Modelling the cost-effectiveness of imaged based DNA-Ploidy as a prognostic marker in prostate cancer

Work in Progress. Not to be quoted.

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Introduction

Prostate cancer is one of the leading causes of male death in the western world with incidence figures rising due to an aging population and with increased use of prostate specific antigen (PSA) testing. In the UK, it is the second most common form of death from cancer in men after lung cancer.[1] Having said this, prostate cancer is often a slow growing cancer, and many men will die with the disease but not of it. The natural course of the disease is highly variable and unpredictable and prognostic markers are unreliable for predicting disease progression. The cancer can be treated and cured using surgery (prostatectomy) or radiation if detected at an early-localised stage. Given the uncertainties around the likelihood and speed of progression, clinicians are faced with the decision to treat radically (with all the inherent risks and reductions in quality of life from possible peri-operative and post-operative complications), or to watch and wait (risking the possibility that the cancer progresses and the patient dies when radical intervention may have lead to cure). In view of the lack of good prognostic indicators, surgeons and patients are often left with having to make treatment choices based on personal preferences.

Disease progression appears to be related to tumour stage and grade[2], however, accurate grading relies on surgical intervention (prostatectomy) as grading from needle biopsy may not be accurate. Tumours can be sub-grouped into well differentiated (Gleason grades 2-4), moderately differentiated (grades 5-7), and poorly differentiated (grades 8-10). There is relatively little controversy about the need to radically treat poorly differentiated tumours. Likewise, well-differentiated tumours, which are less likely to progress, will usually be treated conservatively using active monitoring (watch and wait). Screening using PSA testing is not current policy in the UK, and the majority of prostate cancers diagnosed in the UK are moderately differentiated. It is this most common group of moderately differentiated tumours around which there is most controversy over treatment.

DNA ploidy offers the possibility of being able to detect an abnormal cell line within a population of healthy dividing tissue cells. The important distinction is to differentiate between diploid and non-diploid (aneuploid or tetraploid) cells. The former indicates normal healthy cells, whereas the latter indicate more abnormal cell activity and potentially aggressive cancers thereby indicating the need for radical treatment. Traditionally ploidy has been analysed using flow cytometry and has not been widely accepted as a reliable prognostic marker for prostate cancer. Imaged based DNA-

Ploidy analysis using automated software systems offers the possibility of a more reliable indicator of cancer aggressiveness.

Because of the slow growing nature of these tumours, good quality information about survival, complication rates, quality of life, and the costs of radical treatment versus active monitoring are still years away. Modelling is a particularly useful tool in clinical contexts such as this as demonstrated by the number of previously published modelling papers.[3 4 5 6] This paper presents the results of a modelling exercise designed to investigate the economic viability of image based DNA-ploidy analysis in the prognosis of prostate cancer. An economic model has been constructed in order to estimate the relative effectiveness and cost-effectiveness of radical versus conservative treatment, and a treatment selection policy based on DNA-ploidy analysis. This paper describes the structure and modelling assumptions along with the results and sensitivity analysis.

Methods

Literature

In order to populate the model, relevant published papers were searched using databases including Medline, Embase, Health Economic Evaluation Database (HEED), and NHS Economic Evaluation Database (NEED), and hand searching of reference lists from included studies.

Patient Cohort and Disease States

There is consensus amongst clinicians that older patients with early prostate cancer should be conservatively treated with active monitoring (watch and wait), because older patients are likely to die of other causes before dying of a slow growing prostate cancer. Given this, and given that is it moderately differentiate tumours around which there is most uncertainty over treatment, a theoretical cohort of 1000, 60-year-old men diagnosed with moderately differentiated, early stage prostate cancer has been modelled.

