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Date created: June 2024

Scottish Referral Guidelines for Suspected Cancer Update – Evidence Review (Brain and CNS)

The purpose of this document is to synthesise and critique evidence and insight related to referral guidelines for suspected brain or CNS cancers. Key themes have been determined from the literature. For each key theme e.g. individual symptoms, the papers are summarised separately with some high-level synthesis to provide steer on how this may impact referral guidelines. At the end of the document, a table comparing NICE NG12 and SRG guidelines can be found for reference.

This document includes evidence on the following topics:

- Symptoms (individual and combination)
- Secondary care PPV data
- Investigations, including direct access
- Safety netting and inequalities

Background

Brain and CNS tumours are the 9th most common cancer in Scotland, accounting for 3% of all new cancer cases (data from 2018, 2019 and 2021)[1]. Stage at diagnosis data is not publicly available for brain and CNS tumours in Scotland or any UK nation. Typically, brain or CNS tumours are graded according to the aggressiveness of the tumour (grades 1-4), or whether the tumour is benign or malignant[2]. Symptoms of brain/CNS tumours vary from headaches, seizures, nausea/vomiting, drowsiness/loss of consciousness, visual changes, or behavioural/personality changes[3]. Due to the relatively rare nature of symptoms, most primary care research will combine symptoms into wider symptom groups e.g. 'changes to cognition' or 'loss of cognitive function'.

Being diagnosed via emergency presentation is associated with worse outcomes. Scotland routes to diagnosis data is not publicly available for brain and CNS cancer. In England (2018), among around 9,400 cancer cases with a known route to diagnosis, 39% were

[1] NHS Scotland. Annual Incidence Data. Accessed here: https://www.opendata.nhs.scot/dataset/annual-cancer-incidence
[2]Cancer Research UK. Grades of brain and spinal cord tumours | Cancer Research UK [Internet]. www.cancerresearchuk.org. Available from: https://www.cancerresearchuk.org/about-cancer/brain-tumours/grades
[3]Cancer Research UK. Symptoms of Brain Tumours | Cancer Research UK [Internet]. Cancerresearchuk.org. 2019. Available from: https://www.cancerresearchuk.org/about-cancer/brain-tumours/symptoms

diagnosed via emergency presentation. Currently around 1 in 3 (41%) diagnosed with brain and CNS cancer in Scotland survive their disease for 1 year or more (2015-2019)[4].

There are many challenges to the timely diagnosis of brain and CNS cancers. Multiple consultations prior to referral occur commonly among adults subsequently diagnosed with primary brain tumours. Evaluation of the National Cancer Patient Experience Surveys (England) showed that 39% of brain/CNS cancer patients had three or more pre-referral consultations with a GP compared with an average of 25% for all cancers[5]. National primary care audit data (England) analyses demonstrated longer diagnostic intervals related to multiple primary care consultations: a quarter of brain cancer patients with 3–4 and ≥5 consultations experienced intervals longer than 62 and 166 days respectively[5]. The vast majority of patients with neurological symptoms are diagnosed with benign disease, meaning primary healthcare professionals encounter brain and CNS tumours infrequently[5]. Attributing symptoms and knowing when to seek help can also be challenging for the public, as the subtlety of some changes in symptoms often suggests nothing serious is wrong[6]. Evidence has demonstrated there may be a difference in how health professionals and patients describe the same symptom, potentially leading to missed opportunities to recognise symptoms of brain/CNS cancers (see paper 10 below).

Interventions to encourage the timelier diagnosis of brain/CNS cancers include raising awareness of signs and symptoms and expedited pathways[7]. Evaluation data from a single-centre suggests that updates to NG12 resulted in an increase in the number of urgent referrals received by secondary care, alongside an increase in guideline compliant referrals and an improved rate of brain tumour detection[8].This highlights the importance of referral guidance in supporting primary healthcare professionals to achieve timelier diagnosis of brain/CNS cancers.

Search Strategy

[4] Cancer Research UK. Early Diagnosis [Internet]. crukcancerintelligence.shinyapps.io. 2022. Available from: https://crukcancerintelligence.shinyapps.io/EarlyDiagnosis/
[5] Penfold C, Joannides AJ, Bell J, Walter FM. Diagnosing adult primary brain tumours: can we do better? The British Journal of General Practice [Internet]. 2017 Jun 1 [cited 2021 Nov 28];67(659):278–9. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5442949/
[6]Scott SE, Penfold C, Saji S, Curtis S, Watts C, Hamilton W, et al. "It was nothing that you would think was anything": Qualitative analysis of appraisal and help seeking preceding brain cancer diagnosis. Shilling V, editor. PLOS ONE. 2019 Mar 22;14(3):e0213599.
[7]Grant R, Dowswell T, Tomlinson E, Brennan PM, Walter FM, Ben-Shlomo Y, et al. Interventions to reduce the time to diagnosis of brain tumours. Cochrane Database of Systematic Reviews. 2020 Sep 4;2020(9).
[8]M C, IC C, S. S. Impact of the updated NICE referral pathway for patients with suspected brain cancer on a neuroscience service. British Journal of Neurosurgery. 2020 Oct 5;1–5.

