brainstrust
the brain cancer people

Earlier, prompt or faster diagnosis of a brain tumour?

Why do we need to have this conversation?

Understanding the available evidence and complexities around making a brain tumour diagnosis may help people diagnosed with a brain tumour, and their caregivers, to accept perceived delays and reduce anxiety and frustration.

This paper reflects *brainstrust*'s position on early diagnosis, one that is grounded in research evidence and reflects the current state of play. We know that there is conflicting opinion about this topic in the current landscape, some of which is biased, not evidence-based and not always in the best interests of the people living and working with brain tumours. Such conflict can lead to anxiety and misconceptions at a time when people feel vulnerable and threatened and are already cycling through fear, sadness and anger. Having the facts and understanding the complexity around early diagnosis may help people to focus on what matters to them. If we can get the conversation right, it would settle better with the community – there would be less anger, more healing, less feeling out of control and more resilience.

The purpose of this paper is to address:

- How does a brain tumour present?
- What is the current context around an early diagnosis of a brain tumour?
- What does the National Cancer Research and Analysis Service (NCRAS) data tell us about early diagnosis?
- What research evidence is there about early diagnosis?
- Why is diagnosing a brain tumour challenging?
- Do diagnostic delays in a brain tumour diagnosis matter?
- What is on the horizon?

Having read this paper, you will:

- have a better understanding of the issues that come with early diagnosis
- understand that early diagnosis isn't 'one size fits all'
- have the best current evidence so that you can make informed decisions
- have better conversations about early diagnosis
- understand clinical judgement and stakeholder decisions
- either be assured that you are doing the best you can or feel comfortable and confident in exploring further options

How does a brain tumour present?

Symptoms of a brain tumour can present in different ways:

a) New, progressive focal neurological deficit. A focal neurological deficit is a problem that affects a specific location in the body, such as a right arm, or manifests as a speech, language, vision or hearing problem. If it is progressive, this means it becomes worse over a period of time.

b) New epileptic seizures starting after 18 years of age.

c) New, progressive headache that suggests raised pressure inside the head (raised intracranial pressure).

d) Cognitive or personality change, with or without headache.

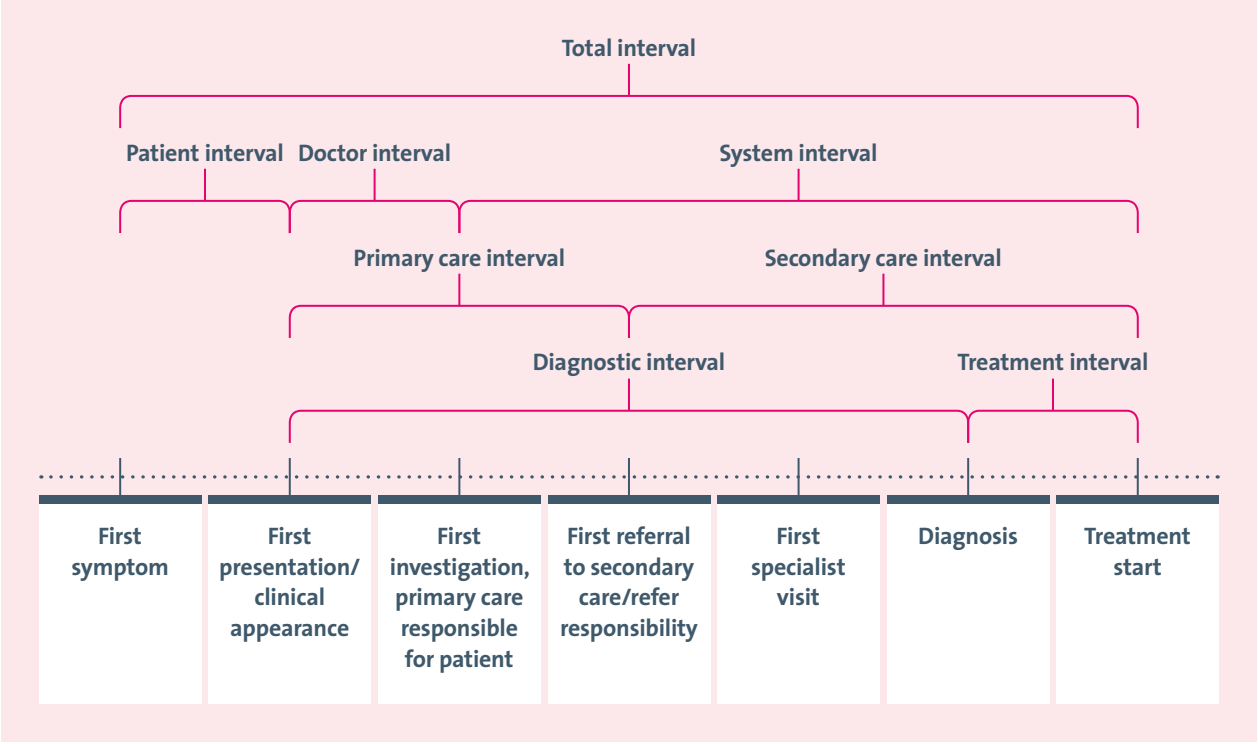
The time to diagnosis is called the total diagnostic interval. This is broken down into different intervals:

