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Health Economics for Personalised Medicine
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Is There Large Underused Potential in Using Genetic Tests to Better Stratify Patients to Established Therapies?

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REVIEW OF NET BENEFIT OF PM, 2009-2019

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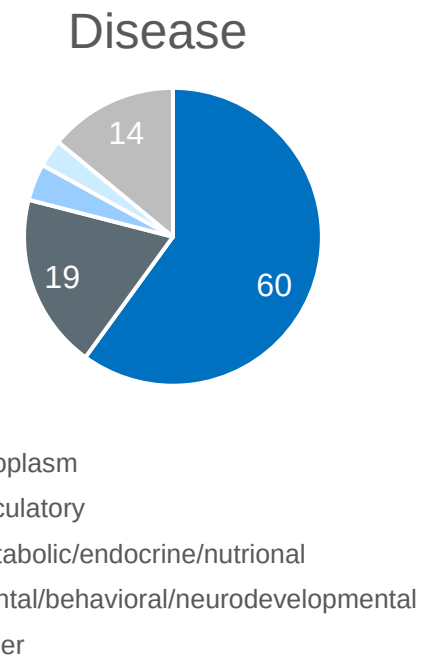
Systematic Literature Review

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

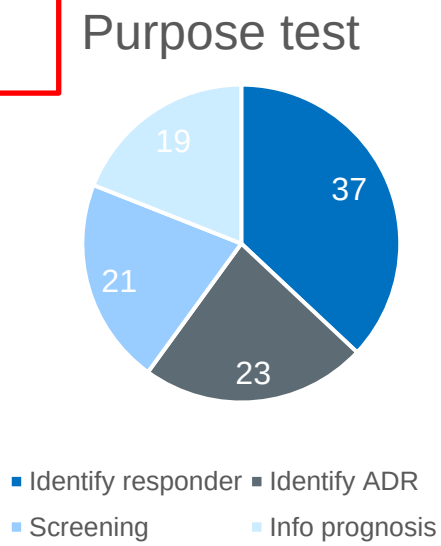


- Focuses on genetic and genomic test-treatment combinations
- 128 studies providing cost-effectiveness data for 279 PM interventions
- High-income and upper-middle-income countries (48% US, 16% UK)

Vellekoop et al., Value in Health 2022 25(8):1428–1438

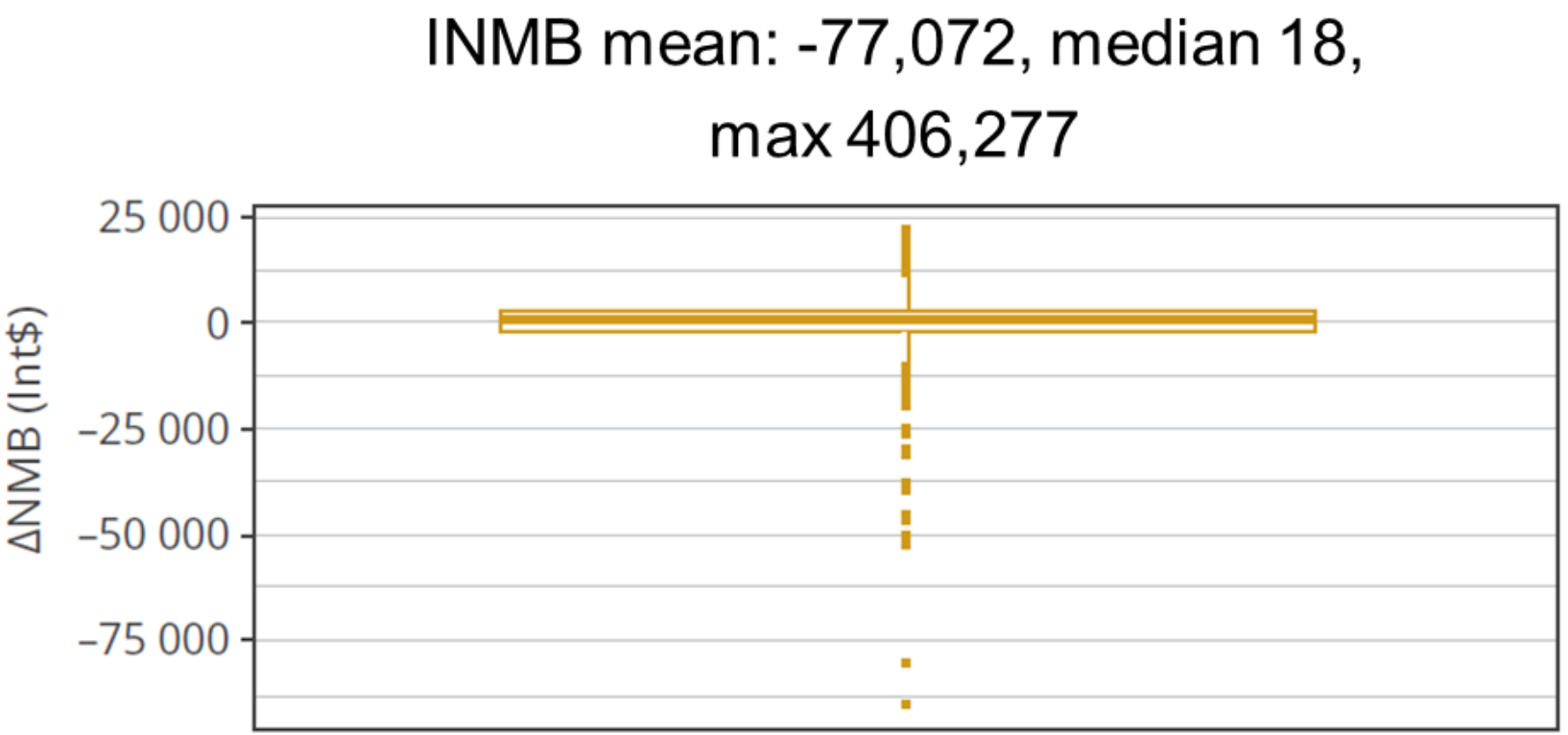
PERSONALISED MEDICINE (TEST-TREATMENT COMBI)

- 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



Vellekoop et al., Value in Health 2022 25(8):1428–1438

MEDIAN NET MONETARY BENEFIT WAS JUST ABOVE ZERO



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

Vellekoop et al., Value in Health 2022 25(8):1428–1438

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

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]

- 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."

THREE CASE STUDIES OF GENETIC TESTING FOR EITHER **INNOVATIVE** THERAPY OR **ESTABLISHED** THERAPY

Identify responders to **INNOVATIVE** THERAPY
NTRK case
Testing for NTRK gene-fusions to identify **responders** to histology-independent therapy

Better stratification to **ESTABLISHED** THERAPY
MODY case
Patient group screening for the presence of Maturity Onset Diabetes of the Young

Dose adjustment of **ESTABLISHED** THERAPY
ToxNav© case
Testing for **DPYD mutations causing ADR** from breast cancer chemotherapy

NMB is likely to vary a.o. by:

1) test-strategy (2 cases)

2) country (all cases)

IT’S TIME FOR A POLL

- **What is the most important facilitator for increasing the use of genetic tests to stratify patients to existing therapies?**

  - Patients’ awareness
  - Available evidence
  - Reimbursement of test
  - Guideline-recommendations
  - Compliance to clinical testing guidelines
  - Motivation to act upon test-result
  - Capacity testing-infrastructure

Multiple choice question, 1 possible answer

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Companion-diagnostic test for NTRK-fusions followed by entrectinib