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Search terms: PubMed search for combinations of the following terms: brain, glioma, ependymoma, CNS, CNS lymphoma, pineal, vestibular schwannoma, spinal cord, gliosarcoma, cancer, PPV, prevalence, symptomatic, presentation, primary care, symptom (loss of central neurological function, headache, vomiting, papilloedema, neurological deficit, seizure), investigation (MRI, CT, direct access), recognition, referral, stage, routine, routes to diagnosis, comorbidity, risk stratification

Date: 2015 – present. In the table summaries, the only papers included from pre-2015 are those that are relevant for explaining differences in Scottish Referral Guidelines (SRG) and NICE NG12 guidelines. These have been gathered from NICE NG12 Evidence Review document.

Peer-reviewed literature

Note: grey rows in the table represent studies that have already been summarised earlier in the document.

Topic: Symptoms
Summary: The findings broadly support the symptoms included in the current guidelines. Those diagnosed with CNS cancers present most commonly with CNS symptoms (63% of those diagnosed with CNS cancers) and non-specific symptoms (21% of those diagnosed with CNS cancers). Paper 1 reported the most common symptom of CNS cancers was loss of central neurological function (31% of those diagnosed, specific symptoms not specified), followed by headache (19%), and seizures (15%). The PPV of symptoms for brain and CNS cancers rarely exceeds 1%. In paper 2, the only symptom that exceeded 1% was: • new-onset seizure for those aged >18 years (PPV: 1.2% (95% CI; 1–1.4)) • new-onset seizure those aged 60-69 years (PPV: 2.3% (95% CI: 1.6–3.3)). These findings are supported by Hamilton et al (2007)[9], which reported that the only symptom that exceeded 1% risk was new-onset seizure in all patients.

[9] Hamilton, W., Kernick, D., Hamilton, W. & Kernick, D. (2007) Clinical features of primary brain tumours: a case-control study using electronic primary care records. British Journal of General Practice, 57: 695-699.

Paper 3 further supported this finding, reporting a PPV of 1.6% for seizures for brain tumours (note: this study included primary and secondary[10] brain tumours). Weakness and confusion also exceeded 1% in this study (1.5% and 1.4%, respectively). Paper 3 reported that for most of the symptoms included in the study, the diagnostic odds ratios were highest in those aged <60 years.

Paper 3 analysed symptom combinations, for which the PPV was higher than for individual symptoms in the 6 months prior to diagnosis*:

- Headache + cognition: 5.9%
- Headache + weakness: 4.4%
- Headache + nausea: 2.0%
- Cognitive** + headache: 7.2%
- Cognitive + weakness: 9.6%
- Cognitive + nausea: 3.5%

It may be worth considering whether symptom combinations should be included in referral guidelines.

Paper 5 found that for those with new onset fatigue, the observed site-specific risk of brain cancer diagnosis was 3-4x greater in men and 2-4x greater in women than the expected site-specific cancer risk in the general population. Fatigue is not noted specifically in SRG or NG12 but health professionals may relate this to symptom groups included in the guidelines, such as behavioural changes and/or drowsiness.

* Note: some symptoms were grouped due to small numbers e.g. 'visual' and 'cognition'.
** includes composite of cognition, concentration and confusion symptoms

Paper number	Study	Cancer	Summary	Notes
1	Zakkak N, Barclay ME, Swann R, McPhail S, Rubin G, Abel GA, et al. The presenting symptom signatures of incident cancer: evidence from the English 2018	CNS	This study aimed to (1) examine the relative frequency of presenting symptoms by cancer site (the 'symptom signature' of each cancer site), and (2) to examine the relative frequency of cancer sites	Data from 2018 National Cancer Diagnosis Audit (England) N=55,122 (total cohort)

[10] Defined as a cancer that developed somewhere else in the body, but spread to brain/CNS