Model structure and disease pathways

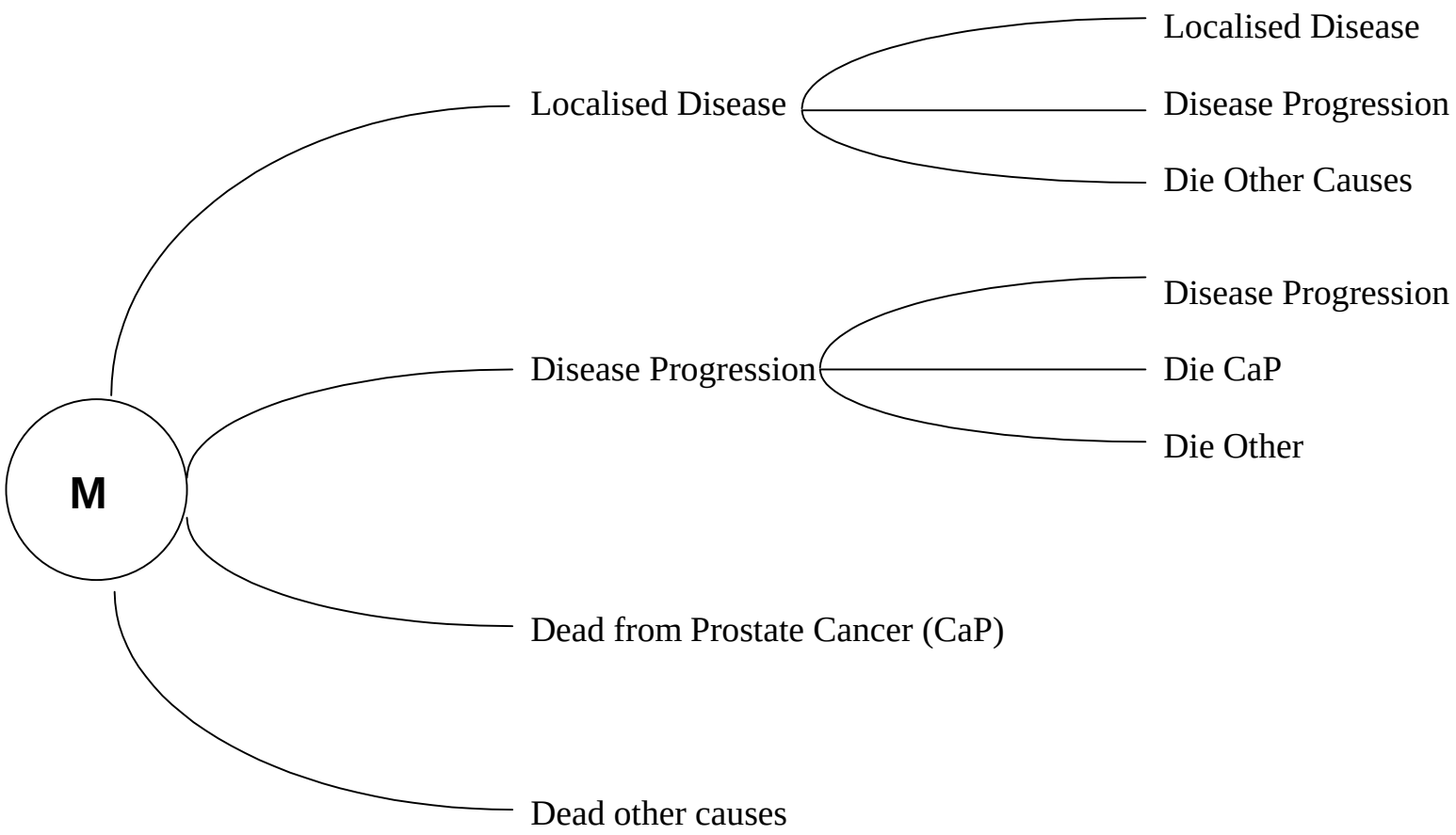
The model takes the form of a Markov model bolted on to a decision tree analysis framework and was built using Microsoft Excel™. The Markovian structure of the model is represented in Figure 1 which depicts the following simplifying assumptions. The patient cohort is initially assigned to the state of having being diagnosed with, and living with, early-localised prostate cancer. Patients then either remain in this

state (redefined as disease free for patients undergoing radical prostatectomy), transfer to the progressive (metastatic) cancer state, or transfer to the end state "dead from other causes". Three transitional states are also defined for those patients who progress to the metastatic disease state. These are: 'living with metastatic disease'; 'dead from prostate cancer'; and 'dead from other causes'. For simplification, radical treatment is assumed to be by radical prostatectomy only.

Survival and disease progression assumptions

Johansson et al.[7] presents the results of a 15-year survival analysis for untreated prostate cancer patients.[7](check this reference and remove earlier one) The Swedish study is particularly appropriate in the context of our model in that it provides detailed survival and disease progression information about a large cohort of north European patients followed up for a sufficiently long period. Like the UK, Sweden had no systematic screening policy during the period of recruitment to their study. A screening programme would inevitably mean that cancers would be diagnosed at an earlier stage than in a non-screening context. Although, 12% of the total Swedish cohort (average age 72) progressed to metastases, an analysis of the sub-group of patients aged under 70 years old indicates that 19% of patients progressed to metastases. This data supports the expectation that a greater proportion of younger patients progress to metastatic disease. Given that we model a cohort of 60-year-olds, it has been assumed that 22% of the cohort are 'true metastatic' (that is, they would progress to metastases if left untreated and avoided death from other causes). This assumption results in 19% of the untreated cohort progressing to metastatic cancer, and 14% dying from prostate cancer by 15 years if untreated. These results reflect outcomes for the Johansson study for patients under 70 years of age.

Figure 1: Markov Representation of Prostate Cancer Model



The 78% of patients assumed not to have metastatic disease ('true localised') are assumed to have a survival function defined by that for 60-year-old UK men adjusted to exclude deaths from prostate cancer. These annual probabilities of death for men aged 60 to 100 were obtained from the Government Actuarial Department.[8] The same survival function is used to determine the probability of death from causes other than prostate cancer for the 'true metastatic' population.

The annual probability of disease progression for the 22% of the cohort assumed to be 'true metastatic' is also taken from Johansson[7] who reports a 15 year progression free survival figure of 6.2% for patients with metastases at diagnosis. Assuming an exponential survival curve, this represents an annual probability of metastatic progression risk of 0.169 for the true metastatic sub-group. Johansson et al. also report a 15-year disease specific survival rate of 5.7% for patients diagnosed with metastases. Again, making the exponential assumption, patients who have progressed to metastatic disease are assumed to have an annual risk of dying from prostate cancer of 0.174.

Treatment Policies

Three policy options are modelled:

1. Conservative monitoring (watch and wait) for all;
2. Radical prostatectomy for all;
3. A selection based policy, using DNA-ploidy as a prognostic marker.

