Healthcare Improvement Scotland | SHTG Advice on health technologies

SHTG Assessment
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Pre-treatment DPYD genetic testing for patients who are prescribed chemotherapy involving fluoropyrimidines

What were we asked to look at?

NHS National Services Scotland asked us to look at the economic case for routine pretreatment DPYD genetic testing for patients who are prescribed fluoropyrimidine-based chemotherapy.

Why is this important?

Fluoropyrimidines are chemotherapy drugs frequently used in the treatment of several types of cancer. Approximately 10% to 30% of patients treated with fluoropyrimidines experience severe (grade≥3) treatment-related toxicities. Changes to the DPYD gene can lead to dihydropyrimidine dehydrogenase (DPD) enzyme deficiency, which can lead to the accumulation of cytotoxic chemotherapy compounds in the body and cause severe side effects. Pre-treatment genetic testing could facilitate the delivery of tailored chemotherapy dosing schedules and reduce severe fluoropyrimidine-related toxicity in patients.

What was our approach?

We undertook an SHTG Assessment that included a literature review of the clinical effectiveness, safety and cost effectiveness evidence, followed by *de novo* economic modelling for NHSScotland. Information on our SHTG Assessment product can be found on the Healthcare Improvement Scotland website.

What next?

The SHTG Assessment will be incorporated into a business case being submitted to the National Patient Public and Professional Reference Group (NPPPRG)/National Specialist Services Committee (NSSC). The business case will aid decision making around securing funding for the implementation and delivery of routine DPYD genetic testing in NHSScotland.

Key findings

- Two systematic reviews and an individual patient data meta-analysis reported clinically significant increases in risk of severe (grade ≥3) fluoropyrimidine (FP)-related toxicity in patients with DPYD gene variants c.1905+1G>A, c.2846A>T, c.1679T>G, or c.1236G>A/Hap B3. No clinically significant increase in risk of severe toxicity was found in patients with DPYD variant c.1601G>A.
- Four cohort studies – two prospective and two retrospective – explored the feasibility and effects of DPYD genetic testing in routine clinical practice.
    - All four studies reported successful implementation of DPYD genetic testing, with subsequent individualisation of FP dose for patients with clinically relevant DPYD variants.
    - The two comparative prospective studies demonstrated a significant reduction in risk of severe (grade ≥3) treatment-related toxicity in patients with DPYD variants treated with reduced doses of FP compared with historical cohorts receiving a full dose.
    - In one of the prospective studies the frequency of treatment-related severe (grade ≥3) toxicity in patients with DPYD variant c.1905+1G>A, receiving reduced doses of FP, was similar to that of wild-type variant patients receiving a full FP dose. In the second prospective study, despite FP dose reduction, the risk of severe toxicity remained elevated in patients with DPYD variants c.1236G>A or c.2846A>T compared with wild-type variant patients
- Four published costing studies found that a pre-treatment testing strategy for DPYD gene variants is likely to be cost saving compared to reactive testing.
- SHTG conducted an economic analysis using Scottish incidence and cost data. The model compared the costs and adverse events associated with a strategy of prospective DPYD genetic testing for patients eligible for FP based chemotherapy versus a strategy of no testing.
    - Prospective testing was the dominant strategy. This meant it was less costly and led to fewer adverse events and associated hospital admissions compared to a no-testing strategy.
    - The model predicted that up to 24 serious adverse events could be averted for every 1,000 patients tested.
    - The incremental costs of DPYD testing are expected to be offset by lower expenditure on acute and in-patient care for patients experiencing adverse events.

Contents

Definitions

Allele: one of two or more versions of a gene. Each individual inherits two alleles for each gene, one from each parent[1].

Heterozygous and homozygous: heterozygous refers to an individual who inherited two different alleles of a gene – one from each parent. Homozygous refers to an individual who inherits the same allele for a particular gene from both parents[1].

Wild-type gene: a gene when it occurs in its natural, non-mutated (unchanged) form[2].

Literature search

A systematic literature search was carried out between 24 and 26 February 2020. The Medline, Medline in process, and Embase databases, were searched. All search results were limited to studies published in English between 2000 and 2020. Searches were not limited by study design.

Concepts used in all searches included: fluoropyrimidines (5-fluoroucil, 5FU, flucytosine, capecitabine, tegafur); DPD, DPYD or dihydropyrimidine dehydrogenase. A full list of resources searched and terms used are available on request.

Research question

Is routine pretreatment DPYD genetic testing for patients prescribed fluoropyrimidine-based chemotherapy for treating cancer feasible and cost effective?

Introduction

Fluoropyrimidines (FP) are chemotherapy drugs predominantly used in the treatment of colorectal, oesophageal, gastric, breast, and head and neck cancers[3]. Approximately 10-30% of patients treated with FP experience severe (grade 3-5) treatment-related toxicity[3, 4]. These toxicities include mucositis (inflammation and ulceration of the digestive tract), hand-foot syndrome (redness, swelling, pain and blisters on the palms and soles of feet), breathlessness, hair loss, neutropenia (low white blood cell count), thrombocytopenia (low blood platelets), cardiac toxicity, and death[5, 6].