	National Cancer Diagnosis Audit. British Journal of Cancer [Internet]. 2024 Feb 1 [cited 2024 Feb 1];130(2):297–307.		by presenting symptom (the 'cancer site case-mix' of each symptom), among incident cancer cases. The proportion of patients with CNS (defined as ICD-10 codes C70-72) cancers presenting with the following symptom groups was: • CNS: 63% • Non-specific: 21% • Upper abdominal: 3% • Musculoskeletal: 2% • Lower abdominal: 1% • Respiratory: 1% • Urological: 1% Mean number of symptoms for CNS cancers: 1.3 Of all patients diagnosed with CNS cancers the proportion that experienced *x* symptom were as follows: • Loss of central neuro function: 31% • Headache: 19% • Other: 17% • Seizure: 15% • Visual loss: 6% • Fatigue: 4% • Weight loss, nausea/vomiting, back pain: 2% • Loss of appetite, LUTS, bone pain: 1%	**Limitations:** this is a case-only analysis (only patients with diagnosis of cancer were included), so cannot make inferences about PPV
2	Schmidt-Hansen M, Berendse S, Hamilton W. Symptomatic	Brain/CNS	This review assessed evidence from studies aiming to quantify the risk of brain/central nervous system	Systematic review. Studies published from

	diagnosis of cancer of the brain and central nervous system in primary care: a systematic review. Family Practice. 2015 Oct 14;32(6):618–23.		(CNS) cancer in patients presenting in primary care with relevant symptoms. For all symptoms analysed in the included studies (undifferentiated headache, headache, primary headache, motor loss, confusion, weakness, memory loss, visual disorder), the PPV for patients of any age did not exceed 1%. The only symptom PPV that did exceed 1%: • new-onset seizure for those aged 18 years and above (PPV: 1.2% (95% CI; 1–1.4)) • new-onset seizure those aged 60-69 (PPV: 2.3% (95% CI: 1.6–3.3)). Two of the studies also reported information on the PPV of symptom combinations, none of which exceeded 1%. • Headache + any second symptom (including: motor loss, new onset seizure, confusion, weakness, memory loss, visual disorder) in those aged 18 years and above: 0.39% (95% CI=0.31-0.48). • Vomiting + unsteadiness in those aged 0-14 years: 0.15% (95% CI: 0.01–0.1) • Vomiting + visual difficulties in those aged 0-14 years: 0.088% (95% CI: 0.005–0.6) • Headache + unsteadiness in those aged 0-14 years: 0.085% (95% CI: 0.005–0.6).	1980-2014, all conducted in the UK. N=6 studies with 159,938 patients Ages 0-24 years included **Limitations:** several of the studies included used case–control methods, which can lead to bias from patient selection and reduce accuracy of the results

3	Ozawa M, Brennan PM, Zienius K, Kurian KM, Hollingworth W, Weller D, et al. The usefulness of symptoms alone or combined for general practitioners in considering the diagnosis of a brain tumour: a case-control study using the clinical practice research database (CPRD) (2000-2014). BMJ Open [Internet]. 2019 Aug [cited 2020 Jan 19];9(8):e029686.	Brain	This study aimed to evaluate the risk associated with different symptoms, alone or combined, presented to primary care in 6 months prior to an adult brain tumour diagnosis. Note: some symptoms were grouped due to small numbers e.g. 'visual' and 'cognition'. **PPV reported for individual symptoms:** • Seizure: 1.6% • Weakness: 1.5% • Confusion: 1.4% • Speech: 0.8% • Cognition: 0.7% • Visual: 0.5% • Ataxia: 0.4% • Appetite, consciousness: 0.3% • Weight, sensation, nausea, headache, fatigue, falls, dizziness, concentration: 0.2% • Anxiety, cough, depression, pain, sleep, vertigo: 0.1% Other than for depression, symptoms among patients younger than 70 years showed greater diagnostic odds ratios for brain cancer, compared to those aged >70 years. For confusion, the largest diagnostic OR was seen in the 60 to 69 year age group (OR 96.4). For anxiety, headache, nausea, changes to sleep and change to	Matched case-control study, using data from Clinical Practice Research Datalink (2000–2014) from primary care consultations in the UK. 1:4 case to control ratio N= 8184 cases and 28,110 controls Included those aged 18+, diagnosed with a record of either a primary or secondary brain tumour, diagnosed between 2000-2014. **Limitations:** for some symptoms and symptom combinations, the authors had to aggregate symptom groups to increase the sample size

			vision, the greatest diagnostic ORs were in those aged <60 years. **PPV reported for combination symptoms:** Headache + cognition: 5.9% Headache + weakness: 4.4% Headache + nausea: 2.0% Cognitive* + headache (6 months): 7.2% Cognitive + weakness (6 months): 9.6% Cognitive + nausea (6 months): 3.5% *includes composite of cognition, concentration and confusion symptoms Some symptoms e.g. headache were equally predictive for both primary and secondary tumours. Cognitive symptoms were more common for primary tumours and generalised symptoms such as lack of appetite were more common in secondary tumours.	
4	Ozawa M, Brennan PM, Zienius K, Kurian KM, Hollingworth W, Weller D, et al. Symptoms in primary care with time to diagnosis of brain tumours. Family Practice. 2018 Feb 6;35(5):551–8.	Brain	This study aimed to examine how different symptoms and patient demographics predict variations in time to brain tumour diagnosis. The most common symptom group recorded was focal neurology including stroke (33.2%), followed by episodic attacks— 'fits, faints or falls' (20.8%) and headache (20.8%).	Secondary analysis of brain tumour cases from National Audit of Cancer Diagnosis in Primary Care (England 2009-2010). N=226 cases

