Diagnostic test accuracy and cost-effectiveness of tests for codeletion of chromosomal arms 1p and 19q in people with glioma (Review)

McAleenan A, Jones HE, Kernohan A, Robinson T, Schmidt L, Dawson S, Kelly C, Spencer Leal E, Faulkner CL, Palmer A, Wragg C, Jefferies S, Brandner S, Vale L, Higgins JPT, Kurian KM

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Diagnostic test accuracy and cost-effectiveness of tests for codeletion of chromosomal arms 1p and 19q in people with glioma

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A B S T R A C T

Background

Complete deletion of both the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q), known as 1p/19q codeletion, is a mutation that can occur in gliomas. It occurs in a type of glioma known as oligodendroglioma and its higher grade counterpart known as anaplastic oligodendroglioma. Detection of 1p/19q codeletion in gliomas is important because, together with another mutation in an enzyme known as isocitrate dehydrogenase, it is needed to make the diagnosis of an oligodendroglioma. Presence of 1p/19q codeletion also informs patient prognosis and prediction of the best drug treatment. The main two tests in use are fluorescent in situ hybridisation (FISH) and polymerase chain reaction (PCR)-based loss of heterozygosity (LOH) assays (also known as PCR-based short tandem repeat or microsatellite analysis). Many other tests are available. None of the tests is perfect, although PCR-based LOH is expected to have very high sensitivity.

Objectives

To estimate the sensitivity and specificity and cost-effectiveness of different deoxyribonucleic acid (DNA)-based techniques for determining 1p/19q codeletion status in glioma.

Search methods

We searched MEDLINE, Embase and BIOSIS up to July 2019. There were no restrictions based on language or date of publication. We sought economic evaluation studies from the results of this search and using the National Health Service Economic Evaluation Database.

Selection criteria

We included cross-sectional studies in adults with glioma or any subtype of glioma, presenting raw data or cross-tabulations of two or more DNA-based tests for 1p/19q codeletion. We also sought economic evaluations of these tests.

Data collection and analysis

We followed procedures outlined in the *Cochrane Handbook for Diagnostic Test Accuracy Reviews*. Two review authors independently screened titles/abstracts/full texts, performed data extraction, and undertook applicability and risk of bias assessments using QUADAS-2. Meta-analyses used the hierarchical summary ROC model to estimate and compare test accuracy. We used FISH and PCR-based LOH as alternate reference standards to examine how tests compared with those in common use, and conducted a latent class analysis comparing FISH and PCR-based LOH. We constructed an economic model to evaluate cost-effectiveness.

Main results

We included 53 studies examining: PCR-based LOH, FISH, single nucleotide polymorphism (SNP) array, next-generation sequencing (NGS), comparative genomic hybridisation (CGH), array comparative genomic hybridisation (aCGH), multiplex-ligation-dependent probe amplification (MLPA), real-time PCR, chromogenic in situ hybridisation (CISH), mass spectrometry (MS), restriction fragment length polymorphism (RFLP) analysis, G-banding, methylation array and NanoString. Risk of bias was low for only one study; most gave us concerns about how patients were selected or about missing data. We had applicability concerns about many of the studies because only patients with specific subtypes of glioma were included. 1520 participants contributed to analyses using FISH as the reference, 1304 participants to analyses involving PCR-based LOH as the reference and 262 participants to analyses of comparisons between methods from studies not including FISH or PCR-based LOH.

Most evidence was available for comparison of FISH with PCR-based LOH (15 studies, 915 participants): PCR-based LOH detected 94% of FISH-determined codeletions (95% credible interval (CrI) 83% to 98%) and FISH detected 91% of codeletions determined by PCR-based LOH (CrI 78% to 97%). Of tumours determined not to have a deletion by FISH, 94% (CrI 87% to 98%) had a deletion detected by PCR-based LOH, and of those determined not to have a deletion by PCR-based LOH, 96% (CrI 90% to 99%) had a deletion detected by FISH. The latent class analysis suggested that PCR-based LOH may be slightly more accurate than FISH. Most other techniques appeared to have high sensitivity (i.e. produced few false-negative results) for detection of 1p/19q codeletion when either FISH or PCR-based LOH was considered as the reference standard, although there was limited evidence. There was some indication of differences in specificity (false-positive rate) with some techniques. Both NGS and SNP array had high specificity when considered against FISH as the reference standard (NGS: 6 studies, 243 participants; SNP: 6 studies, 111 participants), although we rated certainty in the evidence as low or very low. NGS and SNP array also had high specificity when PCR-based LOH was considered the reference standard, although with much more uncertainty as these results were based on fewer studies (just one study with 49 participants for NGS and two studies with 33 participants for SNP array).

G-banding had low sensitivity and specificity when PCR-based LOH was the reference standard. Although MS had very high sensitivity and specificity when both FISH and PCR-based LOH were considered the reference standard, these results were based on only one study with a small number of participants. Real-time PCR also showed high specificity with FISH as a reference standard, although there were only two studies including 40 participants.

We found no relevant economic evaluations. Our economic model using FISH as the reference standard suggested that the resource-optimising test depends on which measure of diagnostic accuracy is most important. With FISH as the reference standard, MLPA is likely to be cost-effective if society was willing to pay GBP 1000 or less for a true positive detected. However, as the value placed on a true positive increased, CISH was most cost-effective. Findings differed when the outcome measure changed to either true negative detected or correct diagnosis. When PCR-based LOH was used as the reference standard, MLPA was likely to be cost-effective for all measures of diagnostic accuracy at lower threshold values for willingness to pay. However, as the threshold values increased, none of the tests were clearly more likely to be considered cost-effective.