Changes to genes involved in drug metabolism can affect how patients respond to treatment, and are associated with increases in the number and severity of adverse drug reactions. The DPYD gene codes for an enzyme called dihydropyrimidine dehydrogenase

(DPD) which breaks down FP into non-cytotoxic metabolites[4]. Changes to the DPYD gene can lead to DPD enzyme deficiency, which may cause cytotoxic compounds to build up in the body resulting in severe treatment-related toxicity in patients treated with FP[3]. An estimated 39-61% of patients who experience severe treatment-related toxicity following chemotherapy with FP have been found to have a DPD enzyme deficiency[4].

Chemotherapy toxicities lead to disruption or discontinuation of treatment and often require hospitalisation of the patient, thereby impacting on patient prognosis, quality of life and healthcare costs[7]. Pre-treatment genetic testing could potentially facilitate the delivery of tailored dosing schedules to patients eligible for FP-based chemotherapy, and thereby prevent severe treatment-related toxicity.

Health technology description

There is currently no routine pre-treatment DPYD genetic testing in NHSScotland, although individually requested DPYD testing is performed (Ms K O'Rourke, Programme Manager, NHS National Services Division. Personal communication, 10 Jan 2020).

In Scotland, the majority of testing for DPYD gene variants uses polymerase chain reaction (PCR) followed by Sanger single gene sequencing. PCR amplifies - makes numerous copies of – DNA[8]. The Sanger technique then sequences the DPYD gene using fluorescent dyes to detect variants associated with adverse reactions to FP. The Sanger technique can only analyse a short section of DNA from one patient at a time.

An alternative test of interest in the Scottish context is the Elucigene® DPYD multiplex assay. This assay allows for rapid simultaneous detection of six known DPYD variants, including those that affect DPD enzyme function[9].

There are four DPYD variants of potential interest in NHSScotland (table 1).

The Clinical Pharmacogenetics Implementation Consortium (CPIC) have produced guidelines on the interpretation of DPYD genetic tests for the purpose of fluoropyrimidine dose adjustment[10].

Table 1: DPYD gene variants of interest to NHSScotland[4, 10]

DPYD variant	Alternative identifier	Effect on DPD activity in heterozygous variant carriers	Estimated carrier frequency (heterozygotes) *
c.1905+1G>A (IVS14+1G>A)	DPYD*2A	50% reduction	1-1.2%
c.2846A>T	DPYD*9B	25% reduction	0.8 -1.4%
c.1679T>G	DPYD*13	50% reduction	0.1%
c.1236G>A / Hap B3 (includes c.1129-5923C>G)	–	25% reduction	4.1 – 4.8%

* in Caucasian population

Epidemiology

An estimated 3-5% of the European population have a partial DPD enzyme deficiency, which reduces their ability to metabolise FP by approximately 50%[4, 11]. Total DPD enzyme deficiency is much rarer, affecting an estimated 0.01% to 0.2% of the European population[4, 6]. Although estimated carrier frequency of DPYD gene variants in other populations is not known, Caucasians may have greater genetic pre-disposition to being DPD deficient. There is insufficient evidence to suggest that race should be used as selection criteria to restrict access to genetic testing. The prospective testing strategy, which is the subject of this assessment, would ensure equal access to genetic testing by all patients suitable for FP based chemotherapy irrespective of racial background.

FP chemotherapy is most frequently used in patients with colorectal, oesophageal, gastric, breast, or head and neck cancer. Table 2 presents incidence and prevalence data for these cancer types in Scotland.

Table 2: Scottish incidence and prevalence data on cancers[12]

Cancer	Incidence (new cases in 2017)	Prevalence in population (all ages surviving up to 20 years)
Breast*	4,742	0.89%
Colorectal	3,800	0.45%
Gastric	620	0.03%
Head and neck	1,281	0.11%
Oesophageal	972	0.03%

* male and female

Approximately 10-30% of patients treated with FP-based chemotherapy experience severe (grade ≥3) treatment-related toxicities[3, 4]. These toxicities include mucositis (inflammation and ulceration of the digestive tract), hand-foot syndrome (redness, swelling, pain and blisters on the palms and soles of feet), breathlessness, hair loss, neutropenia (low white blood cell count), thrombocytopenia (low blood platelets), and cardiac toxicity. Up to 1% of patients experience a fatal toxicity[4].

A retrospective cohort study in cancer patients treated with FP in the UK (n=430) reported that 24% of patients experienced severe (grade ≥3) treatment-related toxicity, including diarrhoea (16%), neutropenia (10%) and mucositis (4%)[13]. No treatment-related mortality was reported, although treatment was discontinued for 31 patients (7.2%) due to severe toxicity. Twenty-three percent (24/104) of patients who experienced a severe treatment-related toxicity (grade ≥3) were found to have one or more DPYD gene variant.

