EcoPerMed
Health Economics for Personalised Medicine

DYPD GENOTYPING

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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

RATIONALE

- 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)

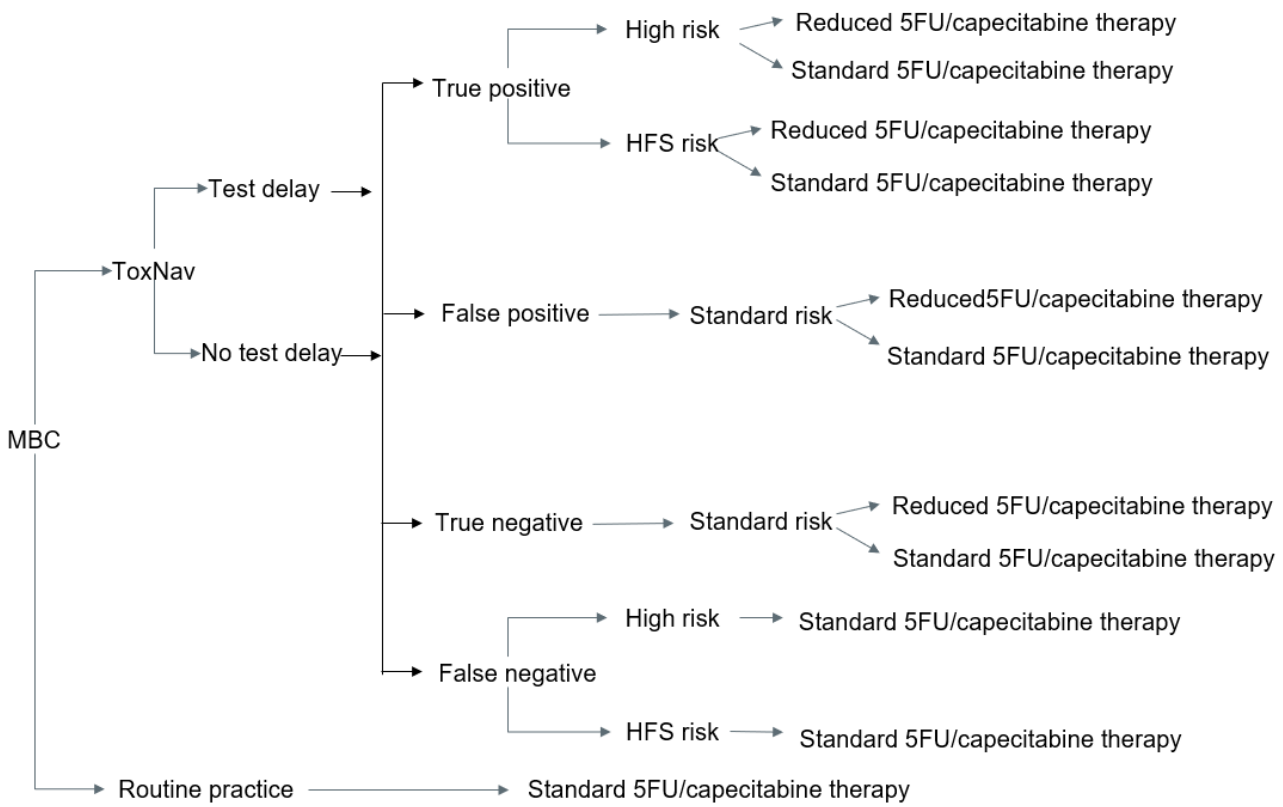
TOXNAV TEST

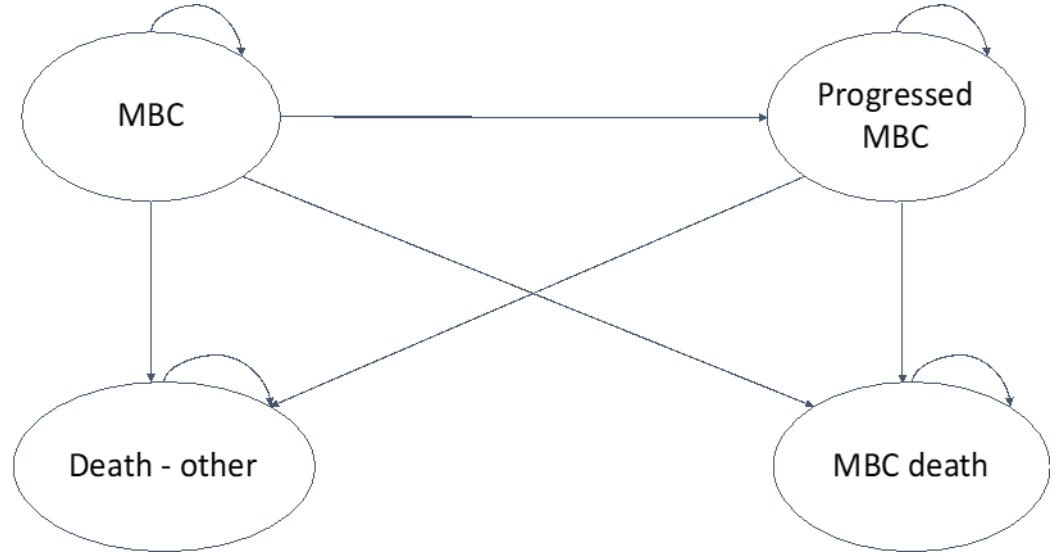
- Currently, only 4 genomic variants in the DPYD gene are tested for, yet 50% of patients with severe toxicity do not have these variants
- ToxNav test developed to allow for testing a broader panel of variants that may have correlation with 5FU and capecitabine toxicities. These included three of the 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**

METHODS

- Target population: women with MBC aged 60 years
- Two part model – decision tree + cohort Markov model, 10 000 simulated women, MS Excel
- Decision tree reflects the testing period: from administering the ToxNav test to start of treatment
- Markov model – 4 health states: MBC, progressive MBC, death from disease, death from other causes
- Included treatments: standard capecitabine/5FU and reduced capecitabine/5FU containing regimens
- Observational study
- Cycle length: 2 months
- Time horizon: lifetime
- Perspective: UK healthcare
- Discount rate: 3.5%
- Uncertainty – DSA & PSA

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%.

TOXNAV MODEL KEY PARAMETERS

- The cost of the ToxNav test was assumed to be £200

- Costs and adverse events rates are based on a propensity score matched (PSM) analysis of 2,022 cancer patients treated at the Oxford NHS Trust

- Performed PSM to estimate adverse events according to grades for ToxNav and Routine practice strategies:
  - Risk of adverse events:
    - haemoglobin Grade 1-2 and Grade 3-4;
    - neutrophils Grade 1-2 and Grade 3-4;
    - white cells Grade 1-2 and Grade 3-4;
    - temperature Grade 1-2 and Grade 3-4.
  - The risk of adverse events by type and grade is used in the Markov model only to estimate the dis-utilities accrued by patients related to these events

