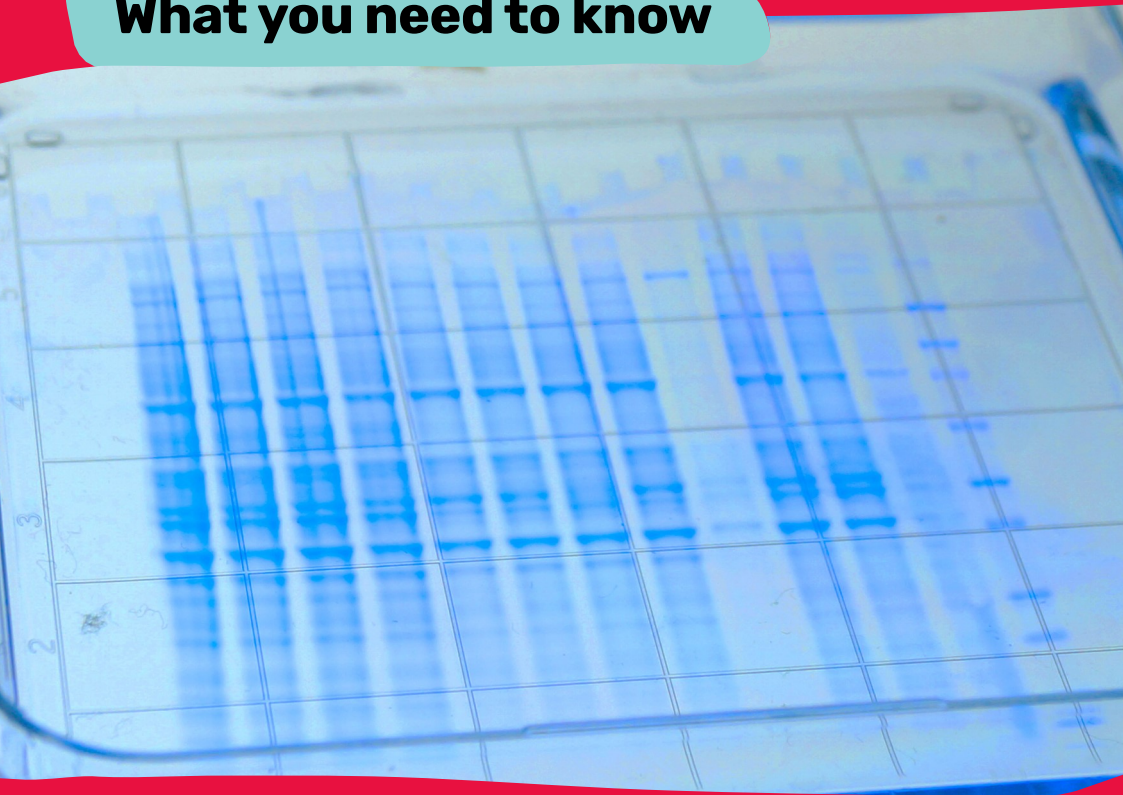


Brain tumour biomarkers

What you need to know



What is a tumour biomarker?

A biomarker is a biological marker or indicator of a certain process happening in the body.

In a brain tumour, it might be a change in a gene in the tumour's DNA or it could be a molecule found in the tumour.



CARE CAN'T WAIT

If you'd like to talk to someone about how you're feeling, or would like to find out where you can get further support (including details of support groups), you can contact The Brain Tumour Charity's Information and Support Team:

Phone: **0808 800 0004**

(free from landlines and most mobiles)

Email: support@thebraintumourcharity.org

Live chat: thebraintumourcharity.org/live-chat

Website: thebraintumourcharity.org/getsupport

Closed Facebook groups:

thebraintumourcharity.org/facebook-support

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Biomarkers and brain tumours

If you have a brain tumour, a biomarker test **may** be used to look at the genes associated with your type of tumour.

With brain tumours, biomarker tests can be used to see if your tumour has certain changes in its genes that **may** be used to:

- help diagnose the type of tumour you have
- predict how fast your tumour will grow
- suggest how you may respond to certain treatments, such as chemotherapy and, possibly, radiotherapy.

