainability. For PM to be routinely implemented in clinical and public health practice, both patients and health professionals should be aware of the possibilities offered and how to

professionals should be aware of the possibilities offered and how to make the most of them.

Given the need for informed, empowered, engaged and responsible fetters, there is a neet to deepen digital literacy, knowledge of health data, public trust in institutions and easily accessible, reliable and understandable sources of medical information. Informed, accountable and empowered health service providers are also essential. The safe repossible and optimal use of health information and research results required for PM should be routine in clinical settings. Clinical decisions should go through multidisciplinary teams, integrating new health professions. Clinicians and researchers, and all relevant stakeholders, should work closely together to support the rapid development and implementation of PM solutions. The considerable global burden of non-communicable diseases and limited healthcare resources put the spotlight on the need for health promotion and disease prevention, diagnosis and treatment for the benefit of patients. To loster the adoption of new policies,





# Working Group 2

### Innovation and market

This WG's activities focused on Big Data and ICT solutions and on bringing innovation to market.

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Big Data refers to datasets that are unprecedented in size and complexity, made possible by recent advances in automated collection of large-scale molecular and clinical data and the creation of large-scale molecular and clinical data and the creation of ICT solutions. Big Data raises several issues for public policy markets, including personal data ownership and protection, skill gaps in labour markets and an emerging new digital divide. Hence, policies in this field are fundamental for three appects. Bediest his prime example of disruptive innovation in the context of Big Data, the innovation copyriem is similarly important to translating basic research and innovation progress into PM solutions in the hands of end users and eventually patients and citizens. The working group inhighlyted the importance of targeted innovation incentives design principal displayed the importance of targeted innovation incentives growing market apolytion and uptake of new approaches is central to bringing innovation to market.



A cluster and patents-termined approach is required to provide guidance to to researchers and developers. Health budget constraints must be considered early on, and novel reimbursement measures are potentially necessary where cost- effectiveness is an issue. Innovations on personalized prevention measures in particular demand a holistic view on budget and should not be limited to healthcare.

### Working Group 3 Research and clinical studies in PM

This WG's activities focus on translating basic clinical research and beyond, and on research funding. In order for PM to reach its anticipated impact on human health and wellbeing translation of discoveries and communication across the continuum of research is required. This starts with the integration of all "omics" data to generate and implement meaningful interventions. Such processes should be supported by redessifying diseases at the molecular level and by developing preclinical models to validate hypotheses resulting from molecular analyses. A Europe-wide process to evaluate and validate biomarkers, together with inorptudinal and in-depth studies to further characterize diseases and their progression would support ongoing efforts towards integration and re-dissification. The development of new clinical trial designs that are adapted to these new approaches and the integration of preclinical testing with innovative clinical trials may further improve the effectiveness of interventions.



Collaborative pre-competitive and trans-disciplinary research and cross-sector collaborations need to be promoted and supported by suitable funding mechanisms, in order to truly bridge all steps of the PM research continuum.

### PM requires integrated approach



Citizens

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in the International Consortium



TRAINED AND UP-TO-DATE

HEALTHCARE WORKFORCE

### **IC2PerMed actions**

Based on the activities of WP1 and WP2, the IC2PerMed consortium developed a Roadmap which presents the main topics and priorities that emerged during the discussions held within the project. This document aims to propose, through the actions listed below, the items to deepen and promote alignment and creation of a common ground for European and Chinese collaborations on PM.



### IMPROVING

HEALTH LITERACY

EMPOWERED AND RESPONSIBLE



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EDUCATION & ETHICS

The future of healthcare professionals

ine truture or neatmeare professionais training relies on multidisciplinary collaborations. Fostering collaborations between professionals from different specialties and between professionals and stakeholders, while establishing more partnerships among countries, to facilitate sharing of best practice.