				Limitations: see safety netting section
5	White B, Rafiq M, Gonzalez-Izquierdo A, Hamilton W, Price S, Lyratzopoulos G. Risk of cancer following primary care presentation with fatigue: a population-based cohort study of a quarter of a million patients. British Journal of Cancer [Internet]. 2022 Feb 18 [cited 2023	Brain	This study aimed to establish the risk of cancer among patients who presented with 'new onset' fatigue to their GP. New onset fatigue was not fully defined in this paper. According to NICE Guidelines, there is no universally applied definition of fatigue. The authors developed medical code lists used to identify fatigue. Variation in severity and duration of fatigue may be possible, but the codes used are likely representative of how fatigue is recorded in primary care. For men with new onset fatigue, the observed site-specific risk of brain cancer diagnosis was 3-4x greater than the expected brain cancer risk in the general population. For women with new onset fatigue, the observed site-specific risk of brain cancer diagnosis was 2-4x greater than the expected brain cancer risk in the general population.	Cohort study of patients with a record of fatigue in primary care in England between 2007-2013, using electronic health records (EHRs) from the Clinical Practice Research Datalink (CPRD) GOLD N=250,606 **Limitations:** some instances of a patient's presentation with fatigue may not be recorded by the GP, due to its non-specific nature, which could underestimate prevalence of fatigue
6	Zienius K, Chak-Lam I, Park J, Ozawa M, Hamilton W, Weller D, et al. Direct access CT for	Brain	This study aimed to explore the predictive value of NICE 2005 referral guidelines (see appendix) and Kernick referral guidelines when applied to a	Retrospective analysis using referral forms

	suspicion of brain tumour: an analysis of referral pathways in a population-based patient group. BMC Family Practice [Internet]. 2019 Aug 20 [cited 2020 Feb 4];20(1).		population referred for direct access CT of the head from primary care. Kernick referral criteria present 3 symptom groups: • red flag symptoms indicate the probability of an underlying tumour is ≥1% • orange flag symptoms indicate that the probability is between 0.1 and 1% • yellow flag symptoms indicate a probability of less than 0.1%, but above the population rate of 0.01%. From 2,938 scans, 53 patients (1.8%) had intracranial tumours diagnosed, of which 42 were significant. This was defined as if clinical details correlated with imaging findings, or if the imaging findings alone were suggestive of requiring further investigations irrespective of the symptoms. This led to a diagnostic yield of 1.43%. Brain tumours occurred in each of the Kernick categories with the expected frequencies: red flag 3.7% (expected > 1%), orange flag 0.7% (expected 0.1 to 1%) and yellow flag 0.09% (expected 0.01 to < 0.1%). Kernick's red-flag group was the only group with a significantly increased risk of brain tumour, compared to other groups in the guideline (orange and yellow flags) (OR 5.73, 95% CI 2.21–14.84).	and imaging reports in South-East Scotland Aged 16+ years, referred for direct access CT (DACT) between 2010-2015 n=2938 records reviewed **Limitations:** this study is based on 2005 NICE referral guidelines, which is no longer used, limiting applicability of findings to current healthcare practices

			Using the NICE 2005 referral guidelines, 'symptoms related to CNS' had significantly elevated odds ratio for presence of a brain tumour (OR 5.21, 95% CI 1.81–14.92) compared to the symptoms recommended for non-urgent referral.	

Topic: Secondary care PPV data
Summary: It is important to note that secondary care PPV data are likely to be over-estimates, as they are calculated using a selected population at greater risk. However due to the sample sizes required, this is often the most feasible study design. Paper 7 reported that headaches were the most common symptom prompting referral (62.7%), followed by visual disturbance (32.0%) and nausea and vomiting (27.5%). PPV estimates from secondary care data (paper 7): • Symptoms suggestive of cranial nerve palsy: 25.0% (95% CI 4.2–71.8) • Gait abnormalities: 11.1% (95% CI 2.0–43.7) • Memory impairment: 10.0% (95% CI 1.8–40.5) • Sensory loss: 6.7% (95% CI 1.2–29.5) • Limb weakness: 5.3% (95% CI 1.0–24.3 • Visual disturbance: 4.1% (95% CI 1.5–10.4) Paper 8 reported PPV data for symptoms related to CNS cancers. Symptoms related to the central nervous system, including seizures, demonstrated the highest PPV for CNS cancer (4.1%), followed by rapidly progressive subacute focal deficit, including cognitive, behavioural or personality change (3.7%), and headaches accompanied by features suggestive of raised intracranial pressure (1.2%). PPV data from primary care suggests that seizures, weakness and confusion are the individual symptoms with the highest PPV for brain/CNS cancers, which broadly correlates with secondary care data. However, secondary care studies report much higher PPV compared to primary care.

