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

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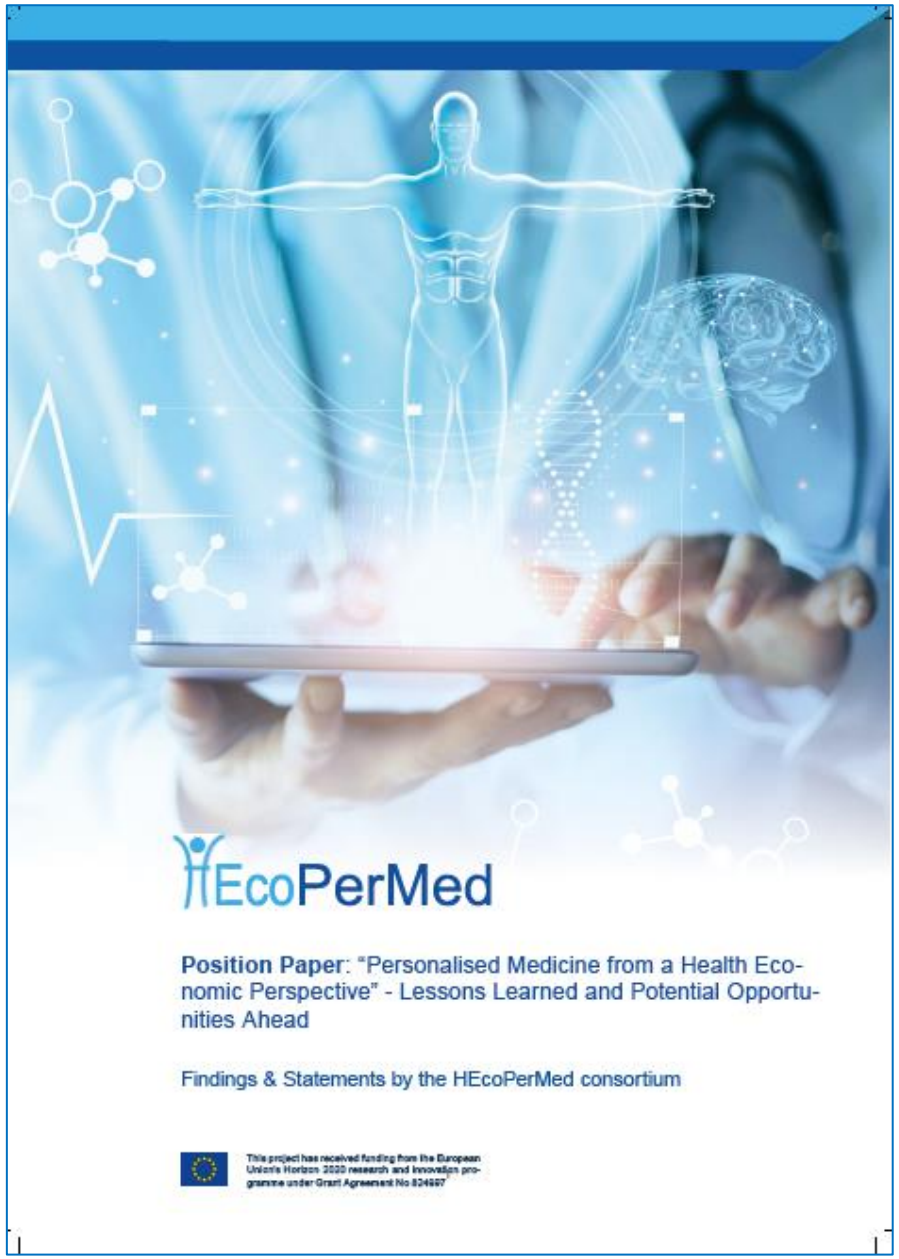
EcoPerMed
Position Paper: "Personalised Medicine from a Health Economic Perspective" - Lessons Learned and Potential Opportunities Ahead
Findings & Statements by the HEcoPerMed consortium
This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824697

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

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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

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- 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