1. Conservative watch and waiting (active monitoring)

Under the active monitoring arm of the model, all patients are assumed to have conservative treatment consisting of PSA tests every 6 months for the first two years of treatment and every 12 months thereafter. These tests continue until the patient dies or progresses to metastatic disease. The survival and disease progression functions described above are used to model conservatively managed patients.

2. Radical prostatectomy for all

The 'radical prostatectomy for all' policy arm of the model assumes that all the patient cohort are given a prostatectomy following diagnosis of localised disease. One percent of radical prostatectomies are assumed to result in a 30 day peri-operative death as assumed by Yoshimura et al[3] in their modelling work, using evidence from Dillioglugil et al.[9] The model requires an assumption about the

proportion of the otherwise true metastatic cancers that would be cured by an early stage prostatectomy. Given the lack of randomised controlled trials with long-term follow-up for conservative management versus radical prostatectomy, the evidence for this variable is poor. In a modelling paper by Kattan et al,[4] a baseline assumptions for 10-year freedom from metastases implies that 25% of patients avoid metastases following early stage treatment with radical prostatectomy. Based on our assumption that 22% of untreated early disease patients are 'true metastatic', the model indicates that around 15% of the patient cohort would progress to metastases even after surgery (assuming they survive death from other causes). This figure is compatible with the 10-year 85% metastases free survival figure reported by Folwer in Selley et al.[2]

Patients surviving surgery are assumed to have survival and progression functions for metastatic and metastases free patients as described above. Patients assumed to be cured of metastatic cancer as a result of their prostatectomy are then assumed to have the survival function experienced by 'true localised' patients.

3. DNA-Ploidy based selection policy

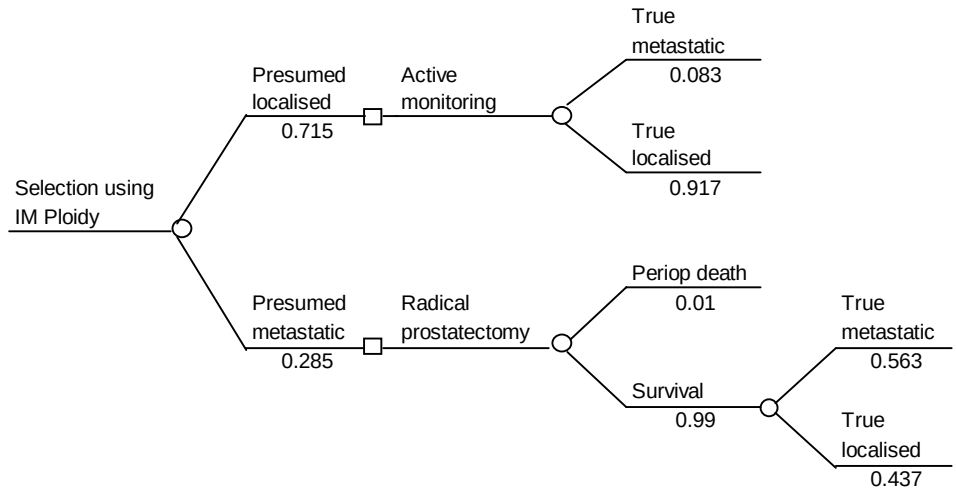
The third and final arm of the model requires sensitivity and specificity assumptions for the image based DNA ploidy marker test. Patients with a diploid test are presumed to have localised disease, and are treated using conservative monitoring. Patients with a non-diploid test are assumed to have metastatic cancers and are treated with a radical prostatectomy. Having assumed that 22% of the patient cohort are 'true metastatic', and having made sensitivity and specificity assumptions for the DNA-ploidy test, Bayes theorem can be used to indicate the proportion of patients with both diploid and non-diploid DNA test results which are 'true metastatic'. Assuming a test sensitivity of 73% and a specificity of 84%, for example, and a true metastatic cancer prevalence of 22%, positive and negative predictive values are calculated to be 0.56 and 0.92 respectively (table 1 and figure 2).

Table 1: Relationship between sensitivity, specificity, and predictive values

	Presumed metastatic	Presumed localised	
True metastatic	0.161(a)	0.059 (b)	0.22 (a+b)
True localised	0.125 (c)	0.655 (d)	0.78 (c+d)
	0.285 (a+c)	0.715 (b+d)	1.0 (a+b+c+d)

The cell "a+b" indicates prevalence of metastatic cancer (22%). Sensitivity and specificity were set to be 0.73 (a/a+b) and 0.84 (d/c+d), respectively. Positive and negative predictive values were then calculated to be 0.563 (a/a+c) and 0.917 (d/b+d), respectively.

Figure 2: Decision tree depicting the incorporation of positive and negative predictive values derived for the DNA –ploidy test.



Again, the model assumes that radical prostatectomy cures 25% of true metastatic cancers. The patient cohort then experience the appropriate survival and disease progression functions previously described depending on their true progression status and whether or not they undergo surgery.