- At the patient level, the appraisal and health-seeking interval occurs while the patient and family become aware of symptoms and decide whether to seek advice from their GP.
- At a primary health system level, the GP (recognition of symptoms) interval is the time taken for the primary care practitioner to assess symptoms and make an assessment to justify investigation or referral, plus the processes associated with the initiation of investigation or referral.
- The secondary healthcare system interval is the time taken to make arrangements for assessment, physician/surgeon recognition of symptoms and the processes of performing diagnostic investigations.
- The pre-treatment interval is the time taken to initiate the first treatment after diagnosis. In brain tumours, this is normally the time until the date of primary surgery.[1]

This means that there can be significant variance in the timing of presentation. There can be delays in all these intervals. Avoiding delays would shorten the total diagnostic interval:

1 Weller, D, P Vedsted, G Rubin, F M Walter, J Emery, S Scott, and others, 'The Aarhus Statement: Improving Design and Reporting of Studies on Early Cancer Diagnosis', *British Journal of Cancer*, 106/7 (2012), 1262–67.

The Aarhus Statement



What is the current context around an earlier diagnosis of a brain tumour?

In 2015, the James Lind Alliance published its list of the top 10 clinical uncertainties in neuro-oncology.[2] Early diagnosis was identified as a priority.

Does earlier diagnosis improve outcomes for people diagnosed with a brain or spinal cord tumour?

We know through our daily interaction with the brain tumour community that early diagnosis is a concern – people feel that if there had been an earlier diagnosis, then outcomes may have been very different for the people they love. This view is also reinforced by NHS England's cancer strategy, which highlights the importance of people receiving the highest-quality care from the moment cancer is suspected.

To improve earlier diagnosis of cancer, the NHS Long Term Plan[3] mapped out how it would introduce a new Faster Diagnosis Standard[4] from October 2021 to ensure most patients receive a definitive diagnosis or ruling out of cancer within 28 days of referral from a GP or from screening.

2 'Neuro-oncology', *James Lind Alliance*, https://www.jla.nihr.ac.uk/priority-setting-partnerships/neuro-oncology, accessed 17 Mar. 2023.

3 NHS England, *Achieving World Class Cancer Outcomes: Taking the strategy forward* (NHS England, 2016), https://www.england.nhs.uk/wp-content/uploads/2016/05/cancer-strategy.pdf, accessed 17 Mar. 2023.

4 NHS England, *NHS Cancer Programme: Faster Diagnosis Framework* (NHS England, 2022), https://www.england.nhs.uk/wp-content/uploads/2019/07/B1332-NHS-Cancer-Programme-Faster-Diagnosis-Framework-v5.pdf, accessed 17 Mar. 2023.

In addition, the Faster Diagnosis Standard is being underpinned by a radical overhaul of the way diagnostic services are delivered for patients with suspected cancer. The rollout of rapid diagnostic centres (RDCs) across the country started in 2021 (to complete in 2024), upgrading and bringing together the latest diagnostic equipment and expertise, building on ten models piloted with Cancer Research UK. These have focused on diagnosing cancers where patients often present with non-specific symptoms and may go to their GP many times before being sent for tests, such as for blood and stomach cancers. Both of these initiatives mean that patients with cancer may have quicker access to diagnosis and begin their treatment sooner. The expectation of the RDCs is that the majority of people will not have a cancer diagnosis, but that those who do will be accessing the care they need more quickly.

Secondary care also plays an important role in the diagnosis of cancer. Updated cancer referral guidance from the National Institute for Health and Care Excellence (NICE) also aims to help GPs diagnose cancer earlier.[5] Referral conversations with GPs are some of the first interactions people have with health professionals on their cancer journey. It is important that people have a beneficial experience of these conversations.

Diagnosing a brain tumour, however, is very complex, making early diagnosis difficult. Non-specific symptoms, as well as the lack of a cost-effective test to triage patients in primary care, have resulted in increased time to diagnosis in a cohort of patients in which some will have a poor prognosis. Public Health England (NCRAS) tracks routes to diagnosis and routes from diagnosis.[6] A study into the routes to diagnosis tracks the route the patient follows to the point of diagnosis, so that it can be categorised.[7] This means we can examine the demographic, organisational, service and personal reasons for delayed diagnosis. Results have since been updated to include patients diagnosed from 2006 to 2016.