Research is still in early stages and it's important to know that :

- biomarkers are not treatments
- biomarker tests are only available for certain types of tumours (*see Tables 1 and 2 on pages 8 and 9*), but research is continually discovering more biomarkers
- biomarkers often don't give absolute answers, but suggest likely tumour behaviour
- not all hospitals offer biomarker tests (although you may be able to be referred to another hospital that does)
- there are advantages and disadvantages to testing.

Advantages

Biomarker test results can be useful in giving more detailed information about your tumour type. This can help to give a more accurate diagnosis and plan appropriate, more personalised treatment.

For certain tumour types, they may also suggest how your tumour may respond to certain treatments and also give information that can help estimate your prognosis (likely outcome of your treatment).

The results may also help give an indication as to which clinical trials may be suitable for you.



For more information about clinical trials, see our Clinical trials webpage and fact sheet: thebraintumourcharity.org/clinical-trials

Disadvantages

While many scientists believe that biomarker testing is helpful, others argue that the results are sometimes unclear due to a number of factors. For example:

- mistakes in detecting the marker
- not enough of the tumour was available to test
- the heterogeneity of the tumour.

What is tumour heterogeneity?

Many tumours are heterogeneous. This means all the cells are not the same. Instead, some cells, or groups of cells, throughout the tumour will have different genetic mutations (changes in the genes) or a different molecular make-up.

If a sample is taken from a part of a tumour that's different to the rest of the tumour, it may show different results to a sample taken from elsewhere in the same tumour.

This means that the results of the biomarker test may not truly reflect the tumour and its likely behaviour.

Some people prefer not to know too much detail about their tumour and how this might predict their prognosis.

For example, if you have a biomarker test which suggests your tumour type doesn't respond well to treatment, this is likely to be difficult news. If you've been working hard to maintain a positive frame of mind on a day-to-day basis, this could set you back.

Quite often biomarker testing is done routinely, so you may not be consulted before this is done. You can, of course, choose not to be told the result.

Ask your healthcare team if testing is done routinely and, if it's not, think about it carefully and discuss it with them and your family before deciding whether to ask for it.

Things to be aware of about biomarkers for brain tumours

- None of the predictions from biomarkers are perfect.
- Some people's tumours will respond differently to what the test predicts.
- Biomarker testing isn't suitable for everyone with a brain tumour and The Brain Tumour Charity is unable to advise on your individual case.
- Biomarker tests can only be carried out on a sample of your tumour, either removed during a craniotomy or biopsy operation, and the sample has been analysed.
- It doesn't matter how long ago the biopsy was performed, so previous samples can be used, if they've been stored appropriately.



For more information about biopsies, see our Neurosurgery for brain tumours webpage and fact sheet.

thebraintumourcharity.org/treatments/neurosurgery-adults

- Testing for biomarkers is a relatively new practice, so it's availability can vary widely, as the time taken to implement the new molecular tests will be different between centres.

Are there tests suitable for my tumour?

Based on increasing evidence, NICE* is now recommending the use of particular biomarker testing for particular brain tumours.

Brain tumour biomarkers (Table 1)	1p/19q co-deletion	ATRX	BRAF	Histone H3.3 K27M	IDH1 & IDH2	MGMT methylation	TERT
High grade tumours							
Glioblastoma (grade 4)		✓			✓	✓	✓
Anaplastic astrocytoma (grade 3)		✓			✓	✓	?
Anaplastic oligodendroglioma (grade 3)	✓				✓	✓	✓
Diffuse midline glioma [previously DIPG] (grade 4)				✓	✓		
Some other high grade gliomas (<i>Speak to your healthcare team to see if it's relevant in your case</i>)					✓	✓	?

✓ = Tests are frequently suitable for these tumours, but it may be only in some circumstances.
 ? = Some evidence has suggested suitability for these tumours, but more evidence is needed.