Most patients (84.3%) presented with more than one symptom in this study, which is also supported by primary care data.				
Paper number	**Study**	**Cancer**	**Summary**	**Notes**
7	Ceronie B, Hart T, Belete D, Ramani L, Anish Bahra. Isolated headache is not a reliable indicator for brain cancer: the 2-week wait pathway for suspected CNS malignancies. Clinical medicine. 2021 Nov 1;21(6):e648–55.	CNS	This study aimed to examine the predictive value of symptoms and signs of CNS cancer; examine previous and current referral criteria for diagnosing CNS cancer; and to make recommendations to optimise diagnosis and resources in the management of brain cancer. Ten CNS tumours were identified. Four were CNS cancers: two primary CNS cancers and two cerebral metastases. Both primary cancers were glioblastoma. Most patients (84.3%) presented with more than one symptom. Headaches were the most common symptom prompting referral (62.7%). This was further subdivided into headaches with features suggestive of raised intracranial pressure (worse in the morning, lying flat, associated with nausea or vomiting, or increased on coughing or straining; 29.4%) and those without (33.3%). The next most common symptoms were visual disturbance (32.0%) and nausea and vomiting (27.5%, but not in isolation) Reported PPV of symptoms within this cohort referred to secondary care: • symptoms suggestive of cranial nerve palsy (25.0% (95% CI 4.2–71.8)), • gait abnormalities (11.1% (95% CI 2.0–43.7)), • memory impairment (10.0% (95% CI 1.8–40.5)),	Single-centre evaluation (England data) of all urgent referrals for brain cancer between 2009 and 2016 N=153, small numbers of brain/CNS tumours **Limitations:** this study is based in secondary care, potentially reducing applicability to practice in primary care. It also included secondary cancers and benign tumours which may limit the representativeness of the findings to primary CNS cancers.

			• sensory loss (6.7% (95% CI 1.2–29.5)), • limb weakness (5.3% (95% CI 1.0–24.3)) • visual disturbance (4.1% (95% CI 1.5–10.4)).	
8	Mohammad HR, Boardman J, Howell L, Mills RJ, Emsley HCA. Urgent referral for suspected CNS cancer: which clinical features are associated with a positive predictive value of 3 % or more? BMC Neurology. 2016 Aug 26;16(1).	CNS	This study aimed to analyse (1) the diagnostic performance of the NICE referral guidance criteria from 2005 (see appendix), with a clinical and radiological diagnosis of CNS cancer as the primary outcome, (2) symptom frequencies amongst all referred patients and amongst those with CNS cancer, and (3) incidental findings. Twelve patients were found to have CNS cancer. This constitutes 3.1% of the total number of referred patients who attended their appointment and 4.2% of patients who underwent imaging. Symptoms related to the central nervous system, including seizures, demonstrated the highest PPV for CNS cancer (4.1%), followed by rapidly progressive subacute focal deficit, including cognitive, behavioural or personality change (3.7%), and headaches accompanied by features suggestive of raised intracranial pressure (1.2%).	Single-centre evaluation (England data) of all patients referred urgently for suspected CNS cancer between 2012-2013 N=288, small numbers of brain/CNS tumours **Limitations:** this study is based in secondary care, potentially reducing applicability to practice in primary care.

Topic: Investigation findings
Summary: There is limited evidence on primary care initiated investigation of suspected brain/CNS cancers. The two papers below summarise findings related to direct access CT for diagnosis of brain/CNS cancers. Paper 6 also highlights that there are important, positive consequences of using direct access investigations for other diseases. Currently, direct access to MRI scan of the brain (or CT scan if MRI is contraindicated) is recommended in NG12 for those with progressive, sub-acute loss of central neurological function. Direct access to investigation is not noted in SRG.

Paper 9 suggests that unrestricted direct access CT (DACT) has the potential to increase the percentage of patients diagnosed promptly. The paper reports that the use of unrestricted DACT (all people with signs and symptoms of brain/CNS cancers referred) means no patients are diagnosed via other pathways, reducing number requiring secondary care assessment. Whereas when using criteria DACT (for patients with red flag symptoms only), almost 40% of patients have DACT, 25% follow other pathways and 37% have no further contact other than GP visits.