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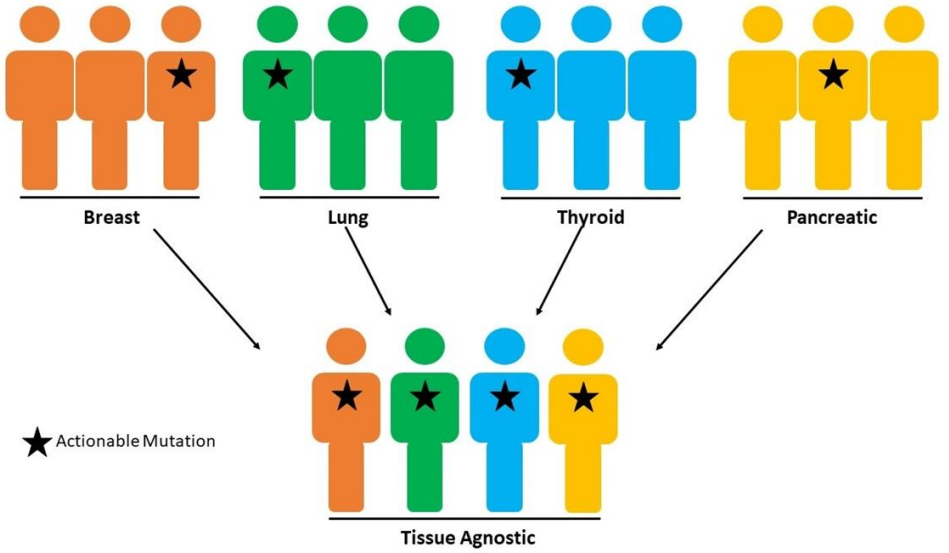
Prof. Maureen Rutten-van Mölken, PhD (presenter) **m.rutten@eshpm.eur.nl**

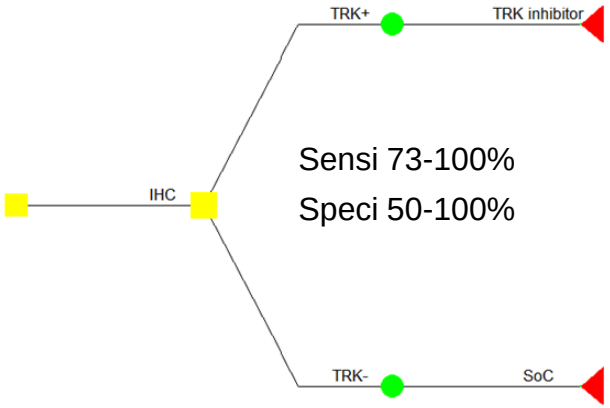
CASE OF HISTOLOGY-INDEPENDENT THERAPY ENTRECTINIB

- 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 approved by FDA and EMA based on single-arm basket trials
- Prescribed for patients with locally advanced or metastatic solid tumours and oncogenic *neurotrophic tyrosine receptor kinase* (NTRK) gene fusions
- NTRK fusions are rare: 0.3-1% of locally advanced or metastatic solid tumours
- NTRK testing not part of SoC



TESTING STRATEGIES

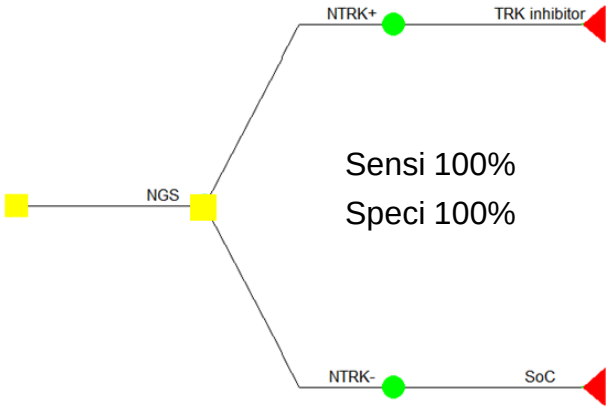
1. IHC for all



Sensi 73-100%

Speci 50-100%

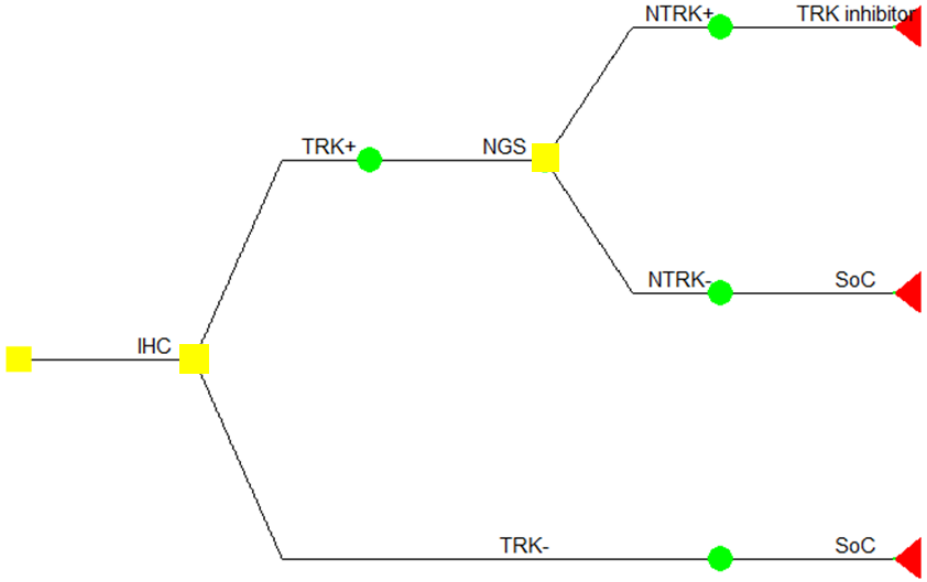
2. RNA-NGS for all



Sensi 100%

Speci 100%

3. IHC then RNA-NGS



4. Stratified

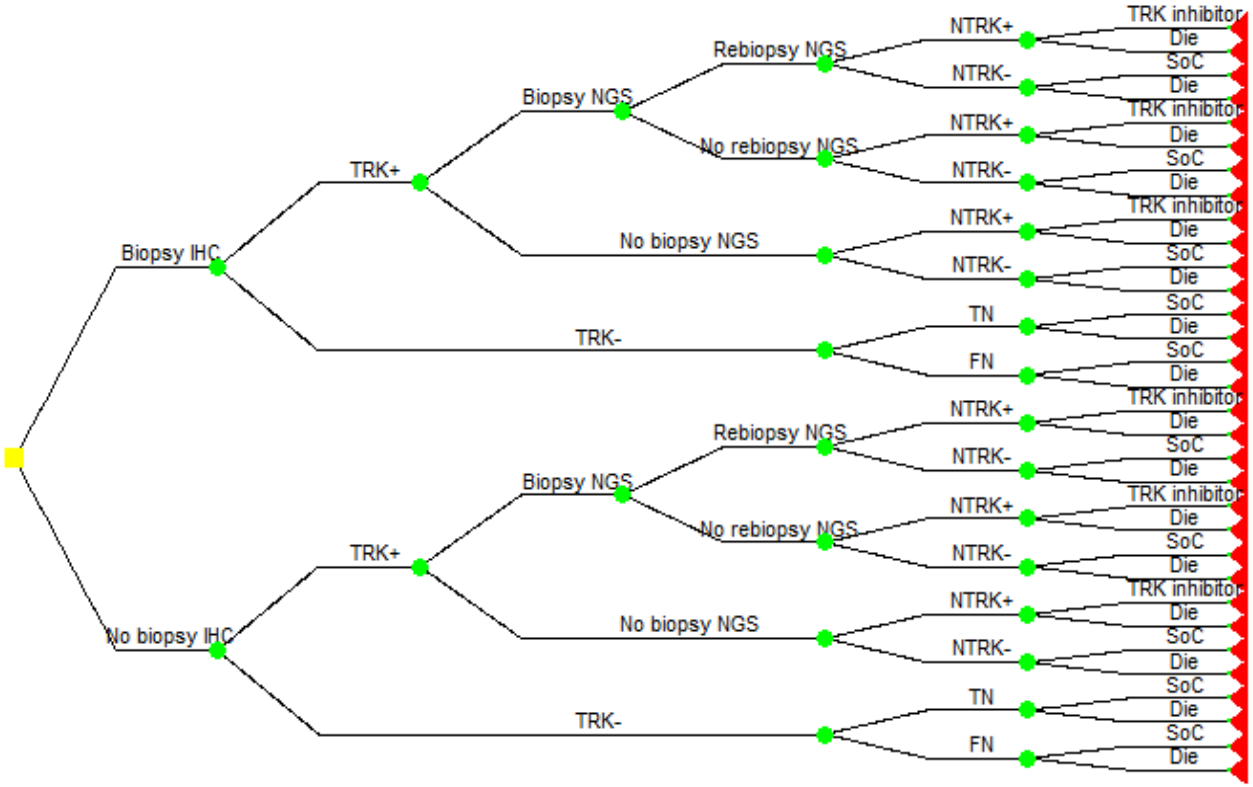
- IHC then RNA-NGS, for tumour types with low prevalence of NTRK gene fusions and no wild-type TRK protein expression
- RNA-NGS for the others