What does the NCRAS data say?

Brain tumour patients are more likely to be diagnosed through an emergency department than any other cancer site. In 2006, 64% of patients were diagnosed through this route, although there is a downward trend, to 49% in the 2016 cohort.[8,9] This is reflected in an increase in GP referrals in the same time period, from 15% (2006) to 22% (2016). As yet, we don't know why this shift has happened. During this period, the NICE guidance for GP referral for brain tumours was reviewed, which may have influenced this data. Or it could be that we have an increased number of scanners. This is a problem with data: it can give us facts, but it also generates questions, which then need to be answered. For example, we could say it is good that fewer people are being diagnosed in A&E, but on the other hand, we know that people diagnosed via the emergency route have speedier access to diagnostic testing and access the system more quickly.

5 National Institute for Health and Care Excellence, *Suspected cancer: recognition and referral*, (NICE, 2015), https://www.nice.org.uk/guidance/ng12, accessed 17 Mar. 2023.

6 'Routes To Diagnosis', *CancerData*, https://www.cancerdata.nhs.uk/routestodiagnosis, accessed 17 Mar. 2023.

7 Elliss-Brookes, L, S McPhail, A Ives, M Greenslade, J Shelton, S Hiom, and others, 'Routes to Diagnosis for Cancer – Determining the Patient Journey Using Multiple Routine Data Sets', *British Journal of Cancer*, 107/8 (2012), 1220–26.

8 'Routes To Diagnosis', *CancerData*, https://www.cancerdata.nhs.uk/routestodiagnosis, accessed 17 Mar. 2023.

9 National Cancer Intelligence Network, *Routes to diagnosis 2015 update: brain tumours*, (NCIN, 2015), http://www.ncin.org.uk/view?rid=3177, accessed 17 Mar. 2023.

The remaining patients are diagnosed through two-week wait (TWW), GP referral, other outpatient, inpatient elective, death certificate only or through an unknown route:

Route	Description
Emergency presentation	An emergency route via A&E, emergency GP referral, emergency transfer, emergency consultant outpatient referral or emergency admission or attendance.
Two-week wait	Urgent GP referral with a suspicion of cancer, using the two-week-wait guidelines.
GP referral	Routine and urgent referrals where the patient was not referred under the two-week-wait referral route.
Other outpatient	An elective route starting with an outpatient appointment, either self-referral, consultant to consultant or other referral.
Inpatient elective	A route where no earlier admission can be found prior to admission from a waiting list, booked or planned.
Death certificate only	No data available from inpatient or outpatient Hospital Episode Statistics (HES), Cancer Waiting Times (CWT), screening and with a death-certificate-only diagnosis flagged by the registry in the cancer analysis system.
Unknown	No data available from inpatient or outpatient HES, CWT, screening within set time parameters or an unknown referral.

Diagnostic imaging data

The diagnostic imaging dataset (December 2019) shows that the proportion of brain MRI referrals made by GPs was the lowest, at 11%, compared to the proportion of ultrasounds on the abdomen or pelvis, at 45%.[10] We know that the median period from a test being requested to being performed is longer for GP direct access; tests on emergency admissions have shorter waits. GP-referred reporting periods were also slightly longer. The median period between the test being requested by the GP and the test being performed was 22 days for a brain MRI (a decrease from 25 days in 2013). Median time to the report being issued to the GP after the test was done was three days. In a six-year period (2013–2019), there was a growth of 8% in all patients being referred for a brain MRI, and a growth of 6.3% in GP brain MRI referrals.

10 NHS England and NHS Improvement, *Diagnostic Imaging Dataset Annual Statistical Release 2018/19*, (NHS England and NHS Improvement, 2019), https://www.england.nhs.uk/statistics/wp-content/uploads/sites/2/2019/12/Annual-Statistical-Release-2018-19-PDF-1.9MB.pdf, accessed 17 Mar. 2023.

A study also confirms that the median time to diagnosis is shorter for patients diagnosed following emergency admission, compared to patients presenting via outpatients.[11] This suggests that patients access the diagnostic services they need more rapidly than via other routes when diagnosis is via accident and emergency. We also know from this study that patients diagnosed following emergency admission had a median overall survival of 181 days, compared with 386 when diagnosed via the outpatient route. However, these patients may have disease that is further advanced by the time they present at A&E, or they may have more aggressive tumours. This highlights the complexity of trying to understand the challenges around earlier diagnosis.

These are quantitative facts; behind every number, we know there is a person, and that person's story humanises the data. We know that people have different experiences of being diagnosed, and that this is where the challenge lies. It is all too easy to hear the negative stories.

What research evidence is there about early diagnosis?

