EcoPerMed
Health Economics for Personalised Medicine

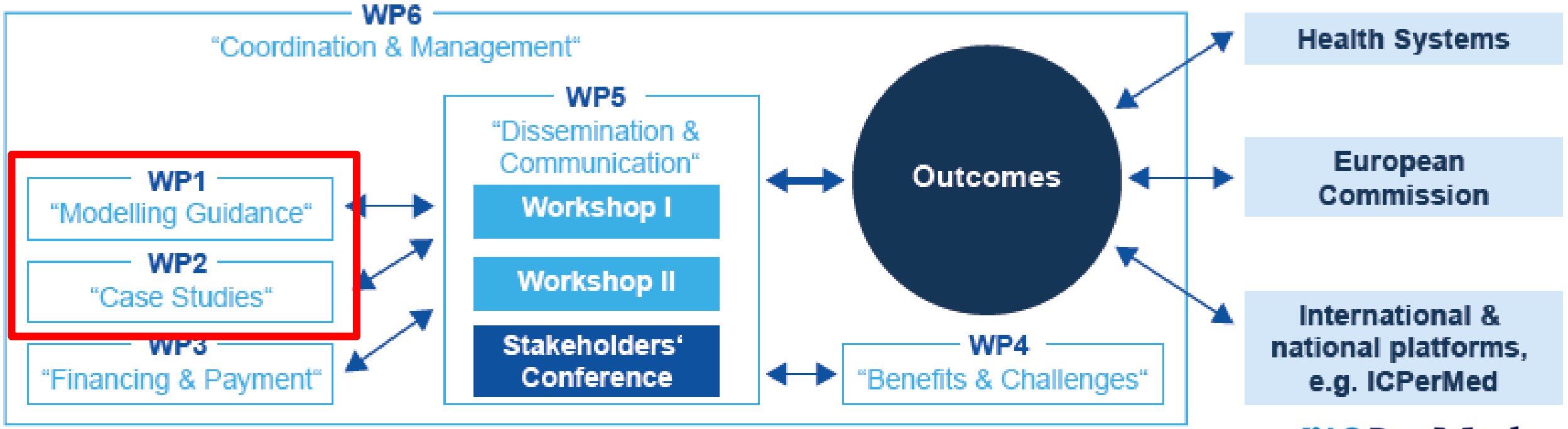
The net benefit of personalized medicine

Heleen Vellekoop, Simone Huygens, Matthijs Versteegh, Maureen Rutten-van Mölken (IMTA/EUR)
László Szilberhorn, Tamás Zelei, Balázs Nagy (Syreon)
Rositsa Koleva-Kolarova, Apostolos Tsiachristas, Sarah Wordsworth (UOXF)
Maren Wallenbach & Wolfgang Ballensiefen (DLR)
Doris Schartinger & Manuela Kienegger

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

INTRODUCTION TO HECOPERMED

The comprehensive approach of HEcoPerMed will fill a gap identified by the ‘International Consortium for ‘Personalised Medicine’ (ICPerMed) and support their efforts in the evaluation and promotion of personalised medicine in Europe and beyond.



GUIDANCE ON HE-MODELLING OF PM

- 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.

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

SYSTEMATIC REVIEW

Check for updates

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

EXAMPLES OF RECOMMENDATIONS

TEST-TREATMENT COMBINATIONS

- When a new treatment requires the introduction of a(n additional) test to stratify patients into eligible and non-eligible patients, the test affects the cost-effectiveness of the treatment. Hence, we should evaluate the test-treatment combination.
- The following consequences should be included in the economic evaluation of the treatment:
  - **Costs of the test** (if the test is not part of standard care);
  - Testing costs for **all tested patients** (including those with negative test results);
  - **Adverse events** of testing;
  - **Further testing and treatment** stimulated by the test results;
  - **False-positive and –negatives** may face poorer health outcomes leading to additional costs.

9. When a treatment requires the use of a test to stratify patients, include the **(downstream) costs and health outcomes of testing** for both individuals who test **positive** and individuals who test **negative** in the model.

REVIEW *NET* BENEFIT OF PM

ELSEVIER

ScienceDirect

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

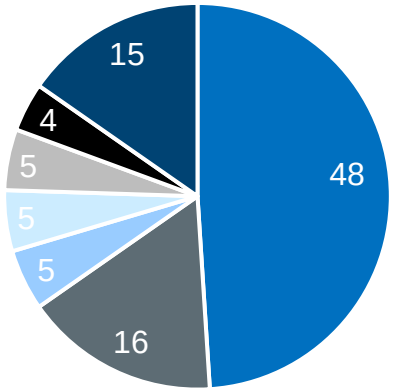
Systematic Literature Review

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

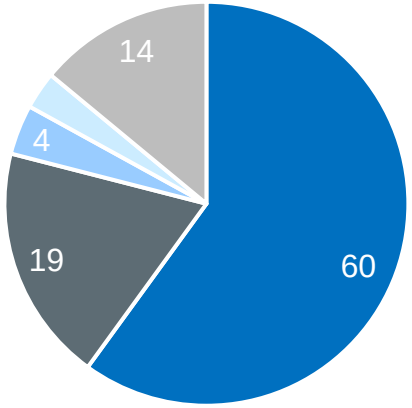
REVIEW 279 PM INTERVENTIONS / 128 STUDIES 2009-2019

