A cost analysis of non-invasive blood-based microRNA testing versus CT scans for follow-up in patients with testicular germ cell tumors

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Conflicts of interest statement: The authors declare no potential conflicts of interest. For information, NC and MJM are developing and validating the technical and clinical performance of the non-invasive blood-based miRNA test described in this manuscript. RA is assisting NC and MJM in translating the test into clinical practice. HA, CB, DC, MF, and KT worked with RA to identify potential healthcare savings following future implementation of the miRNA test.

Keywords: cost analysis; CT scan; germ cell tumor; microRNA; non-invasive; serum; testis cancer

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Abstract

Background: Our group has developed a non-invasive blood-based microRNA (miRNA) test for improving diagnosis, disease-monitoring and relapse detection in malignant testicular germ cell tumors (TGCTs). Performance analysis suggests the test is likely to have comparable sensitivity and specificity in detecting TGCT as CT, thus reducing the need for serial CT scans for follow-up monitoring, with associated reductions in cumulative radiation burden and second cancer risk. To facilitate clinical adoption, we undertook a cost analysis to identify the budget impact of replacing CT scans with miRNA testing within healthcare systems.

Methods: The TGCT aftercare pathway was mapped out using National Comprehensive Cancer Network guidelines. A Markov model was built to simulate the impact of the miRNA test on TGCT aftercare costs. Incidence, treatment probabilities, relapse rate and death rate data were collected from published studies to populate the model.

Results: Applying our model to the US healthcare system, the miRNA test has the potential to save up to $69M/year in aftercare expenses related to TGCT treatment; with exact savings depending on the adoption rate and test price.

Conclusions: This analysis demonstrates the potential positive budget impact of adopting miRNA testing in place of CT scans in the clinical management of TGCTs.

Introduction

Germ cell tumors (GCTs) occur throughout life from childhood through to late adulthood. They may arise at gonadal (testicular/ovarian) or extragonadal sites. Testicular GCTs (TGCTs) are the most common solid malignancy in males aged 20-35 years (1). TGCTs are subdivided into seminoma or nonseminoma, the latter group which includes yolk sac tumor, embryonal carcinoma and choriocarcinoma (2). Although the cause of testicular cancer is still poorly understood, there is increased risk amongst first-degree relatives (1), confirmed by recent genome-wide association studies (3).

Global incidence of TGCTs was 1.5/100,000 in 2008, but is higher in Western Europe at 7.8/100,000 (2015 figures) (4). Remission rates are generally high, with 5-year overall survival reaching 98%. Following definitive treatment [orchidectomy and chemotherapy/radiotherapy according to disease stage (5,6)], there is a risk of recurrence. Follow-up schedules generally last for ten years to monitor for this risk and for late-effects of treatment (6,7).

Follow-up typically comprises regular physical examination, serum biomarker measurement [alpha-fetoprotein (AFP) and human choriogonadotropin (HCG)] (6), chest X-rays, and CT scans (7). However, doubt has been cast on the clinical value of physical examination (8,9), chest X-ray (10,11), and AFP/HCG markers, which are, for example, elevated in just 3% of seminoma patients at relapse (6). Thus for many patients, detection of relapse is dependent upon serial CT scans, which are associated with cumulative radiation burden and increased second cancer risk (12). Consequently, there is a clear need for a universal, reliable alternative to current biomarkers and CT scans for disease-monitoring purposes, both during and after treatment (7).

MicroRNAs (miRNAs) are short, non-coding RNAs which regulate gene expression (2). Global miRNA expression profiles classify cancer more effectively than protein-coding messenger RNAs (mRNAs) and reflect the developmental lineage of tumors (13). Our previous work showed that all malignant GCTs overexpress miRNAs from the miR-371~373 and miR-302/367 clusters, independent of patient age (pediatric or adult), tumor histological subtype (seminoma, yolk sac tumor or embryonal carcinoma) or anatomic site (gonadal or extragonadal), and are not coordinately overexpressed in any other cancer or disease state, demonstrating their biomarker potential (2,6). Furthermore, using PCR methodology incorporating a pre-amplification step, these miRNAs were elevated in serum at the time of malignant GCT diagnosis, and fell to normal levels during successful treatment (14). This and further work (6,15-18), subsequently replicated by others (e.g. (19-22)), has for example shown that miRNA marker sampling is also highly sensitive for detecting relapse in TGCT follow-up (17). MiR-371a-3p use as a serum biomarker has been shown to achieve a sensitivity/specificity of 88.7/93.4%, respectively, with an area under the curve (AUC) on receiver operator characteristic analysis of 0.94 (20). The combined use of miR-371a-3p together with miR-373-3p and miR-367-3p under pre-amplification conditions was found to yield sensitivity of 92% and specificity of 91% (22). Serial testing of miRNAs (as is currently undertaken with AFP/HCG), would therefore put miRNA testing in contention with CT scanning for TGCT recurrence monitoring, which itself has a sensitivity and specificity of 92.8% and 98.6%, respectively (23). Indeed, an independent review highlighted the translational potential of this non-invasive blood-based miRNA test, stating that the data thus far ‘provides convincing evidence for the use of miRNAs as biomarkers for (germ cell) testicular cancer’ and that the ‘introduction of miRNA measurements is anticipated for the clinical management of patients with TGCTs in the near future’ (24).

However, prior to the introduction of novel nucleic acid based biomarkers such as circulating miRNAs or tumor DNA (ctDNA) into routine clinical practice for cancer management, we believe that cost analysis assessments first need to be undertaken. The aim of this study was therefore to estimate the net cost impact of non-invasive miRNA testing in place of CT scanning for TGCT follow-up ('aftercare'), performed from the perspective of the US healthcare system under various pricing scenarios. This study will facilitate a better understanding of the health economic value this tool has in improving management for patients with TGCTs, which can be used as a model for other novel biomarkers in different cancer types - a perspective not often considered when contemplating a shift of clinical protocol.

Methods

This study was a cost analysis of miRNA testing versus CT scans for follow-up assessments in patients previously treated for TGCTs. The model predicted the expected cost of aftercare per patient under CT scan based follow-up. The analysis was then repeated, substituting miRNA testing for CT scans, and the cost difference between the two was examined. We repeated the analysis for different utilization rates of the miRNA test relative to CT scanning alone.