Other published research evidence has the same resonating conclusion: non-specific symptoms make it hard to diagnose a brain tumour, while acknowledging that a shorter time to diagnosis can reduce anxiety and despair.[12, 13, 14, 15, 16, 17] The paradox is that people who present quickly have a poorer prognosis and more aggressive tumours. Currently, there is no clear evidence that an earlier diagnosis would change the prognosis: 'Emergency presentation is a poor prognostic factor not influenced by an earlier diagnosis.'[18] This may be the case for other cancers, where the patient is screened and where treatments can cure. But where there are no curative treatments, an early diagnosis can mean that patients and their families can be living longer with the knowledge that they have a life-limiting brain tumour, with limited treatment options, but the outcome will still be the same. This is called lead-time bias. Measuring the delay is different as a result of diagnosis earlier in the natural history of the cancer, but this will have no effect on the outcome.[19]

11 Aggarwal, A, N Herz, P Campbell, L Arkush, S Short, and J Rees, 'Diagnostic Delay and Survival in High-Grade Gliomas – Evidence of the "Waiting Time Paradox"?', *British Journal of Neurosurgery*, 29/4 (2015), 520–23.

12 Salander, P, A T Bergenheim, K Hamberg, R Henriksson, 'Pathways from Symptoms to Medical Care: A Descriptive Study of Symptom Development and Obstacles to Early Diagnosis in Brain Tumour Patients', *Family Practice*, 16/2 (1999), 143–48.

13 Hamilton, W and D Kernick, 'Clinical features of primary brain tumours: a case–control study using electronic primary care records', *British Journal of General Practice*, 57(542) (2007), 695–699.

14 Neal, R D, 'Do Diagnostic Delays in Cancer Matter?', *British Journal of Cancer*, 101/S2 (2009), S9–S12.

15 Neal, R D, P Tharmanathan, B France, N U Din, S Cotton, J Fallon-Ferguson, and others, 'Is Increased Time to Diagnosis and Treatment in Symptomatic Cancer Associated with Poorer Outcomes? Systematic Review,' *British Journal of Cancer*, 112/S1 (2015), S92–S107.

16 Penfold, C, A J Joannides, J Bell, and F M Walter, 'Diagnosing Adult Primary Brain Tumours: Can We Do Better?', *British Journal of General Practice*, 67/659 (2017), 278–79.

17 Walter, F M, C Penfold, A Joannides, S Saji, M Johnson, C Watts, and others, 'Missed Opportunities for Diagnosing Brain Tumours in Primary Care: A Qualitative Study of Patient Experiences', *British Journal of General Practice*, 69/681 (2019), e224–e235.

18 Aggarwal, A, N Herz, P Campbell, L Arkush, S Short, and J Rees, 'Diagnostic Delay and Survival in High-Grade Gliomas – Evidence of the "Waiting Time Paradox"?', *British Journal of Neurosurgery*, 29/4 (2015), 520–23.

19 Neal, R D, 'Do Diagnostic Delays in Cancer Matter?', *British Journal of Cancer*, 101/S2 (2009), S9–S12.

Why is diagnosing a brain tumour challenging?

The challenges are varied. Nobody would want to miss a diagnosis of a brain tumour, but it happens. It happens in other cancers too. Brain tumours are a less common cancer (as opposed to rare), with an incidence of less than six in 100,000. As we don't have large cohorts of patients, it is hard to compare symptoms. Symptoms could be due to other conditions and are often related to more benign, common illnesses. A systematic review shows that apart from recent-onset headache and epilepsy, symptoms have a low positive predictive value (PPV) for a brain tumour.[20] A PPV is the probability that people with a positive screening test truly have the disease. So the chances of being diagnosed with a brain tumour from the symptoms people associate with a brain tumour are low.

Poor symptom specificity means that people will often visit their GP more than once. The *National Cancer Patient Experience Survey 2018* shows that 22% of brain cancer patients visited their GP three times or more prior to being referred, and 32%, two times. This compares to 3.7% for breast cancer but is similar to other cancers.[21] A third of patients reported a decline in health while waiting to see a hospital doctor, compared to a fifth of patients across all tumour groups.[22]

One qualitative study of patient experiences identified themes in people's narratives prior to diagnosis:

- People experienced changes, rather than specific symptoms, that were noticed by others.
- Often changes were multiple and subtle.
- Not all seizures are the same – some can be normalised or explained away as panic attacks, déjà vu, sleepwalking or daydreams.
- Quality of communication between the patient and the GP.[23]

But it isn't all down to symptoms. Patient factors also come into play. Patients can normalise symptoms or are unable to act with proper judgement or appropriately due to the tumour. They may put changes down to ageing, stress or change in lifestyle, or dismiss them if the changes are not threatening their way of life. Some patients develop workarounds to a change, so that this then becomes the new normal. This in turn can delay the time to seek help,[24] and when help is sought, a lack of clarity about symptoms can be a barrier to diagnosis.