Country



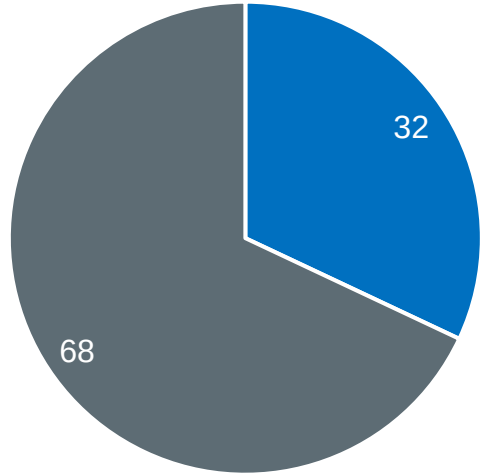
US
UK
Germany
China
Netherlands
Canada
Other

Disease



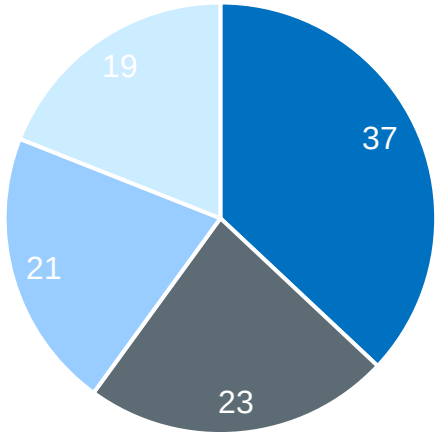
Neoplasm
Circulatory
Metabolic/endocrine/nutrional
Mental/behavioral/neurodevelopmental
Other