Clinical effectiveness and safety

Associations between DPYD variants, DPD enzyme deficiency, and FP toxicity

The value of pre-treatment DPYD genetic testing is dependent on evidence of a clinically significant association between specific DPYD gene variants and increased FP chemotherapy-related toxicity. An overarching review of systematic reviews, and an individual patient data (IPD) meta-analysis published after the overarching review search period, were identified that assessed the relationship between DPYD variants of interest and severe (grade ≥3) FP-related toxicity[14, 15].

The overarching review incorporated two systematic reviews relating to DPYD gene variants of interest: Rosmarin *et al* (2014) who assessed the c.1905+1G>A variant, and Terrazino *et al* (2013) who considered the c.1905+1G>A and c.2846A>T variants[14]. Any severe (grade ≥3) FP-related toxicity was the primary outcome in both of these reviews (table 3). The systematic review by Rosmarin *et al* (2014) found a clinically significant increase in the odds of all severe treatment-related toxicities in patients with DPYD variant c.1905+1G>A who received infusional FP. There was no significant association between this DPYD variant and toxicity in patients treated with capecitabine. Terrazino *et al* (2013) described a clinically significant increase in the odds of severe FP-related toxicities in patients with either DPYD variant c.1905+1G>A or c.2846A>T. The increase in relative risk of all FP-related toxicities was greater for patients with c.2846A>T in analyses that were limited to prospective studies (odd ratio (OR) 18.14, 95% confidence interval (CI) 6.26 to 52.58, p<0.001, 4 studies) or to patients treated with 5-fluorouracil (OR 21.38, 95% CI 6.71 to 68.15, p<0.001, 3 studies). Neither Rosmarin *et al* (2014) nor Terrazino *et al* (2013) conducted subgroup analyses based on patient ethnicity, FP dose, or cancer type.

Table 3: results from two systematic reviews exploring the association between specific DPYD variants and severe (grade ≥3) FP-related toxicity[14]

DPYD variant	Tx	Toxicity type	Patients (studies)	OR (95% CI)	p-value
Rosmarin *et al* (2014): allele test of association model					
c.1905+1G>A	Capecitabine	All	1,035 (2)	3.02 (0.78 to 11.7)	NS
		Diarrhoea	1,035 (2)	3.14 (0.71 to 13.0)	NS
		Hand-foot syndrome	1,033 (2)	1.98 (0.52 to 7.54)	NS
c.1905+1G>A	Infused FP	All	732 (2)	6.71 (1.66 to 27.71)	0.0075
		Diarrhoea	720 (2)	7.71 (1.61 to 36.9)	0.011
Terrazino *et al* (2013): heterozygous vs. homozygous wild-type					
c.1905+1G>A	FP	All	3,499 (13)	5.42 (2.79 to 10.52)	<0.001
		Haematological	1,554 (7)	15.77 (6.36 to 39.06)	<0.001
		Diarrhoea	1,526 (6)	5.54 (2.31 to 13.29)	<0.001
		Mucositis	1,015 (5)	7.48 (3.03 to 18.47)	<0.001
c.2846A>T	FP	All	2,308 (6)	8.18 (2.65 to 25.25)	<0.001
		Diarrhoea	721 (3)	6.04 (1.77 to 20.66)	0.004

Tx = treatment type; NS = not significant

The IPD meta-analysis measured the relative risk of severe (grade ≥3) FP-related toxicity in patients with one of three DPYD variants: c.1679T>G, c.1236G>A/Hap B3, c.1601G>A[15]. Of the eight included cohorts (n=7,365) individual patient data were available for six studies, one of which was an unpublished cohort from the meta-analysis authors' institution, and study-level data were used for the remaining two cohorts. Table 4 presents the results from the IPD meta-analysis. All analyses compared variant allele carriers (heterozygous or homozygous) with patients who did not have variant DPYD alleles. There was a clinically

significant increased risk of any severe (grade ≥3) treatment-related toxicity in patients treated with FP regimens if they had DPYD gene variant c.1679T>G or c.1236G>A/Hap B3. No significant increase in risk of severe FP-related toxicity was found for patients with DPYD variant c.1601G>A. The analyses for total severe toxicities in patients with DPYD variants c.1679T>G or c.1601G>A contained substantial heterogeneity (85% and 91% respectively).