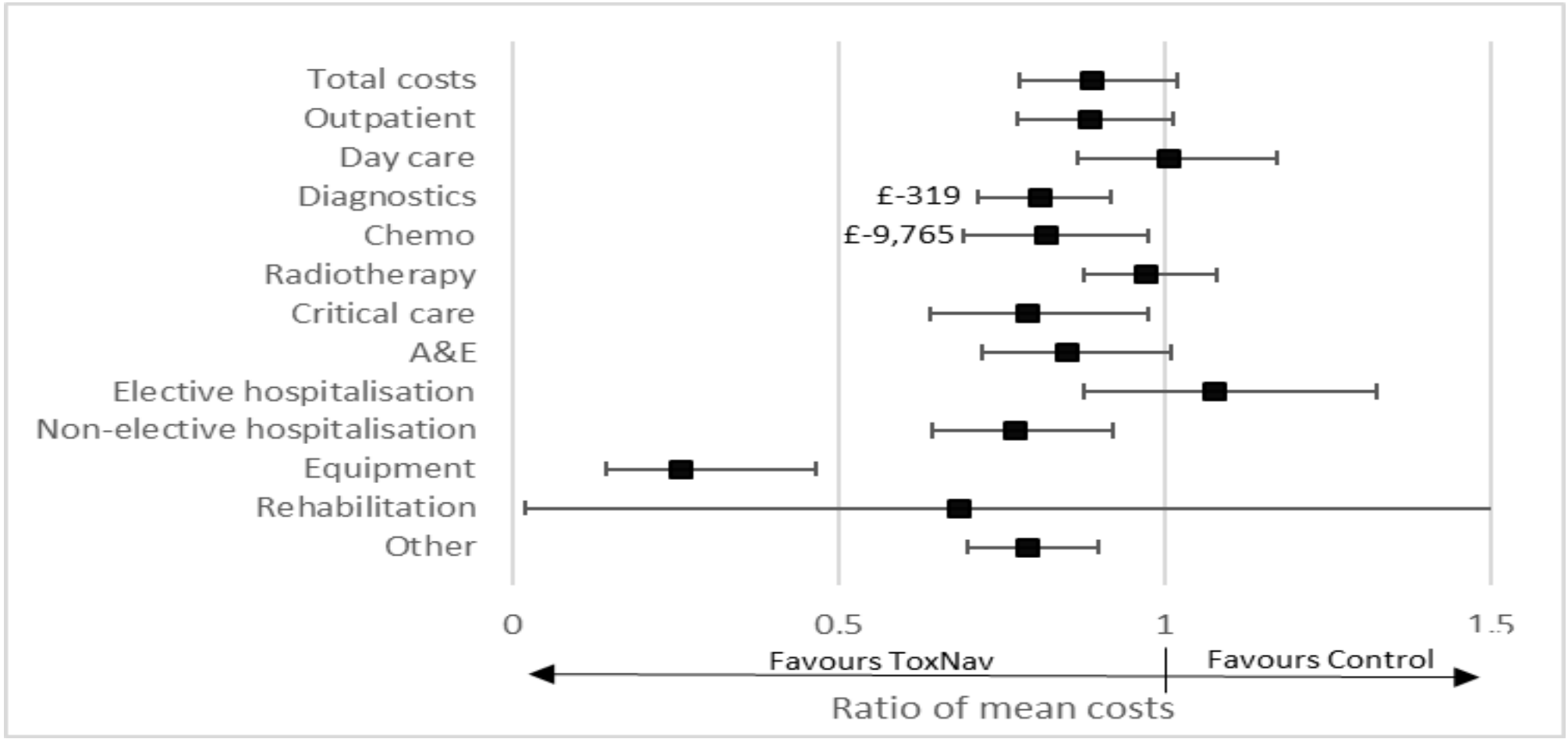
UTILITIES

- Utilities for MBC and progressive MBC states were based on UK specific estimates;

- Dis-utilities for adverse events based on published economic studies and are not country specific:

Utility weights	
MBC	0.715
Progressed MBC	0.443
Neutrophil count Grade 1-2	-0.100
Neutrophil count Grade 3-4	-0.120
Haemoglobin Grade 1-2	-0.1714
Haemoglobin Grade 3-4	-0.1914
White cell count Grade 1-2	-0.100
White cell count Grade 3-4	-0.120
Temperature Grade 1-2	-0.130
Temperature Grade 3-4	-0.150