(Table 1 - High grade tumours - page 8)

(Table 2 - Low grade tumours - page 9)

*NICE = National Institute for Health and Clinical Excellence

Brain tumour biomarkers (Table 2)	1p/19q co-deletion	ATRX	BRAF	Histone H3.3 K27M	IDH1 & IDH2	MGMT methylation	TERT
Low grade tumours							
Oligodendroglioma (grade2)	✓				✓	?	✓
Diffuse astrocytoma (grade 2)		✓	?		✓	?	?
Pilocytic astrocytoma (grade 1)			✓		✓		?
Some other low grade gliomas (<i>Speak to your healthcare team to see if it's relevant in your case</i>)					✓		?
These tests are the main tests which are available for brain tumours.							
<i>The Brain Tumour Charity's research funding has contributed to the development of some of these tests.</i>							

Biomarkers for predicting response to treatment and prognosis

1p/19q co-deletion test

What is the 1p/19q test?

The 1p/19q test **may** predict long-term survival in people who have some types of brain tumour.

The test can also be useful in diagnosing certain types of brain tumours and, therefore, in making decisions about the most appropriate treatment for you.

Is the 1p/19q test suitable for me?

The types of brain tumour that may be suitable for 1p/19q testing are:

- Oligodendrogliomas

How does the test work and what does it show?

Our bodies are made up of cells. Each cell has 23 pairs of chromosomes, which carry your genes (DNA). One chromosome of each pair is inherited from your mother, and the other from your father. Each pair of chromosomes are numbered 1 to 22, then XX or XY.

The 1p/19q test looks at genetic changes to chromosomes 1 and 19 to see whether they have a section missing. If the sections called the p section of chromosome 1 and the q section of chromosome 19 are missing, this means that the genes carried in those sections are also missing.

These genes seem to be involved in resistance to chemotherapy drugs. So if you're found to be missing both those sections, you're more likely to have a better response to chemotherapy and longer overall survival.

Histone H3.3 K27M

What is the histone H3.3 K27M test?

The histone H3.K3 27M test may predict response to treatment for certain types of tumour.

Is the histone H3.3 K27M test suitable for me?

The histone H3.3 K 27M test is suitable for:

- Paediatric diffuse midline gliomas (previously called DIPG)

How does the test work and what does it show?

Up to 80% of paediatric diffuse midline gliomas have a mutation of the histone H3. A histone is a group of proteins that your DNA wraps round in your chromosomes.

The tumours which have this mutation tend to respond less well to treatment.

IDH1 and IDH2 mutation test

What is the IDH1/IDH2 test?

The IDH1/IDH2 test may predict long-term survival in people who have certain types of brain tumour. It may also be useful in predicting how effective a particular treatment is likely to be.

Is the IDH1/IDH2 test suitable for me?

If you have a glioma, you may be suitable for IDH1/IDH2 testing, but speak to your neuro-oncologist for information and advice.

Gliomas that may be suitable include:

- Diffuse astocytomas (grade 2)
- Anaplastic astrocytomas (grade 3)
- Oligodendrogliomas
- Glioblastomas, in particular secondary glioblastomas (tumours that evolved from lower grade gliomas)

How does the test work and what does it show?

IDH1 and IDH2 are genes. A change (mutation) in the IDH1/IDH2 genes has been found in about 80% of astrocytomas, oligodendrogliomas and secondary glioblastomas.

Tumours that have the change are known as IDH-mutant, and those without the change are known as IDH-wildtype.

For people with high grade types of these glioma, those whose tumours are IDH-mutant tend to have better long-term survival rates than those who are IDH-wildtype.

It's not yet clear how mutations of the IDH1/IDH2 genes link to outcomes for people with low grade brain tumours - both in terms of long-term survival and also treatment outcomes. However, there's some evidence that, similar to high grade gliomas, people whose tumours are IDH-mutant have better long-term survival rates than those who are IDH-wildtype.

Further research needs to be carried out before clear conclusions can be drawn, but it may be that chemoradiotherapy (a combination of chemotherapy and radiotherapy) is more effective for some people with grade 2 gliomas who have the IDH1/IDH2 mutation, than those who don't. (See TP53/ATRX mutations section further on.)