Model structure

Following initial diagnostic work-up, an orchidectomy is performed with pathological confirmation and disease staging using CT. Subsequent treatment depends on staging - stage I tumors may be observed in many circumstances, whereas stage II-IV tumors require further definitive therapy, usually chemotherapy according to International Germ Cell Consensus Classification (IGCCC) risk groups (5,6). The patient then enters aftercare, where the program of follow-up depends upon the previous indication, treatment type, stage of disease and the number of years in remission.

A Markov model was developed to estimate the trajectory of patients following initial treatment as they entered into long-term monitoring (Supplementary Data). The (US) National Comprehensive Cancer Network (NCCN) guidelines for TGCTs recommend a 10-year window of monitoring following treatment for all patients (7); consequently the time horizon of the model was 10 years. A 1-year transition period for the model was chosen because much of the clinical literature supporting transition rates utilised annual data collection windows.

As the focus of the study was on patient aftercare, parameters relating to initial presentation, diagnosis (via orchidectomy) and subsequent staging were omitted, and the model

commenced post-orchidectomy, immediately prior to subsequent management (Figure 1). Patients entered the model stratified into one of three possible clinical stages I, II, and III; based on tumor size, evidence of lymph node involvement, and/or presence of metastases (7) of seminoma or nonseminoma [it should be noted that NCCN guidelines for TGCTs exclude stage IV as a prognostic grouping (7)].

The majority of patients with TGCTs enter remission following treatment, which was modelled as a series of 'follow-up' tunnel states unique to the patient's original disease staging (Figure 1). Resource usage rates for aftercare at each year of follow-up (Table 1) were based on NCCN management guidelines (7) and supplemented by interview with consultant oncologists from the UK. Patients within a given year of follow-up could either progress to the next year of follow-up, or encounter a relapse. A relapse event was modelled as an instantaneous occurrence with a corresponding risk of successful recovery or disease progression. Patients with a successful recovery were assumed to have returned to the year one follow-up state corresponding to their original diagnosis stage, while patients who progressed would receive salvage therapy. It should be noted that death was only modelled following a transition into the relapse state, supported by the low mortality rates from active TGCT disease and high success rates of treatment (25).

In the US, according to the Surveillance, Epidemiology, and End Results (SEER) database, 58.3% of TGCT patients have seminoma while 41.7% have nonseminoma (26). Year 0 starting stages were based on the distribution of tumor stages at diagnosis (26). The model was populated with data for recurrence risk and relapse mortality from a number of TGCT clinical studies (Table 2). A discount rate of 5% was selected based on prior health economic precedent to account for the time-value of longitudinal treatments (27).

Unit costs for different elements of the aftercare pathway, comprising clinical examination, conventional serum AFP/HCG estimation, chest X-rays and CT scans, were obtained from a prior analysis examining TGCT treatment costs in the United States Medicaid Medicare systems (28) (Table 2). As we knew the unit cost of the proposed miRNA test but not the charge price (which includes e.g. workforce and physician costs, hospital overheads) we utilised a cost-to-charge ratio of 3.54. This value represents the mark-up typically set by healthcare providers for any services delivered to patients, as a scaling factor relative to their original procurement price, which in this case was assumed to be equal to manufacturing cost (29). Consequently, from an initial unit cost of $55.43, this yielded an estimated charge price of $196.21 per test.

Sensitivity between miRNA and CT scanning (92% and 92.8%, respectively) was assumed to be equivalent for the purposes of this analysis. The difference in specificity (91% miRNA *vs.* 98.6% CT), however, was determined to be too substantial to exclude from further analysis; a lower specificity leads to a higher false positive rate and the need for unnecessary confirmatory CT scans. To account for this, the model assumes independence between repeat tests, and adds the cost of an additional confirmatory miRNA test to follow any positive reading from the initial screen, reflecting routine clinical practice where AFP/HCG levels are repeated when results increase above the reference range in follow-up.

Approach to analysis

The model reported annualised probabilities of patient status across different stages of seminoma and nonseminoma, namely: follow-up monitoring, recurrence, or death. Based upon different patient states, we reported annualized expected treatment and aftercare costs, and aggregate distribution of pre-determined expenses within the care process. The results of this

analysis and expected service utilization rates were used to project what cost saving impacts miRNA testing might have on individuals and the US healthcare system (Supplementary Data; Markov model). A one-way sensitivity analysis of all model attributes was conducted to understand cost drivers in the aftercare process.

Results

Face validity

After 1, 5, and 10 years of follow-up, the model predicted overall survival (OS) at 99.34%, 98.65%, and 98.30% for TGCT patients, respectively (Figure 2). This compares favorably with available national-level data. A Cancer Research UK (CRUK) survival analysis of TGCT patients indicated 1, 5, and 10-year survival of 99.1%, 98.3%, and 98.2%, respectively, suggesting the model has very strong face validity (Table 3) (30).

Typical cost of care

The expected costs of providing aftercare services to a patient with TGCT over 10 years were calculated to be approximately $19,493 (Figure 3). Of the different services provided, CT scans made up the majority of the cost by far, at 56.4% of total expenses, followed by physical exams (18%), conventional tumor markers (15.3%), relapse treatment (9.4%) and X-rays (0.9%). The majority of expenses were encountered early in the aftercare process, in concordance with the increased rate of service utilization during the initial years of post-treatment follow-up.

Cost of care - miRNA test

At a 20% early adoption rate of miRNA testing, the expected cost of providing aftercare services to patients with TGCTs over 10 years was estimated to be approximately $17,781, which represented a 9% saving in total expenditure compared with CT only (Figure 2). Increasing adoption to 100%, the expected cost of aftercare services fell further to $10,933, representing a 44% saving.

To understand how these savings translated to a systems level, a model of testicular cancer incidence was developed using historical data (Appendix A; Supplementary Data) and used to estimate the number of new cases annually between 2018 and 2027. Using this model, the predicted annual average cost of aftercare services for the US healthcare system was $157M over 10 years. Utilization rates of 20% or 100% for miRNA testing would result in 10-year US healthcare expenditure savings of $138M and $688M, respectively. Given that the total cost of testicular cancer treatment for the US healthcare system has been estimated to be $201M annually, including initial treatment (28), the full implementation of miRNA testing has the potential to reduce that figure by $69M annually, a 34% reduction in total annual expenditure for this disease.