Paper 6 reported that referral guidelines assessed in this study were insufficient to stratify patients adequately, based on the likelihood that a tumour will be found on brain imaging. This highlights the risks associated with inadequate guidelines stratifying people onto an inappropriate pathway/management strategy. Of those with non-tumour findings, 39% of referrals with an imaging abnormality that met the NICE 2005 'non-urgent classification' would still have been referred for further imaging or specialist opinion. (Note: this referral guideline has since been updated)

Paper number	Study	Cancer	Summary	Notes
9	Keeney E, Mohiuddin S, Zienius K, Ben-Shlomo Y, Ozawa M, Grant R, et al. Economic evaluation of GPs' direct access to computed tomography for identification of brain tumours. European Journal of Cancer Care. 2020 Nov 13;30(1).	Brain	This study aimed to develop a cost-effectiveness model to explore whether unrestricted DACT for patients with a suspected brain tumour might be more cost-effective than DACT based on higher risk symptoms (criteria DACT) or no DACT. 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. The use of unrestricted DACT means no patients are diagnosed via other pathways.	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 **Limitations**: the model has had to make several assumptions due to data limitations. For example, assuming perfect sensitivity

			When using criteria DACT (for patients with red flag symptoms*), almost 40% of patients have DACT, 25% follow other pathways and 37% have no further contact other than GP visits. The differences in outcomes between the diagnostic strategies are small (0.01 QALYs), reflecting the limited evidence that small reductions in diagnostic interval improve survival. The incremental net monetary benefit (iNMB) of unrestricted DACT compared to no DACT is positive, indicating that DACT has the potential to be cost-effective for the NHS. Overall, this study suggests that unrestricted DACT has the potential to reduce the costs of brain tumour diagnosis and to increase the percentage of patients diagnosed promptly. *defined as: papilloedema, significant alterations in consciousness, memory, confusion, or coordination, new epileptic seizure, new onset cluster headache, headache with a history of cancer elsewhere particularly breast and lung, headache with abnormal findings on neurological examination or other neurological symptoms	of CT in identifying clinically important tumours.
-	Zienius K, Chak-Lam I, Park J, Ozawa M, Hamilton W, Weller	Brain	This study aimed to explore the predictive value of NICE 2005 referral guidelines (see appendix) and	See above.

	D, et al. Direct access CT for suspicion of brain tumour: an analysis of referral pathways in a population-based patient group. BMC Family Practice [Internet]. 2019 Aug 20 [cited 2020 Feb 4];20(1). **This paper is also summarised above, see paper 6.**		Kernick referral guidelines when applied to a population referred for direct access CT of the head from primary care. Kernick referral criteria present 3 symptom groups: • red flag symptoms indicate the probability of an underlying tumour is ≥1% • orange flag symptoms that the probability is between 0.1 and 1% • yellow flag symptoms indicate a probability of less than 0.1%, but above the population rate of 0.01%. From 2,938 scans, 53 patients (1.8%) had intracranial tumours diagnosed, of which 42 were significant. This was defined as if clinical details correlated with imaging findings, or if the imaging findings alone were suggestive of requiring further investigations irrespective of the symptoms. This led to a diagnostic yield of 1.43%. Of those with non-tumour findings: • 18.6% of imaging abnormalities were determined to require no further follow-up but did explain the presenting symptom. • 38.4% of radiologically reported abnormalities did not explain the patient's presenting symptoms, but care could be managed in primary care.	

			• 34.2% of patients required referral for further imaging or specialist assessment. • **38.7% of referrals with an imaging abnormality that met the NICE 2005 'non-urgent classification' would still have been referred for further imaging or specialist opinion** Whilst 100% of Kernick red flag cases were also classified as refer urgently according to the NICE 2005 guidance, there was overall quite a lot of disagreement between the two guidelines. These findings suggest that the guidelines were suitable for identifying those with high-risk symptoms, but a significant proportion of those with non-brain tumour findings would have been referred for further imaging or specialist opinion.	

Topic: Safety Netting
Summary: In Paper 4, 30% of brain tumour cases had experienced three or more consultations prior to referral. In around one-third of the cases GPs considered there may have been avoidable delays to diagnosis. Paper 10 summarised reasons why missed opportunities may have occurred in primary care, including: • people experience 'changes' rather than 'symptoms', which can be subtle and difficult to verbalise • seizures are not all the same and few come 'out of the blue'. Some described them as panic attacks or deja vu. This highlights the difference in how health professionals and patients may describe the same symptom, potentially leading to missed opportunity to recognise potential symptoms of brain/CNS cancers.

- the quality of patient– GP communication. Often, patients were either falsely reassured, or dismissed, both of which reducing the likelihood of re-presenting if symptoms persisted.