Table 4: results from an IPD meta-analysis measuring the association between specific DPYD variants and FP-related toxicities[15]

Toxicity	Total	Adjusted relative risk (RR) (95% CI)	p-value
c.1679T>G			
All	5,616	4.44 (2.08 to 9.30)	<0.0001
Gastrointestinal		5.72 (1.40 to 23.33)	0.015
Haematological		9.76 (3.03 to 31.48)	0.00014
Hand-foot syndrome*		–	–
c.1236G>A/HapB3			
All	4,261	1.59 (1.29 to 1.97)	<0.0001
Gastrointestinal		2.04 (1.49 to 2.78)	<0.0001
Haematological		2.07 (1.17 to 3.68)	0.013
Hand-foot syndrome		1.11 (0.70 to 1.77)	0.65
c.1601G>A			
All**	3,900	1.52 (0.86 to 2.70)	0.15
Gastrointestinal**		1.44 (0.96 to 2.17)	0.078
Haematological**		1.40 (0.86 to 2.17)	0.31
Hand-foot syndrome**		0.83 (0.48 to 1.45)	0.50

*No patients experienced hand-foot syndrome in this analysis

**Results are from meta-analysis after exclusion of an outlier study

DPYD genetic testing in clinical practice

Four cohort studies explored the feasibility and effects on patient safety of pretreatment DPYD genetic testing followed by FP dose modification (if appropriate)[7, 11, 16, 17]. The first of these studies was a small (n=66) retrospective cohort study evaluating the implementation of routine pre-treatment DPYD genetic testing in patients with metastatic breast cancer treated with capecitabine at a large hospital in London[17]. Four DPYD variants were tested for in this study: c.1905+1G>A, c.2846A>T, c.1679T>G, and c.1601G>A. Although DPYD variant c.1236G>A was identified in the study introduction as clinically relevant, it was not tested for in this cohort of patients. Five patients (8%) were found to be heterozygous for one of the DPYD gene variants. Two of these patients received a 50% reduction in capecitabine dose, and three were treated with an alternative chemotherapy regimen, possibly due to uncertainty about the safety and effectiveness of FP dose reduction at the time of treatment. The study authors concluded that a rapid turnaround time for DPYD testing and the relatively low cost of testing contributed to successful implementation of pre-treatment DPYD testing in routine clinical practice.

The other three cohort studies – two prospective and one retrospective – were all conducted in the Netherlands. The most recent study (2018) was a prospective cohort of patients with cancer scheduled for FP chemotherapy at one of 17 hospitals[11]. One thousand-one hundred-three evaluable patients were tested for one of four clinically relevant DPYD gene variants: c.1236G>A, c.2846A>T, c.1905+1G>A, and c.1679T>G. Eighty-five patients (8%) were found to be heterozygous DPYD gene variant carriers and were prescribed reduced doses of FP. Despite dose reduction, thirty-three patients with a DPYD gene variant (39%) experienced grade ≥3 toxicity compared with 23% (n=231/1,018) of patients with the wild-type DPYD gene, p=0.0013. Grade ≥4 toxicities were reported by a similar proportion of patients with DPYD variants and wild-type patients: 5% versus 3%, p=0.49. The results were compared with a historical cohort of patients who had a DPYD gene variant but still received a full dose of FP (table 5). The historical cohort was derived from a meta-analysis; the validity of comparing this historical cohort with the current cohort is unclear as no information is provided on patient characteristics in the historical cohort. Despite FP dose reduction, the risk of severe (grade ≥3) treatment-related toxicity remained elevated in patients with DPYD variants c.1236G>A or c.2846A>T compared with wild-type. Based on comparisons between the study cohort and the historical cohort, toxicity risk was reduced for patients with DPYD gene variants when prescribed reduced doses of FP.

Table 5: relative risk of severe (grade ≥3) FP-related toxicity in patients with DPYD variants, treated with reduced dose or full dose FP, compared with wild-type[11]

DPYD variant	n	Current study patients tx with reduced dose	n	Historical cohort treated with full dose
c.1236G>A	51	RR 1.69 (95% CI 1.18 to 2.42)	177	RR 1.72 (95% CI 1.22 to 2.42)
c.2846A>T	17	RR 2.00 (95% CI 1.19 to 3.34)	85	RR 3.11 (95% CI 2.25 to 4.28)
c.1905+1G>A	16	RR 1.31 (95% CI 0.63 to 2.73)	60	RR 2.87 (95% CI 2.14 to 3.86)
c.1679T>G	1	-	11	RR 4.30 (95% CI 2.10 to 8.80)

The second prospective cohort study explored pre-treatment screening for variant c.1905+1G>A followed by FP dose individualisation (50% dose reduction in heterozygous patients)[7]. Results for patients with the c.1905+1G>A gene variant were compared with a concurrent wild-type patient group and a historical comparator group. The historical comparator group was derived from published studies of patients with the c.1905+1G>A variant who received a full FP dose during treatment.

Severe (grade ≥3) treatment-related toxicity in patients included in this study and a historical cohort are reported in table 6. A total of 2,038 consecutive patients were tested, with 1.1% (n=22) found to be heterozygous for c.1905+1G>A. Eighteen patients (82%) with the DPYD variant received an initial reduction in FP dose, with 33% of these patients then having the FP dose escalated during subsequent treatment cycles: median genotype-guided dose 48%, range 17% to 91%. Five patients (28%) with the DPYD gene variant experienced grade ≥3 toxicity even with a reduced dose of FP. The historical cohort consisted of 3,974 patients extracted from 14 studies. Patients in the historical cohort tended to be treated more often with 5-fluoroucil compared with patients in the current study. Fifty-one patients (1.1%) in the historical cohort had the c.1905+1G>A variant; 48 went on to receive a full dose of FP chemotherapy. There were statistically significant reductions in the proportion of grade ≥3 toxicity and treatment-related mortality in the DPYD variant group treated with a reduced dose of FP compared with the historical cohort. Severe toxicity rates was similar in the DPYD variant reduced dose cohort and wild-type patients.

