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Economic Evaluation of GPs' Direct Access to Computed Tomography for Identification of Brain Tumours

DACT for Brain Tumours: An economic evaluation

Edna Keeney¹, edna.keeney@bristol.ac.uk

Syed Mohiuddin¹, syed.mohiuddin@bristol.ac.uk

Karolis Zienius², zienius.k@gmail.com

Yoav Ben-Shlomo¹, y.ben-shlomo@bristol.ac.uk

Mio Ozawa¹, mio.ozawa@ucl.ac.uk

Robin Grant², robin.grant7@gmail.com

Willie Hamilton³, w.hamilton@exeter.ac.uk

David Weller⁴, david.weller@ed.ac.uk

Paul M Brennan^{5,6}, paul.brennan@ed.ac.uk

William Hollingworth¹, william.hollingworth@bristol.ac.uk

¹ Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK.

² Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK.

³ Primary Care Diagnostics, University of Exeter Medical School, College House, St Luke's Campus, University of Exeter, Exeter, UK.

⁴ Centre for Population Health Sciences, University of Edinburgh, Edinburgh, UK.

⁵ Translational Neurosurgery Unit, Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK.

⁶ Brain Tumour Research Group, University of Bristol, Institute of Clinical Neuroscience, Learning and Research Building, Southmead Hospital, Bristol, UK.

Corresponding author: Edna Keeney, Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK. edna.keeney@bristol.ac.uk, Tel: 01174283118

Declarations

Availability of data and materials

The data that support the findings of this study are available from the CPRD but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the CPRD.

Authors' contributions

All the authors were involved in the conception of the study. E.K. analysed the data and performed the decision tree component of the cost-effectiveness analysis. S.M. performed the Markov model component of the cost-effectiveness analysis and integrated this with the decision tree component. All the authors helped

with interpretation of the data and results. EK, SM and WH co-wrote the first draft of the paper which was then modified after comments and suggestions from the other authors

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Conflict of Interest statement

The authors declare that they have no competing interests.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Abstract

Background

When GPs suspect a brain tumour, a referral for specialist assessment and subsequent brain imaging is generally the first option. NICE have recommended that GPs have rapid direct access to brain imaging for adults with progressive sub-acute loss of central nervous function; however, no studies have evaluated the cost-effectiveness.

Methods

We developed a cost-effectiveness model based on data from one region of the UK with direct access computed tomography (DACT), routine data from GP records and the literature, to explore whether unrestricted DACT for patients with suspected brain tumour might be more cost-effective than criteria-based DACT or no DACT.

Results

Although criteria-based DACT allows some patients without brain tumour to avoid imaging, our model suggests this may increase costs of diagnosis due to non-specific risk criteria and high costs of diagnosing or 'ruling out' brain tumours by other pathways. For patients diagnosed with tumours, differences in outcomes between the three diagnostic strategies are small.

Conclusions

Unrestricted DACT may reduce diagnostic costs; however, the evidence is not strong and further controlled studies are required. Criteria-based access to CT for GPs might reduce demand for DACT, but imperfect sensitivity and specificity of current risk stratification mean that it will not necessarily be cost-effective.

Keywords: Brain tumour; Direct access CT; Cost-effectiveness model; Economic evaluation; Diagnosis; Risk stratification

Background

Brain tumours are the 9th most common cancer in the UK, accounting for 3% of all new cases in 2015 (Cancer Research UK, 2018). Since the 1990s, brain tumour incidence has increased by around a third in the UK and is projected to rise further to 22 cases per 100,000 people by 2035 (Cancer Research UK, 2018). Patients with glioblastoma, the most common type of malignant brain tumour, have a 1-year survival rate of only 30% (Brodbelt et al., 2015). Current therapy includes surgery, radiotherapy or chemotherapy. Previous studies have shown that earlier detection of tumours, when they are more amenable to surgery, may be beneficial (Stummer et al., 2006).

The symptoms associated with brain tumour are often non-specific, making diagnosis difficult. About 30% of cases have three or more GP consultations before referral (Ozawa et al., 2018). The median interval from patient recognition of symptoms to specialist assessment is 24 days (Ozawa et al., 2018). In one study, GPs considered that 16.9% of patients had an avoidable delay in diagnosis (Swann et al., 2018). Only 9.3% had imaging investigations prior to referral (Swann et al., 2018), so earlier and easier access to brain imaging may have helped. In practice, GP direct access to imaging varies markedly by region (Nicholson, Oke, Rose, & Mant, 2016).

Whilst direct access to brain imaging may reduce the diagnostic interval, there are potential disadvantages. Imaging is relatively expensive and has an opportunity cost if scarce imaging resources are diverted away from more urgent cases. An incidental finding might trigger a cascade of unwarranted diagnostic tests and treatments. The anxiety caused to these patients may counterbalance the reassurance provided to patients with no abnormal findings (Howard L, 2005). If computed tomography (CT) imaging is to be used more widely in patients with a lower prevalence of cancer, the benefits must also be balanced against the harm from radiation exposure (Smith-Bindman R, 2009).

