HEcoPerMed

Health Economics for Personalised Medicine

Deliverable

Conference Report, D5.3

Report Information	
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Duration:	42 months
Coordinator:	Doris Schartinger

This project has received funding from the European Union’s Horizon 2020 research and innovation programme under Grant Agreement No 824997.

History of changes			
Version	Date	Changes	Author
1	27.06.2022		Walgenbach
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3	30.06.2022		Walgenbach

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SUMMARY

The final conference “Health Economics of Personalised medicine” took place in Brussels on April 28th 2022. This by invitation only event was planned and organised onsite, but has been streamed via YouTube channel. The main purpose of this conference, as originally planned, was to give an overview of the results and findings of the project and the introduction of a strategic document describing specific approaches and challenges for the health economic evaluation of PM approaches. Therefore, the so-called HEcoPerMed “Position Paper” was launched and presented together with the main scientific results of the CSA to experts, stakeholders, funders and policy representatives.

The event and the achievements were of particular interest to the European Commission as well as for ICPerMed (International Consortium for Personalised Medicine) and the related EC funded projects. Thus, this event was a successful conclusion of the 3,5-years HEcoPerMed project and showed the results and finding of the CSA and gave an outlook on the upcoming activities and initiatives.

The agenda and some impression as well as a report will be available on the project’s webpage: Final Conference – HEcoPerMed

The Coordination and Support Action (CSA) HEcoPerMed started with a kick-off meeting in January 2019, Brussels. The project consortium consists of six partners from five European countries. It represents four academic institutions such as universities and university-based scientific institutes (Institute for Medical Technology Assessment-iMTA, Erasmus School of Health Policy (ESHPM) of Erasmus University of Rotterdam**,** The University of Oxford), research and technology organisations (AIT), a funding organisation (DLR) and an SME (Syreon).

The duration was originally planned for three years, but has been extended for 6 months due to the ongoing pandemic situation. Within work package 5 "Communication and Dissemination", two scientific and strategic workshops and a final conference were originally planned. The 1st workshop was planned in September 2020 and the 2nd workshop in March 2021. Due to the ongoing Covid-19 pandemic, the 1st workshop was postponed two times and replaced by two online workshops dedicated to the scientific work packages.

The 2nd workshop had also been postponed twice and finally took place in a hybrid format in October 2021, Budapest. In this event the recent project results and findings were presented and discussed along with a 1st version of a so called HEcoPerMed "Position Paper”.

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BACKGROUND OF THE EVENT

On behalf of HEcoPerMed consortium ("Healthcare- and pharma-economics in support of the International Consortium for Personalised Medicine – ICPerMed"), DLR organised a final conference with international experts and representatives from a wide range of stakeholders, experts and researchers. These included, for example health economics and personalised medicine researchers, policy and funders, e.g. the European Commission, ICPerMed, other CSAs related to ICPerMed (the so called 'ICPerMed family') and regional funders, healthcare payers as well as test technology developers/manufacturers and national competence authorities.

Originally the final conference should have been taken place already in September 2021. After postponing the previous workshop twice because of the still ongoing COVID-19 pandemic and the extension of the CSA by six months, the consortium decided to hold the final conference on April 28th in Brussels in order to get the presented documents ready and to allow European representatives from the EC, but also from other European organisations to join the even in person. The event and the report are a task within work package five (WP5). The conference has also been announced as by invitation only on the HEcoPerMed webpage: News – HEcoPerMed

AIM OF THE EVENT

The major aim of the event was to give an overview of the results and findings of the project and present and discuss the HEcoPerMed "Position Paper" as well as the latest project achievements. The "Position Paper "and the final conference agenda were sent to all invited experts before the conference for their information. At the event, the finalised document was presented and discussed in plenum. Together with the strategic "Position Paper" also the HEcoPerMed Short Scenarios Brochure was launched at this event. Furthermore, the main project achievements were presented and discussed in plenum.

ORGANISATION AND PREPARATION OF THE EVENT

For the conference, the consortium selected and invited over 150 experts from all relevant areas and sectors across Europe and beyond. Excluding the consortium partners, 50 experts had confirmed their participation and travelled to Brussels. In addition, the conference was streamed live via a dedicated YouTube link on the HEcoPerMed webpage. On average, 25 additional viewers were online via this link.

Only registered participants received information material one week prior to the conference, that included the final conference agenda, the finalised "Position Paper", a declaration of consent and organisational information about the hotel/venue and the travel reimbursement (see also under 10. Appendix of this document).

At the conference, after the welcome by the responsible head of units for the CSA of the EC, Carmen Laplaza-Santos, the ICPerMed chair, Ejner Moltzen and the coordination of HEcoPerMed Doris Schartinger, the main scientific results of HEcoPerMed, incl. three specific PM approach case studies were presented.

The HEcoPerMed conference on "Health Economics of Personalised medicine" was hosted at the Bedford Hotel & Conference Centre, Brussels. The basis of the conference were the achievements of the partners in the WP 1, 2, 3, 4 and 5 as well as the specifically developed "Position Paper".

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THE FINAL CONFERENCE COURSE OF EVENTS

The conference was divided into a plenary session and a concluding round table. In the plenary session, the individual results of the CSA and the finalised “Position Paper” were presented. At the subsequent round table, research and Implementation of Personalised Medicine in the light of the HEcoPerMed findings as well as other crucial settings and developments where discussed in a panel format. The participants of the panel represented crucial aspects of PM research, health economic evaluation and the implementation step. These included representatives of the EC and a national funding agency, industry/efpia, ICPerMed, a scientific partner of HEcoPerMed. Unfortunately, despite intense effort the organisers could not manage to get a patient organisation representative to join the panel and he discussion. For further information, please see agenda in the appendix.

Plenary Session: Welcome

On Tuesday 28 April, first, the responsible head of Unit for HEcoPerMed at the European Commission, Carmen La Plaza Santos and after her the ICPerMed chair Ejner Moltzen, Danish Innovation Fonds (DIF), welcomed the participants to the final meeting. Afterwards, Doris Schartinger, Austrian Institute of Technology (AIT), the coordinator of the CSA HEcoPerMed, introduced the HEcoPerMed consortium to the auditorium and gave a brief overview of how the CSA came into being. The HEcoPerMed CSA was launched in 2019 and is a CSA with a high proportion of scientific tasks and deliverables. Thus, the project consortium consists of six partners from five European countries. It represents four academic institutions such as universities and university-based scientific institutes, research and technology organisations (AIT), a funding organisation (DLR) and a SME (Syreon). The plenary session has been moderated by Tamas Zelei, HEcoPerMed partner from Syreon Research Institute, Budapest, Hungary.

Part One of the Conference, Update on HEcoPerMed Results and Achievements

Rositsa Koleva-Kolarova, HEcoPerMed partner from Oxford University, United Kingdom, presented the project results and achievements on behalf of the consortium. These include, among others, a **systematic review**, an article on “***Guidance for the Harmonisation and Improvement of Economic Evaluations of Personalised Medicine***”, three personalised medicine related health economic **case studies** and an accepted manuscript about “***Reimbursement and Payment of Personalised Medicine***”.

Afterwards, the results of different Personalised Medicine approaches (Modelling Case Studies), have been presented. Heleen Vellekoop, Institute for Medical Technology Assessment (IMTA), The Netherlands, presented the results of the study “Tumour-agnostic treatments for NTRK gene fusion-positive (NTRK+) cancers”, Sarah Wordsworth, Oxford University, United Kingdom, presented DPYD genotyping prior to fluorpyrimidine-based chemotherapy – ToxNav and Balazs Nagy, Syreon Research Institute, Budapest, Hungary, presented the trial “Maturity onset diabetes of the young – MODY”.

At the end of the first part of the conference, different possible perspectives of personalised medicine in the future were presented by Doris Schartinger, Austrian Institute of Technology. A related brochure described the process and outcome of this task with WP4 briefly. The document is ready for download on the project’s webpage. Also, around these talks and results a lively and interesting discussion took place at the event.

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Part Two of the Conference, HEcoPerMed Position Paper and Round Table Discussion

The second part of the conference was moderated by Doris Schartinger.

First, Maureen Rutten-van Molken, HEcoPerMed partner from Institute for Medical Technology Assessment (IMTA), The Netherlands, introduced the "HEcoPerMed Position Paper", which was officially launched at the conference (see appendix). The general concept of this paper has been developed by DLR and a first version was presented at the Budapest workshop in October 2021. This version was intensively edited by Sarah Wordsworth. Following the discussions at the hybrid event in Budapest and internal discussions the document was intensively rearranged an adapted by all HEcoPerMed partners under the coordination of Maureen Rutten van-Molken. The final document was also published at the HEcoPerMed website.

Maureen Rutten-van Molken started in her presentation (see appendix) with the explanation why HTA is needed and appropriate also for the evaluation for PM approaches. Then she explained the context, aim and target groups of the "Position Paper". This strategic document is largely based on the findings of the scientific efforts and achievements from HEcoPerMed as well as other publications in the field. It highlights the needs and the contribution that different economic evaluations bring to decisions related to personalised medicine (PM) approaches. Thus, they give the scientific basis for the allocation of the limited resources in health care. In particular, the role of health economic models in the context of HTA are presented. It is also shown that cost effectiveness analyses need modelling which is even more challenging for PM approaches. The document explains and defines important phrases, like Health Economics, Health Technology Assessment (HTA) and Health Economic Evaluation. Finally, **12** specifics scientific, strategic and policy **statements** are listed and described. The presentation highlighted some of these aspects and was followed by an open discussion with the audience in the plenum.

The conference closed by a round table panel discussion, which was moderated by Wolfgang Ballensiefen (HEcoPerMed and DLR). Participants of the round table were Carmen Laplaza Santos (EC), Ejner Moltzen (ICPerMed, DIF), Matthijs Versteegh (HEcoPerMed, iMTA) and Iain Bennett (Roche, Global Evidence Leader & efpia). Unfortunately, no patient representative could be found for the discussion. In preparation for the discussion, 10 guiding questions (see below), the position paper and the preliminary agenda of the conference were forwarded to the participants about one week before the conference.

These were the prepared guiding questions:

- What are the main statements and aspects from the "Position Paper" for you personally and did any conclusion or interpretation surprize you?
- Are health economic evaluations, models and HTA suitable and up-to-date for the assessment of PM and other innovative approaches?
- Are all aspects of diagnosis, treatment, benefit and preference of the patient adequately considered in the economic evaluation, especially for PM?
- Some of the main challenges for health innovations are the commitment of the private sector, regulatory assessment and economic considerations towards implementation. How and by whom could/should the system be further optimised to increase success rates and accelerate innovation?
- How could personalised prevention strategies be evaluated according to health economic aspects and models?
- Could a feedback loop from payers, providers and patients be feasible and beneficial for a continuous economic assessment of innovative PM approaches?

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- Like in some European Research Area Network for PM (ERA PerMed) calls could an early consideration of health economic aspects in research projects improve the impact of the related research?
- If the majority of health-related PM and health economic research is supported by public funding should this be considered in the health economic evaluation and in prizing?
- Are there significant variations to your knowledge in economic evaluation of PM across Europe?
- How do the objectives of European Medicine Agency (EMA) and/or national competent authorities' influence the reimbursement process in Member States and could it be optimised?

The discussion with the participants and the plenum was intensively and very constructive.

OUTLOOK AND NEXT STEPS

This report will be published together with the "Position Paper" and other conference related information and pictures on the HEcoPerMed webpage and disseminated through various channels, e.g. of ICPerMed, by the partners and the EC. This includes also the printed version of the "Position Paper" and the PM scenarios which were also available at the ICPerMed workshop in June (21st/22nd 2022) in Brussels entitled: "*Personalised Medicine: How to Ensure Value-Based Implementation*".

Also, several representative of HEcoPerMed were actively participating in this event. Furthermore, HEcoPerMed was presenting their results and finding at serval other events of the so called "ICPerMed Family" before and after the conference in April 2022.

Additionally, it is likely that the HEcoPerMed results, findings and publications will be a valuable input for upcoming ICPerMed activities, considerations of the EC as well as the planning of the upcoming European partnership for Personalised Medicine (EP PerMed). The consortium will publish further papers on health economy related to personalised medicine, such as a special issue within the next weeks. Also, further presentation and communication opportunities will be identified, e.g. at the annual ISPOR conferences as well as other personalised medicine and health economics related event and meetings

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Agenda

Thursday, April 28th 2022

HEcoPerMed Conference
"Health Economics of Personalised medicine"

Venue: Bedford Hotel & Congress Centre 135-137 Rue du Midi, B-1000 Brussels, including ***live streaming*** *under:* dlr-pt - YouTube

12:15 – 13.00h Registration

Part 1

Moderation: Tamas Zelei, Syreon Research Institute, Budapest, Hungary

13:00h Welcome (Plenum & Streaming)

- *Carmen Laplaza Santos, European Commission (EC), Health Innovations*
- *Ejner Moltzen, ICPerMed chair, Danish Innovation Fonds (DIF)*
- *Doris Schartinger, Introduction to HecoPerMed and this event, Austrian Institute of Technology (AIT)*

13:45h Update on HEcoPerMed Results and Achievements

- *A European outlook for incentivizing Personalised Medicine: the financing and reimbursement perspective, Apostolos Tsiachristas, Oxford University, United Kingdom*
- *Different Personalised Medicine approaches (Modelling **Case Studies**)*
    1. *Tumour-agnostic treatments for **NTRK** gene fusion-positive (NTRK+) cancers, Heleen Vellekoop, Institute for Medical Technology Assessment (IMTA), The Netherlands*
    2. *DPYD genotyping prior to fluorpyrimidine-based chemotherapy - **ToxNav**, Rositsa Koleva-Kolarova, Oxford University, United Kingdom*
    3. *Maturity onset diabetes of the young - **MODY**, Balazs Nagy, Syreon Research Institute, Budapest, Hungary*
- *Personalised medicine different perspectives for the future, Doris Schartinger, Austrian Institute of Technology*

14:45h Coffee / Break

Part 2

Moderation: Doris Schartinger, Austrian Institute of Technology

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15:00h HEcoPerMed "Position Paper": *Personalised Medicine from a Health Economic Perspective: Lessons Learnt and Potentials Ahead*"

- Maureen Rutten-van Mölken, *HEcoPerMed and Erasmus University Rotterdam, The Netherlands*
- Introduction to the "HEcoPerMed Position Paper" and the major findings followed by an open discussion with the audience in Brussels

15:45h Roundtable – Research and Implementation of Personalised Medicine in the light of the HEcoPerMed findings as well as further settings and developments

- Panel Discussion moderated by Wolfgang Ballensiefen, HEcoPerMed and DLR project management agency, Germany
- *Participants: Carmen Laplaza Santos (EC), Ejner Moltzen (ICPerMed, DIF), Matthijs Versteegh (HEcoPerMed, iMTA) and Iain Bennett (Roche, Global Evidence Leader & efpia).*

16:45h Closing Remarks and Outlook

Sarah Wordsworth, Oxford University, United Kingdom

Part 3

17:00 – 19:15h Exchange and Networking Opportunity

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The International Consortium for Personalised Medicine

Ejner K. Moltzen

Innovation Fund Denmark, Chair of IC PerMed

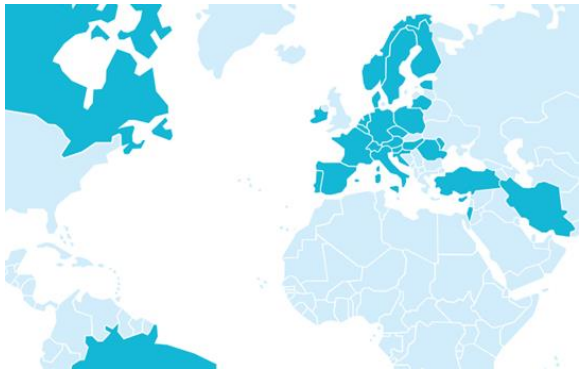
HEcoPerMed: Health Economics of Personalised medicine, Brussels, 28 April 2022

ICPerMed – An International Consortium

Overall aim:

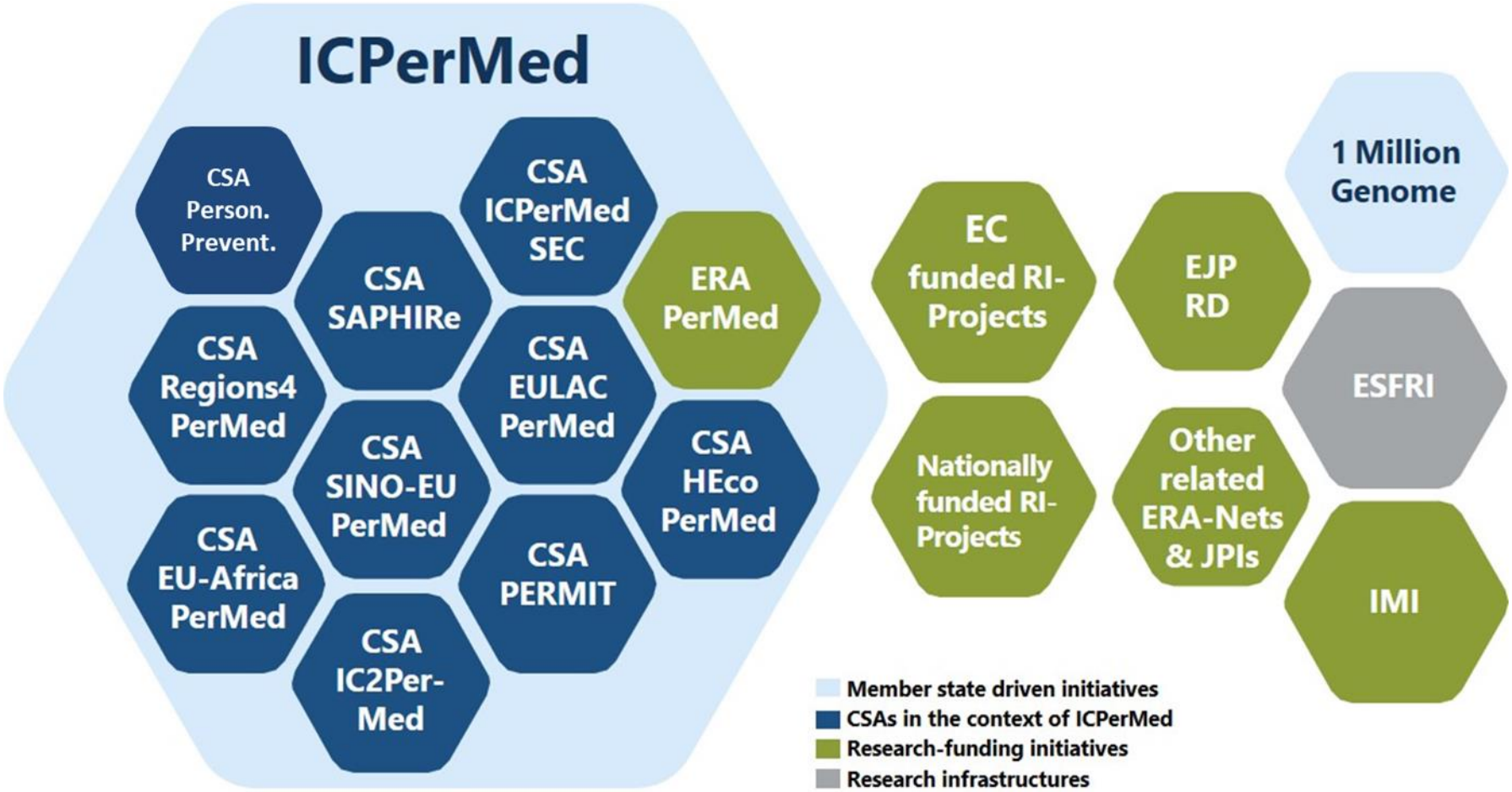
To coordinate and promote research along the full value chain to develop, evaluate and support implementation of personalised medicine approaches

- Almost 50 European and international partners
- Members include public and private `not-for-profit` health research funding and policy organisations and the European Commission
- Secretariat is funded by the European Commission
- Started in 2016 and will continue until 2023



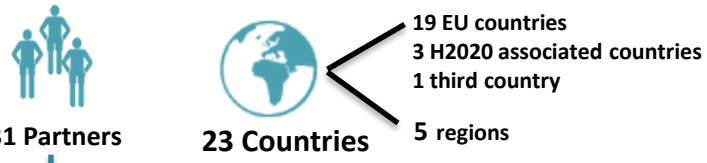
Internal networking - Events – publications – communications – various database tools

ICPerMed „Family“ and related initiatives



ERA PerMed – Joint Transnational Calls

EU co-funded JTC2018

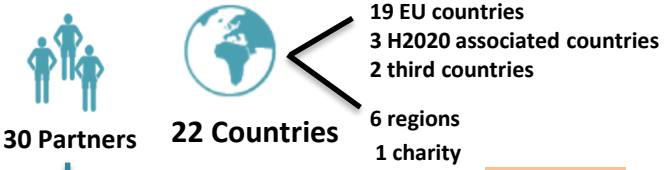


28,3 M€

Joint Call Secretariat (JCS)

National Institute of Health Carlos III (ISCIII)
SPAIN

non EU co-funded JTC2019

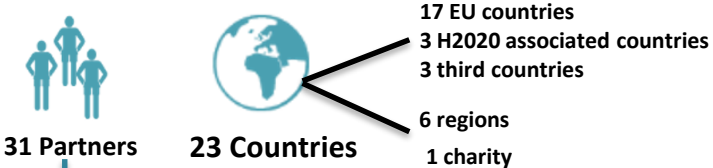


24,6 M€

Joint Call Secretariat (JCS)

French National Research Agency (ANR)
FRANCE

non EU co-funded JTC2020

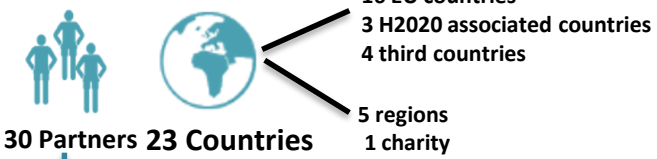


23,3 M€

Joint Call Secretariat (JCS)

German Aerospace Center (DLR)
GERMANY

non EU co-funded JTC2021 (in progress)



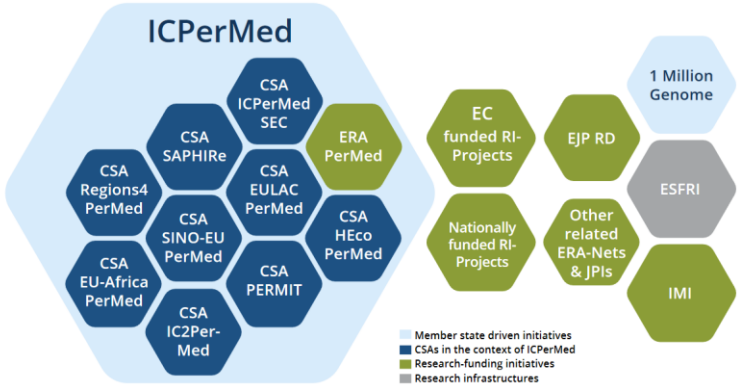
~ 24 M€

Joint Call Secretariat (JCS)

Italian Ministry of Health (IT-MoH)
ITALY

Additional non EU co-funded JTC2022 has been launched

Increasing commitment for and investment in PM



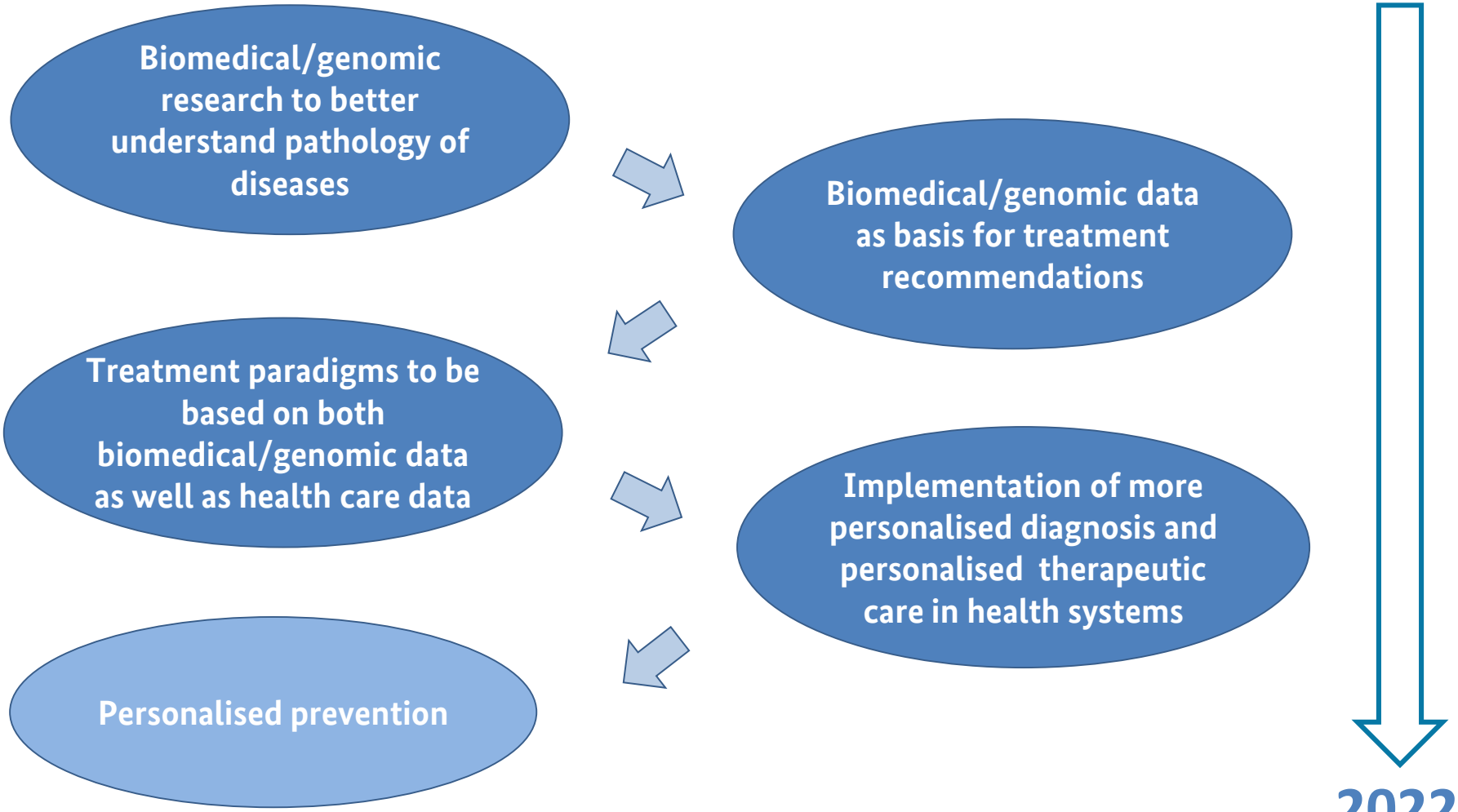
Since FP7 and during Horizon 2020, the EC provided a budget of more than 2 billion Euros into PM.

European Commission

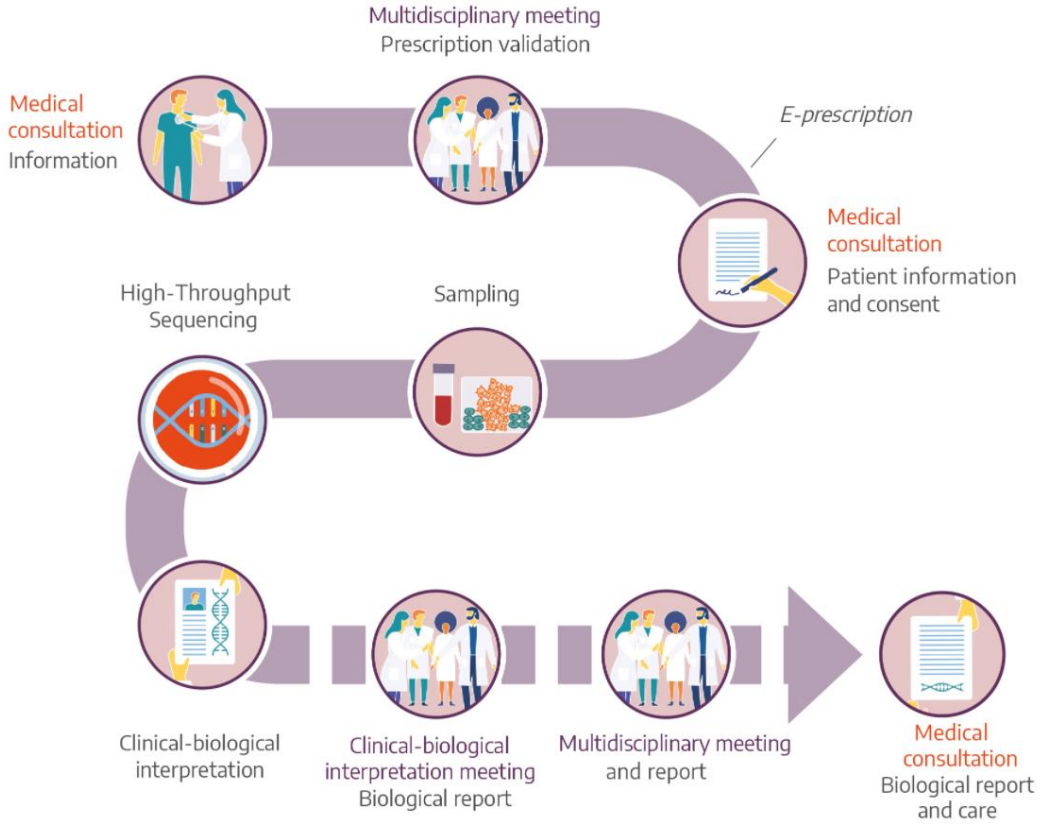
National, regional and cross-national level

- MedeA – Pharmacogenetics Personlised Prescription
- PERSEPHONE project
- MASTER – Innovation Driver for Personalised Oncology
- Electronic medical records (EMR) for personalised treatment
- 2025 France Genomic Medicine Initiative
- The "HAZLO" project
- Strimvelis® Gene Therapy
- Genomic Medicine Sweden
- Pharmacogenetic Recommendations for PM
- Navarra 1,000 Genomes Project
- Network Genomic Medicine (NGM) Lung Cancer

Personalised medicine is developing rapidly!



2025 France Genomic Medicine Initiative

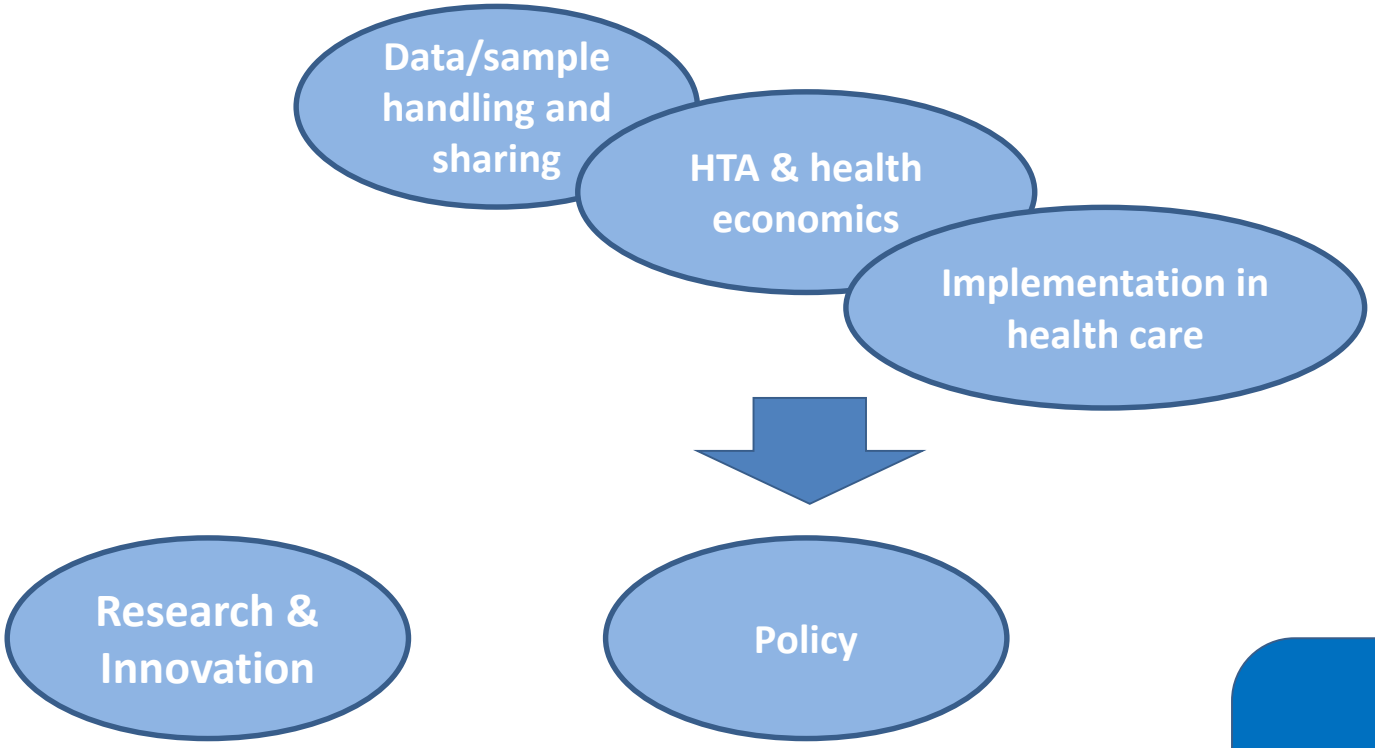


FRANCE MÉDECINE GÉNOMIQUE 2025
aviesan

"Precise genomic medicine represensts a revolution in the fields of health care and prevention. It is fostering huge hopes – legitimately so – in people. It is changing how we define disease and how we help the sick"

Yves Lévy, President of Aviesan

Overall PM landscape perspectives



Vision of PM:
Implementation of personalised medicine approaches for the benefit of patients, citizens, and society

Challenges & opportunities going forward

- R&I: Funding landscape overall for PM is good, but there is still main focus on cancer and rare diseases
- Access to relevant biomedical and healthcare data is necessary for both PM research and for PM-based treatment of patients
- Legislative frameworks are necessary to ensure privacy and security of data access.
- Patient involvement and engagement needed in relation to generation of real-world data (RWD)
- More outcome data needed in order to obtain broader health economic/HTA related evaluations of PM-approaches
- Implementation of PM-approaches in health systems will require major reforms

"Conceptually, PM may be seen as a natural evolution of medicine. However, in practical terms it may well represent a major disruption for healthcare systems, implying a shift from public health concepts traditionally developed for populations to a focus on the individual"

Investment in the future:
European Partnership for Personalised Medicine 2023-33

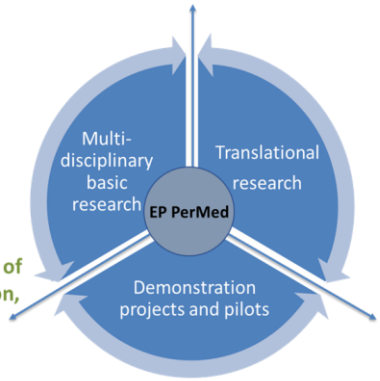
ICPerMed
INTERNATIONAL CONSORTIUM

ERA PerMed

Concept based on experiences from ICPerMed and ERA PerMed

Based on experience

Improved health outcomes for citizens and patients



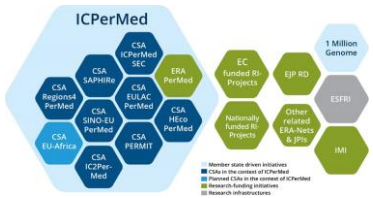
Europe at the forefront of Research and Innovation, in collaboration with international partners

Optimised and sustainable healthcare

The vision of the European Partnership for Personalised Medicine is to improve health outcomes within sustainable healthcare systems through research and the development and implementation of personalised medicine approaches for the benefit of patients, citizens, and society

Supported by
PM SRIA and priority setting
Suitable policy and regulatory frameworks
Dissemination, knowledge exchange, communication
and
Participation of all keyplayers

Knowledge & value transfer



Cooperation

EP PerMed

The necessary support

Member states & EC
Regions
International partners
Stakeholders

(1) Innovative Health Initiative (IHI)	2022-2032
(2) Global Health Partnership	2022-2032
(3) Transformation of Health Systems (THCS)	2023-2033
(4) Chemicals Risk Assessment	2022-2032
(5) ERA for Health (ERA4Health)	2023-2033
(6) Rare Diseases	2024-2034
(7) One-Health / Anti-Microbial Resistance	2024-2034
(8) Pandemic Preparedness	2024-2034

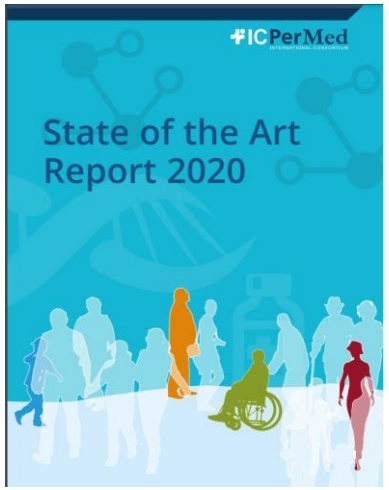
ICPerMed Stakeholder Forum

If you are interested to become an ICPerMed Stakeholder, please join the Stakeholder Forum here:

https://www.icpermed.eu/en/services-stakeholder-forum.php

More info on ICPerMed in State of the Art report:

https://www.icpermed.eu/media/content/ICPerMed%20State%20of%20the%20Art%20report%202020.pdf



Mail: ICPerMed@dlr.de Internet: www.icpermed.eu

ICPerMed
INTERNATIONAL CONSORTIUM

Thanks for your attention

and thanks a lot to the HEcoPermed team for doing a great and important job

Mail: ICPerMed@dlr.de Internet: www.icpermed.eu

EcoPerMed
Health Economics for Personalised Medicine

WELCOME TO THE HECOPERMED FINAL EVENT

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824997.