Authors' conclusions

In our review, most techniques (except G-banding) appeared to have good sensitivity (few false negatives) for detection of 1p/19q codeletions in glioma against both FISH and PCR-based LOH as a reference standard. However, we judged the certainty of the evidence low or very low for all the tests. There are possible differences in specificity, with both NGS and SNP array having high specificity (fewer false positives) for 1p/19q codeletion when considered against FISH as the reference standard. The economic analysis should be interpreted with caution due to the small number of studies.

P L A I N   L A N G U A G E   S U M M A R Y

Comparing different methods of determining whether gliomas are missing arms 1p and 19q of the chromosomes

Why is improving the detection of 1p/19q codeletion in glioma important?

Gliomas are a type of brain tumour (cancer). There are different types of glioma, with different changes in their genetic material. One of the possible genetic changes is the loss of parts of two of our 23 chromosomes. When both a specific part of chromosome 1 and a specific part of chromosome 19 are missing, it is known as '1p/19q codeletion'. 1p/19q codeletion is used to diagnose a glioma known as an oligodendroglioma. Presence of 1p/19q codeletion can also tell us how long a patient with a glioma may survive and which is the best medicine to treat that patient.

What is the aim of this review?

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We wanted to find out which is the most accurate and cost-effective way to identify 1p/19q codeletion in gliomas.

What is studied in the review?

The review examined and compared all methods to detect 1p/19q codeletion that are based on the deoxyribonucleic acid (DNA, which contains the information for an organism to develop, survive and reproduce) of the tumour. These include tests known as FISH and CISH, which are performed directly on tumour tissue and a number of other tests that are based on DNA extracted from the tumour tissue including: PCR-based LOH, real-time PCR, MLPA, SNP array, CGH array and NGS. None of these tests is perfect, so there is no 'gold standard' against which to compare them. The two most commonly used tests (FISH and PCR-based LOH) were used as the best available reference tests against which to examine the others.

What are the main results of the review?

We found 53 studies. Most tests were good at identifying instances of 1p/19q codeletion (meaning they were tests with good 'sensitivity') that had been identified by either of the two common tests. However, there were some differences in how well the tests were able to rule out 1p/19q codeletion when it did not seem to be present (the 'specificity' of the test). NGS and SNP arrays were better at this (i.e. having fewer 'false-positives' results) when considered against FISH as the reference test. The cost per correct diagnosis was lowest for MLPA, although this was not a firm finding because the amount of evidence was small.

How reliable are results of the studies in this review?

Our certainty in the evidence was low or very low, because there were few studies for most of the tests and there were limitations to almost all the studies. Similarly, the economic analysis must be interpreted with caution due to the relatively small number of studies.

To whom do the results of this review apply?

The ways in which the tests were performed were thought to be representative of how they would be performed in practice. However, many of the studies included people with specific types of gliomas, so the results might not be representative of all people with gliomas.

What are the implications of this review?

The limited evidence suggests that currently used techniques show good sensitivity for detection of 1p/19q codeletion. NGS and SNP arrays may have higher specificity when FISH is the reference standard, but this comes at greater cost per test.

How up-to-date is this review?

The latest search for studies took place in August 2019.

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SUMMARY OF FINDINGS

Summary of findings 1.   Accuracy of tests for 1p/19q codeletion in people with glioma: assuming FISH is the reference standard

Review question: what is the best method to detect 1p/19q codeletion in gliomas?

Patients/population: adults with glioma

Role: 1p/19q status is used for diagnosis, to inform treatment decisions and to give information on prognosis (survival)

Index tests: any test

Threshold for index tests: any threshold

Reference standards: FISH

Studies: cross-sectional studies

Setting: any setting; gliomas are typically diagnosed by a neuropathologist

Test	Number of participants (studies)	Accuracy		Overall prevalence (95% CrI)	Interpretation: **a**ssuming 31 people out of 100 with glioma will have a FISH-detected 1p/19q codeletion and 69 people without the codeletion.	Certainty of the evidence (GRADE)
		Sensitivity (95% CrI)	Specificity (95% CrI)			
CISH	38 (1)	1.00 (0.84 to 1.00)	0.92 (0.33 to 1.00)	0.31	31 people will be given the correct positive result and 0 people will be given a false-negative result. 63 people will be given a correct negative result and 6 people will be given a false-positive result.	**Low-certainty evidence:** downgraded due to high imprecision.
PCR-based LOH	915 (15)	0.94 (0.83 to 0.98)	0.94 (0.87 to 0.98)	0.31	29 people will be given the correct positive result and 2 people will be given a false-negative result. 65 people will be given a correct negative result and 4 people will be given a false-positive result.	**Low-certainty evidence:** downgraded due to risk of bias and indirectness.
Real-time PCR	40 (2)	0.81 (0.20 to 0.99)	1.00 (0.95 to 1.00)	0.31	25 people will be given the correct positive result and 6 people will be given a false-negative result. 69 people will be given a correct negative result and 0 people will be given a false-positive result.	**Very low-certainty evidence:** downgraded due to high risk of bias, high imprecision and indirectness.
MLPA	33 (2)	0.96 (0.44 to 1.00)	0.68 (0.20 to 0.95)	0.31	30 people will be given the correct positive result and 1 person will be given a false-negative result.	**Very low-certainty evidence:** downgraded due to risk of bias,

