Early economic evaluation to guide development of a spectroscopic liquid biopsy for the detection of brain cancer

Running title: Evaluation of brain cancer spectroscopic liquid biopsy

Ewan Gray[1], James M. Cameron[2], Holly J. Butler[3], Michael D. Jenkinson[4], Mark G. Hegarty[3], David S. Palmer[2,3], Paul M. Brennan[5], Matthew J. Baker[2,3]*

[1] Independent Health Economics Consultant

[2] Department of Pure and Applied Chemistry, University of Strathclyde

[3] ClinSpec Diagnostics Limited

[4] Institute of Translational Medicine, University of Liverpool & The Walton Centre NHS Foundation Trust

[5] Translational Neurosurgery, Department of Clinical Neurosciences, Western General Hospital, Edinburgh

*Corresponding Author, Address: WestCHEM, Department of Pure and Applied Chemistry, University of Strathclyde, Technology and Innovation Centre, 99 George Street, Glasgow G1 1RD, UK. Telephone: 0141 548 4700. Email:matthew.baker@clinspecdx.com

Objectives: An early economic evaluation to inform the translation into clinical practice of a spectroscopic liquid biopsy for the detection of brain cancer. Two specific aims are: [1] to update an existing economic model with results from a prospective study of diagnostic accuracy, and [2] explore the potential of brain tumour type predictions to affect patient outcomes and healthcare costs.

Methods: A cost-effectiveness analysis from a UK NHS perspective of use of spectroscopic liquid biopsy in primary and secondary care settings, as well as a cost-consequences analysis of the addition of tumour type predictions were conducted. Decision tree models were constructed to represent simplified diagnostic pathways. Test diagnostic accuracy parameters were based on a prospective validation study. Four price points (GBP 50-200, EUR 57-228) for the test were considered.

Results: In both settings use of liquid biopsy produced QALY gains. In primary care, at test costs below GBP 100 (EUR 114) testing was cost saving. At GBP 100 (EUR 114) per test the ICER was GBP 13,279 (EUR 15,145) while at GBP 200 (EUR 228) the ICER was GBP 78,300 (EUR 89,301). In secondary care, the ICER ranges from GBP 11,360 (EUR 12,956) to GBP 43,870 (EUR 50,034) across the range of test costs. .

Conclusions: Results demonstrate potential for the technology to be cost-effective in both primary and secondary care settings. Additional studies of test use in routine primary care practice is needed to resolve the remaining issues of uncertainty - prevalence in this patient population and referral behaviour.

Keywords: ‘Spectroscopy, Fourier Transform Infrared’,’ Brain Neoplasms’, ‘Economic Model’

Introduction

Brain tumours have among the worst prognosis of all cancer types. In England, the 1-year survival rate is 40 percent while the 5-year survival rate is as low as 15 percent [1]. This, at least in part, may relate to late presentation and diagnosis. The symptoms experienced by patients with a brain tumour can be vague and non-specific and as such have only a poor predictive value from a diagnostic perspective [2][3]. Headache, the most common symptom of brain tumours in adults, also occurs in 4.4 percent of all primary care consultations but has a positive predictive value of only 0.09 percent [2]. A study of symptom-based referral pathways for suspected brain tumour reported a positive predictive value (PPV) of 2.8 percent for severe red flag symptoms in terms of detecting a brain tumour on subsequent brain imaging [4]. There is clinical need for new tests to support brain tumour diagnosis that both reduce diagnostic delay and reduce unnecessary imaging.

The liquid biopsy proposed here is based on Fourier-transform infrared (FTIR) spectroscopy applied to serum from a standard blood sample. The spectral data is collected and analysed using pattern recognition and machine learning algorithms to detect disease-specific signatures [5]. Liquid biopsy results predict presence or absence of cancer and may also suggest cancer type.

The test was developed using data from 433 patient blood samples, including those with and without brain tumours. Using a 5-fold cross-validation strategy to assess accuracy in the development data a sensitivity of 92.8 percent and specificity of 91.5 percent was reported [6]. This result was further validated in a larger retrospective cohort of 724 patients with sensitivity of 93.2 percent and specificity of 92.8 percent reported [5].