Table 6: FP-related toxicity in patients with DPYD variant c.1905+1G>A treated with reduced dose FP, compared with wild-type patients and with DPYD variant patients who received a full dose of FP therapy[7]

Toxicity	c.1905+1G>A (reduced dose)	Wild-type (full dose)	Historical cohort c.1905+1G>A (full dose)
Any grade ≥3	5 (28%)	373 (23%)	35 (73%)
Grade ≥3 haematological	3 (17%)	159 (10%)	27 (66%)
Grade ≥3 diarrhoea	1 (6%)	133 (8%)	23 (56%) *[GI toxicity]*
Grade ≥3 hand-foot syndrome	2 (11%)	86 (5%)	-
Grade 5 (death)	0 (0%)	-	5 (10%)

The final study was a retrospective cohort of patients intended for FP therapy who were prospectively tested for DPYD variants as part of routine practice[16]. Of 314 patients with a recorded prescription for FP, 273 (89.6%) had a pre-treatment DPYD test result. Fourteen patients (5.1%) were found to have one or more DPYD gene variant. Based on the results of the DPYD testing, an initial FP dose reduction was recommended for 11 patients with a DPYD gene variant, subsequently adjusted in practice for eight patients (90% adherence to dose adjustment recommendation). None of the patients who received a reduced dose of FP experienced severe (grade ≥3) toxicity. The authors concluded that DPYD genetic testing could be successfully implemented in routine clinical practice, but due to the small number of patients with DPYD variants the study cohort they could not reach any conclusions on the impact of DPYD testing on patient safety.

Cost effectiveness

Published evidence

Four studies investigating the cost effectiveness of pretreatment DPYD variant genetic testing were identified. The consensus amongst these studies was that a prospective testing strategy is likely to be cost neutral, if not cost saving, compared with reactive testing.

Two studies were conducted in the Netherlands. In the first, 2,038 patients were prospectively tested for the variant c1905+1G>A, of whom 1.1% tested positive. Heterozygous carrier patients were treated with 48% median dose intensity FP chemotherapy. The risk of grade ≥3 toxicity for this group of patients was significantly

reduced from 73% in historical controls (n= 548) to 28% by genotype-guided dosing (p=0.001), and drug-induced death was reduced from 10% to 0%. In the base case cost analysis, the expected total cost per patient in the screening strategy was €2,772 (£2,435) compared with €2,817 (£2,475) in the non-screening strategy, resulting in a cost savings of €45 (£40) per patient [17]. A second study produced similar results, based on a cost-minimisation analysis alongside the large prospective trial described in the clinical effectiveness section[11]. Expected total costs of the screening strategy were €2,599 (£2,284) per patient compared with €2,650 (£2,328) for non-screening, resulting in a net cost saving of €51 (£44) per patient [18].

An Italian economic analysis of DPYD-guided toxicity management was conducted in a sample of 571 patients who were retrospectively genotyped. A generalised linear regression model was used to estimate cost differences for the two patient groups. DPYD extensive metabolisers (528 patients) had greater effectiveness and lesser cost, representing a cost-saving option over DPYD intermediate and poor metabolisers (43 patients)[19].

A cost analysis of prospective screening for DPYD variants versus current usual care was carried out in Ireland. Out of a total of 134 patients experiencing severe (grade ≥3) toxicity from FP-based chemotherapy, 23 patients (17%) tested positive for DPYD variants. The cost of hospital admission for severe chemotherapy-related toxicity was found to be significantly higher than the cost of prospectively testing all patients commencing FP chemotherapy[20].