					47 people will be given a correct negative result and 22 people will be given a false-positive result.	high imprecision and indirectness.
CGH	75 (4)	0.95 (0.59 to 1.00)	0.99 (0.90 to 1.00)	0.31	29 people will be given the correct positive result and 2 people will be given a false-negative result.	**Low-certainty evidence:** downgraded due to risk of bias and imprecision.
					68 people will be given a correct negative result and 1 person will be given a false-positive result.	
aCGH	39 (3)	1.00 (0.89 to 1.00)	0.91 (0.55 to 0.99)	0.31	31 people will be given the correct positive result and 0 people will be given a false-negative result.	**Very low-certainty evidence:** downgraded due to risk of bias, imprecision and indirectness.
					63 people will be given a correct negative result and 6 people will be given a false-positive result.	
SNP array	111 (6)	0.90 (0.57 to 0.99)	0.97 (0.84 to 1.00)	0.31	28 people will be given the correct positive result and 3 people will be given a false-negative result.	**Very low-certainty evidence:** downgraded due to risk of bias, imprecision and indirectness.
					67 people will be given a correct negative result and 2 people will be given a false-positive result.	
NGS	243 (6)	0.94 (0.75 to 0.99)	1.00 (0.99 to 1.00)	0.31	29 people will be given the correct positive result and 2 people will be given a false-negative result.	**Low-certainty evidence:** downgraded due to risk of bias and indirectness.
					69 people will be given a correct negative result and 0 people will be given a false-positive result.	
MS	10 (1)	1.00 (0.60 to 1.00)	1.00 (0.70 to 1.00)	0.31	31 people will be given the correct positive result and 0 people will be given a false-negative result.	**Very low certainty evidence:** downgraded due to high risk of bias and imprecision.
					69 people will be given a correct negative result and 0 people will be given a false-positive result.	
NanoString	16 (1)	0.85 (0.11 to 1.00)	0.80 (0.10 to 1.00)	0.31	26 people will be given the correct positive result and 5 people will be given a false-negative result.	**Very low certainty evidence:** downgraded due to high risk of bias and high imprecision.
					55 people will be given a correct negative result and 14 people will be given a false-positive result.	

aCGH: array comparative genomic hybridisation; CGH: comparative genomic hybridisation; CrI: credible interval; CISH: chromogenic in situ hybridisation; FISH: fluorescent in situ hybridisation; LOH: loss of heterozygosity; MLPA: multiplex-ligation-dependent probe amplification; MS: mass spectrometry; NGS: next-generation sequencing; PCR: polymerase chain reaction; SNP: single nucleotide polymorphism.

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Summary of findings 2.   Accuracy of tests for 1p/19q codeletion in people with glioma: assuming PCR-based LOH is the reference standard

Review question: what is the best method to detect 1p/19q codeletion in gliomas?

Patients/population: adults with glioma

Role: 1p/19q status is used for diagnosis, to inform treatment decisions and to give information on prognosis (survival)

Index tests: any test

Threshold for index tests: any threshold

Reference standards: PCR-based LOH

Studies: cross-sectional studies

Setting: any setting; gliomas are typically diagnosed by a neuropathologist

Test	Number of participants (studies)	Accuracy		Overall prevalence (95% CrI)	Interpretation: assuming 31 people out of 100 with glioma will have a PCR-detected 1p/19q codeletion and 69 people without the codeletion	Certainty of the evidence (GRADE)
		Sensitivity (95% CrI)	Specificity (95% CrI)			
FISH	915 (15)	0.91 (0.78 to 0.97)	0.96 (0.90 to 0.99)	0.31	28 people will be given the correct positive result and 3 people will be given a false-negative result. 66 people will be given a correct negative result and 3 people will be given a false-positive result.	**Low-certainty evidence:** downgraded due to risk of bias and indirectness.
Real-time PCR	10 (1)	1.00 (0.77 to 1.00)	NA	0.31	31 people will be given the correct positive result and 0 people will be given a false-negative result. Results are not provided for those without the codeletion.	**Very low-certainty evidence:** downgraded due to risk of bias, imprecision and indirectness.
MLPA	18 (1)	1.00 (0.74 to 1.00)	1.00 (0.83 to 1.00)	0.31	31 people will be given the correct positive result and 0 people will be given a false-negative result. 69 people will be given a correct negative result and 0 people will be given a false-positive result.	**Very low-certainty evidence:** downgraded due to high risk of bias, imprecision and indirectness.
CGH	151 (6)	0.94 (0.74 to 0.99)	0.98 (0.91 to 1.00)	0.31	29 people will be given the correct positive result and 2 people will be given a false-negative result. 68 people will be given a correct negative result and 1 people will be given a false-positive result.	**Low-certainty evidence:** downgraded due to risk of bias and indirectness.

Test	N (studies)	Sensitivity	Specificity	Prevalence	Natural frequencies	Certainty
aCGH	57 (4)	1.00 (0.97 to 1.00)	0.96 (0.75 to 1.00)	0.31	31 people will be given the correct positive result and 0 people will be given a false-negative result. 66 people will be given a correct negative result and 3 people will be given a false-positive result.	**Low-certainty evidence:** downgraded due to high risk of bias.
SNP array	33 (2)	0.97 (0.50 to 1.00)	1.00 (0.92 to 1.00)	0.31	30 people will be given the correct positive result and 1 person will be given a false-negative result. 69 people will be given a correct negative result and 0 people will be given a false-positive result.	**Very low-certainty evidence:** downgraded due to risk of bias and high imprecision.
NGS	49 (1)	1.00 (0.86 to 1.00)	0.98 (0.64 to 1.00)	0.31	31 people will be given the correct positive result and 0 people will be given a false-negative result. 68 people will be given a correct negative result and 1 people will be given a false-positive result.	**Very low-certainty evidence:** downgraded due to risk of bias, imprecision and indirectness.
MS	50 (1)	1.00 (0.85 to 1.00)	1.00 (0.94 to 1.00)	0.31	31 people will be given the correct positive result and 0 people will be given a false-negative result. 69 people will be given a correct negative result and 0 people will be given a false-positive result.	**Very low-certainty evidence:** downgraded due to risk of bias and imprecision.
G-banding	21 (1)	0.00 (0.00 to 0.20)	1.00 (0.78 to 1.00)	0.31	0 people will be given the correct positive result and 31 people will be given a false-negative result. 69 people will be given a correct negative result and 0 people will be given a false-positive result.	**Very low-certainty evidence:** downgraded due to high risk of bias, high imprecision and indirectness.