Promoting health literacy is a prerequisite for better citizens' and patients' improving healthcare professionals' literacy and expertise, engagement and empowerment. Considering the emergence of digital valuing integrity and ethics, could help foster PM. Resort technologies and the role of digital tools in supporting the engagement process, aimed at identifying methods that are more effective should be digital literacy whould be improved. Given the advancement of genomics and be promoted.

We are a province the end of the professionals' literacy should be considered, as they are a proxy for public engagement in self-management of considered, as they are a proxy for public engagement in self-management of considered, as they are a proxy for public engagement in self-management of considered, as they are a proxy for public engagement in self-management of considered, as they are a proxy for public engagement in self-management of considered as the consi



### RESEARCH

Fostering needs-assessment research and communication activities in the field of citizens' and patients' education related to Personalised Medicine could lead to





Scientific research, public organization and private institutions are key innovation actors in PM. Sustaining public trust and collaborations between different institutions, on a national and international scale, is the drive for healthrace transformation and public health promotion. In addition, public trust should be foretered and strengthened, in order to protect patients' right, knowle fleet after agovernance in accordance with the Helsinki Declaration and GDPR, implementing technical solutions to safeguard cyber security, citizens and health practitioner engagement, and developing comprehensive consent procedures where needed.



This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 874694

# **LE IC2Per**Med Roadmap



HEALTHCARE SYSTEMS' SUSTAINABILITY



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A better allocation of resources on PM can foster the sustainability of health systems. In particular, the identification of a large investment stream for the long-term storage of data is a fundamental perequisite for implementing PM strategies. In investment priorities for product and process innovation should be defined, considering the relationship between

.. product and process innovation should be defined, considering the relationship between results and costs, also by identifying new payment models for public relmbursement.





Ethical, Legal and Social Implications (ELSI) aspects and related costs should always be considered in the process of Personalised Medicine policymaking, evaluation, and management of technological innovation.





Multidisciplinary and cross-sectoral collaborations for PM can promote the sustainability of health systems. Public-

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Integrating China in the International Consortium for Personalised Medicine



# BRINGING

INNOVATION TO MARKET



The application of personalised diagnostics and therapeutics should be geared towards lowering economic costs and barriers to market uptake. With regard to diagnostics, promoting research in PM aimed at a more appropriate use of diagnostic tools (avoiding overuse, overdiagnosis and overtreatment) could lead to an optimal use of resources in the field of overtearment; ocusi lead to an optimal use or resources in the relate of healthcare. Interest of the consequently an increase in the value of healthcare. Health insurance providers should extend their coverage to innovative and high value Phositutions and refinement of services should be promoted or attempts should be made to reduce barriers to reimbursement. In implementation processes, economic, cost-effectiveness and relative value analyses should take into account both. social and health budgets as well as non-optimal resource use in the



New solutions on the market must put the emphasis on maximisi health outcomes for patients. An early, intensive, coordinated a continuous dialogue between all PM stakeholders involved is needed.





The various PM actors should follow a set of shared principles and universal guidelines on data sharing and exchange. Innovations that aim for higher therapeutic value should be rewarded. Social value assessment should be systematically applied.



Stakeholders stimulating innovation should take a holistic and long-term perspective on the balance sheet. The interconnection and mutual dependence between diagnostic and therapeutic innovations and potential for inappropriate use/ overuse must be taken into account.



### ADOPTING

BIG DATA AND ICT SOLUTIONS



To promote PM, Big Data needs to be analysable, comparable and interoperable across borders. The need emerges to carefully identify the type of information to be retained, increasingly favoring those related to health outcomes that ninformation with no proven clinical or management value. To facilitate data exchange procedures, greater cooperation between academia, healthcare systems (including providers and payers) and industry would be advisable.