20 Schmidt-Hansen, M, S Berendse, and W Hamilton, 'Symptomatic Diagnosis of Cancer of the Brain and Central Nervous System in Primary Care: A Systematic Review', *Family Practice*, 32/6 (2015), 618–23.

21 NHS England, *National Cancer Patient Experience Survey 2018* (NHS England, 2018), https://www.ncpes.co.uk/2018-results/, accessed 17 Mar. 2023.

22 Lyratzopoulos, G, R D Neal, J M Barbiere, G P Rubin, and G A Abel, 'Variation in Number of General Practitioner Consultations before Hospital Referral for Cancer: Findings from the 2010 National Cancer Patient Experience Survey in England', *The Lancet Oncology*, 13/4 (2012), 353–65.

23 Walter, F M, C Penfold, A Joannides, S Saji, M Johnson, C Watts, and others, 'Missed Opportunities for Diagnosing Brain Tumours in Primary Care: A Qualitative Study of Patient Experiences', *British Journal of General Practice*, 69/681 (2019), e224–e235.

24 Weller, D, P Vedsted, G Rubin, F M Walter, J Emery, S Scott, and others, 'The Aarhus Statement: Improving Design and Reporting of Studies on Early Cancer Diagnosis', *British Journal of Cancer*, 106/7 (2012), 1262–67.

We know that communication between the GP and the patient and their caregiver could be improved. Time pressures of the ten-minute appointment mean that nuance can be missed. When it works well, GPs elicit the right information from patients, prompting a wider picture to be painted over a period of time. Continuity of care has a key role here too – follow-up appointments need to be time-bound and made at the time of the initial consultation. Patients and their caregivers should be encouraged to keep a symptom diary so that symptoms are presented better, and GPs should trust intuition if patients have repeated appointments with vague symptoms.

And then there is the capacity bottleneck. We don't have enough diagnostic resource – not enough technology (or at least, technology that is of a 21st century standard) and not enough people, with shortages of radiologists (the people who read the scans).[25] Our system is calibrated to investigate only when the suspicion of cancer is high, as the diagnostic gateway is too narrow because of constrained resources. We hear daily in the press how overstretched GPs and A&E departments are, and that there isn't enough resource, as vacancies aren't being filled and there aren't enough beds. The UK has one of the worst survival rates for primary brain tumours compared to other EU countries (we rank 21 out of 27 countries);[26] we have fewer doctors, less time for consultations and insufficient imaging resources. Just under a third of patients wait for more than six weeks for an MRI scan (collected data January 2022), and there has been a 44% increase in requests for a scan in 2021–2022.[27] Although the direction of travel toward more scanners and open-access MRI was specified in the NICE guideline *Suspected cancer: recognition and referral* (NG12) in 2015,[28] gaps in availability and open access remain. COVID has added to the complexity of accessing resources, with fewer face-to-face appointments, issues with accessibility of GPs and people not wanting to be a burden to an overloaded system.

And in brain cancer, we have issues every step of the way: we have a poor grasp of brain tumour biology; patients aren't educated in the signs and symptoms; it is a less common cancer, so the mindset is that it won't be a brain tumour (it usually isn't); brain cancer isn't staged like other cancers, so it is harder to track progression; population-level screening wouldn't work for brain tumours (the return on investment wouldn't justify the costs); there is a lack of training; money is being wasted on catching up; and we don't have the cures.

Do diagnostic delays in brain tumour diagnosis matter?

We don't know. There are so many ways in which they could matter – for instance, in symptoms, disability, survival and psychological impact. It's all very well diagnosing a high-grade brain tumour earlier, but we don't as yet have any treatments that are curative or that can preserve

25 'The NHS does not have enough radiologists to keep patients safe, say three-in-four hospital imaging bosses', *The Royal College of Radiologists*, https://www.rcr.ac.uk/posts/nhs-does-not-have-enough-radiologists-keep-patients-safe-say-three-four-hospital-imaging, accessed 17 Mar. 2023.

26 Allemani, C, T Matsuda, V Di Carlo, R Harewood, M Matz, M Nikšić, and others, 'Global Surveillance of Trends in Cancer Survival 2000–14 (Concord-3): Analysis of Individual Records for 37,513,025 Patients Diagnosed with One of 18 Cancers from 322 Population-Based Registries in 71 Countries', *The Lancet*, 391/10125 (2018), 1023–75.

27 NHS England and NHS Improvement, *NHS Diagnostic Waiting Times and Activity Data*, (NHS England and NHS Improvement, 2022), https://www.england.nhs.uk/statistics/wp-content/uploads/sites/2/2022/05/DWTA-Report-March-2022_17J0T4.pdf, accessed 17 Mar. 2023.