aCGH: array comparative genomic hybridisation; CGH: comparative genomic hybridisation; CrI: credible interval; CISH: chromogenic in situ hybridisation; FISH: fluorescent in situ hybridisation; LOH: loss of heterozygosity; MLPA: multiplex-ligation-dependent probe amplification; MS: mass spectrometry; NGS: next-generation sequencing; PCR: polymerase chain reaction; SNP: single nucleotide polymorphism.

BACKGROUND

Gliomas are a group of brain tumours arising within the central nervous system. Different types of gliomas can show different changes in genetic information. Some of these genetic changes can serve as diagnostic, prognostic and predictive biomarkers. Diagnostic biomarkers help to establish which specific type of glioma is present. Prognostic biomarkers give information about the likely clinical outcome or prognosis for a patient with glioma, and predictive biomarkers indicate the likelihood of response to a particular treatment. One of the possible genetic changes that may be present is the loss of parts of chromosome 1 and chromosome 19, known as codeletion of chromosomal arms 1p and 19q. 1p/19q codeletion is most commonly found in a type of glioma called an oligodendroglioma and is a diagnostic biomarker for this glioma. In addition, 1p/19q codeletion acts as a prognostic and predictive biomarker for glioma because it informs patient prognosis and treatment strategy.

In this review, we aimed to determine the most accurate way of testing whether a glioma has codeletion of chromosomal arms 1p and 19q. There are costs to patients, their families, health services and society in general associated with glioma. One review of studies found that the estimated cost of clinical care for a patient with glioma ranged between USD 4755 and USD 42,907 (reported costs were all converted into 2013 US dollars using an exchange rate based on purchasing power parities) (Messali 2014). These studies were carried out before particular chemotherapies became the standard of care for different types of glioma, which would also increase the treatment costs. In addition to an integrated full review of economic evaluations, this review features an economic decision model as a further level of evidence synthesis. The use of an economic decision model allows consideration of the resource implications of tests for diagnosis of codeletion of chromosomal arms 1p and 19q. We used this approach because we anticipated that we would identify limited economic evidence for inclusion in the review.

Target condition being diagnosed

Gliomas are thought to arise from stem or progenitor cells in the central nervous system and they share some features with glial cells. Glial cells have several functions including supporting and insulating neurons. Age-adjusted incidence rates for all gliomas (ICD-O-3 morphology codes 9380–9480) range from 4.67 to 5.73 per 100,000 persons, with varied survival rates (Ostrom 2014). One review of population-based studies found that the lowest grade glioma, called pilocytic astrocytoma (World Health Organization (WHO) grade I), has the highest five-year relative survival rate at 57.3% to 97.3%; while the highest grade glioma, glioblastoma (WHO grade IV), has the poorest survival with only 0.1% to 8.9% of people surviving five years after diagnosis (Ostrom 2014).

Loss of a chromosome arm can be complete (where the whole chromosome arm is lost) or partial (where only part of the chromosomal arm is lost). Complete deletion of both the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q) (1p/19q codeletion) is a mutation that can occur in gliomas. The codeletion is thought to be an early event in the development of cancer (Pinkham 2015), that is due to an unbalanced whole-arm translocation between chromosomes 1 and 19 with the loss of the resulting hybrid chromosome (Griffin 2006; Jenkins 2006). As described below, the 1p/19q codeletion is a diagnostic, prognostic

and predictive biomarker in glioma. We are not interested in partial loss of 1p or 19q (or both), as these partial deletions do not share the diagnostic, prognostic and predictive abilities of the complete 1p/19q codeletion.

According to the WHO, the diagnosis of oligodendroglioma (a type of glioma) and anaplastic (high-grade) oligodendroglioma requires the demonstration of both an isocitrate dehydrogenase (IDH) gene family mutation and 1p/19q codeletion (Louis 2016).

One systematic review and meta-analysis of the prognostic value of chromosomal 1p/19q codeletion in low-grade (WHO grade II) and high-grade/anaplastic (WHO grade III) tumours found a summary hazard ratio (HR) for mortality of 0.28 (95% confidence interval (CI) 0.13 to 0.62; 9 studies) favouring 1p/19q codeletion after adjusting for age, extent of resection, IDH-1 mutation and type of therapy (Hu 2016). Another systematic review and meta-analysis that evaluated the association between codeletion (versus no codeletion) of 1p/19q and overall survival among people with different grades and types of gliomas found that 1p/19q codeletion was associated with increased overall survival (HR 0.43, 95% CI 0.35 to 0.53; 14 studies) (Zhao 2014). There were similar results in both low-grade tumours (HR 0.45, 95% CI 0.30 to 0.68; 5 studies) and high-grade gliomas (HR 0.41, 95% CI 0.31 to 0.53; 6 studies). This is akin to the results also seen for astrocytic tumours (HR 0.52, 95% CI 0.36 to 0.75; 3 studies) and oligodendroglial tumours (HR 0.41, 95% CI 0.30 to 0.56; 9 studies) (Zhao 2014). This review also observed no evidence of a difference in the HR for overall survival between studies using two different techniques (polymerase chain reaction (PCR)-based loss of heterozygosity (LOH) and fluorescence in situ hybridisation (FISH)) to assess the status of chromosomal arms 1p and 19q (Zhao 2014).