Quality of life

Years spent alive are quality adjusted using utility values where perfect health is represented by a utility score of one, and death is represented by a value of zero. Kind et al.[10] report age related utility scores for healthy UK males. The average 60-year-old UK man, for example, has been estimated to have a utility score of 0.78. This falls to 0.75 by the age of 75. These utility scores have been used in the model to represent the quality of life experienced by those men cured of early-localised prostate cancer following radical prostatectomy. Other health utility values have been derived using utilities estimated by Cowen et al.[11] Conservatively treated patients living with prostate cancer are assigned a utility of 0.72, which is fixed until death or

progression to metastatic disease. Once disease has progressed to metastases a utility of 0.42 is assumed until death.

Patients surviving radical prostatectomy are assigned an average utility score of 0.70 to reflect the reduced quality of life experienced by a proportion of surgery patients through peri and post-operative complications, (notably persistent incontinence and/or impotence). A meta-analysis of complication rates presented by Selly[2] implies that 48% of radical prostatectomy patients become impotent and remain impotent 18 months after surgery. Similar analysis of Selley's figures for incontinence, imply 18% with long-term incontinence at 18 months. Cowen quotes utility scores for living with impotence and incontinence of 0.69 and 0.57 respectively. Making the simplifying assumption that half of the incontinence patients suffer from both complications and assigning a combined utility score of 0.50 (multiplicative assumption assuming a ceiling utility of 0.78), a weighted average utility score for patients suffering complications of 0.64 has been estimated. Based on the Selley data and our modelling assumptions, this utility score has been assigned to 57.3% of all patients undergoing radical prostatectomy. Table 2 summarises the key quality of life utility assumptions used in the model.

Table 2: Quality of life Utility Assumptions

Health State	Utility	95% CI (range)	Source
Healthy UK male age <75	0.78		Kind et al.[10]
Healthy UK male age 75+	0.75		Kind et al.[10]
living with localised CaP	0.72	0.63 – 0.80	Cowen et al.[11]
Metastatic CaP	0.42	0.33 – 0.51	Cowen et al.[11]
Impotence	0.69	0.61 – 0.77	Cowen et al.[11]
Incontinence	0.57	0.46 – 0.68	Cowen et al.[11]

Treatment Costs

An NHS costing perspective is taken so that direct patient costs and indirect costs to the economy are ignored. Prices have been inflated in the model to 2000/01 financial year prices using hospital and community health services (HCSH) inflators[12] to 1999/2000 and an RPI[13] of 2.26% for 2000/01.

All patients alive and free of metastases are assumed to have 2 PSA tests for the first 2 years after diagnosis, and annually thereafter. The blood test itself is assumed to cost £6 per test in 1995/6 prices.[14] It is assumed that hospital

consultants will want to review patients so that PSA testing takes place during a hospital outpatient visit. Each outpatient consultation is assumed to cost at an additional £58 (1999/00 prices).[12]

Patients progressing to metastatic disease are assumed to have hormone treatment. This can be administered medically or surgically (castration), however, patient preference for a reversible procedure dictates that treatment is now almost exclusively administered by the reversible medical method. The model therefore assumes that all hormone treatment is administered medically using LH-RH analogues (e.g.Goserelin). The BNF[15] quotes a 28-day cost of £122.27 for Zoladex, which converts to an annual cost estimate of £1,589 per patient year. This cost assumption is used in the model, and the treatment regime is assumed to continue until death

The cost of radical prostatectomy for early localised prostate cancer has been estimated using HRG data[16] (Prostate or Bladder Neck Open Procedure <70, (L26)) which indicates a mean cost of £1,844 (1999/00 prices) per inpatient consultant episode, and a range for 50% of NHS trusts from £1,203 to £2,219.

The costs of DNA-ploidy analysis have been estimated using confidential information provided by an imaging company. It is assumed that the specimen slide used in the ploidy analysis is obtained from the same needle biopsy undertaken to measure tumour grading. As such, the cost of needle biopsy is not included in the model as it is not a marginal economic cost. Table 3 summarises the assumptions made to derive a cost per ploidy analysis. The table is divided into equipment costs and staff cost estimates. The equipment costs comprise estimates of purchase costs for hard and software, which are then annualised by making assumptions about expected equipment life and assuming a 6% discount rate. The result is an estimated equipment cost per test of £6.68.

Table 3: DNA ploidy analysis costs

Equipment costs

	Purchase cost	Capital life years	Discount rate	Discounted Cost p.a.	Tests Per year	Cost Per test
Total	£81,400	5-10	6%	£20,043	3000*	£6.68

* Assumes 15 tests per day, 5 days per week for a 40 week working year

Staff time costs

	Prep of slide (mins)	Ploidy analysis (mins)	Reporting/ diagnosing (mins)	Total (mins)	Salary Cost Per hour	Cost Per test
Technician	30	5		35	£14.81**	£8.64
Pathologist		15	5	20	£83.85***	£27.95
Clinician			5	5	£83.85***	£6.99
Total						£43.58

** University of Sheffield pay scales (Medical laboratory scientific officer, grade 2, point 5)
*** Netten & Curtis, Unit costs of health and social care, 2000 inflated to 2000/01 prices

Summary

Total	£50.26

Table 3 also indicates staff time estimates required to operate an automated imaging analysis system along with estimated hourly staff costs. The results indicate that it is the staff, and not the equipment costs that dominate the costs of ploidy analysis (£43.58 compared with £6.68), resulting in an estimated total cost per test of £50.26.