De-novo economic model

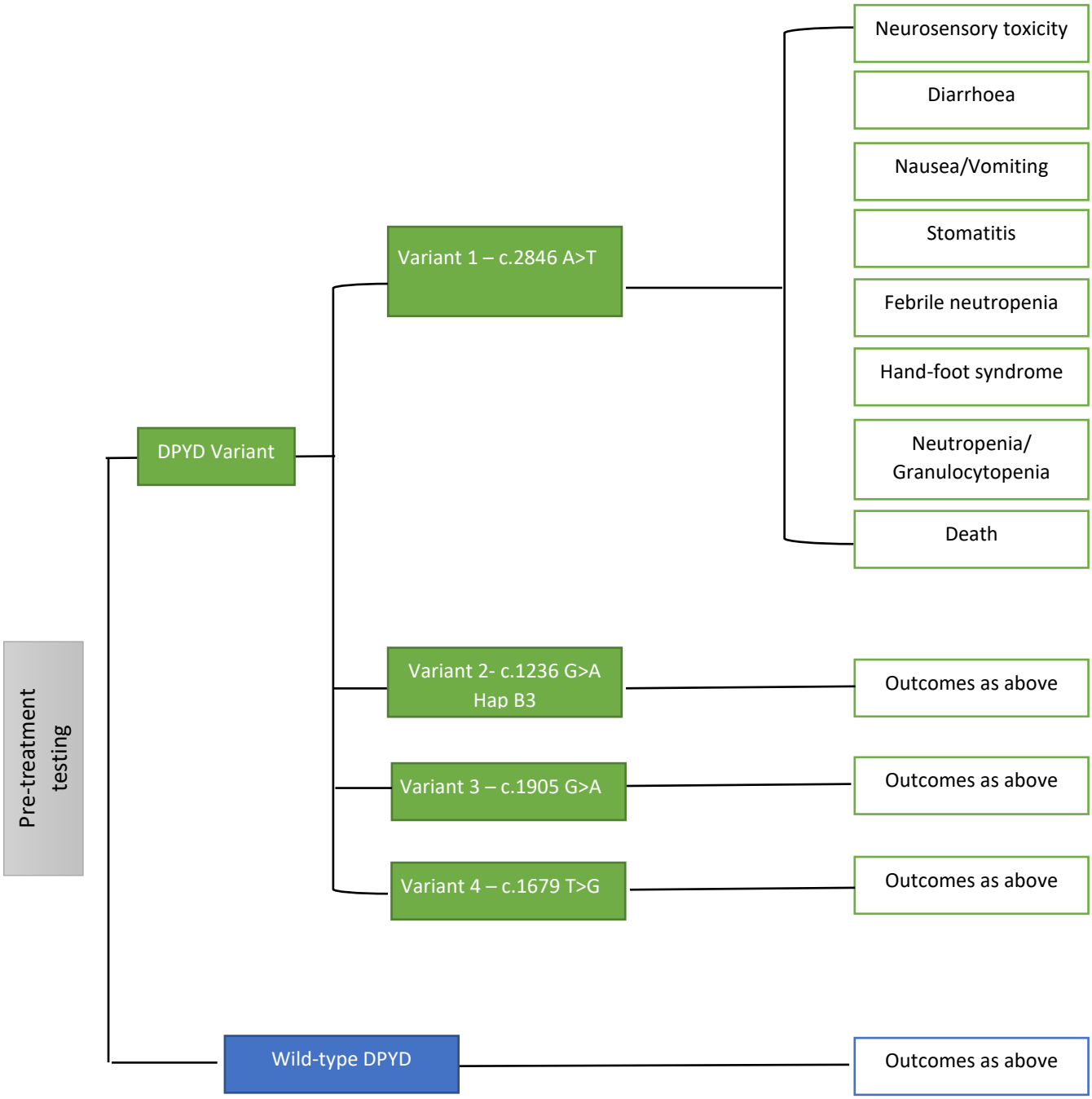
SHTG developed a de-novo economic model to assess the cost-effectiveness of pretreatment DPYD genetic testing within the NHSScotland context.

The economic analysis was based on a decision tree model that compared the costs and outcomes associated with a strategy of prospective DPYD genetic testing for patients eligible for FP-based chemotherapy versus a strategy of no testing. Figure 1 presents the structure of the model for the 'testing' arm. Patients in the pretreatment testing cohort entered the model and were identified - via a genetic test - as either having one of the four DPYD gene variants leading to DPD deficiency, or being a wild-type carrier with no DPD deficiency. The same structure applies to the 'no-testing' arm of the model.

The primary outcomes for the model were the number of serious adverse events (grade 3-5) and deaths associated with each strategy.

Figure 1: decision-tree model structure

(figure presented for prospective testing strategy; identical structure used for no-testing strategy)



In the pretreatment testing strategy, patients with a DPYD gene variant would be identified and subject to reduced dosage of chemotherapy, thereby resulting in lower incidence of adverse events. In the no-testing strategy, patients with DPYD gene variants would receive full chemotherapy dosage with an increased likelihood of developing adverse events. The model also predicted total days in an intensive care (ICU) or high dependency unit (HDU) experienced by DPD deficient patients in both strategies.

Parameters and sources

Table 7 presents the key parameters used in the model. The incidence of DPYD variants detected through genetic testing was based on pilot data from the four NHSScotland laboratories – in Aberdeen, Dundee, Edinburgh and Glasgow. A total of 992 tests were conducted with 86 variants detected (8.67%). Testing figures included the c.1601 G>A variant which was not included in this analysis as it is not associated with a significant increase in risk of severe (grade ≥3) FP-related toxicity[14]. The combined detection rate for all clinically relevant variants was 5.14%.

The probabilities for developing various toxicity-related adverse events were based on incidence rates from a non-inferiority trial investigating the effectiveness of a fluorouracil based chemotherapy (FOLFOX4) versus capecitabine based chemotherapy (XELOX) [21]. The trial did not differentiate between wild-type and DPYD variant patients. A relative risk adjustment was applied in order to reflect the increased risk of toxicity for DPYD variant carriers treated with reduced dosage relative to wild-type patients. In the testing arm, the relative risk adjustments were obtained from a Dutch trial[10]. For the no testing arm, the relative risk adjustment for DPYD variant carriers treated with full dose was based on results of a meta-analysis[14].