1p/19q codeletion predicts response to chemotherapy in anaplastic oligodendrogliomas. The European Organisation for Research and Treatment of Cancer (EORTC) study 26951 was a phase III trial comparing radiotherapy (RT) with RT plus adjuvant chemotherapy with procarbazine, lomustine and vincristine (PCV) in people with newly diagnosed anaplastic oligodendroglioma (van den Bent 2013). An exploratory analysis of long-term follow-up found a trend towards increased survival for people with 1p/19q codeletion from adjuvant PCV. In people with 1p/19q codeletion, fewer than half died during follow-up in the RT plus PCV group (and therefore median overall survival was not reached) versus a median survival of 112 months in the RT group (HR 0.56, 95% CI 0.31 to 1.03) (van den Bent 2013). In people with non-codeleted 1p/19q, the median overall survival was 25 months in the RT plus PCV group versus 21 months in the RT group (HR 0.83, 95% CI 0.62 to 1.10) (van den Bent 2013). Similarly, long-term follow-up of the Radiation Therapy Oncology Group (RTOG) study 9402, which also compared PCV plus RT with RT alone in people with pure and mixed anaplastic oligodendrogliomas, found that the median survival of those with codeleted tumours treated with PCV plus RT was twice that of people receiving RT (14.7 years with PCV plus RT versus 7.3 years with RT; HR 0.59, 95% CI 0.37 to 0.95; P = 0.03) (Cairncross 2013). For people with non-codeleted tumours, there was no evidence of a difference in median survival by treatment arm (2.6 years with PCV plus RT versus 2.7 years with RT; HR 0.85, 95% CI 0.58 to 1.23; P = 0.39) (Cairncross 2013).

1p/19q codeletion 1p can be absolute (i.e. loss in the presence of the normal number of other chromosomes), or relative if it occurs in the presence of polysomy (when cells contain at least

one more copy of a chromosome than normal) or polyploidy (when cells contain more than two sets of chromosomes). Several studies have suggested that people with relative 1p/19q codeletions (deletions in the presence of polysomy or polyploidy) have a worse prognosis (progression-free survival or overall survival) than people with absolute 1p/19q codeletions, with some studies suggesting that prognosis in people with relative codeletions may be similar to that of people with no codeletion (Chamberlain 2015; Jiang 2014; Ren 2013; Snuderl 2009). In all these studies, classification of polysomy occurred when more than 30% of nuclei had more than two 1q and 19p signals, as assessed by FISH. Although there are limitations to these studies, for example treatment was not standardised, these findings suggest that diagnosing absolute deletions is more important. In this review, our interest was primarily in detection of absolute deletions. We were also interested in diagnosing situations where one copy of 1p/19q had been lost and the other copy duplicated (also termed copy-neutral LOH). Combinations of chromosomal deletions in oligodendrogliomas and the corresponding signals in FISH are presented in a schematic representation in Figure 1.

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Figure 1. Combinations of chromosomal deletions in oligodendrogliomas and the corresponding signals in fluorescent in situ hybridisation (FISH) in a schematic representation. In all parts of the figure, chromosome 1 and chromosome 19 are presented in separate frames to visualise the combination of FISH signals. The 1p probes and the 19q probes are red, and the reference probes (1q and 19p) are green. The approximate labelling sites are indicated in the chromosomal schematics. An unrelated chromosome (2) is also shown. Below each frame a schematic representation of the nuclear hybridisation signals as they appear on FISH images. (A): normal cell with diploid set of chromosomes. There are two red signals each, for chromosomal arms 1p and 19q, as well as two green signals each for chromosomal arms 1q and 19p. (B): the most common constellation in oligodendrogliomas with absolute 1p/19q codeletion in a diploid set of chromosomes. Loss of one red signal in chromosome 1p and in 19q and two green signals for each 1q and 19p. (C): relative codeletion with example of polysomy of chromosome 19 and chromosome 2. (D): 1p/19q codeletion in tetraploid cells, resulting in two red and four green signals for both, 1p and 19q tests. (E): complex deletion patterns can be found in a small proportion of oligodendrogliomas, often associated

with anaplastic histological types. In this example, there are diploid cells (left, 30%), triploid cells (centre, 30%) and tetraploid cells (right, 40%).