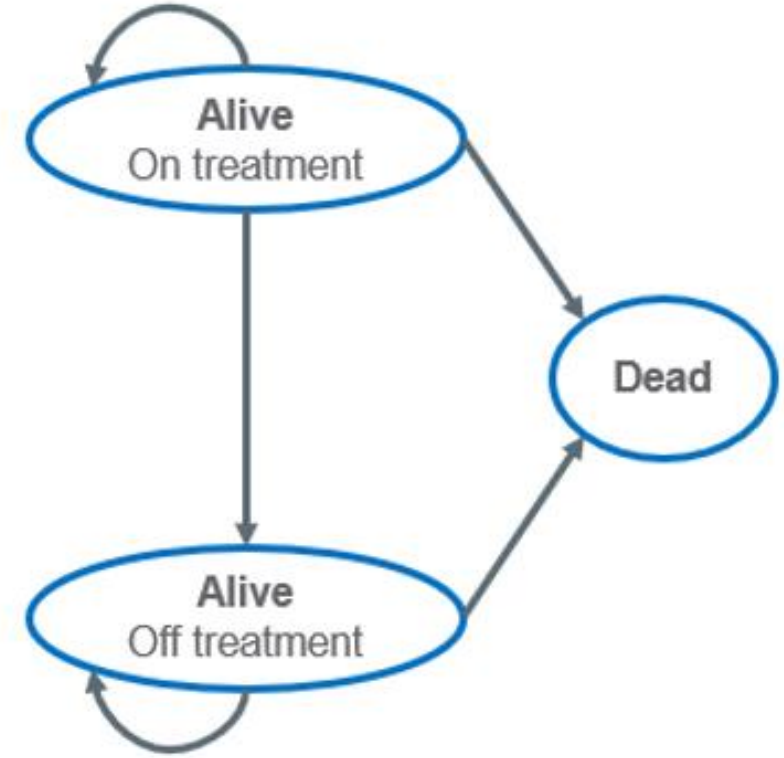
COSTS OF TESTS AND TREATMENT (INPUT PARAMETERS)

	Cost of test (int€)		
	EN	HU	NL
RNA-NGS	334	1,347	1,552
IHC	143	202	356

	Monthly cost of treatment (int€)		
	EN	HU	NL
SoC	2,964	1,768	1,741
Entrectinib	4,994	9,851	4,938

DECISION TREE + MICROSIMULATION MODEL





entrectinib vs SoC=synthetic control adjusted for the prognostic value of NTRK+; HR NTRK+ overall survival 1.44; HR TTDiscontinuation NTRK+ 1.37

Decision to receive additional treatment

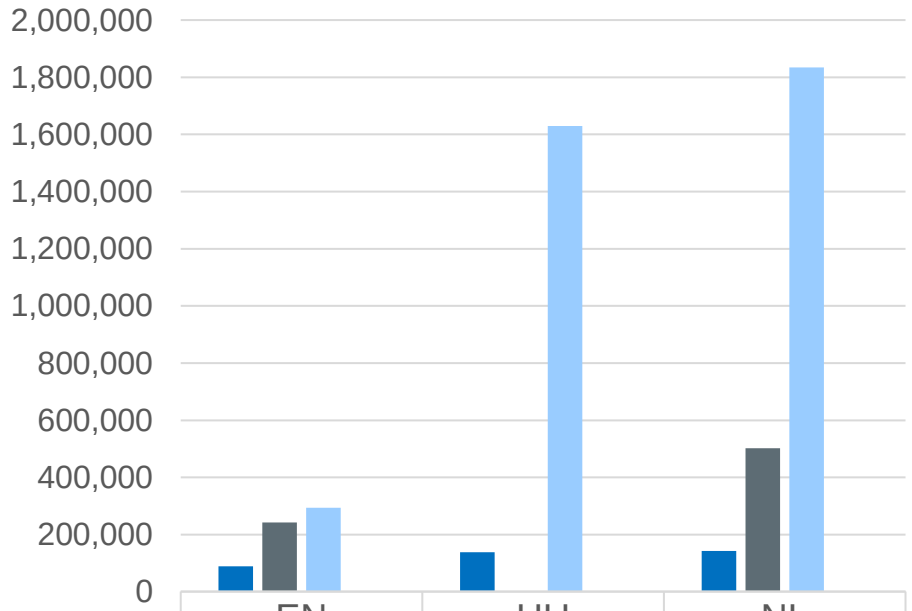
Start treatment

Death

Huygens, Vellekoop et al., ViH 2022, available online

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

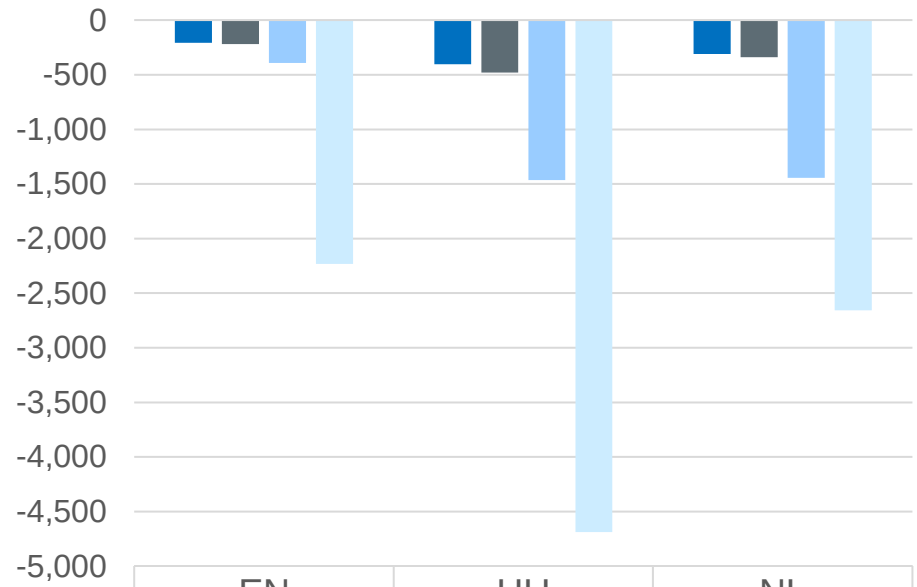
Incremental cost-effectiveness ratio (int€)



	EN	HU	NL
IHC then NGS	89,196	138,135	142,663
Stratified	242,668	0	502,431
RNA-NGS for all	293,640	1,629,295	1,834,617
IHC for all	0	0	0

IHC then NGS Stratified RNA-NGS for all IHC for all

Incremental net monetary benefit versus no testing (int€)



	EN	HU	NL
IHC then NGS	-206	-404	-310
Stratified	-218	-480	-338
RNA-NGS for all	-391	-1,465	-1,445
IHC for all	-2,231	-4,687	-2,657