It's important to be aware that people with gliomas that have the IDH1/IDH2 mutation tend to be younger adults and older children, which may partially account for their longer survival.

MGMT promoter methylation test

What is the MGMT methylation test?

For people with certain tumour types, the MGMT methylation test helps to predict how effective chemotherapy treatment is likely to be, although there are many other factors that also affect response to treatment. This can be used to help plan a suitable, individualised treatment plan.

Is the MGMT methylation test suitable for me?

NICE (National Institute for Health and Care Excellence) recommends that all high grade glioma tumours should be tested for MGMT promoter methylation to inform prognosis and guide treatment.

The types of brain tumour suitable for MGMT biomarker testing include:

- Glioblastoma
It can only predict your response to the chemotherapy drug, temozolomide (TMZ)
- Anaplastic gliomas (grade 3)
 - anaplastic astrocytoma
 - anaplastic oligodendroglioma

You may have heard of recent research that suggested that the MGMT test **may** also be useful for predicting prognosis in grade 2 gliomas. This research is in very early stages and is not evidence-based. More research is needed to confirm if this is the case.

What does the test show?

In summary, the test looks at the amount (percentage) of something called methylation. If your tumour is found to be:

- MGMT methylated, you're more likely to respond well to TMZ chemotherapy.
- MGMT unmethylated, you're less likely to respond to TMZ chemotherapy.

This helps your healthcare team decide on the best course of treatment for you. For example, if your tumour is unmethylated, giving you high doses of chemotherapy may give you lots of unpleasant side-effects, but with little benefit in terms of reducing your tumour.

If you do decide to have the test, you need to be aware that it may be found to be unmethylated. Speak to your healthcare team about what would happen next if this turned out to be the case.



There are other factors that influence the effectiveness of chemotherapy, so there'll always be 'good' and 'poor' responders in both the methylated and unmethylated groups.

How does the test work?

If you'd like to understand the test more:

- MGMT is a protein in cells, including tumour cells, that repairs damage to the cell's DNA.
For example, the damage caused by chemotherapy drugs to tumour cells.
- The more MGMT protein that the tumour produces, the less effective the chemotherapy drug is expected to be, as the protein will repair the damage to the tumour.
- The production of the MGMT protein is controlled by the MGMT gene.
- Some tumour cells have a change in their MGMT gene. This change is called methylation.
- If the MGMT gene is methylated, it effectively turns the gene off.
- If the MGMT gene is turned off, less MGMT protein is produced in that cell.
- If there's less MGMT protein to repair the tumour cell, a chemotherapy drug is more likely to be effective.
- The more cells in the tumour that are methylated, the more cells will be damaged by the chemotherapy drug.
- The MGMT test estimates how much of the MGMT protein is likely to be produced in the tumour cells and states it as the amount (percentage) of methylation.

There's some debate about what percentage marks a tumour as methylated and what as unmethylated. As a result, the test isn't 100% accurate.

TERT promoter mutation test

When found with 1p/19q co-deletion and IDH-mutant biomarkers, the TERT promoter mutation suggests a diagnosis of oligodendroglioma, and predicts greater benefit from chemotherapy and radiotherapy and longer survival, particularly in grade 2 and 3 gliomas.

However, when the TERT mutation is found on its own in grade 2 and 3 gliomas, it predicts poorer survival. This suggests the need for early, more aggressive treatment.

When the TERT mutation is found with IDH-wildtype, this suggests a diagnosis of glioblastoma. In higher grade gliomas, such as glioblastoma, the TERT mutation is associated with poor overall survival.

It's thought that the TERT mutation may also worsen the poor response to treatment (temozolomide and radiotherapy) in MGMT unmethylated glioblastomas.

Biomarkers used mainly for confirming diagnosis

ATRX and TP53

Frequently found in adult diffuse gliomas (grades 2 and 3) and often in astrocytomas with IDH1/2 mutations, these biomarkers are useful in confirming the diagnosis of these tumours.

Tumours that are IDH-mutated and have mutations in ATRX and TP53 grow more slowly than tumours without the IDH-mutation, but have also been found to be resistant to radiotherapy.