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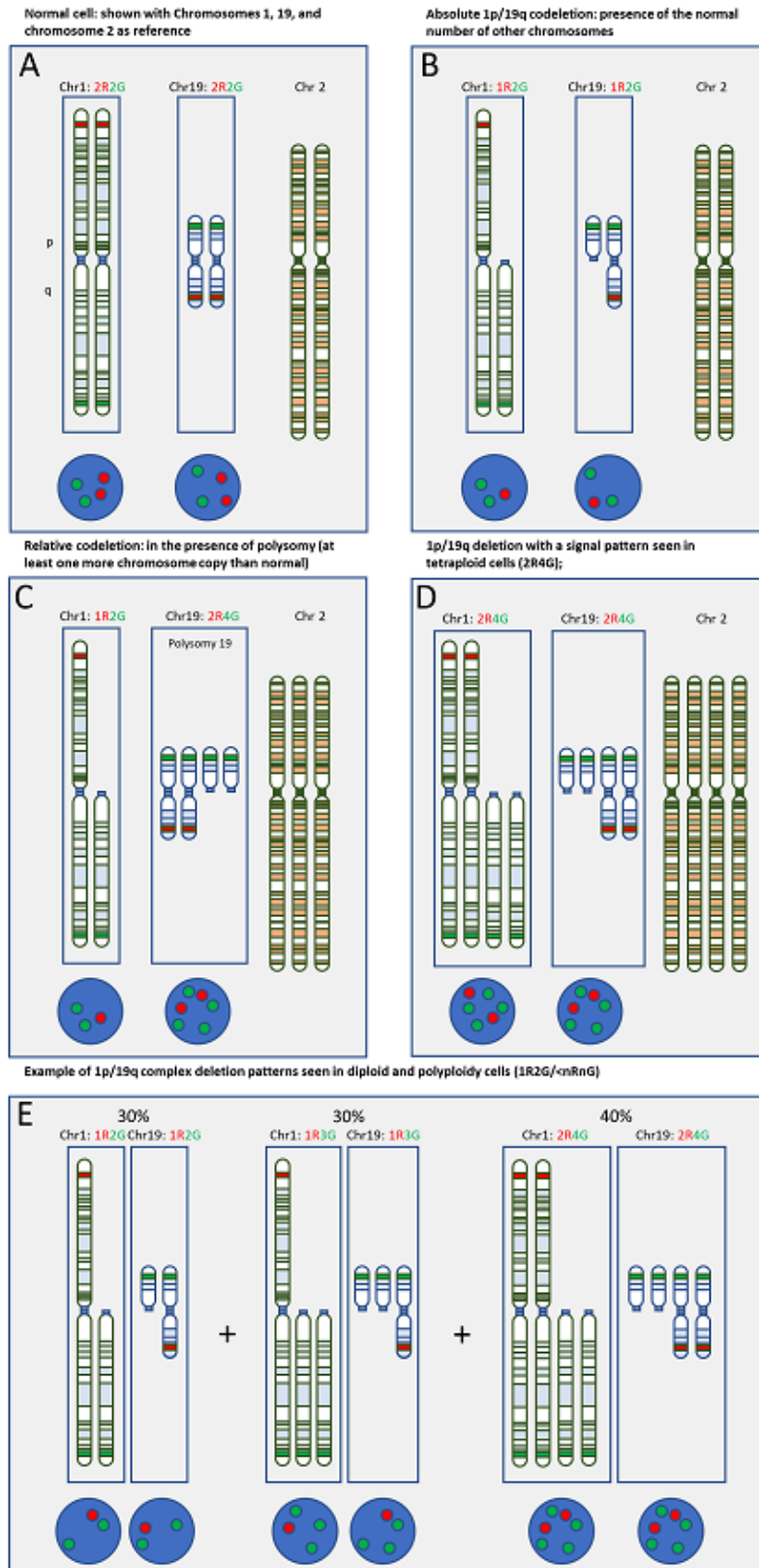
Index test(s)

This review assessed the sensitivity and specificity of any deoxyribonucleic acid (DNA)-based techniques that can be used on tumour tissue to directly evaluate 1p/19q codeletion status. These include the following.

- Fluorescent in situ hybridisation (FISH).
- Chromogenic in situ hybridisation (CISH).
- PCR-based LOH assays (also known as PCR-based – short tandem repeat or microsatellite analysis).
- Restriction fragment length polymorphism (RFLP) analysis.
- Comparative quantitative PCR (a form of real-time PCR).
- Multiplex-ligation-dependent probe amplification (MLPA).
- Comparative genomic hybridisation (CGH).
- Array comparative genomic hybridisation (aCGH).
- Single nucleotide polymorphism (SNP) arrays.
- Methylation arrays.
- Next-generation sequencing (NGS).

These techniques are briefly described in Table 1. There is no perfect (100% sensitive, 100% specific) 'gold standard' test for 1p/19q codeletion status: each of the above tests could theoretically produce false-positive or false-negative (or both) results, as described in Table 2.

Clinical pathway

Prior test(s)

Before testing for 1p/19q codeletion status, tumours undergo histological assessment. 1p/19q status is determined in tumours with histological appearances of gliomas, typically with morphological appearances suggestive of oligodendroglioma and usually after an initial set of histological special stains (immunohistochemistry) assessing the status of the most common IDH mutation (R132H) and of ATRX expression. Within IDH-mutation tumours, 1p/19q codeletion tumours have different prognosis and different treatments, so 1p/19q deletions are only relevant for diagnosis of oligodendroglioma if there is IDH mutation (although there are very rare exceptions to this).

Role of index test(s)

As described previously, the codeletion has diagnostic, prognostic and predictive abilities in glioma. The results of testing for 1p/19q status are used for diagnosis, to inform treatment decisions and to give information on prognosis (survival). It is usual for testing to be done once, using one technique. Patients may be misdiagnosed, are likely to receive suboptimal treatments (although there is no good evidence on what the effect of this will be), and receive inaccurate prognostic information if given false-positive or false-negative results for 1p/19q status.

Alternative test(s)

All DNA-based techniques that are used to determine 1p/19q status in tumour tissue were eligible.

Rationale

European guidelines recommend that 1p/19q status is evaluated to support a diagnosis of oligodendroglioma and for prognosis, and that treatment decisions are based on the 1p/19q status (Stupp 2014; Weller 2017). WHO guidelines required the demonstration of both an IDH mutation and 1p/19q codeletion for the diagnosis of oligodendroglioma and anaplastic oligodendroglioma (Louis 2016). Current guidance from the National Institute for Health and Care Excellence (NICE) recommend testing 1p/19q codeletion to identify oligodendrogliomas, and the adjuvant chemotherapeutic recommended after surgery for people with grade III glioma varies according to 1p/19q status (NICE 2018).

cIMPACT-NOW 2 (the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy) guidance has suggested that in the setting of a diffuse astrocytic-appearing WHO grade II or III glioma that has IDH mutation as well as loss of ATRX nuclear expression or strong, diffuse p53 immunopositivity, a diagnosis of diffuse astrocytoma, IDH-mutant or anaplastic astrocytoma, IDH-mutant can be rendered in the absence of 1p/19q testing (Louis 2018). However, for the diagnosis of oligodendroglioma and anaplastic oligodendroglioma assessment of both 1p/19q codeletion and IDH mutation is still required.

