What can be learned from the 3 HEcoPerMed case studies?

Balázs Nagy, PhD, Habil
balazs.nagy@syreon.eu

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HECOPERMED

- Healthcare- and pharma-economics in support of the International Consortium for Personalised Medicine
- To support research and implementation of personalised medicine in Europe and beyond

Produced:

- Guidance for the harmonisation and improvement of economic evaluations of personalised medicine
- Position paper: Lessons learnt and potential opportunities ahead
- 6 scientific papers
- Special issue in ‘Personalized Medicine’ : 7 papers (coming soon)

- Website: https://hecopermed.eu/

HECOPERMED CASE STUDIES

ToxNav: A genetic test that identifies **breast cancer** patients at risk of adverse effects due to fluorpyrimidine based chemotherapy (5-FU and capecitabine) caused by genetic deficiency in the function of the dihydropyrimidine dehydrogenase (DPD).

Genetic testing to initiate tumour agnostic treatment for solid tumours with **NTRK fusions** (Larotrectinib and Entrectinib).

Genetic testing of **monogenic diabetes**, caused by mutations in the GCK, HNF1A or HNF4A genes (MODY 1-3).

CASE OF NTRK

- Histology-independent (tumour-agnostic) therapy = prescribed based on genetic markers of tumour, regardless of tissue of origin
- Entrectinib
  - Recently approved by FDA and EMA
  - inhibitor of TRK proteins, prescribed for patients with locally advanced or metastatic solid tumours and oncogenic neurotrophic tyrosine receptor kinase (NTRK) gene fusions
- Around 0.3-1% of locally advanced or metastatic solid tumours contain these NTRK-fusions
- NTRK-fusion positive patients recieve entrectinib - testing is not standard practice

- **Is it cost effective to test for NTRK positive patients?**

NTRK – DATA CHALLENGES

- efficacy is determined with single-arm basket trials
  - patients with different tumour locations and possibly heterogeneous treatment effects
  - creates challenges for the assessment of the relative treatment effectiveness and cost-effectiveness as required by reimbursement authorities
- lack of a comparator arm
  - raises the need for indirect comparisons to historical control data.
  - the control data need to be adjusted to account for the prognostic value of NTRK-fusions that is largely unknown.
- Small study size, n=58

- Take away: **Data problems can occur often when targeting a small subgroup of patients with little history/information about their potential to improve**

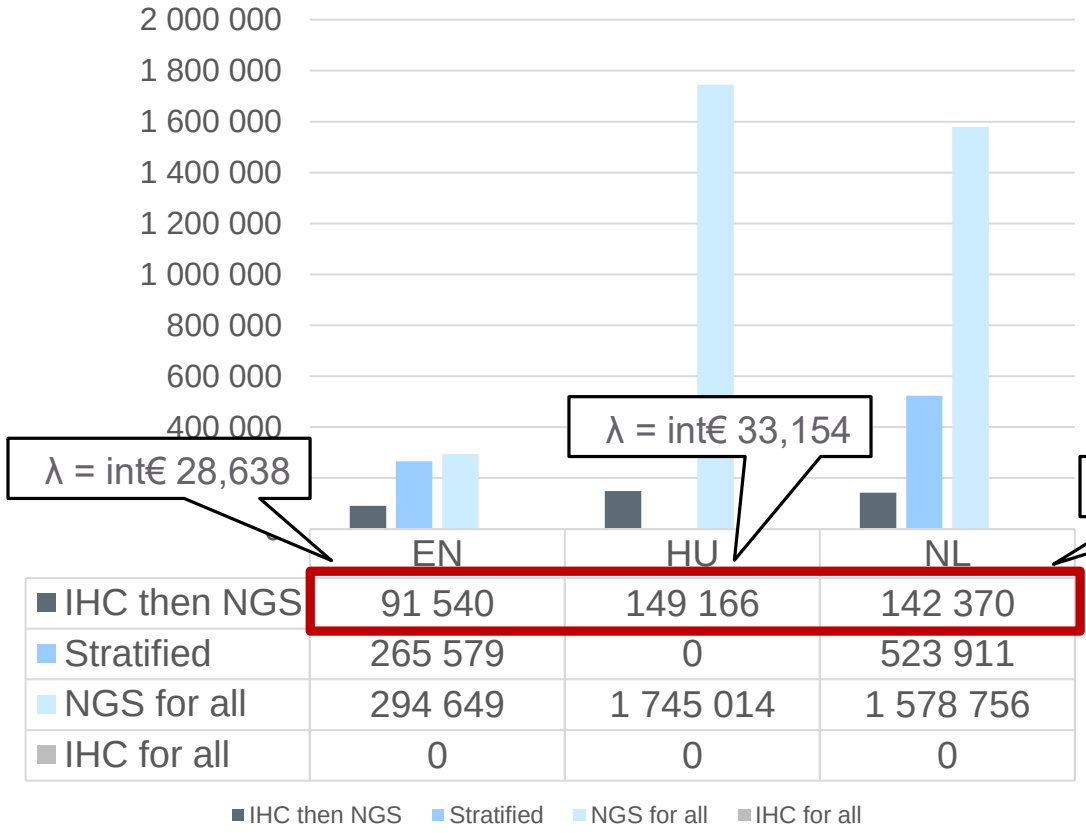
NTRK – VARIOUS STRATEGIES FOR PERSONALIZATION