This means radiotherapy is less likely to kill these tumour cells, and so is less effective in tumours with these mutations.

However, in low grade gliomas, if the radiotherapy is combined with chemotherapy drugs that block the repair of DNA, this can result in longer survival than receiving radiotherapy alone.

TP53 has also been found to help predict prognosis in the sub-type of medulloblastomas known as SHH (sonic hedgehog) type. SHH types of medulloblastoma with a mutation in TP53 tend to have a worse prognosis.

BRAF

There are 2 different mutations in the BRAF gene that may be of interest. These are the KIAA1549-BRAF fusion gene in childhood brain tumours and the BRAF V600E mutation in adult brain tumours.

What is the BRAF test?

The BRAF test (along with other investigations) can sometimes help determine whether a tumour is a pilocytic astrocytoma (a type of grade 1 tumour) rather than another type of (non-pilocytic) astrocytoma, if there's uncertainty. These tumours are more common in children than adults.

There is some evidence that a mutation in the KIAA1549-BRAF fusion gene can cause poorer outcomes in low grade gliomas in children.

The BRAF V600E mutation in adults may increase the growth and spread of tumour cells. This is being investigated as a target for various drugs.

Is the BRAF test suitable for me?

BRAF testing is only clinically useful in a few selected tumour types and is most commonly used to determine whether a tumour is a pilocytic astrocytoma.

If you're interested in BRAF testing, please speak to your neuro-oncologist for information and advice.

How does the test work and what does it show?

BRAF is a gene that makes a protein called B-raf. The B-raf protein is important because it sends signals to direct the growth of cells within our body. This is known as the MAPK pathway inside the cell.

Research has found that some brain tumours (types of grade 1 and 2 astrocytoma, including grade 1 pilocytic astrocytoma) may have a fault with their BRAF gene.

The fault leads to the BRAF gene permanently sending signals that make cells divide and create copies of themselves. This uncontrolled growth of cells contributes to tumour formation.

Other biomarkers you may hear about

Research into the molecular structure of brain tumour cells is ongoing and is leading to increased understanding of the role genes play in a tumour's behaviour. As a result, other possible biomarkers are of interest.

Many of these other genes and mutations have shown some association with survival and tumour behaviour, but many of these tests are very experimental and remain under investigation. As a result, they're not yet routinely offered as their value in clinical practice has yet to be determined.

EGFRvIII

A mutation in the EGFRvIII gene is found in about 20-30% of glioblastomas, and is tumour-specific. This means it's not found in normal brain tissue.

As a result, its presence can confirm a diagnosis of glioblastoma. Although it's important to note that its absence doesn't mean it's not a glioblastoma.

As it only appears in tumour cells, it could also be used as a target for treatments, as well as predicting prognosis. Research is underway and this test isn't routinely offered.

Whole chromosome markers

Recent research has identified markers, which can predict prognosis, in particular sub-types of childhood medulloblastomas - the sub-types known as SHH (with TP53 wildtype), Group 3 and Group 4.

A pattern of chromosome gains and losses was found that could separate these sub-types, normally classified as standard-risk, into favourable-risk and high-risk categories.

Those in the favourable-risk group would need less intensive, aggressive chemotherapy, and so have fewer side-effects.

YAP1

Sometimes when a cell is dividing, a mistake can be made and 2 separate genes can fuse together. These fusion genes can make fusion proteins.

It's been found that children with certain types of brain tumour **and** fusions of the YAP1 protein had better prognoses than children without the fusion, known as YAP1-wildtype. These include childhood supratentorial subependymomas and ependymomas.

Many other genes and mutations have been associated with survival and tumour behaviour. However, many of these remain under investigation and aren't yet routinely used.

How can I get biomarker testing?

The number of centres offering biomarker testing is growing as research in the area develops. In some centres, biomarker testing is now done routinely (when your neuro-oncologist thinks a particular test would be appropriate to your tumour type) and in line with NICE recommendations.