Sensitivity analysis

Sensitivity analysis of all variables was conducted under conditions of 20% early test adoption. Results showed that the price of a CT scan remained the most influential factor in determining the total cost of care (Figure 4). Unsurprisingly, the miRNA utilization rate had a larger impact on cost than the price of the miRNA test itself, as higher adoption acted to offset the utilization of costly CT scanning in favor of the less expensive blood-based test. Price was more sensitive to increases in nonseminoma incidence as compared with seminoma, a reflection of the more aggressive nature of nonseminoma, with higher rates of relapse and disease-associated mortality.

Discussion

To our knowledge, this report represents the first health economic analysis to assess the utility of a non-invasive miRNA test in TGCT clinical practice, with particular regard to reducing the use of CT imaging. Reducing the reliance on CT during TGCT follow-up monitoring has not only a clinical benefit, but offers significant cost savings to patients, providers, and healthcare systems. Previous economic assessments of oncology protocols have typically focused on the potential savings obtained through early diagnosis, which requires less treatment and is associated with a lower chance of recurrence and higher subsequent quality of life (31). TGCTs are atypical in that patients tend to present early and there is a pre-existing, low-cost diagnostic protocol in place via ultrasound and orchidectomy. Additionally, TGCT treatment is relatively inexpensive in comparison with most other oncology schedules, and is very effective; TGCT has one of the highest cancer survival rates (25). Consequently, the analysis presented here focuses on the costs arising from aftercare, particularly the substitution of imaging studies with lower-cost alternatives.

The sensitivity and specificity of CT in detecting intra-testicular lesions is 92.8/98.6% (23), however, small lesions are often incidental and benign findings (32). Based on prior analyses (20,22), the miRNA test developed by our group is likely to have a comparable level of sensitivity in detecting TGCT as CT, with sensitivity and specificity of 92% and 91%, respectively (22); the lower cost of the test *vs.* CT offsets the lower specificity. Indeed, very recent data would suggest the superiority of miRNA testing over CT scans for assessing patients after chemotherapy for the presence of residual active malignant disease (33). Thus, early data suggest that a miRNA test could potentially substitute for a CT scan in aftercare, without compromising patient outcomes. The results presented here show that the miRNA test, at a basic charge price of $196.21, has the potential to offset a large proportion of aftercare

costs as a replacement for CT. Indeed, complete replacement could result in a $688M saving to the US healthcare system over a 10 year period.

Whilst these potential cost savings are compelling for US health insurers, the views of physicians and patients should also be considered. Whilst physicians consider cost-savings within their practice, this is always a secondary motivator in adoption of new protocols. Indeed, multiple behavioral factors influence adoption of such protocols by physicians; one study showed that patients received recommended care only 55% of the time (34). Therefore, an alternative protocol offering only cost-savings for similar standard-of-care may struggle to gain widespread adoption in the short-to-medium term. Importantly, our analysis shows that tangible cost-savings would still be accrued even with a modest initial 20% rate of replacement over CT scans. For the patient perspective, see Appendix B, Supplementary Data.

Our model and analyses have a number of potential limitations. Firstly, the variability of treatment given and the aftercare process, based on the stage and type of TCGT disease, meant that the care pathway required simplification in order to build the model structure. Secondly, the healthcare prices used in the model were derived from Medicare/Medicaid claims data, which typically underestimates the prices charged for patients with private health insurance. This could lead to an underestimate of the cost-savings that could be achieved from the miRNA test. In contrast, in other non-US healthcare systems the costs for CT are likely to be lower and consequently cost-savings more modest. Thirdly, it is acknowledged that the NCCN guidelines for CT scan frequency are not particularly evidence-based, and a more measured approach to scanning is adopted in some healthcare systems; such an approach would also impact on potential cost-savings. Fourthly, we have assumed that the sensitivity and specificity of the miRNA test will be the same at the time of radiologically identified relapse as at primary diagnosis. It should be noted that large-scale prospective clinical trials are

underway to confirm this assumption. Finally, the initial 20% miRNA test adoption rate was selected as the starting value based on interviews with clinical experts, but the real value may differ depending upon the degree of clinical evidence, marketing efforts, and other tertiary factors that influence the adoption of novel biomarkers. We have however made the model available so that it may be adjusted for these and other factors in different healthcare systems (Supplementary Data; Markov model).

In calculating the final cost-offset, miRNA testing frequency and pattern was made comparable to the current NCCN guidelines for CT scanning. It is highly likely that when implemented in clinical practice, however, the guidelines for miRNA testing will be consistent with the more frequent conventional serum tumor marker analyses. Of note, we retained conventional AFP/HCG tumor marker utilization in the follow-up care pipeline. Given the relatively limited performance of these markers for detecting TGCT relapse, particularly for seminoma patients, the potential for replacing both CT scanning and AFP/HCG analysis with a single serum miRNA test should also be considered in such cohorts. Further confirmatory work will be required to ensure that the sensitivity of the miRNA test is indeed comparable to CT scans during aftercare in a clinical setting. Our results provide a strong incentive for such work to be conducted. Once undertaken, confirmatory CT will only need to be performed in positive miRNA test cases, to allow assessment of radiological extent of disease. Early evidence shows that the miRNA test is positive at the time of malignant TGCT relapse and that these novel biomarkers may precede clinical or radiological evidence of disease (6,17).

Conclusion. Significant costs in TGCT care are incurred by the healthcare system during the 10-year follow-up or 'aftercare' period. We demonstrate the potential cost-offset of adopting miRNA testing over CT scans in TGCT aftercare. Our analyses show potential cost-savings at a range of adoption levels over CT scans and price points for the test. Following confirmatory studies, it will be important to establish miRNA testing in routine TGCT clinical management, at which stage the cost effectiveness of this approach can be formally assessed and demonstrated.

Clinical Practice Points

- It is already known that the current conventional serum markers alpha fetoprotein (AFP) and human chorionic gonadotropin (HCG) have limited sensitivity in assisting the diagnosis and longitudinal follow-up of testicular (germ cell) cancer, as they are typically negative in certain malignant subtypes, including seminoma and embryonal carcinoma.

- It is also known that clinical examination and chest X-ray are of very little use for diagnosing relapse in clinical follow-up of testicular cancer patients.

- Consequently, testicular cancer aftercare relies heavily on CT scanning in follow-up, with associated radiation burden and concerns regarding second cancer risk, as well as health economic implications.