Industry sponsored



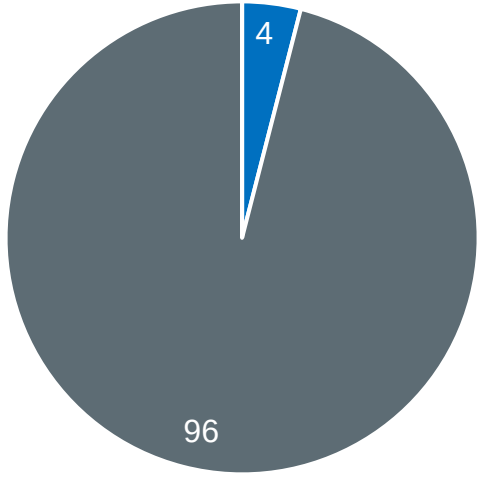
Yes
No

Purpose test



Identify responder
Identify ADR
Screening
Info prognosis

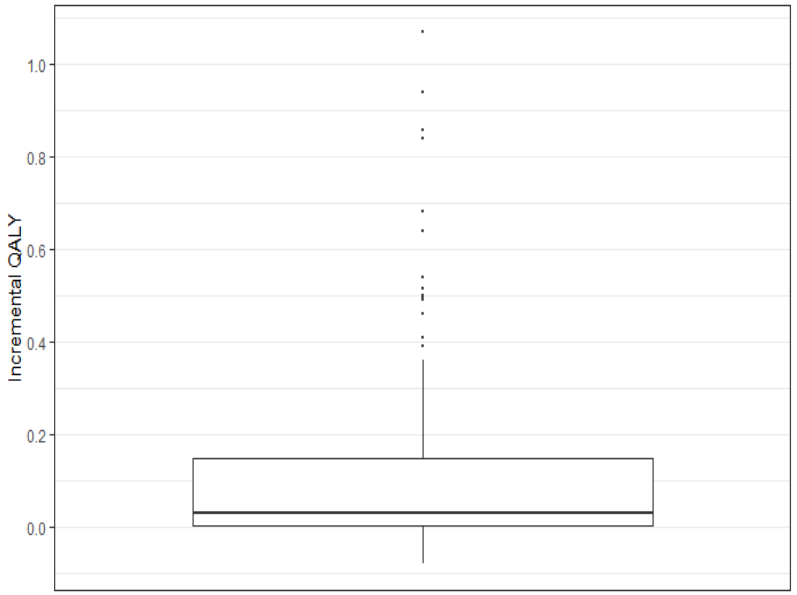
Gene therapy



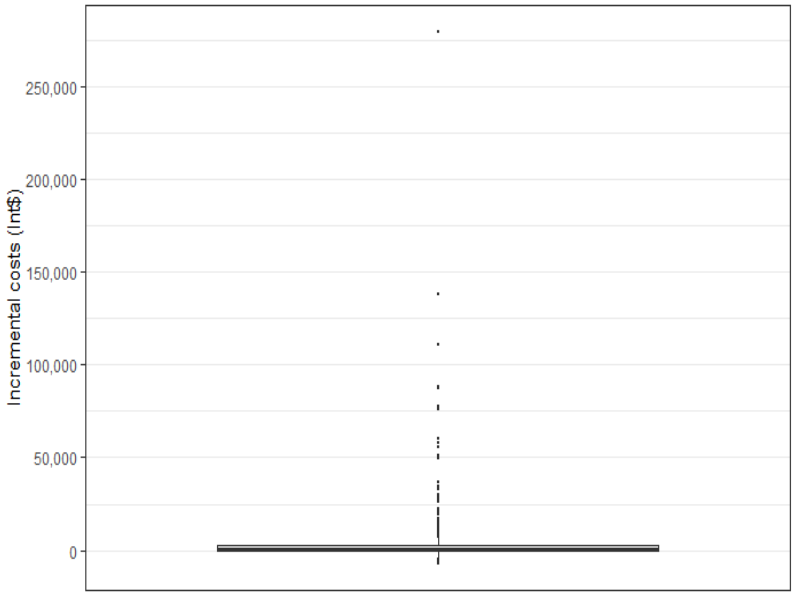
Yes
No

INCREMENTAL QALY, COST (INT$ 2020), NMB (INT$) OF PM VS NON-PM (HC PERSPECTIVE)