In 2015, the UK National Institute for Health and Care Excellence (NICE) recommended that GPs have rapid direct access to brain imaging in adults with progressive sub-acute loss of central nervous function; however, they were unable to identify studies evaluating the cost-effectiveness of primary care direct access to brain imaging (NICE, 2015). We developed a cost-effectiveness model based on data from one region of the UK with direct access CT (DACT), routine data from GP records and the available literature, to explore whether unrestricted DACT for patients with a suspected brain tumour might be more cost-effective than DACT predicated on higher risk symptoms (criteria DACT) or no DACT. There is little high-quality evidence on the causal relationship between delayed diagnosis and the costs and outcomes of brain tumour. Therefore, our model is designed to provide preliminary estimates of the potential cost-effectiveness of unrestricted and criteria DACT, identify key drivers of cost-effectiveness and guide future research, rather than provide a definitive evaluation of cost-effectiveness.

Methods

We developed a decision model to evaluate DACT in adult primary care patients with symptoms suggestive of brain tumour which do not require urgent emergency department (ED) referral. The model was used to estimate costs and patient outcomes in quality adjusted life years (QALYs). We used a decision tree and Markov model to compare the costs and diagnostic accuracy of three diagnostic strategies at the point of diagnosis and the long-term costs and outcomes for patients who have a brain tumour (Figure 1 and Figure 2). Costs and QALYs were discounted annually at 3.5% (National Institute for Clinical Excellence (NICE), 2013). The model was built in Microsoft Excel®, and programmed in Visual Basic for Applications®.

Model structure

In the 'unrestricted DACT' strategy, all patients in whom the GP suspects brain tumour will be imaged. In 'criteria DACT', GPs can only access CT in patients with symptoms indicating higher risk of tumour. We modelled the criteria DACT strategy based on the risk stratification published by Kernick et al. (Kernick et al., 2008). The Kernick classification (Appendix A), categorises signs and symptoms as red (tumour probability >1%), orange (0.1% to 1%), or yellow flags (<0.1%, but above the population rate of 0.01%). We assumed that patients with red flag symptoms would meet the criteria for DACT. Those with orange or yellow flags will not have DACT. In 'no DACT', GPs cannot directly access CT.

Three pathways represent the potential diagnostic routes of patients not referred for DACT: (1) referral to a specialist, (2) presentation at the Emergency Department (ED), and (3) re-presentation to the GP with more overt symptoms and direct admission to hospital as an emergency. Patients will have a 'prompt' or 'delayed' diagnosis of brain tumour, or no tumour. Patients with no tumour may have normal or radiologically abnormal findings such as arteriovenous malformation or infarct. We focused on the role of DACT in improving the cost-effectiveness of care for brain tumours, therefore long-term costs and outcomes of treating other radiologically abnormal findings are not modelled. The Markov model for patients with brain tumour consisted of five health states: low-grade tumour, high-grade tumour, progression, metastases and all-cause death.

Decision tree parameters

Two main data sources were used to inform the decision tree parameters as specified in Table 1. DACT in the Lothian region of Scotland is available for GPs to diagnose or exclude a serious intracranial pathology where emergency hospital admission is not more appropriate. We used data from 2,938 patients referred for DACT in Lothian to estimate the prevalence of tumour, abnormal, and normal findings by presenting symptom (Zienius et al., 2019). 53 of 2,938 patients had intracranial tumours, but only 42 (1.4%) were considered to be clinically significant. 559 (19.2%) patients had other abnormalities and the remaining 2,326 (79.2%) had normal findings (Zienius et al., 2019).

1,141 (39%) of 2,938 patients had a 'red flag' feature qualifying for DACT in the 'criteria DACT' strategy (**Table 2**). The prevalence of tumour in this subgroup was 2.8% (32/1,141). 225 (22%) of 1,141 patients with red flags had other abnormalities. The sensitivity (0.76) and specificity (0.61) of red flag symptoms for identifying patients with tumours (based on the Lothian data) are moderately high, but about one quarter of patients with tumours would not meet the red flag criteria for DACT and many without tumours would be imaged. We evaluated the robustness of model findings to improvements in risk stratification by varying these estimates of sensitivity and specificity in a one-way sensitivity analysis. We assumed that patients with clinically significant tumours identified by DACT would be urgently referred for a specialist assessment and treatment. GP review of the presenting symptoms and imaging findings in the 570 patients with either non-clinically significant tumours or a potentially significant non-tumour imaging findings suggested that specialist referral might be required in 201 (35%) patients.