Translation of entirely new diagnostic technologies to the clinic is highly challenging with complex and internationally varying regulatory and reimbursement decision making [7]. Early economic evaluation has been proposed as a method to guide the development of medical tests from the lab to the clinic [8]. By obtaining estimates of cost-effectiveness before the final stage clinical research or commercialisation, efficiency in translation can be improved. Clinical applications that are unlikely to be able to demonstrate cost-effectiveness can be halted while more promising applications can be progressed [9].

In an early economic evaluation [10], we mapped a clinical pathway integrating spectroscopic liquid biopsy as a triage test in both primary and secondary care. Patients would be tested with a liquid biopsy prior to referral for brain imaging studies, those testing positive would be prioritised to urgent imaging (within 1 week) while those testing negative would have standard referral (around 4 weeks) or follow-up without further investigation. It is expected that all patients seen in secondary care would ultimately receive imaging tests while many in primary care could forgo imaging for the time being if they received a negative liquid biopsy result. Under current standard of care all patients would be referred for brain imaging via either specialist or open-access services.

Cost-effectiveness analysis results suggested the potential for the technology to be cost-effective subject to confirmation of diagnostic accuracy and test cost. The next stage in translation was identified to be a prospective validation study of test accuracy with patient blood samples gathered prior to diagnosis and treatment. This study required symptomatic patients only, without ‘healthy’ controls, as would be the case in the proposed clinical setting. A study of this type has now reached a pre-planned interim analysis [Brennan et al, under review], necessitating an update of the economic evaluation to inform the next stage of development. A cohort study design was used, recruiting from high-risk settings in secondary care. At the pre-planned interim analysis when recruitment had reached 400 patients the

prospective validation study reported test sensitivity of 81 percent and specificity of 80 percent. This iteration of the early economic evaluation updates the cost-effectiveness analysis with these estimates to help inform the next stage of translation of the technology.

We also examine a new extension of the clinical pathway. Recent research has established that there is scope to differentiate between brain tumour types as part of the same liquid biopsy based on FTIR serum spectroscopy [11]. The ability to provide a prediction of the tumour type may have additional diagnostic value. This could be particularly beneficial in cases when brain imaging is inconclusive for the tumour type. For example, the aggressive grade IV glioma, glioblastoma (GBM), may have similar radiological appearance with primary central nervous system lymphoma (PCNSL) and brain metastases, but all have very different treatment pathways [12,13]. This issue was highlighted as an important problem by clinical experts in focus groups [10]. Therefore, in this study we sought to explore the impact of providing tumour type classification on healthcare costs and patient management pathways through an extension of the cost-effectiveness model.

This study aims to inform development of the test in two ways:

[1] Estimate the cost-effectiveness of the spectroscopic liquid biopsy in both primary and secondary care in the UK NHS based on prospective diagnostic performance.

[2] Estimate the cost-consequences of providing additional tumour type predictions to clinicians at the point of confirmation of brain tumour diagnosis by imaging.

Methods

A cost-effectiveness analysis was conducted from a UK NHS perspective to evaluate the effect of the addition of triage blood test for brain cancer to standard diagnostic practice. Life

years (LY), quality-adjusted life years (QALY) and healthcare costs were estimated for both current standard practice and practice with the addition of the test. The time horizon of the analysis is two years. Unit costs used a price year of 2017/2018. Costs in GBP were converted to EUR at a rate of 1.1405 [14].

A cost-consequences analysis was conducted to explore the consequences of providing additional information of the probability of tumour types. The analysis applies only to patients with a tumour confirmed by imaging. Healthcare costs, probability of surgery, and probability of biopsy were compared between standard practice and practice when predicted probability of different tumour types is available. Surgery is both the major resource item and a significant source of possible harm for patients [15]. Reducing unnecessary surgery is the principal outcome of interest in addition to total healthcare costs.

A decision-analytic model was constructed to represent the alternative clinical pathways for suspected brain tumour patients with or without a triage blood test available [10]. A decision tree structure was selected because this can feasibly represent the alternative diagnostic pathways and outcomes over a short time horizon. A two year time horizon was selected because of the short duration of survival in this patient group, less than 20 percent are expected to survive beyond 2 years [16]. The model structure is shown in Figure 1. The figure shows the decision tree for the diagnostic pathway using a spectroscopic liquid biopsy. Without the spectroscopic liquid biopsy all patients in both primary and secondary care receive a standard referral to imaging. A positive liquid biopsy test provides the opportunity for a fast-track referral and consequently earlier diagnosis. . The clinical pathways of patients presenting in primary and secondary care were evaluated separately. A key difference is that in primary care a proportion of patients who have tested negative may forgo imaging referral while in secondary all will receive at least a standard imaging referral. This feature also means that there may be harms from false negative results in primary care leading to a longer