IHC then NGS Stratified RNA-NGS for all IHC for all

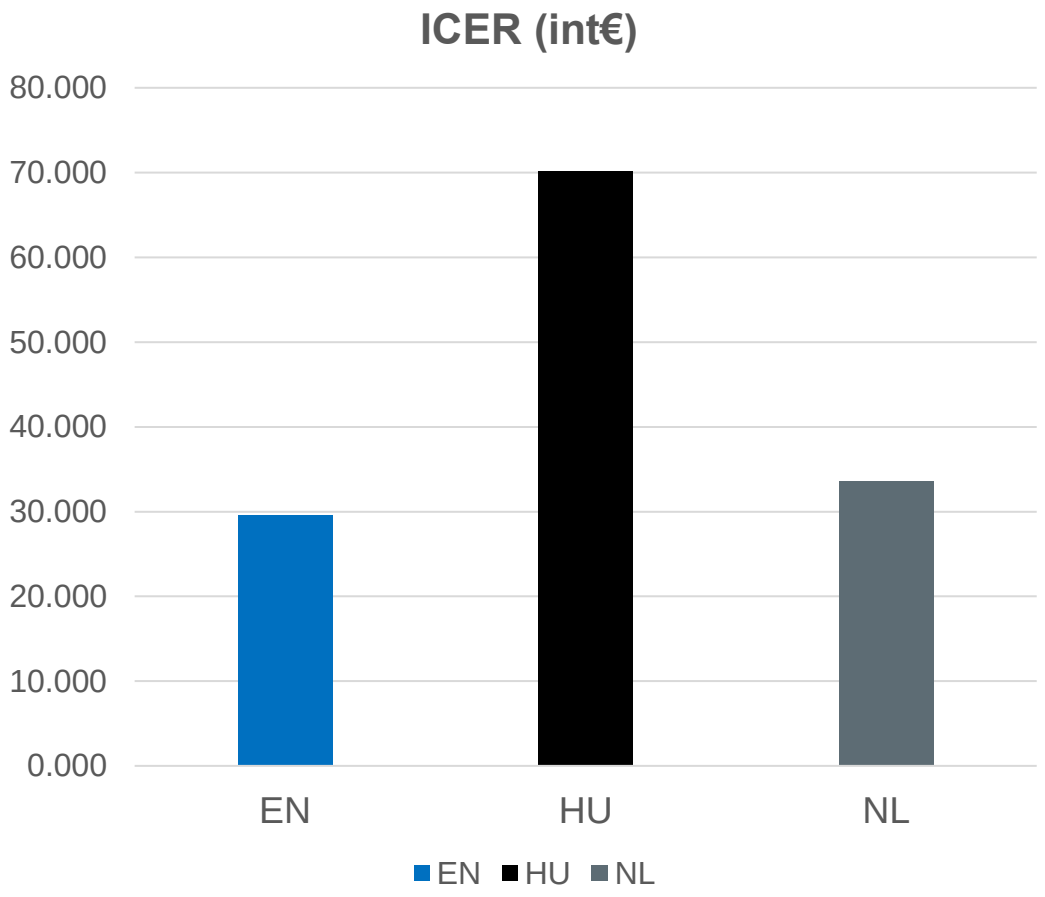
0 = (extendedly) dominated

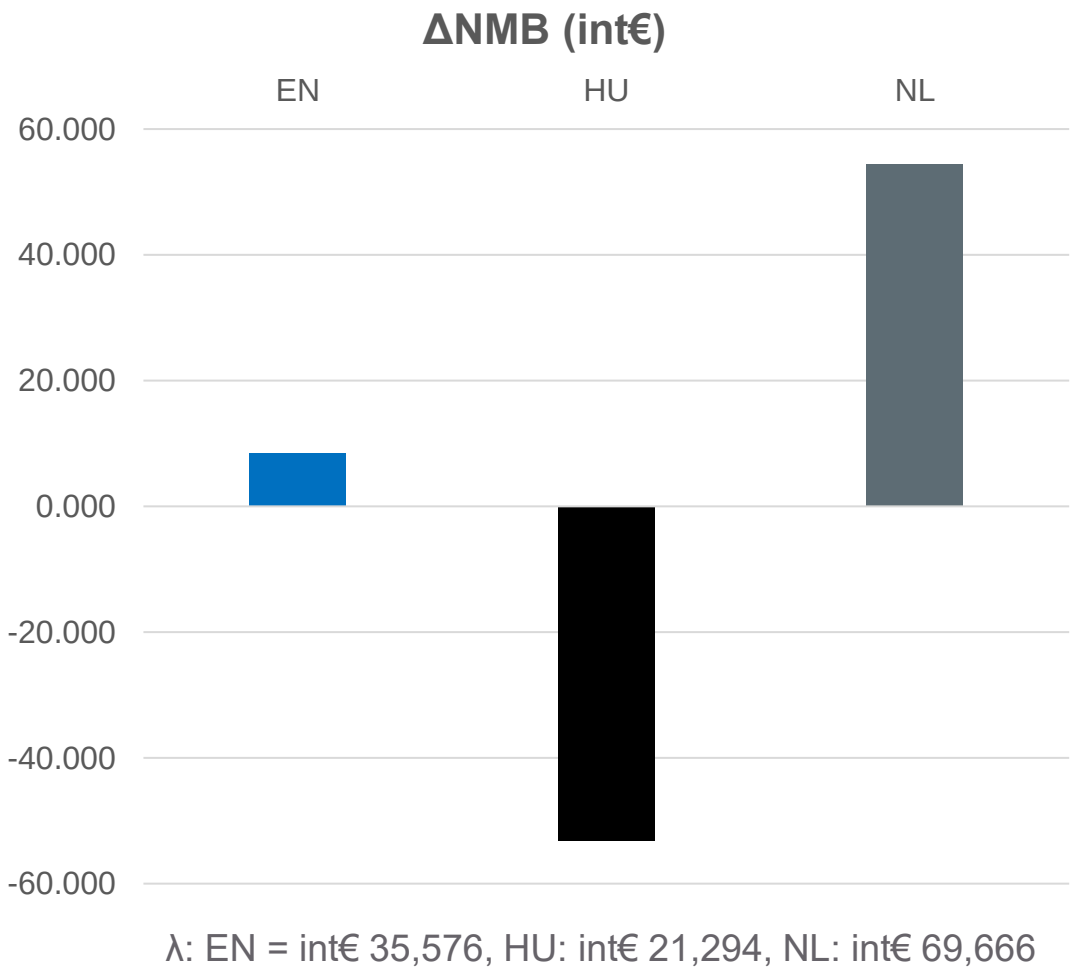
λ: EN = int€ 35,576, HU: int€ 21,294, NL: int€ 69,666

Huygens, Vellekoop et al., ViH 2022, available online

Vellekoop et al., Pers Med, in press

WHAT IF WE WOULD DISREGARD THE TESTING PHASE?





λ: EN = int€ 35,576, HU: int€ 21,294, NL: int€ 69,666

Huygens, Vellekoop et al., ViH 2022, available online

Vellekoop et al., Pers Med, in press

BUDGET IMPACT (HEALTH CARE PERSPECTIVE; VERSUS SOC)

Strategy	Five-year incremental budget impact (int€)			Percentage test costs		
	EN	HU	NL	EN	HU	NL
IHC then NGS	156,347,606	37,874,049	76,879,546	65.85	52.19	81.39
Stratified	162,707,341	43,612,999	81,027,374	66.50	57.76	81.95
NGS for all	247,205,447	117,721,977	233,475,628	74.22	81.90	92.65
IHC for all	1,066,761,912	340,863,660	326,279,464	8.80	4.32	15.62
	Percentage of total public health care expenditure			Percentage of total cancer care expenditure		
IHC then NGS	0.02	0.11	0.03	0.27	1.23	0.29
Stratified	0.02	0.12	0.03	0.28	1.41	0.31
NGS for all	0.03	0.34	0.08	0.42	3.81	0.88
IHC for all	0.11	0.97	0.11	1.82	11.03	1.23

Huygens, Vellekoop et al., ViH 2022, available online
Vellekoop et al., Pers Med, in press

TAKE AWAY MESSAGES

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

- In **England** and the **Netherlands**, the implementation of entrectinib was also not found to be cost-effective, though the results from a subgroup analysis of NTRK+ patients suggested that entrectinib has the potential to be cost-effective. (EN: Cancer Drug Fund, NL conditionally reimbursed)

- **Reducing the costs of stratification** is necessary, especially when NNT is high, but it may not be sufficient.
  - In the Netherlands, the cost of RNA-NGS would have to be **reduced by 90%** for implementation of entrectinib to become CE.
  - In England and Hungary, the net benefit to society remains negative, even if the test was provided **for free.**
  - A reduction in the drug price is needed.