RESULTS: IMPACT OF TOXNAV TESTING ON HOSPITAL COSTS

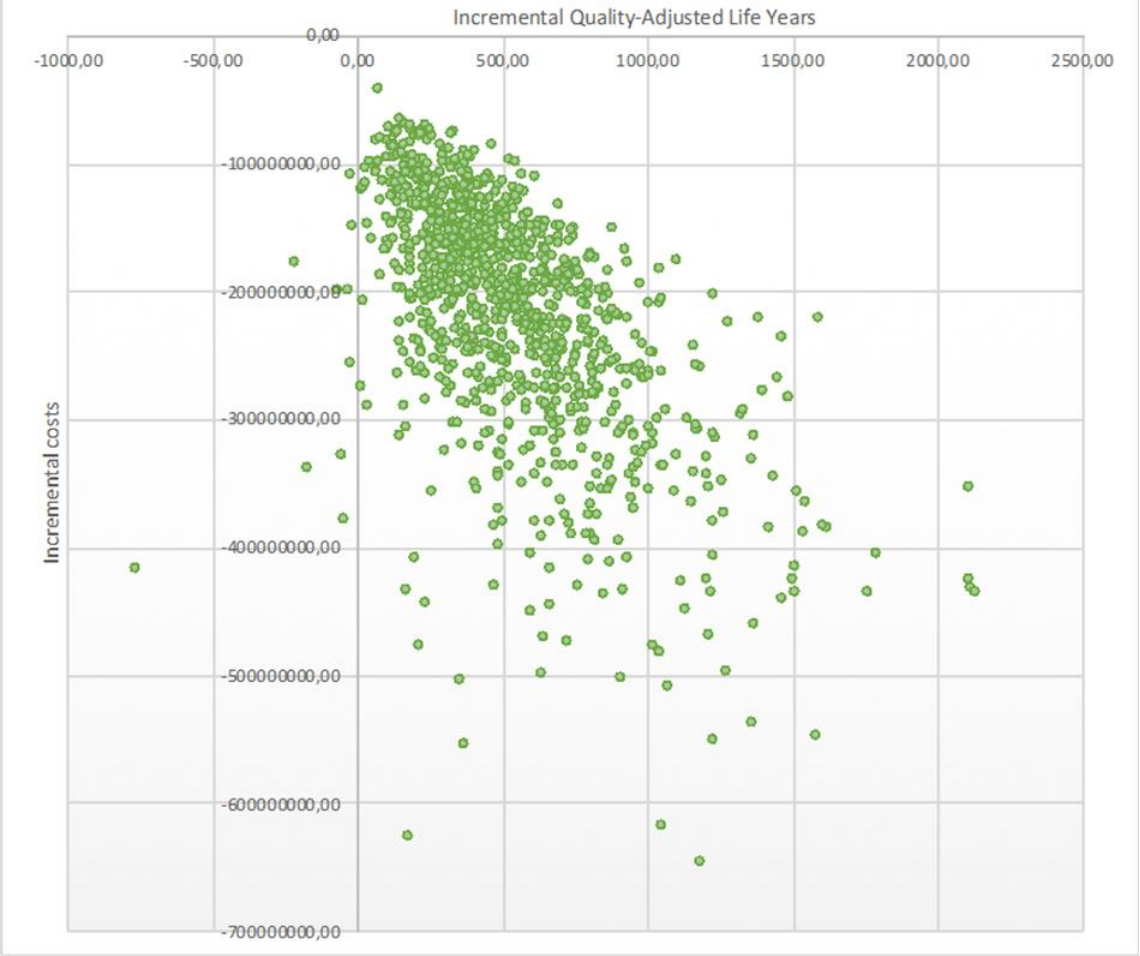


RESULTS: PRELIMINARY COST-EFFECTIVENESS

Base case for a cohort of 10,000 women with mean age of 60

Strategy	Costs (in £)	QALYs	ICER
Standard of Care	555,3	17243.5	
ToxNav strategy	241,9	17988.3	
Incremental	-313,4	744,8	dominant

HIGH CERTAINTY THAT TOXNAV IS DOMINANT



DISCUSSION

- 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 has impact on lowering the likelihood of some AEs and increasing others; might have some positive impact on mental heath (pain reduction)

- Guidance implementation:
  - Effectiveness data (11) – perhaps consider adding that effectiveness data can be obtained from RWD, especially when new genetic tests are developed for long existing treatments with proven benefit.