We used CPRD Gold (the largest UK GP database with 13 million patient records) to estimate the probabilities of referral to secondary care, A&E attendance or hospital admission in patients who are not eligible for DACT (Herrett et al., 2015). This study was approved by the CPRD's Independent Scientific Advisory Committee (ISAC), protocol number: 16_222R. The total data extract included 8,184 people with brain tumours (cases) and 33,350 age, sex and practice matched controls. The medical codes used to define patients with a diagnosis of brain tumour are given in Appendix B. For each patient, the index date was defined as the first date on which a brain tumour diagnosis code was recorded in the GP record. Controls were assigned the same index date as their matched case. We restricted our analysis to the subset of patients who had linked Hospital Episode Statistics (HES) data and to patients who had one or more GP consultations for symptoms potentially related to brain tumour in the six months prior to their index date. To do this, we matched symptoms in the Kernick et al guidance (Kernick et al., 2008) to the diagnostic (Read) codes in the CPRD dataset (Appendix C). This resulted in 1,004 patients (510 cases and 494 non-cancer) presenting with orange/yellow flag symptoms. Referrals potentially related to brain tumour symptoms were identified by NHS specialty (Appendix D1), and consultant specialty was used to identify admissions potentially related to brain tumour symptoms (Appendix D2). We excluded ED attendances coded as being due to a road traffic accident, assault, deliberate self-harm, or any other accident.

We assumed that all patients with brain tumours would eventually be diagnosed either via specialist referral (pathway 1), via ED attendance (pathway 2), or via an emergency hospital admission (pathway 3). Patients with cancer were categorised as pathway 1_c if the first event was a specialist referral or the hospital admission was from a consultant clinic. Patients were categorised as pathway 2_c if the first event was an ED attendance or the hospital admission was from ED. Patients admitted to hospital without any evidence of referral or an ED attendance were categorised as following pathway 3_c. In each pathway, we estimated the delay between first GP presentation with symptoms and the date of diagnosis. Patients without cancer

can also be referred to a specialist (pathway 1_{nc}), attend ED (pathway 2_{nc}) or be admitted to hospital (pathway 3_{nc}). In addition, they may be managed in primary care (pathway 4_{nc}).

The CPRD data indicated that 193 of 510 (38%) patients with orange and yellow flag symptoms and brain tumours were initially referred to a specialist (pathway 1_c), 191 (37%) initially attended ED (pathway 2_c) and 45 (9%) were admitted directly to hospital. The remaining 81 (16%) had no secondary care contacts recorded prior to the diagnosis date. 61 of 494 (12%) patients without brain tumour were referred to a specialist (pathway 1_{nc}), 51 (10%) attended ED (pathway 2_{nc}), 2 (0.4%) were admitted to hospital (pathway 3_{nc}), and the remaining 380 (77%) had no secondary care contacts recorded. It is possible that the 81 patients with brain tumours, but no secondary care contacts recorded were diagnosed by a different route (e.g. DACT or private healthcare) or data on the diagnostic pathway may be missing from the GP record. In our primary analysis, we inflated the proportion of patients in the other pathways to adjust for this potential missing data (**Table 3**). We tested the impact of reducing the percentages of patients without brain tumour who are referred to a specialist, attend ED or are admitted to hospital in sensitivity analyses.

Markov model parameters

Based on data from the Lothian DACT cohort (Zienius et al., 2019), patients with tumours had a mean age of 60 years; 45% (19/42) of the cohort started in the low-grade, 14% (6/42) in the high-grade and 41% (17/42) in the metastases state (Appendix E). Disease progression was modelled monthly over the lifetime. In the absence of European data on median progression free survival (PFS) and overall survival (OS) by brain tumour type, we used Japanese registry data on PFS and OS for low- and high-grade primary brain tumours (Narita, Shibui, & Committee of Brain Tumor Registry of Japan Supported by the Japan Neurosurgical, 2015). We estimated a 5-year PFS rate of 68.0% (995/1,463) and 18.7% (638/3,408) for low- and high-grade tumours respectively and converted these to monthly transition probabilities (**Table 6**).

Non-cancer mortality was estimated from age- and gender-specific ONS UK life-tables for the years 2014-2016 (Office for National Statistics, 2017). The transition probability from progression to all-cause death was derived by subtracting the age-specific non-cancer mortality probability from the Japanese registry data on overall mortality probability (Narita et al., 2015). We used a North American cohort study reporting overall median survival time of 7.16 months in 3,940 patients with brain metastases to estimate transition probabilities for these patients (Sperduto et al., 2012). We assumed that patients have a constant risk of death (i.e. exponential survival function).

There is no high-quality evidence demonstrating a causal relationship between earlier diagnosis of brain tumours and increased survival. A systematic review of 209 articles estimating the association between time to diagnosis and clinical outcomes in all symptomatic cancers found just one article evaluating brain/CNS tumours (Neal et al., 2015). The authors concluded that it was reasonable to assume that expedited diagnosis of cancer was likely to have benefits for patients in improved survival and quality of life and that these benefits were likely to vary between cancers. In order to explore the potential impact

of expedited diagnosis by DACT, we initially assumed that diagnosis was delayed by 30 days without DACT (i.e. some patients progress before diagnosis). We then varied this assumption in sensitivity analyses (SA) by assuming delays of 15 (SA1) and 45 (SA2) days.

Costs and Utilities

Our analysis was conducted from a Health Service perspective. All costs related to diagnosis were estimated from the NHS reference costs 2015-2016 (DOH, 2016) or the Unit costs of Health and Social care 2016 (Curtis, 2016) (**Table 4**). Based on CPRD data on GP visits, specialist referrals, ED attendances and admissions, we estimated the pathway costs between first symptoms and diagnosis of brain tumour. Pathway costs can be substantial, particularly for patients admitted to hospital prior to diagnosis (**Table 5** and Appendix E). Costs were lower for patients who did not have brain tumours.