time-to-diagnosis. Prevalence of brain tumours of patients presenting in secondary care (3 percent) is higher than in primary care (1 percent)[10]. Prevalence in each setting was determined in the prior evaluation based on evidence from observational data and clinical expert opinion on the population that would be selected for testing in practice [10]. LY and QALY gains are driven by a reduction in delays to diagnosis for those patients with a brain tumour, leading to increased expected survival time, explained in more detail in [10]. The selected prevalence and test accuracy in the base case imply a false negative rate per 10,000 patients tested of 57 in secondary care and 19 in primary care, with a corresponding false positive rate of 1,940 in secondary care and 1,980 in primary care.

An extension of this decision tree was constructed for tumour type information (Figure 1). Tumour type classification probabilities allow varying diagnostic protocols for patients that test positive and have a tumour confirmed by imaging study (i.e. true positive for a brain tumour for the serum spectroscopy test). Three possible management routes were included in the model. Those who are predicted to have high grade glioma/GBM go directly to surgery. A prediction of primary central nervous system lymphoma (PCNSL) leads to a biopsy and medical therapy. Predicted metastatic cancer of unknown origin leads to further imaging investigation (with avoidance of brain surgery or biopsy in most cases). Under standard care all these patients would be presumed to have a GBM and directed to surgical resection, with alternative diagnosis happening during or after the surgery.

Unit cost parameters are listed in Supplementary Table 1,Decision tree parameters are listed in Supplementary Table 2. Outcomes (healthcare costs, remaining LY and QALYs) for each leaf of the decision tree were specified as in [10]. Survival, quality of life and cost parameters for the cost-consequences analysis are displayed in Supplementary Table 3. Prices for imaging studies and surgery were sourced from NHS reference costs (2017-2018).

Cost-effectiveness results for the base case analysis were summarized by the incremental cost-effectiveness ratio (ICER) at four selected spectroscopic liquid biopsy price points. Key parameters of prevalence and effect of delay on survival were varied in one-way sensitivity analysis (OWSA), these are presented on a cost-effectiveness plane. OWSA of test sensitivity and specificity is available in [10]. A probabilistic sensitivity analysis (PSA) was conducted to understand uncertainty across all key model parameters arising from sampling uncertainty. The PSA results are reported on a cost-effectiveness plane and as a cost-effectiveness acceptability curve (CEAC).

Results

In the base case of the cost-effectiveness analysis (Table 1), updated with prospective validation results, spectroscopic liquid biopsy testing would lead to a gain of 15.4 QALYs per 10,000 patients in primary care use and 65.4 QALYs per 10,000 patients in secondary care use. In primary care, at test costs below GBP 100 (EUR 114) testing was cost saving. At GBP 100 (EUR 114) per test the ICER was GBP 13,279 (EUR 15,145) while at GBP 200 (EUR 228) the ICER was GBP 78,300 (EUR 89,301). In secondary care, the ICER ranges from GBP 11,360 (EUR 12,956) to GBP 43,870 (EUR 50,034) across the range of test costs. The results of the previously published, first iteration of the early evaluation using retrospective data are available in Supplementary Table 4 to see the effect of the attenuation of diagnostic performance on cost-effectiveness.

OWSA on prevalence (Supplementary Figure 1) and HR for delay to diagnosis (Supplementary Figure 2) show that these parameters are highly influential. Both are strong determinants of the QALY difference between diagnostic strategies and therefore influence cost-effectiveness. For example, at a test cost of GBP 100 (EUR 144) if prevalence were 0.5

percent instead of 1 percent in primary care then the ICER would be >GBP 20,000 (EUR 22,810) and the technology may not be considered cost-effective.

The CEAC plot (Figure 2) demonstrates that at a test cost of GBP 100 (EUR 114) there is approximately a 75% probability of being cost-effective in primary care and a 50% probability of being cost-effective in secondary care at a ICER threshold of GBP 20,000 (EUR 22,810). At the lower end of the range of test costs (GBP 50, EUR 57) testing is highly likely to be cost-effective at any ICER threshold in primary care and at thresholds above GBP 15,000 (EUR 17,108) in secondary care. Supplementary Figure 3 shows the PSA results on the cost-effectiveness plane. This highlights the importance of uncertainty about effectiveness in both scenarios and uncertainty about costs for the primary care scenario only.