TESTING HECOPERMED RECOMMENDATIONS

15 of 23 recommendations were applied in our case study

- Our case study managed to address 15 out of 23 recommendations; 7 items were not applicable for our case, 1 item was not included.

	ToxNav
Addressed	15
Not applicable	7
Not included	1

Guidance items	Recommendations	Application to the ToxNav case study
Perspective and Discounting	1. For economic evaluations of PM, use the standard perspective as recommended by national HTA guidelines in the base case.	applied
	2. For economic evaluations of PM, use the standard discount rates as recommended by national HTA guidelines in the base case.	applied
Test-Treatment Pathways	3. Identify all relevant test-treatment pathways and justify why the pathways included in the model were selected.	applied
	4. When treatment requires the use of a test to stratify patients, include in the model the (downstream) costs and health outcomes of testing for both individuals who test (false-)positive and individuals who test (false)negative.	applied
	5. Ensure that the data used to estimate the diagnostic accuracy of a testing technology are appropriate to the patient population in the model.	applied
	6. When different cut-off values are in use to determine test results, clearly define the cut-off value assumed in the base case. Investigate the effect of alternative cut-off values on cost-effectiveness results using a sensitivity analysis.	not applicable
	7. When multiple tests are modelled in sequence, consider the interdependence between test results.	not applicable
	8. If there is a notable risk of increased morbidity or mortality as a result of waiting periods, incorporate in the model the costs and health outcomes due to the waiting periods.	applied
	9. Confirm that the assumed testing costs are accurate in the setting of interest and consider possible variations in costs across laboratories.	applied
	10. If relatives of index patients become eligible for genetic testing when the index patients test positive for a specific genetic marker, include the costs and health outcomes of testing relatives in the economic evaluation of the index patients.	not applicable
Effectiveness Data	11. Where possible, use effectiveness data from trials with two (or more) alternative treatment strategies.	applied
	12. When surrogate outcomes are used to estimate final outcomes, specify which data sources were used to estimate the relationship between surrogate and final outcomes and justify any assumptions made about the relationship	not applicable
	13. When the effectiveness of the comparator is estimated using external data, account for a possible time trend in the effectiveness.	not applicable
	14. When the effectiveness of the comparator for patients with a specific genetic marker is estimated using external data, account for the prognostic value of the genetic marker and differences in its prevalence across the different data sources.	not applicable
	15. Specify which data sources were used to estimate the association between the genetic marker(s) of interest and clinical outcomes and justify any assumptions made about the association.	applied
Extrapolating Survival	16. When extrapolating survival data beyond the study period, use expert opinion alongside statistical fit to choose the survival model.	applied
	17. When extrapolating survival data beyond the study period, account for any excess mortality and morbidity among long-term survivors.	not applicable
Additional Elements of Value	18. Only include elements of value recommended by national HTA guidelines in the base case. If additional elements of value are included in a sensitivity analysis, ensure possible elements of negative value are equally considered and included for both the intervention and the comparator.	applied
Incorporating Compliance	19. Include parameters reflecting patient and clinician compliance in economic evaluations for decision-makers who require cost-effectiveness results under realistic circumstances.	applied
	20. When including patient and clinician compliance in economic evaluations, confirm that the assumed compliance is accurate in the setting of interest and consider possible variation in compliance across societal groups.	applied
Uncertainty Analysis	21. When expert judgement is used to estimate values for the input parameters in the model, synthesise the elicited values into a probability distribution to be included in a sensitivity analysis.	applied
	22. Identify uncertainties in structural assumptions and decisions and investigate their impact on cost-effectiveness results through a sensitivity analysis. Parameterise structural aspects where possible.	applied
Managed Entry Agreements	23. If a managed entry agreement is being considered for intervention, including its conditions in the model evaluating the intervention.	not included

POLLING

- Should the use of real world evidence in economic modelling of personalised medicine (PM) be more acceptable than in other clinical areas, considering the data and randomisation challenges in PM?

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THANK YOU!

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