28 National Institute for Health and Care Excellence, *Suspected cancer: recognition and referral*, (NICE, 2015), https://www.nice.org.uk/guidance/ng12, accessed 17 Mar. 2023.

or improve quality of life while living with an aggressive brain tumour. In fact, most treatments are detrimental to quality of life. So potentially all this would mean is that people are living longer with the knowledge that they have a brain tumour. This would apply to any brain tumour. It would appear that people are living longer, but in actual fact, they aren't – it's just that they had the diagnosis earlier. An early diagnosis may be beneficial if the person is living with a high symptom burden, but treatments also come at a price, as does the anxiety and fear. So it is important that we are able to answer the question.

The bottom line, therefore, is that we really don't know. Evidence is based on observational studies, so there is a dearth of trial evidence (where an intervention is researched to reduce delays). In addition, confounding issues mean that it is incredibly hard to find a definitive answer to this question:

- There are different definitions of what we mean by 'delay'.
- The NHS systems are set up so that we have a variety of ways of presenting with a brain tumour.
- Different ways of measuring the delay are confounded by the way patients give information and the questions they are asked, the data collected and missing data.
- Brain tumour patients are a small cohort with a wide range of subsets of tumours, so comparison is difficult.
- Brain tumours present and grow very differently. Low-grade tumours will grow over time with more insidious changes; high-grade gliomas can lead to a quicker diagnostic journey but with rapid progression. This leads to patients with a worse prognosis having a shorter diagnostic delay. For example, a grade 1 pilocytic astrocytoma detected early when small is more likely to be resectable than a larger tumour diagnosed late but promptly. Surgery for non-malignant tumours can be curable if they are removed completely. This could also be applied to incidental, asymptomatic meningiomas. Early detection of these tumours means they are more likely to be curable with surgery. The landscape is not so clear for malignant tumours. The overall prognosis is dictated by the molecular and genetic make-up. Being diagnosed when the tumour is still small means quality of life will be better than for a person with a larger symptomatic tumour diagnosed at a later stage. But this still means living longer with the knowledge that you have a life-limiting diagnosis – so whether an early diagnosis is a good thing depends on the person's values, their context and their appetite for risk. And of course, all of this depends on where the tumour is sited. Options for surgery are limited if it is on the brain stem or in an eloquent area.
- Measurement outcomes vary, and quality of life is a measure that is often secondary to overall survival. And yet it is the outcome measure that is most important to patients and their caregivers.

What is on the horizon?

To address the challenges of an early diagnosis, we need:

- shared ownership of the problem if there has been a delay
- a new approach to diagnostics that isn't based on screening
- people to be educated in the signs and symptoms, and to understand the challenges that exist around diagnosis of a brain tumour

- a proper plan for workforce expansion
- a mindset shift from an *early* diagnosis to a *faster* diagnosis.

Many of these are being addressed by the collaborative efforts of the Tessa Jowell Brain Cancer Mission (TJBCM). The TJBCM serves as a national convening body, uniting professional, patient, charity and government groups to share information and work together to eradicate brain tumours. The mission puts patients first and foremost, and its aim is to selflessly share insights, knowledge and resources. The TJBCM runs a national programme portfolio, which consists of eight programmes. These focus on:

- novel therapeutics
- supporting clinical trials and trial infrastructure (the Brain Matrix)
- further training for medical professionals through the Tessa Jowell Academy, research workshops and fellowships
- Tessa Jowell Centres of Excellence for adults and paediatrics
- The Minderoo Precision Brain Tumour Programme

Improving diagnostic accuracy

Combinations of symptoms

We have outlined the challenges in diagnosing a brain tumour. Research that has analysed primary care data from 8,184 brain cancer patients and 28,110 patients without brain cancer demonstrated that combinations of symptoms, such as headache and cognitive symptoms or weakness, improved the diagnostic accuracy of a brain tumour, but it still means that fewer than eight people in every hundred with these symptoms will actually have a brain tumour.[29]

The lack of a good correlation between these symptoms and the likelihood of having a brain cancer contributes to delays in diagnosis for people who do have cancer, and unnecessary brain imaging for people who don't but whose symptoms suggest that they might. So we need other approaches.

Headache plus

Headaches are common and do not usually have a serious cause. However, headache plus (headache plus another symptom) may suggest that further investigation is needed. Headaches affect 90% of the population at some time and account for 4% of adult GP visits.[30,31] Most are infrequent, episodic headaches, such as migraine or tension-type headaches or chronic daily

29 Ozawa, M, P M Brennan, K Zienius, K M Kurian, W Hollingworth, D Weller, and others, '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*, 9/8 (2019).