The costs of treatment and subsequent care for patients with brain tumours were based on a study of 2,115 adults (De Oliveira et al., 2017) which estimated initial, continuing and terminal phase costs. We converted these costs (GBP 1 = CAD 1.7515) (HM Revenue & Customs, 2018) and inflated to 2016 values (**Table 6**) (HM Treasury, 2018). We used initial phase costs for the low- and high-grade states up to 6 months and continuing phase costs for any subsequent months before progression/death and terminal phase costs. We assumed that the cost of being in the metastases state would be the initial phase cost (up to 6 months) and the terminal phase (subsequent months).

Each health state was assigned a 'utility' value (on a scale from 0 'death' to 1 'best health'); QALYs were estimated by multiplying the state-specific utility value by the time spent in that state (Weinstein, Torrance, & McGuire, 2009). We identified one study that used the EQ-5D-3L preference-based measure in 100 patients with low-, high-grade, or recurrent brain tumours to estimate utility values for these states (Vera, Acquaye, Mendoza, Gilbert, & Armstrong, 2018). A second study used the EQ-5D-3L to estimate utility values among 122 patients with brain metastases (Miller et al., 2017). As in previous economic models in brain tumour patients (Garside et al., 2007; Qian et al., 2017; Waschke et al., 2018), we applied a time-dependent utility decrement of 0.02 per consecutive month, up to a maximum of 24 months (0.48 decrement), spent in the progression or the metastases state, to represent likely deterioration of health in these states. In a **sensitivity analysis** (SA3), we decreased the initial utility values by 5% for all health states.

Presentation of Results

We performed probabilistic sensitivity analysis (PSA), which reflected the joint uncertainties in model inputs. Appropriate distributions around model parameters were used to reflect uncertainty in the model (Tables 2, 3, 5, 6). Gamma distributions were used to represent the uncertainty in the cost parameters because these values are constrained to be zero or positive. Beta distributions were used to represent

the uncertainty in the probability and utility parameters because these values are defined on the interval with a minimum (0) and maximum (1) value. Wherever possible, the parameters for these distributions were chosen to reflect the uncertainty reported in the primary data sources.

PSA was performed using 10,000 Monte Carlo iterations to empirically estimate the model uncertainty. Based on the results of PSA, we produced the cost-effectiveness acceptability curves to demonstrate how the NHS willingness-to-pay threshold for an additional QALY affects the probability that a strategy is considered cost-effective. We also produced the cost-effectiveness plane to demonstrate the spread in simulated costs and QALYs for unrestricted DACT compared to criteria DACT and no DACT. We presented incremental cost-effectiveness ratios, described as the difference in mean costs divided by the difference in mean QALYs between two strategies. We estimated the cost-effectiveness of unrestricted DACT versus no DACT and criteria DACT versus no DACT based on the incremental net monetary benefit (iNMB):

$$iNMB = \lambda (QALY_{unrestricted/criteria\ DACT} - QALY_{no\ DACT}) - (Cost_{unrestricted/criteria\ DACT} - Cost_{no\ DACT}),$$

where λ represents the maximum amount that the NHS is willing to pay to gain one QALY. We used the upper UK NICE willingness-to-pay threshold of £30,000 (λ) per QALY gained to calculate the iNMBs. An iNMB value greater than zero indicates that a strategy is cost-effective.”

Results

With unrestricted DACT all patients receive a CT scan, at a cost of £99, with a small percentage (those identified as having tumours and a percentage of those with abnormalities) receiving a further referral (**Table 7**). The use of unrestricted DACT identifies brain tumours, if present, promptly and no patients are diagnosed via other pathways. With criteria DACT (for patients with red flag symptoms), almost 40% of patients have DACT, 25% follow other pathways and 37%, who do not have brain tumour, have no further contact other than GP visits.

Although risk stratification allows some patients who do not have brain tumour to avoid CT imaging, our model suggests that this may in fact increase the costs of diagnosis (mean total cost per patient £121 for criteria DACT versus £110 for unrestricted DACT). This is partly because the risk stratification is not very specific, so that many patients still get CT imaging. Furthermore, the savings from avoiding direct access CT in lower risk patients are counterbalanced by the high costs (e.g. ED attendances or specialist visits) of diagnosing or ruling out brain tumours by other pathways.

With no DACT, the mean total cost per patient estimated is higher than either of the other strategies. Approximately 50% of patients would still present to secondary care (via specialist, ED or admission).

The longer term Markov model analysis showed that the differences in outcomes between the diagnostic strategies are small (0.01 QALYs) (**Table 9**) reflecting the limited evidence that small reductions in diagnostic delay improves survival. The incremental net monetary benefit (iNMB) of unrestricted DACT compared to no DACT is positive (£39; £7 to £71) indicating that DACT has the potential to be cost-effective for the NHS. There is greater uncertainty about whether criteria DACT is cost-effective, due to the uncertainty about the diagnostic accuracy of the risk stratification. The uncertainty is demonstrated in the cost-effectiveness plane (Figure 3) which shows that the incremental costs and QALYs for unrestricted DACT compared to both strategies lie across the north-east and south-east quadrants, suggesting slightly increased QALYs but uncertainty as to cost differences. The majority of the points for unrestricted DACT compared to no DACT lie in the south-east quadrant, however, indicating decreased costs. The cost-effectiveness acceptability curve (Figure 4) demonstrates that unrestricted DACT has a greater than 75% probability of being the most cost-effective strategy at any willingness to pay threshold.