Paper 11 reported emergency presenters with brain cancer were most likely to report no prior consultations, using colon cancer as a reference. This suggests that those with brain cancer are less likely to present to primary care with symptoms prior to emergency presentations than other cancers.

Inequalities exist in brain cancer outcomes. Paper 12 reported that women and those in the most deprived groups had greater risk of emergency presentation than men and those from least deprived groups for brain cancer. The risk of emergency presentation increased with age across all age groups. Paper 4 reported younger patients (those aged <60 years), those presenting with memory loss, headache or non-specific neurological signs are more likely to experience longer pathway intervals.

Paper number	Study	Cancer	Summary	Notes
-	Ozawa M, Brennan PM, Zienius K, Kurian KM, Hollingworth W, Weller D, et al. Symptoms in primary care with time to diagnosis of brain tumours. Family Practice. 2018 Feb 6;35(5):551–8. **This paper is also summarised above, see paper 4.**	Brain	This study aimed to examine how different symptoms and patient demographics predict variations in time to brain tumour diagnosis. 30% of cases had experienced three or more consultations prior to referral. In around 1/3 of cases, GPs felt that, or were unsure if, there had been avoidable delays. In around 20% the GPs felt that rapid access to investigations would have been helpful. Headache, behavioural/cognitive changes and nonspecific symptoms were associated with at least three or more presentations before referral. This was most marked for: headache only (OR=7.92, 95% CI = 1.80-34.8) and memory complaints (OR=6.09, 95% CI = 1.30-28.6)	Secondary analysis of brain tumour cases from National Audit of Cancer Diagnosis in Primary Care (England 2009-2010). N= 226 cases **Limitations:** reporting of potentially avoidable delays and whether further investigation would have helped was done retrospectively by the GPs, so may have

			Younger patients (aged <60 years) had longer delays along the pathway. There were marked variations in the pathway interval by symptom group. The shortest time was seen for episodic attacks – 'fits, faints or falls' (10 days) whilst the longest interval was seen for memory loss (62 days). Compared to 'fits, faints or falls', patients with headache and non-specific neurological symptoms were more likely to have a longer primary care interval (OR=6.47, 95% CI = 1.22-34.3 and OR=11.9, 95% CI = 1.82-77.8, respectively). Patients presenting with headache only (i.e. headache without any other reported features) and altered memory as a single symptom only were more likely to have a longer total interval, primarily driven by a longer primary care interval (OR=4.11, 95% CI = 1.10-15.5 and OR=4.82, 95% CI = 1.15-20.1, respectively). Investigations in primary care before referral were also associated with longer time to referral and longer overall pathways.	been biased by the actual patient outcomes
10	Walter FM, Penfold C, Joannides A, Saji S, Johnson M, Watts C, et al. Missed opportunities for diagnosing brain tumours in primary	Brain	This study aimed to explore patients' experiences of symptom appraisal, help seeking, and routes to diagnosis. Key themes were identified in participants' narratives: • people experience 'changes' rather than 'symptoms', which are often first noticed by others. It is often	Qualitative study Semi-structured interviews conducted face to face with adults who had been very recently diagnosed

	care: a qualitative study of patient experiences. British Journal of General Practice [Internet]. 2019 Mar 11 [cited 2020 Jan 19];69(681):e224–35.		multiple subtle changes that precede brain tumour diagnosis. Continuity of care was noted as an important factor, so that GPs are more likely to notice symptom changes over time. • not all seizures are the same and few come 'out of the blue' • quality of patient– GP communication. **Participants frequently described 'changes' or 'something not quite right' rather than 'symptoms'.** These related to their body, daily living activities, work, hobbies, or relationships. Some changes were very subtle and difficult to notice; sometimes the participant was unaware of a change until someone else pointed it out. Experiencing these changes or symptoms often led to less engagement, less interest in or a change in ability to carry out work, hobbies, caring responsibilities, and daily living activities. **Not all seizures are the same or come 'out of the blue'** Participants spoke of experiences that were 'out of the norm' yet still 'understandable' e.g. déjà vu, panic attacks, sleepwalking, or intrusive daydreams. Participants explained their symptoms as a response to being tired, overexercising, or not eating.	(within 4 weeks) with a primary brain tumour in the East and North West of England n=39 **Limitations:** this is a small scale qualitative study, which may not be representative of the experiences of the wider population