QALY mean: 0.26, median 0.03

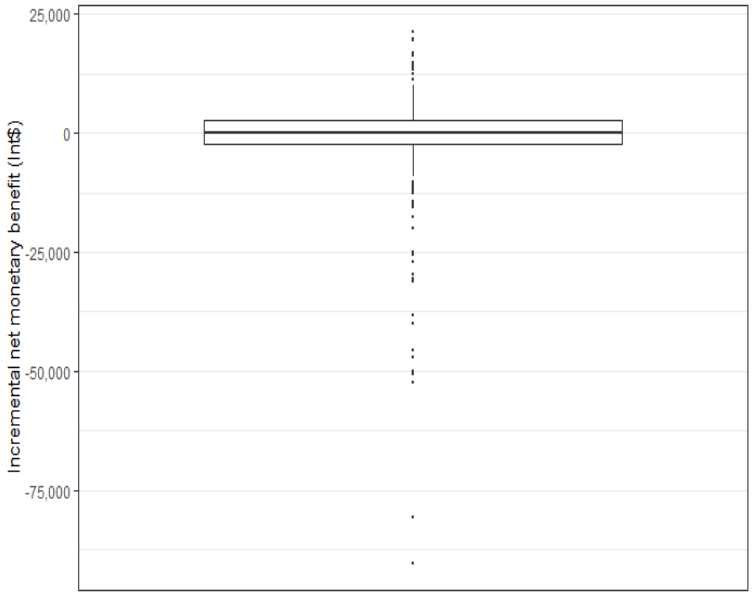


Cost mean: 99,777, median 575



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

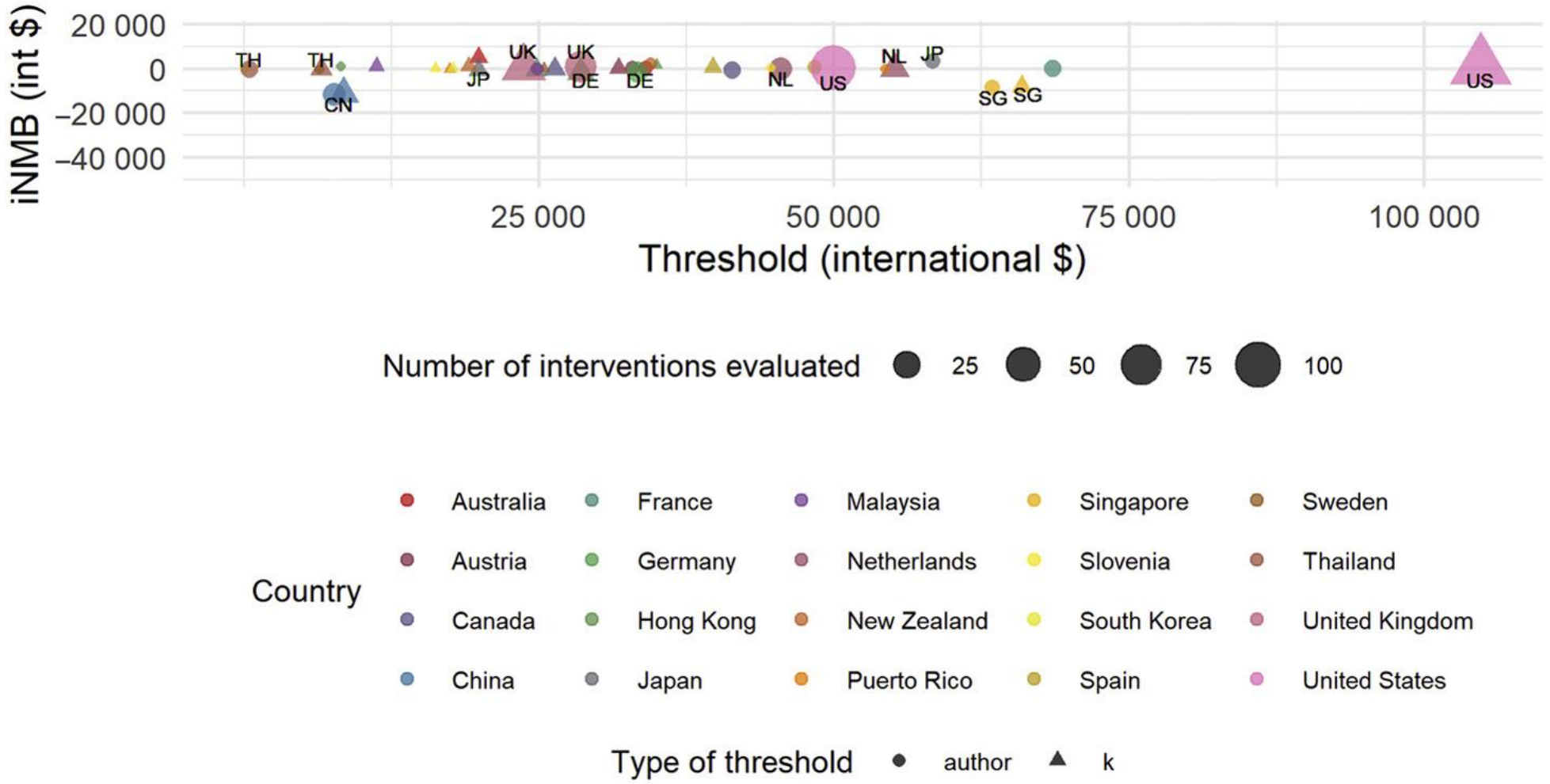
NMB mean: -77,072, median 18



$\Delta NMB_{ij} = \Delta h_i * k_j - \Delta c_{ij}$, 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

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

FINDINGS SIMILAR ACROSS COUNTRIES



Vellekoop H, Versteegh M, Huygens S, Ramos IC, Szilberhorn L, Zelei T, Nagy B, Tsiachristas A, Koleva-Kolarova R, Wordsworth S, Rutten-van Mölken M. The Net Benefit of Personalized Medicine: A Systematic Literature Review and Regression Analysis. Value in Health. 2022 Mar 2.

HETEROGENEITY

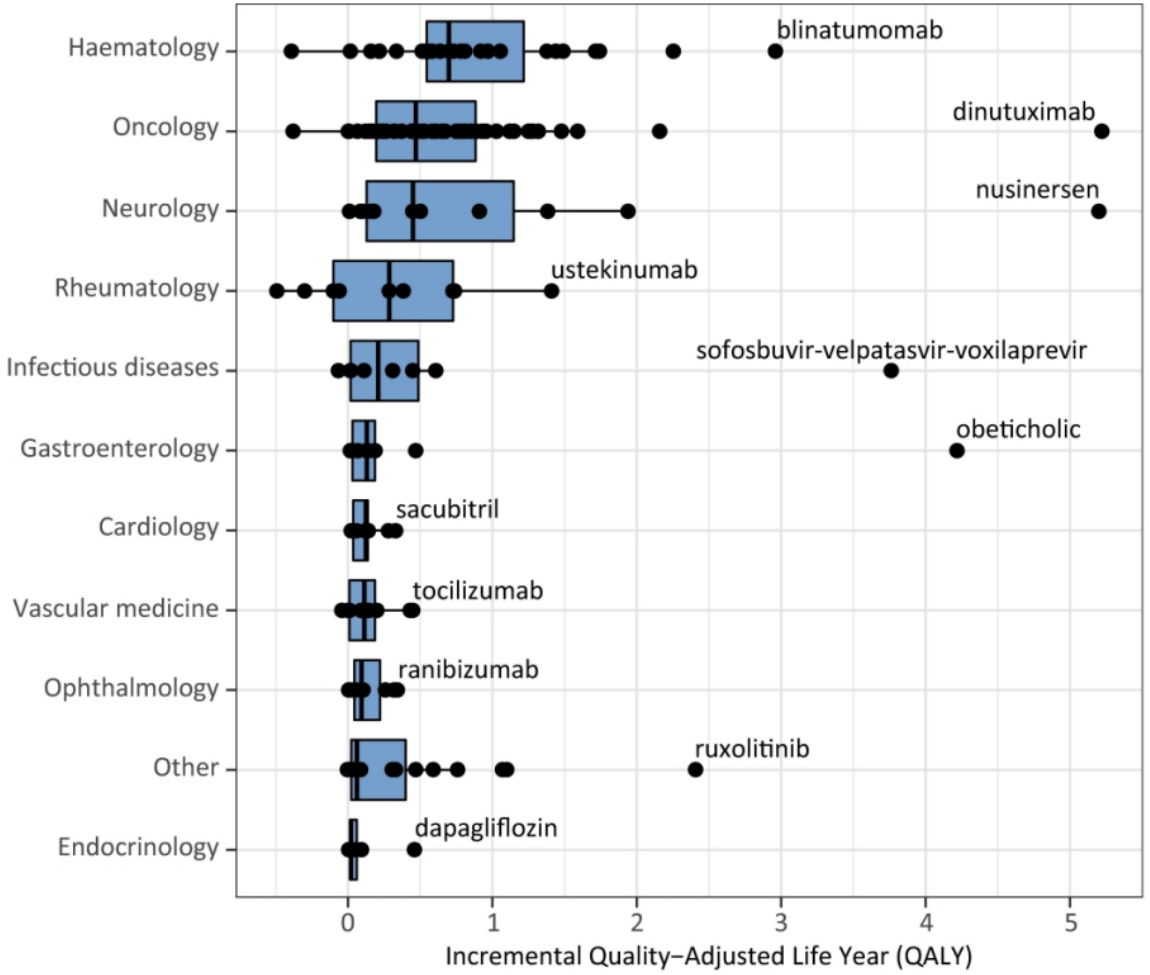
Dependent variable: ΔNMB				
Intercept		152 210	[−144 118 to 448 539]	1.02
Purpose of test*	Info prognosis	−126 431	[−445 368 to 192 505]	−0.78
	Identify responders	−221 146	[−535 623 to 93 331]	−1.39
	Identify ADR	176 913	[−156 155 to 509 981]	1.06
Type of treatment†	Pharmaceutical	3479	[−251 023 to 257 981]	0.03
	Combination	99 635	[−475 897 to 675 166]	0.34
Gene therapy	Gene therapy	**−868 759**	[−1 307 289 to −430 229]	−3.94
Sponsorship	Industry	92 109	[−103 308 to 287 527]	0.94
Disease classification‡	Non-neoplasm	**−380 950**	[−638 867 to −123 032]	−2.94