Sensitivity analyses

Even if criteria DACT was perfectly sensitive (i.e. correctly identified all patients with brain tumours), the cost of this strategy would only decrease marginally from £121 to £117 as many patients without tumour would still follow an expensive pathway to diagnosis (**Table 8**). If criteria DACT was perfectly specific (i.e.

only patients with brain tumours were referred for DACT), the cost of the strategy would increase from £121 to £122 as more expensive pathways would be required to rule out tumours in the other patients.

Further sensitivity analysis demonstrated that if the percentages of 'non-tumour' patients being referred, admitted, or attending ED were reduced by 20% then criteria DACT became marginally less expensive than unrestricted DACT (£108 compared to £110). The percentages of patients without tumour following pathways 1, 2, or 3 would need to be reduced by 35% in order for no DACT to become less expensive than unrestricted DACT (£108 compared to £110) (**Table 8**).

The model assumes that CT scanning for brain tumours is perfectly sensitive. Relaxing this assumption to assume 80% sensitivity increases the cost of all strategies by a relatively even amount, with unrestricted DACT still being the least expensive option (Table 8). This is because rather than being treated directly, the patients with tumours that are missed will eventually be admitted as an emergency.

The sensitivity analyses exploring delays in diagnosis of 15 (SA1) and 45 (SA2) days without DACT (base case 30 days) had little impact on conclusions about cost-effectiveness (**Table 9**), with unrestricted DACT still being the dominant strategy. The sensitivity analysis exploring 5% reduction in all initial utility values (SA3) similarly had very little impact on conclusions about cost-effectiveness (**Table 9**).

Discussion

This economic evaluation of GPs' direct access to CT for identification of brain tumours suggests that unrestricted DACT has the potential to reduce the costs of brain tumour diagnosis and to increase the percentage of patients diagnosed promptly. However, uncertainty about the diagnostic pathway patients would follow if DACT were not available and limited causal evidence linking prompt diagnosis to improved outcomes means that the results should be interpreted with caution. The imperfect sensitivity and specificity of current risk stratification methods means that while criteria-based access to CT for GPs may reduce demand on open access services, it will not necessarily be cost-effective.

Comparison with other studies

There is limited literature on the most cost-effective diagnostic pathways in patients with a suspected brain tumour. Simpson et al (Simpson, Forbes, Teasdale, Tyagi, & Santosh, 2010) performed a cost evaluation of GPs' direct access to CT in Glasgow, using GP questionnaire data on choice of referral path in the absence of DACT. They estimated that without DACT, 90% of patients would have been referred to a consultant outpatient appointment and DACT was therefore associated with cost-savings. This is in line with our findings, which used clinical data to look in more detail at pathways of care, as opposed to clinical opinion.

A more recent study by Gray et al (Gray et al., 2018) performed a model-based cost-effectiveness analysis of a serum-based spectroscopic tool for suspected brain tumours as an alternative to MRI or CT, to reduce diagnostic delays. They found that the use of this tool in primary care has the potential to be both more effective and cost saving for the health service. They similarly found no direct evidence linking early diagnosis to improved outcomes and concluded that prospective trials are required to provide definitive evidence on the likely impact of reducing diagnostic delays.

The Routes to Diagnosis study (Elliss-Brookes et al., 2012) categorised cancers registered in England (2006-2015) into one of eight pathways: screen detected; two-week wait; emergency presentation; GP referral; inpatient elective; other outpatient; death certificate only; or unknown. Their findings suggest that 51% of brain cancers are diagnosed via an emergency presentation, 45% via a referral (GP or inpatient/outpatient elective), 2% via an urgent two-week wait referral and 3% unknown. Although our analysis used different datasets and looked specifically at patients who had attended their GP with symptoms suggestive of a brain tumour in the 6 months before their diagnosis, these estimates are in line with our findings from the CPRD data which suggest that the two main pathways to diagnosis are referrals and emergency presentations.

Strengths and Limitations of Study

This study has used the best available evidence from a well-characterised cohort of patients who received DACT in Lothian to model the implications of a wider introduction of direct access imaging for GPs. However, we were unable to observe the counterfactual (i.e. diagnostic pathways in the absence of DACT) so had to estimate it based on routine data, GP opinion and assumptions. Controlled studies of DACT are

needed to verify our findings and inform policy. Through our analysis, we have identified key drivers of cost-effective diagnosis. Risk stratification may help GPs and radiologists manage demand for DACT, but it is unlikely to be clearly cost-effective unless more sensitive and specific strategies are developed based, potentially, on new biomarkers. Broadening access to DACT for primary care may be appropriate, but any such service redesign needs to be coupled with careful monitoring, analysis and quality control to minimise unintended consequences such as overwhelming of imaging services, and diversion of resources from potentially more efficient pathways.