- Test strategies:
  - RNA-NGS test for all tumour types
  - IHC test for all tumour types
  - IHC test followed by RNA-NGS in patients with a positive IHC test result for all tumour types
  - Stratified test strategies depending on the NTRK fusion prevalence and TRK wild-type protein expression of the tumour types

- Take-away: **Patient pathways are not easy te set up!**

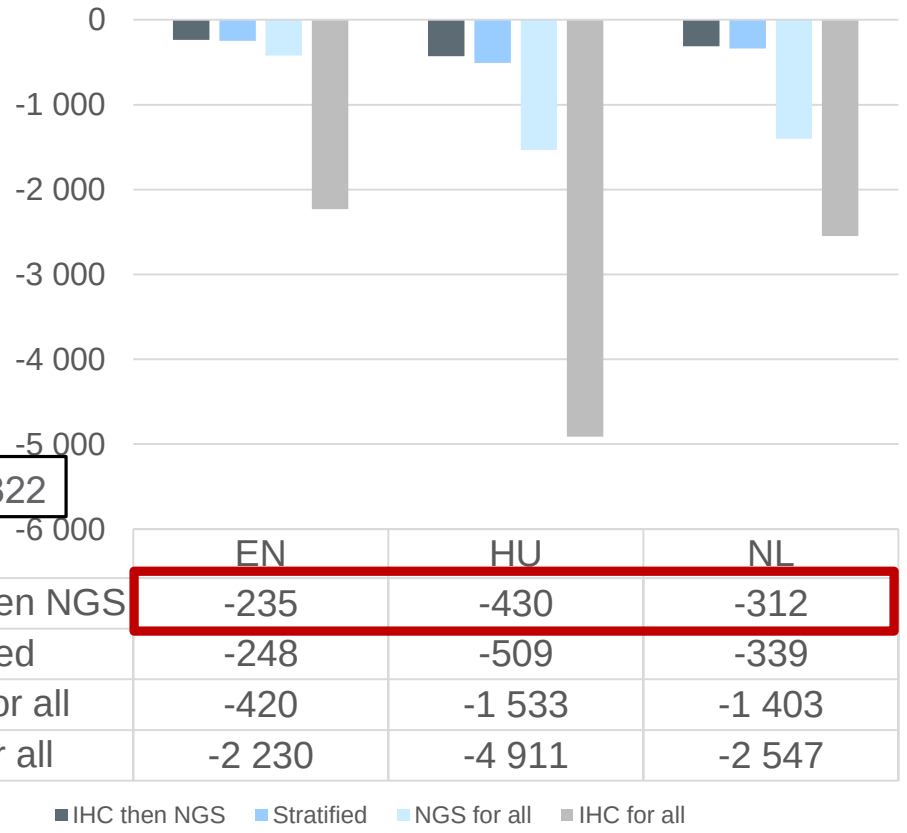
IHC then NGS is the best strategy… but not cost-effective vs. SoC

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

Incremental net monetary benefit (int€)