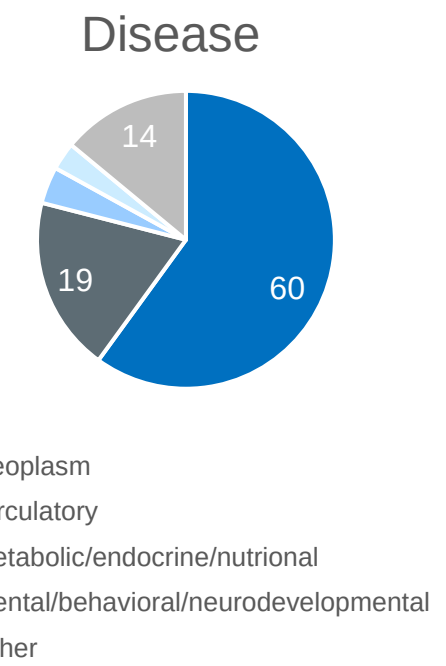
ScienceDirect

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

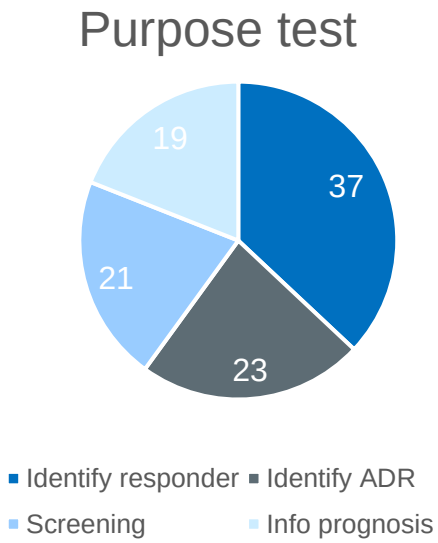
Heleen Vellekoop, MSc, Matthijs Versteegh, PhD, Simone Huygens, PhD, Isaac Corro Ramos, PhD, László Szilberhorn, PhD, Tamás Zelei, PhD, Balázs Nagy, PhD, Apostolos Tsiachristas, PhD, Rositsa Koleva-Kolarova, PhD, Sarah Wordsworth, PhD, Maureen Rutten-van Mölken, PhD, on behalf of the HEcoPerMed consortium



- 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)

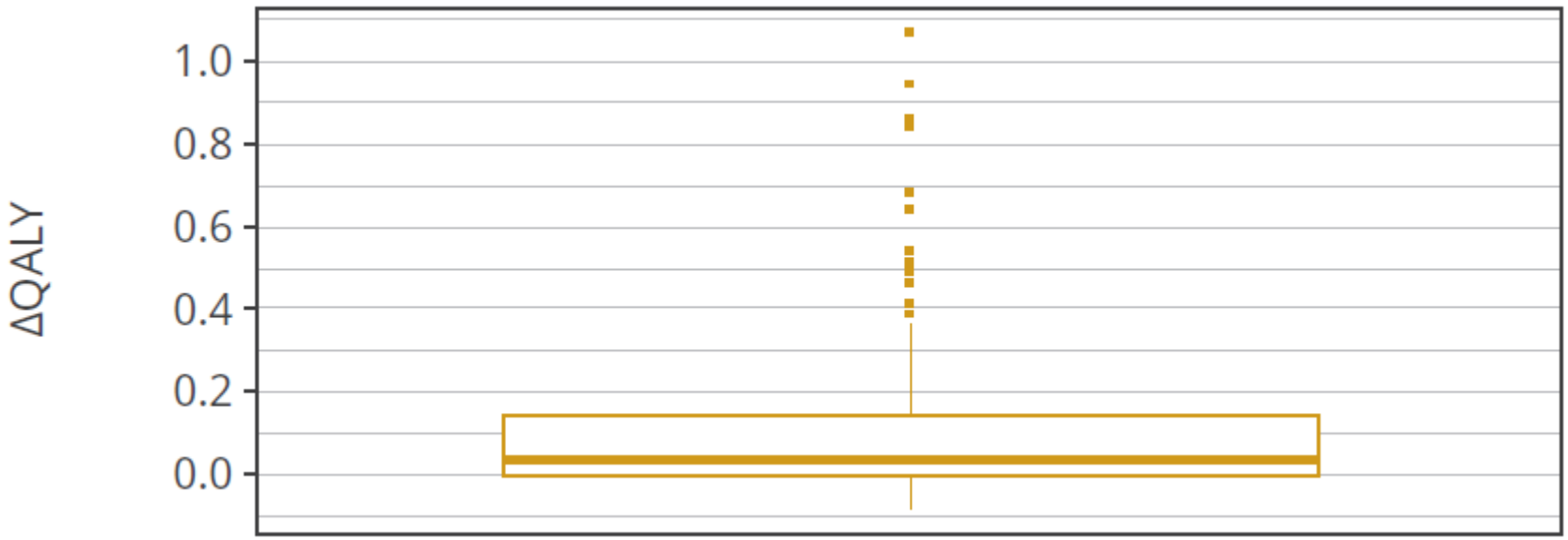
PERSONALISED MEDICINE (TEST-TREATMENT COMBI)