30 All-Party Parliamentary Group on Primary Headache Disorders, *Headache Services in England: A report of the All-Party Parliamentary Group on Primary Headache Disorders 2014* (House of Commons, 2014), https://migrainetrust.org/wp-content/uploads/2022/07/APPGPHD-Report-on-Headache-Services-in-England-%E2%80%93-Full-Report.pdf, accessed 17 March 2023.

31 Latinovic R, M Gulliford, and L Ridsdale, 'Headache and Migraine in Primary Care: Consultation, Prescription, and Referral Rates in a Large Population', *Journal of Neurology, Neurosurgery & Psychiatry*, 77/3 (2005), 385–87.

headaches, and there is no underlying structural cause. Secondary headache is caused by an underlying medical or structural condition (e.g. a brain tumour), and imaging is mandatory. Primary care clinicians have to distinguish between primary headaches and secondary headaches, based on clinical history and examinations, and know when to consider referral to secondary care for a neurological opinion regarding diagnosis or management or open-access imaging. Many patients with secondary headache will in addition have subtle cognitive changes or other findings (headache plus).

Improving diagnostic pathway times

Some key targeted actions would improve the pathway times. We need:

- the time to see a neurologist to be reduced
- an increase in the number of CT and MR imaging facilities, including the human resource to support this increase
- to utilise faster access pathways for people who present with certain symptoms, such as headache plus
- an increased availability of direct-access cerebral imaging for GPs
- a utilisation of the optometry pathway when the GP is uncertain about optic disc swelling, which suggests raised intracranial pressure.

We know that headache suspicious of a brain tumour is a common worry for GPs and patients. We know that imaging can identify a brain tumour, but imaging may also identify incidental findings of no importance, or non-specific brain changes that are difficult to interpret and may lead to people being treated unnecessarily – called overtreatment. This has happened in breast cancer. So while it may sound beneficial to have more access to new, state-of-the-art technology, this is not going to be a game-changer for diagnosing brain tumours.

First of all, we need to make sure that the human interface is in place – GPs who are ready to refer for a scan, and patients who understand the risk involved (they may have an incidental finding) – and most of all, we need to have neuroradiologists to read the scans.

Imaging can bring its own challenges, though. Imaging can identify tumours but may also identify incidental findings of no importance, or non-specific brain changes that are difficult to interpret in the context of headaches. Imaging will not identify potentially serious conditions, such as headache due to idiopathic intracranial hypertension, which can cause raised intracranial pressure and blindness – a normal scan may give false reassurance. MRI imaging, if available to GPs, is expensive, and there can be delays in reporting due to radiologist shortages. CT scanning has shorter waiting times but uses radiation, and usually contrast is not given, meaning it is less sensitive than MRI scanning and may miss some infiltrating tumours.

Research about headache plus is ongoing to see if this would be a good diagnostic tool for brain tumours.[32]

32 Ozawa, M, P M Brennan, K Zienius, K M Kurian, W Hollingworth, D Weller, and others, 'Symptoms in Primary Care with Time to Diagnosis of Brain Tumours', *Family Practice*, 35/5 (2018), 551–58.

A blood test

Neuro-oncology clinicians in Scotland and Liverpool have recognised the importance of improving the diagnostic pathway for patients with suspected brain cancer.[33] They have developed a blood test to differentiate patients likely to have a brain cancer from non-cancer patients. A drop of patient blood is analysed in a tabletop spectrometer using infrared spectroscopy: light is shone on the blood through a crystal, and the resulting pattern of light (spectrum) can be analysed. By comparing these spectral patterns between patients, patterns have been identified that are predictive of a brain cancer, and others that are predictive of not having brain cancer. Unlike most other blood tests that try to detect cancer, this test is assessing all the molecules in a patient's blood, not just a single specific molecule of interest. This makes it more sensitive and accurate.

However, this is not an approved diagnostic screening test. It has a 20% false-positive rate. This means that 20% of people having the blood test would be told they have a brain tumour, but further investigation would show that they don't have a brain tumour. This would cause unnecessary psychological harm in thousands of people. It also doesn't diagnose all types of tumours. If used for population-level screening, the 20% false-positive rate would mean thousands will live in fear for the rest of their lives and require frequent scanning. This required increase in scanning would not be economically viable. This blood test does not replace a doctor's clinical decision-making about a patient and is not a substitute for gold-standard brain imaging.

Artificial intelligence (AI)

AI is showing potential to help with the speedier diagnosis of a brain tumour, but this is at the time when the biopsy is done and will not impact on the time of diagnosis intervals.[34] In this study, a machine-learning approach provided the intraoperative diagnosis without needing to go through the pathologist pathway. It is quicker, which saves time during surgery, and would potentially improve outcomes and cut costs as a result, or it could bring a service to a location that isn't currently served.