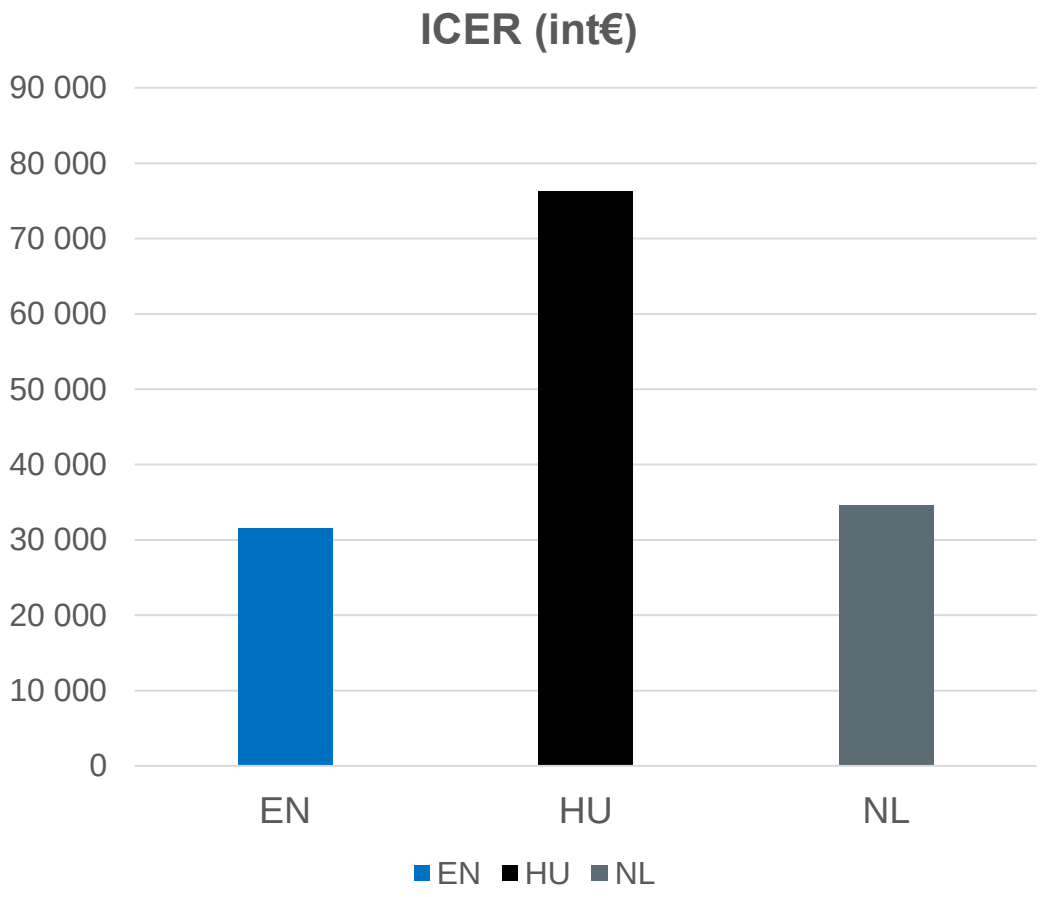


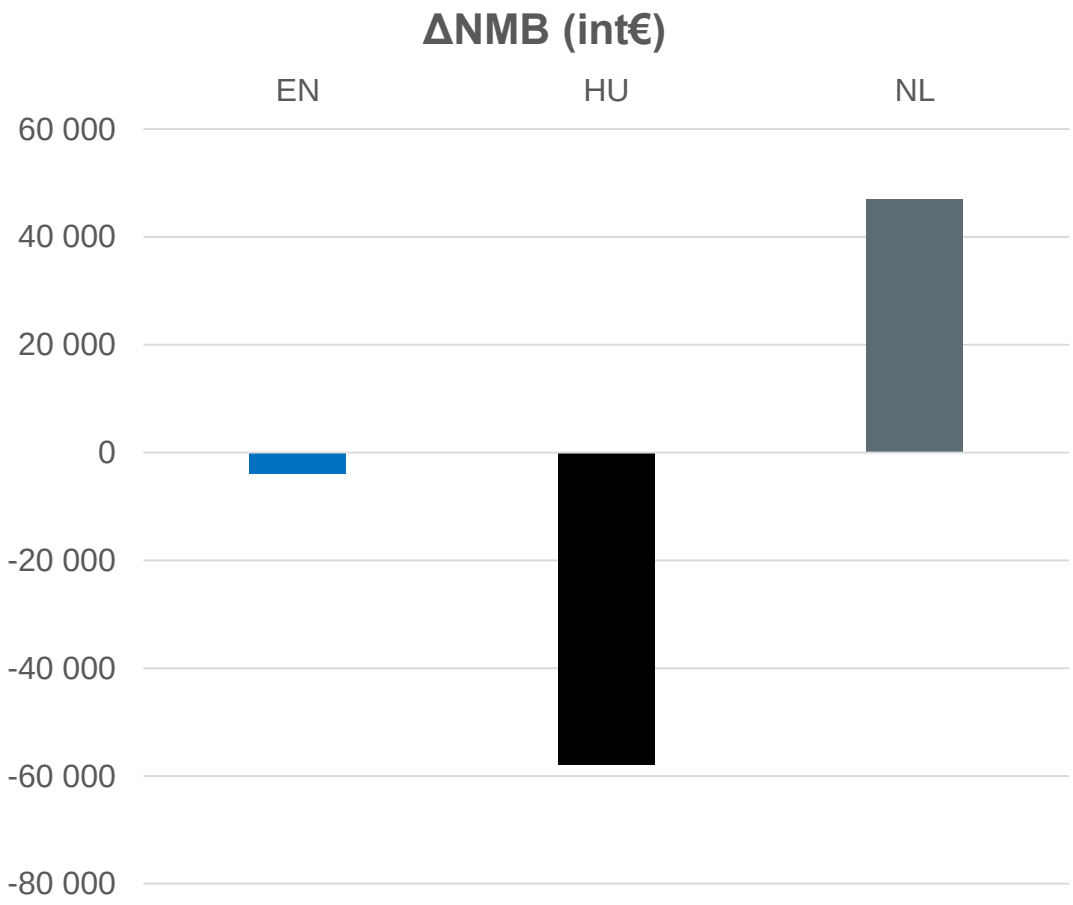
	EN	HU	NL
IHC then NGS	-235	-430	-312
Stratified	-248	-509	-339
NGS for all	-420	-1 533	-1 403
IHC for all	-2 230	-4 911	-2 547

0 = (extendedly) dominated

Take away: **Combination of lower prevalence and expensive innovative therapy**

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





Take away: **reduction of the stratification burden can be key**

NTRK IV.- BUDGETARY IMPACT CAN DRAMATICALLY CHANGE BY JURISDICTIONS

Strategy	Five-year incremental budget impact (int€)			Percentage test costs		
	UK	***HU***	***NL***	***UK***	***HU***	***NL***
IHC then NGS	180,289,572	39,803,379	73,944,040	65.56	51.55	81.17
Stratified	187,583,081	45,766,968	77,925,852	66.23	57.13	81.73
NGS for all	284,637,684	122,760,610	224,183,436	74.01	81.52	92.55
IHC for all	1,228,043,140	359,777,624	305,898,512	8.77	4.25	15.98
Proportion of total expenditure						
	Percentage of total health expenditure			**Percentage of total cancer care expenditures**		
IHC then NGS	0.02	0.11	0.02	0.31	1.29	0.28
Stratified	0.02	0.13	0.03	0.32	1.48	0.29
NGS for all	0.03	0.35	0.07	0.49	3.97	0.84
IHC for all	0.13	1.03	0.10	2.10	11.64	1.15

Take away: **The burden of PM can dramatically change by jurisdictions**

THE CASE OF TOXNAV

- Fluoropyrimidine-based chemotherapy drugs, including capecitabine and 5-fluorouracil (5FU)
  - to treat several solid tumour types
  - cause severe adverse drug reactions (ADR) due to genetic mutations
  - 10-15% of patients poorly metabolize chemotherapy and have an increased risk of severe toxicity
  - germline mutations in DPYD gene causing a DPD enzyme deficiency

- Extended DPYD genotyping with ToxNav test before chemotherapy help identify poor metabolisers prior to chemotherapy and allow for dose adjustment, potentially avoiding severe toxicities

- **Is it cost effective to use ToxNav test for breast cancer patients before capecitabine and 5-fluorouracil chemotherapy?**