For values in bold, the 95% confidence interval does not cross 0.
Δcost indicates incremental cost; ΔNMB, incremental net monetary benefit; ΔQALY, incremental quality-adjusted life-year; ADR, adverse drug reaction.
*Reference category is "screening."
†Reference category is "nonpharmaceutical interventions."
‡Reference category is "neoplasms."

Generalised linear mixed models with random intercepts for country and restricted maximum likelihood (REML) estimation

Vellekoop H, Versteegh M, Huygens S, Ramos IC, Szilberhorn L, Zelei T, Nagy B, Tsiachristas A, Koleva-Kolarova R, Wordsworth S, Rutten-van Mölken M. The Net Benefit of Personalized Medicine: A Systematic Literature Review and Regression Analysis. Value in Health. 2022 Mar 2.

MEDIAN OF 185 QALY ESIMTATES OF NICE SUBMISSION 2010-2020 = 0,27



Polak, Cuccihi, Darrow, Versteegh. Incremental benefits of novel pharmaceuticals in the United Kingdom: A cross-sectional analysis of NICE technology appraisals from 2010 – 2020. BMJ Open 2022

CASE STUDY: COST-EFFECTIVENESS OF PM

CASE 2: NTRK-INHIBITOR ENTRECTINIB VERSUS STANDARD OF CARE

- Entrectinib is a tumor-agnostic treatment for adult patients with locally advanced or metastatic solid tumours caused by neurotrophic receptor tyrosine kinase (NTRK) fusions (prevalence 0.3-1%)

- It is an inhibitor of TRK A/B/C proteins, designed to cross the blood-brain barrier and remain in the central nervous system. It has a durable response and long survival (median OS 33.8 months). Costs: €5,900 per month