Model Outputs

In each model state, patients incur treatment costs and are assigned an assumed quality of life utility. Costs and benefits are accrued over the patient's lifetime or until 40 years have elapsed, whichever occurs first. The model then calculates total costs and quality adjusted life years (QALYs) for each of the three treatment regimes. Future costs and benefits are discounted for time preference at a rate of 6% per annum. The model facilitates the calculation of incremental costs per QALY for the three treatment policy options.

Results

Watch and wait versus radical prostatectomy

The central case assumptions described above were input to the model. Ignoring the ploidy selection policy for the moment, the policies of conservative monitoring and radical prostatectomy for all can be compared. Table 4 presents 15-year progression and survival outputs from the model for these two treatment regimes.

Table 4: Fifteen Year progression and survival outputs

	Conservative monitoring	RP for all
Progressed to metastases	19%	14%
Died of CaP	14%	11%
Observed survival	56%	58%

The progression rates and prostate cancer mortality rates for conservative monitoring are comparable with Johansson's results.[7] Progression and mortality rates are lower under the radical prostatectomy policy because some patients are cured of the metastatic disease that they would have otherwise experienced. Observed (total) survival rates from the model are higher than those experienced by the Swedish cohort. This is because the average age of the Swedish patients is 72 years, compared to 60 in our model, and so fewer of the modelled patients are dying of other causes at 15 years after diagnosis. Table 5 presents the central case scenario cost and QALY model outputs for the two non-ploidy polices.

Table 5: Modelled Cost and QALY outcomes*

	WW for all	RP for all
Total QALYs	7,095	7,033
Total Costs	£1,659,051	£3,329,823

* costs and QALYs discounted at 6%

Conservative monitoring produces more quality adjusted life years than does a policy of radical prostatectomy for all. The difference is smaller than 1% however. A policy of 'surgery for all' generates the smallest number of QALYs because the gains in lives saved are outweighed by losses from peri-operative deaths and reductions in quality of life from complications following surgery. Many modelled patients suffering these losses would not have progressed to metastatic cancer if left untreated. The bigger contrast is in the total discounted costs of the two policies, radical prostatectomy for all costing double that of conservative monitoring at £3.3m. In decision analytic terms, conservative monitoring dominates the policy of radical prostatectomy in that conservative monitoring under the defined central scenario is both more effective and less costly than a policy of radical prostatectomy for all.

Ploidy based selection policy

The only published evidence for sensitivity and specificity values for DNA ploidy found in the literature were those published by Ross et al.[17] These sensitivity and specificity values (78% and 96% respectively) are not appropriate for use in our model because Ross was interested in ploidy as a predictor of grade shifting and not metastatic progression. Given the lack of published figures for sensitivity and specificity of image based ploidy analysis in the prediction of metastatic cancer, the tables below present the cost and QALY model outputs for a range of possible test sensitivities and specificities. Table 6 indicates the number of discounted QALYS varying sensitivity and specificity between 50% and 100%. The table demonstrates the expected increase in QALYs with increasing test sensitivity and specificity.

Table 6: Total QALYs* from ploidy based selection policy

		Specificity					
		0.5	**0.6**	**0.7**	**0.8**	**0.9**	**1**
Sensitivity	**0.5**	7064	7088	7112	7136	7160	7184
	0.6	7082	7106	7130	7154	7178	7202
	0.7	7100	7124	7148	7172	7196	7220
	0.8	7118	7142	7166	7190	7214	7238
	0.9	7135	7160	7184	7208	7232	7256
	1	7153	7178	7202	7226	7250	7274

*Discounted by 6%

Significantly, the number of QALYs never falls below the total achieved in the central scenario for the radical prostatectomy for all policy, implying that the ploidy selection based policy is always more effective than radical prostatectomy for all. Furthermore, it is only for the three cells in the top left hand corner of the table that QALYs from the ploidy policy are lower than from the conservative monitoring policy.

Table 7 presents total discounted costs for the same range of sensitivities and specificities. Under the full range of scenarios, total discounted costs for the ploidy selection policy lie between the base case costs presented for the other two policies.

Table 7: Total Discounted Costs of Ploidy Policy

Sensitivity	Specificity					
	0.5	**0.6**	**0.7**	**0.8**	**0.9**	**1.0**
0.5	£ 2,544,697	£ 2,398,289	£ 2,251,881	£ 2,105,473	£1,959,064	£1,812,656
0.6	£ 2,565,366	£ 2,418,958	£ 2,272,550	£ 2,126,142	£1,979,733	£1,833,325
0.7	£ 2,586,035	£ 2,439,627	£ 2,293,219	£ 2,146,810	£2,000,402	£1,853,994
0.8	£ 2,606,704	£ 2,460,296	£ 2,313,888	£ 2,167,479	£2,021,071	£1,874,663
0.9	£ 2,627,373	£ 2,480,965	£ 2,334,557	£ 2,188,148	£2,041,740	£1,895,332
1.0	£ 2,648,042	£ 2,501,634	£ 2,355,225	£ 2,208,817	£2,062,409	£1,916,001

Discount rate of 6%

Table 7 indicates that the ploidy based selection policy dominates the policy of radical prostatectomy, under all sensitivity and specificity combinations examined. That is, the ploidy based selection policy is always more effective and less costly than the radical prostatectomy policy. Table 8 presents the incremental cost utility ratios (costs per QALY) for the ploidy based selection policy compared with conservative monitoring. The same figures are presented graphically in figure 3. £20,000 to £30,000 per QALY is a commonly quoted threshold range of acceptability for healthcare interventions in the UK. With this in mind, table 8 indicates that a ploidy based selection policy is cost-effective for all scenarios except where cells are shaded. The more sensitive and specific ploidy analysis is in predicting metastatic cancer, the more cost-effective it becomes. Sensitivities and specificities below 65% make ploidy begin to look less cost-effective compared to conservative monitoring. The three cells in the top left hand corner of the matrix indicate that ploidy is dominated by conservative monitoring (i.e. less effective and more costly).