However, the translation of AI research techniques into the clinic presents a new frontier. This study was with a small sample of patients, and it would be hard to scale. We need robust evaluation to ensure that AI systems are safe and effective, using performance measures that go beyond measures of technical accuracy. These should include how AI affects the quality of care, the variations, efficiency and productivity of clinical practice and, most importantly, patient outcomes. We don't yet know about any unintended consequences, including bias, nor do we know much about human–algorithm interactions. There is still a way to go before this translates safely into the clinic, and one would hope that AI would combine strengths to improve things overall. This is the ideal approach for institutions with resources, whereas in parts of the world where intraoperative diagnosis is harder to confirm (where neuropathologists are a rare entity), AI could be an invaluable tool.

33 Butler, Holly J., Paul M. Brennan, James M. Cameron, Duncan Finlayson, Mark G. Hegarty, Michael D. Jenkinson, and others, 'Development of High-Throughput ATR-FTIR Technology for Rapid Triage of Brain Cancer', *Nature Communications*, 10/1 (2019).

34 Hollon, T C, B Pandian, S S S Khalsa, R D'Amico, M B Sisti, J N Bruce, and others, 'Near Real-Time Intraoperative Brain Tumor Diagnosis Using Stimulated Raman Histology and Deep Neural Networks', *Neurosurgery*, 66/Supplement 1 (2019), 310–634.

A deeper understanding of symptom combinations, referral pathways and protocols is available in the NCRI position statement on early diagnosis of brain tumours.[35]

Managing expectations: Is early detection always an advantage?

Finally, it comes down to the person at the centre of this, the person with the potential diagnosis of a brain tumour and the communication that needs to sit around this. Earlier diagnosis must surely be a good thing. The NHS has targets for speedy diagnosis and offers screening for a wide range of cancers. Millions of pounds are poured into research, screening, imaging and diagnostic testing. But suppose there is no cure for your cancer. This doesn't address the failure to communicate the rather darker side of earlier diagnosis. We do not know the benefits and harms of early detection, in terms of lives saved, and unnecessary and harmful treatment, let alone the anxiety and stress that this brings. For example, there is an assumption that an earlier diagnosis means the tumour is easier to remove, but this is often not the case (e.g. if it is in an eloquent area, on the brain stem or deep within the brain), so you are told you have a brain tumour, but surgery is not an option for you. And treatments will cause significant impact on quality of life, which is possibly already compromised by the tumour.

There is a surge of attention being given to earlier detection of disease, with a 36-fold increase in articles about early detection from the 1950s to the 2010s.[36] There is a significant imbalance (2:1) between the articles on benefits and harms, with the advantages of early detection being taken for granted. There needs to be a better balance of information provided about the pros and cons of earlier diagnosis. We would argue for a shift in the discourse around earlier diagnosis, which is fraught with confusion. We advocate that the word *early* should become *prompt*. A prompt diagnosis would mean that if you feel something is not right, then you have a proper examination and diagnosis (which may be no diagnosis) promptly. This is not screening, which attempts early diagnosis of people who are symptom-free. This type of early diagnosis has the potential to bring with it early misdiagnosis, anxiety, needless treatment and harm.

Underpinning this are the stories we hear. We hear of repeated visits to the GP, of inexplicable symptoms (which may or may not be linked to a brain tumour), of brain tumours the size of oranges because they have been left too long (size isn't the only factor; grade is more important) and of how things would have been different if only there had been an earlier diagnosis. These stories are told to confirm everything we've been led to believe about early diagnosis – that it's a good thing, that we'd live longer with an earlier diagnosis, that we'd get the treatment we need. We tell stories to make sense of life, or to kid ourselves that life makes sense. And in our need to do this, we can be tempted to make clearer sense of the data than it is really telling us – we read what we want to read and hear what we want to hear, as long as it confirms our beliefs, which may or may not be the right ones.

Such is the wealth of information available on the Web and via apps, and the focus on biomarkers, that we are now all capable of diagnosing our illnesses and monitoring our health in our own homes. This needs to be tempered with the understanding that this may not create better health for people but can, and does, lead to overtreatment, trauma and living our lives defined by illness. It is also a huge waste of resource. Until we know more about the progression of disease, including

35 National Cancer Research Institute position statement on early diagnosis of brain tumours (NCRI, 2023).

36 Hofmann, B and J-A Skolbekken, 'Surge in Publications on Early Detection', *BMJ*, 357:j2102 (2017).

brain cancer, we should be better communicating the benefits and harms of early detection and treatment, and encouraging people to be more comfortable with living with uncertainty and to explore their fear of illness. Helping people to seek a faster diagnosis, rather than an early diagnosis, is a start.

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