- 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

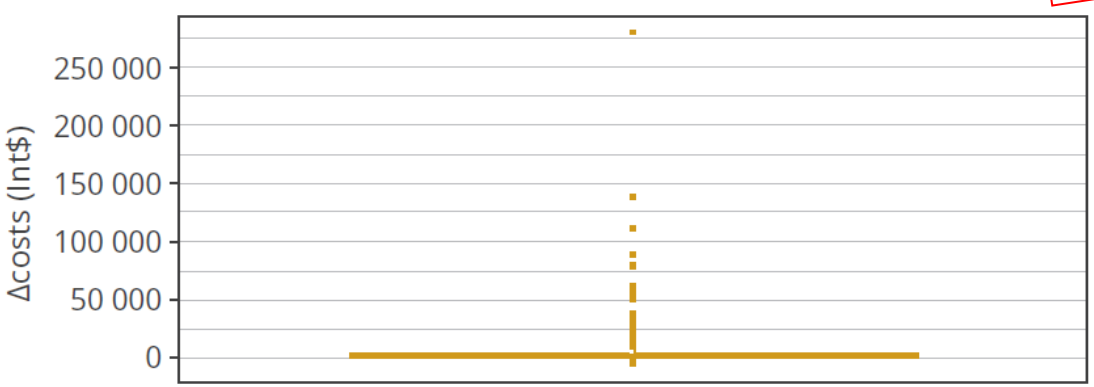
HEALTH GAINS FOR AN INDIVIDUAL DO NOT AUTOMATICALLY TRANSLATE INTO SUBSTANTIAL ADDED VALUE FOR SOCIETY

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

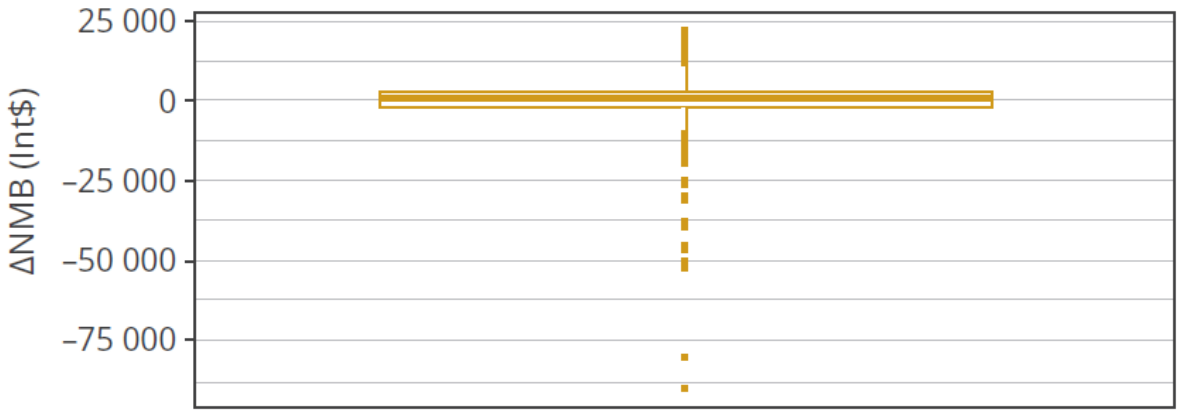
Cost mean: 99,777, median 575, max 8.1 mln

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

CASE STUDY: TRK-INHIBITOR ENTRECTINIB

With testing

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

Without testing

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

THERE IS A WORLD TO WIN WHEN USING GENETIC TESTS TO BETTER STRATIFY PATIENTS TO **ESTABLISHED** RATHER THAN NEW THERAPIES

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."

CASE STUDY: TOXNAV® DNA-TEST

***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

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%

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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

TOOLS TO MEASURE ADDITIONAL ELEMENTS OF VALUE

iMTA

Study types | Questionnaires | Publications | Tools
Clinical Areas | HEOR Courses | News | Team
Contact us →