Table 8: Cost per QALY Ratios (ploidy versus active monitoring)

		Specificity					
		0.5	**0.6**	**0.7**	**0.8**	**0.9**	**1.0**
Sensitivity	**0.5**	Dominated	Dominated	£34,277	£10,784	£4,580	£1,714
	0.6	Dominated	£68,380	£17,421	£7,874	£3,844	£1,621
	0.7	£187,995	£26,885	£11,935	£6,315	£3,368	£1,554
	0.8	£41,470	£17,064	£9,216	£5,343	£3,035	£1,504
	0.9	£23,749	£12,669	£7,592	£4,679	£2,790	£1,465
	1.0	£16,850	£10,177	£6,512	£4,197	£2,601	£1,434

Figure 3: Costs per QALY by Sensitivity and Specificity

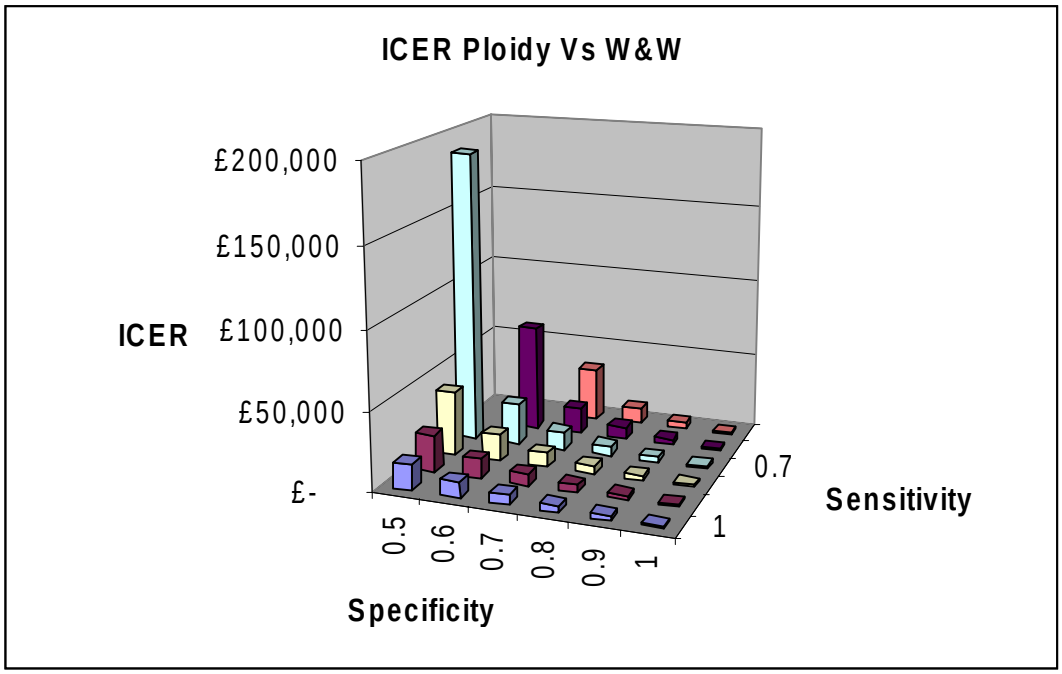
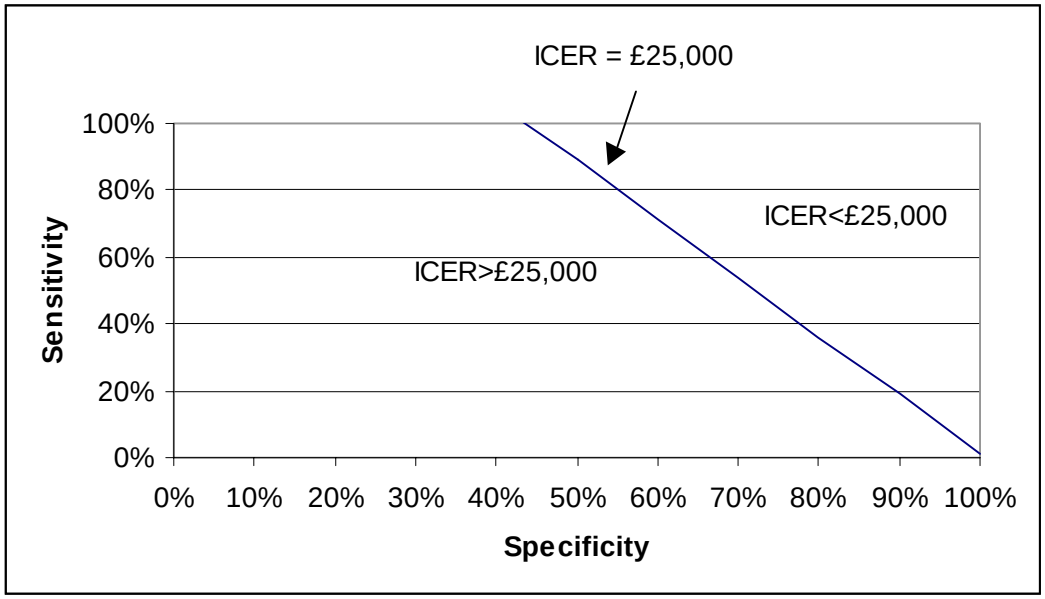