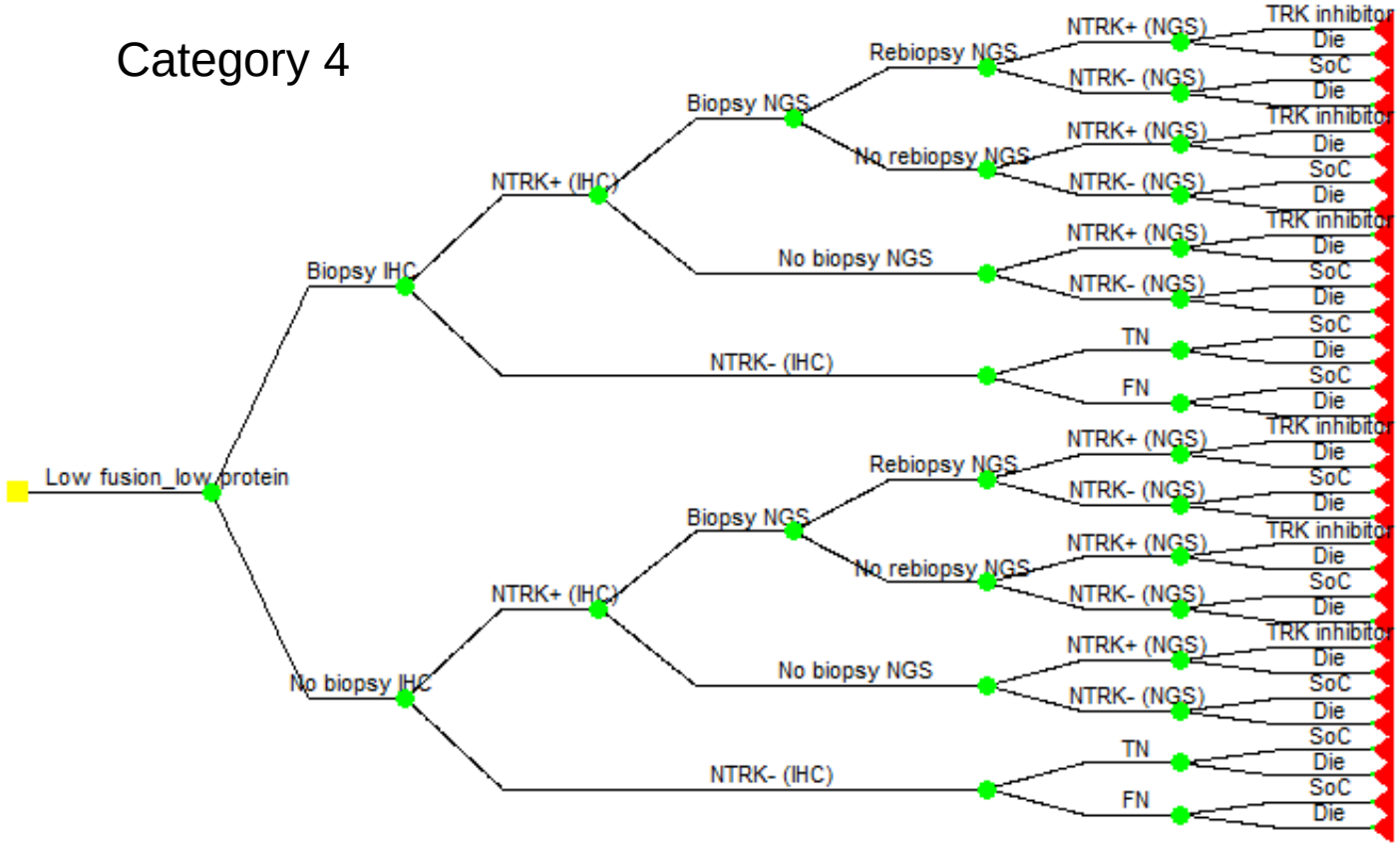
- Two tests: IHC (~€400) and NGS-RNA (~€1700).
- To model the testing phase, the tumour types were categorised into 4 a priori groups
  - Based on 2020 “Consensus report” developed by group of experts, which outlines envisioned NTRK testing policy in Dutch clinical practice

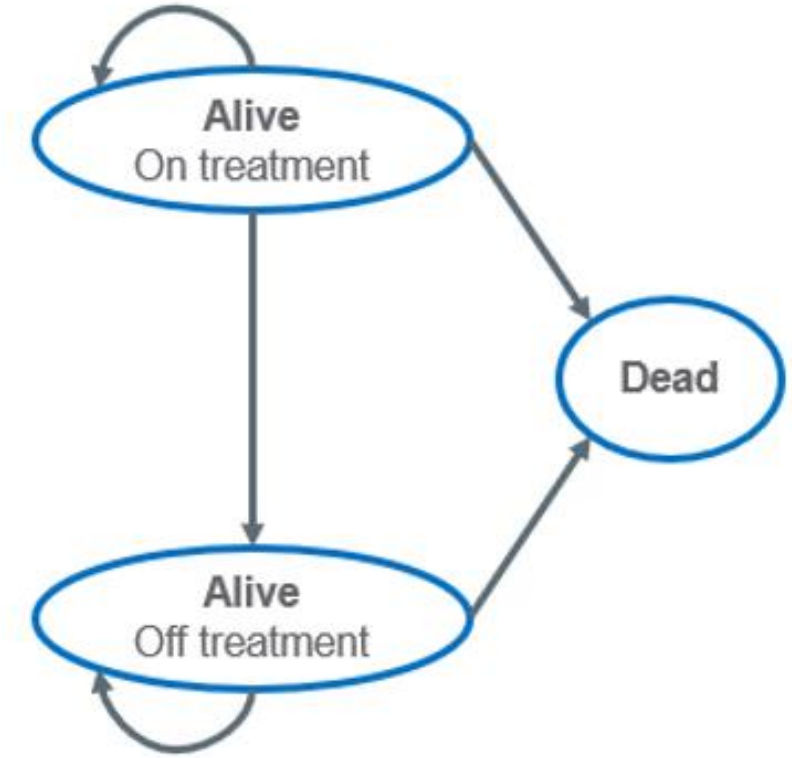
1. **Non-small cell lung cancer (NSCLC): no new test**
2. **Tumour types with high NTRK fusion prevalence: NGS-RNA**
3. **Tumour types with low NTRK fusion prevalence but wild-type* TRK protein expression: NGS-RNA**
4. **Tumour types with low NTRK fusion prevalence and no/very little wild-type* TRK protein expression: IHC+NGS-RNA**