iDBC

Tools
- iDBC ›
- PAID ›
- Costing tool ›
- iCARE ›

An easy tool to calculate burden of disease

A free online R-based calculator

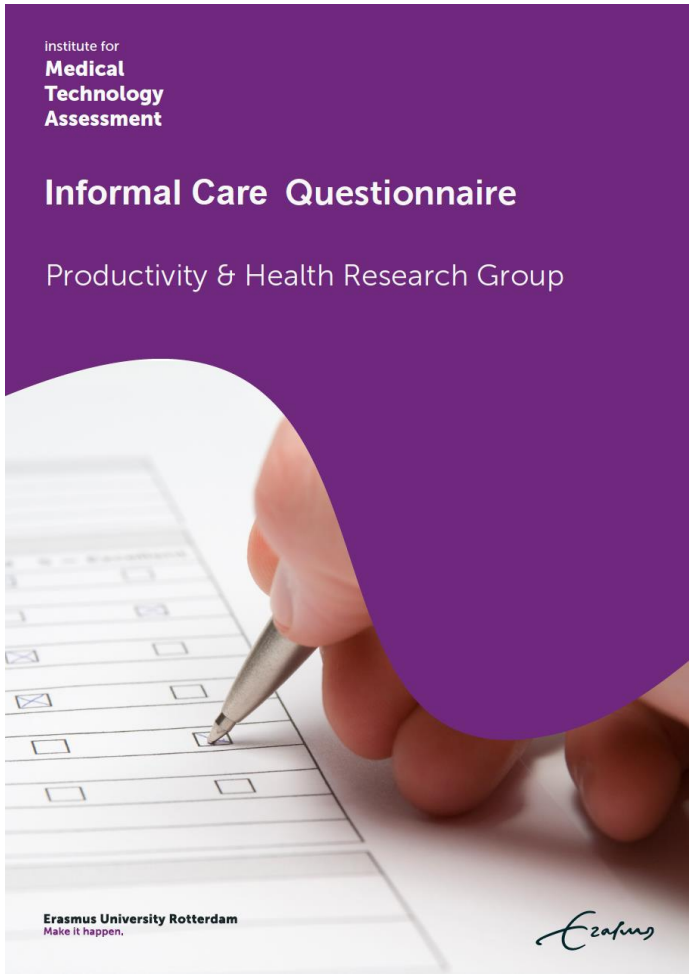
In The Netherlands, the cost-utility threshold depends on burden of disease: when a condition has a higher burden of disease, a higher threshold applies. The highest threshold is 80,000 euro per Quality Adjusted Life Year, which applies for conditions with a high burden of disease.

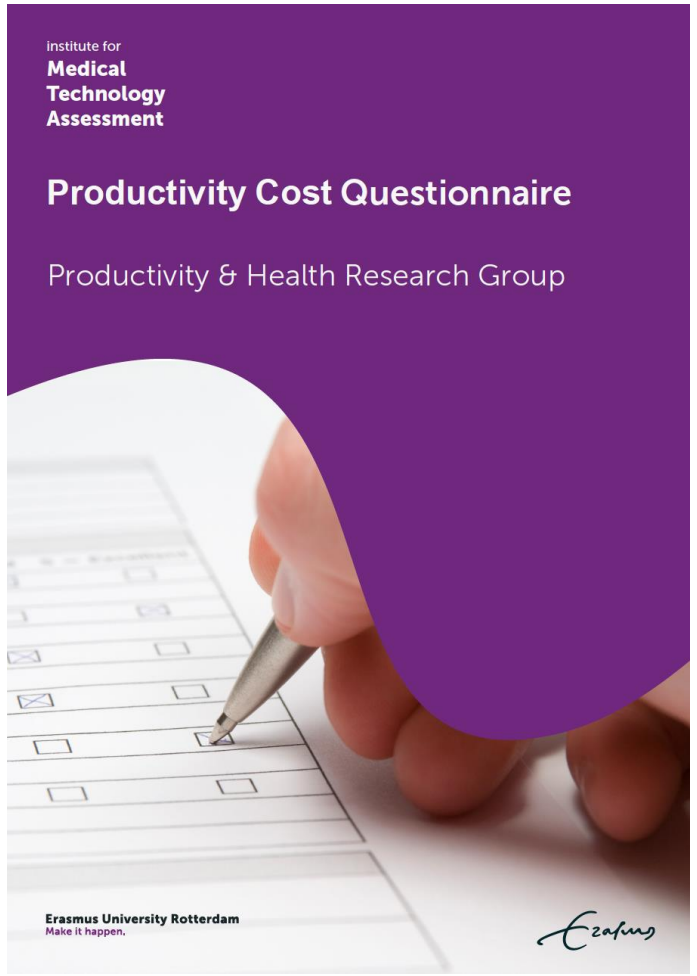
An important challenge is the uniform assessment of burden of disease. iMTA developed a practical tool that can be used in to calculate the 'proportional shortfall' of a condition and the 'absolute shortfall' of a condition. The tool is referred to as the iMTA Disease Burden Calculator (iDBC) and enhances a uniform assessment.

The iDBC is available for the following countries:

- Netherlands
- USA
- Spain
- Germany
- UK
- Norway

The iDBC is available here.