The cost-consequences analysis results of providing tumour type information are reported in Table 2. Tumour type predictions have the potential to reduce surgeries by approximately 8 per 100 brain tumour cases. The additional healthcare cost savings are approximately GBP 58,000 (EUR 66,149) per 100 cases. These estimates are sensitive to the relative frequency of GBM, PCNSL and metastatic disease in the patient population (Supplementary Figure 4). There are significantly larger cost-savings possible when other tumour types are relatively more prevalent among cases compared to GBM. The total budget impact for the NHS in England and Wales if this was rolled-out nationally would be approximately GBP 1.3-2 million (EUR 1.5-2.3 million) assuming 50-80% of the 4,500 malignant brain tumours diagnosed each year [17] had received testing.

Discussion

A prospective study of diagnostic accuracy has brought a spectroscopic liquid biopsy for brain cancer one step closer to being ready for clinical use. The updated cost-effectiveness results reported here demonstrate potential for the technology to be cost-effective in both

primary and secondary care settings. Compared to the base case result in the previous iteration of the evaluation, effectiveness is reduced due to the attenuation of diagnostic accuracy in the prospective data. This iteration of the early economic evaluation also extended the clinical pathway to include a new feature of the technology - classification of tumour type. The cost-consequences analysis demonstrated some additional utility and cost-savings from providing tumour type classification probabilities.

New evidence in relation to diagnostic accuracy may emerge as more data is collected in ongoing studies. This can then be used to update the economic evaluation in a further iteration. Machine learning based classification systems can require large numbers of observations to achieve optimal performance therefore it is possible that improvements in diagnostic accuracy may occur after more training data is collected. Prospective data from primary care would also be useful to determine if diagnostic accuracy is the same in this setting and alleviate concerns about possible spectrum bias.

This economic evaluation provides support for the continued development of a serum spectroscopy test for brain tumours. Remaining issues relate to the feasibility of integrating the test into routine practice. An important aspect of this is understanding how patient selection by clinicians would influence disease prevalence in the tested population. This was highlighted as an important parameter in the sensitivity analysis. Another issue, identified in the previous iteration of early evaluation [10], is to what extent brain imaging studies would actually be reduced in primary care, i.e. what proportion of test negative patients would not be subsequently referred to imaging.

The major limitations of this analysis are related to the lack of direct evidence of how alternative diagnostic pathways will influence patient survival and quality of life. In the absence of this data we have relied on extrapolation from observational data. While this data

is available from a cohort studies [18,19], treating the association between time to treatment and survival as causal requires strong assumptions.

An open question is whether or not a randomised trial of alternative diagnostic strategies (test vs no test) is required to demonstrate patient benefit for this technology. Whether a randomised trial(s) is desirable or not can be considered within existing frameworks [20]. This requires the judgement of all relevant stakeholders regarding the feasibility of a trial as well as the validity of assuming survival and quality of life benefits of early diagnosis. While a randomised trial offers the best possible evidence on which to base an adoption decision, the scale of the trial that would be required may prove prohibitively expensive to undertake, and it is well recognised that randomised trials for diagnostic tests are often unfeasible [21]. The vast majority of tests in clinical practice today do not have evidence of patient benefit from a randomised trial. A feasible solution in this case may be a post-marketing study, forgoing randomisation in favour of a cohort study design. It has been suggested that an observational study assessing time to diagnosis and treatment may be optimal for a triage test when a randomised design is infeasible [20]. A study of the hypothetical clinical utility of test results using a questionnaire survey among primary care clinicians may be a useful preceding step. These types of studies could address the two key remaining areas of uncertainty; prevalence in the referred population and clinical decision making in response to negative test results. Clear benchmarks for clinical utility could be determined and a risk sharing model for reimbursement [22] may be useful to explore. Determining the optimal design of future studies requires a full exposition and consultation with stakeholders, beyond the scope of this early economic evaluation.

Translation of the economic model to other countries or health systems will also require refining the above parameters and may need further development of the economic model. In the preceding evaluation the USA healthcare system was considered using Medicare unit

prices [10]. We now believe that differences between UK and USA health systems may necessitate a different model structure. Validation or adaption of the diagnostic and clinical pathway represented in the model to health systems in the United States is part of ongoing research.