- Recently, serum microRNA testing has shown much research promise as a potential universal biomarker of diagnosis and relapse for all malignant germ cell cancers, including testicular cancer.

- Prior to the introduction of novel nucleic acid based biomarkers such as circulating microRNAs or tumor DNA (ctDNA) into routine clinical practice for cancer management, cost analysis assessments need to be undertaken.

- Here, our cost analyses demonstrate a potential cost-offset of adopting miRNA testing over CT scans in testicular cancer aftercare.

- Following confirmatory prospective studies, it will be important to establish microRNA testing in routine testicular cancer clinical management

Legends to Figures and Tables

Figure 1. Markov Chain summarising testicular germ cell tumor (TGCT) aftercare model flow structure. At the point marked 'start' post-treatment patients are divided into having had either seminoma or nonseminoma based upon disease incidence rates of each indication, and subsequently divided into stages using similar methods. With the assumption that each patient had been treated and is currently in remission, each year of follow-up care is entered. At each point, there is a unique risk of relapse that decreases over time. A patient entering relapse either successfully recovers, at which point they will return to the beginning of the follow-up cycles, or are assumed to have disease progression which leads to death. Patients progress through each unique year of follow-up until they reach the Year 10 state, which repeats indefinitely for any additional model cycles.

Figure 2. Each possible Markov state following 10 cycles of the testicular germ cell tumor (TGCT) aftercare model is shown (A). The horizontal axes represents each individual Markov cycle, with point zero showing initial patient stratifications based on disease and stage incidence data. The vertical axes represent the total probability of a patient progressing through the model being in that particular state (follow-up, relapse, or death) having had either seminoma or nonseminoma stages 1, 2 or 3. For each cycle, all model states cumulatively add up to 100% probability. The overall survival for patients with seminoma and nonseminoma, combined, is shown with data from CRUK superimposed for comparison (B).

Figure 3. The costs of different testicular germ cell tumor (TGCT) aftercare services are shown under a 20% miRNA test adoption rate scenario. The absolute expected aftercare costs, stratified by service, are shown for each year of follow-up for 10 model cycles (A). The cumulative cost of each individual service over 10 model cycles, discounted at a rate of 5% per

cycle, is combined to highlight the total expected, discounted, cost of aftercare services (B). The impact of varying the miRNA test utilization rate on the total discounted cost of aftercare services for individual as well as health system cost is shown (C).

Figure 4. A sensitivity analysis of the testicular germ cell tumor (TGCT) aftercare model was conducted under the 20% miRNA test adoption scenario, with each model input varied by -20% (low) or +20% (high) from its basal condition (Table 2). The impact on total discounted cost of aftercare services was then calculated. Results were sorted top-down in order of largest absolute difference between low and high cases.

Table 1. Annual frequency of different follow-up service utilization by initial stage and condition. The four major follow-up services, namely physical examination, tumor marker screening, X-ray and CT scanning, together with miRNA testing, are mapped according to stage and either germ cell tumor subtype – either seminoma or nonseminoma. For each year of follow-up care after initial treatment, the number of annual recommended service utilizations is shown.

Table 2. Markov model inputs. Parameters for input into the model are shown below. The upper panel is separated into seminoma and nonseminoma. The lower panel includes treatment costs for different follow-up services and relapse treatment.

Table 3. Face validity comparison between model and validation data. Pooled overall survival (OS) from both seminoma and nonseminoma branches of the Markov model at various time-points are compared against comparable epidemiological data available for CRUK.

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Table 1. Annual frequency of different follow-up service utilization by initial stage and condition. The four major follow-up services, namely physical examination, tumor marker screening, X-ray and CT scanning, together with miRNA testing, are mapped according to stage and either germ cell tumor subtype – either seminoma or nonseminoma. For each year of follow-up care after initial treatment, the number of annual recommended service utilizations is shown.

Condition	Stage	Service	Year of Follow-up Care					
			1	2	3	4	5	6+
Seminoma	I	Physical exam	4	4	2	2	1	1
		Tumor markers	4	4	2	1	1	1
		X-ray	0	0	0	0	0	0
		CT Scan	2	2	1	1	1	1
		miRNA test	2	2	1	1	1	1
	II	Physical exam	4	2	2	2	2	2
		Tumor markers	4	2	2	2	2	2
		X-ray	2	2	1	1	1	1
		CT scan	2	2	1	1	1	1
		miRNA test	2	2	1	1	1	1
	III	Physical exam	6	4	2	2	2	2
		Tumor markers	6	4	2	2	1	1
		X-ray	6	4	2	2	1	1
		CT scan	4	4	4	4	2	2
		miRNA test	4	4	4	4	2	2
Nonseminoma	I	Physical exam	12	6	4	4	2	1
		Tumor markers	12	6	4	4	2	1
		X-ray	0	0	0	0	0	0
		CT scan	4	4	2	2	1	1
		miRNA test	4	4	2	2	1	1
	II	Physical exam	4	4	2	2	2	1
		Tumor markers	4	4	2	2	2	1
		X-ray	6	6	4	2	2	1
		CT scan	2	2	1	1	1	1
		miRNA test	2	2	1	1	1	1
	III	Physical exam	6	4	2	2	2	1
		Tumor markers	6	4	2	2	2	1
		X-ray	6	6	4	2	2	1
		CT scan	2	2	1	1	1	1
		miRNA test	2	2	1	1	1	1

Table 2. Markov model inputs. Parameters for input into the model are shown below. The upper panel is separated into seminoma and nonseminoma. The lower panel includes treatment costs for different follow-up services and relapse treatment.