Figure 4 illustrates the threshold combinations of sensitivities and specificities that produce a cost per QALY of £25,000. Combinations above and to the right of the isoquant indicate costs per QALY below £25,000, and vice versa below and to the left of the isoquant.

Fig 4: Threshold analysis showing cost per QALY of £25,000 for ploidy selection policy in relation to conservative monitoring



A base case central scenario

In order to present a sensitivity analysis for the other variables in the model a base case ploidy analysis sensitivity and specificity scenario needs to be defined. In view of the lack of published evidence for these figures, it was determined that published sensitivity and specificity figures for Gleason grading (the next best alternative) should be used. A trawl of the literature searched for this study, revealed a paper by Veltri et al.[18] in which Gleason grade sensitivities and specificities of 73% and 84% respectively were reported for the prediction of progression in patients with clinically localised prostate cancer. Assuming that ploidy will do at least as well as these sensitivity and specificity estimates, these figures have been used to define a base case central scenario. The resulting discounted costs and QALYs for the ploidy scenario are £2,094,448 and 7187 respectively. The incremental cost per QALY is £4,719 comparing ploidy with conservative monitoring, a ratio which augers well for the cost-effectiveness of ploidy analysis. The ploidy policy dominates the radical prostatectomy policy using the assumptions of the base case scenario.

Sensitivity analysis

To test the robustness of the base case central scenario to changes in other key model variables, a threshold sensitivity analysis has been undertaken. A cost per QALY of £20,000 to £30,000 is a commonly quoted threshold range of acceptability for healthcare interventions in the UK. On the basis of this, a threshold figure of £25,000 per QALY was identified. A threshold analysis was undertaken using the model, to demonstrate by how much key input assumptions needed to change, in order to raise incremental cost-effectiveness ratios (ICERs) to £25,000. The exercise was undertaken for both the ICER for the ploidy selection based policy with respect to conservative monitoring, and then for the radical prostatectomy for all policy with respect to the ploidy policy. The results of the analysis are presented in table 9.

Table 9: Threshold Sensitivity Analyses

Variable	Base case Assumption	Ploidy Vs W&W ICER*=£25,000	RP Vs Ploidy ICER*=£25,000
Sensitivity	73%	29%	<0%
Specificity	84%	59%	16%
% True Metastatic	22%	10%	60%
% Cured by RP	25%	13%	>100%
15yr Progression free survival	6.2%	36%	<0%
15yr Disease specific survival	5.7%	>100%	<0%
Utility (living with local CaP)	0.72	0.76	0.69
Utility (metastatic)	0.42	>1	<0
Impotence (Utility)	0.69	0.62	0.75
Impotence (%)	48.4%	87%	17%
Incontinence (Utility)	0.57	0.37	0.73
Incontinence (%)	17.8%	35%	4%
P(peri-op death)	1%	5.3%	<0%
Pathologist Cost per hour	£83.85	£5,697	£15,345
Cost of RP	£1,885	£8,441	<£0
Cost per ploidy test	£50.26	£1,921	£5,137
Discount rate	6%	18%	<0%

*ICER = Incremental cost effectiveness ratio

Comparing first the cost-effectiveness of the ploidy based selection policy with that of conservative monitoring, the ploidy based policy appears to be robust to changes in most of the model input variable assumptions. Ploidy test sensitivity, for example, would have to fall to 29% from 73% before the cost-effectiveness of a ploidy selection based policy starts to look questionable. Specificity, on the other hand, would need to fall to 59% from 83%, indicating that cost-effectiveness is more responsive to specificity than it is to test sensitivity. The proportion of the population cohort defined as true metastatic would need to fall from 22% to 10% before the incremental cost per QALY rises to £25,000. The percentage of prostate cancers cured by radical prostatectomy would need to fall from 25% to 10%, or the peri-operative death rate increase from 1% to 5.3%. Progression free survival would need to increase from 6.2% to 35.5%. The ploidy based selection policy remains cost-effective under all possible values for the disease specific survival rate for patients who develop metastatic cancer. It is also unresponsive to the costs of ploidy analysis, and the costs of the radical prostatectomy operation would need to increase from £1,885 to £8,441 before the cost-effectiveness of a ploidy selection based policy might be questioned.

The ploidy ICER with respect to conservative monitoring is most responsive to some of the quality of life assumptions in the model. The cost-effectiveness of the ploidy based selection policy is most responsive to the utility assumption of 0.72 for quality of life when living with the knowledge that a patient has localised prostate cancer.