THE HECOPERMED PARTNERS

AIT Austrian Institute of Technology (AT)

- Doris Schartinger, Beatrix Wepner

DLR Deutsches Zentrum fuer Luft- und Raumfahrt (DE)

- Wolfgang Ballensiefen, Maren Walgenbach

IMTA Institute for Medical Technology Assessment (NL)

- Matthijs Versteegh, Simone Huygens, Heleen Vellekoop

Erasmus University of Rotterdam (NL)

- Maureen Rutten-van Mölken (IMTA/EUR)

Syreon Research Institute (HU)

- Balázs Nagy, László Szilberhorn, Tamás Zelei

University of Oxford (UK)

- Rositsa Koleva-Kolarova, Apostolos Tsiachristas, Sarah Wordsworth

THE HECOPERMED PROJECT (2019-22)

- **Develop** Healthcare- and pharma economic models
  - in support of IC PerMed, the International Consortium for Personalised Medicine
- **Respond** to the demand for health economic models
  - Robust evidence
  - Alternative payment and reimbursement models
  - Budget impact models
  - Innovative ways of funding R&D
  - Institutionalisation
- **Future health care**
  - With the aim of rapid development and uptake of PM based innovations in European health care systems
  - For the Health of the future society

HECOPERMED ACTIVITIES

HE Modelling related Activities

- Systematic literature reviews
- Generation of empirical evidence in three case studies (NTRK, ToxNav, Mody)

Community-building activities

- Involvement of experts and stakeholders in different formats
- Workshops
- Interviews
- Focus groups

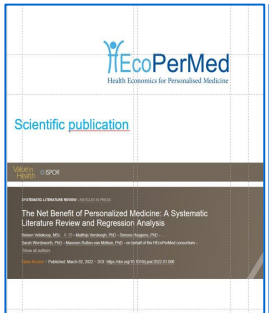
Strategic policy advice activities

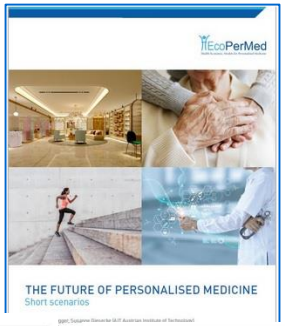
- Translate scientific evidence for decision makers
- Develop future scenarios
- Identify challenges and drivers of implementation

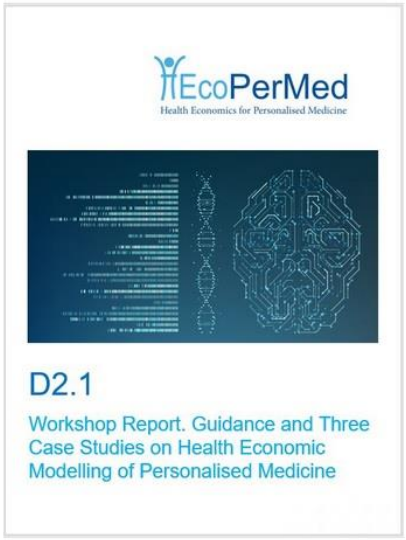
HECOPERMED RESULTS

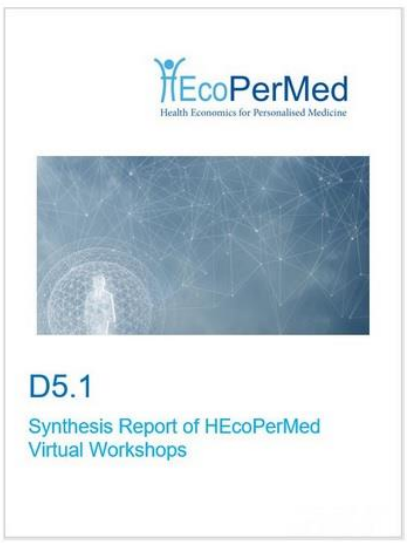
HECOPERMED RESULTS

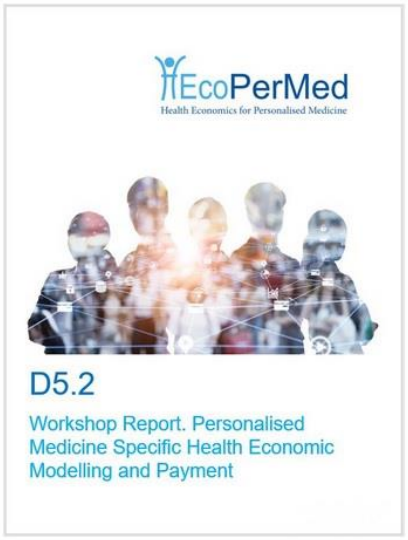
HECOPERMED RESULTS



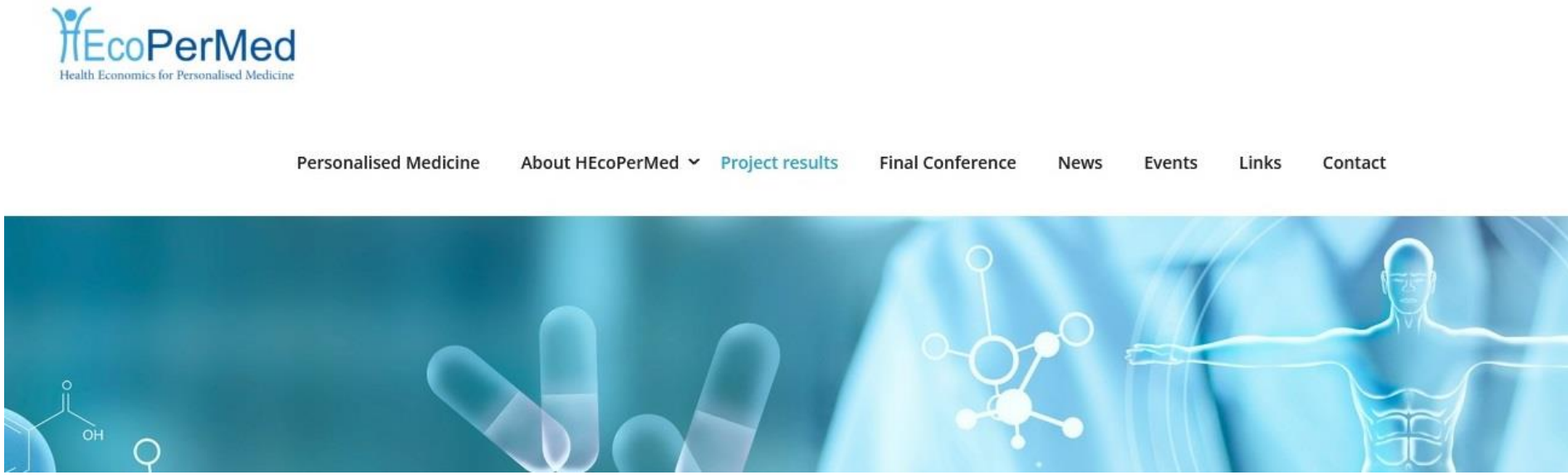








BEYOND HECOPERMED: WEBSITE



https://hecopermed.eu/

BEYOND HECOPERMED

EcoPerMed
Health Economics for Personalised Medicine

- Health care systems
- European Commission
- Strategic platforms

ICPerMed
INTERNATIONAL CONSORTIUM

EP PerMed

OBJECTIVES FOR THIS EVENT

- Present insights and findings
  - Financing and reimbursement perspective
  - Economic modelling results from 3 case studies (NTRK, ToxNav, Mody)
  - Future implementation perspective
- Translate and discuss scientific evidence with a wider audience
  - Present Position Paper
  - Panel discussion
  - Open discussion
- Exchange and networking

EcoPerMed
Health Economics for Personalised Medicine

THANK YOU

Doris Schartinger, April 28th, 2022

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824997.

EUROPEAN OUTLOOK FOR INCENTIVIZING PERSONALISED MEDICINE

Rositsa Koleva-Kolarova, Sarah Wordsworth, Apostolos Tsiachristas

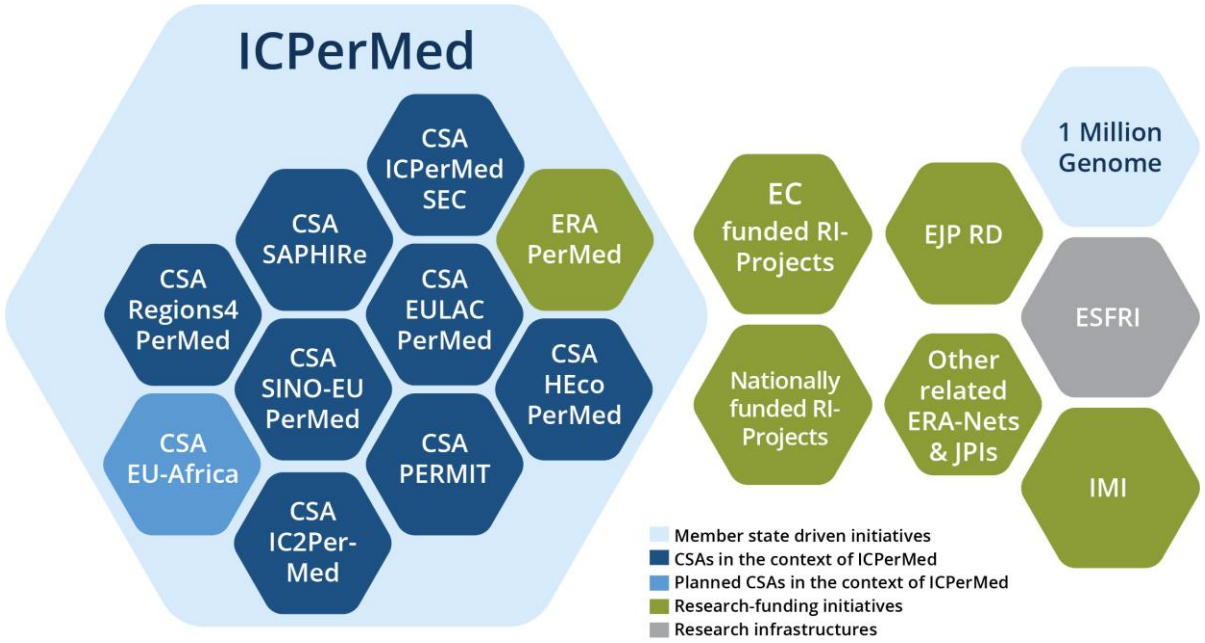
on behalf of the HEcoPerMed team

HEcoPerMed Final Conference Brussels 28 April 2022

INCREASING APPROVAL OF AND FUNDING FOR PERSONALIZED MEDICINE

Approved gene therapies		Gene therapies in advanced development	Gene & gene editing therapies in earlier development
USA	Imlygic Kymriah Yescarta Luxturna	GS010 NSR-REP1 Valoctocogene roxaparvovec AMT-061 AVXS-101 Alferminogene tadenovec RT-100 Ofranergene obadenovec Pexastimogene devacirepvec Beperminogene perplasmid VM202 LentiGlobin Elivaldogene tavalentivec GSK2696274	SPK-9001 ABO-102 AAV1-Follistatin Mydicar Lisocabtagene maraleucel bb2121 DNX-2401 ONCOS-102 Sepravir Vocimagene amiretrorepvec NY-ESO-1 OTL-101 G1XCGD SB-728-T CRISPR/Cas9
EU	Imlygic Strimvelis Zalmoxis		
China	Gencidine Oncorine		
Russia	Neovasculgen		
Korea	Tonogenchoncel-L		

Source: Sinclair 2018



- €3.2 billion EU investment in PM research in 2017
- Over US$4 billion government investment in genetic R&D and translation in 14 countries in 2019

TRANSLATION OF PERSONALISED MEDICINE INTO CLINICAL PRACTICE

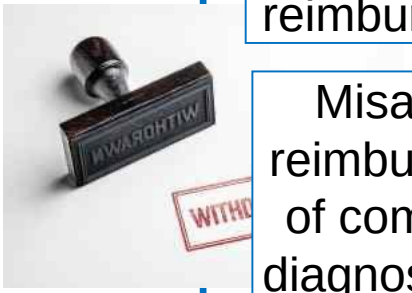
Trastuzumab

OncotypeDX

Luxturna

Vitrakvi

ChondroCelect
MACI
Provenge
Glybera



Variable reimbursement

Misaligned reimbursement of companion diagnostics and treatments

Mismatch between price and value

2006

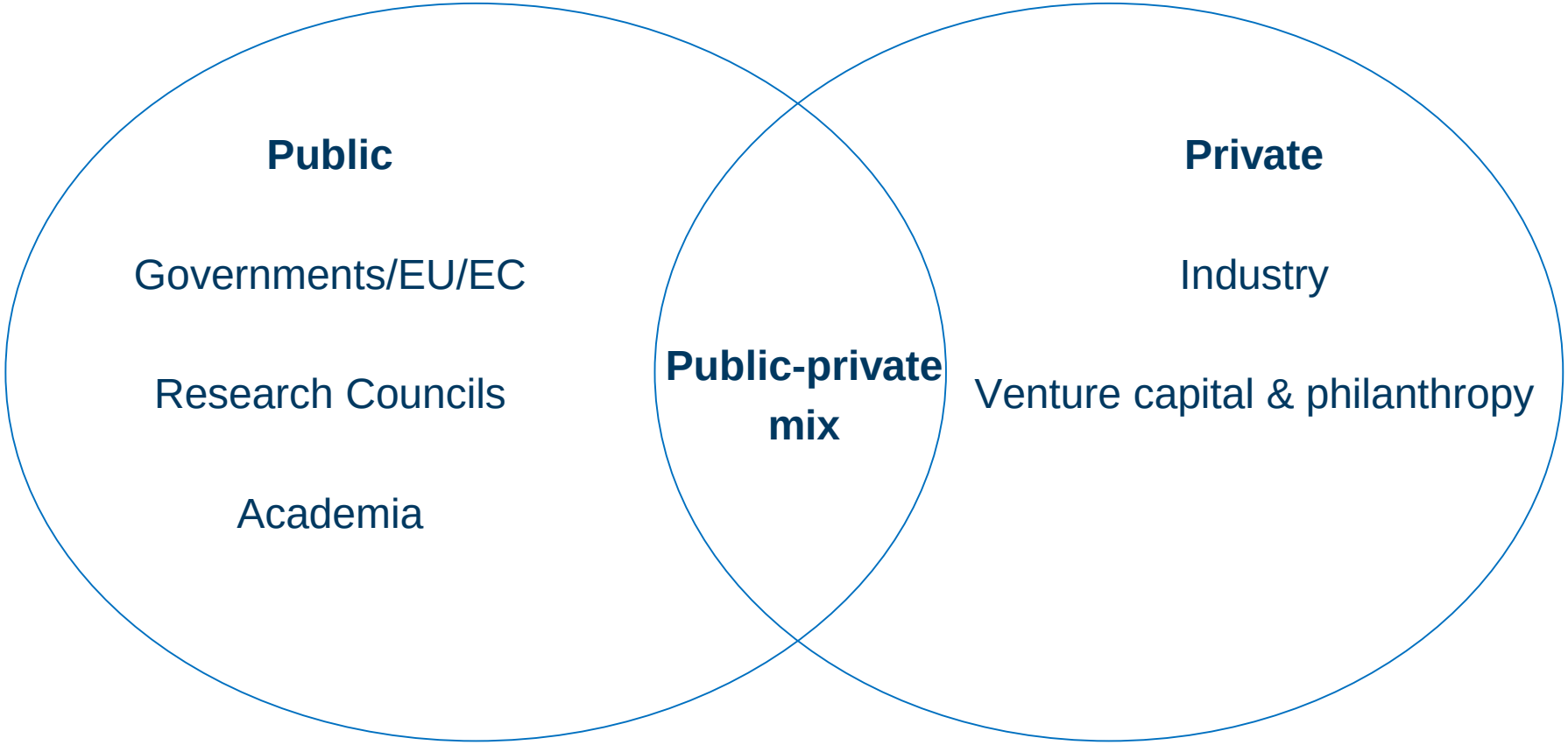
2011

2018

2020

2009-20

FINANCING MODELS

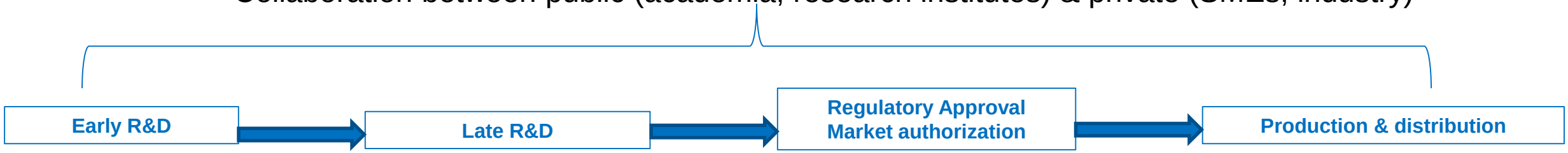


Public
Academia research institutes

Private
SMEs, Industry

co-production as business partners

Collaboration between public (academia, research institutes) & private (SMEs, industry)



ACTIONS FOR ADEQUATE FINANCING OF PM

Barriers and disincentives

- **Lack of strong links** between academic researchers and private endeavours
- Issues related to **legal, privacy/ethics, data-sharing, and generation of evidence**
- **Misaligned research priorities** at international, national and regional level

Maintain and upscale current financing

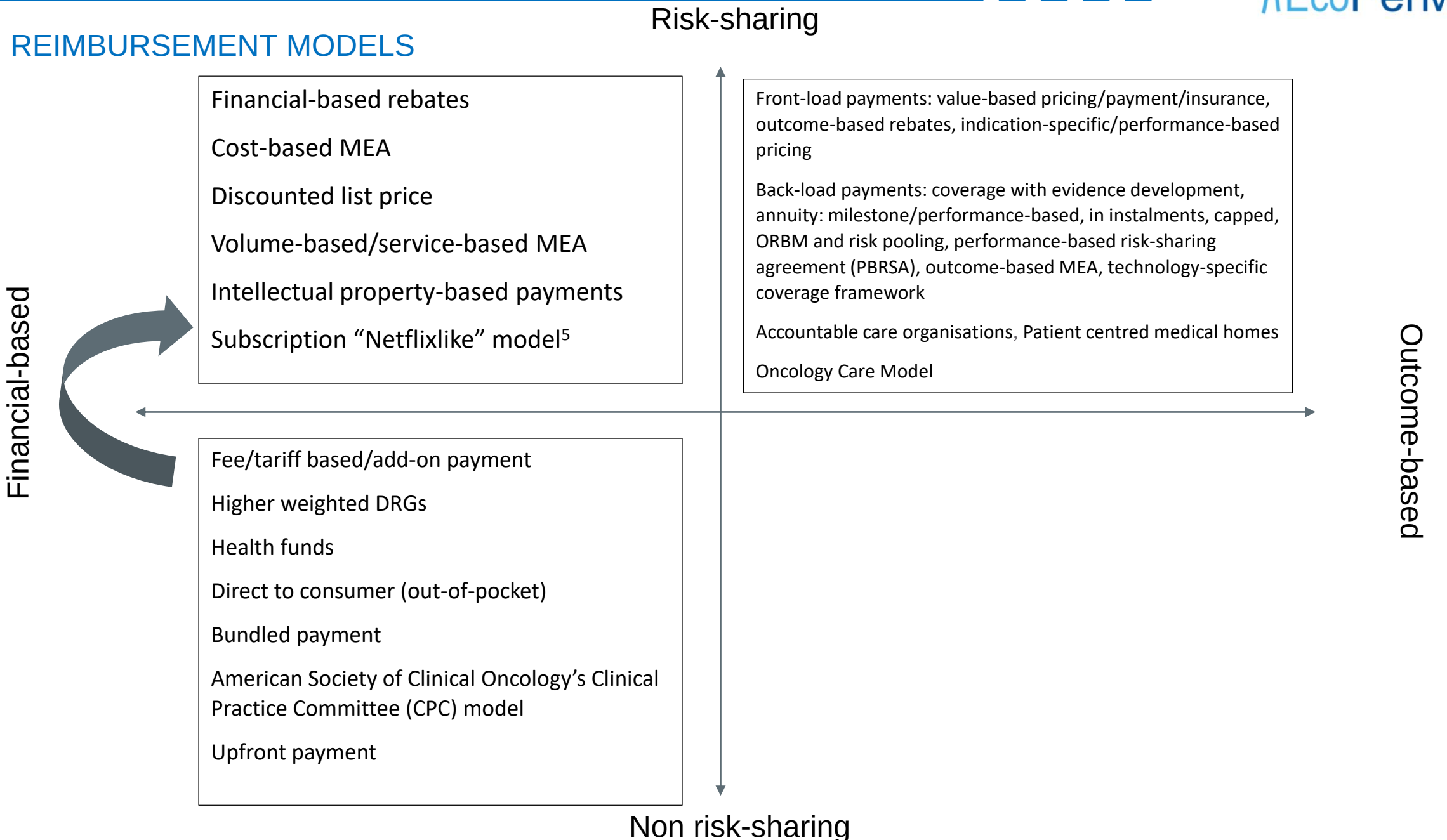
Establish research links between public and private partners

Overcome issues in legal, privacy/ethics, data-sharing, and generation of evidence

Align research priorities at international, national and regional level

	Short term	Medium Term	Long Term
Maintain and upscale current financing	• Public investment in R&D accounted in the price • Promote open innovation • Raise public and philanthropic investment	• Funds to support early research • Encourage/support universities and SMEs • Partial financial protection if R&D fails	• Sustainable funding for upstream basic and applied research
Establish research links between public and private partners	• Create showcase platform	• Encourage wider collaboration between public and private funders, as well as SMEs and bigger corporations in the private sector	• EU member states should engage in international coordination and discussion to enhance cooperation between public and private partners
Overcome issues in legal, privacy/ethics, data-sharing, and generation of evidence	• Establish information governance frameworks that facilitate data sharing agreements	• Legal, technical, and financial support for building large bio- and databanks that can be shared for research purposes • Integrate health outcomes into budgeting process	• Legislation to use biomedical data for research • Payers should engage to establish data platforms and promote data sharing
Align research priorities at international, national and regional level	• Discussions at regional and local levels, and regions, to improve their understanding on funding for R&D of PM.	• National foundations, research centres, and agencies should engage with EU Commission bodies to ensure funding and promote transborder research collaboration	• Use the assessment of Expected Net Present Value and Real Option Analyses to prioritise public investment in PM

REIMBURSEMENT MODELS



ACTIONS FOR ADEQUATE REIMBURSEMENT

Barriers and disincentives

- Lack of demonstrable benefit/value and **evidence for clinical utility**
- **Affordability**
- **Current reimbursement models**
- **Current assessment paradigms** (including HTA) and **reimbursement systems**

Evidence generation

Type of reimbursement models

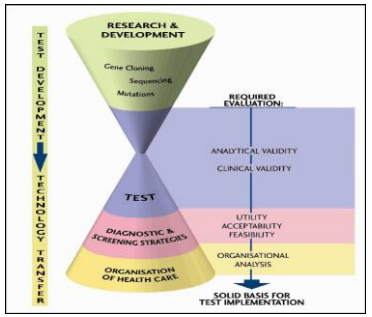
Sharing financial risk

HTA and other regulatory frameworks

	Short term	Medium Term	Long Term
Evidence generation	• Agreement between payers and manufacturers about relevant outcomes and measures • Adapting or developing relevant HTA processes and procedures	• Collect clinical/health outcomes for all PM treatments or test-treatment combinations • Patient involvement in monitoring and reporting the outcomes	• Public investment in creating databases that include clinical, patient outcomes, as well as incidental findings
Type of reimbursement model	• Consider financial-based models in case of budget constraints in the short-term • Consider performance-based models when clinical uncertainty is high • Apply the relevant units of payment that are different for the different type of PM	• Establish dedicated reimbursement pathway for PM • Bundle the reimbursement of companion diagnostics and drugs.	• In the long run adaptive payments or switching models of reimbursement could be considered
Sharing financial risks	• Couple financial- and performance-based models with an evidence generation scheme with clear criteria for reimbursement coverage	• Early access to new promising treatments	• Apply frameworks that capture the long-term effects
HTA and other regulatory frameworks	• Outline the requirements for coverage with evidence development and clear stop/continue criteria to inform evidence generation • Adapt or develop relevant HTA processes and procedures	• Dedicated pathway for evaluating different types of PM and subsequent value-based reimbursement • Apply horizon scanning and the pre-approval initiatives supported by HTA to ensure timely access to PM with proven benefit.	• Re-assess benefit, value and budget impact when competitors appear or patents expire

MAIN TAKE AWAY MESSAGES

- The use of collaborative financing models for R & D of tests and treatments in PM is important and needed
- Different evidence requirements of European regulatory and Member State reimbursement authorities delay access to PM
- Reimbursing PM based on performance could alleviate the burden of upfront payments, and share risks and benefits between payers and providers/manufacturers
- Need to invest and build: Trust , Databases, Assessment & legal frameworks, Communication/coordination



EcoPerMed
Health Economics for Personalised Medicine

THANK YOU!

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EcoPerMed
Health Economics for Personalised Medicine

Evaluating the cost-effectiveness of NTRK testing followed by the histology-independent treatment entrectinib in England, Hungary and the Netherlands

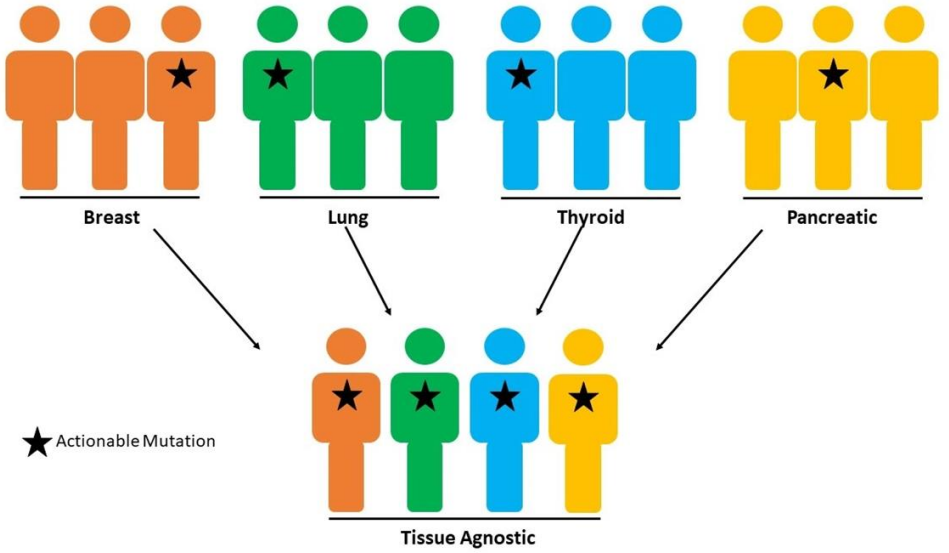
Heleen Vellekoop, MSc
Simone Huygens, PhD
Matthijs Versteegh, PhD
Prof. Maureen Rutten-van Mölken, PhD

CASE STUDY: HISTOLOGY-INDEPENDENT THERAPY ENTRECTINIB

- Histology-independent (or tumour-agnostic) therapies = prescribed based on genetic markers of tumour, regardless of tissue of origin

- Larotrectinib and entrectinib first histology-independent therapies with FDA and EMA approval
  - Inhibitors of TRK proteins

- Prescribed for patients with locally advanced or metastatic solid tumours and oncogenic *neurotrophic tyrosine receptor kinase* (NTRK) gene fusions



CHALLENGES FOR ECONOMIC EVALUATION

- No RCT data
  - Small trial of NTRK+ patients receiving entrectinib
  - **No control arm**

- Limited knowledge on health outcomes in SoC for NTRK+ patients
  - Historical data only on mixed populations (NTRK+ and NTRK- combined)
  - Outcomes for NTRK+ patients may be different because of **prognostic value of NTRK gene fusions**

- **NTRK testing** not part of SoC
  - To be introduced to enable implementation of entrectinib
  - NTRK testing to be included in evaluation

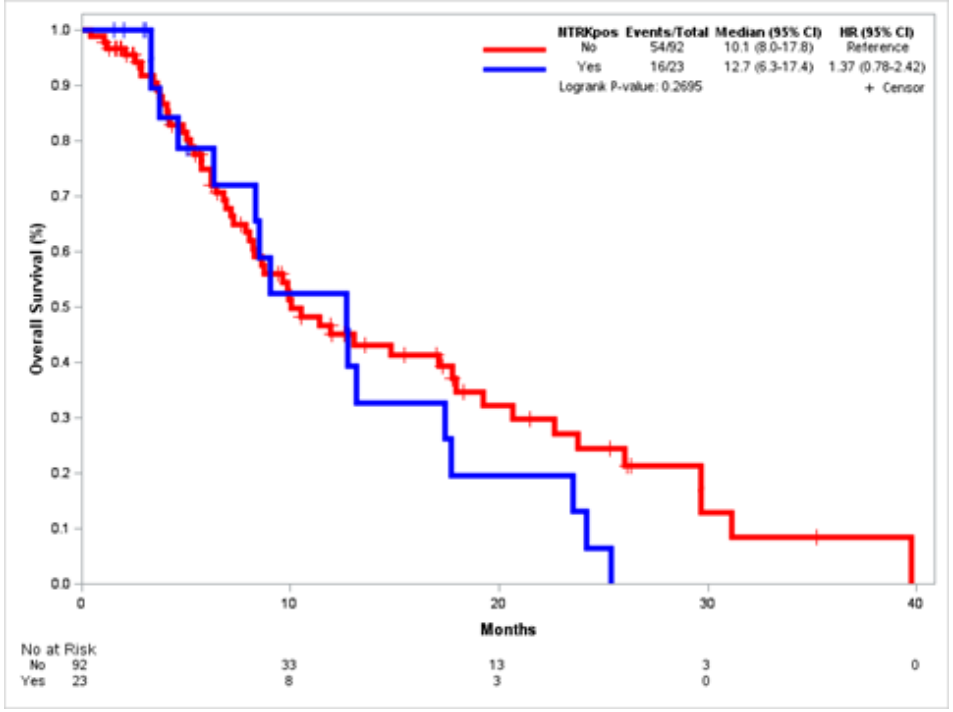
CONSTRUCTING A CONTROL ARM

- Real-world data from Hartwig database (CPCT-02 study)
  - Whole-genome sequencing was performed for metastatic cancer patients (n=3,547 with known tumour location)
  - Clinical data also collected

- Survival (and time to treatment discontinuation) were estimated on NTRK- patients who received SoC
  - Parametric distributions were fitted per tumour type

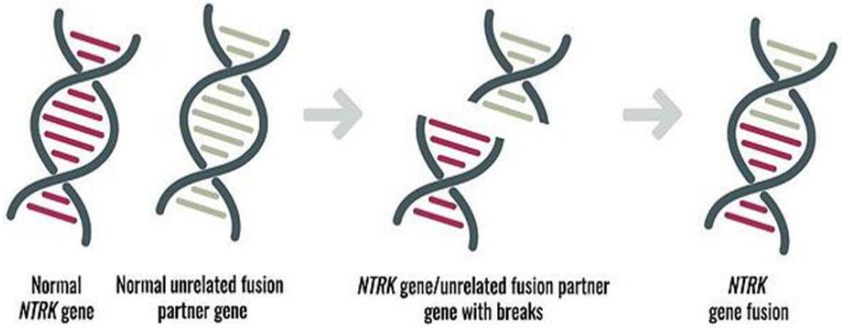
PROGNOSTIC VALUE OF NTRK FUSIONS

- 23 NTRK+ patients were matched with 92 NTRK- patients
- In an unadjusted analysis
  - HR for NTRK+ patients was 1.37 [95% CI: 0.78, 2.42]
- After adjusting for age, gender and previous line of treatment, a multivariable Cox regression found
  - HR of **1.32** [95% CI: 0.74, 2.35], confirming the results of the unadjusted analysis



NTRK TESTING

- NTRK fusions are rare
  - Present in 0.3-1% of locally advanced or metastatic solid tumours

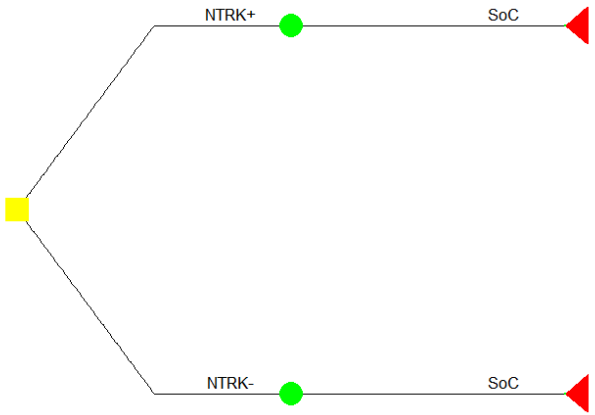


- Main tests:

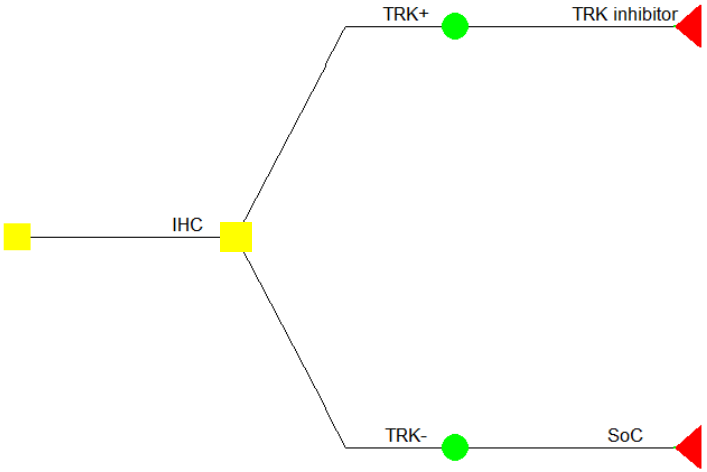
Type of test	Pros	Cons
Next-generation sequencing of the tumour RNA (**RNA-NGS**)	High sensitivity and specificity	Expensive
Immunohistochemistry (**IHC**) testing for TRK protein expression	Cheaper	Lower sensitivity and specificity

TESTING STRATEGIES UNDER EVALUATION (1/2)

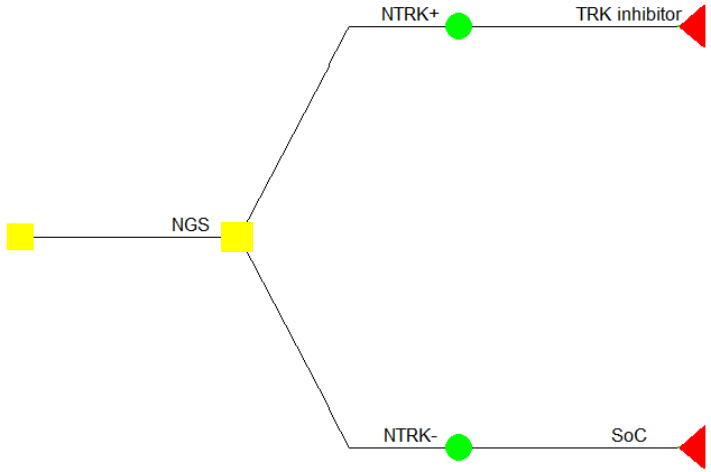
No testing (SoC for all)



IHC

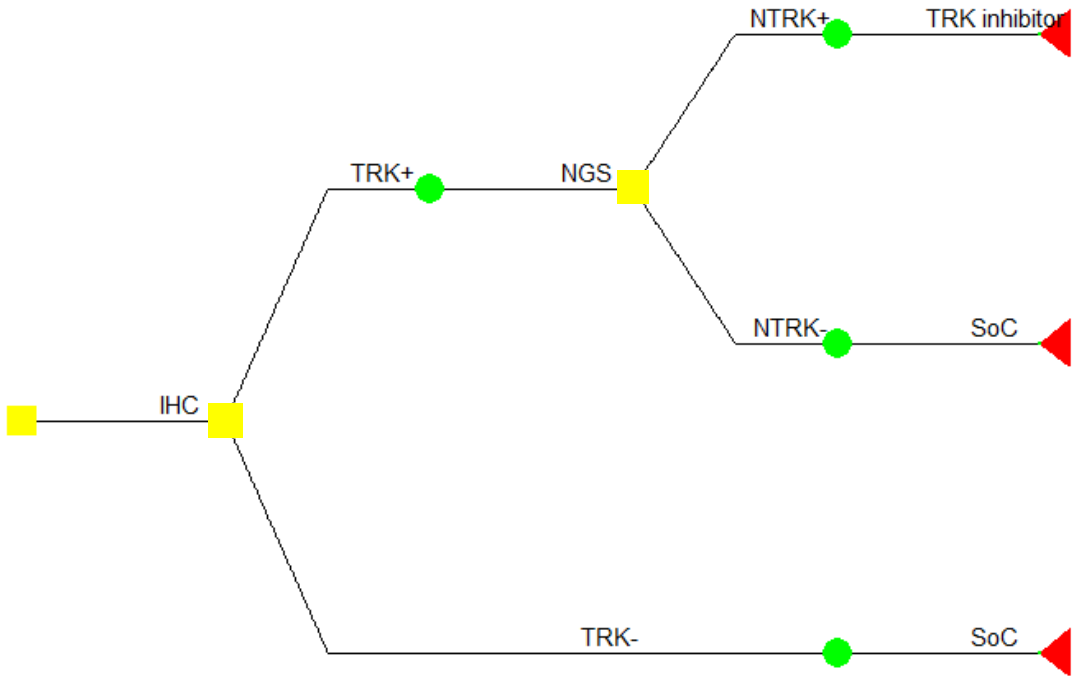


NGS



TESTING STRATEGIES UNDER EVALUATION (2/2)

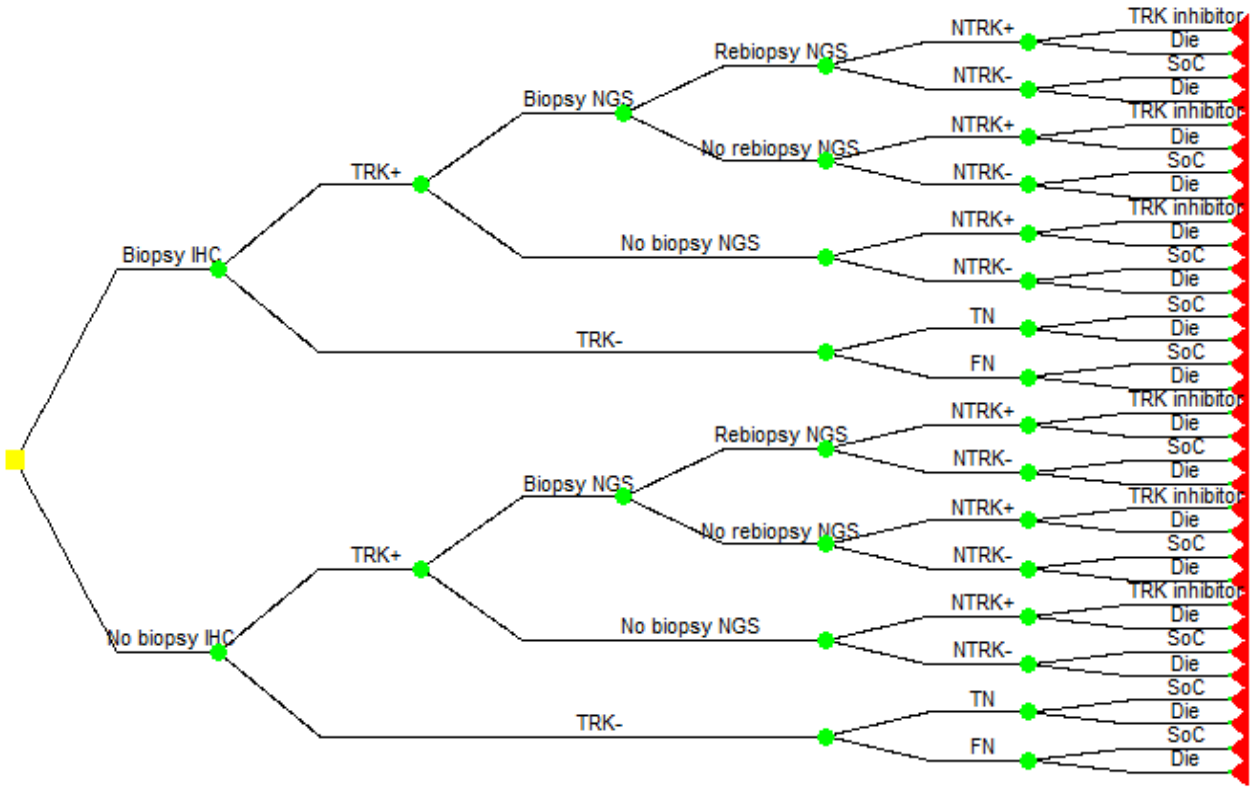
IHC then NGS

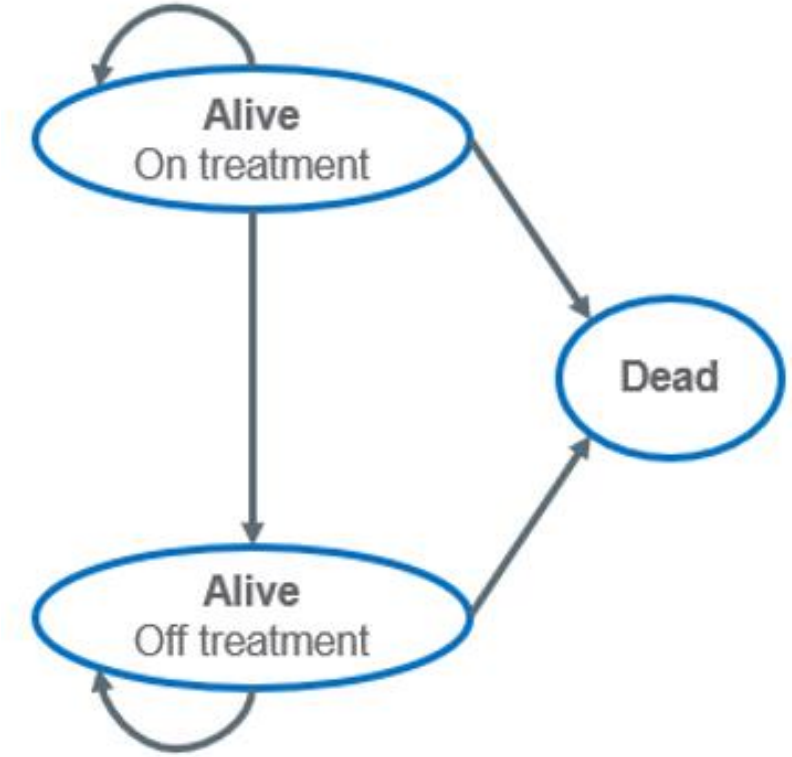


Stratified

High prevalence of NTRK gene fusions	Wild-type TRK protein expression	Testing strategy
☑	☒	NGS
☒	☑	NGS
☒	☒	IHC then NGS

DECISION TREE + MICROSIMULATION MODEL





Decision to receive additional treatment

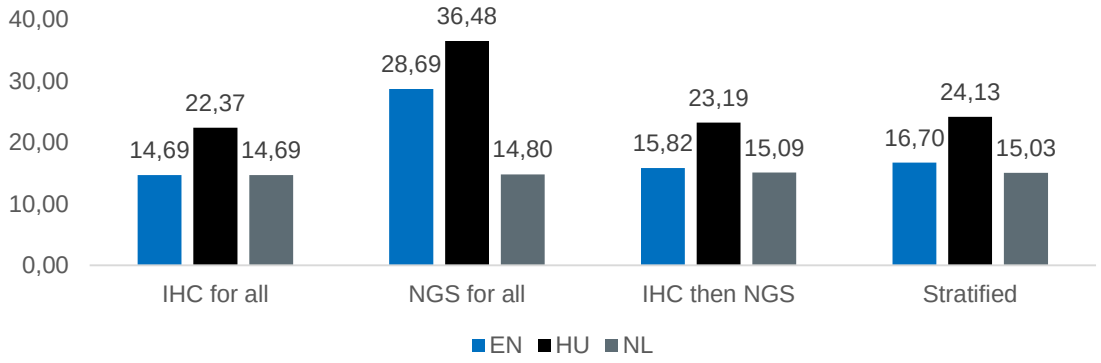
Start treatment

Death

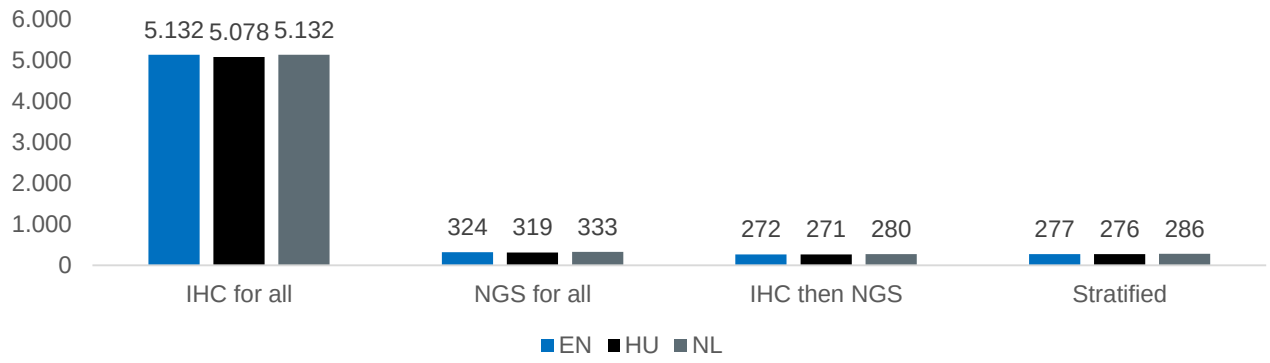
RESULTS

INTERMEDIATE OUTCOMES

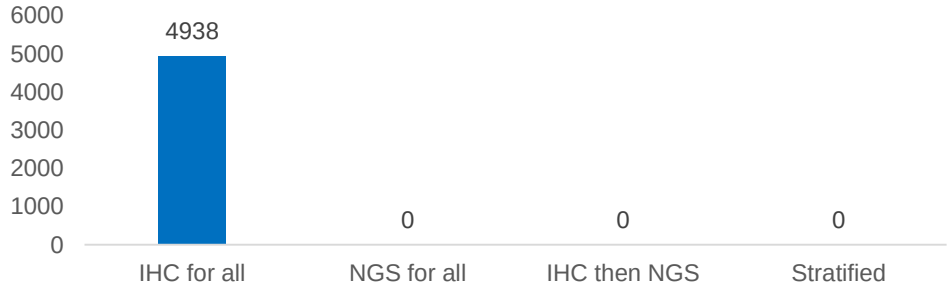
Average **waiting time** (in days)



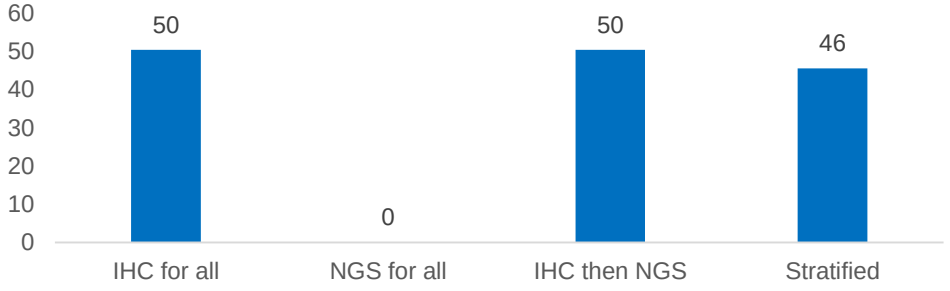
Number of patients **treated with entrectinib**



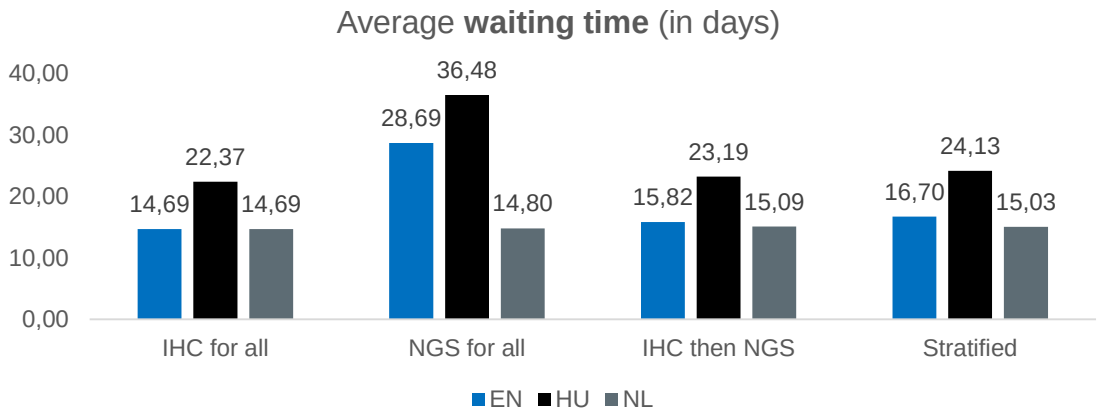
Number of **false positives** per 100,000 patients

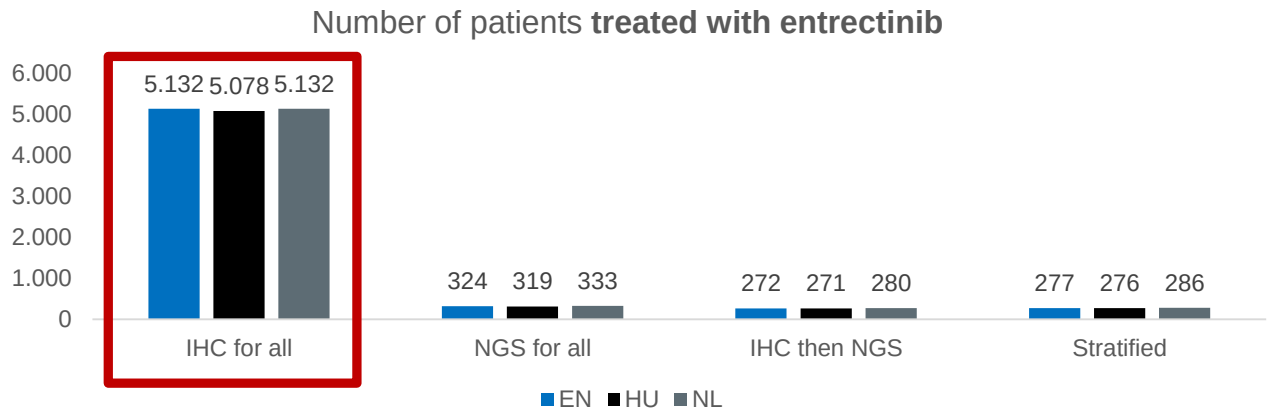


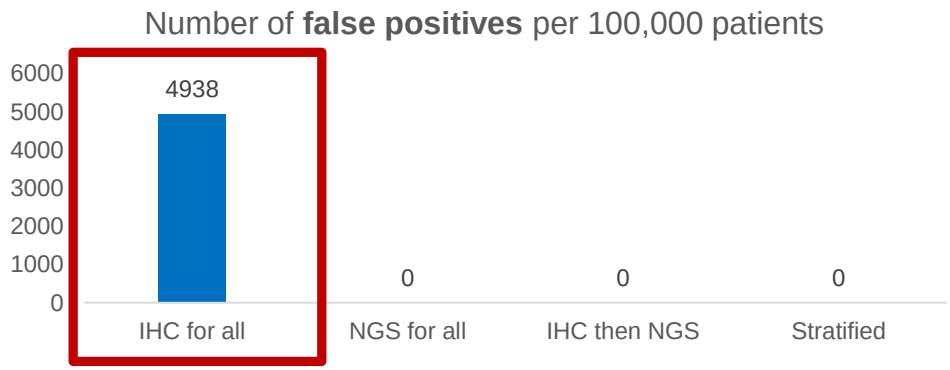
Number of **false negatives** per 100,000 patients

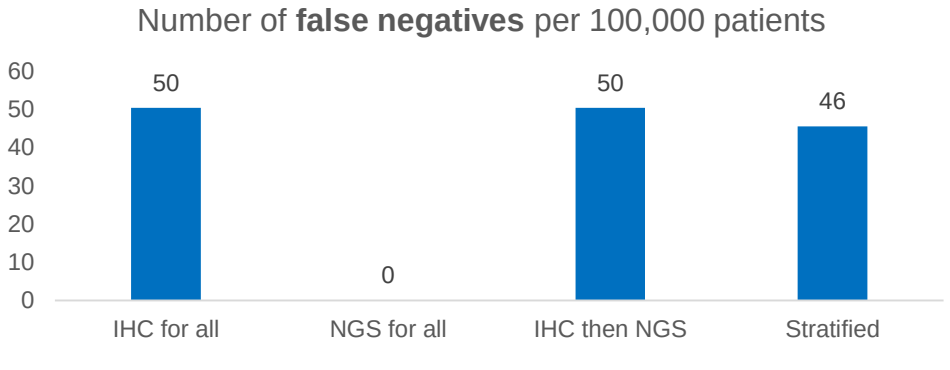


IHC: high number of patients treated with entrectinib because of many false positives

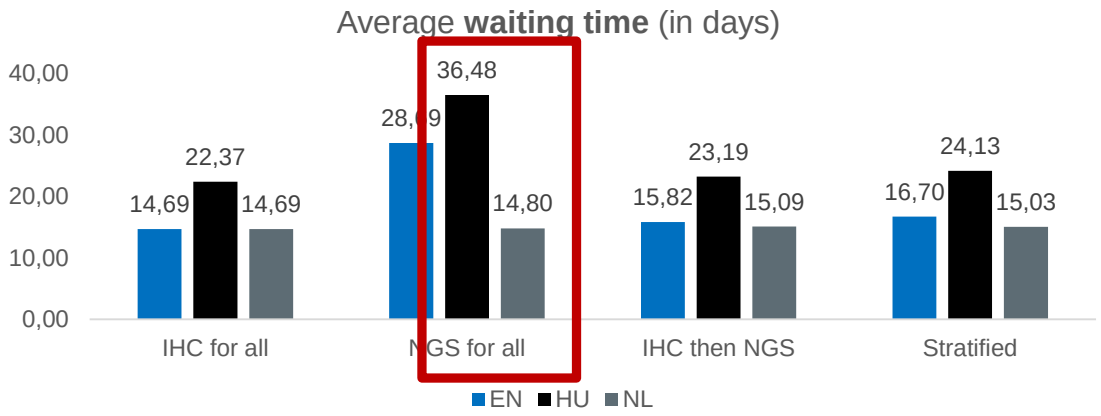


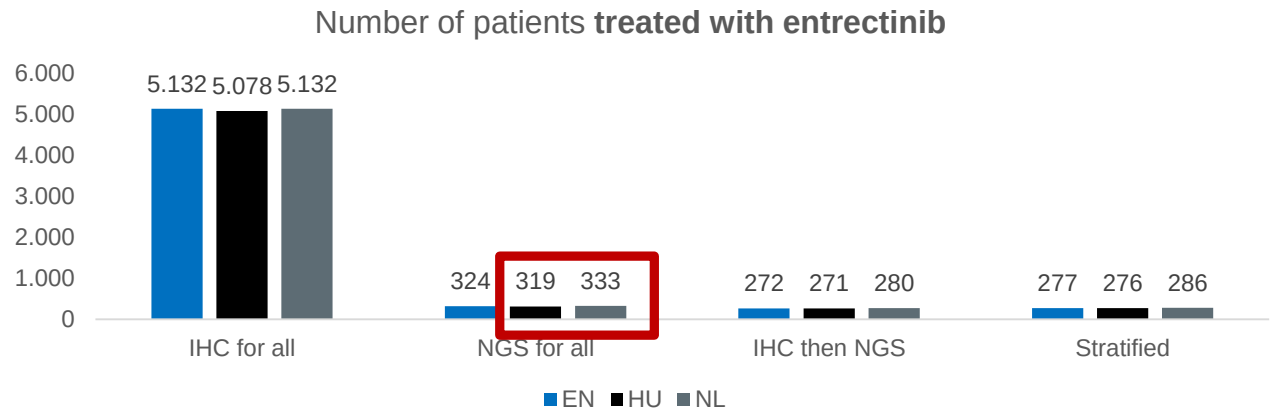


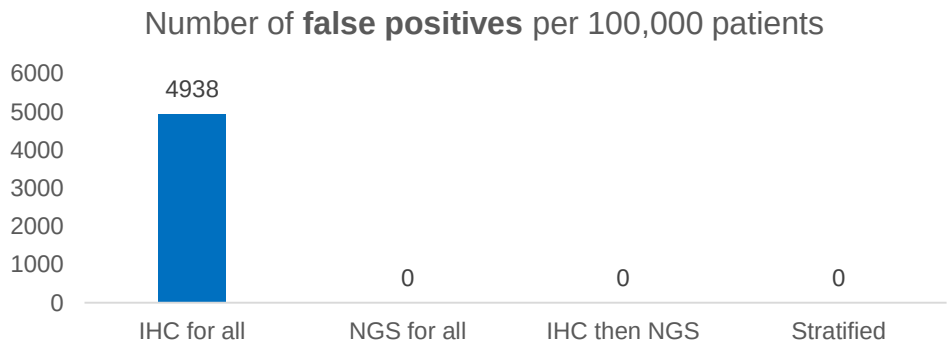


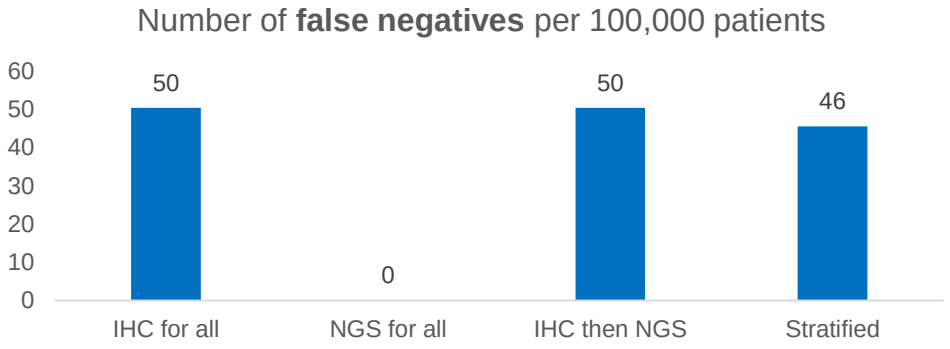


Longer average waiting time results in less patients treated with entrectinib

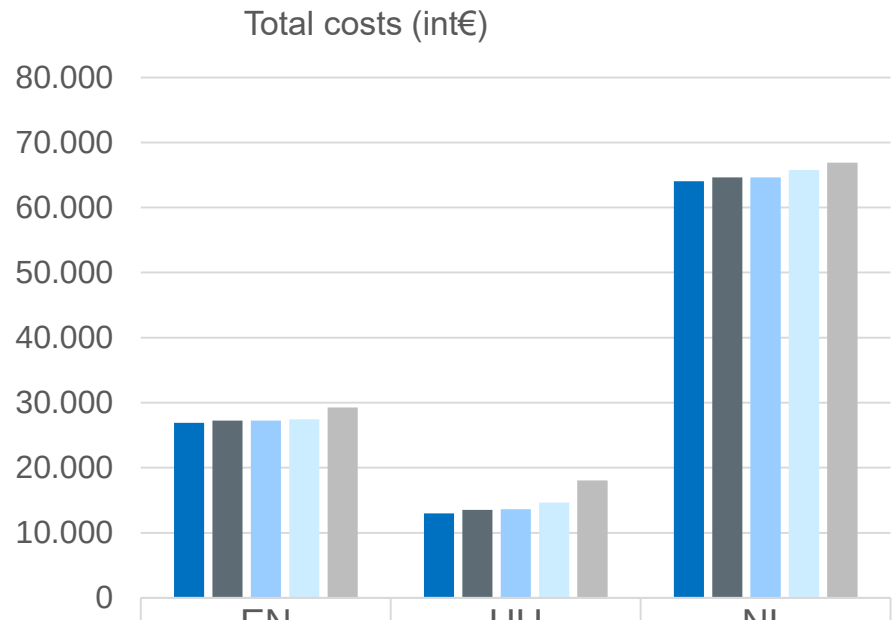




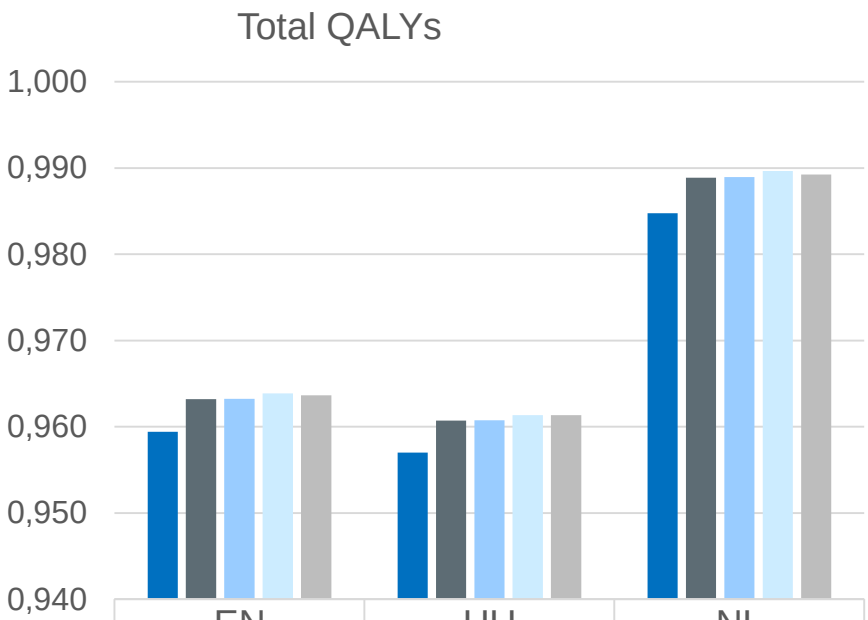




COST AND QALY OUTCOMES

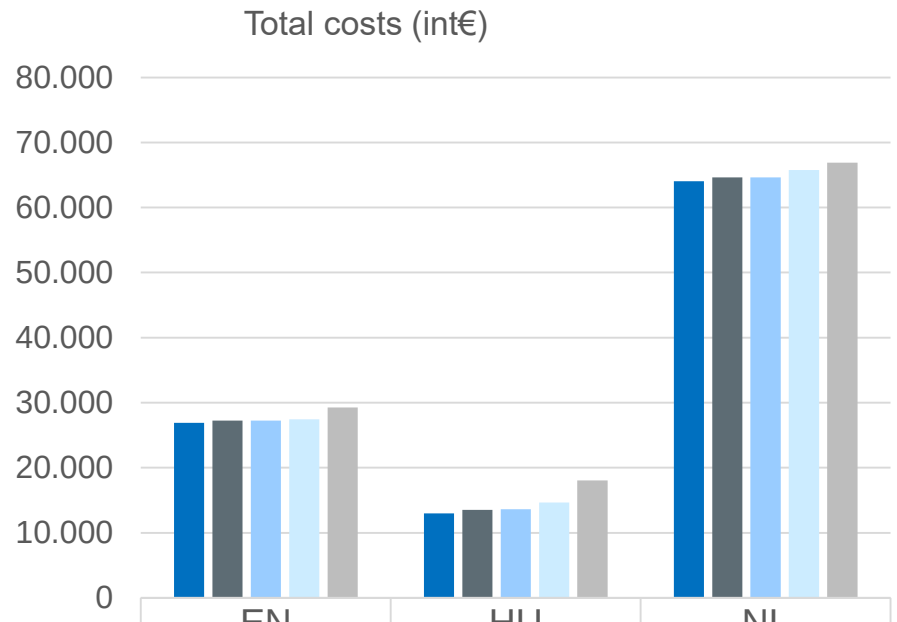


	EN	HU	NL
No testing	26.899	12.981	64.024
IHC then NGS	27.241	13.534	64.612
Stratified	27.255	13.615	64.642
NGS for all	27.446	14.658	65.754
IHC for all	29.249	18.036	66.872



	EN	HU	NL
No testing	0,959	0,957	0,985
IHC then NGS	0,963	0,961	0,989
Stratified	0,963	0,961	0,989
NGS for all	0,964	0,961	0,990
IHC for all	0,964	0,961	0,989

Most QALYs with ‘NGS for all’ because no false positives/negatives



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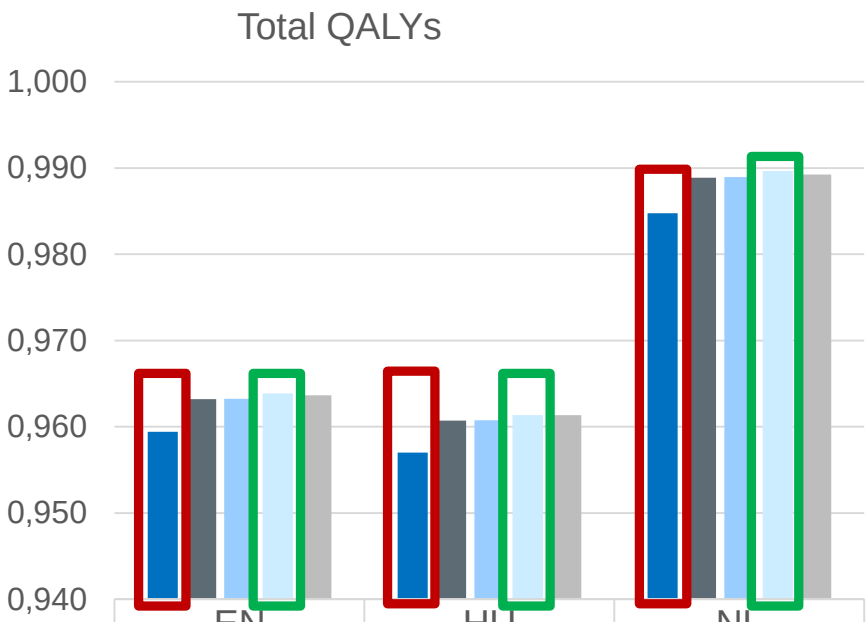