			People experiencing a seizure often did not seek help initially, unless the seizure involved a collapse. However, not all patients collapsed, and some chose to visit their GP rather than the emergency department for seizure symptoms. **GP communication** Patients discussed some of the changes or symptoms with their GP, but often failed to mention all the changes they had noticed because they forgot, were uncertain of which symptoms were important or found the consultation too short. If patients felt their symptoms were dismissed, this prompted them to downplay their symptoms and their motivation to re-consult was low. On the other hand, patients spoke of being given false reassurance, which sometimes gave patients less incentive to re-attend when symptoms progressed or persisted. Commonly, a brain tumour was not initially considered by the GP or the patient. Other diagnoses such as infection, hormonal changes (thyroid or menopause), eye problems, or mental health issues were considered more likely and investigated first.	
11	Abel GA, Mendonca SC, McPhail S, Zhou Y, Elliss-Brookes L, Lyratzopoulos G. Emergency diagnosis of cancer and previous	Brain	This study aimed to examine primary care consultations for relevant symptoms prior to diagnosis via an emergency route.	Secondary analysis of patient survey data from the 2010 English Cancer Patient Experience

	general practice consultations: insights from linked patient survey data. British Journal of General Practice [Internet]. 2017 Jun 1;67(659):e377–87.		People diagnosed with brain cancer via an emergency route were more likely to report no prior consultations compared to other cancer types (adjusted OR: 2.08 using colon cancer as a reference). This suggests that those with brain cancer are less likely to present to primary care with symptoms prior to emergency presentations than other cancers.	Survey (CPES), previously linked to population-based data on diagnostic routes. N=4647 **Limitations:** the data used in this study is relatively dated, and based on survey data which may reduce reliability of the findings
12	Abel GA, Shelton J, Johnson S, Elliss-Brookes L, Lyratzopoulos G. Cancer-specific variation in emergency presentation by sex, age and deprivation across 27 common and rarer cancers. British Journal of Cancer. 2015 Mar;112(S1):S129–36.	Brain	This study aimed to examine cancer-specific variation in emergency presentation by sex, deprivation group and age among patients with common and rarer cancers. There was evidence that women and those in the most deprived groups are at greater risk of emergency presentation than men for seven cancers, including brain cancer. For brain cancers, the risk of emergency presentation increased with age across all age groups.	Retrospective analysis using cancer registration records, Hospital Episodes Statistics and National Cancer Waiting Times were linked at person tumour level (England) N= 749,645 incident tumours **Limitations:** no information is provided on symptom at presentation, nor about

				the exact circumstances preceding emergency presentation e.g. how often they presented in primary care prior to EP

Suspected Cancer Referral Guidelines: NG12 and SRG

NG12	SRG
Consider an urgent, direct access, MRI scan of the brain (or CT scan if MRI is contraindicated; to be done within 2 weeks) to assess for brain or central nervous system cancer in adults with progressive, sub-acute loss of central neurological function. [2015]	**Emergency (same day) referral** Headache Patients with headache and/or vomiting with papilloedema **Urgent suspicion of cancer referral** Neurological deficit: Progressive neurological deficit (including personality, cognitive or behavioural change) in the absence of previously diagnosed or suspected alternative disorders (such as multiple sclerosis or dementia) Seizure: Any new seizure Seizures which change in character such as post–ictal deficit, headache, increased frequency, etc. **Good practice Points** Consider urgent investigation/referral for patients with non-migrainous headaches of recent onset, when accompanied by "red flag" features suggestive of raised intra cranial pressure (for

	example: woken by headache; vomiting; drowsiness), progressive neurological deficit or new seizure disorder All NHS Boards have pathways for investigation of headaches which should include primary care direct access to imaging If any uncertainty about the presence of papilloedema, the person should be urgently referred to an optometrist for assessment. If there are red-flags suspicious of cancer as detailed above, a simultaneous urgent suspicion of cancer referral to secondary care should be made. If papilloedema is confirmed, the optometrist should refer directly to secondary care An urgent, suspicion of cancer pathway should exist in all NHS Boards for optometrists to refer directly to secondary care for people with optic discs suspicious of papilloedema

Appendix: NICE 2005 Referral Guidelines

Refer urgently symptoms related to the CNS, including:

- progressive neurological deficit
- new-onset/suspected recent onset seizures
- headaches
- mental changes
- cranial nerve palsy
- unilateral sensorineural deafness

in whom a brain tumour is suspected

Headache of recent onset accompanied by features suggestive of raised intracranial pressure, for example:

- vomiting
- drowsiness
- posture-related headache
- pulse-synchronous tinnitus
- or by other focal or non-focal neurological symptoms, for example blackout, change in personality or memory
- a new, qualitatively different, unexplained headache that becomes progressively severe

Consider urgent referral for patients with rapid progression of:

- sub-acute focal neurological deficit
- unexplained cognitive impairment, behavioural disturbance or slowness, or a combination of these
- personality changes confirmed by a witness and for which there is no reasonable explanation

Consider non-urgent referral for patients with:

- unexplained headaches of recent onset: either present for at least 1 month, or not accompanied by features suggestive of raised ICP