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Genetic testing of Maturity Onset Diabetes of the Young (MODY)

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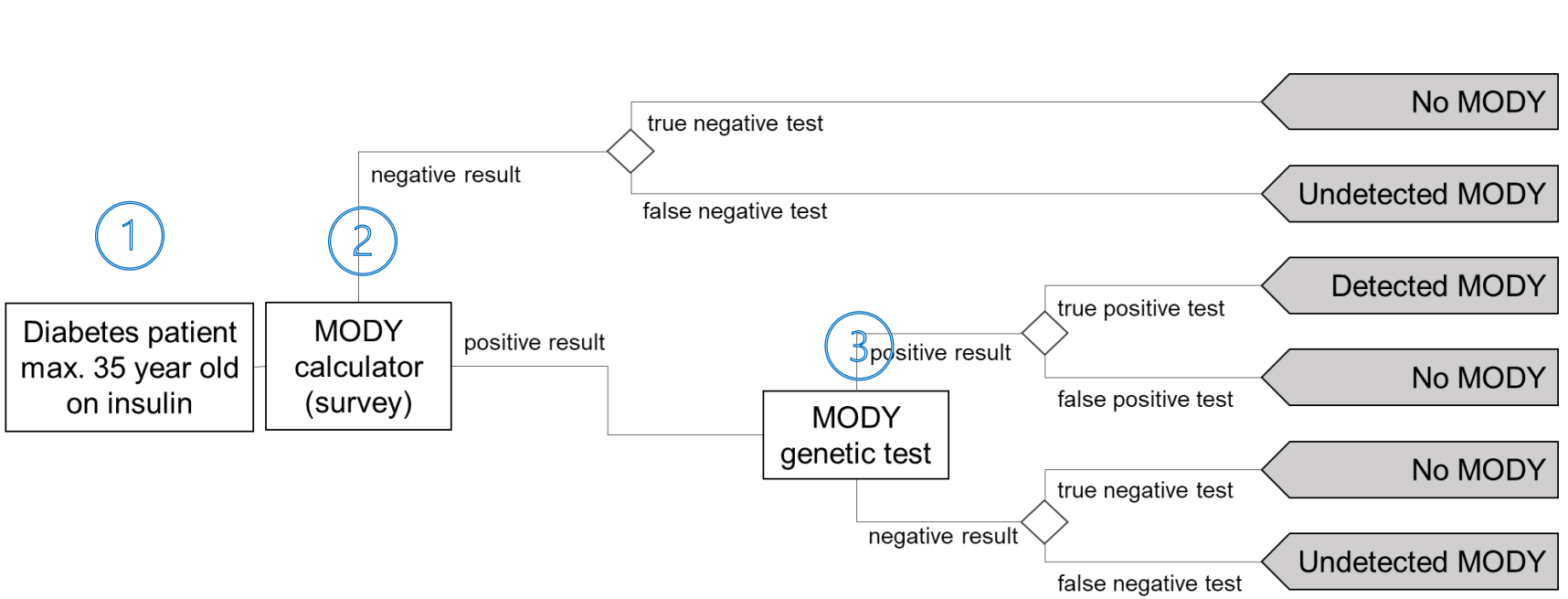
This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824997.

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 insulin 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

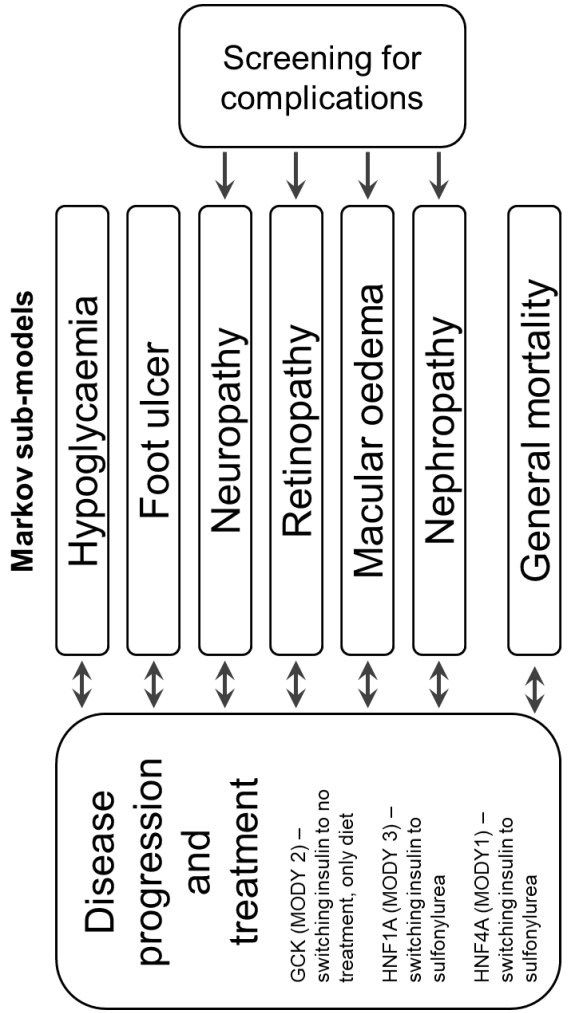
Is it cost-effective and affordably to diagnose MODY patients by genetic testing?