There are several different methods for determining 1p/19q status and no clear consensus regarding the optimal method. The two most common methods for routine diagnostic use are FISH- and PCR-based LOH assays (Woehrer 2015). In the 2017 UK Cytogenomic External Quality Assessment Service (CEQAS) report, of the 35 enrolled laboratories, 25 laboratories used FISH, one laboratory used MLPA, four laboratories used arrays and one laboratory used quantitative PCR.

This review should go some way to answering the question "Do molecular subtyping techniques improve treatment selection, prediction and prognostication in people with brain and spinal cord tumours?", one of the top 10 topics identified by the James Lind Alliance Neuro-Oncology Priority Setting Partnership (James Lind Alliance). The National Cancer Research Institute Brain Clinical Studies Group has identified this as an area for future research.

The final element of the review was to consider the costs and cost-effectiveness of alternative methods of assessing 1p/19q status. Each method of 1p/19q assessment incurs costs such as staff costs, laboratory costs and clinic costs.

OBJECTIVES

To estimate the sensitivity and specificity and cost-effectiveness of different deoxyribonucleic acid (DNA)-based techniques for determining 1p/19q codeletion status in glioma.

Secondary objectives

If sufficient studies are identified, we aimed to break down each technique by relevant features, for example the region analysed/ probes used and the cut-off used to classify 1p/19q status.

We further aimed to critically appraise and summarise current evidence on the resource use, costs and cost-effectiveness of techniques for determining 1p/19q status in gliomas (conduct a full integrated review of economic evidence) and assess the cost-effectiveness of the different approaches of determining 1p/19q status using a decision model.

METHODS

Criteria for considering studies for this review

Types of studies

Types of studies for diagnostic test accuracy review

Cross-sectional studies that used two or more DNA-based tests to assess 1p/19q status in tumour tissue from the same set of people.

To be included, studies needed to present either raw data or classified results for patients for at least two DNA-based tests. Studies that reported only on concordance of test results were excluded. Studies with data for just one person were excluded.

Types of studies for the full integrated review of economic evidence

We sought economic evaluations (cost-effectiveness analyses, cost-utility analyses and cost-benefit analyses) conducted alongside any study designs or as part of a modelling exercise.

Participants

Adults aged 18 years or over with glioma or any subtype of glioma, which would typically be diagnosed by a neuropathologist.

Studies of people recruited because they were all determined by a specific technique to be 1p/19q codeleted (or all 1p/19q non-codeleted) were excluded.

Index tests

Any DNA-based technique that is used to determine 1p/19q status in tumour tissue.

Studies that assessed 1p/19q status by immunohistochemistry were excluded.

Studies that assessed 1p/19q status from blood samples or by imaging (i.e. magnetic resonance imagining, computed tomography, positron emission tomography) were excluded.

Target conditions

Absolute 1p/19q codeletion (1p/19q codeletion in the absence of polysomy).

Reference standards

As described in Table 2, each test can potentially generate false-positive and false-negative results. As such, there is no true 'gold standard' reference test. However, in order to estimate the sensitivity and specificity of each test, we considered two alternative reference standards. These were selected as the two tests that are most commonly used so are most familiar to people considering using alternative tests.

- Using FISH as the reference standard, which can be interpreted as assuming that FISH has 100% sensitivity and 100% specificity.
- Using PCR-based LOH assays as the reference standard, which can be interpreted as assuming that PCR-based LOH assays have 100% sensitivity and 100% specificity.
- No reference standard: using latent class methodology, it is theoretically possible to estimate the sensitivity and specificity of a number of tests without making the strong assumption that

any one test is 100% sensitive and 100% specific, although other strong assumptions are required. Further details are provided in the 'Statistical analysis and data synthesis for the diagnostic test accuracy review' section.

Use of FISH or PCR-based LOH assays was not an eligibility criterion: all studies that used two or more tests to assess 1p/19q status in tumour tissue from the same set of people were included in the review.

Search methods for identification of studies

Electronic searches

Electronic searches for the diagnostic test accuracy review

We searched MEDLINE Ovid (from 1946 to 31 July 2019), Embase Ovid (from 1974 to 2019 week 30) and BIOSIS Citation Index (from 1969 to 1 August 2019). The search strategies are given in Appendix 1.

We also searched for studies available in PubMed that were not available in MEDLINE using the syntax 'pubmednotmedline[sb]' (all years).

There were no restrictions based on language or date of publication.

Electronic searches for the full integrated review of economic evidence

We screened the search in MEDLINE and Embase in Appendix 1 for suitable economic evaluation studies at the same time as screening for study inclusion in the diagnostic test accuracy (DTA) review. In addition, we searched the NHS Economic Evaluation Database (EED) up to the end of March 2015, when the last records were added to that database. This search used key individual clinical terms from the main search strategy (Appendix 1), both alone and in combination, to identify suitable economic evaluations.