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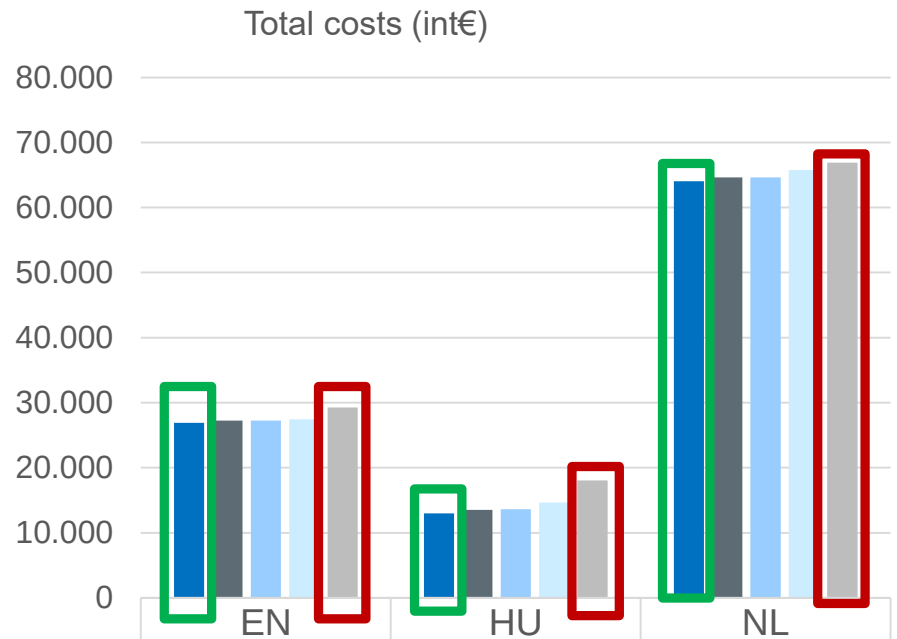
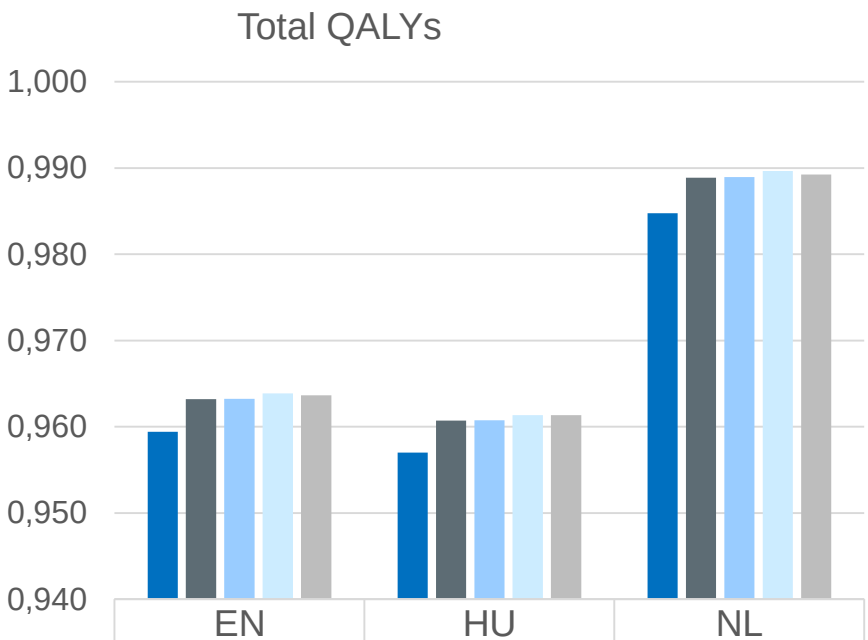
No testing	0,959	0,957	0,985
IHC then NGS	0,963	0,961	0,989
Stratified	0,963	0,961	0,989
NGS for all	0,964	0,961	0,990
IHC for all	0,964	0,961	0,989

Highest costs with ‘IHC for all’ due to many patients treated with entrectinib



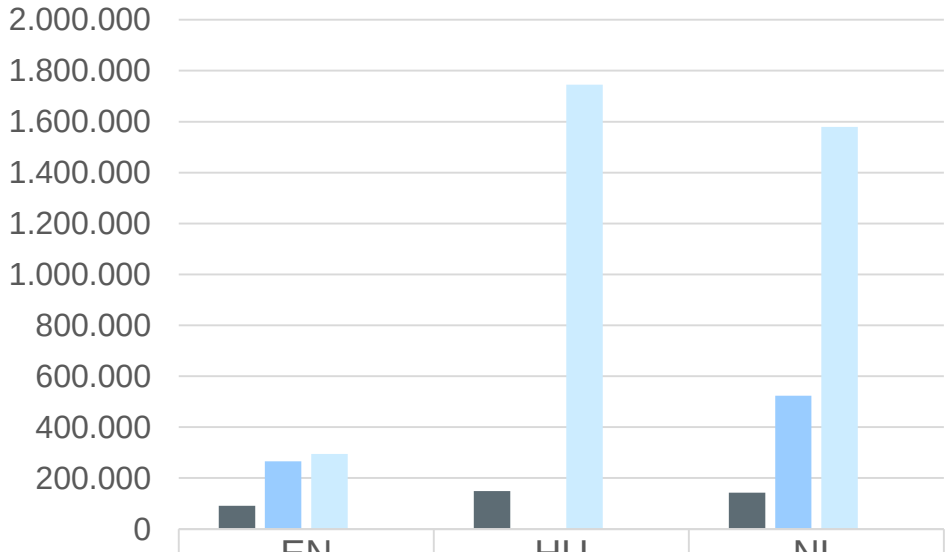
	EN	HU	NL
No testing	26.899	12.981	64.024
IHC then NGS	27.241	13.534	64.612
Stratified	27.255	13.615	64.642
NGS for all	27.446	14.658	65.754
IHC for all	29.249	18.036	66.872



	EN	HU	NL
No testing	0,959	0,957	0,985
IHC then NGS	0,963	0,961	0,989
Stratified	0,963	0,961	0,989
NGS for all	0,964	0,961	0,990
IHC for all	0,964	0,961	0,989

COST-EFFECTIVENESS OUTCOMES

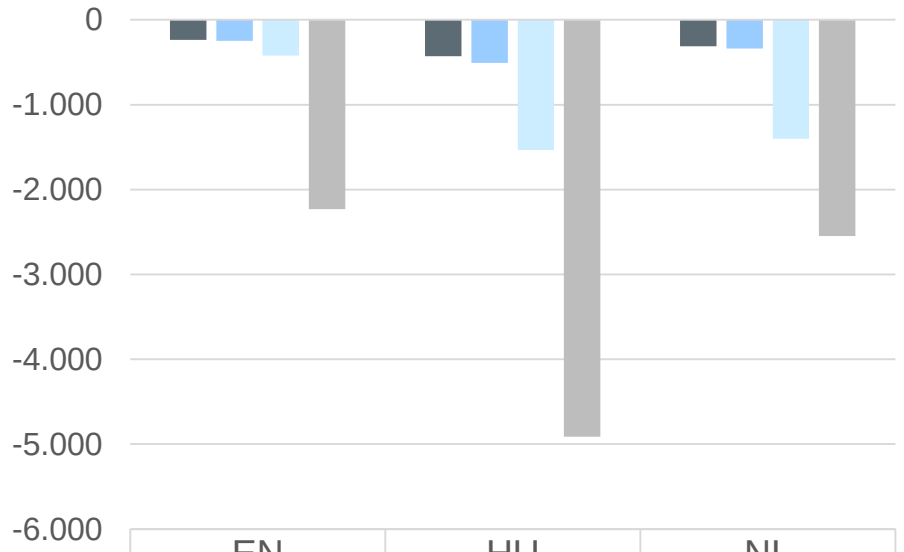
Incremental cost-effectiveness ratio (int€)



	EN	HU	NL
IHC then NGS	91.540	149.166	142.370
Stratified	265.579	0	523.911
NGS for all	294.649	1.745.014	1.578.756
IHC for all	0	0	0

IHC then NGS Stratified NGS for all IHC for all

Incremental net monetary benefit (int€)



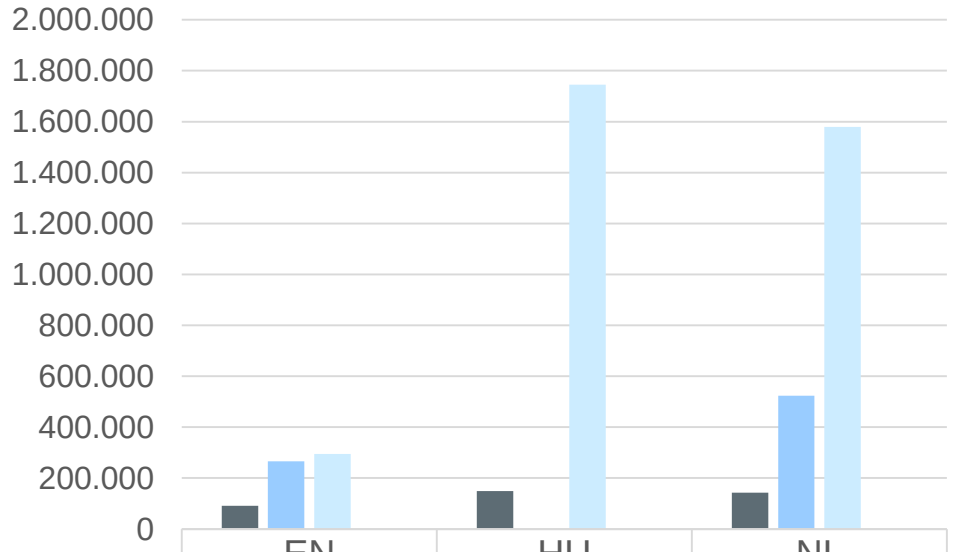
	EN	HU	NL
IHC then NGS	-235	-430	-312
Stratified	-248	-509	-339
NGS for all	-420	-1.533	-1.403
IHC for all	-2.230	-4.911	-2.547

IHC then NGS Stratified NGS for all IHC for all

0 = (extendedly) dominated

IHC then NGS is the best strategy…

Incremental cost-effectiveness ratio (int€)



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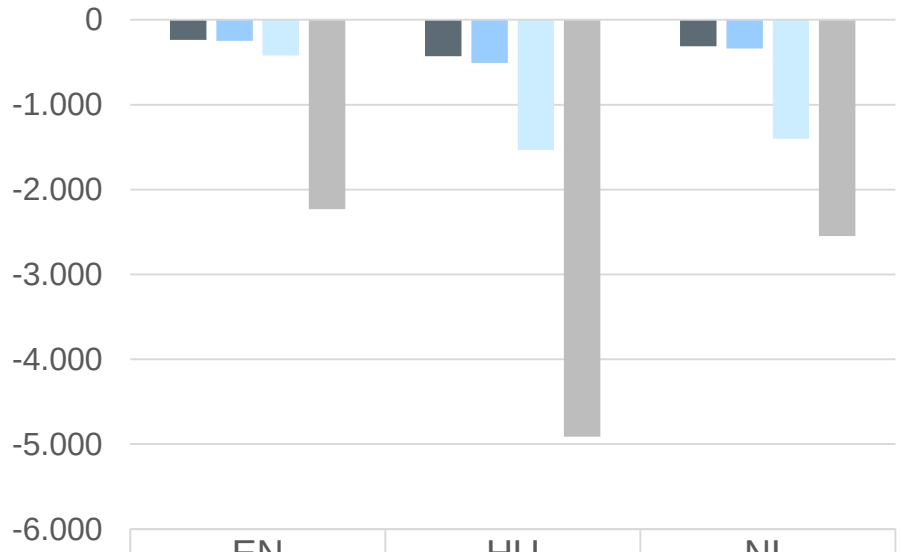

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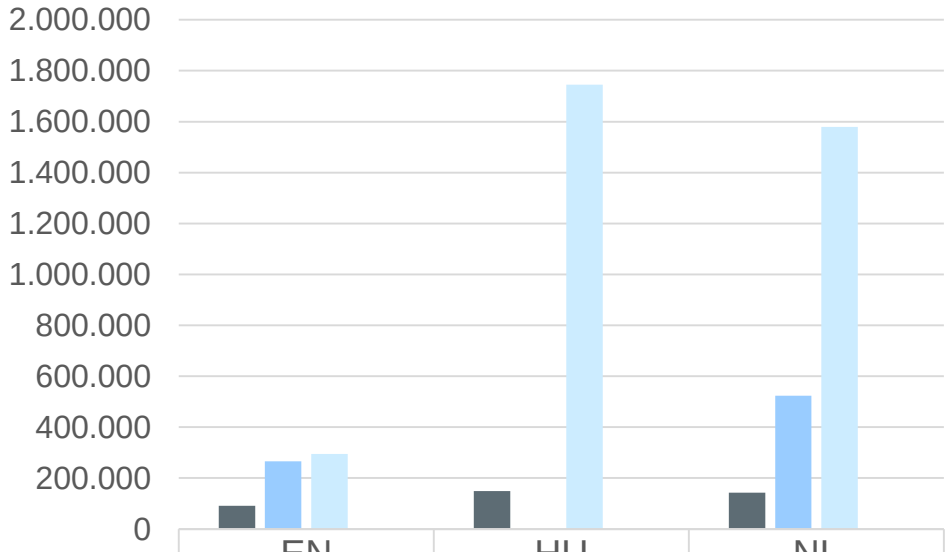
IHC then NGS is the best strategy… but not cost-effective vs. SoC

Incremental cost-effectiveness ratio (int€)



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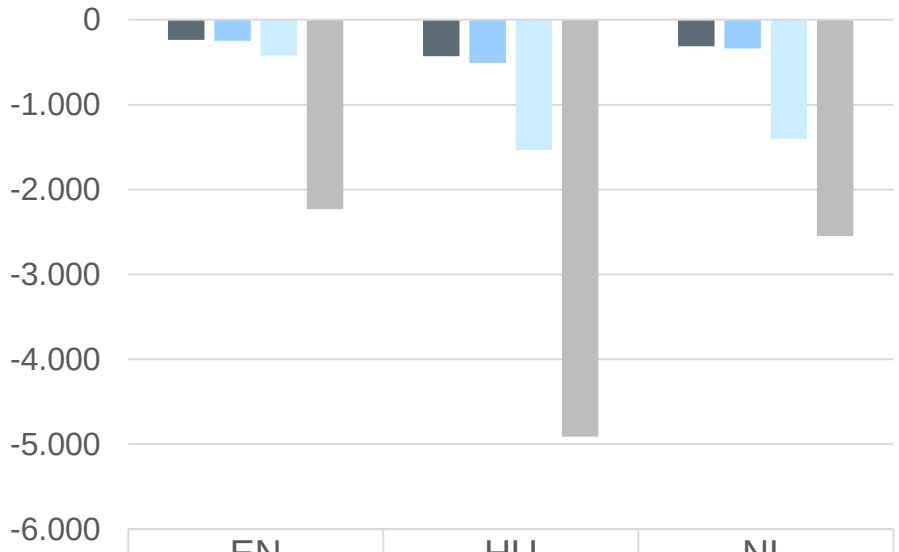

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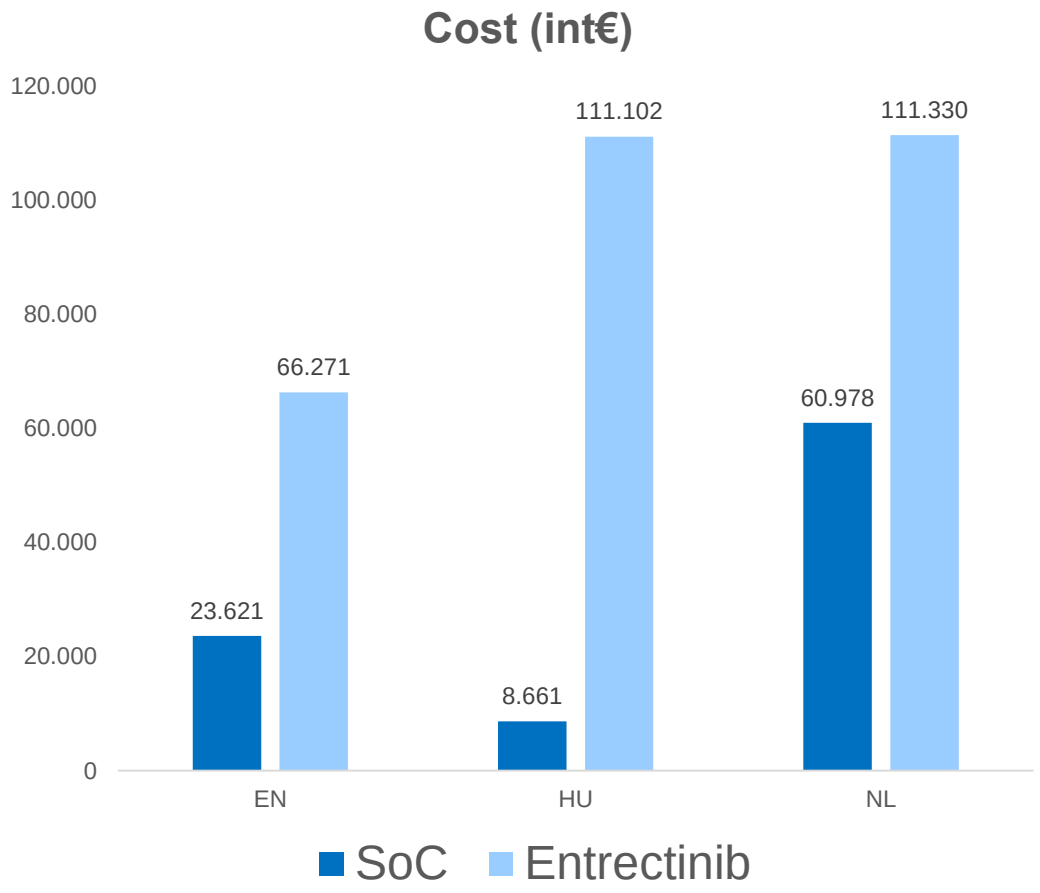
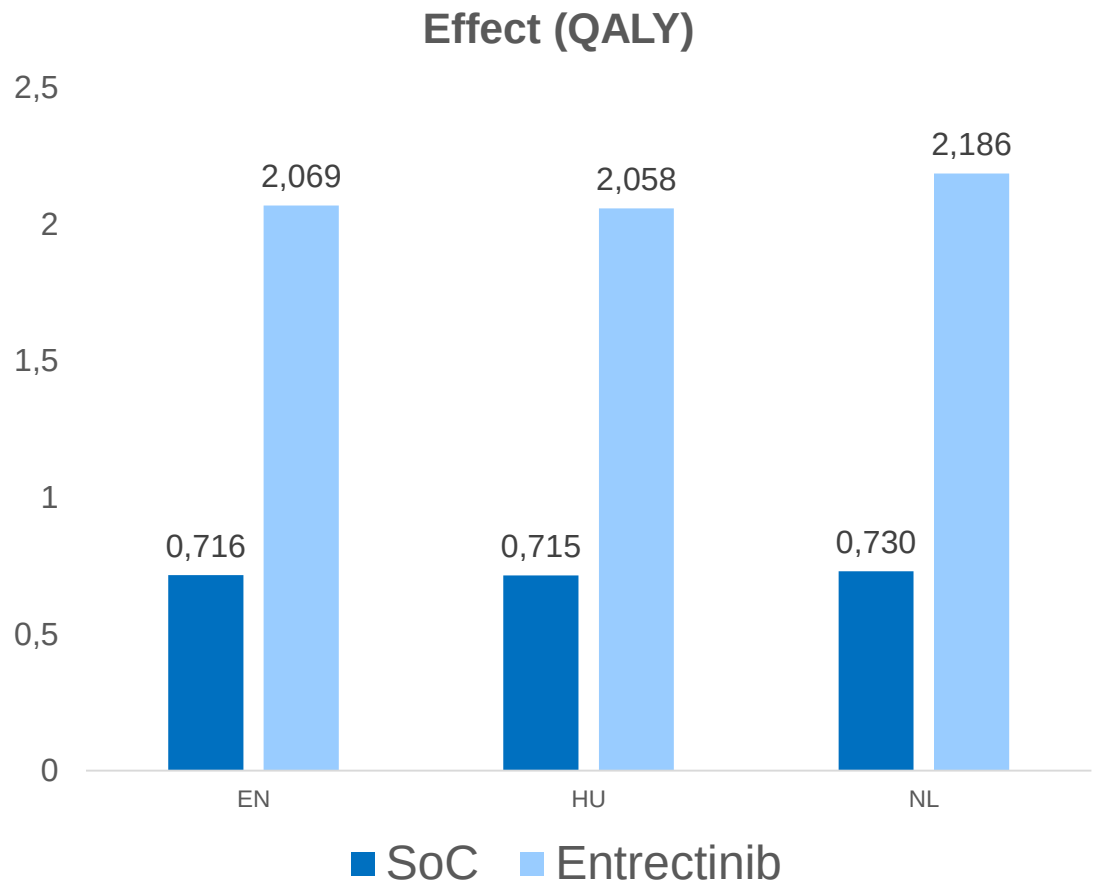
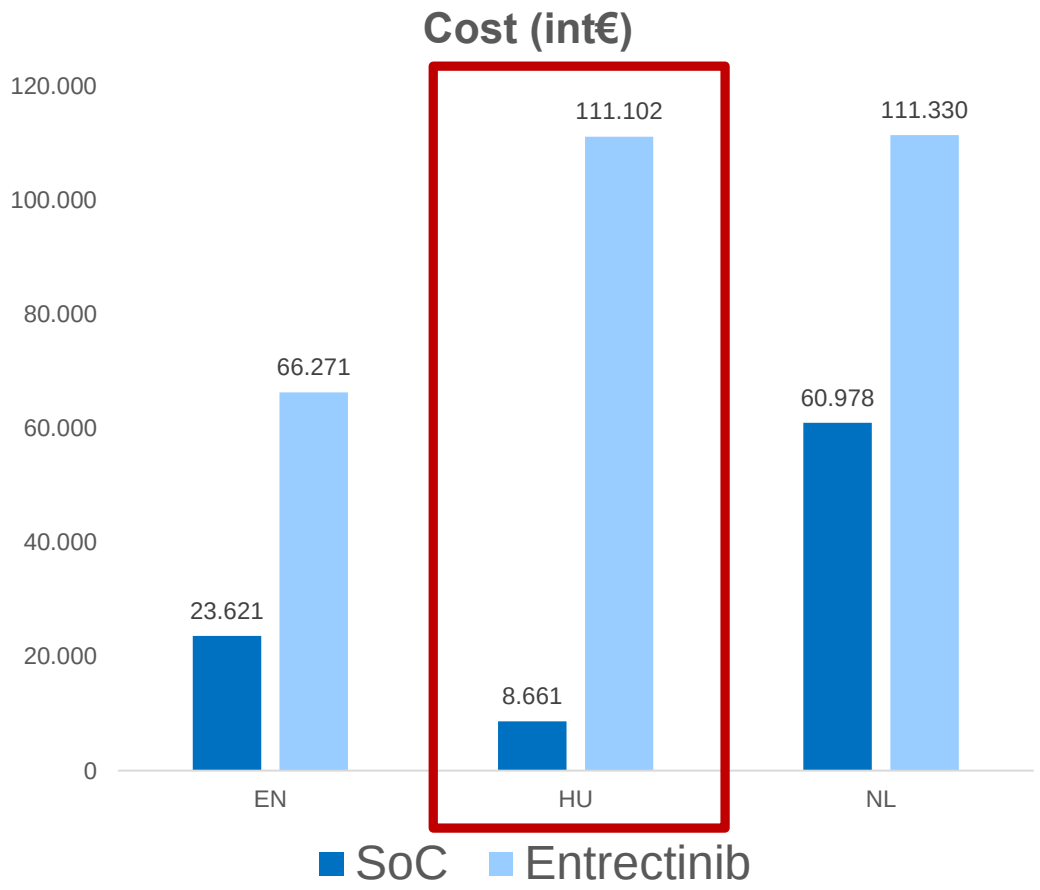
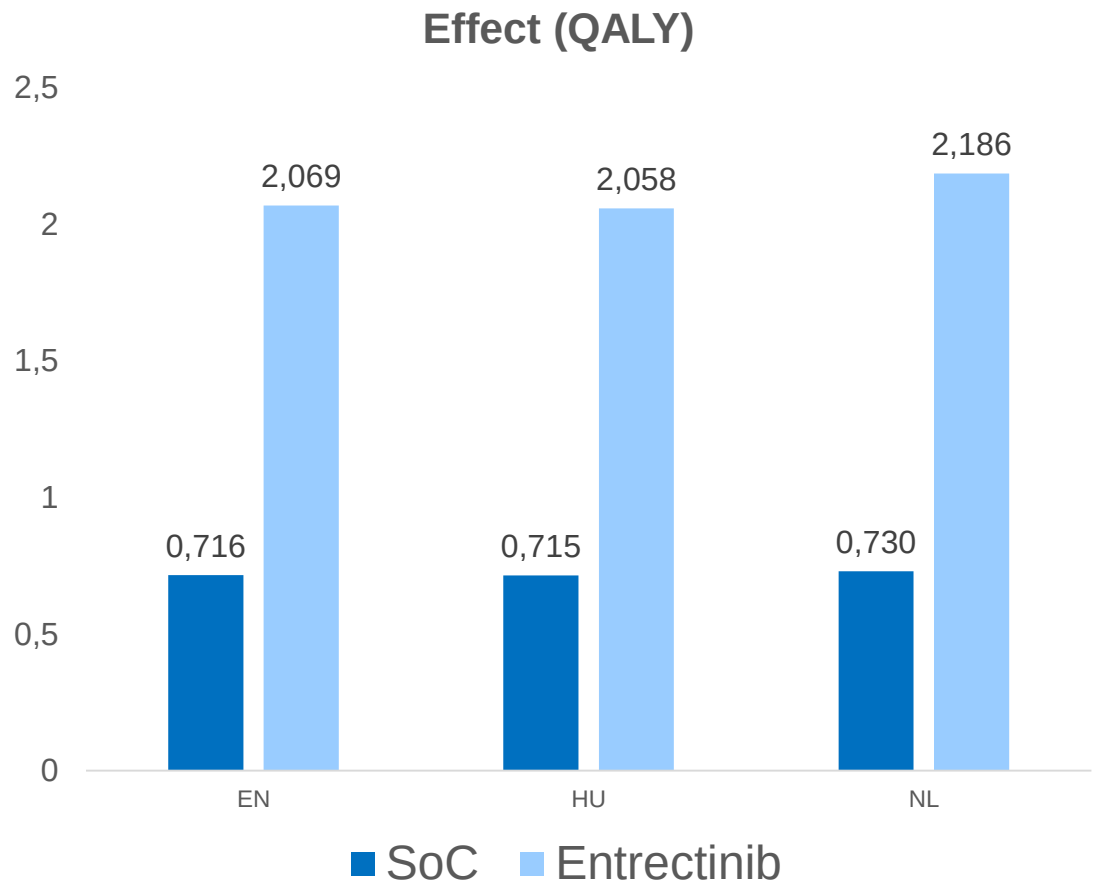
SUB-GROUP ANALYSIS: NTRK+ PATIENTS ONLY, WITHOUT TESTING
Large QALY gains at high costs



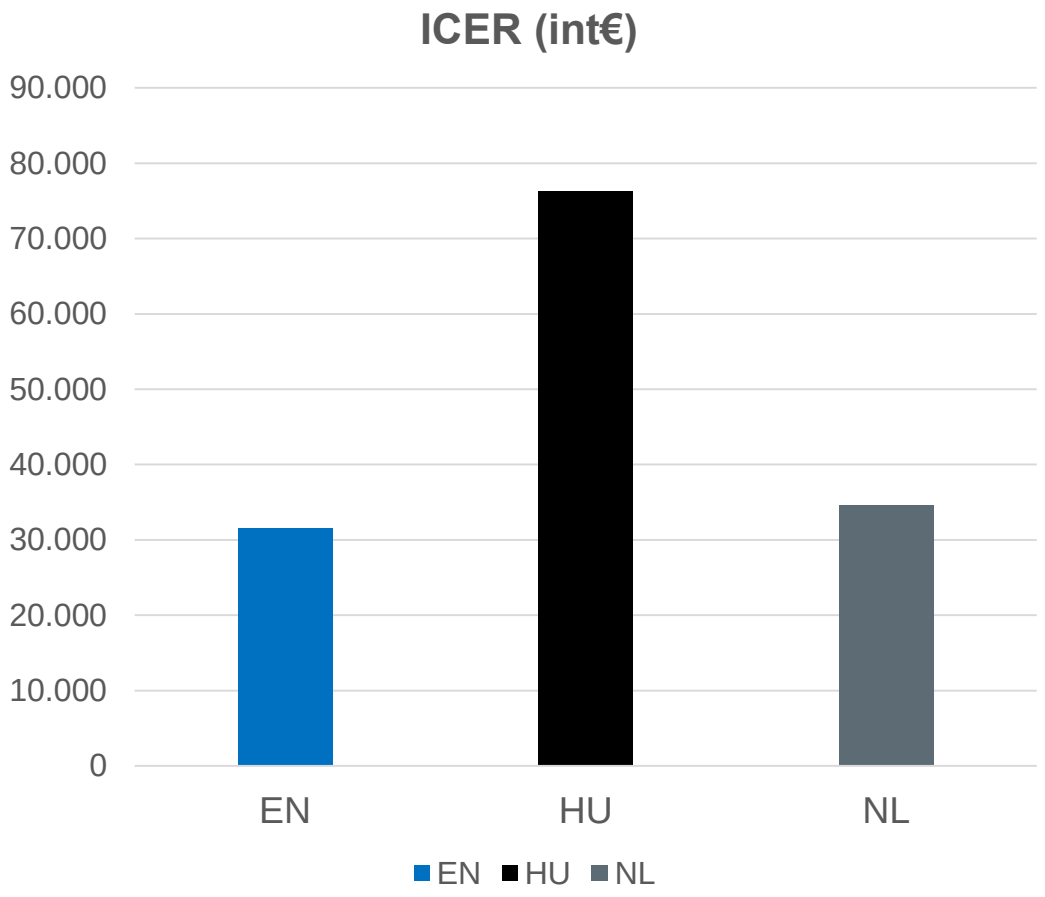


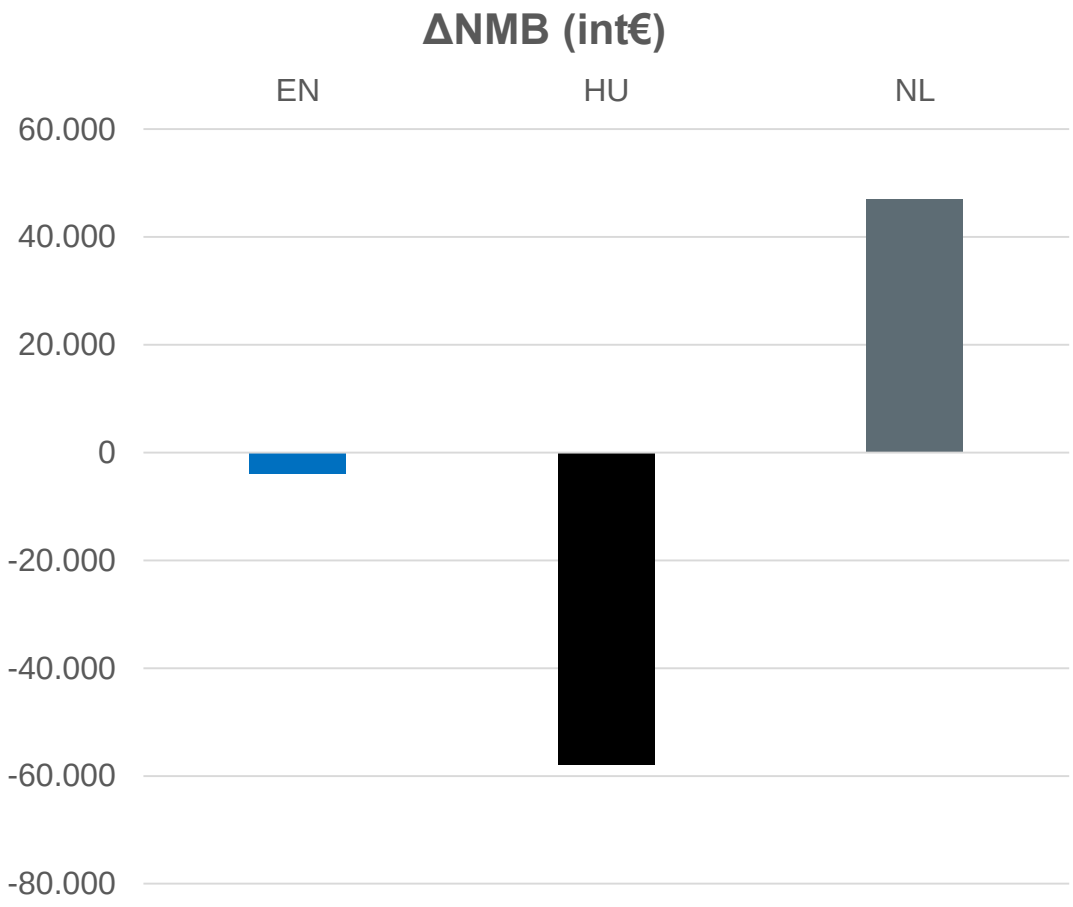
SUB-GROUP ANALYSIS: NTRK+ PATIENTS ONLY, WITHOUT TESTING
Large QALY gains at high costs





SUB-GROUP ANALYSIS: NTRK+ PATIENTS ONLY, WITHOUT TESTING
Positive NMB for the Netherlands, negative NMB for England and Hungary





MAXIMUM COST RNA-NGS

- *NGS for all*: most accurate targeting of treatments because of test sensitivity and specificity
- Sequencing costs expected to decrease
- How much does NGS cost need to decrease for implementation entrectinib to become cost-effective?
  - NGS cost at which ΔNMB is no longer negative (becomes zero)

Country	Maximum cost (int€)	Current cost (int€)	Reduction compared to current cost
England	Not cost-effective compared to 'No testing' at zero price	334	-
Hungary	Not cost-effective compared to 'No testing' at zero price	1,347	-
The Netherlands	140	1,857	91%

CONCLUDING REMARKS

- Implementation of entrectinib likely not cost-effective in Hungary
  - More benefit to society if other care is implemented first

- In England and Netherlands the implementation of entrectinib has the potential to be cost-effective
  - Cost of RNA-NGS would have to be reduced 91% in NL for implementation entrectinib to become CE
  - In England, entrectinib has been included in Cancer Drugs Fund after managed access agreement with pharmaceutical company

- Genomic databases (including clinical data) can be used to estimate control arm for single-arm trial data
  - However, unclear to what extent populations in trial arm and control arm are comparable
  - Second-best option as better trial data is preferred

- Challenge for PM interventions: Country adaptations might require additional attention/work, given that testing pathways may vary across countries

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THANK YOU!

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This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824997.

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DPYD Genotyping

prior to fluorpyrimidine-based chemotherapy (ToxNav)

Rositsa Koleva-Kolarova, **Sarah Wordsworth, Apostolos Tsiachristas**

on behalf of the HEcoPerMed team

HEcoPerMed Final Conference Brussels 28 April 2022

Funded by European Union's Horizon 2020 research and innovation programme; Grant Agreement no. 824997.