MODY – PATIENT STRATIFICATION: RISK ASSESSMENT + GENETIC TEST

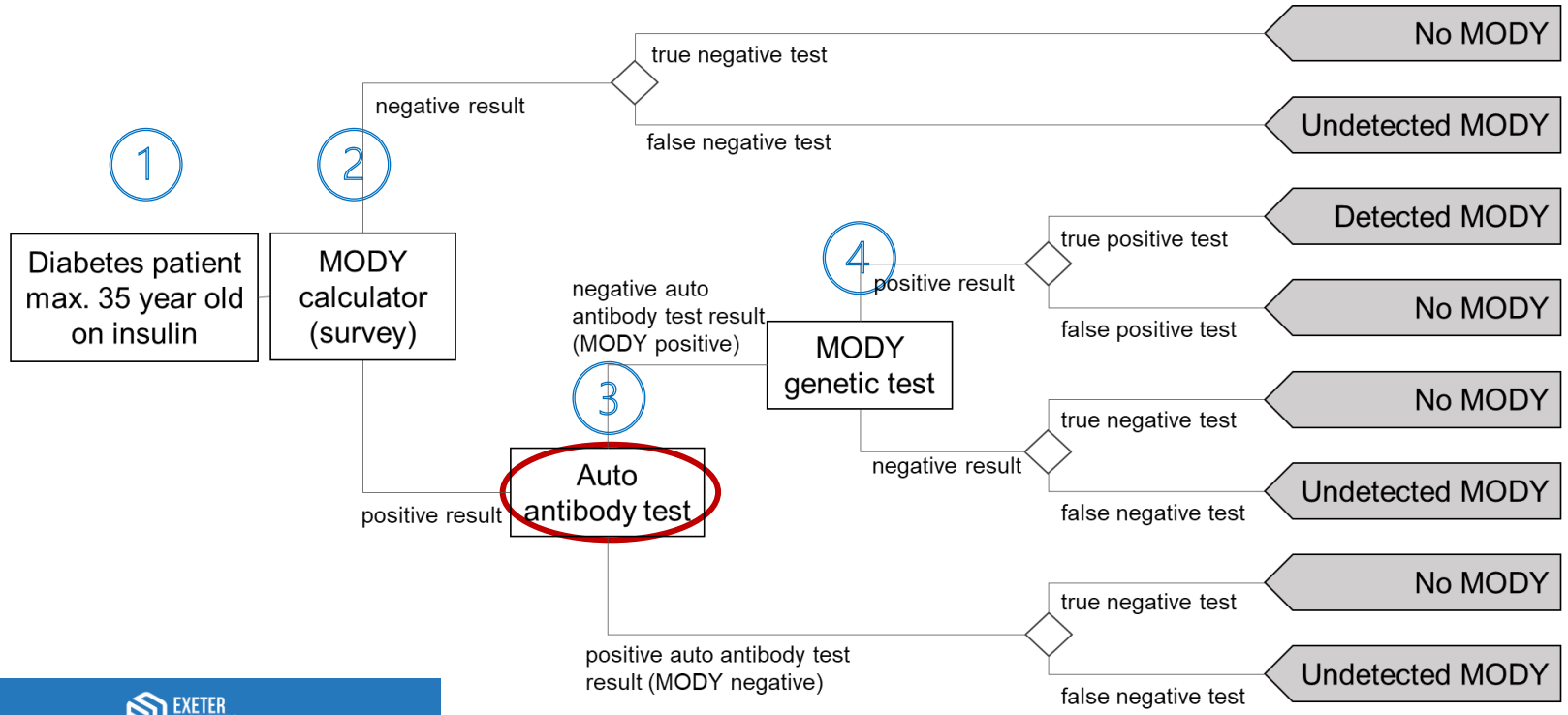


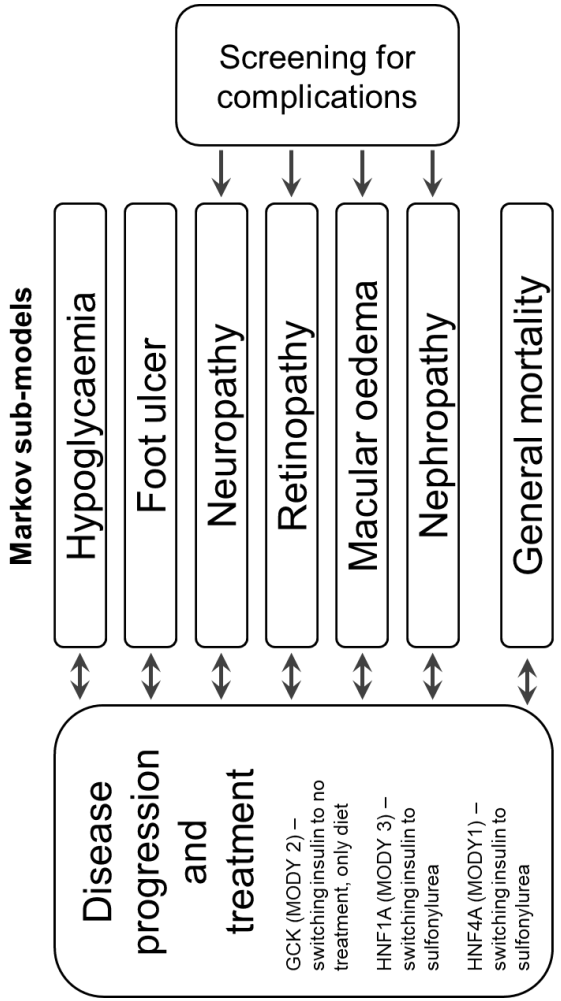
EXETER DIABETES

MODY Probability Calculator



MODY – PATIENT STRATIFICATION: RISK ASSESSMENT + LAB TEST + GENETIC TEST



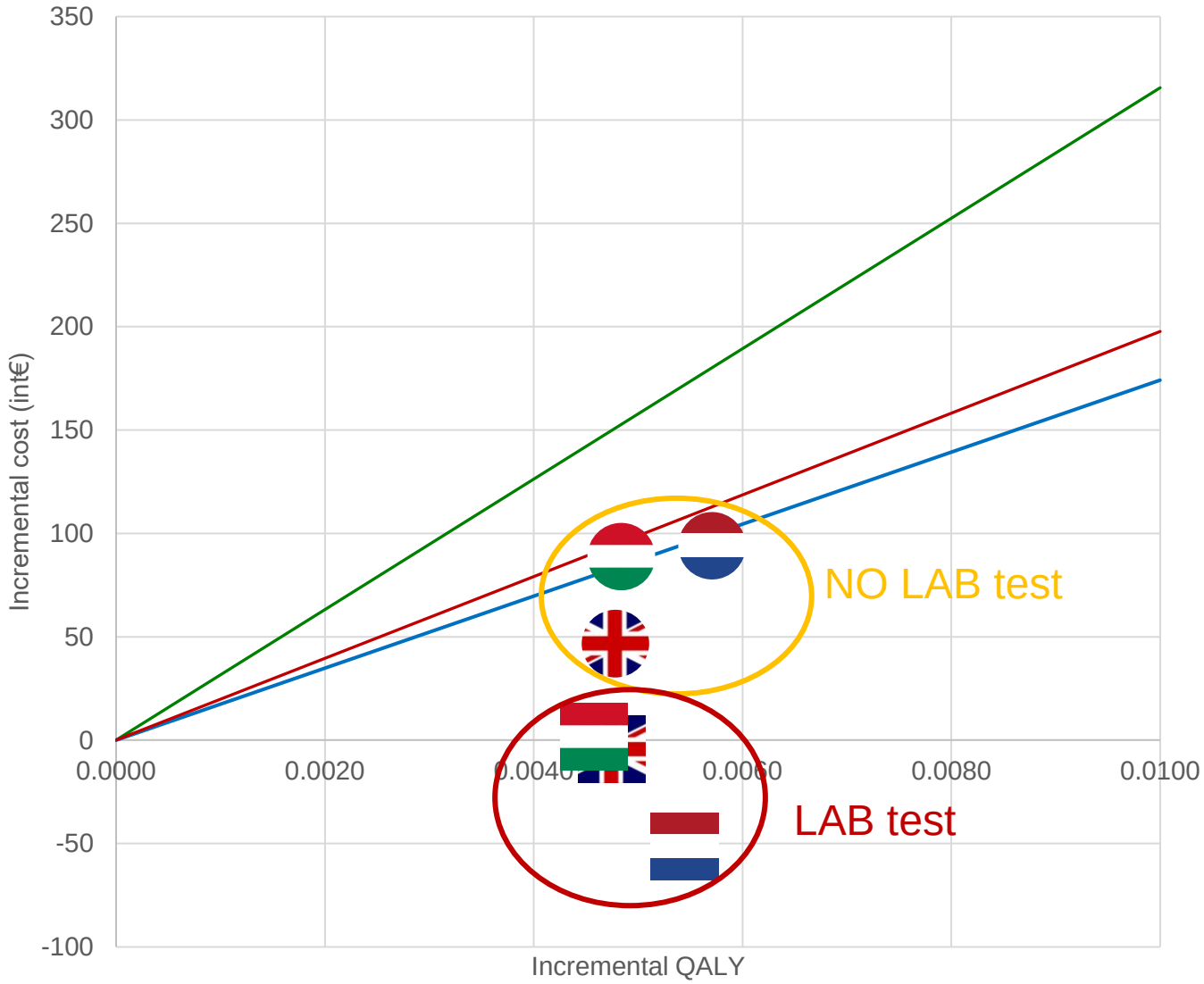


EXETER DIABETES

MODY Probability Calculator

Autoantibody Lab test

MODY – RESULTS FOR THREE COUNTRIES, TWO STRATEGIES



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

MODY - BUDGET IMPACT

Strategy	Five-year incremental budget impact (int€)		
	UK	***HU***	***NL***
MODY screening without autoantibody test vs. No screening	221,452,636	2,333,912	11,396,869
MODY screening with autoantibody test vs. No screening	146,699,297	373,996	2,060,035
	Percentage of public healthcare spending		
MODY screening without autoantibody test vs. No screening	0.025%	0.005%	0.004%
MODY screening with autoantibody test vs. No screening	0.017%	0.001%	0.001%

PREVALENCE OF TYPE 1 DIABETES

Country/Territory	2000	2011	2021
Europe	N/A	N/A	294.9
Russian Federation	-	-	38.1
Germany	-	-	35.1
United Kingdom	-	-	31.6
France	-	-	27.1
Turkey	-	-	25.8
Spain	-	-	17.2
Italy	-	-	13.7
Poland	-	-	12.5
Sweden	-	-	9.2
Ukraine	-	-	6.7
Netherlands	-	-	6.4