Estimates for the proportion of adverse events which would require a HDU or ICU stay – and the average length of stay - were informed by clinical opinion and peer review (incl. Dr J Graham, Medical oncologist; NHS Greater Glasgow and Clyde. Personal communication 28 March 2020).

Cost estimates were obtained from a variety of sources as displayed in Table 7. The impact of clinical and cost parameters on results was explored via deterministic sensitivity analysis.

Table 7: parameters included in cost-effectiveness model

Parameter	Base case input		Source	Sensitivity analysis
DPYD variant incidence				
c.1905+1 G>A	1.01%		Pilot testing data	+/-20%
c.2846 A>T	1.01%			
c.1679 T>G	0.30%			
c.1236G>A / Hap B3	2.82%			
Baseline incidence of adverse events [f]				
Neurosensory toxicity	17%		Cassidy et al (2011)	N/A
Diarrhoea	16%			
Nausea/vomiting	8%			
Stomatitis	2%			
Neutropenia/granulocytopenia	26%			
Febrile neutropenia	3%			
Hand-foot syndrome	4%			
Death	1%		Meulendijks *et al* (2016) [4]	
Variant Relative Risk	**Test**	**No test**		
c.1905+1 G>A	1.31	2.87	Test – Henricks *et al* (2018) [10]	95% confidence interval
c.2846 A>T	2	3.11	No Test – Meulendijks *et al* (2015) [14]	
c.1679 T>G	n/a*	4.30		
c.1236G>A / Hap B3	1.69	1.72		
In-patient care				
HDU	10%	40%	Clinical expert opinion	+/-20%
ICU	5%	10%		
Mean length of stay				
HDU	5 days	10 days	Assumption	+/-20%
ICU	7 days	30 days		

Costs			
Neurosensory toxicity	£1,000	Assumption	0, +/-20%
Diarrhoea	£336	Erlotinib NICE single technology appraisal (2006)	
Nausea/vomiting	£340		
Stomatitis	£266		
Neutropenia/granulocytopenia	£531		
Febrile neutropenia	£5,076	Homes *et al* (2004)	
Hand-foot syndrome	£250	Assumption	
Death	£6,610	Nuffield Trust (2014)	+/-20%
HDU stay	£6,883	Public Health Scotland – specialty costs/activity (2018)[22]	+/-20%, medical oncology ward costs, general medicine ward costs
ICU stay	£8,872		
General ward	£619		
Elucigene® Test	[redacted]	Pilot testing data*	+/-20%
Sanger PCR Test	£28.64		+/-20%

∫ Baseline values reflect the pre-relative risk incidence of events occurring amongst wild type carrier patients.
* Testing costs inclusive of kit/reagents and staff time. Cost of the Elucigene test is commercially sensitive due to discounts negotiated with the laboratories. The analysis assumed that 50% of tests would be conducted using the Elucigene kit.

Results

The base case analysis found prospective DPYD testing to be a dominant strategy. This means that DPYD testing was associated with lower costs and led to better outcomes compared to a no testing strategy.

Table 8 presents a breakdown of the results. The testing cost of £38,565 was offset by treatment cost savings (£19,292) and inpatient resource savings (£246,983).

The model predicted that for every 1,000 patients tested prospectively for a DPYD variant, up to 24 serious (grade ≥3) adverse events could be avoided. This would also lead to a reduction in the number of HDU/ICU admissions and a subsequent HDU/ICU stay. It is estimated that NHSScotland could achieve between £90,000 and £227,000 of resource savings by implementing a testing strategy.

Table 8: results of base case analysis

Outcome	Testing	No-testing	Difference
Grade ≥3 adverse events	**67**	**91**	**-24**
Events needing HDU stay	*7*	*36*	*-29*
Events needing ICU stay	*3*	*9*	*-6*
Events with day case admission	*57*	*45*	*12*
Total HDU stays (days)	**34**	**362**	**-328**
Total ICU stays (days)	**24**	**271**	**-247**
Adverse event treatment costs	*£663,369*	*£682,661*	*- £19,292*
Hospital in-patient costs	*£111,384*	*£357,367*	*- £245,983*
Testing costs	*£38,565*	*£0*	*£38,565*
Total costs	**£813,317**	**£1,040,842**	**- £227,524**
Adverse events	**Reduction per 1,000 patients**		
Neurosensory toxicity	5.38		
Diarrhoea	4.91		
Nausea/vomiting	2.37		
Stomatitis	0.47		
Neutropenia/granulocytopenia	7.78		
Febrile neutropenia	0.95		
Hand-foot syndrome	1.11		
Death	0.32		

Sensitivity analysis and limitations

Deterministic sensitivity analysis was performed to test the robustness of the economic model. Varying the parameters by their 95% confidence intervals or +/- 20% of the base case values led to changes in the level of cost savings achieved but crucially, did not alter the conclusion of the model. Alternate scenarios were constructed to test the impact of varying multiple parameters simultaneously, but none of the scenarios found the testing strategy to be associated with incrementally higher costs.