* i.e. naturally occurring in the type of tissue in which the cancer is located

DECISION TREE + MICRO SIMULATION MODEL

Category 4





Decision to receive additional treatment

Start treatment

Death

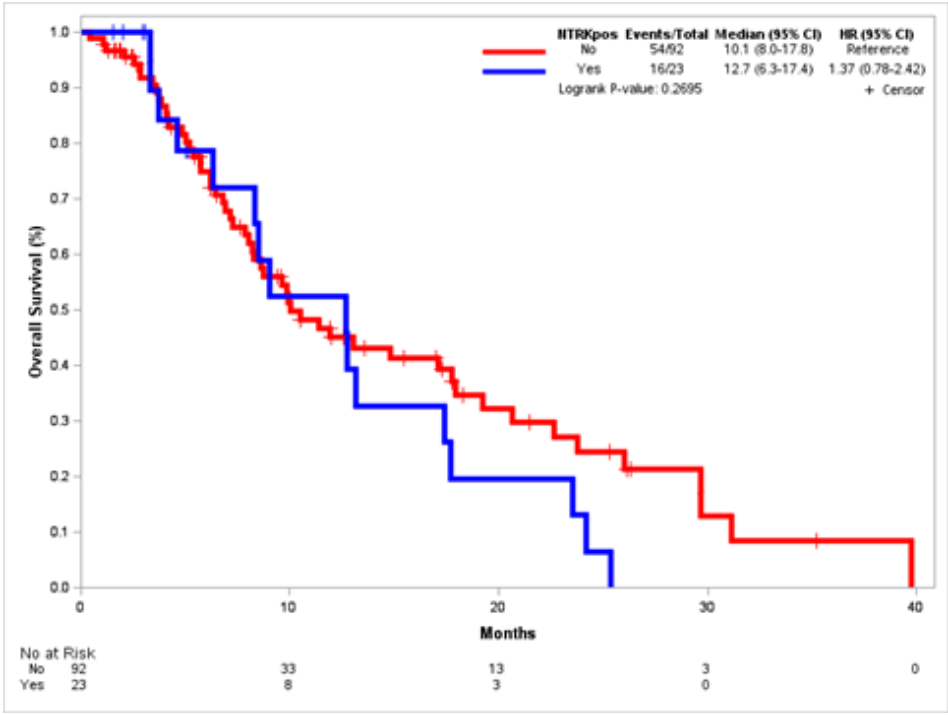
EXTERNAL DATA FROM HARTWIG MEDICAL FOUNDATION

- CPCT-02 study, in which whole-genome sequencing was performed for metastatic cancer patients (n=3,547 with known tumour location)

- 23 NTRK+ patients were matched with 92 NTRK- patients

- In an unadjusted analysis,
  - median OS from the first post-biopsy treatment was
    - 12.7 months [95% CI: 6.3, 17.4] for NTRK+
    - 10.1 months [95% CI: 8.0, 17.8] for NTRK–
  - HR for NTRK+ patients was 1.37 [95% CI: 0.78, 2.42]

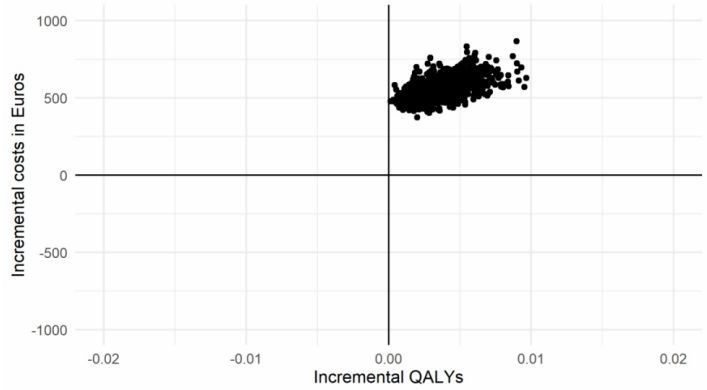
- After adjusting for age, gender and previous line of treatment, the multivariable Cox regression found an HR of **1.32** [95% CI: 0.74, 2.35], confirming the results of the unadjusted analysis.