Parameter	Value	Reference*	Parameter	Value	Reference*
Seminoma			**Nonseminoma**		
Incidence	58.29%	(26)	Incidence	41.71%	(26)
Stage At Diagnosis			**Stage At Diagnosis**		
Stage I	80.21%	(26)	Stage I	58.20%	(26)
Stage II	15.04%	(26)	Stage II	23.34%	(26)
Stage III	4.75%	(26)	Stage III	18.46%	(26)
Recurrence Risk			**Recurrence Risk**		
Stage I			**Stage I**		
Year I	5.4%	(9)	Year I	15.0%	(9)
Year II	4.2%	(9)	Year II	2.3%	(9)
Year III	2.2%	(9)	Year III	0.7%	(9)
Year IV	1.35%	(35)	Year IV	0.68%	(35)
Year V	0.46%	(35)	Year V	0.65%	(35)
Year VI	0.37%	(35)	Year VI	0.53%	(35)
Year VII	0.28%	(35)	Year VII	0.41%	(35)
Year VIII	0.19%	(35)	Year VIII	0.28%	(35)
Year IX	0.09%	(35)	Year IX	0.16%	(35)
Year X	0.0%	(35)	Year X	0.04%	(35)
Stage II			**Stage II**		
Year I	3.1%	(25)	Year I	3.1%	(25)
Year II	1.0%	(25)	Year II	1.0%	(25)
Year III	1.0%	(25)	Year III	1.0%	(25)
Year IV	1.0%	(35)	Year IV	0.71%	(35)
Year V	1.0%	(35)	Year V	0.40%	(35)
Year VI	0.82%	(35)	Year VI	0.36%	(35)
Year VII	0.63%	(35)	Year VII	0.31%	(35)
Year VIII	0.45%	(35)	Year VIII	0.26%	(35)
Year IX	0.26%	(35)	Year IX	0.22%	(35)
Year X	0.08%	(35)	Year X	0.17%	(35)
Stage III			**Stage III**		
Year I	3.1%	(25)	Year I	3.1%	(25)
Year II	1.0%	(25)	Year II	1.0%	(25)
Year III	1.0%	(25)	Year III	1.0%	(25)
Year IV	0.51%	(35)	Year IV	0.93%	(35)
Year V	0.0%	(35)	Year V	0.85%	(35)
Year VI	0.0%	(35)	Year VI	0.74%	(35)
Year VII	0.0%	(35)	Year VII	0.62%	(35)
Year VIII	0.0%	(35)	Year VIII	0.50%	(35)
Year IX	0.0%	(35)	Year IX	0.38%	(35)
Year X	0.0%	(35)	Year X	0.26%	(35)
Relapse Survival			**Relapse Survival**		
Stage I	99.1%	(36)	Stage I	99.0%	(36)
Stage II/III	32.7%	(5)	Stage II/III	39.7%	(5)
Treatment Costs					
Cost Physical Exam	$164.29	(28)	Cost Radiotherapy (RT) Course	$12,927.48	(28)
Cost Tumor Markers	$142.68	(28)	Cost Surgery	$11,595.09	(28)
Cost Chest X Ray	$29.95	(28)	Cost Total Seminoma Relapse	$11,918.29	(28)
Cost CT Scan	$898.30	(28)	Cost Total Nonseminoma Relapse	$11,314.16	(28)
Cost miRNA	$196.21	See Appendix	Cost Salvage Chemotherapy	$21,804.75	(28)
Cost Bleomycin, Etoposide, Cisplatin (BEP) Course	$8,239.87	(28)			

*Detailed data derivations from sources used are available in Supplementary Data

Table 3. Face validity comparison between model and validation data. Pooled overall survival (OS) from both seminoma and nonseminoma branches of the Markov model at various time-points are compared against comparable epidemiological data available for CRUK.

Time Point	Model Overall Survival	CRUK Validation Cohort Overall Survival	% Error
1 Year	99.34%	99.1%	0.24%
5 Year	98.65%	98.3%	0.35%
10 Year	98.30%	98.2%	0.10%