NICE recommends the following tests should be carried out for all gliomas:

- IDH1/IDH2
- ATRX - to identify IDH mutant astrocytomas and glioblastomas
- 1p/19q co-deletion - to identify oligodendrogliomas
- BRAF fusion and gene mutations - to identify pilocytic astrocytoma
- Histone H3.3 K27M mutations in diffuse midline gliomas - previously called DIPG or brain stem gliomas

NICE also recommends:

- MGMT promoter methylation for all high grade gliomas - to inform prognosis and guide treatment
- Consider testing IDH-wildtype gliomas for TERT promoter mutations - to inform prognosis.

As many of these NICE recommended biomarkers are also now part of the latest WHO classification system of brain tumours, they should be offered by all neuro-oncology centres. (WHO= World Health Organisation.)

You may have had it done without realising. Speak to your healthcare team if you want to know if this is the case.

If it hasn't been done routinely and you're interested in having a biomarker test, the first thing you'll need to do is speak to your neuro-oncologist. They'll be able to tell you whether they think it's suitable for you. You can ask this question at any time.

If they feel it would be beneficial, they may arrange for the test to happen at the hospital you're being treated at. If the hospital doesn't carry out such tests, they may refer you elsewhere.

It's important to note that the tests won't necessarily influence your treatment plan at the hospital you attend. So, as the hospital has to pay for the test, unless the neuro-oncologist is going to change your treatment on the basis of the test result, they may not feel that testing is necessary.

If your neuro-oncologist doesn't believe that biomarker testing would be beneficial to you, you can ask them to talk through with you how they've made their decision.

If, after this, you'd still like to pursue biomarker testing, you may wish to ask your medical insurers, if you have private medical insurance, if they would pay for them. Or you may wish to have the testing done privately and pay for it yourself. Either way, you'll need to provide information, and possibly biopsy samples. To obtain these, speak to your neuro-oncologist.

It's important to be aware that any biomarkers outside the NICE recommended group are unlikely to be funded outside of a research study (clinical trial).

What if I have further questions?

You may have heard your neuro-oncologist use some of the terms mentioned in this fact sheet when referring to your specific tumour type. If you're finding this overwhelming or difficult to understand, you're not alone. Speak to your healthcare team if you have questions, or please contact our Information and Support Team:

Phone: **0808 800 0004**

(free from landlines and most mobiles)

Email: **support@thebraintumourcharity.org**

Live chat: **thebraintumourcharity.org/live-chat**

Website: **thebraintumourcharity.org/getsupport**

Closed Facebook groups:

thebraintumourcharity.org/facebook-support

About this information resource

The Brain Tumour Charity is proud to have been certified as a provider of high quality health and social care information by The Information Standard - an NHS standard that allows the public to identify reliable and trustworthy sources of information.

Written and edited by our Information and Support Team, the accuracy of medical information in this resource has been verified by leading health professionals specialising in neuro-oncology. Our information resources have been produced with the assistance of patient and carer representatives and up-to-date, reliable sources of evidence.

We hope that this information will complement the medical advice you've already been given. Please do continue to talk to your healthcare team if you're worried about any medical issues. If you'd like a list of references for any of our information resources, or would like more information about how we produce them, please contact us.

We welcome your comments on this information resource, so we can improve. Please give us your feedback via our Information and Support Team on **0808 800 0004** or **support@thebraintumourcharity.org**

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About The Brain Tumour Charity

Going further for a cure

As the UK's leading brain tumour charity, we're here to accelerate a positive change in how people affected by brain tumours are diagnosed, supported and cured.

At The Brain Tumour Charity, we believe that no-one should have to live with a brain tumour or lose a loved one to a brain tumour. Advances in both treatments and quality of life care need to be made - and they need to be made quickly.

We know that if we put our heads together, we're more than up to the challenge. So we're building a movement of people from every walk of life - all coming together to accelerate a cure.

Find out more and get involved:
thebraintumourcharity.org



**WE'RE
HERE FOR YOU
AT EVERY STEP**

thebraintumourcharity.org

Registered office: Hartshead House, 61-65 Victoria Road,
Farnborough, Hampshire GU14 7PA.

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