Our model does not quantify all factors relevant to the policy decision. DACT may provide reassurance (if imaging findings are normal) or anxiety and further healthcare costs (due to potentially incidental abnormal findings) (Howard L, 2005). DACT will result in small increases in cumulative radiation dose. This latter factor suggests caution in recommending DACT without robust evidence of safety and (cost-) effectiveness. We also do not quantify the costs and benefits of DACT for the small proportion of patients who have clinically important abnormalities other than tumour. If these patients also benefit from prompt diagnosis, the cost-effectiveness of unrestricted DACT would likely increase.

Our model does not take account of the impact of DACT on delays in imaging for other patients. It is likely that with GPs referring more patients for DACT the time to imaging would increase. Also, if DACT were to become more widespread, funds would then need to be invested in additional CT equipment and staff. On the other hand, if patients are diverted from specialist referral lists through the use of DACT, then resources could be freed up and waiting lists could decrease in secondary care to diagnose and manage other neurological conditions.

The model has had to make several assumptions due to data limitations. We assumed perfect sensitivity of CT in identifying clinically important tumours. We also assumed that diagnosis is delayed by 30 days without DACT, impacting on progression of tumours. These parameters were varied in sensitivity analyses however and had little impact on results. Published data on median progression free survival and overall survival by brain tumour type are not available from the UK and US brain tumour registries and no alternative source for the cost of care could be identified. Therefore, we assumed that these estimates were transferable from other high-income countries (Japan and Canada). These parameters were varied in the probabilistic sensitivity analysis and, as only a very small proportion of patients presenting to GPs actually have tumours, had negligible impact on the conclusions of the model.

Conclusions and Policy Implications

As far as we are aware, no previous study has estimated the cost-effectiveness of unrestricted DACT compared to criteria DACT and no DACT. Our findings suggest that DACT has the potential to reduce the cost of diagnosis; however, the evidence is not strong and further controlled studies are required before widespread implementation. The wide variation in access to DACT across the UK creates a 'natural' experiment which might be exploited for such a study. Current risk stratification tools are limited in their

capacity to accurately categorise patients. Therefore, improved risk stratification methods are needed to manage demand for DACT and increase the speed and efficiency of brain tumour diagnosis. High-quality registry-based studies of survival after brain tumour diagnosis are needed to better understand the causal relationship between prompt diagnosis and improved outcomes.

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Table 1. Decision tree data sources and parameters informed by each

Data source	Parameters informed
Lothian DACT data	Prevalence of tumour, abnormal and normal findings in total cohort and in red, orange and yellow flag patients Probability of specialist referral when findings are abnormal Mean age of patients with tumours Percentage low grade, high grade and metastatic tumours at diagnosis
CPRD data	Probability of referral to secondary care, A&E attendance or hospital admission based on symptoms at GP attendance (red, orange or yellow flags) Cost of diagnostic pathways to diagnosis

Table 2 Probability of tumour conditional on red/orange/yellow flag symptom status*

	n/N	Probability (95% CI)	Distribution in probabilistic sensitivity analysis
Probability red flag	1,141/2,938	0.39 (0.37 to 0.41)	Beta (1141, 1797)
Probability tumour given red flag	32/1,141	0.03 (0.02 to 0.04)	Dirichlet (32, 193, 916)
Probability abnormal findings given red flag	255/1,141	0.22 (0.20 to 0.25)	Dirichlet (32, 193, 916)
Probability normal given red flag	854/1,141	0.75 (0.72 to 0.77)	Dirichlet (32, 193, 916)
Probability orange or yellow flag	1,797/2,938	0.61 (0.59 to 0.63)	Beta (1797, 1141)
Probability tumour given orange or yellow flag	10/1,797	0.01 (0 to 0.01)	Dirichlet (10, 186, 1601)
Probability abnormal findings given orange or yellow flag	315/1,797	0.18 (0.16 to 0.19)	Dirichlet (10, 186, 1601)
Probability normal given orange or yellow flag	1,472/1,797	0.82 (0.80 to 0.84)	Dirichlet (10, 186, 1601)
Sensitivity		0.76 (0.63 to 0.89)	
Specificity		0.61 (0.46 to 0.76)	

*Based on Lothian DACT data

Table 3 Probabilities for model from CPRD data – adjusted for missing data*

	Orange/yellow symptoms		Red/orange/yellow symptoms	
	Cancer	No cancer	Cancer	No cancer
Referred to specialist (pathway 1)	0.45	0.21	0.36	0.24
Attend ED (pathway 2)	0.44	0.18	0.53	0.22
Admitted to hospital (pathway 3)	0.11	0.01	0.11	0.01
Managed in primary care	0	0.61	0	0.53

* patients with brain tumours but no secondary care contacts coded were allocated to pathways 1, 2 and 3 in accordance with the percentages of patients with tumours who had been coded. The same degree of missing data was assumed and adjusted for in the patients without brain tumour