This utility value only has to rise to 0.76 to increase the cost per QALY ratio to £25,000. The ratio is less responsive to the utility and risk assumptions associated with impotence and incontinence complications following radical prostatectomy. Having said this, the utility associated with impotence only needs to fall from 0.69 to 0.62. Cost-effectiveness of ploidy with respect to conservative monitoring is not responsive to the utility assumption of 0.42 for those with metastatic cancer.

Table 9 also indicates that the cost-effectiveness of the ploidy policy is relatively insensitive to changes in the discount rate. With no discounting, the ICER of ploidy compared with conservative monitoring falls to £1,600 per QALY. This reflects the fact that discounting tends to penalise interventions where the costs of the intervention are incurred early, but the benefits are experienced further into the future.

The second set of threshold sensitivity analyses measure the responsiveness of the ICER of the policy of radical prostatectomy for all compared with a ploidy based selection policy. Table 9 indicates that many of the modelled input variables can be changed to their extremes, and still the policy of radical prostatectomy does not become cost effective compared with a ploidy testing policy. The shaded boxes highlight those results where a feasible threshold value is observed, but where radical prostatectomy is still dominated by the policy of conservative monitoring, rendering the ICER for radical prostatectomy compared with ploidy irrelevant. Once again, it is the quality of life assumptions in the model that provide the greatest scope for variability in the ICER. The utilities of living with localised prostate cancer or living with impotence only need to fall from 0.72 to 0.69, or rise from 0.69 to 0.75 respectively, before the policy of radical prostatectomy becomes cost-effective compared to a ploidy based policy.

Discussion

This paper presents the results of a modelling exercise estimating the cost-effectiveness of image based DNA-ploidy analysis as a prognostic marker for metastatic prostate cancer. The lack of long-term follow up randomised controlled trial data in this disease makes modelling an ideal analytical tool in this context. Published evidence has been used to populate a decision analytic Markov model with survival and disease progression functions, quality of life, and costing

assumptions. Model outputs have been validated using published evidence such as that presented by Johansson.[7]

Modelling has indicated that a treatment selection policy based on DNA-ploidy analysis may well be a cost-effective prognostic marker for patients diagnosed with moderately differentiated tumours (Gleason grades 5-7). This holds true over a wide range test sensitivities and specificities. Above sensitivity and specificity of 65%, the model indicates that DNA ploidy has a cost per QALY lower than £25,000 compared to conservative monitoring. A scenario using Gleason grade sensitivity and specificity figures as a proxy for a base case ploidy scenario again indicates that ploidy is cost effective and that this result is robust for a wide range of input assumptions. Having said this, no published evidence for appropriate sensitivity and specificity figures could be found in the literature although personal communications with a company involved in marketing ploidy analysis software indicates that data is about to be published in Norway. It is up to the protagonists of image based ploidy analysis to demonstrate good evidence for cost-effective sensitivity and specificity estimates. If it can be demonstrated that ploidy has better sensitivity and specificity values than 73% and 84% respectively, then a selection based policy based on ploidy will be even more cost-effective than our base case scenario demonstrates.

The ICER for the DNA-ploidy based selection policy is however sensitive to quality of life assumptions used for patients living with the knowledge that they have untreated localised prostate cancer. The thresholds required to bring the cost-effective result into doubt lie within the 95% confidence intervals for this variable reported by Cowen[11] and Kattan.[4] The result is also relatively sensitive to the frequency and quality of life assumptions associated with the modelled post-operative complications (impotence and incontinence) associated with radical prostatectomy. Improvements in these variables would enhance both the cost-effectiveness of a ploidy based selection policy with respect to conservative monitoring, and the cost-effectiveness of radical prostatectomy compared with the alternative policies. Having said that, these utility scores would need to vary independently and relative to other utility scores used in the model. Further research concerned with guiding treatment policy for early-localised prostate cancer should ensure data collection on quality of life variables.

A by-product of our modelling work suggests that a policy of 'radical prostatectomy for all' is not cost-effective compared with conservative monitoring for patients with moderately differentiated tumours. The surgical policy has been shown to be both less effective and significantly more costly than the more conservative policy. This conclusion is subject to the caveats of the sensitivity analysis results discussed above and in particular assumptions made about quality of life and surgical complication rates.

Our model has only considered prostatectomy as a radical treatment option. It has been suggested that radiotherapy has similar costs and effectiveness to prostatectomy so that the results of our analysis may be transferable. Our model has not considered tumour progression to locally advanced stage. Had the model done so, it may well have benefited policies involving early treatment options, although this would need to be confirmed by further modelling work.

This paper does not address the implications of ploidy for prostate cancer screening in the UK. The sensitivity and specificity of ploidy testing for a broader spectrum of tumours than has been modelled in this report needs to be demonstrated before this can happen. The introduction of screening in the UK will lead to the identification of earlier stage tumours than are currently being diagnosed without a screening policy. With increasing demand and supply of PSA testing in the UK, and the subsequent increase in the numbers of men being diagnosed with early localised prostate cancer, the current treatment dilemma will have even greater healthcare and resource implications for the NHS in coming years. The cost-effectiveness of DNA-ploidy testing under a screening regime, and for a broader spectrum of prostate cancers is clearly of interest, and should be considered in further research.

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