Country/Territory	2000	2011	2021
Finland	-	-	5.4
Belgium	-	-	4.3
Czechia	-	-	4.3
Israel	-	-	4.1
Romania	-	-	3.9
Norway	-	-	3.8
Austria	-	-	3.6
Hungary	-	-	3.5
Ireland	-	-	3.4
Denmark	-	-	3.1
Greece	-	-	2.9

source: IDF Diabetes Atlas 2021

MODY- TAKE AWAY MESSAGE

- **High prevalence health problem, treated with existing (cheap) care is cost effective**
- **The exact method of patient stratification was a game changer**
- **Differences in cost-effectiveness were not crucial**
- **Differences in affordability was linked with prevalence and costs (NOT with wealthiness)**

DPYD mutation testing prior to fluoropyrimidine-based chemotherapy in metastatic breast cancer

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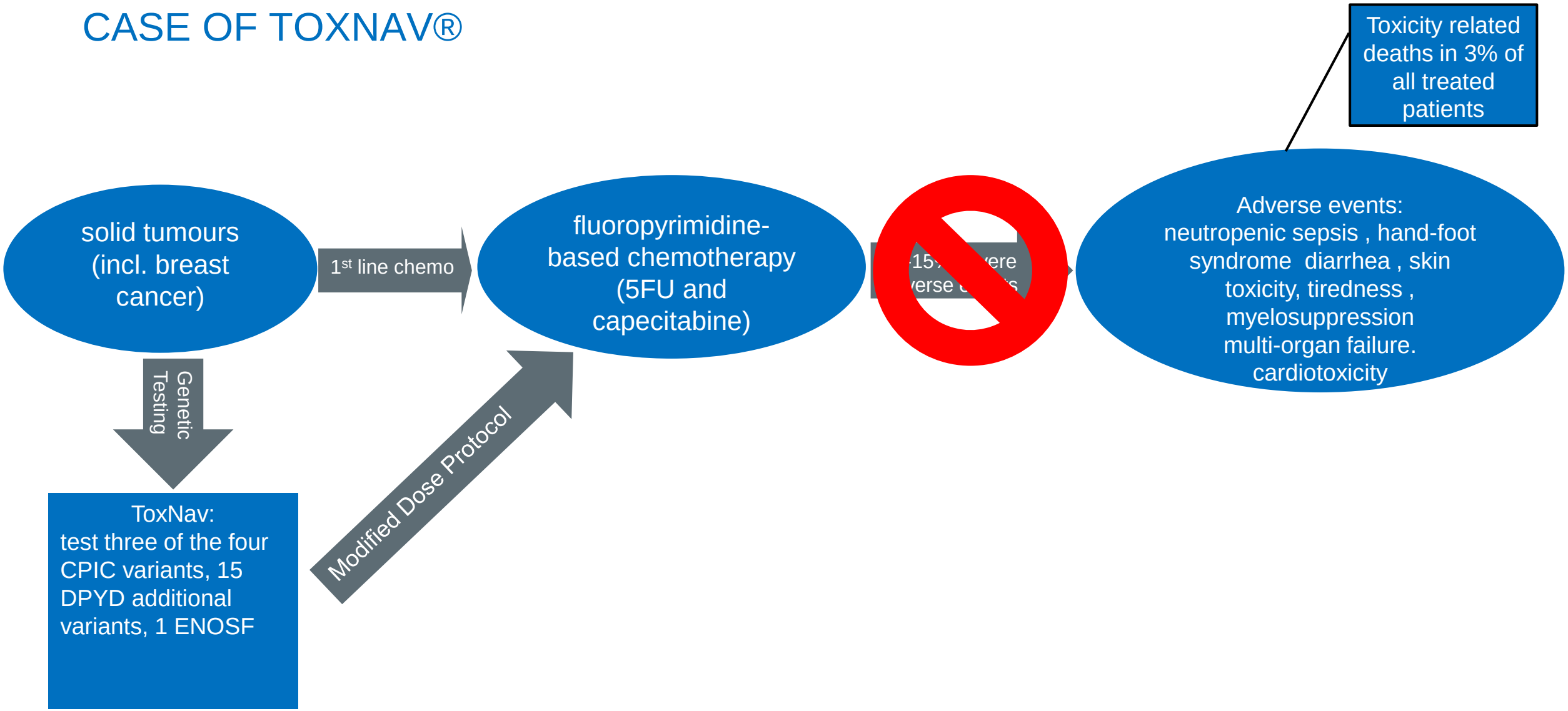
This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824997.