TOXNAV (DPYD GENOTYPING) BEFORE FLUOROPYRIMIDINE CHEMOTHERAPY IN METASTATIC BREAST CANCER (MBC)

- In cancer, fluoropyrimidine-based chemotherapy drugs, including capecitabine and 5-fluorouracil (5FU), used widely for to treat several solid tumour types
- 10-15% of patients develop severe adverse drug reactions (ADR) due to genetic mutations
- Mostly germline mutations in DPYD gene causing a DPD enzyme deficiency
- Patients poorly metabolize chemotherapy and have an increased risk of severe toxicity
- Following standard-of-care dosing, side effects can include: diarrhoea, hand-foot syndrome, skin toxicity, tiredness, myelosuppression, and multi-organ failure

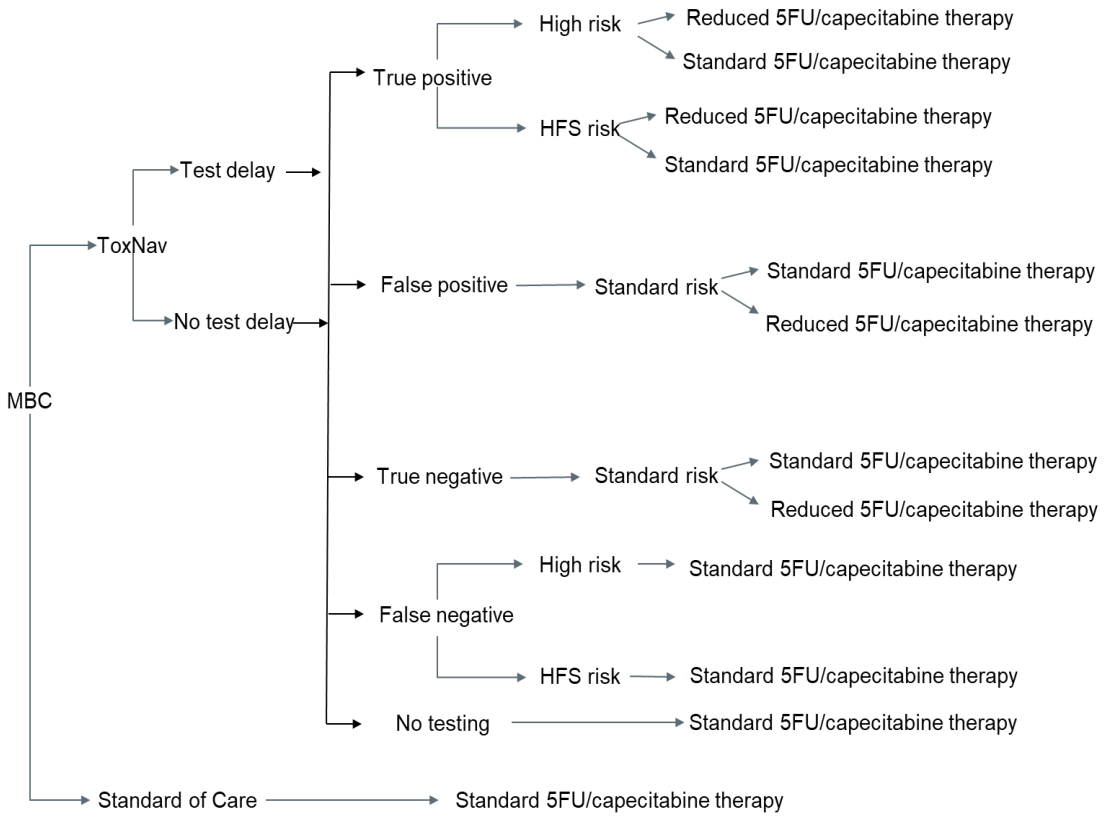
REASON FOR STUDY

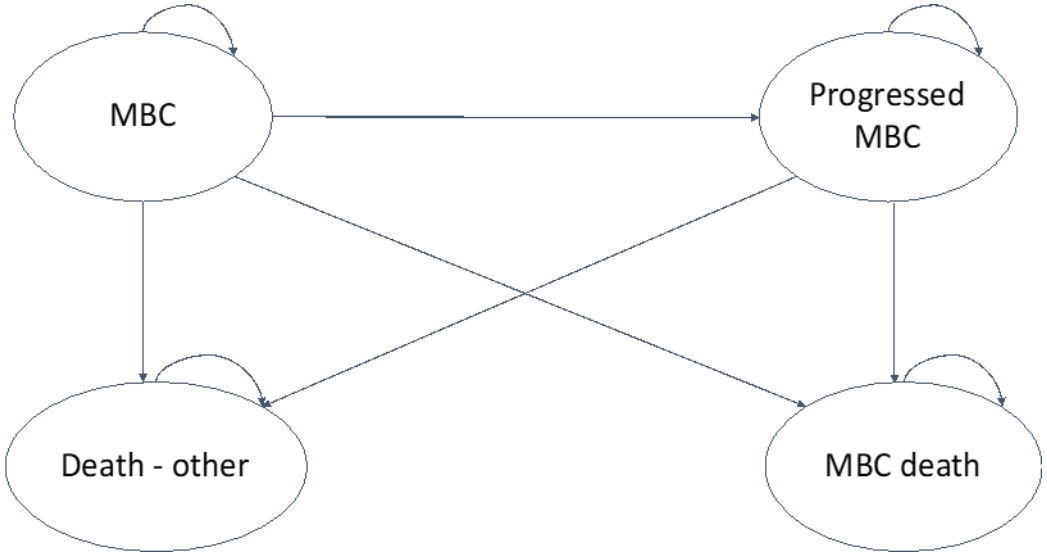
- Upfront DPYD genotyping has not been universally implemented in daily clinical practice (except the Netherlands);
- Oxford Oncology Directorates report: 600 patients per year are treated with 5-fluoruracil and capecitabine, 20% of patients experience side effects;
- In 2019 mandatory ToxNav (DPYD) testing was introduced in Oxford and Horton prior to treatment initiation (466 pts/1,556 pts).

TOXNAV TEST

- Currently, only 4 genomic variants in the DPYD gene are tested for, yet 50% of patients with severe toxicity do not have these variants
- ToxNav test developed to allow for testing a broader panel of variants that may have correlation with 5FU and capecitabine toxicities. These included three of the four CPIC variants, 15 DPYD additional variants
- Identifying poor metabolisers prior to chemotherapy would allow for dose adjustment, potentially avoiding severe toxicities
- **Study aims: Evaluate the cost-effectiveness of upfront DPYD testing for patients with metastatic breast cancer prescribed capecitabine/5FU from the UK healthcare perspective**

DECISION TREE + MARKOV MODEL



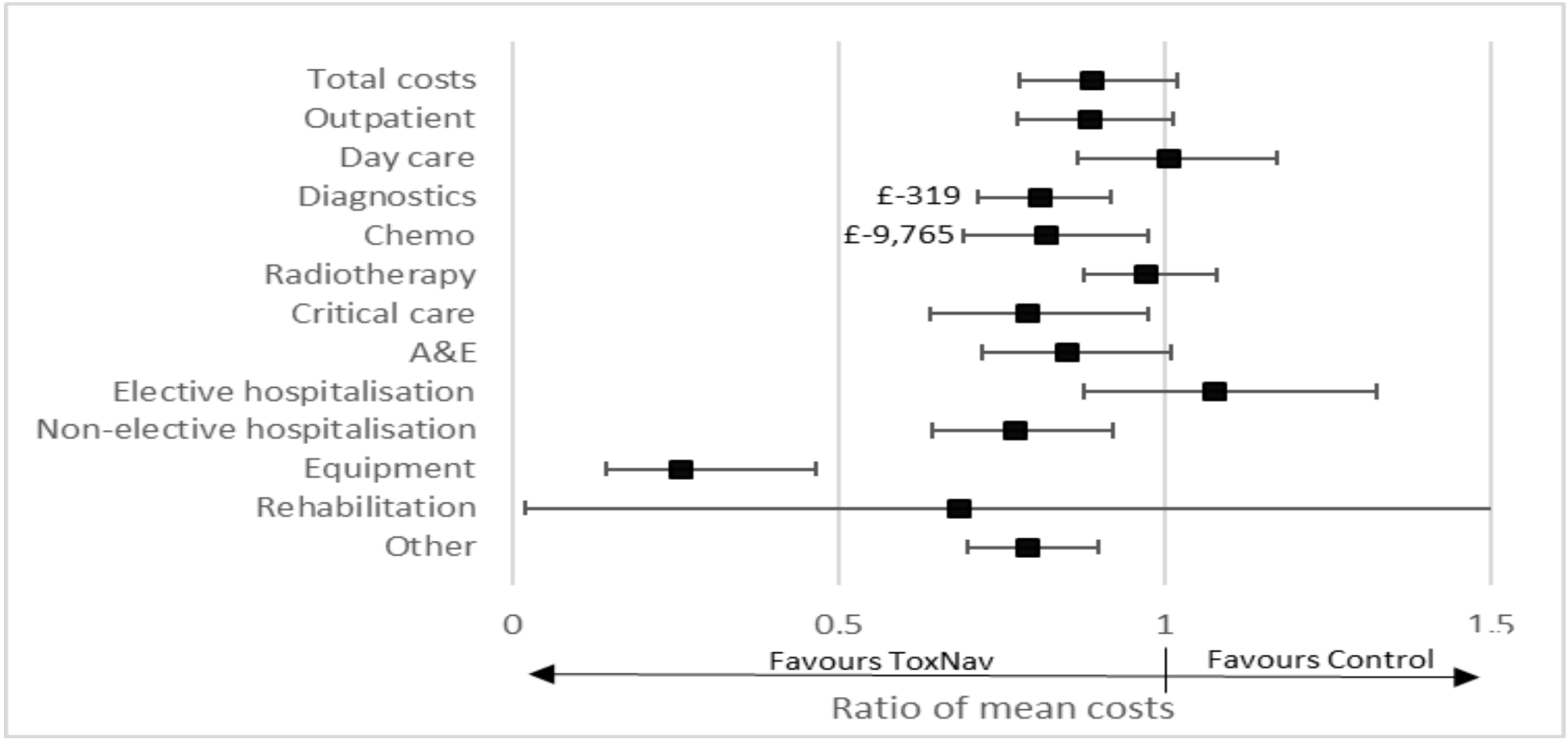


- P(mild ADR) and P(severe ADR), leading to utility decrement and costs
- ADR related to haemoglobin, neutrophil count (NC), white cell count (WCC), and temperature.

Sensitivity ToxNav 100%. Specificity 98%.

Prevalence DPYD mutation 5%.

RESULTS
IMPACT OF TOXNAV TESTING ON HOSPITAL COSTS

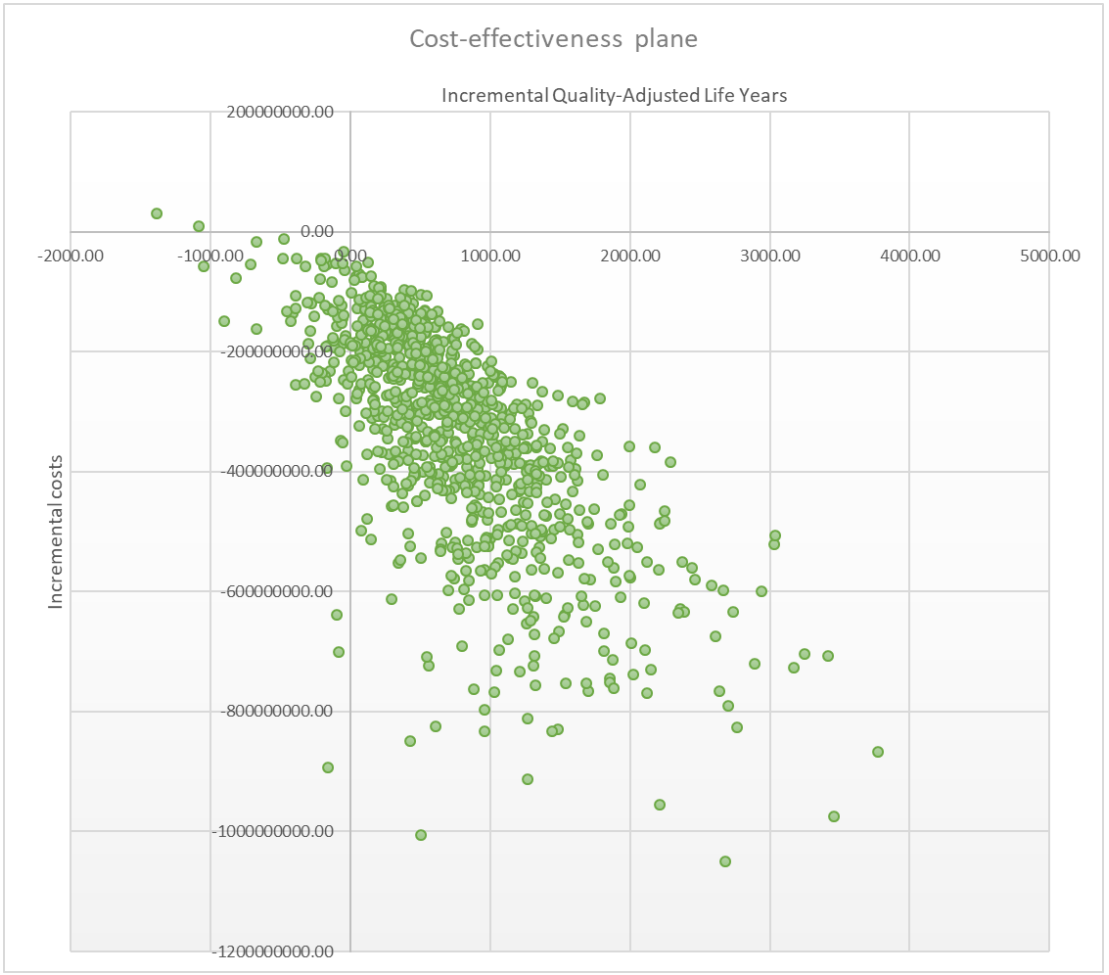


RESULTS: PRELIMINARY COST-EFFECTIVENESS

Main analysis for a cohort of 10,000 women with mean age of 60

Strategy	Costs (in £)	QALYs	ICER
ToxNav strategy	262,4	18,466.6	-
Standard of Care	572,6	17,729.3	-
Incremental	-310,2	737.3	dominant

HIGH CERTAINTY THAT TOXNAV IS DOMINANT IN MOST SIMULATIONS



WHAT DID WE LEARN FROM THE TOXNAV CASE STUDY?

- Toxnav data analysis:
  - Genetic test has impact on initial dosing of capecitabine/5FU
  - Critical/high risk variants contributing to 80% increase in hospital costs as compared to no variants; no significant difference between HFS variants and no variants
  - Genetic testing can lower the likelihood of some AEs and increasing others; might have some positive impact on mental heath (pain reduction)

- Guidance implementation:
  - Including compliance to testing (of patients and clinicians) and test results is important
  - Effectiveness data – can be obtained from RWD, especially when new genetic tests are developed for long existing treatments with proven benefit.

MAIN TAKE AWAYS

- DPYD Genotyping prior to fluorpyrimidine-based chemotherapy with ToxNav is a good value for money
- Compliance of healthcare providers to genetic testing and results from it can impact cost-effectiveness
- Real world data of PM effectiveness can be used in the absence of trial data

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SCREENING FOR MATURITY ONSET DIABETES OF THE YOUNG

László Szilberhorn, Dávid Nagy, Gábor Kovács, Tamás Zelei, Balázs Nagy
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This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824997.

MODY - MATURITY ONSET DIABETES OF THE YOUNG

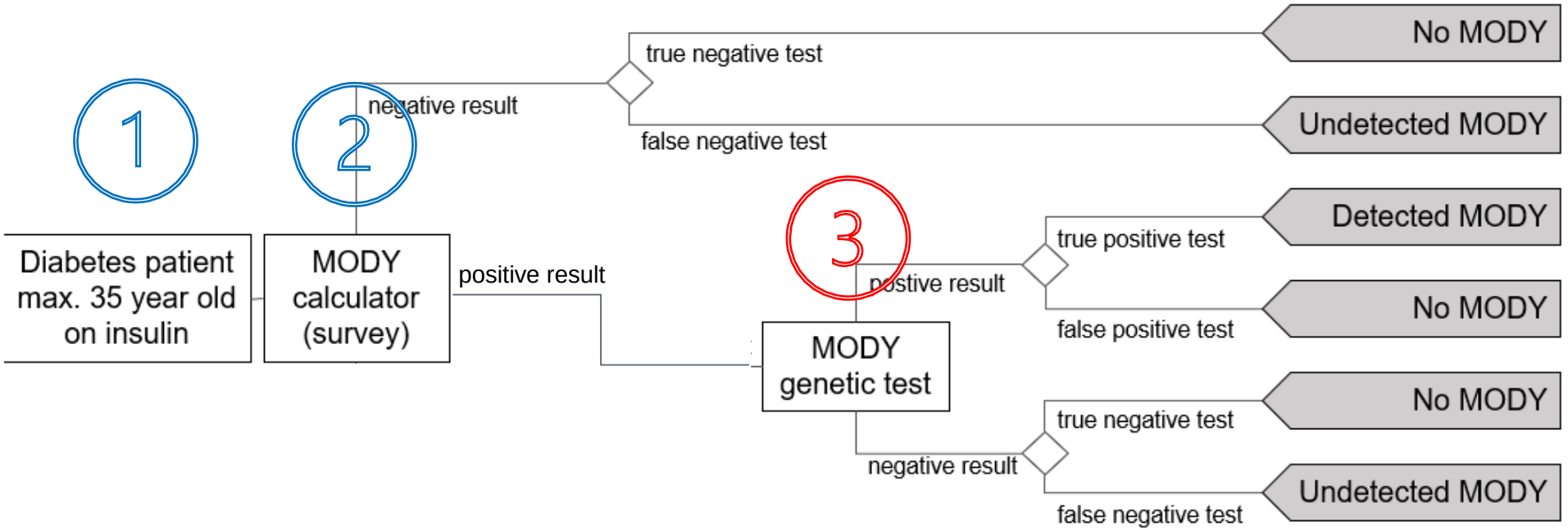
- MODY is the most common form of monogenic diabetes, caused by 13 mutations
- Accounts for at least **1%-5%** of all diabetes cases
- Age of onset typically **<35 years**
- The three most common mutation types
  - Hepatocyte Nuclear Factor 1 Alpha (**HNF1A**)-MODY
  - Glucokinase (**GCK**)-MODY
  - Hepatocyte Nuclear Factor 4 Alpha (**HNF4A**)-MODY

95% of all monogenic diabetes patients

WHY BOTHER WITH DIAGNOSIS?

- Most of MODY cases are **misdiagnosed** as type 1 or type 2 diabetes
- With proper diagnosis **no insuline** treatment is required
  - **Dietary intervention alone** is usually enough for GCK-MODY patients
  - HNF1A-MODY and HNF4A-MODY patients are able to maintain optimal glycaemic control with **sulphonylurea**
- Correct determination of the MODY subtype informs decisions regarding appropriate treatment and prognosis

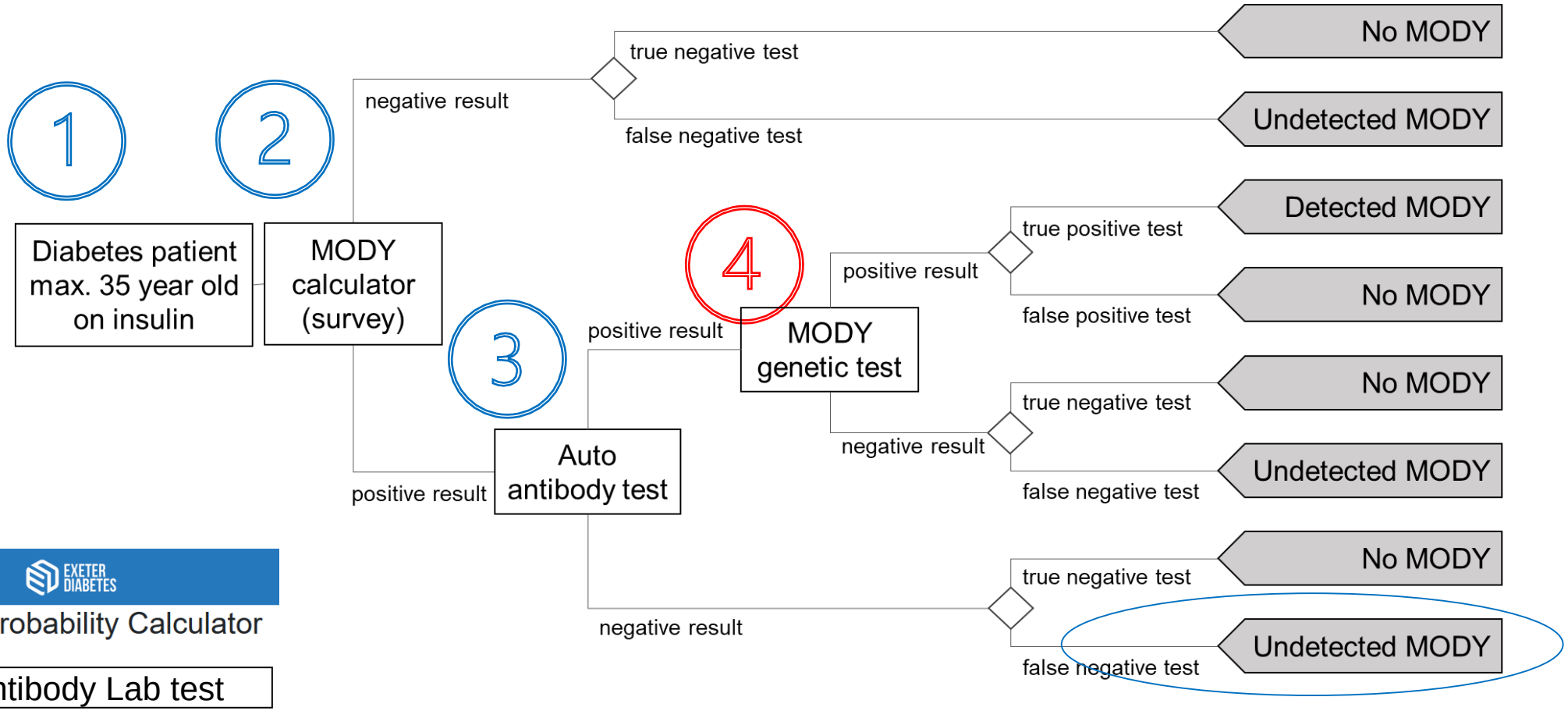
SCREENING FOR MODY PATIENTS - SCENARIO 1



EXETER DIABETES

MODY Probability Calculator

SCREENING FOR MODY PATIENTS - SCENARIO 2



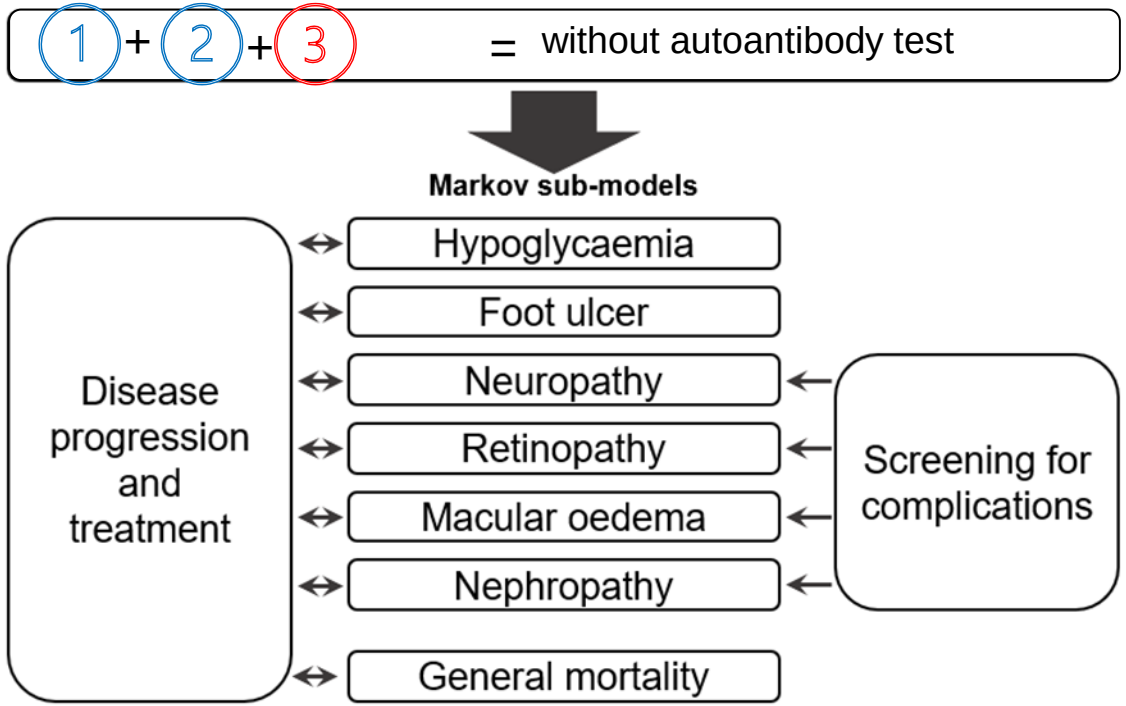
EXETER DIABETES

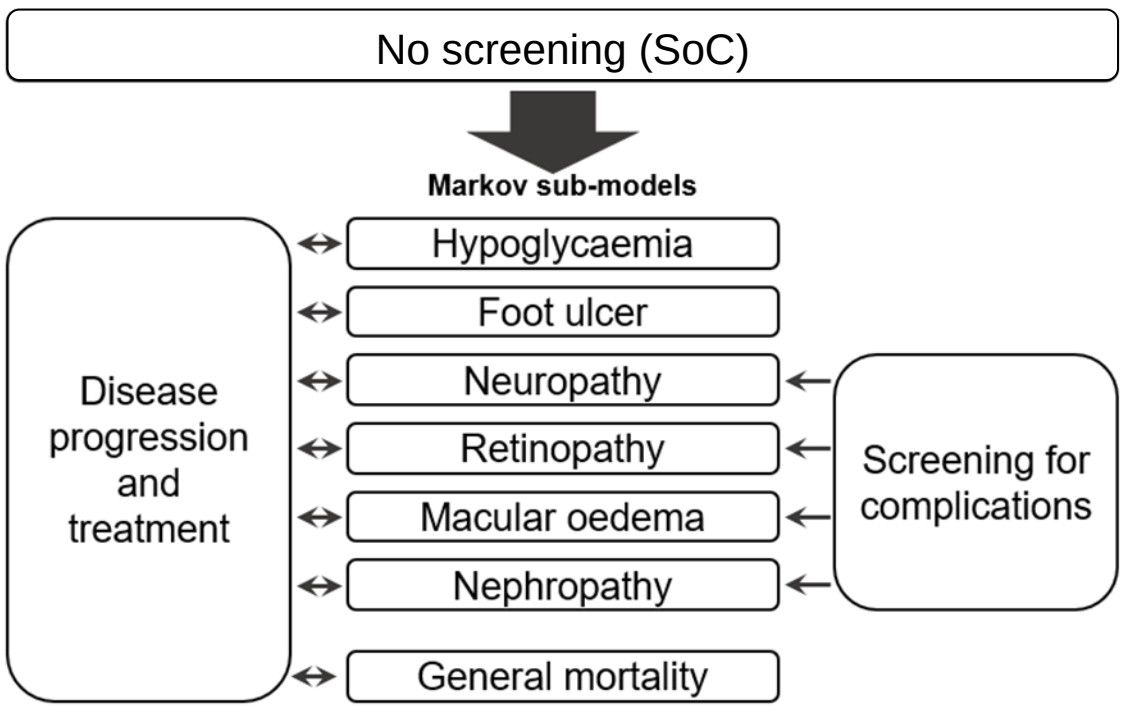
MODY Probability Calculator

Autoantibody Lab test

MODEL STRUCTURE

Scenario 1



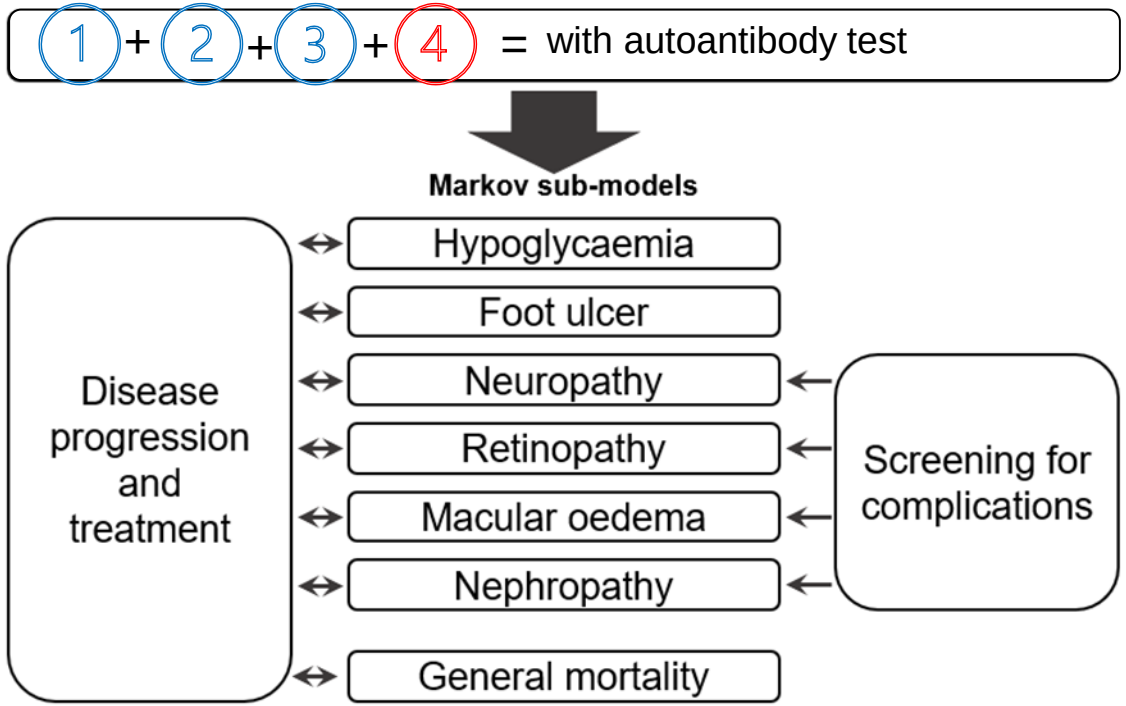


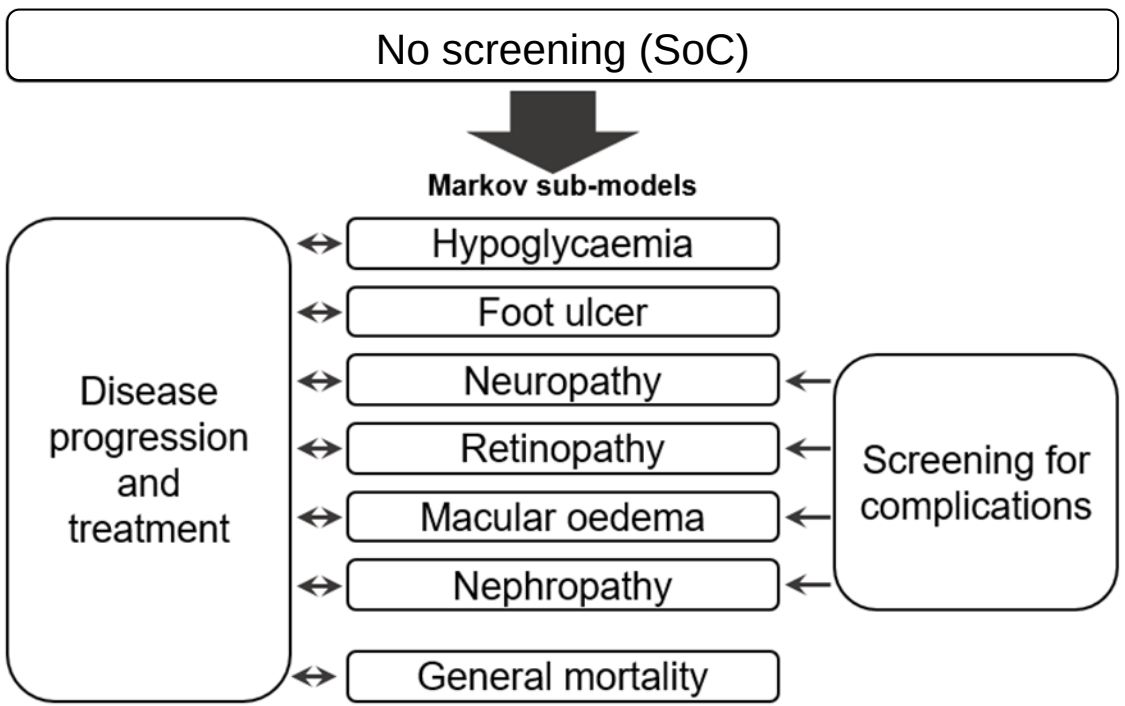
Simulation model for diabetic complications and mortality: Nagy et al 2016

Time horizon: 20 years

MODEL STRUCTURE

Scenario 2





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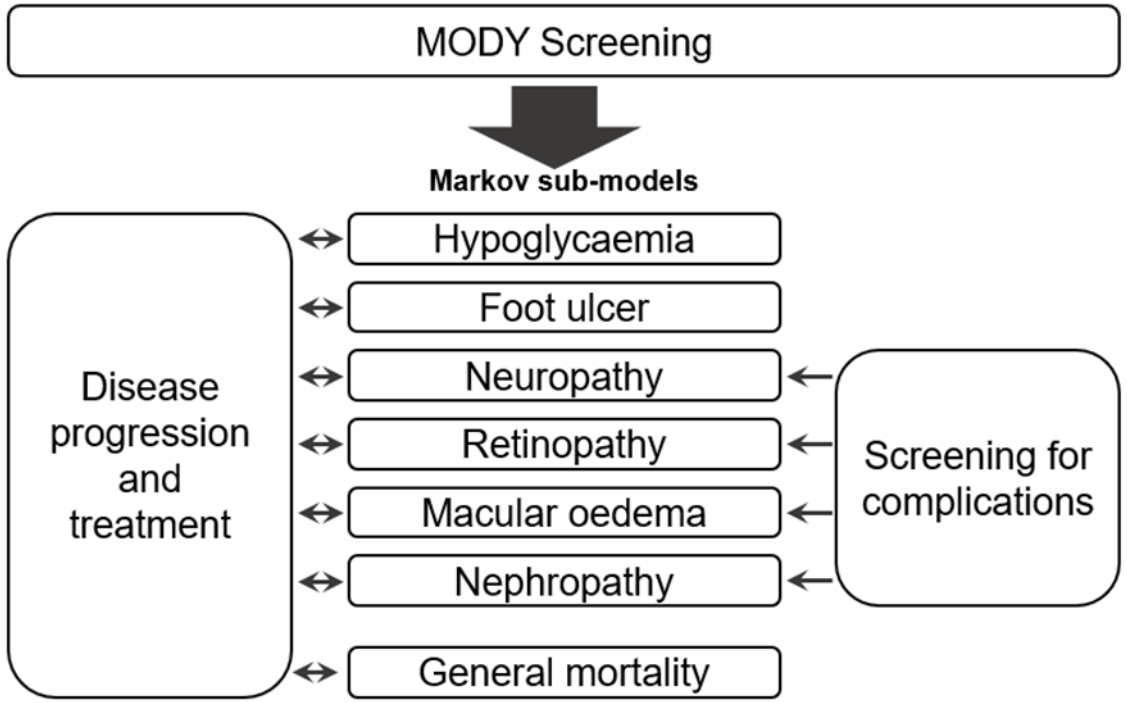
CONSEQUENCES OF SCREENING



BOTH SCREENING STRATEGIES

- Less therapeutical costs + better quality of life
  - avoid hypoglycaemic events
  - less frequent complications (better HbA1c control)
- Extra costs of
  - genetic test: 730.9 EU
  - autoantibody test: 3.8 EU
  - MODY questionnaire: 2.0 EU