MAIN ANALYSIS RESULTS PER 10,000 SIMULATED WOMEN FOR LIFETIME HORIZON, INT €, COST YEAR 2020/2021, COUNTRIES UK, THE NETHERLANDS, HUNGARY

Country	Strategy	Costs	QALYs	Incremental costs	Incremental QALYs	ICER
United Kingdom	ToxNav© strategy	€327.1 mln	22,670.8	-	-	-
	Standard of Care	€714.4 mln	21,740.0	€-387.3 mln	930.8	Dominant
Country	**Strategy**	**Costs**	**QALYs**	**Incremental costs**	**Incremental QALYs**	**ICER**
The Netherlands	ToxNav© strategy	€108.8mln	27,121.3	-	-	
	Standard of Care	€110.0mln	26,180.8	€-0.8 mln	940.5	Dominant
Country	**Strategy**	**Costs**	**QALYs**	**Incremental costs**	**Incremental QALYs**	**ICER**
Hungary	ToxNav© strategy	€62.3 mln	22,725.8	-	-	-
	Standard of Care	€61.3 mln	21,792.5	€0.9 mln	933.3	€987.1

TOXNAV – TAKE AWAY

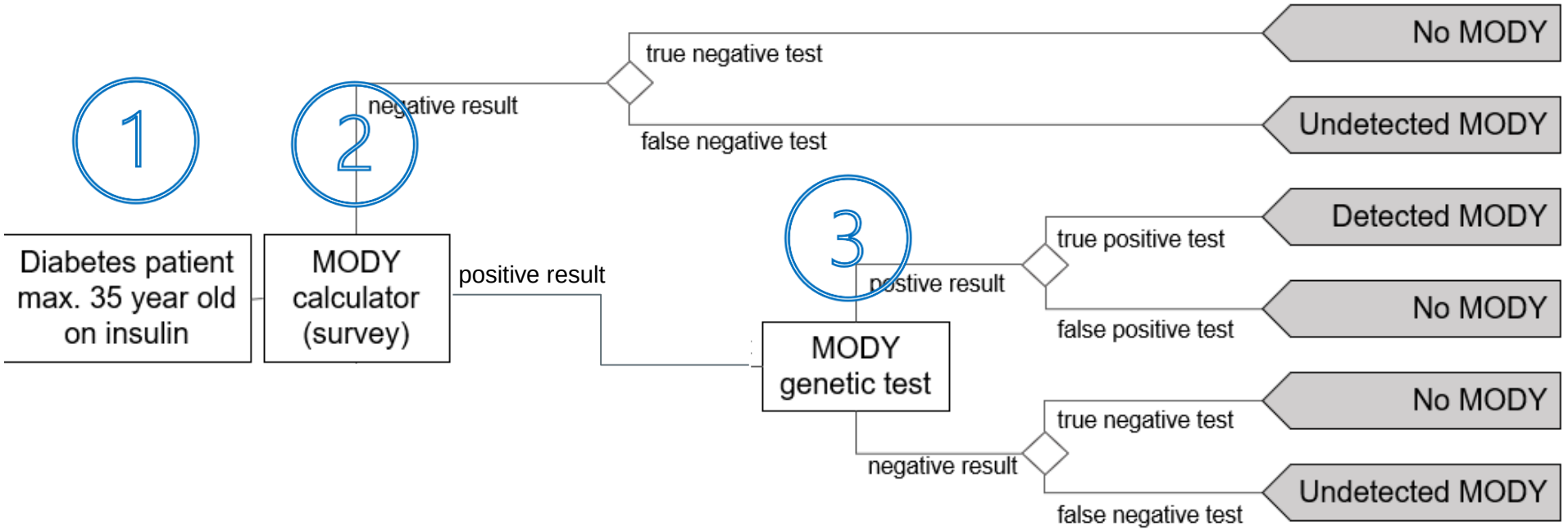
- Personalization of high prevalence health problem treated with existing (cheap) care has great potential to be cost effective
- In the absence of trial data effectiveness data can be obtained from RWD, especially when new genetic tests are developed for long existing treatments with proven benefit.