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

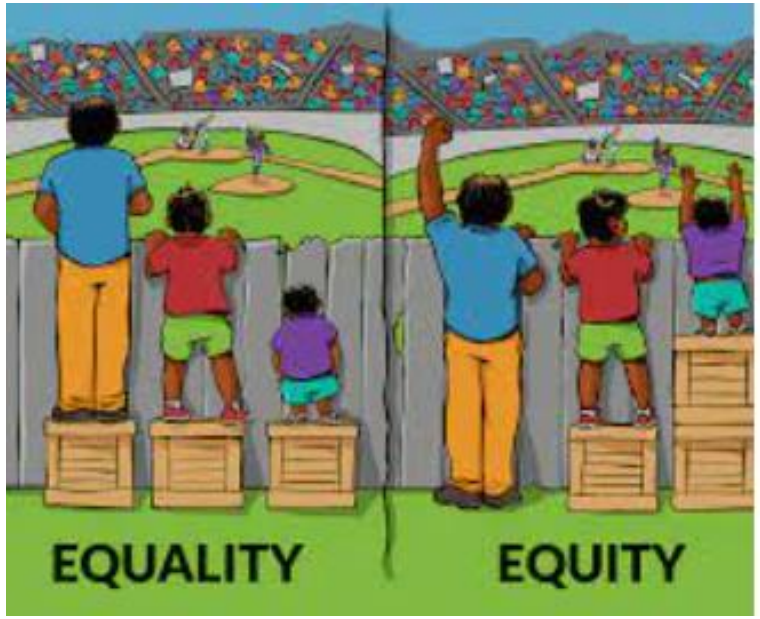
Threshold €50,000

Treatment	QALY	cost	Value of hope	Net Health Benefit
Standard CEA				
A	2	€80,000	-	+0.4
B (would be adopted)	2.5	€80,000	-	+0.9
CEA incl. Value of hope				
A (would be adopted)	2	€80,000	€30,000	+1
B	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

JUST PROVIDING EVIDENCE IS NOT SUFFICIENT

- We need **implementation-strategies** that stimulate the adoption of proven cost-effective PM
- Requires a **behavioral change** among professional care providers and patients
- Incorporate economic evidence in **clinical guidelines and clinical decision support tools** that stimulate the appropriate use of PM (i.e., value-base health care)
- Incentivizing appropriate use of PM by designing **appropriate payment and reimbursement models**
  - **dedicated codes** for companion diagnostics and genetic tests that reflect their value
  - aligning the reimbursement of companion diagnostics and targeted therapies by combining these into a **reimbursement packag**e
  - implementing **performance-based payment models** that will decrease the financial risk for payers in the case of treatment failure especially for highly priced gene, cell and targeted therapies
  - agreements on **coverage with evidence development** to generate real-world data regarding the performance of the PM to re-evaluate reimbursement decisions

Applied Health Economics and Health Policy
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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

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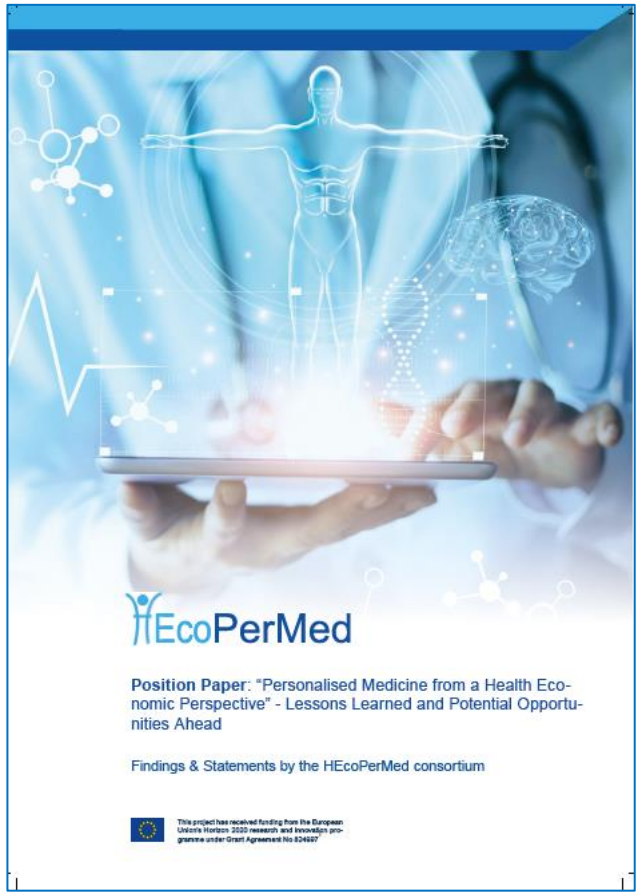
THANK YOU!

@hecopermed

m.rutten@eshpm.eur.nl



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