SCREENING WITH AUTOANTIBODY TEST

- 1% of patients is not detected

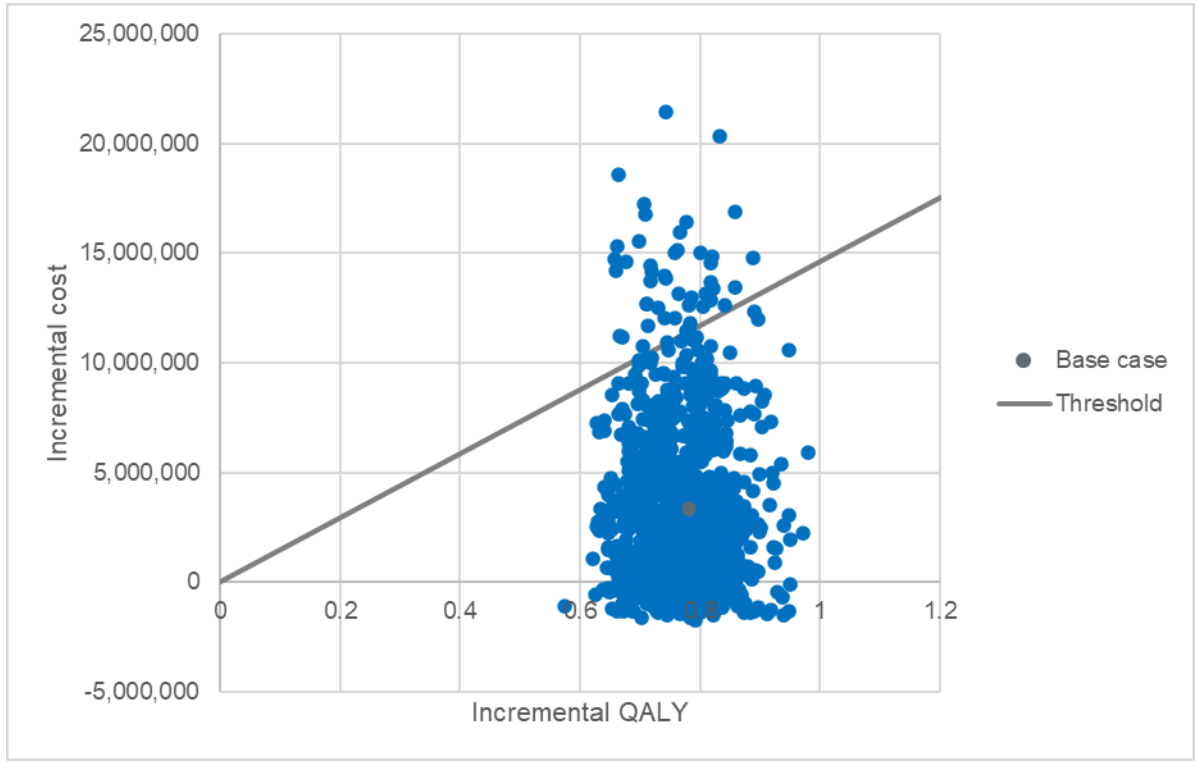
COST-EFFECTIVENESS RESULTS - HUNGARY

	Cost (in €)	QALYs	Incremental Cost (in €)	Incremental QALYs	ICER	
No screening	7,516	12.1488	-	-	-	
MODY screening with autoantibody test	7,503	12.1535	-12	0.004707	**dominant**	**Scenario 2**
MODY screening without autoantibody test	7,574	12.1536	58	0.004754	**12,244**	**Scenario 1**

*extended dominance of scenario 2 over scenario 1

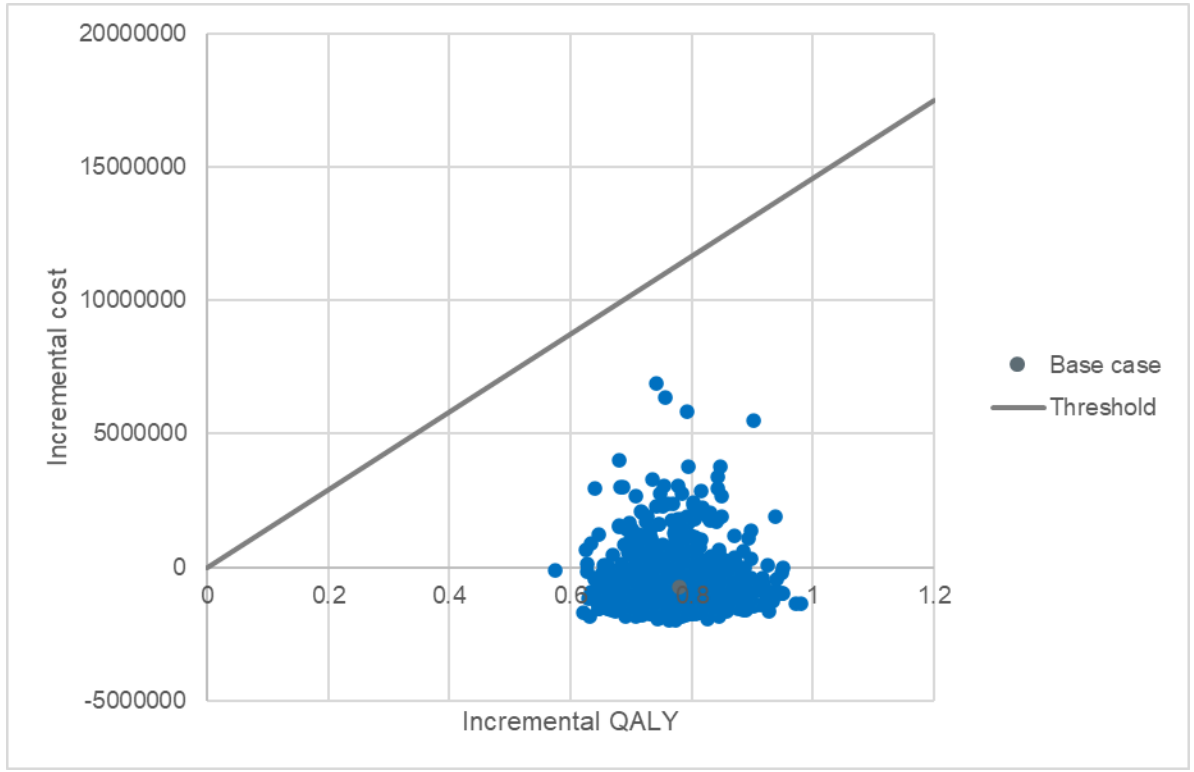
Willingness to pay threshold of the society: 41,544 €/QALY

PROBABILISTIC SENSITIVITY ANALYSIS



SCREENING WITH GENETIC TEST ONLY

SCENARIO 1



PRE-SCREEING WITH AUTOANTIBODY TEST + GENETIC TEST

SCENARIO 2

COST-EFFECTIVENESS RESULTS – THE NETHERLANDS

	Cost (in €)	QALYs	Incremental Cost (in €)	Incremental QALYs	ICER	
No screening	26,375	14.6121	-	-	-	
MODY screening with autoantibody test	26,313	14.6177	-62	0.005614	**dominant**	**Scenario 2**
MODY screening without autoantibody test	26,484	14.6177	109	0.005670	**19,141***	**Scenario 1**

*extended dominance of scenario 2 over scenario 1

Lowest possible willingness to pay threshold of the society: 20,000 €/QALY

WHAT WE LEARNED FROM THE MODY CASE I

„Identify all relevant test-treatment pathways and justify why the pathways included in the model were selected.”

- Inclusion of autoantibody testing is false negative in 1% of the MODY population
- We take the risk of loosing QALYs for 1% of patients but save costs
- IT WAS A GAME CHANGER

WHAT WE LEARNED FROM THE MODY CASE II

"Include the costs and health outcomes of testing relatives of index patients with inheritable genetic mutations in the model."

- Which relatives could have been included?
  - Siblings, easy to identify - **YES**
  - Parents, too old (>35) to switch original therapy - **NO**
  - Children – in a great distance of time to capture in a model – **NO**

- IT WAS NOT A KEY FACTOR

OUR TAKE-AWAY

A. Screening with genetic testing for MODY patients is good value for money

But...the context of screening could make significant difference

- Specify the target population
- Consider all screening pathways
- Pay attention and adjust to the context (country)

B. Personalized medicine can be modelled with standard methods

But...attention to personalized medicine specific features is necessary

- Check what could be an issue – use our guidance!
- Adjust when there is a real issue

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THANK YOU!

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syreon Research Institute

UNIVERSITY OF OXFORD

Personalised Medicine

DIFFERENT PERSPECTIVES FOR THE FUTURE

Doris Schartinger, Beatrix Wepner, Sabine Neuberger, Manuela Kienegger, Susanne Giesecke

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824997.

HECOPERMED

- HEcoPerMed aims
  - Responding to the demand for HE models
  - studying and stimulating the adoption of PM in health care systems

- Future perspective of citizens and patients and other stakeholders on the trneds related to personalised medicine (scenarios)
- Real-time perspective of citizens, patients and other stakeholders on the current challenges and drivers around implementation
- process aims
  - identifying and approaching stakeholders and including them in a debate,
- explorative aims
  - seeking to identify their perspectives on drivers and challenges
  - And the role of HE therein

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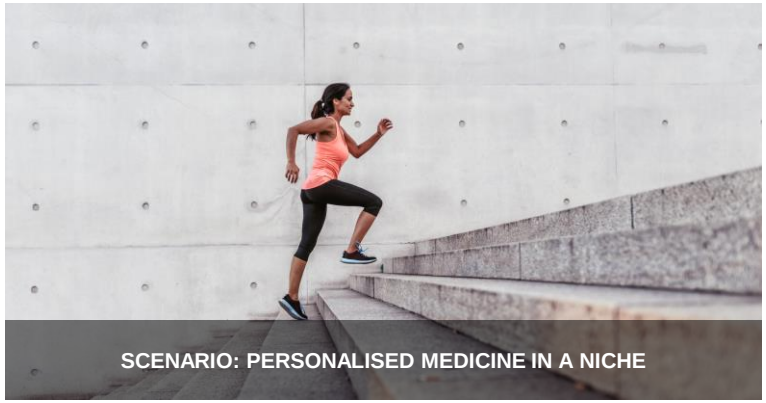
FUTURE PERSPECTIVE

Scenarios

SCENARIOS OF FUTURE PERSONALISED MEDICINE



FOUR SCENARIOS

Scenario 1: Privatization:

- PM is for wealthy people who go “health shopping” at international scale.
- Investments for PM are mostly from the private sector

Scenario 2: Cooperation :

- PM advances through open and intense cooperation by all actors
- Pan-European exchange of data and patients
- People work longer hours and extended working life-time

Scenario 3: Niche - Scepticism:

- The health insurance system is solidarity based but does not provide a lot of funds for advanced medical research, treatment or PM
- Society questioning ever more evidence-based health care and has loss of trust in data-driven health-care systems due to privacy breaches.

Scenario 4: Technology-driven:

- Donating one’s own data is the entry to this health care system.
- Rapid decrease in genome sequencing costs, affordable for everyone, also expected from everyone.

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REAL-TIME PERSPECTIVE

How to proceed from innovation niches

TWO DIFFERENT BUDGETS

- Health care budgets
- evidence-based reimbursement logic
- If personalised medicine compared to standard of care does not prove cost effective, it should not be implemented.

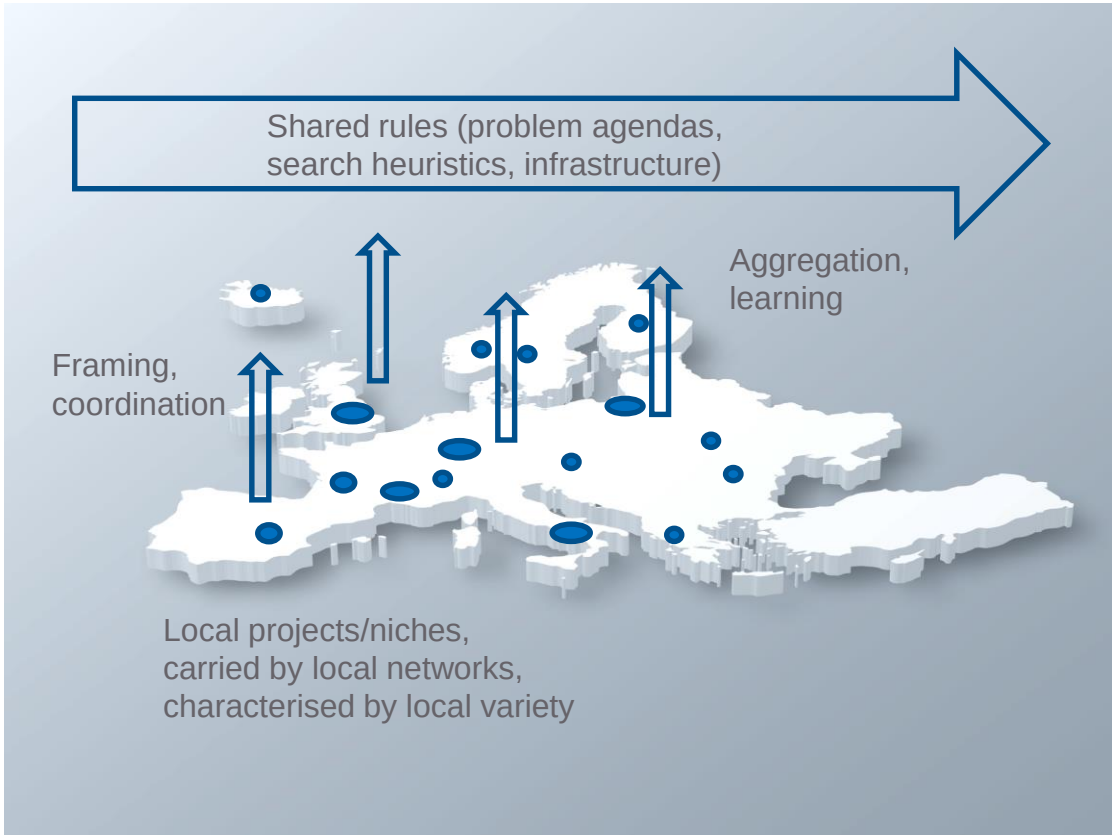
- Research and innovation budgets
- an investment logic
- “It is still the early days.”
- Hence, poor performance and high costs, yet hopeful because of new valued functionalities.

- These are of two kinds of perspectives exist in parallel AND are at the same time in conflict with each other.
- Countries and regions where innovation funding and healthcare reimbursement mechanisms are organised more closely are likely to have an advantage in the transition from the research phase to the actual implementation in healthcare.

FROM INNOVATION NICHES TO SYSTEM CHANGE

Regime level

Niche level



Adapted from: Geels and Raven 2006

HOW COUNTRIES APPROACH: INNOVATION NICHES

- Countries have implemented niches already.

- Aggregate learning across Europe, so that others in other countries do not make the same mistakes, but build on the past experiences

- Innovation niches around infrastructure.
- Innovation niches around stages of the disease.
- Innovation niches around a catalogue of criteria.
- Innovation niches around particularly promising technologies.

THE EUROPEAN ROLE

- Despite health essentially being a national agenda, there is a general agreement that there are several roles for European level governance in personalised medicine.

- Setting up European Learning Structures/Platforms for Sharing Evidence

- Maintaining pace: agenda and priority setting.
  - Priority setting
  - EU level as a facilitator, committed to the future opportunities of wellbeing, inclusion and competitiveness.
  - National level: often different debates, trade-offs

EcoPerMed
Health Economics for Personalised Medicine

THANK YOU

Doris Schartinger, April 28th, 2022

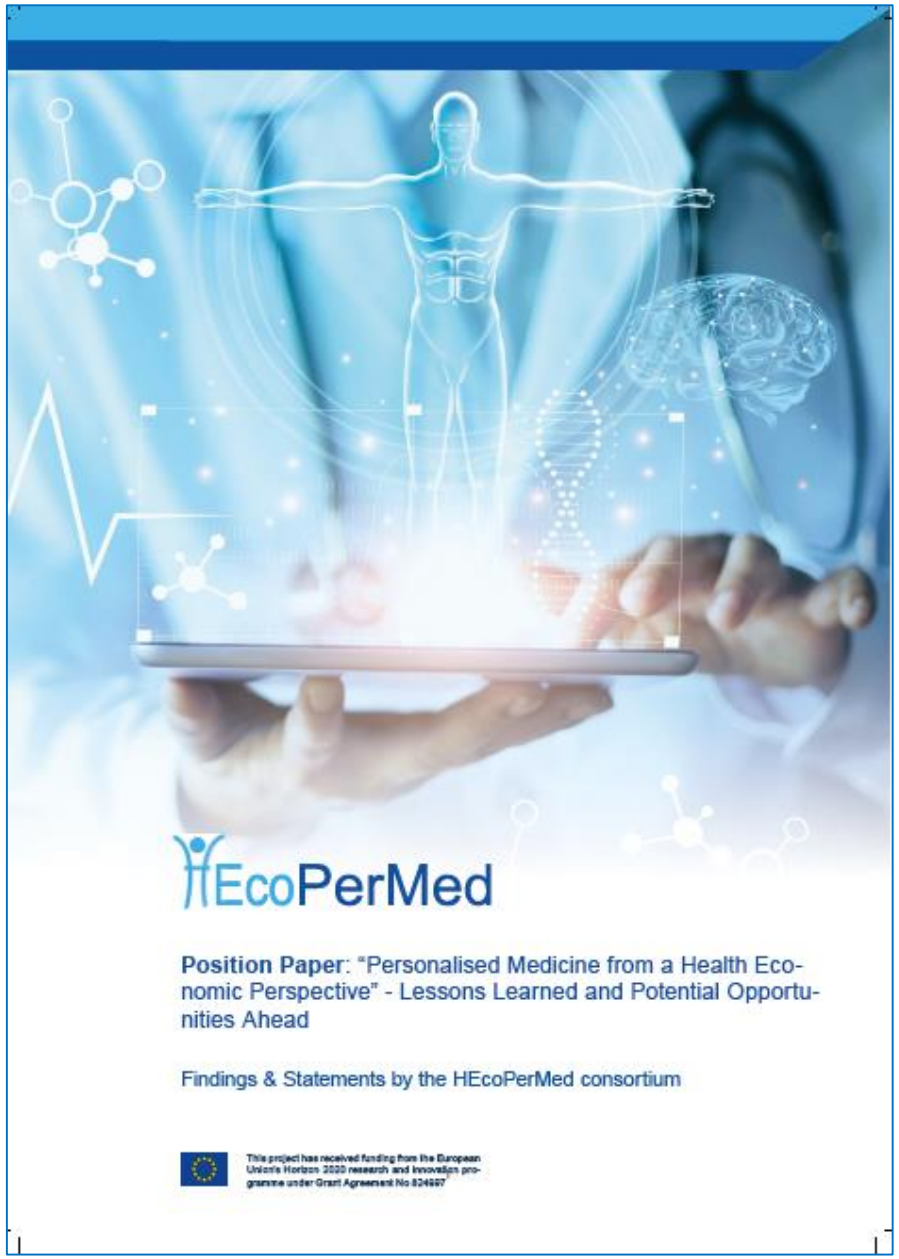
This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824997.

EcoPerMed
Health Economics for Personalised Medicine

Position paper
Personalised Medicine from a Health Economic Perspective

Maureen Rutten-van Mölken, Matthijs Versteegh, Balázs Nagy, Sarah Wordsworth

Funded by European Union's Horizon 2020 research and innovation programme; Grant Agreement no. 824997.


EcoPerMed
Position Paper: "Personalised Medicine from a Health Economic Perspective" - Lessons Learned and Potential Opportunities Ahead
Findings & Statements by the HEcoPerMed consortium
This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824987

WHY IS THERE A NEED FOR HTA OF PM?

Health care

- Budget and workforce constraints
- € spend on particular PM we have to forgo another treatment

Increase taxes/premiums

Climate

Education

Health care

- Problem of displacement is expanded into the wider economy

- Maximise health gain by prioritizing interventions which generate most health per € invested

Cost-effectiveness analysis

$$ICER = \frac{C_a - C_b}{E_a - E_b}$$

$ICER < \lambda$

$INHB > 0$

- Also used to determine the highest price at which the ICER stays below λ, i.e. the headroom price, which can be starting point of negotiations on value-based price

COST-EFFECTIVENESS ANALYSIS REQUIRES MODELLING

01

Combine different data from different sources of evidence

02

Extrapolate results of clinical trials to longer time horizons

03

Expand the number of comparators beyond that used in a clinical trial

04

Simulate real world conditions

MODELLING NOT SPECIFIC TO PM, BUT MORE COMPLEX IN PM

01

More complex treatment pathways due to risk stratification

02

Greater data needs as the downstream consequences of testing have to be modelled for all subgroups

03

Greater uncertainty as more subgroups and less patients per subgroup are inherent to stratification

04

Comparative effectiveness data may not be available for all subgroups

PharmacoEconomics (2021) 39:771–788
https://doi.org/10.1007/s40273-021-01010-z

SYSTEMATIC REVIEW

Guidance for the Harmonisation and Improvement of Economic Evaluations of Personalised Medicine

Heleen Vellekoop[1] · Simone Huygens[1] · Matthijs Versteegh[1] · László Szilberhorn[2] · Tamás Zelei[2] · Balázs Nagy[2] · Rositsa Koleva-Kolarova[3] · Apostolos Tsiachristas[3] · Sarah Wordsworth[3] · Maureen Rutten-van Mölken[1,4] on behalf of the HEcoPerMed Consortium

Accepted: 15 February 2021 / Published online: 16 April 2021

- Paper with 23 recommendations addressing the modelling of test-treatment combinations, non-randomized controlled data, additional elements of value, premature survival data, uncertainty, managed entry agreements and other issues.

REVIEW OF NET BENEFIT OF PM, 2009-2019

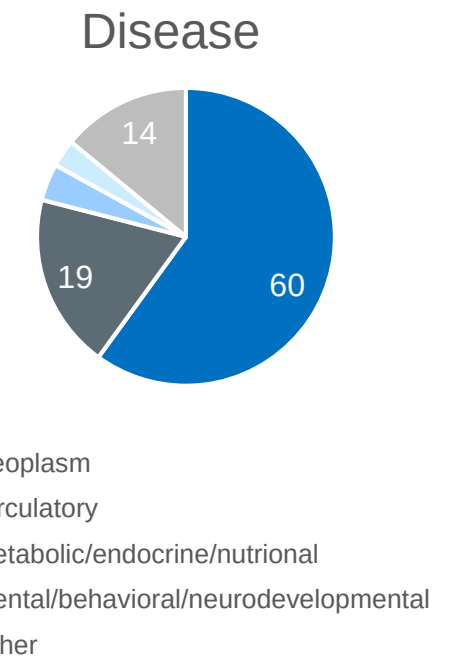
ScienceDirect

Contents lists available at **sciencedirect.com**
Journal homepage: **www.elsevier.com/locate/jval**

Systematic Literature Review

The Net Benefit of Personalized Medicine: A Systematic Literature Review and Regression Analysis

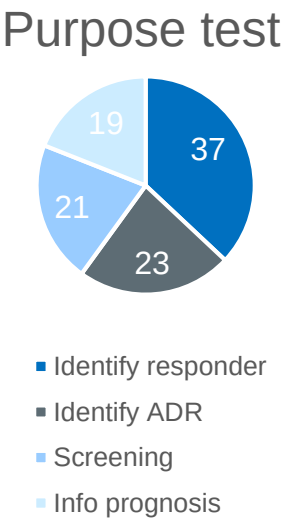
Heleen Vellekoop, MSc, Matthijs Versteegh, PhD, Simone Huygens, PhD, Isaac Corro Ramos, PhD, László Szilberhorn, PhD, Tamás Zelei, PhD, Balázs Nagy, PhD, Apostolos Tsiachristas, PhD, Rositsa Koleva-Kolarova, PhD, Sarah Wordsworth, PhD, Maureen Rutten-van Mölken, PhD, on behalf of the HEcoPerMed consortium



- Focuses on genetic and genomic test-treatment combinations
- 128 studies providing cost-effectiveness data for 279 PM interventions
- High-income and upper-middle-income countries (48% US, 16% UK)

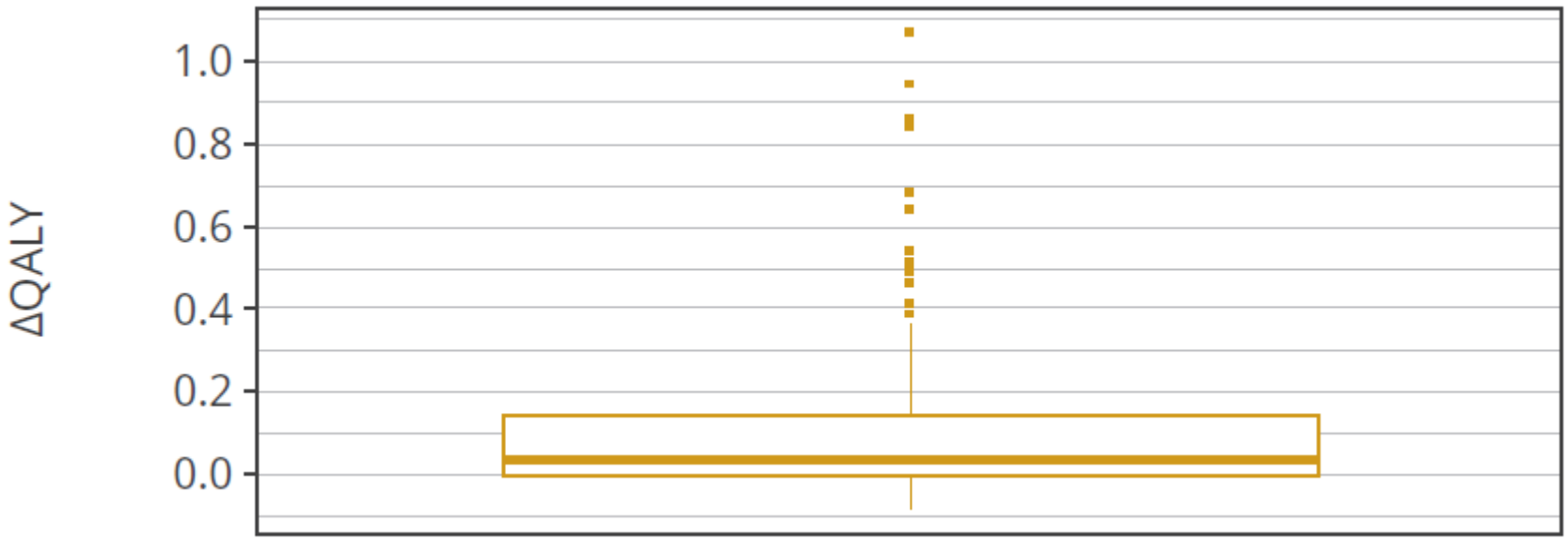
PERSONALISED MEDICINE (TEST-TREATMENT COMBI)

- Identify likely (non-)**responders** to treatment (37%)
  - E.g. testing for NTRK gene fusions followed by TRK inhibitors in NTRK+
- Identify **adverse drug reactions**: test for mutations increasing susceptibility to side-effects/adverse events (23%)
  - E.g. DPYD mutations that affect metabolisation of chemotherapy
- Obtain information about **disease prognosis to tailor treatment** (21%)
  - E.g. OncotypeDX Breast Recurrence Score test
- **Personalised screening** for presence of risk factors or disease (19%)
  - E.g. increased screening frequency for patients at increased risk of hypertrophic cardiomyopathy
- **Cell and gene therapies (4%)**
  - E.g. Car-T cell therapy, Zolgensma for spinal muscular atrophy



HEALTH GAINS CAN BE SUBSTANTIAL, BUT HETEROGENEITY IS LARGE

QALY mean: 0.26, median 0.03, max 11.8



- 16 interventions (6%) rendered more than 1 ΔQALY
- Gene therapies were found to have larger health benefits than other PM interventions (regression coefficient 3.22 (95% CI 2.69-3.75)

The bottom and top 5% of values have been left out of the boxplot

PERSPECTIVE MATTERS

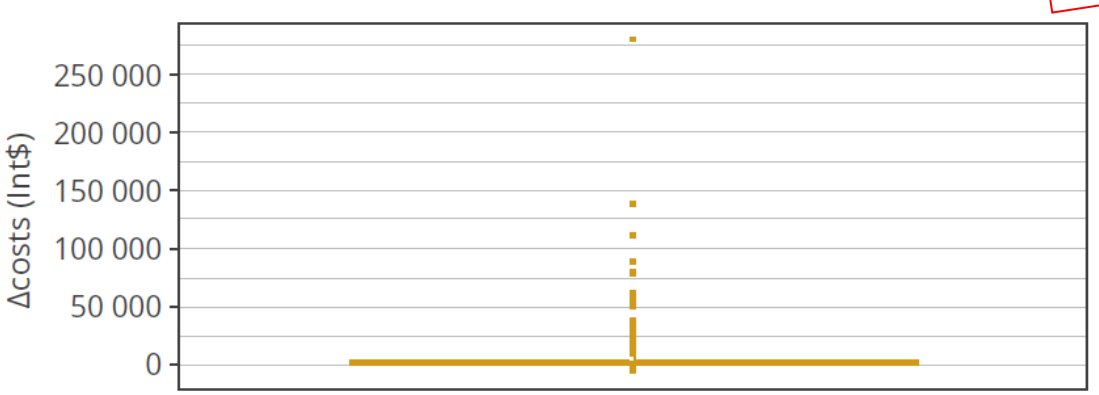
HEALTH GAINS FOR AN INDIVIDUAL DO NOT AUTOMATICALLY TRANSLATE INTO SUBSTANTIAL ADDED VALUE FOR SOCIETY

COST CONSEQUENCES LARGER THAN USUALLY IDENTIFIED THEY CAN OFFSET THE VALUE OF THE HEALTH GAINS ENTIRELY

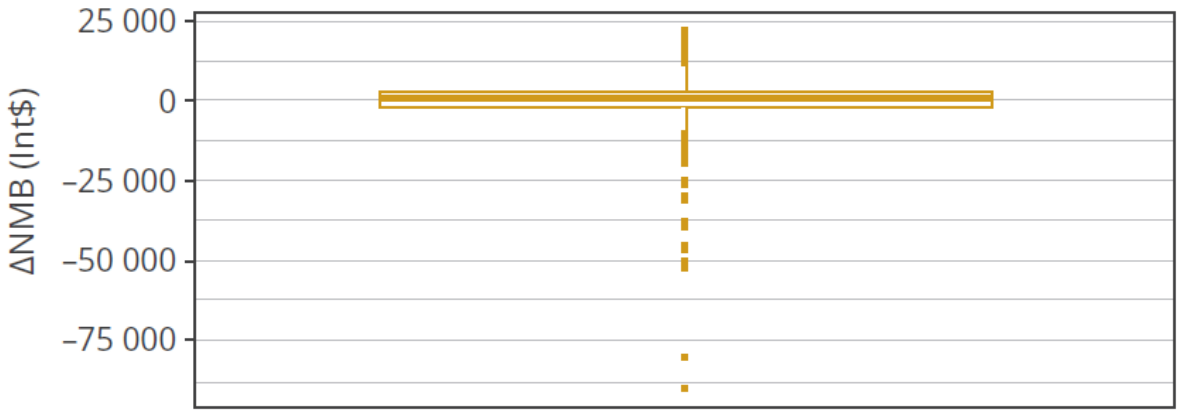
Cost mean: 99,777, median 575, max 8.1 mln

ENTRECTINIB CASE

INMB mean: -77,072, median 18, max 406,277



Differential costs were inflated to 2020 prices using country-specific inflation rates, and converted to PPP using conversion factors from the World Bank Global Economic Monitor



$\Delta NMB_{ij} = \Delta h_i * k_j - \Delta c_{ij}$, where h_i = ΔQALYs for intervention *i*, k_j = cost-effectiveness threshold in country *j*, and c_{ij} = Δcosts for intervention *i* in country *j*. k thresholds were mostly taken from Woods et al, Value in Health 2016, 19(8):929-35

- Large-scale testing, for the benefit of a few, can be costly
- Cost of testing-infrastructure to obtain the data to personalise treatment
- Costs of setting up the infrastructure to deliver the therapy (e.g,. CAR-T)
- Lifetime health gains and cost-savings of PM are commonly factored into the price

The bottom and top 5% of values have been left out of each boxplot

SUBSTANTIAL EFFICIENCY GAINS TO BE MADE BY INVESTING IN PM INTERVENTIONS THAT TARGET **EXISTING** CARE BETTER

Dependent variable: ΔNMB			
Intercept		152 210	[−144 118 to 448 539]
Purpose of test*	Info prognosis	−126 431	[−445 368 to 192 505]
	Identify responders	−221 146	[−535 623 to 93 331]
	Identify ADR	176 913	[−156 155 to 509 981]
Type of treatment†	Pharmaceutical	3479	[−251 023 to 257 981]
	Combination	99 635	[−475 897 to 675 166]
Gene therapy	Gene therapy	**−868 759**	[−1 307 289 to −430 229]
Sponsorship	Industry	92 109	[−103 308 to 287 527]
Disease classification‡	Non-neoplasm	**−380 950**	[−638 867 to −123 032]

TOXNAV CASE

- many interventions included in "**identifying ADR"** aim to better stratify patients to existing treatments instead of new treatments
- many interventions in the "**identify responders**" stratify toward new treatments, which are still patented and may be costly

*Reference category is "screening."
†Reference category is "nonpharmaceutical interventions."
‡Reference category is "neoplasms."

WHERE COULD PHARMACOGENETICS HELP?