Figure 1

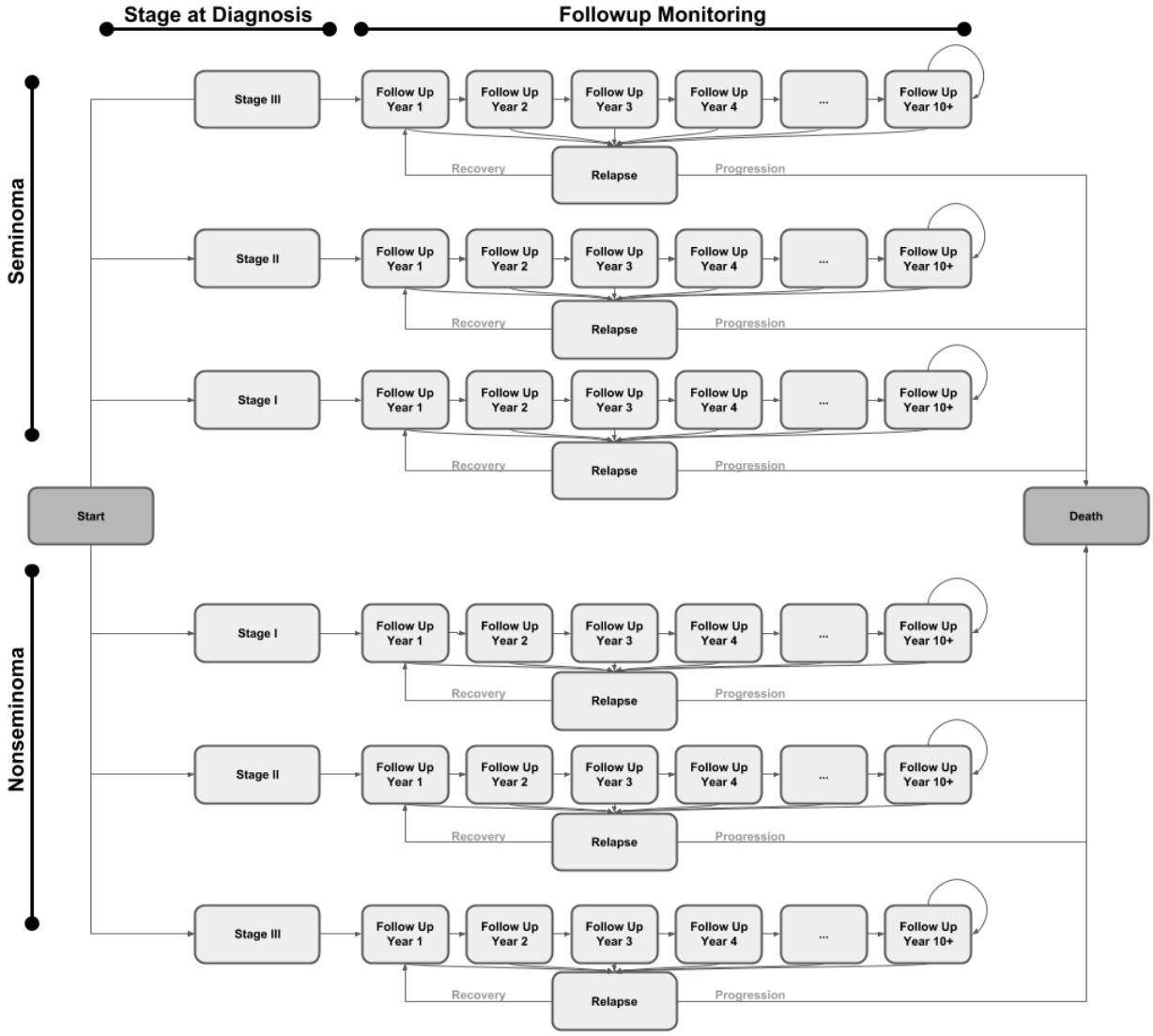

Stage at Diagnosis
Followup Monitoring
Seminoma
Nonseminoma
Start
Death
Stage III
Stage II
Stage I
Stage I
Stage II
Stage III
Follow Up Year 1
Follow Up Year 2
Follow Up Year 3
Follow Up Year 4
...
Follow Up Year 10+
Recovery
Relapse
Progression

Figure 2

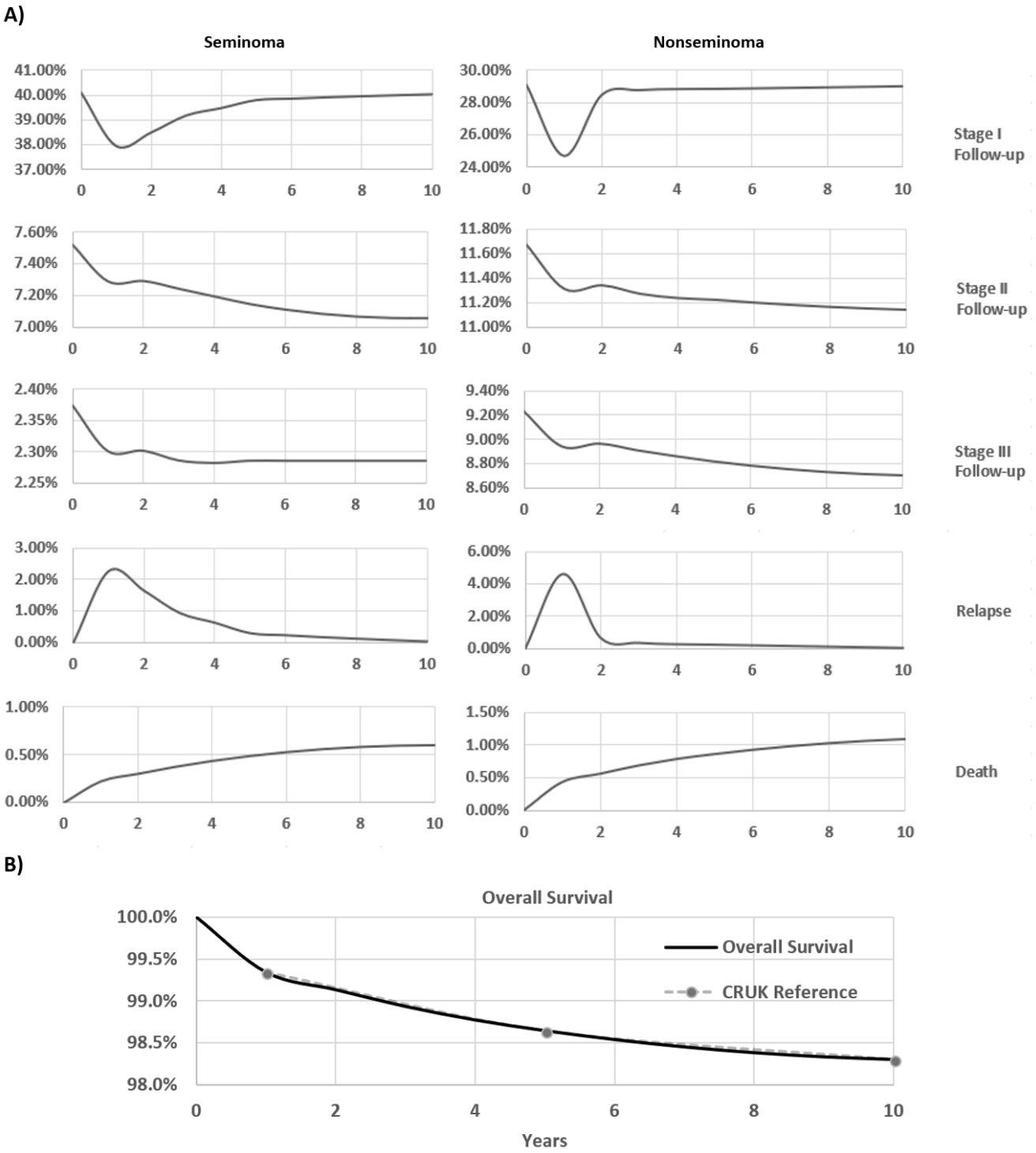

A)
Seminoma
Nonseminoma
Stage I Follow-up
Stage II Follow-up
Stage III Follow-up
Relapse
Death
B)
Overall Survival
Overall Survival
CRUK Reference
Years