CASE OF MODY

- Maturity Onset Diabetes of the Young is a form of monogenic diabetes, caused by 13 mutations
- Accounts for at least **1%-5%** of all diabetes cases, age of onset typically **<35 years**
- 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**
- Diagnosis of MODY subtype drives appropriate treatment and prognosis

Is it cost-effective to diagnose MODY patients by genetic testing?

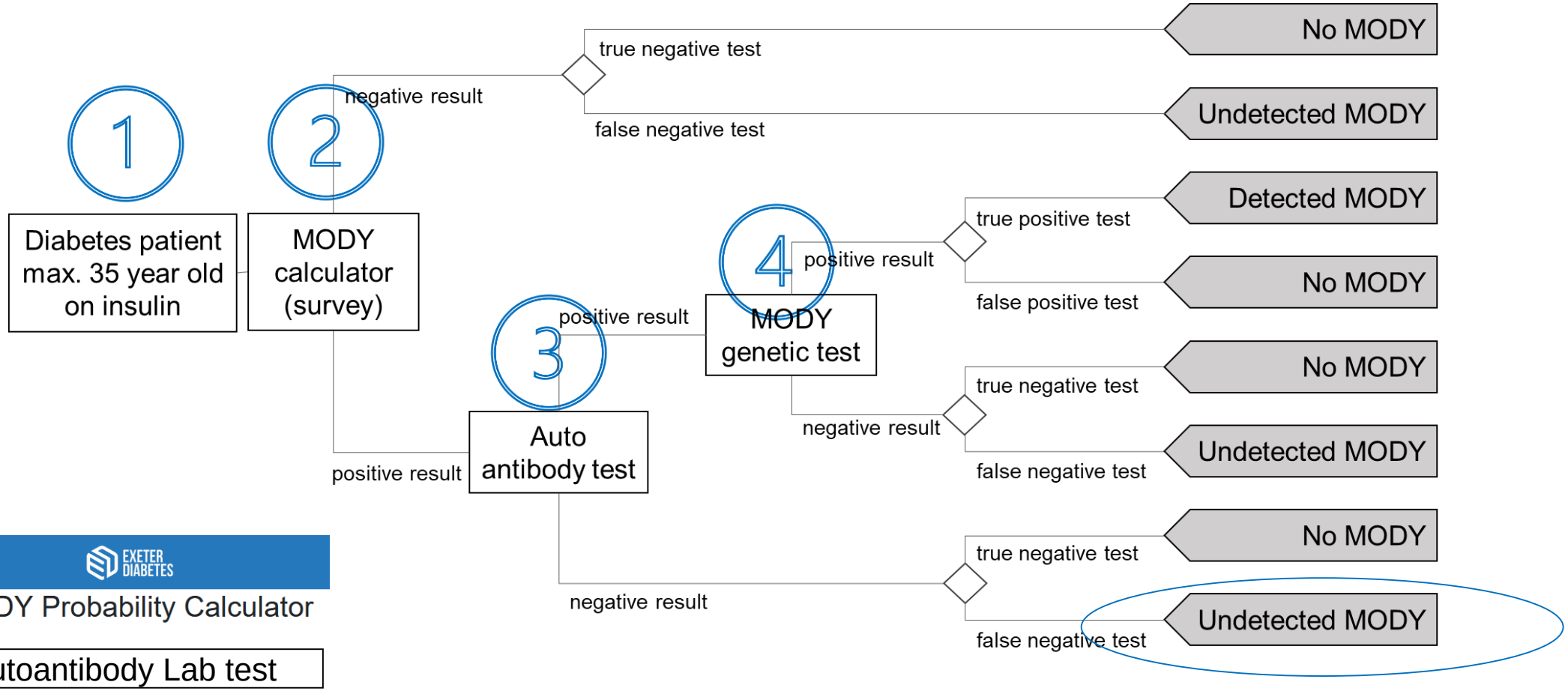
SCREENING FOR MODY PATIENTS - SCENARIO 1