The parameters with the greatest impact on the level of cost savings were adverse event risk for DPD deficient patients in the non-testing arm, the proportion of adverse events

requiring HDU admission and the inpatient cost of an HDU admission. A conservative scenario, which assumed a lower relative risk for DPD deficient patients, a higher proportion of adverse events in the testing arm leading to HDU admission and a 20% reduction in hospitalisation costs, was tested. Results indicated that the testing strategy could lead to cost savings of approximately £90,000.

Despite the stability of the model, there is uncertainty around some underlying assumptions, which, if modified, could affect results.

- The model assumes that each adverse event occurs only once per patient. If data regarding the mean/median number of episodes were available that indicated multiple episodes for some adverse events, its incorporation into the model could further improve estimates of cost-effectiveness. However, for adverse events of grade three and above it seems unlikely that clinicians would be willing to risk the recurrence of such an event in a patient after they experience it once.
- Owing to wide variation in clinical presentation of symptoms associated with adverse events, there remains a high level of uncertainty regarding the proportion of events that would require in-patient care as well as the median length of stay for HDU/ICU admissions. Further, the in-patient costs applied in the model were based on a cost per stay basis (obtained by dividing net annual expenditure by annual cases) and not specific to the patient population eligible for testing.
- The comparator strategy of no-testing is not completely representative of current practice, which maintains a level of reactive testing for those patients who do develop adverse events on FP chemotherapy. Hence in actuality, the comparator strategy would include some testing costs and adverse event incidence for DPD deficient patients could potentially be lower.
- The model assumes that FP chemotherapy dose reduction in DPYD variant carriers does not lead to different treatment outcomes in terms of survival (e.g. overall survival, event free survival, progression free survival). Whilst the impact of dose reduction on outcomes was outwith the scope of this assessment, evidence suggesting otherwise would require revised modelling to be undertaken as this could alter conclusions regarding cost-effectiveness.
- Two types of tests have been trialed within Scotland – the Elucigene® testing kit and in-house Sanger PCR testing. The choice of testing method can vary between laboratories based on capacity, staff preferences and other factors. The base case model assumes that 50% of the tests will be performed using the more expensive Elucigene® kit. Hence, there is some scope for variation in total testing costs.

The savings achieved in reality will depend on the types of toxicity-related adverse events patients develop as well as variations in local practice for treatment and hospitalisation. Ongoing data collection from the pilot sites is encouraged to help inform future analyses.

Conclusion

There is evidence from two systematic reviews and a meta-analysis of a clinically significant increase in the risk of severe (grade ≥3) FP-related toxicity in patients with DPYD gene variants c.1905+1G>A, c.2846A>T, c.1679T>G, or c.1236G>A/Hap B3. No equivalent increase in risk of severe treatment-related toxicity was reported for patients with DPYD variant c.1601G>A. Evidence from four observational studies indicates that DPYD genetic testing for these clinically relevant DPYD variants can be successfully implemented within routine clinical care in order to individualise FP dose reduction in affected patients. Use of reduced FP doses in patients with DPYD variants appears to result in a reduction in the risk of severe (grade ≥3) treatment-related toxicity compared with historical controls who received full dose FP therapy.

Economic modelling by SHTG suggests that prospective genetic testing for four variants is likely to result in resource savings for NHSScotland. A prospective testing strategy is associated with lower incidence of serious (grade ≥3) adverse events in affected patients, due to pre-emptive FP dose reduction, and lower rates of hospitalisation. The incremental costs of DPYD testing are expected to be offset by lower expenditure on acute and in-patient care for patients experiencing adverse events.

Equality and diversity

Healthcare Improvement Scotland is committed to equality and diversity in respect of the nine equality groups defined by age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion, sex, and sexual orientation.

The expression of genetic variants which affect DPD activity in a clinically relevant manner can vary by race. Although estimated carrier frequency of DPYD gene variants associated with FP toxicity is estimated to be higher amongst Caucasian populations, genetic testing should not be restricted to this group. The prospective strategy assessed by SHTG would ensure equal access to genetic testing by all patients suitable for FP based chemotherapy irrespective of racial background.

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Appendix 1: abbreviations

CI	confidence interval
DNA	deoxyribonucleic acid
DPD	dihydropyrimidine dehydrogenase
FP	fluoropyrimidine
5-FU	5-fluoroucil
HDU	high dependency unit
ICU	intensive care unit
IPD	individual patient data
NA	not applicable
NPPPRG	National Patient, Public and Professional Reference Group
NS	not significant
NSSC	National Specialist Services Committee
OR	odds ratio
PCR	polymerase chain reaction
RR	relative risk
Tx	treatment