Figure 3

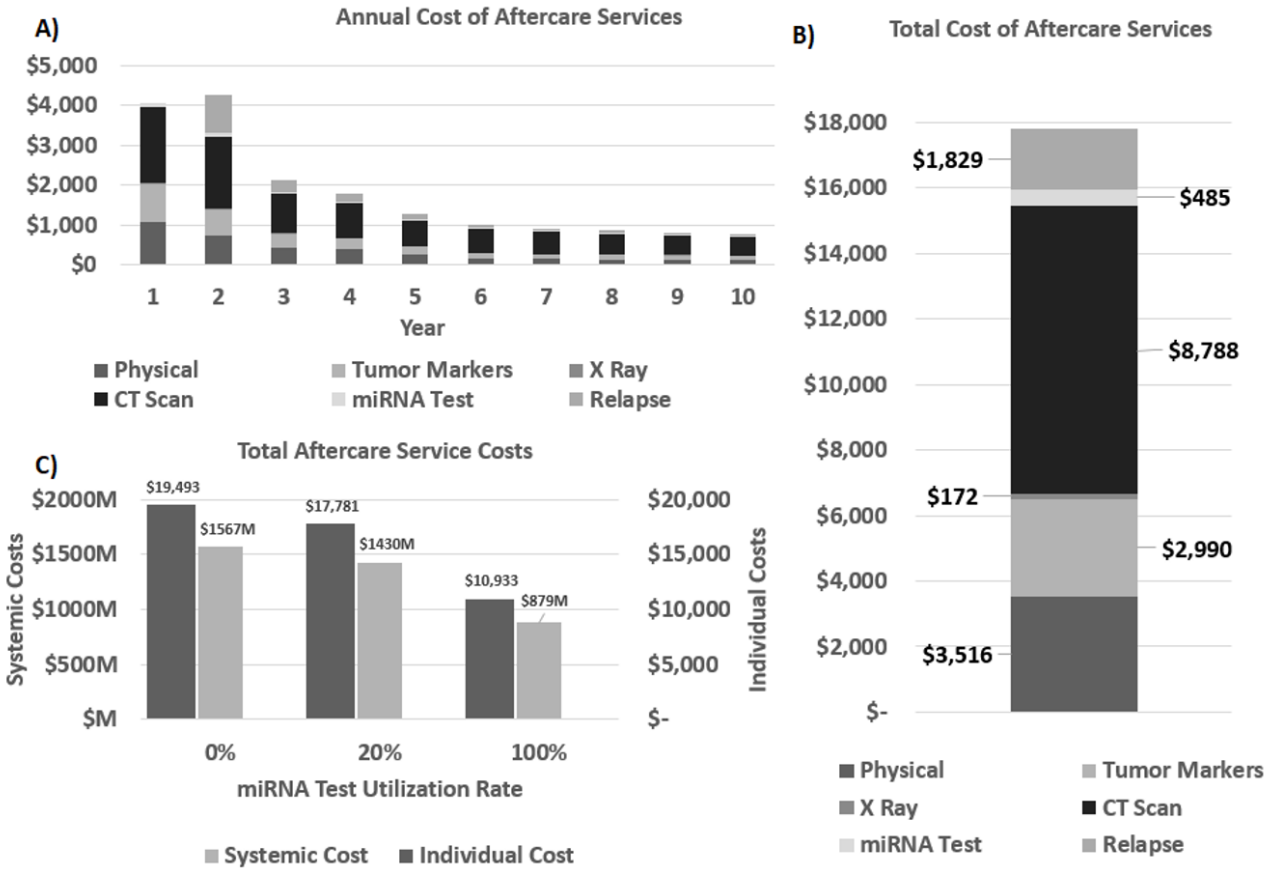
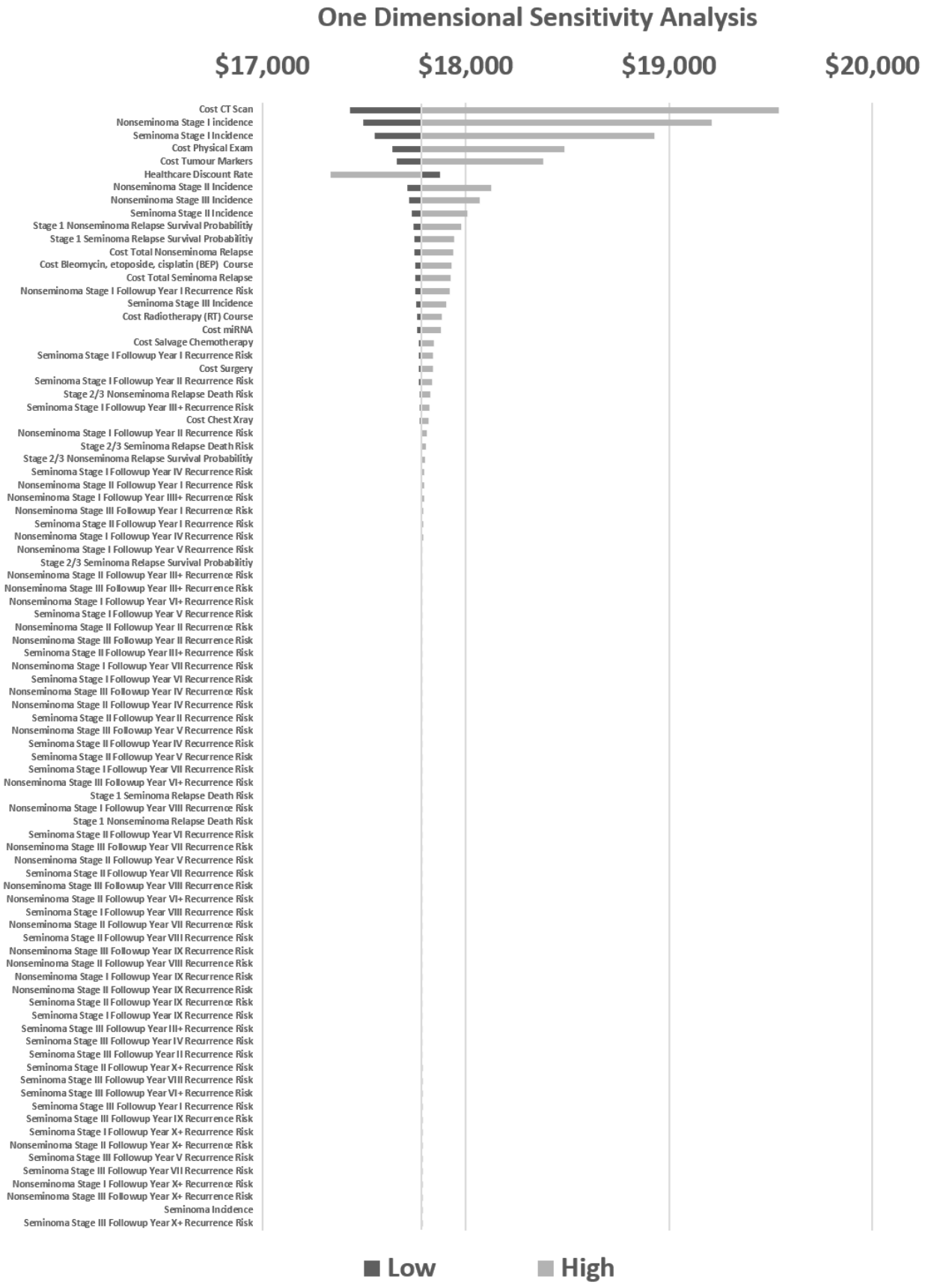