Early economic evaluation has been useful in guiding the development of this liquid biopsy test for brain tumours. Making an early assessment of both costs and consequences of other novel tests in the domain of liquid biopsies for cancer may improve the focus of clinical research efforts in this area. Ultimately, comparative cost-effectiveness analysis with both existing diagnostic pathways and all potential new alternatives would be most useful for clinicians, patients and health system decision makers.

A logical next stage of development for spectroscopic liquid biopsy for brain tumours is a large scale, pragmatic programme of test use in routine primary care practice. Additional studies in this setting are needed to resolve the remaining issues of uncertainty - prevalence in this patient population and referral behaviour - and would demonstrate feasibility in real-world clinical practice.

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Conflicts of Interest: M.J.B. (Chief Scientific Officer), H.J.B. (R & D Director), M.G.H. (Chief Executive Officer), P.M.B. (Clinical Advisory Board Lead) and D.S.P. (Chief Data Officer) and E.G. (Health Economics Consultant) are all employees/consultants of ClinSpec

Diagnostics Ltd, J.M.C. and M.D.J. declare no conflicts of interest. P.M.D reports grants from Innovate UK, grants from Cancer research UK, other from ClinSpec Dx, during the conduct of the study. M.J.B, D.S.P. and H.J.B. have patents issued for technology related to liquid biopsy for brain tumours. M.J.B. reports personal fees from ClinSpec Diagnostics Ltd., during the conduct of the study; personal fees from ClinSpec Diagnostics Ltd. , outside the submitted work; In addition, M.J.B. has a patent Discerning Brain Cancer Type 2019 - PE959914GB pending to ClinSpec Diagnostics Ltd., a patent Infra-Red Spectroscopy System March 2017 - GB2018/050821 pending to ClinSpec Diagnostics Ltd., a patent Method of Diagnosing Proliterative Disorders - WO 2014/076480 issued to ClinSpec Diagnostics Ltd., a patent Analysis of bodily fluids using infrared spectroscopy - GB2018/050821 pending to ClinSpec Diagnostics Ltd., and a patent Sample Container - PCT/GB2019/052898 pending to ClinSpec Diagnostics Ltd. H.J.B. reports grants and other from ClinSpec Diagnostics, during the conduct of the study; grants and other from ClinSpec Diagnostics, from null, outside the submitted work; In addition, H.J.B. has a patent Methods of diagnosing proliferative disorders issued. M.G.H. reports personal fees from CLINSPEC DIAGNOSTICS LIMITED, during the conduct of the study; personal fees from CLINSPEC DIAGNOSTICS LIMITED, outside the submitted work; In addition, M.G.H. has a patent Infra-Red Spectroscopy System March 2017 - GB2018/050821 licensed to CLINSPEC DIAGNOSTICS LIMITED, and a patent Sample Container - PCT/GB2019/052898 licensed to CLINSPEC DIAGNOSTICS LIMITED. D.S.P. reports grants and other from ClinSpec Diagnostics Limited, during the conduct of the study; other from ClinSpec Diagnostics Limited, outside the submitted work; In addition, D.S.P. Palmer has a patent relating to brain tumour diagnosis issued.

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Tables

Table 1 - Cost-effectiveness analysis base case results

	Primary			Secondary		
Serum spectroscopy cost (GBP)	ΔQALY per 10,000 referred	ΔCost per 10,000 referred GBP (EUR)	ICER GBP (EUR)	ΔQALY per 10,000 referred	ΔCost per 10,000 referred GBP (EUR)	ICER GBP (EUR)
50	15.38	-295,780 (-337,337)	Dominates* (-19,232) (-21,934)	46.14	524,130 (597,770)	11,360 (12,956)
75	15.38	-45,780 (-52,212)	Dominates (-2,977) (-3,395)	46.14	774,130 (882,895)	16,778 (19,135)
100	15.38	204,220 (232,913)	13,279 (15,148)	46.14	1,024,130 (1,168,020)	22,197 (25,316)
200	15.38	1,204,220 (1,373,413)	78,300 (89,301)	46.14	2,024,130 (2,308,520)	43,870 (50,034)

*More effective and less expensive

Table 2 Cost-consequences per 100 cases with and without type information

Category	Liquid biopsy sub-type information available	Standard Care	Difference
Surgical resection	100	92.1	-7.9