Data security measures are a priority in the development of sew ICT solutions, which are crucial at global level and not only focusing on high-income countries. Social and cultural differences between Europe and China should also be considered when it comes to public trust in government and state authorities, trying to read a common understanding of shared challenges within PM. Public engagement can improve awareness and understanding of the benefits of data sharing, how data will be used beyond improving personal draw, and companies and order companies and protection options pertaining to personal data, and can help to develop frameworks that treflect broader societal consensus.



In the field of PM, It is essential to study solutions aimed at effectively combining data from different sources (genetics, clinical data) and regions, focusing on their standardization of effective usage. Standards for data use should be adopted and implemented, allow with a view to establishing common policies and global efforts for cross-border data sharing.

# **尼2Per**Med Roadmap



### **FOSTERING**

RESEARCH FUNDING



Funding agencies should tailor investments to the needs of patients. There is a need to promote the voice of patients (and caregivers) at all stages of PM research, from co-design research projects to advisory roles and enhancing educational initiatives to improve the scientific literacy of patients and researchers. Defining unmet needs and potential incremental innovation could help in Javing the groundwork for new international collaborations.

Investment plays an important role in the entire value chain and is needed from basic science to the implementation of and is needed into meast science or the imperimentation or PM in healthcare. Funders, both public and private, act as a first filter on the prioritisation of resource allocation, and this should be done responsibly. Furthermore, adequate investments are crucial in the research translation system.









Establishing synergies between funders and the research community is the first step in implementing PM as a community in the first step in implementing PM as a community funding programmes could promote collaboration and knowledge sharing between different countries and foster data sharing. Collaborations between funders should be established to align on research themes and to fund larger projects that are bold and cutting-edge, and enable risk sharing.



### TRANSI ATING

BASIC CLINICAL RESEARCH AND REYOND



Omics sciences are fundamental to the development of PM. Phenotyping patients, following defined standards, could identify similar platents. Beidise genomics, applications of different omics sciences and technologies should be promoted and used for the identification of biomarkers suitable for PM. Innovative methods that have shown great promise in the field of PM, including but use of induced pulmoptent stem cell and organ-on-chips models, should be evaluated and adopted, valuing literational partnerships.

Standardising approaches, including controlled access models for data sharing and clinical trials, may facilitate their implementation and help in patient stratification. Patient stratification in the field of non-genetic/complex diseases would benefit from research programmes on machine learning algorithms. Furthernow, using specific use cases from the fields of rare diseases and cancer could help in the development of common international standards and tools for research. Exchanges and dialogue between regulatory agencies should be promoted to overcome regulatory problems in PM, in particular on benefit-risk relationships.

## COLLABORATIONS



To promote international collaborations, especially on oncological care and rare diseases, it is important to support non-profit foundations and funding agencies. Establishing incentives and frameworks for public-private collaboration can facilitate academic and industrial access to biological samples and distate research purposes. It is necessary to facilitate and strengthen the discipute with registation yand HTA agencies, companies and discipute with registation yand HTA agencies, companies and researched, and to identify the most appropriate research methods to investigate PM both enrouring patient safety and adapting to the characteristics of study populations.

This project has received funding from the Chinese MOST Intergovernmental Project of National Key R&D programme | grant N#2021YFE0192400



This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 874694





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- Francesco Florindi. EMEA Strategic Partnerships Manager, Predictive Genomics
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- Luigi Russo. Hygiene and Preventive Medicine Resident Physician
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### Sacro Cuore

- Matti Aapro. President, Sharing Progress in Cancer Care and UICC board member.
- **Melissa Campagno**. Governments and EU Innovation Consultant at G.A.C. Group
- Nicolò Scarsi. Resident University Sacred Heart, Italy
- **Otmar Kloiber**. Secretary General, World Medical Association
- Jens Habermann. Director General BBMRI-ERIC
- Rachel Yang. National Rare Diseases Registry System (NRDRS) China
- Razieh Azari. WFPHA Communications Manager
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- **Terence Xiong**. Vice President, Global Development, Genomics
- **Tommaso Osti**. Resident University Sacred Heart, Italy
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