			% with variant alleles
Psychiatry:	Antidepressants, antipsychotics	CYP2D6, 2C19, 1A2, 3A4	60%
Cardiology:	Clopidogrel (Plavix)	CYPC19	15%
	Metoprolol	CYP2D6	40%
	Statins	SLCO1B1 (521T>C)	20%
	Warfarin	CYP2C9, VKORC1	20%
Oncology:	Tamoxifen (breast)	CYP2D6	10%
	Capecitabine / 5-FU	DPYD (*2A)	2-3%
	6-mercaptopurine (ALL)	TPMT	11%
	Irinotecan (colon)	UGT1A1	15%
Neurology	Phenytoin	CYP2C9, 2C19	20%
	Clobazam	CYP3A4, 2C19	20%
Dermatology	Azathioprine	TPMT	11%
Pain	Codeine, tramadol, oxycodon	CYP2D6	40%
Internal Medicine	Azathioprine (Crohns)	TPMT	11%
HIV	Efavirenz	CYP2B6	5%
	Abacavir	HLA-B*5701	4%
Organ Tx	Azathioprine	TPMT	11%
	Tacrolimus/cyclosporin	CYP3A5, 3A4	20%

Reproduced with permission from prof.dr. Ron van Schaik

THE VALUE OF PM OVER ITS **ENTIRE LIFETIME** IS POORLY UNDERSTOOD

- Focus on **static efficiency**: does PM as currently provided to a cohort of patients offer value for money?
- **Scientific spillovers**: future innovators can build on both successful and failed prior innovations
- What if we would move to **dynamic efficiency**: maximise health benefits by optimally combining interventions over a period of time (i.e., current and future interventions)?
- It would reward innovation with higher prices but would likely **reduce access to current interventions** in exchange for faster access to future innovations

- Value assessment should acknowledge that **prices decline after patents expire**
- There is likely to be too little competition in some of the smaller markets for PM, with **high prices maintained** after patent expiration

IT IS DEBATABLE WHETHER CURRENT ECONOMIC EVALUATIONS FULLY APPRECIATE THE VALUE OF INNOVATIVE PM APPROACHES

Additional elements of value

- Scientific spillovers
- Increased productivity
- Reduced costs of informal care
- Reduction in costs to other sectors
- Severity of disease
- Value of a cure
- Value of hope
- Reduction in uncertainty
- Real option value
- Etc…

Concerns

- How to measure?
- Risk of double counting
- Sole focus on positive value elements
- Threshold should be adjusted

IF WE WOULD INCLUDE ADDITIONAL ELEMENTS OF VALUE, WE MAY ADOPT PM INTERVENTIONS THAT GENERATE THESE ADDITIONAL ELEMENTS **AT THE EXPENSE** OF INTERVENTIONS IMPROVING LENGTH AND QUALITY OF LIFE

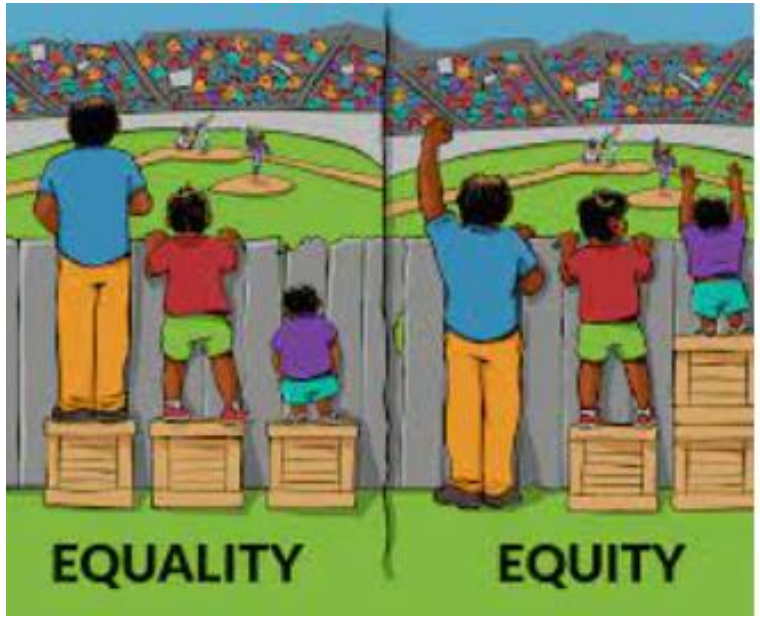
Threshold
€50,000

Treatment	QALY	cost	Value of a cure	Net Health Benefit
Standard CEA				
A	2	€80,000	-	+0.4
B (would be adopted)	2.5	€80,000	-	+0.9

EQUITY ISSUES ARE LARGE AND UNADDRESSED:

- Compared with one-size-fits-all approaches, PM, by definition, increases some forms of inequality, but we must **avoid undesirable effects of inequality on equity**

  - Inequity in **access** to genetic research;
  - **Representation** of vulnerable groups in the databases;
  - **Correlation between biomarkers** used for personalisation **and equity-relevant variables**, such as ethnicity, socioeconomic status, and health-literacy;
  - **Delays in regulatory and reimbursement decision-making**, because of uncertainty on effectiveness of PM in small groups that result from stratification;
  - **Privacy and data protection concerns** about misuse of personal data to discriminate when purchasing insurance or a mortgage;



- Value of PM may be higher in developed countries with an advanced level of health care compared to **lower-income countries where quicker wins** from the wider implementation of **non-PM** are still possible

ACCELERATE ACCESS TO VALUE-BASED PM

- **Horizon scanning**, followed by more **early-HTA**'s to steer R&I of value-based PM
- Stimulate appropriate use of PM in daily practice by **including CE-considerations in clinical guidelines,** policy implementation strategies and decision-making support tools
- Shift from one-time CEA to inform yes/no reimbursement decisions to a **cyclic approach** in which models are regularly updated with routinely-collected data

- Better **align the evidence-requirements** of European regulatory and Member State reimbursement authorities (EU HTA regulation, Dec 2021, joint clinical assessments)
- Share HTA results. Why wouldn't there be room for core **European CE-model** that can be adapted to country-specific needs?

- When uncertainty is high, use more **financial- and performance-based MEA's**, to alleviate the burden of upfront payments, and **share risks and benefits** between payers and providers/manufacturers
- **Dedicated codes** to reimburse **companion diagnostics** and **genetic tests** that reflect the value of the test
- Consider combining the reimbursement of companion diagnostics and targeted therapies into a reimbursement **package**

Applied Health Economics and Health Policy
https://doi.org/10.1007/s40258-021-00714-9

REVIEW ARTICLE

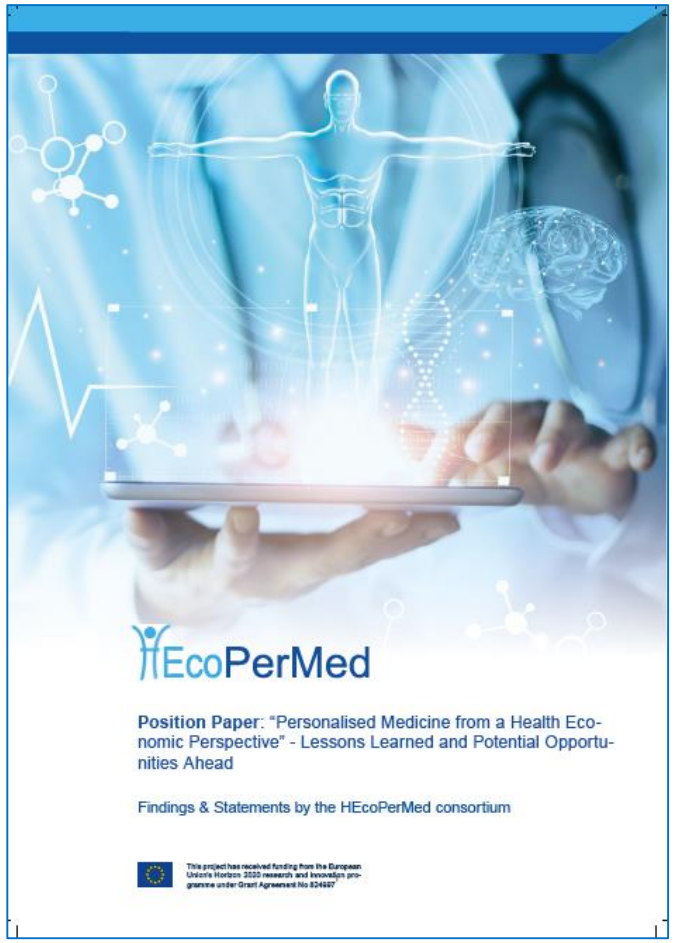
Financing and Reimbursement Models for Personalised Medicine: A Systematic Review to Identify Current Models and Future Options

Rositsa Koleva-Kolarova[1] · James Buchanan[1] · Heleen Vellekoop[2] · Simone Huygens[2] · Matthijs Versteegh[2] · Maureen Rutten-van Mölken[2,3] · László Szilberhorn[4,5] · Tamás Zelei[4] · Balázs Nagy[4] · Sarah Wordsworth[1,6] · Apostolos Tsiachristas[1,6] on behalf of The HEcoPerMed Consortium

Accepted: 28 December 2021

RECAP AND TAKE-HOME MESSAGES

- More and earlier HTA studies into the societal benefits of PM (Guidance / Position papers)
- Health gains of PM can be substantial, but heterogeneity is large (Net benefit paper)
- The cost-consequences of introducing PM are larger than usually identified (NTRK case)
- Substantial efficiency gains to be made by investing in PM interventions that target existing care better (ToxNav/MODY cases)
- The term PM may be too general given that it conceals sizable differences in the net benefit of different interventions. A more precise division into subcategories of PM may be needed to uncover the most promising areas for further investment (Net benefit paper)
- Appropriate use of value-based PM in every day clinical practice needs to be stimulated by incorporating cost-effectiveness considerations in clinical guidelines and decision support tools (Guidance / Position papers)



EcoPerMed
Health Economics for Personalised Medicine

THANK YOU!

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AIT AUSTRIAN INSTITUTE OF TECHNOLOGY
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Institute for Medical Technology Assessment
Erasmus School of Health Policy & Management
syreon Research Institute
UNIVERSITY OF OXFORD

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824997.

HEcoPerMed

Position Paper: “Personalised Medicine from a Health Economic Perspective” - Lessons Learned and Potential Opportunities Ahead

Findings & Statements by the HEcoPerMed consortium

This project has received funding from the European Union’s Horizon 2020 research and innovation programme under Grant Agreement No 824997

GLOSSARY AND ABBREVIATIONS

COVID	Coronavirus SARS-CoV-2
ELSI	Ethical, Legal and Social Implications
EC	European Commission
EEA	European Economic Area
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicine Agency
EP PerMed	European Partnership for Personalised Medicine
EU	European Union
EUnetHTA	European Network for Health Technology Assessment
GDPR	General Data Protection Regulation
HE	Health Economic/Economy
HTA	Health Technology Assessment
HEcoPerMed	HEalthcare and Pharma-Economics in support of ICPerMed
ICER	Incremental Cost-Effectiveness Ratio
ICPerMed	Interanion Consortium for Personalised Medicine
ICT	Information and Communication Technology
NCA	National Competent Authorities (Regulatory Authorities)
NTRK	Neurotrophic Tyrosine-Receptor Kinase
MEA	Management Entry Agreements
MS	Member States
QALY/QALYs	Quality-Adjusted Life Years
Patients W.A.I.T.	Patients Waiting to Access Innovative Therapies. The INDICATOR provides a benchmark of the rate of availability and waiting times in European countries.
PerMed/PM	Personalised Medicine
R&D	Research and Development
VBP	Value-Based Pricing
WGS	Whole Genome Sequencing

TABLE OF CONTENTS

1 INTRODUCTION AND AIM

The HEcoPerMed project **(Healthcare and pharma economics in support of the International Consortium for Personalised Medicine – ICPerMed)** is a cooperation and support action (CSA) funded by the European Commission (EC). It is part of the so-called ICPerMed "family" of projects and initiatives that support the research and implementation of personalised medicine in Europe and beyond.

HEcoPerMed was designed in response to the need for robust evidence on the societal value of Personalised Medicine (PM) to support faster adoption of and wider equitable access to value-based PM. An important part of the evidence required is information on the **long-term effectiveness and cost-effectiveness of distinct PM approaches**, which is the **focus of this position paper.** Industry, reimbursement agencies and healthcare payers require this evidence at various stages of the life cycle to help determine whether to continue the development of PM interventions, introduce them into routine health care, or discontinue reimbursing them. However, to accelerate adoption and broaden access, industry, clinicians and payers require more than just robust evidence. They also need innovative ways of funding research and innovation (R&I), as well as alternative payment and reimbursement models that accelerate the implementation of PM in European healthcare systems. Proposing such innovations in funding and payment was also within the scope of HEcoPerMed.

To date, the **scientific output** from HEcoPerMed includes two systematic literature reviews – one on the net benefit of PM and another on financing and reimbursement models for PM – which are good practice guidelines for modelling the cost-effectiveness of PM, and a demonstration of the application of these guidelines in three purposively selected **case studies** in which:

- an extended genetic panel for DPYD testing (TOXNAV) was used to identify poor metabolizers of fluoropyrimidine-based chemotherapy and to personalize the dose so as to avoid serious toxicity;
- a next-generation sequencing (NGS) RNA test was used to detect the presence of rare neurotrophic receptor tyrosine kinase (NTRK) fusions in tumour tissue to identify those eligible for histology-independent treatment with the NTRK-inhibitor entrectinib
- a genetic test was used to screen for the presence of maturity-onset diabetes of the young (MODY), the most common form of mono-genetic diabetes, in which insulin treatment is not beneficial

Together, these outputs provide the main basis for this position paper, which describes these findings and the lessons learned from HEcoPerMed for an **audience including industry, reimbursement authorities, payers, health economic researchers and policy-makers** at European, national, and regional level, to support their decision-making on the development and implementation of value-based PM approaches. We present these findings and lessons in the form of 12 statements in chapter 3. The position paper starts with a general explanation as to why there is a need for cost-effectiveness research of PM in chapter 2. For readers who are less familiar with health economics and cost-effectiveness research, we have included boxes explaining the main methods.

2 Executive SUMMARY

Purpose of position paper

This position paper discusses the contribution that economic evaluations can make to decisions surrounding the allocation of limited health care resources in personalised medicine (PM). In particular, the paper examines the role that health economic models can play in the context of Health Technology Assessment (HTA).

Why is the paper important?

PM combines data from many different sources and aims to increase treatment effectiveness by individualizing health care interventions, which provides a departure from a common "one-size-fits-all" approach in health care delivery. However, some PMs, such as gene therapies, are considered expensive and it is sometimes unclear what their benefits are. Given that many European countries face the challenge of limited budgets for health care, the HEcoPerMed project was designed to provide evidence on the value of PM to promote the appropriate adoption and equitable access to value-based PM. This position paper reports the information and evidence generated during the HEcoPerMed Project to support the future directions for PM across European health care systems.

Our methods

The position paper was generated by combining the outputs produced during the HEcoPerMED project such as literature reviews, model guidance documents and health economic analyses across several clinical cases studies. These outputs are summarised and shaped into lessons learned from HEcoPerMed for different audiences including industry, reimbursement authorities and policy-makers to support decisions on the development and implementation of value-based PM approaches.

Main findings

Our findings and the lessons learned culminated in 12 statements which cover areas relating to efficiency and equity in the delivery of PM, the value of a PM technology over its entire lifetime, and alternative approaches to the reimbursement of PM and their relative success. We report that the costs of introducing PM may be larger than usually identified. The appropriate use of PM can be enhanced, not only by using cost-effectiveness data in reimbursement decisions, but also by adding evidence into clinical guidelines, policy implementation strategies, and clinical decision support tools. It can further be enhanced by the wider adoption of innovative payment and reimbursement models that accelerate access in exchange for the sharing of risks.

Future directions

When performing economic evaluations of PM in the future, all changes to the care pathway should be identification and all downstream cost and benefits related to patient care pathways should be reported so as to enable policy-makers to make informed choices. To provide more timely access to new PM interventions that are shown to be cost-effective from these economic evaluations, the evaluations should be carried out as early as possible and the results shared among EU Member States. Finally, to be able to fund any cost-effective PM interventions, the evidence requirements of various European regulatory and reimbursement authorities should be better aligned going forward.

3 PERSONALISED MEDICINE – POTENTIALS AND PRECONDITIONS

3.1 Perspective matters

Personalised Medicine (PM) – is essential for improving the effectiveness of many public health and healthcare interventions as it overcomes the current limited approach of "one-size-fits-all" and the unhelpful notion of the "average" individual. There are several definitions for "personalised medicine" but, following ICPerMed, HEcoPerMed uses the definition provided in the European Council Conclusion on personalised medicine for patients (2015/C 421/03). This definition states *"[…] that it is widely understood that personalised medicine refers to a medical model using characterisation of individuals' phenotypes and genotypes (e.g., molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention."*

PM is a **multifaceted concept** that often combines data from many different sources to individualize interventions. When focusing on the use of genetic information to inform clinical decisions, it includes the following examples: 1) testing to screen for diseases or genetic markers in asymptomatic populations to individualize their screening intervals and disease prevention strategies, 2) testing to provide information on disease prognosis to tailor treatment, 3) testing to identify treatment responders and non-responders to provide therapy to those most likely to benefit and avoid side-effects in those unlikely to respond, 4) testing to identify patients who abnormally metabolize drugs, as a result of which they experience adverse drug reactions that may be avoided by adjusting (dose) or modifying the treatment, and 5) gene therapies.

The health gains of PM for the individual patient can be substantial. For example, in cancer, the targeted therapy trastuzumab has increased the cure rate of primary HER2-positive breast cancer and has improved overall disease survival in the adjuvant and metastatic setting.

In our systematic literature review comparing 279 PM interventions involving gene profiling or correcting pathogenic gene mutations with their non-PM counterfactuals, we found a mean gain in quality adjusted life years (QALYs) per patient of 0.26 (median 0.03), with 6 % of PM interventions rendering more than 1 QALY. However, the mean incremental net monetary benefit (see box for further explanation) was negative and the median just above zero. Although there is a lot of variation between interventions, this illustrates that **health gains for an individual patient do not automatically translate into substantial added value for healthcare systems and society.** A potential reason for this, especially regarding rare genetic mutations, is that many people must have an expensive test to identify the few patients that may benefit from PM, which can drive up the costs of test-treatment combinations. In addition, the lifetime downstream health gains and cost savings of PM are commonly factored into the price of PM (especially medicines), which could entirely offset the value of the health gains. Furthermore, unequal access to PM within and between countries – for example, because of budget constraints – might contribute to increasing health inequalities. In addition, unexpected test findings may raise ethical dilemmas or trigger interventions with lifetime consequences for patients and their relatives.

PM approaches can transfer their potentials for the patients into the reality of health care systems only when Health Technology Assessments (HTA) are performed to ensure **net benefits** not only for the individual, but also for society as a whole. For that to happen, reimbursement decision-makers and payers need to make much more use of information resulting from HTA analyses in their decision-making.

3.2 Why is there a need for HTA of personalised medicine?

Healthcare **resources are scarce**. In many EU countries, there is an increasing shortage of staff, hospital bed capacity and a limited budget. During the Covid-19 pandemic, people started to truly understand the meaning of **"displacement"**. While resources were needed to save the lives of those infected, consultations, diagnostic investigations, surgeries, and therapies were postponed for those not needing emergent care. Simply put: healthcare euros can only be spent once, i.e., if we spend it on treatment A we have to forgo treatment B. If the healthcare budget is increased by increasing taxes or premiums for health insurance, the problem of displacement is expanded to the wider economy and a reduced budget may be available for other public goods such as education, climate change, and other public services. Moreover, increasing taxes or insurance premiums beyond a certain point jeopardizes the market competitiveness of countries, which in turn could lead to reduced funds available for healthcare.

In all healthcare systems in the EU and beyond, healthcare interventions compete for financial, technical, and human resources. An **economic evaluation** can help identify interventions that produce the

most health within a given budget and prioritise the allocation of resources to them. The outcome of this type of evaluation is generally expressed as an **incremental cost-effectiveness ratio (ICER)**, which reflects how many additional resources are needed for an intervention so as to generate one additional quality adjusted life year (QALY), in comparison to the next best (in terms of effectiveness) alternative intervention (often the standard of care). This ICER is a valuable estimate in its own right as an efficiency ratio. However, it can also be compared against a **threshold value (i.e., the maximum acceptable ICER)**, which can be defined based on different approaches. This comparison tells us if a new intervention is more (ICER<threshold) or less (ICER>threshold) efficient in creating health than an intervention that could be displaced if the new intervention was introduced in the healthcare system.

An economic evaluation can also play a key role in the price-setting of innovations, as it enables us to determine the maximum price at which the ICER of an intervention stays below the threshold value of the ICER, i.e., the **headroom** of the price.

However, allocation of scarce resources is guided not only by efficiency considerations. Healthcare policy-makers also care about the distribution of health and health gains across different population groups. In some countries, these equity considerations have led to an increase in the threshold value of the ICER for (end-of-life) interventions in severely ill patients or patients with rare conditions. This increases the likelihood of these interventions being reimbursed. Besides efficiency, affordability, and **equity considerations**, societal acceptance also plays a role in resource allocation decisions. Societal acceptance is often guided by common European values such as solidarity for those in greatest need and trust in social justice.

This position paper focuses primarily on the contribution of economic evaluations to the unavoidable need to make choices in healthcare. An economic evaluation can be positioned as the heart of a wider **Health Technology Assessment (HTA)**, which – as defined by the EUnetHTA (European Network for HTA) core model – is a comprehensive evaluation approach of a technology (i.e., healthcare intervention) addressing comparative effectiveness, costs, economic evaluation, safety, ethical, organisational, social, and legal aspects.

The application of economic evaluations often involves the construction of a **cost-effectiveness model** in which different sources of evidence, such as baseline-risks, treatment-effects, costs, and quality-of-life values (utilities), are combined. These models commonly extrapolate the results of clinical trials to the long-term (often to the lifetime of individuals). They can also expand the number of relevant comparators beyond that included in clinical trials, position the investigated technology into the patient pathway, and simulate real-world conditions. Cost-effectiveness modelling is not specific to PM, but its execution can be complicated by several factors leading to greater uncertainty, which include limited data due to small populations inherent in the stratification of patients in PM, lack of or methodologically weak comparative effectiveness studies, complex and country-specific test-treatment combinations, as well as unexpected test findings. In terms of terminology, cost-effectiveness models are also referred to as health-economic models, something that is confusing to people outside this scientific field, as Health Economics is a science that is much broader than HTA (see text boxes for further explanation).

Health Economics

Health economics is a branch of economics concerned with issues related to efficiency, effectiveness, value and behaviour in the production and consumption of health and healthcare. This scientific discipline emerged from the observation that the healthcare market is very different from markets for many common consumer goods and services where the law of supply and demand affects prices. There are several key differences. Firstly, the decision to consume a healthcare service is not made voluntary but is a necessity that results from the occurrence of an illness. Secondly, there is an information asymmetry between doctors (suppliers) and patients (demanders). Contrary to other markets in which consumers know what they want and can judge the quality of a product, doctors have more knowledge and patients depend on doctors to act in their best interest. However, doctors make profit from selling services, which can lead to a conflict of interest. Thirdly, doctors are not paid directly by the patient. Instead, the patient pays money to an insurer in the form of either a premium (if the insurer is a private company) or a tax (if the insurer is the government) and the insurer pays the doctor. Hence, the health insurer is the third-party agent of the principal (i.e., the patient). Health insurance may lead to moral hazard, i.e., patients and doctors order more than is necessary because the insurer will pay anyway. It may also lead to adverse selection, i.e., insurers selecting people in good health who consume fewer services. Universal coverage can prevent that. Fourthly, externalities frequently arise, most notably in the context of health impacts, for example, from an infectious disease such as COVID-19, where vaccination affects people other than the patient vaccinated. These differences explain why extensive government intervention is required, for example, to regulate who pays for insurance and how much (health insurance market), who provides which services (healthcare service provision market), or what an insurer will pay for and how much (healthcare provider market). Health economists analyse these and many other markets that exist in the healthcare sector.

Health Technology Assessment

One of the disciplines in Health Economics is Health Technology Assessment (HTA). HTA is a comprehensive evaluation approach of a technology (i.e., healthcare intervention) addressing comparative effectiveness, costs, economic evaluation, safety, as well as ethical, organisational, social and legal aspects. HTA seeks to inform health policy-makers by using the best scientific evidence available in regard to the aforementioned aspects, for example, to support decision-making on the reimbursement of a technology by healthcare insurance.

Health Economic Evaluation

An essential component of an HTA is a health economic evaluation. This is a comparative analysis of two or more alternative technologies (i.e., healthcare interventions) in terms of both their costs and health consequences. Four different types of economic evaluations are distinguished, which differ in terms of the health consequences that are analysed. In a cost-utility analysis, the health consequences are expressed in quality-adjusted life years (QALYS) and, in a cost-effectiveness analysis, in natural units such as life years or number of events. In a cost-benefit analysis, the health outcomes are translated into a monetary value, and a cost-minimization analysis focuses on comparing the costs as the health consequences of the alternative technologies are equal. The term "cost-effectiveness analysis" is also used as a synonym for economic evaluation in general.

The outcome of a cost-utility analysis is expressed as an incremental cost-effectiveness ratio (ICER) that indicates how much it costs for the new intervention to generate one additional QALY in comparison with standard of care. If the ICER is lower than the maximum acceptable ICER (the threshold value) then the new intervention is cost-effective.

The outcome of a cost-benefit analysis is expressed as the incremental net monetary benefit (INMB) or the incremental net health benefit (INHB). The INMB is calculated as the difference in QALYs between the new intervention and the standard of care times the threshold value minus the difference in costs. The INHB is calculated as the difference in QALYs minus the difference in costs divided by the threshold value. If the INMB and the INHB are greater than zero, the new intervention is cost-effective.

4 FINDINGS AND LESSONS LEARNED

4.1 The cost consequences of introducing PM are larger than usually identified

A challenge for the adoption of PM is that successful provision of PM treatments is dependent on the availability of testing infrastructure that enables stratification of patients to specific treatments or prevention strategies. Data on personal (clinical) characteristics is crucial to match the individual needs of a patient with available interventions. These data can come in many shapes and sizes, such as measuring protein expression, preferences of patients for mode of administration, or whole genome sequencing. Regardless of type, all data for PM can be generated by some form of testing infrastructure. As such, paying for and establishing testing infrastructure is an integral part of a successful strategy in adopting PM.

The acceptance of the test costs as an integral part of PM implies that the costs and benefits associated with testing must be accounted for in any economic evaluations of PM. For instance, a new genetic treatment that benefits a small group of patients may not be very costly, but it may require a wide-scale screening phase which may expose healthcare payers to larger costs than the cost of the genetic treatment itself. A comprehensive health economic model should include the additional costs and benefits of the test infrastructure when adopting PM interventions. Another often overlooked issue when dealing with test infrastructure is that testing itself takes time and may lead to treatment delays. If these delays were associated with increased morbidity or mortality, the costs and health outcomes attributable to these delays should be incorporated into the cost-effectiveness model.

An illustrative example is HEcoPerMed's case study on neurotrophic receptor tyrosine kinase (NTRK) fusion. For patients with (NTRK) positive tumours, we estimated that the cost-effectiveness of the tumour-agnostic treatment was almost €42,000 per QALY (Table 1). This would commonly be considered cost-effective, given the disease severity in patients with locally advanced or metastatic solid tumours. However, when the costs and consequences of screening all eligible patients for NTRK positive tumours were taken into account, the ICER climbed to about €130,000 per QALY (i.e., well above the conventional threshold values) (Table 2). This more than 3-fold increase in the ICER was because many cancer patients had to undergo immunohistochemistry and/or RNA testing due to the very low prevalence of NTRK fusions. The benefit of TRK inhibitors to the very few patients with NTRK positive tumours was diluted across the large number of patients who had been tested (only 0.30% of those who were tested were treated with entrectinib).

***Table 1**. Cost-effectiveness of entrectinib in NTRK+ cancer from a societal perspective (year 2020)*

Strategy	Costs (in €)	QALYs	ICER
Entrectinib for NTRK+	133,285	2.19	
SoC for NTRK+	72,151	0.730	
Incremental	61,134	1.457	41,973

***Table 2**. Cost-effectiveness of testing followed by entrectinib or SoC versus not testing and SoC for all from a societal perspective (year 2020)*

Strategy	Costs (in €)	QALYs	ICER
Testing, Entrectinib for NTRK+ patients, SoC for NTRK- patients	77,213	0.989	
No NTRK testing, SoC for all patients	76,639	0.985	
Incremental	574	0.0044	130,333

4.2 The value of a PM technology over its entire lifetime is poorly understood

There are ongoing discussions as to what extent the current cost-effectiveness models are suitable in the establishment of the long-term benefit of technologies. It is beyond doubt that there are scientific spillovers of new technologies and new scientific knowledge that is generated in an R&I process. Future innovators can build on both successful and failed prior innovations. We may think, for example, of successfully repurposed drugs. It is argued that this element of value would justify a higher price for PM interventions that are scientific breakthroughs, such as cell and gene therapies. Including scientific spillovers in cost-effectiveness analysis would involve the challenge of finding a balance between static efficiency and dynamic efficiency. The current cost-effectiveness framework is focused on static efficiency, which is the maximisation of health benefit with an optimal combination of the interventions currently available. If the evaluation framework was to be moved towards achieving dynamic efficiency, it would maximise health benefits by optimally combining interventions over a period of time (i.e., current and future interventions). Although this framework would stimulate and reward innovation with higher prices, we currently do not have any widely accepted methods which could be used to estimate the future value of innovation in present terms. Moreover, dynamic efficiency would likely reduce access to current interventions in exchange for faster access to future innovations.

The time horizon of a cost-effectiveness model reflects the observation of a cohort of patients often up until their death, while the time horizon of a technology might be longer (or shorter). To achieve a proper assessment of value, these longer time horizons may need to be considered, including, but not limited to price declines after patent expiration or the introduction of competitive interventions, technology obsolesce and replacement estimates, and the large extent of uncertainty in these estimates. Price declines after patent expiration are achieved in Europe by means of a set of interlinked regulations and incentives to stimulate the adoption of cheaper generic alternatives. However, this is mainly observed for small molecule drugs for which production is less complicated and less costly than for biologicals and personalized treatments. Patents might not be the only barrier for new treatments to come to market. There is likely to be too little competition in some of the smaller markets for PM, with high prices maintained after patent expiration unless technologies are replaced by other innovations. From the perspective of the decision-maker, it may therefore be understandable that the desired time horizon of the evaluation is that of a cohort of patients likely to benefit from the drug. Economic models providing that information may, however, be less suitable for the estimation of the total value generated by new PM technologies and whether this value is well-distributed between consumers and producers now and in the future.

4.3 There are still substantial efficiency gains to be made by investing in PM interventions that target existing care better

The term “personalised medicine” may be too general as it conceals sizeable differences in the net benefit of different PM interventions where there were both highly negative and highly positive values across different types of interventions. For example, gene therapies were found to have greater health benefits than other types of PM interventions. However, they were also associated with higher costs and significantly lower net benefit, suggesting that prices for gene therapies are higher than their benefit (as captured with current economic evaluation frameworks). Contrary to that finding, PM interventions where the testing phase focused on identifying patients likely to experience adverse drug reactions had a trend toward a positive net benefit. Many of these risk stratification interventions pertained to existing therapies. There seems to be a lot of potential in better stratifying patients to existing therapies as compared to offering new treatments. This finding points to the large and probably underused potential in improving health and reducing costs by informed targeting of existing therapies. In essence, that would increase the cost-effectiveness of current treatments by personalizing them and, therefore, the efficiency levels of the entire healthcare system.

This finding is substantiated by the ToxNav case study by an extended genetic panel (ToxNav test) that evaluated the cost-effectiveness of introducing an upfront DPYD genetic testing prior to fluoropyrimidine-based chemotherapy (e.g., capecitabine or 5-fluoracil(5-FU) for metastatic breast cancer patients. ToxNav results allowed for the identification of patients who metabolise these drugs poorly due to genetic mutations and in choosing whether to adjust the dosing or provide second-line chemotherapy. The PM intervention was compared to the current Standard of Care in the United Kingdom, which is no genetic testing followed by standard capecitabine and 5-FU dosing. The economic evaluation demonstrated that the Standard of Care strategy led to higher costs and lower QALYs as compared to the ToxNav strategy (£555,30 mln GBP vs £241,90 mln GBP; QALYs 17243.5 vs 17988.3, respectively (Table 3). Consequently, upfront DPYD testing was found to be the dominant strategy, e.g., the one that produces more health gains (QALYs) at a lower cost, which was also confirmed by extensive sensitivity analyses.

***Table 3**. Cost-effectiveness of DPYD testing prior to capecitabine or 5-fluoracil(5-FU) for metastatic breast cancer from a UK healthcare perspective (2019/2020, cohort of 10,000 simulated women)*

Strategy	Costs (in £ mln)	QALYs	ICER
Standard of Care	555.3	17243.5	
ToxNav strategy	241.9	17988.3	
Incremental	-313.4	744.8	dominant

4.4 A cost-effectiveness analysis should model entire patient pathways so as to have more alignment with and impact on clinical guidelines

Instead of isolated models comparing two or a number of alternative options at a particular phase in the patient pathway, it is more useful to assess the impact of risk stratification using a full disease model of the entire patient pathway. Although these models are usually more complex, their benefits become apparent when they are employed to evaluate multiple different healthcare interventions for the same disease. As such, it is feasible to assess testing strategies, test combinations, test-treatment combinations and treatment sequences in one cost-effectiveness model. These features enable decision-makers to judge the cost-effectiveness of not only single PM interventions but also more complex health care strategies. Information from such models is more likely to be utilized in clinical guidelines as well.

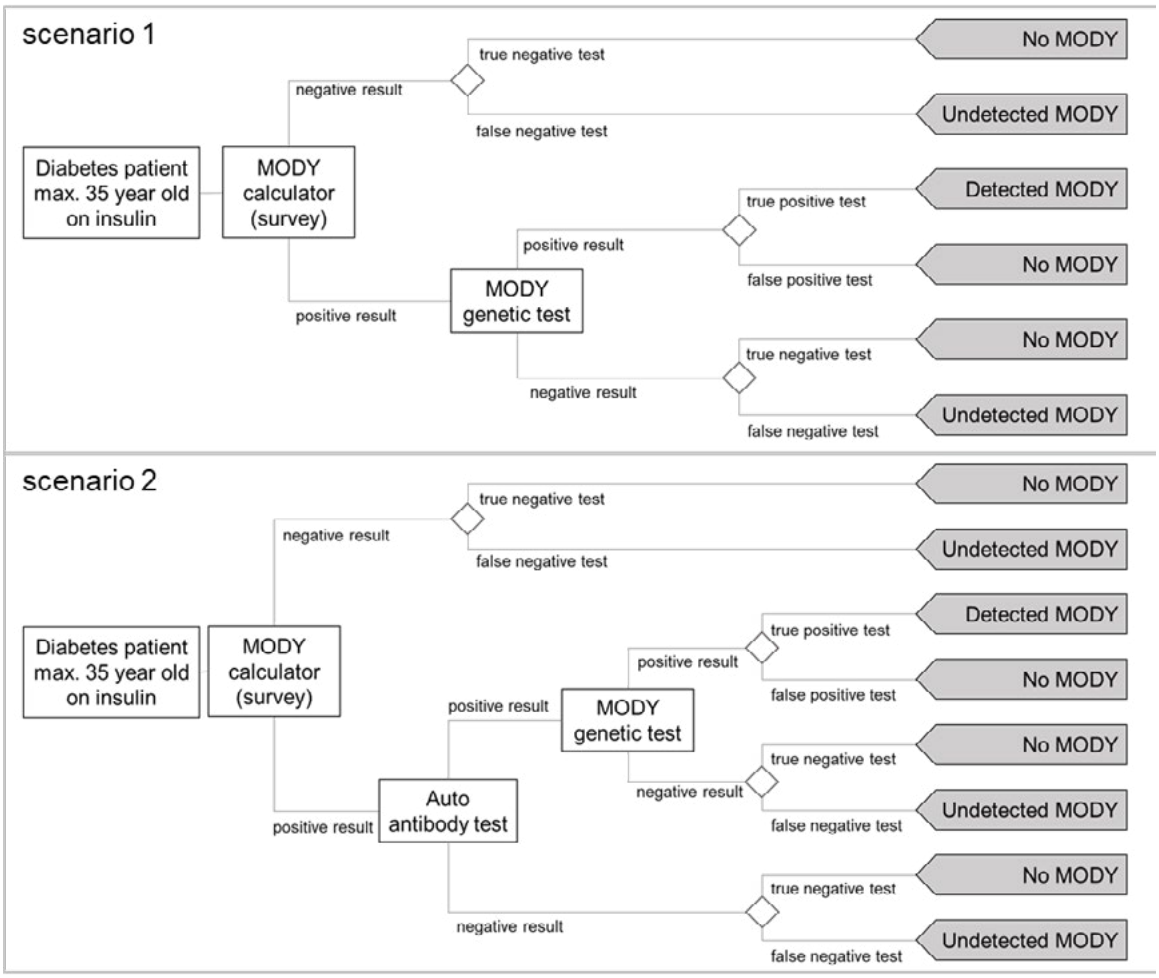
A key consideration for the decision about which diagnostic and treatment routes are to be included should be the extent to which they are relevant given the decision-making context. In HEcoPerMed, we have demonstrated this in our case study on diagnosing Maturity Onset Diabetes of the Young (MODY), which compared different patient stratification methods. The model included a decision tree for the test options and a disease progression and treatment model with sub-models for six important complications of diabetes. Diabetic patients younger than 35 years treated with insulin filled out a risk stratification questionnaire (MODY calculator). Patients with a high-risk profile according to this questionnaire could either be tested with a next-generation sequencing test immediately (scenario 1) or have an auto-antibody test to detect type I diabetes first, followed by a next-generation sequencing test for auto-antibody negative patients only (scenario 2) (Figure 1).