Table 4 Unit costs and probabilities from the literature

	Cost	Distribution in probabilistic sensitivity analysis	Source
CT Scan of one area, without contrast, age 19+, Direct Access	£99	Uniform (£70, £121)	NHS reference costs 2015-16
MRI Scan of one area, without contrast, 19+, Outpatient	£145	Uniform (£113, £174)	NHS reference costs 2015-16
CT Scan of one area, without contrast, 19+, Outpatient	£94	Uniform (£65, £116)	NHS reference costs 2015-16
Outpatient neurology visit	£128	Uniform (£93, £146)	NHS reference costs 2015-16
ED visit (weighted average of all types of ED visit) ¹	£138	Uniform (£113, £159)	NHS reference costs 2015-16
Hospital admission – Non-elective inpatients, brain tumours or cerebral cysts	£3,223	N/A ²	NHS reference costs 2015-16
Hospital admission – Non-elective inpatients, Headache, Migraine or Cerebrospinal Fluid Leak ³	£1,018	N/A ²	NHS reference costs 2015-16
GP visit (Per surgery consultation lasting 9.22 minutes)	£32	Uniform (£27, £36)	Unit costs of Health and Social care 2016
	Probability (95% CI)	Distribution in probabilistic sensitivity analysis	Source
Probability of imaging after referral ⁴	0.15 (0.13 to 0.16)	Beta (530, 3125)	Clarke et al 2010
Probability of imaging in ED ⁵	0.27 (0.23 to 0.30)	Beta (149, 409)	Locker et al 2006
Probability that imaging modality after referral will be MRI ⁴	0.63 (0.59 to 0.67)	Beta (334, 196)	Clarke et al 2010
Probability that imaging modality in ED will be CT	1.00	Fixed	Locker et al 2006

¹ weighted by number of each type of ED attendance

² no distribution assumed as average cost of admissions is pathway dependent and calculated in STATA as number of admissions multiplied by cost

³ average cost of short stay and long stay admission

⁴Clarke et al (Clarke CE1, 2010) collected data on 3,655 patients referred to a consultant-led outpatient headache service. A total of 530 (14.5%) patients were referred for neuroimaging (CT 36.8%, MRI 63.2%).

⁵Locker et al (Locker TE, 2006) recruited a cohort of 589 adult patients presenting to a UK emergency department with non-traumatic headache. One hundred and forty-nine (26.7%) had a CT scan.

Table 5 Patient pathway costs for orange or yellow flag patients*

Patient pathway	GP visits (excluding first visit)	Referrals	ED attendances	Admissions	Total mean cost (95% CI)	Distribution
Pathway 1 _c	£29	£220	£75	£768	£1,092 (£876 to £1,308)	Gamma (98, 11)
Pathway 2 _c	£20	£13	£169	£472	£674 (£502 to £846)	Gamma (60, 11)
Pathway 3 _c	£23	£0	£0	£3,438	£3,464 (£3,218 to £3,709)	Gamma (100, 35)
Pathway 1 _{nc}	£23	£199	£9	£0	£231 (£210 to £252)	Gamma (487, 0)
Pathway 2 _{nc}	£16	£17	£219	£60	£312 (£228 to £396)	Gamma (55, 6)
Pathway 3 _{nc}	£0	£0	£0	£1,018	£1018 (£1,018 to £1,018)	N/A
Pathway 4 _{nc}	£6	£0	£0	£0	£6 (£4 to £7)	Gamma (55, 0)

*based on CPRD data and unit costs from the literature

Table 6 Transition probabilities, cost and utility parameters used in the Markov model

Parameter	Mean estimate	Distribution in probabilistic sensitivity analysis	Source
Transition probabilities (monthly)			
Remaining in low-grade	0.994 = $\exp\{[\ln(995/1463)]/60\}$	$\exp\{[\ln(\text{Beta}(995, 468))]/60\}^c$	Narita et al., 2015
Death from low-grade	Age variant	Fixed	Office for National Statistics, 2017
Remaining in high-grade	0.972 = $\exp\{[\ln(638/3408)]/60\}$	$\exp\{[\ln(\text{Beta}(638, 2770))]/60\}^c$	Narita et al., 2015
Death from high-grade	Age variant	Fixed	Office for National Statistics, 2017
Death from progression	Adjusted ^a	Adjusted ^b	Narita et al., 2015; Office for National Statistics, 2017
Remaining in metastases	0.908 = $\exp\{[\ln(1970/3940)]/7.16\}$	$\exp\{[\ln(\text{Beta}(1970, 1970))]/7.16\}^c$	Sperduto et al., 2012
Costs (monthly)			
Low- and high-grade (initial phase; 6 months)	£3,510	Gamma (1997, 11) ^d divided by 6 ^e	De Oliveira et al., 2017
Low- and high-grade (continuing phase; 12 months)	£406	Gamma (272, 18) ^d divided by 12 ^e	De Oliveira et al., 2017
Progression (terminal phase; 12 months)	£4,117	Gamma (2282, 22) ^d divided by 12 ^e	De Oliveira et al., 2017
Metastases (initial phase; 6 months)	£3,510	Gamma (1997, 11) ^d divided by 6 ^e	De Oliveira et al., 2017
Metastases (terminal phase; 12 months)	£4,117	Gamma (2282, 22) ^d divided by 6 ^e	De Oliveira et al., 2017
Utilities			
Low-grade	0.82	Beta (302, 66) ^d	Vera et al., 2018
High-grade	0.79	Beta (327, 87) ^d	Vera et al., 2018
Progression	0.80	Beta (394, 99) ^d	Vera et al., 2018
Metastases	0.75	Beta (510, 168) ^d	Miller et al., 2017