Biopsy	2	4	2
CT full body	0	7	7
Total costs (GBP)	796,876	738,970	-57,906
	(EUR 908,837)	(EUR 842,795)	(EUR -66,042)

Figure Legends

Figure 1 - Decision Tree Model and Extension

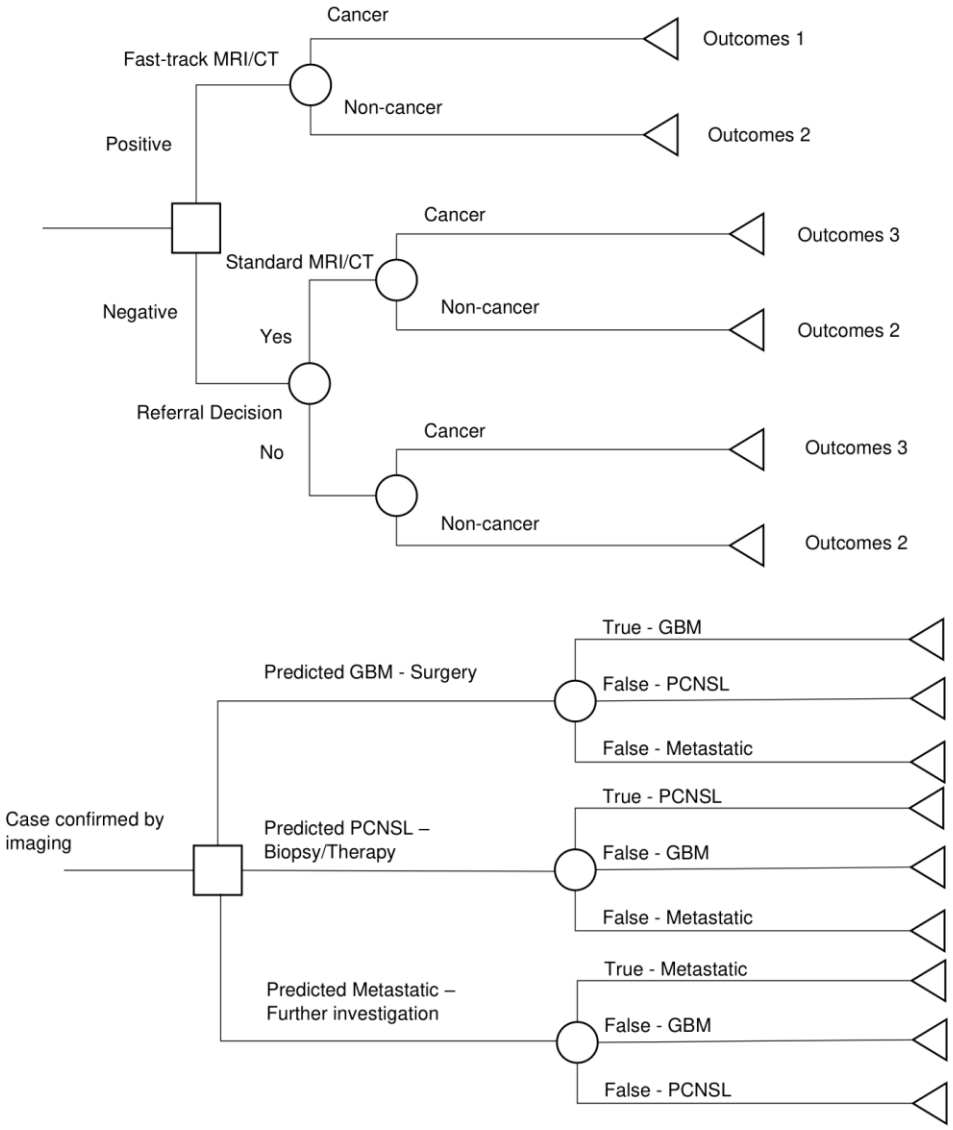

Figure 1 Legend: Outcomes 1: LY 0.80, QALY 0.71. Outcomes 2: LY 2, QALY 2. Outcomes 3: LY 0.58, QALY 0.52. Abbreviations: GBM Glioblastoma, PCNSL Primary Central Nervous System Lymphoma

Figure 2 - Cost-effectiveness acceptability curve, primary care and secondary care scenarios at GBP 50 (EUR 57) and GBP 100 (EUR 114) test cost