COST-EFFECTIVENESS RESULTS (SOCIETAL PERSPECTIVE)

Base case

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**

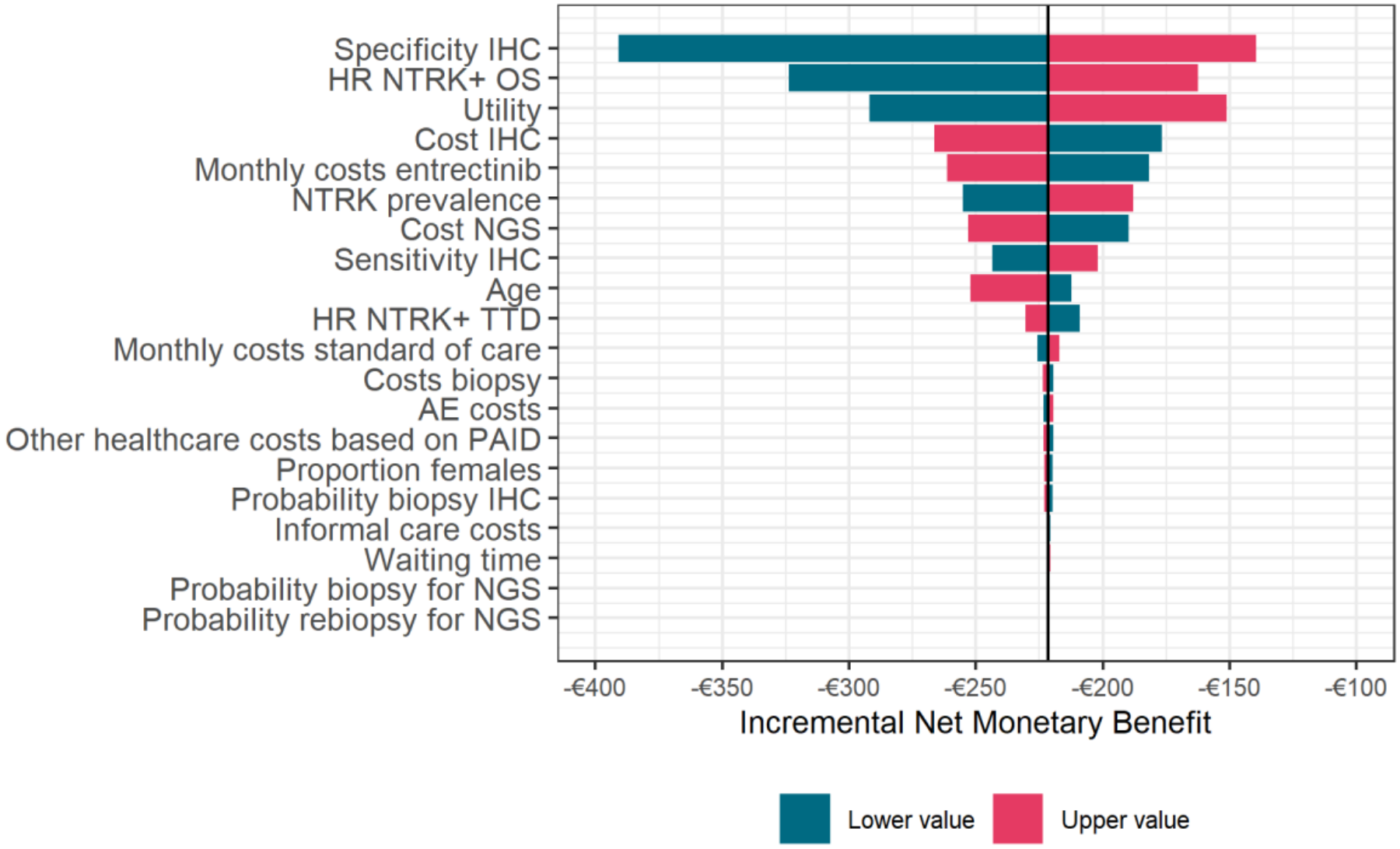


Scenario analysis without the test phase

Strategy	Costs (in €)	QALYs	ICER
Entrectinib for NTRK+	133,285	2,19	
SoC for NTRK+	72,151	0,73	
Incremental	61,134	1,457	**41,973**

MODEL DRIVERS

Base case



OTHER CASE STUDIES

ToXnav in mBRC: identify patients who are poor metabolizers of chemotherapy:

Cost saving and health improving

Screening strategies for MODY:

Cost saving and health improving (with antibody test)
Cost increasing but cost-effectieve (w/out antibody test)

TAKE HOME MESSAGES

The cost consequences of introducing PM are larger than usually identified (NTRK case study)

It appears that the term “personalized medicine” may be too general given that it conceals sizable differences in the net benefit of different PM interventions. A more precise division into subcategories of PM may be needed to uncover the most promising areas for further investment. (Net benefit analysis)

There are still substantial efficiency gains to be made by investing in PM interventions that target existing care better (ToxNav / MODY case studies)

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 paper)

EcoPerMed
Health Economics for Personalised Medicine

THANK YOU!

@hecopermed

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