CASE OF TOXNAV®

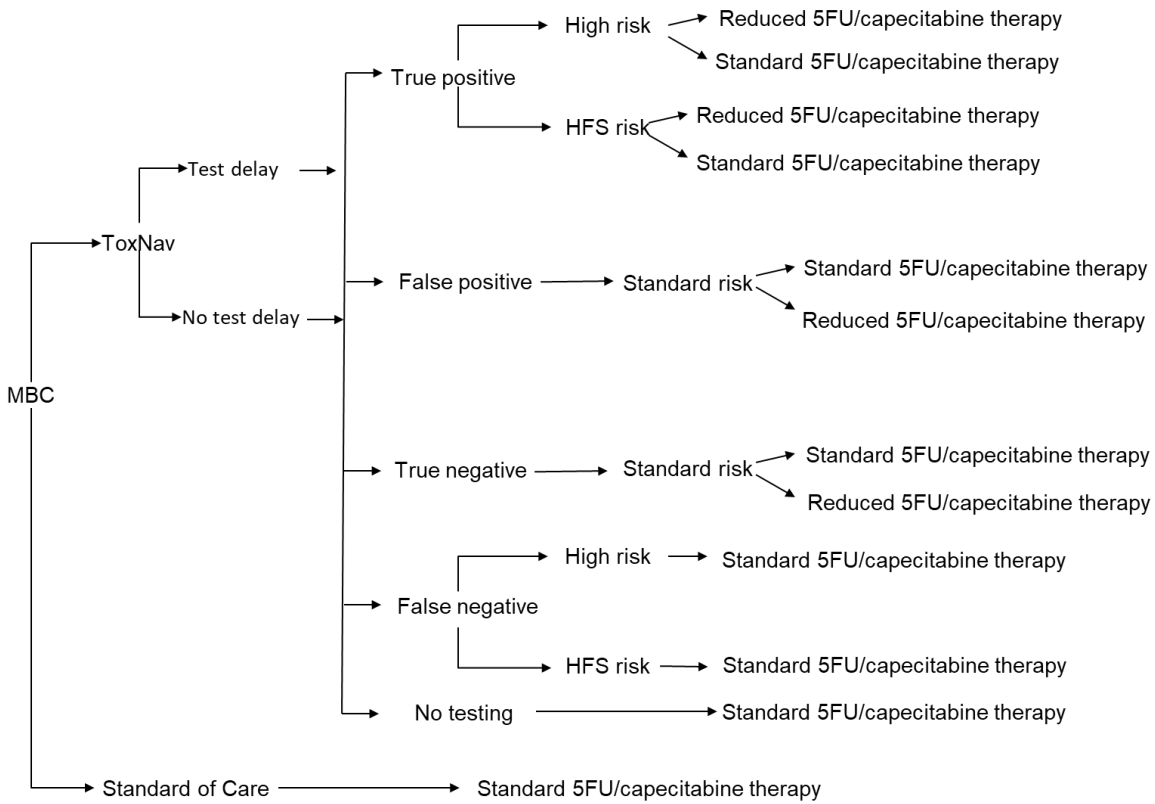


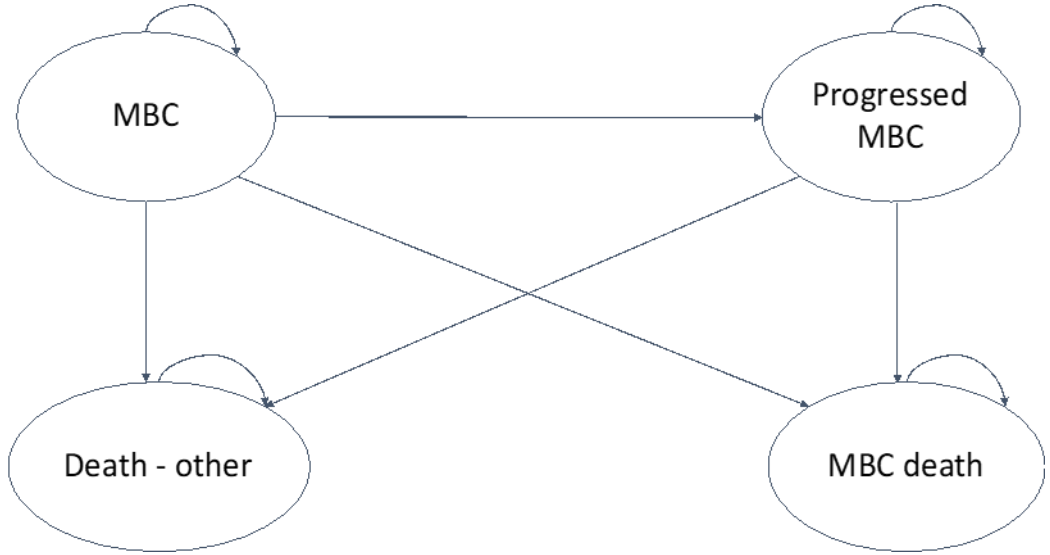
CASE OF TOXNAV

- **Current clinical implementation:**
  -  initiatives to implement DPYD testing across NHS
  -  DPYD testing implemented for all cancer patients assigned to 5FU/capecitabine
  -  not standard of care

- **Is it cost-effective and affordable to test metastatic breast cancer patients for DPYD mutation prior to 5FU/capecitabine?**

TOXNAV - DECISION TREE + MARKOV MODEL





- Adverse events leading to utility decrement and costs
- Rates of adverse events (haemoglobin, neutrophil count, white cell count, and temperature) based on Oxford Oncology Directorates' data
- Local data for costs, disease utilities, general mortality

- MBC = metastatic breast cancer

Sensitivity ToxNav 100%. Specificity 98%.

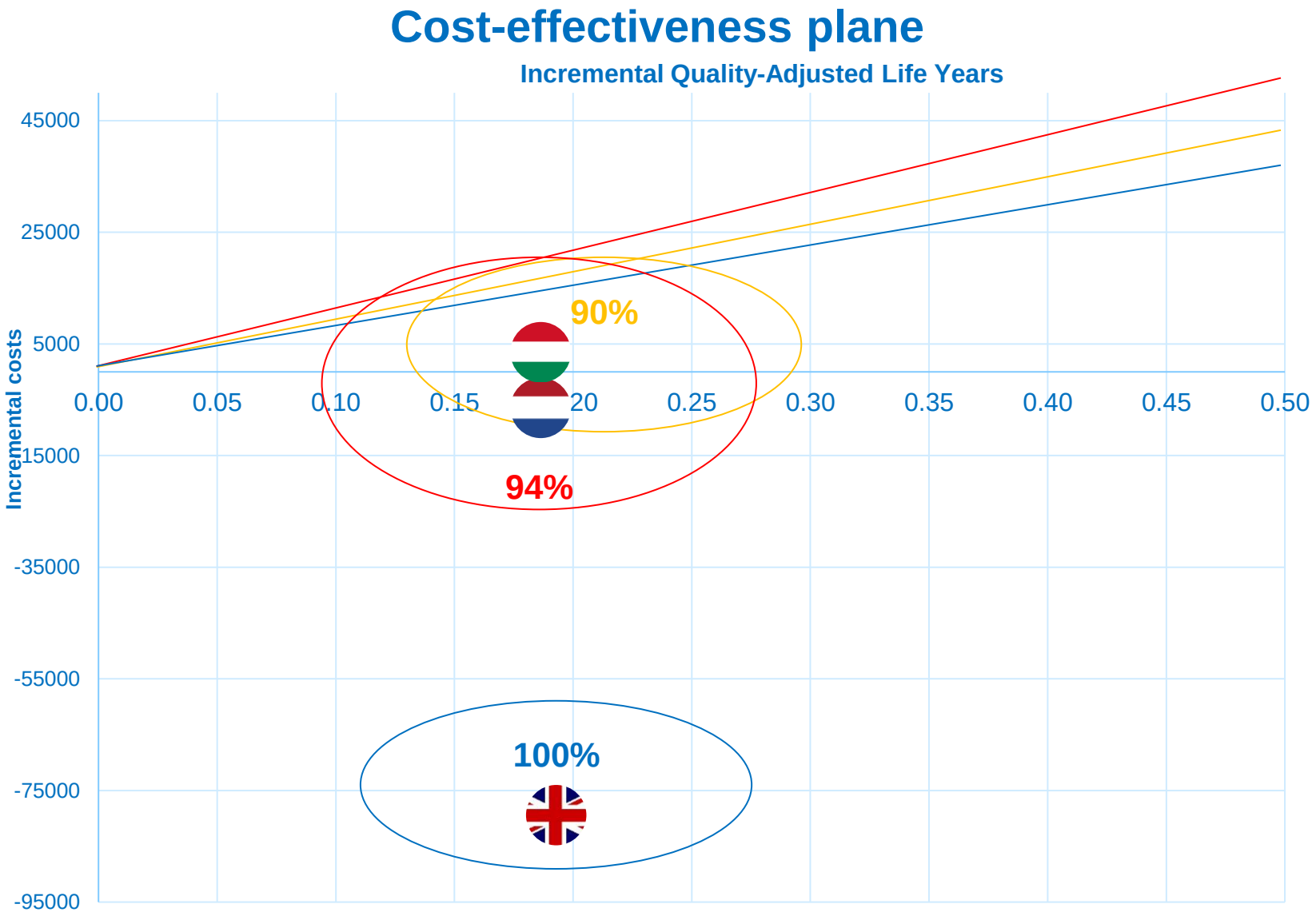
Local prevalence DPYD mutation

Oxford Oncology Directorates' data for compliance and variant prevalence

TOXNAV – RESULTS FOR THREE COUNTRIES

- Cost effectiveness thresholds:
  - Hungary
  - Netherlands
  - United Kingdom

- ToxNav vs No genetic testing:
  - UK – dominant
  - NL – dominant
  - HU – cost-effective



TOXNAV – BUDGET IMPACT RESULTS

Strategy	Five-year incremental budget impact (in mln int€)		
	UK	*HU*	*NL*
ToxNav vs. No genetic testing	-2,984	+1.2	-1.7
ToxNav vs. No genetic testing/ 50% population	-1,492	+1.1	-0.968
ToxNav vs. No genetic testing/ Managed entry agreement for ToxNav in 4 & 5 year	-3,021	+0.600	-0.838

TOXNAV – TAKE AWAY MESSAGES

- **ToxNav for upfront DPYD testing to stratify patients to chemotherapy dose adjustment is cost-effective**
- **Savings in drug and adverse event treatment outweigh cost of testing**
- **Differences in savings depend on the availability of granular costing data**
- **Cost of testing can affect affordability (UK price converted by PPP for NL and HU)**
- **Improved equity by using an extended gene panel (ToxNav), however, different testing strategies for DPYD need to be compared**

WRAP UP

- The TOXNAV©, MODY and NTRK cases seem to confirm the results of our published literature review of the Net Benefit of Personalized Medicine, i.e.

  - the potential for cost-effective application of genetic tests to better stratify patients to established therapies is underused, when compared to

  - the attention that is paid to less cost-effective genetic tests to identify responders to expensive innovative therapies

IT’S TIME FOR A POLL

- **How can we improve affordability of genetic test/expensive treatment combinations?**

Open Ended / Short Answer question, wordcloud