^a we subtracted age-specific ONS death from overall death using: $1 - \exp\{[\ln(1 - (2799/4871))]/60\}$

^b we subtracted age-specific ONS death from overall death using: $1 - \exp\{[\ln(1 - \text{Beta}(2799, 2072))]/60\}^c$

^c we determined the Beta parameters empirically

^d we determined the Gamma and Beta parameters using the methods of moments described elsewhere (Briggs, Sculpher, & Claxton, 2006)

^e divided to obtain monthly cost estimates

Table 7 Results from decision tree modelling

Diagnostic Strategy	Mean total cost per patient (95% CI)	Cost per case detected early*	% DACT	% referred	% attend ED	% admitted by GP	% no further contact
Unrestricted DACT	£110 (£81 to £130)	£7,666	100%	4%**	0%	0%	0%
Criteria DACT	£121 (£103 to £135)	£11,067	39%	12%	11%	0.5%	38%
No DACT	£144 (£128 to £161)	NA	0%	25%	22%	1%	52%

*Assuming hypothetical cohort of 1000 patients

**This represents the 35% of patients with other abnormalities who are referred to secondary care based on the Lothian data

Table 8 Results from decision tree modelling – deterministic sensitivity analysis

Diagnostic Strategy	Mean total cost per patient	Cost per case detected early	% DACT	% referred	% attend ED	% admitted by GP	% not further contacted
Unrestricted DACT	£110	£7,666	100%	4%	0%	0%	0%
Criteria DACT – if Kernick criteria correctly identifies all tumours	£117	£8,190	39%	13%	11%	0.4%	37%
Criteria DACT – if Kernick criteria only identifies patients with tumours	£122	£8,550	1%	21%	17%	0.6%	60%
Criteria DACT – 20% decrease in probabilities of patients without tumour following pathways 1, 2 and 3	£108	£9,953	39%	10%	9%	0.3%	42%
No DACT – 35% decrease in probabilities of patients without tumour following pathways 1, 2 and 3	£108	NA	0%	17%	16%	0.9%	66%
Unrestricted DACT – assuming CT only 80% sensitive as opposed to 100%	£119	£10,416	100%	4%	0%	0.3%	0%
Criteria DACT - assuming CT only 80% sensitive as opposed to 100%	£129	£14,847	39%	13%	11%	0.7%	37%
No DACT - assuming CT only 80% sensitive as opposed to 100%	£150	NA	0%	24%	22%	1.5%	52.5%

Table 9 Results from Markov model

Strategy	Mean total cost per patient ^a	Mean total QALYs per patient ^a	ICER	NMB ^{b, c} (95% CI)	iNMB ^{b, c} (95% CI) compared to no DACT
Unrestricted DACT	£2,084	0.08		£183 (-£124 to £526)	£39 (£7 to £71)
Criteria DACT	£2,094	0.08	Dominated	£166 (-£135 to £506)	£22 (£0 to £45)
No DACT	£2,099	0.07	Dominated	£144 (-£156 to £481)	N/A
Sensitivity analysis (SA1)					
Unrestricted DACT	£2,084	0.08		£183 (-£117 to £538)	£39 (£7 to £70)
Criteria DACT	£2,093	0.08	Dominated	£169 (-£131 to £523)	£24 (£2 to £47)
No DACT	£2,108	0.08	Dominated	£145 (-£155 to £496)	N/A
Sensitivity analysis (SA2)					
Unrestricted DACT	£2,084	0.08		£186 (-£117 to £535)	£39 (£6 to £72)
Criteria DACT	£2,087	0.08	Dominated	£171 (-£130 to £517)	£24 (£0 to £48)
No DACT	£2,089	0.07	Dominated	£147 (-£154 to £487)	N/A
Sensitivity analysis (SA3)					
Unrestricted DACT	£2,084	0.07		£71 (-£215 to £388)	£38 (£6 to £70)
Criteria DACT	£2,094	0.07	Dominated	£54 (-£230 to £367)	£21 (-£1 to £45)
No DACT	£2,099	0.07	Dominated	£33 (-£251 to £342)	N/A

^a deterministic analysis

^b probabilistic sensitivity analysis

QALYs (quality adjusted life years)

NMB (net monetary benefit)

iNMB (incremental net monetary benefit)

ICER (incremental cost effectiveness ratio)

^c at NICE £30,000 per QALY willingness-to-pay threshold

CI (confidence interval) based on the percentile method

Figure 1. Decision Tree

Figure 2. Schematic diagram of the Markov model

Figure 3. Cost Effectiveness Plane

Figure 4. Cost Effectiveness Acceptability Curve