There was an almost 200-fold difference between the cost of the traditional lab test and the high-tech genome sequencing method. Our results showed that, irrespective of the patient stratification process, detecting MODY patients and switching them to a more adequate therapy saved not only on treatment costs but – as a result of better Haemoglobin A1c (HbA1c) control – also on long-term complication-related costs. Patients who tested positive switched from the ineffective insulin treatment to either sulphonylurea or diet adaptation. The patients' quality of life also improved due to this therapy switch and complications were avoided. Our results also showed that placing the auto-antibody test (scenario 2) in between the MODY risk calculator and the expensive genetic test could significantly reduce the cost of finding MODY patients compared to using only the combination of the questionnaire and genetic testing. Patient stratification with the inclusion of an autoantibody test became not only cost-effective but also cost-saving, which was a far more attractive policy scenario for payers. Table 4 summarizes the results of the different MODY screening strategies.

***Table 4.** Results of the MODY screening strategies*

	Costs (in €)	QALYs	Delta Cost (in €)	Delta QALY	ICER
No screening	7,516	12.1488			
MODY screening without autoantibody test	7,574	12.1536	58	0.004754	12,244
MODY screening with autoantibody test	7,503	12.1535	-12	0.004707	-2,640

Figure 1. *Decision tree of the test strategies to diagnose MODY*



4.5 It is debatable whether current economic evaluations fully appreciate the value of innovative PM approaches

It has been argued that the high prices of some types of PM, especially cell and gene therapies, are justified, as PM has benefits that are not captured in conventional cost-effectiveness analysis. As a solution, it was proposed to update the current economic evaluation framework in order to capture additional elements of value. An increasing number of countries is considering moving in this direction by requiring the adoption of a societal perspective and the inclusion of potential gains in productivity and the reduction of informal care costs. Furthermore, some countries already include equity considerations in resource allocation decisions, often by increasing the ICER threshold for end-of-life treatments, severe (life-threatening diseases), or rare diseases.

However, the debate mostly concentrates on which benefits (or elements of value) to include when measuring the value of PM. Some frequently mentioned additional elements of value which it is argued should not be included in the QALY include the value of hope, the value of a cure, real-option value, and insurance value. Individuals may indeed be willing to pay more for a treatment that – in addition to QALY gains – offers hope of being among the long-term responders, the opportunity to lead a “normal” life after being cured of a highly progressive and severely disabling disease, the option of benefiting from a future innovation, and the notion of being insured in case they require very expensive treatments. There are three main concerns associated with including these additional elements of value in economic evaluations. Firstly, there is a high risk of double counting benefits, as some of the additional elements could be (partially) captured by the QALY metric. For example, people’s hopes and dashed hopes (note that the negative impact of PM on additional elements of value is often ignored) for the future are associated with the current level of stress and anxiety that is included in the QALY. The value of being cured is already reflected in the survival gain and the quality of life during these additional

Table 5. *Stylised example of the consequence of including value of hope*

Treatment	Cost-effectiveness threshold (t)	ΔQALY	Δcost	Value of hope	Incremental net monetary benefit*
T1 (standard approach)	$50,000	2	$80,000		**$20,000**
T2	$50,000	2.5	$80,000	0	$45,000
T1 (including value of hope)	$50,000	2	$80,000	**$30,000**	**$50,000****

**Incremental net monetary benefit = (t * ΔQALY) – Δcost*

***Incremental QALYs are higher for T2. However, T1 offers "hope", while T2 does not. In this example, placing a monetary value on "hope" increases the incremental net monetary benefit of T1 from $20,000 to $50,000. This may lead to the prioritisation of T1 over T2, despite T2 offering higher QALY gains.*

years of life. Secondly, the methods for measuring additional elements of value are under development. Thirdly, there is scepticism among reimbursement authorities and academics about including additional elements of value in reimbursement decisions, as this could displace interventions that generate greater gains in length and quality of life than in the additional elements of value, as illustrated with the stylised example in Table 5.

4.6 Appropriate use of value-based PM in everyday clinical practice needs to be stimulated by incorporating cost-effectiveness considerations into clinical guidelines and decision support tools

Historically, cost-effectiveness evidence has primarily been used to inform "yes or no" reimbursement decisions, while its potential to improve efficiency in everyday clinical practice is underutilized. The results of HTA studies can also be used more often to stimulate "appropriate use" of PM in a real-world setting. "Appropriate use" of PM refers to prioritising PM interventions with proven added value over interventions without proven added value (some of which may be even potentially harmful) in the everyday clinical treatment of individual patients, ceteris paribus. This is also referred to as the provision of value-based health care. This requires increased knowledge of existing HTA evidence and behavioural change among professional care providers and patients. Such change can be enhanced through the incorporation of economic evidence in clinical guidelines, policy implementation strategies, and clinical decision support tools that stimulate the appropriate use of PM. Currently, these guidelines and tools frequently rely on the evidence of effectiveness without considering efficiency arguments. However, treatment guidelines could additionally be based on evidence about the amount of health gains per euro invested or the additional cost to the payer of deviating from the clinical guidelines. Specifically, for PM interventions that require costly testing of a large group of people to identify a few candidates for treatment, testing could be performed only after a clear distinction between relevant patients to be screened using pre-screening risk stratification strategies (similar to the MODY case study in HEcoPerMed) or only after preceding tests have ruled out other diagnoses. Another example is the clear definition of the cut-off values of a test, below which further intervention is not efficient.

4.7 The horizon of PM can be scanned and early HTA can be used to identify promising PM interventions and set future price points

Early HTA refers to HTA in the early phases of product development, usually well before a definitive evaluation of cost-effectiveness can be made and the decision for marketing authorisation by regulatory bodies. Exploring the potential value of a PM intervention at its development phase for different potential target populations can help governments, health care payers, and manufacturers to identify potential areas of future disagreement and provide them with options for action at an early stage. Due to personalization (e.g., the composite use of tests followed by an intervention) the accurate identification of these decision principles may become more complicated for PM than for traditional technologies. Stratification of patient/user pathways, evidence generation, data collection, and expectations on

the combined cost-effectiveness of test-treatment interventions are all challenging. On the other hand, when regulators and payers grant early access (e.g., Early Access Programs) to the innovative PM technologies, input from early HTA is a key determinant of decisions. There is a large degree of uncertainty around the efficacy and accuracy of PM data as often only surrogate outcomes are available and the target population and the treatment setting might change. The diagnostic accuracy of the technology is likely to vary depending on disease types and subgroups of the patient population in which the technology is applied and may change over time. Multiple personalized treatment scenarios with regards to settings, population and data may come into play, which will interact with the product development context, e.g., R&I partnerships and exit strategies. Under these circumstances, the judgement on the future of a PM intervention is greatly dependent on several unforeseen factors. Elicitation of expert opinion may have a key role, especially in setting up the direction of future development and determining the evidence that should further be generated to decrease the uncertainty of existing clinical data. Thus, the experience of analysts, decision-makers, experts and the right mixture of knowledge, assumptions, ideas and risk-assessment can be successful.

All in all, early HTA can play a crucial role in the internal decisions of manufacturers, and it will also identify points for (dis)agreement between them and regulators regarding conditional market access and reimbursement at an early stage. Demonstration of uncertainties and directions on further data collection will also be a beneficial by-product of early HTA. Early HTA will help in mapping the missing information in a structured and timely manner and can play a decisive role in the future of PM.

4.8 The use of collaborative financing models for R&I of tests and treatments in PM is urgently needed

There is a need for an appropriate financing ecosystem to enable PM to achieve its full potential and to generate a positive net benefit for society. Traditionally, academia and small and medium-sized enterprises have undertaken early R&I in PM while large scale manufacturers led the commercialisation and translation of personalised diagnostics and treatments. This financing model leads to the suboptimal reward of public institutes for investing in PM discovery and early phases of R&I, as well as to a substantial financial risk exposure of PM manufacturers to the uncertainty surrounding the development and market access phases of PM. As a result, there is limited trust between all parties involved in R&I of PM that obscures optimal investment in innovation.

This approach to research, however, is evolving and large research consortia have been consolidated that could enhance R&I for PM. Involving public and private partners in the financing for R&I of PM could not only pool together substantive investment resources but also provide opportunities for upscaling R&I, as well as sharing research facilities, databases, expertise and experience. Collaborations between academia, government, the pharmaceutical industry and charities provide promising new avenues. Examples of such collaborations include:

a) the Eisai – University College London (UCL) collaborative drug discovery alliance;

b) the Bioscreening Technology Group and the Adhiron Screening Facility utilising funding from academia, government, charities, industry and the European Commission;

c) dedicated centres for oncology research and networks of Centres of Excellence in Europe that connect academic, clinical and industrial partners, small and medium-sized enterprises, as well as governmental and non-profit organisations.

There are also collaborations between governments and the pharmaceutical industry which include pharmacogenetics research in Europe, which access core funding from governments, small industrial contracts and funds from charitable foundations. In addition, the EU Sixth Framework and FP7 Programme provided opportunities for industry to access funding under the Innovative Medicines Initiative (IMI) programme. The European Commission programmes (H2020) for Research and Innovation have also been developed to support innovative small and medium-sized enterprises in the diagnostic area.

Other examples include the International Immuno-Oncology Network that is a collaboration between Brystol Myers and the Netherlands Cancer Institute, the Dana-Farber Cancer Institute, the Royal Marsden NHS Foundation Trust, the Institute of Cancer Research and the Johns Hopkins Kimmel Cancer Centre; Pfizer, Eli Lilly, AstraZeneca and the National Institutes of Health's National Clinical and Translational Sciences programme that funds preclinical and clinical feasibility studies for new uses of shelved compounds.

Health economics can play a pivotal role in these collaborations by providing an estimate of the financial risks involved in the R&I of PM, forecasting the potential benefits for the stakeholders involved in the agreement, and recommending a system to reward each party to the agreement for the contributed investment, undertaken risks, and share of the (future)

value of the PM intervention. Such a system can be realised by linking the reimbursement/payment of PM with the financing of its R&I. For example, innovation in PM can be rewarded by accounting for and paying for value. However, it should be noted that such a reward system should be flexible with regards to the generation of new evidence related to PM value and the emergence of competing PM technologies.

4.9 Reimbursing PM based on performance could alleviate the burden of upfront payments, and share risks and benefits between payers and providers/manufacturers

Currently, PM is reimbursed via existing reimbursement models that commonly do not involve the sharing of financial risk between payers and providers or manufacturers, and do not take into account the performance (i.e., effectiveness) of PM. For example, incorporating the cost of molecular diagnostic tests into existing DRGs and using locally and nationally negotiated tariff-based payments (e.g, in EU5 countries: Germany, France, Spain, Italy and UK) can often result in underpaying or misaligning reimbursement between tests and drugs that could limit the adoption and use of these PM in clinical practice.

Reimbursing PM via performance-based agreements could alleviate the burden of upfront payments and share financial and uncertainty risk between payers and providers. Early pre-approval dialogue between payers and providers/manufacturers to agree on health outcomes that will be assessed and for which data need to be collected could help facilitate the application of performance-based agreements in practice. Coverage with evidence development is often a preliminary step to value-based pricing and reimbursement, and could be used to facilitate the reimbursement and adoption of PM while the necessary clinical and cost-effectiveness evidence is being generated. In addition, such evidence-based schemes can be used to improve patient access, address regulatory concerns, and simplify reimbursement decisions. However, it should be noted that in some healthcare systems it is easier not to grant reimbursement for a PM intervention on the first instance than to withdraw it from the market if the expected benefits are not realised. Recently, gene therapy manufacturers have increasingly offered performance-based agreements in European markets such as outcome-based rebates for treatment failure or payments in instalments for interventions including Kymriah®, Yescarta®, Zynteglo®, Zolgensma® and Strimvelis®, as well as coverage with evidence development for Kymriah® and Yescarta®.

It is generally suggested that financial-based reimbursement models, such as rebates and volume caps, can reduce the impact on the healthcare budget and improve the affordability and cost-effectiveness of new treatments. Financial-based models could also be used as an intermediate step while generating the real-world evidence of the effectiveness and benefit of PM that will help re-evaluate reimbursement decisions. Reimbursement of PM could be further improved by establishing dedicated codes for companion diagnostics and genetic tests that reflect the value of the test, aligning the reimbursement of companion diagnostics and targeted therapies by combining these into a reimbursement package, implementing performance-based models that will decrease the financial risk for payers in the case of treatment failure especially for highly priced gene, cell and targeted therapies, and using real-world data regarding the performance of the PM to re-evaluate reimbursement decisions.

4.10 Equity issues are large and unaddressed: The highly innovative area of personalised medicine makes it challenging to ensure access for all

There is also a tendency in the international domain that research funds are allocated to the development of relatively expensive genomic technologies in wealthier countries. This results in the lack of diversity in the collected genetic data which consequently leads to limited generalizability of evidence across ethnic groups, especially in less economically developed regions. There is a real threat that inequity in access to genetic research, genetic discrimination, and lack of adherence to internationally accepted prerequisites of clinical validity and utility for diagnostic and predictive genetic testing will place patients in low and middle-income countries in a disadvantaged position. Similarly, to overcome the problems of limited generalizability, population diversity in genetic databases and evaluating genetic scores in conjunction with other disease factors will be needed to ensure a more equitable impact of precision medicine.

One can anticipate that the value of PM may be higher in the most developed countries with an advanced level of health care compared to lower-income countries where quicker wins from the wider implementation of non-personalised technologies are still possible. In these jurisdictions, capacity issues, including lack of a specialised work-force and testing/analysing infrastructure, volume restrictions, administrative barriers, lack of population specific data, competency, expertise, and financial support, limit access to expensive PM therapies. However, in lower-income countries with a lower average health status, there is more potential to benefit from high-value care which would meet the vertical equity criteria of providing more access to those with more needs. While higher-income countries in the EU

struggle more with within-country variation, lower-income countries struggle with the equity issues due to their limited financial and infrastructural capacity. One example of such an issue is the reference pricing system that results in a narrow price corridor within the European community and in relatively high prices in European countries with lower purchasing power. Value-based pricing that enables price differentiation of PM between countries can offer a solution to this equity issue, but it requires solutions for other market dynamics such as parallel trade because of the free movement of goods in the EU.

There is no question that equity concerns will vary across European jurisdictions. The above examples show that the toolset of HTA and health economics needs to be applied in a stepwise, cautious manner with respect to country-specific circumstances, and that the consequent implementation of HTA methodologies will be a key prerequisite towards more equitable systems in applying PM across Europe.

4.11 Different evidence requirements of European regulatory and Member State reimbursement authorities delay access to PM

As there is limited overlap between the requirements for European medicine Agency (EMA) approval and for market access in specific Member States, discussions about pricing and reimbursement are potentially longer than necessary. EMA, responsible for assessing the quality, safety and efficacy of a drug, does not bear costs in mind and does not test relative effectiveness as they are not making decisions on reimbursement but on whether a new drug can enter the market. Therefore, evidence submitted to meet EMA requirements does not meet the requirements of several Member States in their reimbursement discussions.

The issue is pressing, as there are increasingly more decisions for market authorization of PM treatments stratified to patients with some genetic biomarkers based on single arm studies. This poses two main challenges. Firstly, the relative effectiveness of PM must be estimated using external data (as it was not collected in the trial). Without a comparator group, it is not possible to identify to what extent a new PM treatment is better than alternatives that are already on the market. However, the estimation of such a comparator is difficult when one has to rely on historical data in which the new genetic test was not included (as it is new). A typical example is the NTRK case study, where both entrectinib and larotrectinib were granted market access by EMA based on a single arm data, only to find local authorities desiring evidence on relative effectiveness, an issue that could not be informed by the trial data. Secondly, the prognostic value of the genetic biomarker is unknown: patients who test positive might have better, worse, or equal prognosis as compared to those who test negative, thereby complicating the assessment of relative effectiveness. In the NTRK case, we estimated the prognostic value of NTRK fusions in a very small number of patients to allow us to estimate a comparator arm. While this approach may constitute a short-term solution for the information needs of national decision-makers, it is a temporary solution at best.

4.12 To improve timely access to cost-effective new therapies, the economic evaluations of PM should be conducted earlier and be shared among EU Member States

While there are public efforts such as EUnetHTA to establish relative efficacy reports, such efforts are not present for economic evaluations, most likely because EU member states differ in opinion about what constitutes a fair price for a new PM intervention as a result of the national decision-making context (such as different national comparators and country-specific societal preferences). Interestingly, the resulting practice is that pharmaceutical companies develop evidence (a central or “global” cost-effectiveness model) that is subsequently submitted to several Member States after some input variables have been adapted to meet national requirements. Independent research is also performed in the academic setting, but this is usually undertaken separately and often does not form any part of the discussions about the value of PM between payers and manufacturers. It is unclear as to why there is no place for the development of a core European economic evaluation model that can be adapted to the national needs of Member States. Such an effort would allow increased transparency on input data and can be developed during EMA procedures to speed up subsequent negotiations between industry and Member States. This is particularly relevant in the context of PM, where an upfront recognition of data limitations and estimates of cost-effectiveness can help identify where current reimbursement frameworks might not be fit for purpose. Recent initiatives such as horizon scanning and purchasing partnerships between Member States indicate that collaboration is possible and should be stimulated.

Centralized assessment, however, still faces issues in connection with the transferability of assumptions, input data and outcome validation. It is essential to separate the transferability of data and methodology from the transferability of recommendations and policy decisions. Consistent methodology can increase the transparency of assessment while decreasing the need for human and financial resources. On the other hand, directly transferring HTA recommen-

dations or policy decisions across countries with potentially different health-care priorities can lead to suboptimal allocation decisions in the local markets.

EUnetHTA was a first and important development in the harmonization of methodologies across countries. They developed the “HTA Core Model” to focus on the joint production of relative effectiveness assessments, which can be used as a basis for national value assessments. As such, the HTA Core Model aims to standardize reporting of HTA, as well as to standardize the effectiveness input data where possible. The approach encourages explicit consideration of the transferability of relative effectiveness assessment across countries and recommends national HTA assessment based on similar methodologies, which ultimately reduces duplication of efforts while adhering to key scientific principles.

When applied to PM, a collective approach to assess the value for money of PM interventions could facilitate the development of joint efforts by member states to strengthen public-private partnerships for financing R&I of PM at EU level that provide larger rewards for investment, share risks among a larger pool of involved parties, and exploit value of synergies (e.g., due to economies of scale). In addition, such an EU-wide HTA model could form the base of unifying reimbursement of PM across the EU by adopting a reimbursement model that accounts for widely agreed elements of value, secures equity between member states, and fulfils the appetite of manufacturers for large markets. Avoiding duplication of work would be even more beneficial for lower-income countries that generally have a worse health status and less public resources for health care. Therefore, they have an even greater need to make well thought-out, evidence-based policy decisions. Joint HTA work organised in a permanent system would strongly support scientific accuracy and the policy relevance of HTA recommendations in all EU countries.

5 CONCLUSION

In all healthcare systems, both in the EU and beyond the EU, healthcare interventions compete for the same financial, technical, and human resources. An economic evaluation can help identify interventions that produce the most health within a given budget and prioritise the allocation of resources to them.

When performing an economic evaluation of PM, a comparison should be made between the new situation, in which PM is implemented, and the current situation. To fully inform policy-makers on the new situation, all changes to the care pathway that are needed for the identification, stratification, and treatment of eligible patients need to be accounted for and all downstream cost and benefits need to be reported. Consequently, the costs of introducing PM may be larger than usually identified. That specifically applies to expensive drugs that require wide-scale expensive upfront testing for rare biomarkers. On the other hand, there seems to be a large and probably underused potential to improve health and reduce costs by informed targeting of existing therapies. In essence, that would increase the cost-effectiveness of current treatments and, therefore, the efficiency levels of the entire healthcare system. To improve timely access to cost-effective new PM interventions, economic evaluations of PM should be conducted earlier and be shared among EU Member States. Furthermore, evidence requirements of European regulatory and reimbursement authorities should be better aligned. However, there are ongoing discussions as to what extent the cost-effectiveness models are suitable to establish the long-term benefits of PM and capture all elements of the value of PM. Our current cost-effectiveness analyses focus on static efficiency. The time horizon is commonly that of the lifetime of a fixed cohort of patients, while the life cycle of a technology used in PM might be longer or shorter. Moving towards dynamic efficiency would likely stimulate and reward innovation but at the expense of access to current interventions. Likewise, including additional elements of value could displace interventions that generate greater gains in length and quality of life than in the additional elements of value. HTA researchers should contribute to raising awareness of this debate among policy-makers. Appropriate use of PM can be enhanced, using not only cost-effectiveness data in reimbursement decisions, but also through the incorporation of this evidence in clinical guidelines, policy implementation strategies, and clinical decision support tools. It can be further enhanced by the wider adoption of innovative payment and reimbursement models that accelerate access in exchange for sharing of risks.

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Financial incentives to promote personalised medicine in Europe: an overview and guidance for implementation

8 IMPRINT

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EcoPerMed
Health Economic Models for Personalised Medicine




THE FUTURE OF PERSONALISED MEDICINE

Short scenarios

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ABOUT HECOPERMED

PERSONALISED MEDICINE

With increasing and ongoing pressure on healthcare budgets in Europe, personalised medicine is the hope of many patients, healthcare professionals and policy makers. Personalised medicine aims to optimally match patient and treatment by assessing the characteristics of patients for whom treatments achieve the best results. In this way, personalised medicine reflects a paradigm shift in healthcare, as it no longer emphasises the effects on group averages, but on the individual differences between patients through in-depth phenotyping. Behind the call for personalised medicine is the implicit promise that healthcare will become more cost-effective through more targeted treatments.

HECOPERMED PROJECT

The Horizon 2020 funded HEcoPerMed project (Health care- and pharma economic models in support of the International Consortium for Personalised Medicine) responds to the demand for economic models that evaluate treatments enabled by innovations in personalised medicine and seeks to identify funding and reimbursement mechanisms that provide financial incentives for the rapid development and adoption of such innovations. HEcoPerMed goes beyond current assessment and payment models to serve the requirements of personalised medicine for more comprehensive cost-effectiveness estimates that incorporate patient and societal perspectives and improve the sustainable affordability of cutting-edge health innovations. HEcoPerMed aims to identify the best modelling and payment strategies for personalised medicine to distinguish between promise and reality.

HECOPERMED SCENARIOS

To demonstrate the value of state-of-the art economic modelling and appropriate financial agreements, HEcoPerMed has created future scenarios that consider, on the one hand, the trends, and drivers, and, on the other hand, the challenges, and benefits of personalised medicine for the European social model of healthcare and its financial viability.

The aim of the HEcoPerMed scenarios is to tell parallel stories of what different futures of personalised medicine might look like from a wider societal perspective. The scenarios are by no means predictions. Rather, the scenarios developed represent plausible alternatives in which different aspects dominate. Scenarios create links between future assessments (i.e., trends, drivers) of a variety of stakeholders and participants in the scenario process and can thus create pictures of the future with greater density and diversity, going far beyond a stringing together of individual trends. Linking trends and drivers in scenarios makes framework conditions and critical issues visible where development could go in different directions. This perspective is especially important for policy makers.

STAKEHOLDER PARTICIPATION

Stakeholders were an integral part of the project through participation in workshops and interviews and had the opportunity to contribute to the scenario building process, to assess the scenarios and elaborate further options for strategy development and policy implications.

We would like to thank all experts participating in the scenario process, especially our HEcoPerMed consortium partners, the advisory board, interview partners and workshop participants for providing valuable information, feedback and context.

SCENARIO: PRIVATIZATION – BOUTIQUE MEDICINE VS. AUTOMATED MEDICINE

Healthcare is largely privatised. The public sector has retreated from supporting a tax-based health system due to ever rising costs. Personalised medicine is something for wealthy people who do "health shopping" on an international scale. Most of the investments for personalised medicine come from the private sector.

SOCIETY

The European social system is reaching its financial limit. Personalised medicine has made considerable progress in diagnostics and treatment of diseases, and a number of personalised medicine therapies are available. However, medical innovation is cost-increasing rather than cost-saving.

HEALTH CARE

The public sector has withdrawn from supporting a tax-based health system due to the ever-increasing costs. A growing proportion of medical care is now based on genome screening and related therapies. Many of the expensive therapies of personalised medicine are only affordable for wealthy people. The emergence of "boutique medicine", where the wealthy patients choose appropriate and tailored treatment, is leading to increasing inequalities in health outcomes between a small segment of wealthy people and the poorer majority who mainly access standard health services. As a result, the rich live longer and healthier lives than the poor because they have access to quality hospitals and therapies. The inequity between the small rich

segment and the large poor segment starts already at a young age because rich people can afford a full genomic sequencing right after birth, and their medical treatment is based on this analysis throughout their lives. From the patient's point of view, the free market allows international shopping for the best tests and treatments and offers a variety of solutions for all those who can afford it.

However, stratified medicine based on Big Data, referred to as "automatic medicine", makes diagnostics and treatment more efficient and cheaper than ever before, benefiting the larger part of the population that cannot afford boutique medicine.

INSURANCE

Private insurance, affordable only to a few, can hardly compensate the existing care deficit. Multinational, diversified companies, which incorporate insurance and pharmaceutical companies, offer a pan-European insurance plan and global health care.

FINANCING & BUSINESS

Medical and technological breakthroughs are provided by public research institutes and universities. Research and development is usually funded with public money. There is no government regulation of prices for specific and personalised treatments or tests.

The small percentage of boutique medicine followers are willing to pay a high price for comprehensive analysis of their health data, which creates incentives for start-ups to develop rapid tests and reliable interpretations. The role of private players in the production and delivery of health services is increasing. They might be willing to lower the prices for treatments in exchange for personal data from (potential) clients.

To provide more incentives to invest in personalised medicine, patent protection has been limited and the costs of research and development have been distributed.

SCENARIO: TECHNOLOGY-DRIVEN – PERSONALISED MEDICINE BY SUBSCRIPTION

Public and private funds are available for technological progress including personalised medicine. Sharing one's own data is the entry point to the healthcare system. Technology-driven medicine that uses e.g., Internet of Things with sensors everywhere allows more flexible healthcare. Rapid decline in genome sequencing costs has made it affordable for everyone and genome screening is expected by everyone.

SOCIETY

The European social system strives for cure for all and at all costs. The top priority of the health care system is to do whatever it takes to prolong life, even if this means that the number of chronically ill people and those in need of intensive care is increasing sharply.

Patients have great trust in technology-driven medicine and the achievements of personalised medicine because of unprecedented advances in biotechnology and medical technology, such as artificial intelligence, quantum computing, Internet of Things, and new methods for analysing and visualising biological functional levels (genomics, proteomics, metabolomics, etc.).

HEALTH CARE

Healthcare professionals are more concerned with genetic deficiencies than with treating people or preventing other illnesses. Processing costs for genome screening are low, and it has become easy to

obtain enormous amounts of biological data. Health data is owned by the collecting institution, and these data companies have become the major players in the health system. Patients willingly provide these companies and pharmaceutical companies with their health data, be it genetic or physiological and behavioural determinants from wearable and (implanted) body sensors. They are convinced that in this way the healthcare system can cure every affliction in the long run. For fear of a predisposition to a genetic disease, citizens are willing to participate in many of the numerous screening programs. A trigger for the extensive sharing of personal health data is also the fact that it is a prerequisite for patients' access to medical treatment. Everyone is under great social pressure to take personal responsibility for their own health, e.g. by proactively undergoing screening programmes.

INSURANCE

Despite tax-funded health insurance schemes, private insurance is becoming common practice because possible genetic diseases or unfavourable epigenetic patterns can never be ruled out, even in healthy people. The focus of healthcare on the genetic causes of health problems has led to the creation of "genetic insurances" that cover all problems arising from a person's genetic pattern. The "Geneflix model" (in reference to the media service Netflix) is the new business model of insurance companies. People take out subscriptions that make them direct payers for research and development on the one hand, and owners of the results, i.e. the free research and development services for treatment, on the other hand.

FINANCING & BUSINESS

Public and private funds are available for technological progress including personalised medicine. The government is committed to maximise the quality of healthcare and takes a "whatever it costs" approach. It also places great trust in personalised medicine to combat any disease and financially supports screening programmes and research in data-intensive healthcare.

Private companies offering screenings at low cost are flourishing. As technologies are often privately owned, care is becoming increasingly commercialised.

SCENARIO: COOPERATION - PERSONALISED AND HOLISTIC MEDICINE

Personalised medicine advances through open and intense cooperation between all actors within the health sector: science, policy, insurance, pharma industry, SMEs, patient organisations. There is a worldwide exchange of health data. The population is quite healthy due to the excellent healthcare system. People are working longer and extending their working lives to finance the high public spending for healthcare.

SOCIETY

The European social system benefits from the overall economic growth. Technological and social innovations have contributed to economic growth with far-reaching positive socio-economic effects on society. The society has a strong sense of community. Every citizen should benefit from the wealth of the country. The population is quite healthy thanks to the excellent healthcare system. However, to finance the high public spending for healthcare, people are working longer and extending their working lives.

HEALTH CARE

Previous crises, such as the COVID-19 pandemic, have underlined the importance of the services provided by health professionals and raised their social prestige. Not only the sick, but also the elderly people and those in need of care who live at home benefit from the high number of people working in the health sector now.

The cooperation and collaboration of all healthcare actors, e.g. patients and patient organizations, doctors, researchers, insurers, medical technology

companies, innovators/start-ups, public funding organisations for health research, health policy makers and related policies, bring together a diversity of knowledge and perspectives and thus increase the benefits of personalised medicine for patients. Transnational alliances for personalised medicine have been fostered to pool knowledge and available resources in specialised transnational centres and reduce the costs for diagnostics in large-scale settings. These centres benefit from the fact that countries worldwide, and to some extent, pharmaceutical companies, support open data policies and make health data openly available worldwide.

Databases for health data are interconnected worldwide and regular data sharing between most countries is now common practice. In general, there is trust in the government and other data owners regarding the security of medical data, as there are strict national and international regulations governing the handling and use of sensitive medical data. All citizens are required to provide their health data to public health centres if they wish to access the state health insurance system scheme.

INSURANCE

The majority of the population uses the tax-based public health insurance system. The entire health care system is based on the "Singapore model", which provides every patient with every type of medical treatment, including personalised medicine. It comprises public and private health insurance schemes, both of which cover the costs of high-quality medical care. Health insurance and benefits depend on a citizen's national status. While Europeans are entitled to subsidised public health services through a compulsory national savings scheme, employed non-Europeans can only use private insurance to cover themselves and their dependents.

FINANCING & BUSINESS

The population is taxed heavily to provide the resources for the healthcare system. In the long run, health insurers expect to save money by restricting certain treatments to patients who are most likely to benefit from the therapy. The people expect the government to reallocate budgetary resources from other sectors of the economy to the health sector. Health policy makers are still working to develop new business models and incentives for pharmaceutical companies to collaborate more closely with public centres in a public-private partnership and to balance the research and development costs of personalised medicine developments and the development risks between the public funders and the business entity who commercializes the medical product or treatment.

SCENARIO: SCEPTICISM - PERSONALISED MEDICINE IN A NICHE

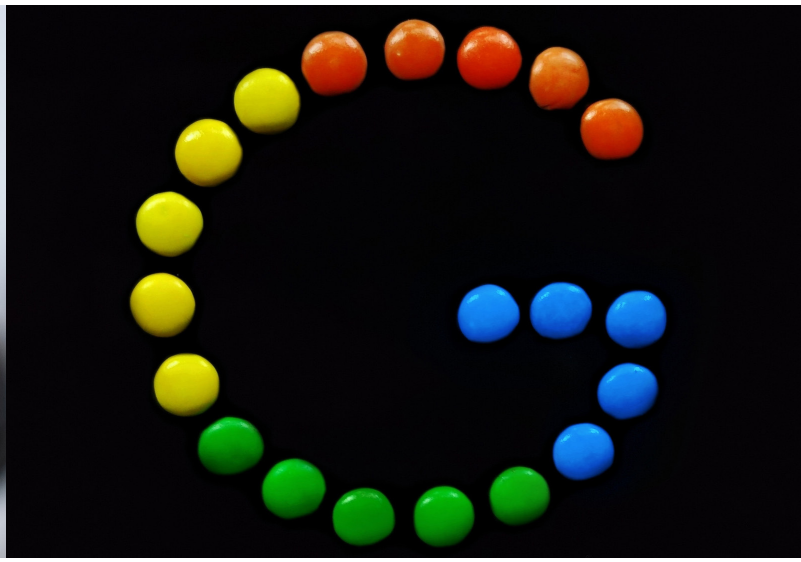
The society is increasingly questioning evidence-based healthcare and has little trust in data-driven health-care systems due to expected data breaches. The health insurance system is solidarity-based but does not provide much funding for advanced medical research, treatment, or personalised medicine.

SOCIETY

The European social system and the society in general is sceptic about innovations, including personalised medicine.

Some private initiatives try to counter the scepticism by strengthening health literacy in relation to personalised medicine, e.g. by involving international celebrities who show how personalised medicine has helped them. These initiatives also argue that good regulations on data ownership and privacy issues could counterbalance the concerns of citizens who do not want to share their health data and fear data breaches. In general, the notion prevails that "the data belongs to me" and should not be shared at a level where individuals can no longer control data use anymore.

At international level, countries are experiencing their isolation from other EU countries and beyond since politicians tend to pursue protectionist strategies. For the health sector, this means less access to treatments developed abroad.



HEALTH CARE

The emphasis is on prevention and healthy lifestyles, which are supported by government agencies and employers.

Blockbuster drugs are more widely used than any personalised medicine because they are more lucrative for pharma companies and more trusted by patients. Personalised medicine, on the other hand, brings with it a new form of threat, namely that of being one of the non-responders and therefore being denied treatment.

This impression is reinforced by the international trend that healthcare treatment is becoming a very expensive undertaking worldwide. Through mergers and acquisitions, the pharmaceutical market has become more and more consolidated, and eventually some pharmaceutical companies have become part of "Google Health" and "Amazon Care".

INSURANCE

The health insurance system is solidarity based but does not provide much funding for advanced medical research, treatment, or personalised medicine. Instead, social networks are very tight, which means that family and community provide support structure for those in need. Most elderly people are cared for by their relatives rather than in nursing homes.

FINANCING & BUSINESS

In this sceptical society, there is less private investment in personalised medicine, but more public investment in long-term care and "warm care", in line with the idea that loss of length of life is compensated by a better quality of life.
There are some private companies producing blockbuster drugs. And, since the COVID-19 pandemic in 2020, there are also public-private enterprises in which the state holds a significant number of shares. This approach has helped set the research and development direction and funding to produce the medication needed to contain epidemics and to copycat therapies of already approved drugs and therapies.

A lag in personalised medicine research is not considered to be a bad thing; in contrary, with a certain time lag there is an opportunity to adopt evidence-based personalised medicine from other countries and benefit from these experiences. Only when personalised medicine therapies are proven to be safe and affordable, health policy makers tend to include them in national health plans.
Among the new proposals to counter scepticism is that patents be owned by universities, public institutions, and governments, not industry.

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