A)
Annual Cost of Aftercare Services
$5,000
$4,000
$3,000
$2,000
$1,000
$0
1
2
3
4
5
6
7
8
9
10
Year
Physical
Tumor Markers
X Ray
CT Scan
miRNA Test
Relapse
B)
Total Cost of Aftercare Services
$18,000
$16,000
$14,000
$12,000
$10,000
$8,000
$6,000
$4,000
$2,000
$-
$1,829
$485
$8,788
$172
$2,990
$3,516
Physical
Tumor Markers
X Ray
CT Scan
miRNA Test
Relapse
C)
Total Aftercare Service Costs
Systemic Costs
$2000M
$1500M
$1000M
$500M
$M
$19,493
$1567M
$17,781
$1430M
$10,933
$879M
$20,000
$15,000
$10,000
$5,000
$-
Individual Costs
0%
20%
100%
miRNA Test Utilization Rate
Systemic Cost
Individual Cost

Figure 4


One Dimensional Sensitivity Analysis
$17,000
$18,000
$19,000
$20,000
Cost CT Scan
Nonseminoma Stage I incidence
Seminoma Stage I Incidence
Cost Physical Exam
Cost Tumour Markers
Healthcare Discount Rate
Nonseminoma Stage II Incidence
Nonseminoma Stage III Incidence
Seminoma Stage II Incidence
Stage 1 Nonseminoma Relapse Survival Probabilitiy
Stage 1 Seminoma Relapse Survival Probabilitiy
Cost Total Nonseminoma Relapse
Cost Bleomycin, etoposide, cisplatin (BEP) Course
Cost Total Seminoma Relapse
Nonseminoma Stage I Followup Year I Recurrence Risk
Seminoma Stage III Incidence
Cost Radiotherapy (RT) Course
Cost miRNA
Cost Salvage Chemotherapy
Seminoma Stage I Followup Year I Recurrence Risk
Cost Surgery
Seminoma Stage I Followup Year II Recurrence Risk
Stage 2/3 Nonseminoma Relapse Death Risk
Seminoma Stage I Followup Year III+ Recurrence Risk
Cost Chest Xray
Nonseminoma Stage I Followup Year II Recurrence Risk
Stage 2/3 Seminoma Relapse Death Risk
Stage 2/3 Nonseminoma Relapse Survival Probabilitiy
Seminoma Stage I Followup Year IV Recurrence Risk
Nonseminoma Stage II Followup Year I Recurrence Risk
Nonseminoma Stage I Followup Year IIII+ Recurrence Risk
Nonseminoma Stage III Followup Year I Recurrence Risk
Seminoma Stage II Followup Year I Recurrence Risk
Nonseminoma Stage I Followup Year IV Recurrence Risk
Nonseminoma Stage I Followup Year V Recurrence Risk
Stage 2/3 Seminoma Relapse Survival Probabilitiy
Nonseminoma Stage II Followup Year III+ Recurrence Risk
Nonseminoma Stage III Followup Year III+ Recurrence Risk
Nonseminoma Stage I Followup Year VI+ Recurrence Risk
Seminoma Stage I Followup Year V Recurrence Risk
Nonseminoma Stage II Followup Year II Recurrence Risk
Nonseminoma Stage III Followup Year II Recurrence Risk
Seminoma Stage II Followup Year III+ Recurrence Risk
Nonseminoma Stage I Followup Year VII Recurrence Risk
Seminoma Stage I Followup Year VI Recurrence Risk
Nonseminoma Stage III Followup Year IV Recurrence Risk
Nonseminoma Stage II Followup Year IV Recurrence Risk
Seminoma Stage II Followup Year II Recurrence Risk
Nonseminoma Stage III Followup Year V Recurrence Risk
Seminoma Stage II Followup Year IV Recurrence Risk
Seminoma Stage II Followup Year V Recurrence Risk
Seminoma Stage I Followup Year VII Recurrence Risk
Nonseminoma Stage III Followup Year VI+ Recurrence Risk
Stage 1 Seminoma Relapse Death Risk
Nonseminoma Stage I Followup Year VIII Recurrence Risk
Stage 1 Nonseminoma Relapse Death Risk
Seminoma Stage II Followup Year VI Recurrence Risk
Nonseminoma Stage III Followup Year VII Recurrence Risk
Nonseminoma Stage II Followup Year V Recurrence Risk
Seminoma Stage II Followup Year VII Recurrence Risk
Nonseminoma Stage III Followup Year VIII Recurrence Risk
Nonseminoma Stage II Followup Year VI+ Recurrence Risk
Seminoma Stage I Followup Year VIII Recurrence Risk
Nonseminoma Stage II Followup Year VII Recurrence Risk
Seminoma Stage II Followup Year VIII Recurrence Risk
Nonseminoma Stage III Followup Year IX Recurrence Risk
Nonseminoma Stage II Followup Year VIII Recurrence Risk
Nonseminoma Stage I Followup Year IX Recurrence Risk
Nonseminoma Stage II Followup Year IX Recurrence Risk
Seminoma Stage II Followup Year IX Recurrence Risk
Seminoma Stage I Followup Year IX Recurrence Risk
Seminoma Stage III Followup Year III+ Recurrence Risk
Seminoma Stage III Followup Year IV Recurrence Risk
Seminoma Stage III Followup Year II Recurrence Risk
Seminoma Stage II Followup Year X+ Recurrence Risk
Seminoma Stage III Followup Year VIII Recurrence Risk
Seminoma Stage III Followup Year VI+ Recurrence Risk
Seminoma Stage III Followup Year I Recurrence Risk
Seminoma Stage III Followup Year IX Recurrence Risk
Seminoma Stage I Followup Year X+ Recurrence Risk
Nonseminoma Stage II Followup Year X+ Recurrence Risk
Seminoma Stage III Followup Year V Recurrence Risk
Seminoma Stage III Followup Year VII Recurrence Risk
Nonseminoma Stage I Followup Year X+ Recurrence Risk
Nonseminoma Stage III Followup Year X+ Recurrence Risk
Seminoma Incidence
Seminoma Stage III Followup Year X+ Recurrence Risk
Low
High