EXETER DIABETES

MODY Probability Calculator

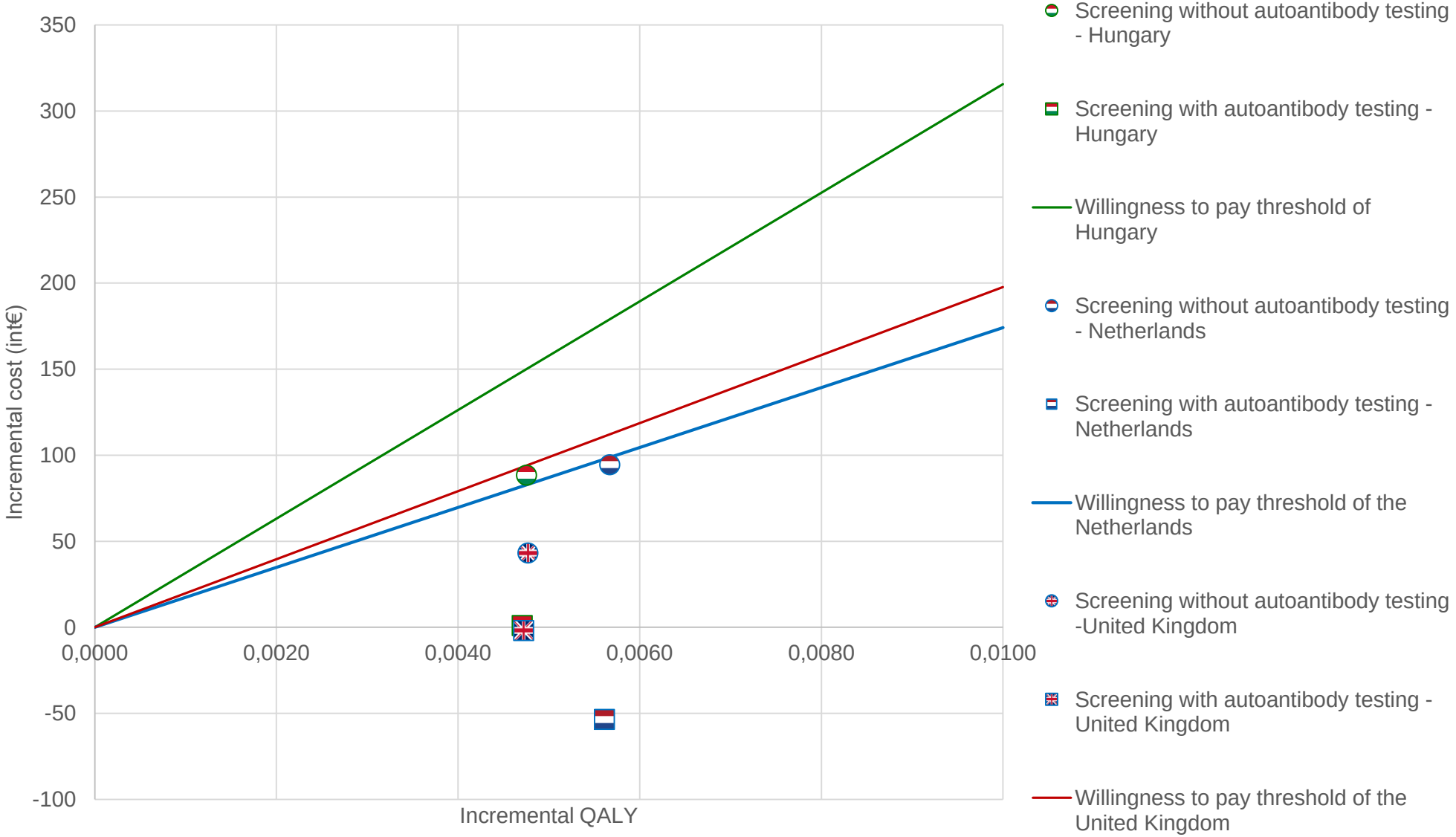
SCREENING FOR MODY PATIENTS - SCENARIO 2



EXETER DIABETES

MODY Probability Calculator

Autoantibody Lab test


350
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Incremental cost (int€)
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Incremental QALY
Screening without autoantibody testing - Hungary
Screening with autoantibody testing - Hungary
Willingness to pay threshold of Hungary
Screening without autoantibody testing - Netherlands
Screening with autoantibody testing - Netherlands
Willingness to pay threshold of the Netherlands
Screening without autoantibody testing -United Kingdom
Screening with autoantibody testing - United Kingdom
Willingness to pay threshold of the United Kingdom

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