Searching other resources

Searching other resources for the diagnostic test accuracy review

We searched Open Grey (www.opengrey.eu/, all available years to 1 August 2019) using the free-text terms from our MEDLINE search ((("chromosome 1" OR 1p) AND ("chromosome 19" OR 19q)) OR (1p19q OR "1p/19q" OR (1p* NEAR/3 19q*))) AND (glioma* OR astrocytoma* OR astroblastoma* OR ependymoma* OR subependymoma* OR oligodendroglioma* OR oligoastrocytoma* OR pleomorphic xanthoastrocytoma* OR glioblastoma* OR GBM* OR ganglioglioma* OR gliosarcoma* OR gangliocytoma* OR ((glial* OR glioneuronal* OR brain*) AND (tumor* OR tumour* OR cancer* OR neoplasm*))).

We searched for relevant material in dissertations and theses using ProQuest Dissertations & Theses Global (search.proquest.com/pqdtglobal/dissertations/), using the same strategy as for Open Grey but limiting to all fields except full text (all available years to 1 August 2019). We also searched the Networked Digital Library of Theses and Dissertations (search.ndltd.org/index.php) (all available years to 1 August 2019).

The Society of Neuro-Oncology (SNO) and its partner associations the EANO and The Japan Society of Neuro-Oncology hold meetings

where relevant research may be presented. We searched for abstracts from these meetings and other relevant conferences via the Web of Science Conference Proceedings Citation Index (CPCI-S) (from 1990 to 1 August 2019). We translated the BIOSIS search for CPCI-S as both databases are hosted on Web of Science.

We also searched for any ongoing studies via the WHO International Clinical Trials Registry Platform (ICTRP) (all available years to 1 August 2019). The search strategy is given in Appendix 1.

We examined the reference lists of included studies to identify any additional studies.

We examined results of searches of these other resources for both the DTA and economic components of the review.

Data collection and analysis

Selection of studies

Selection of diagnostic test accuracy studies

Two review authors independently screened titles and abstracts using EPPI-Reviewer 4 or EPPI-Reviewer Web (Beta). In case of disagreement, a third review author independently screened the title and abstract and decided on potential relevance. Full-text articles were then independently screened in duplicate. Disagreements were resolved by consensus, with discussion with a third review author if necessary.

Selection of economic studies

Studies that met the inclusion criteria for DTAs were screened by one review author to assess if any of the clinically relevant studies could possibly meet the economic inclusion criteria. Had any potentially relevant studies been identified they would have been screened by two review authors.

Data extraction and management

Data extraction and management of diagnostic test accuracy studies

Two review authors independently performed data extraction onto a data extraction form split between Excel and EPPI-Reviewer 4/EPPI-Reviewer Web (Beta). Disagreements were resolved by consensus, with discussion with a third review author if necessary. We extracted data on the following items.

Study characteristics

- Author.
- Year.
- Country.
- Whether the study compared two or compared multiple techniques for determining 1p/19q status.

Population characteristics

- Number of participants.
- Population source and setting.
- Inclusion/exclusion criteria.
- Tumour subtype and grade.
- Prior testing.
- Age.
- Gender.

- Karnofsky performance status.
- First diagnosis or recurrent disease.
- Prevalence of 1p/19 codeletion.

Index tests (per test performed)

- Technique.
- Tumour sample type (i.e. formalin-fixed, paraffin-embedded (FFPE) or frozen tissue).
- Region(s) analysed.
- Cut-off/threshold used to determine 1p/19q status.
- Method of determining threshold and whether it was prespecified.

Raw test result data

We extracted the raw data from each individual study as a contingency table of cross-classified test results. For studies comparing two tests, this was a 2 × 2 table. Regardless of whether the study treated one of the tests as a reference standard, overall in the review we did not label results as true positives but rather 'positive on both tests'; not true negatives but rather 'negative on both tests'; not false positives but rather 'positive on test A and negative on test B'; and not false negatives but rather 'negative on test A and positive on test B'. In situations where more than two tests were compared the data formed tables of higher dimensions. For example, if three tests were compared then the table formed was 2 × 2 × 2, that is, eight cells of cross-classified results.

We extracted the researchers' classifications of test results (i.e. we did not attempt to reclassify test results even if raw data were available if the researchers had made classifications). If raw data were presented and classifications had not been made, but thresholds for classification were reported, we used these to classify test results. In situations where classifications were not made, raw data were presented, and the threshold to be used to interpret the raw data were not specified, we applied a threshold ourselves and explain our choices of threshold in the results.

Data extraction and management of economic evaluation studies

We adapted a data extraction form for economic investigations based on the format and guidelines used to produce structured abstracts of economic evaluations for inclusion in the NHS EED to the specific requirements of this review. The following data were to be collected from the economic studies.

- Type of evaluations.
- Sources of effectiveness data.
- Cost data.
- Sources of cost data.
- Sources of outcome valuations.
- Analytical approach.
- Outcome valuations (e.g. utility values).
- Sources of outcome valuations.
- Cost-effectiveness data (e.g. incremental cost-effectiveness ratios (ICER)).
- Analytic approach.

Assessment of methodological quality

Assessment of methodological quality in included diagnostic test accuracy studies

Two review authors independently assessed the applicability and risk of bias of included studies using the QUADAS-2 tool (Whiting 2011). We resolved disagreements by consensus, with discussion with a third review author if necessary. We tailored the tool to our review, and the tailored form of the tool, along with how we judged risk of bias and applicability in each study is described in Appendix 2. We illustrated assessments using the robvis tool (McGuinness 2020).

Assessment of methodological quality in included economic studies

If any relevant economic evaluations were identified then these were to be assessed for bias in two stages. The first stage was to involve assessing the risk of bias from the sources of the DTA effectiveness data. Summary effect sizes from systematic reviews used as data inputs in model-based economic evaluations were to be assessed using the ROBIS tool (Whiting 2016). The second stage was to assess the overall methodological quality of the economic component of the evaluation. Evaluations carried out alongside studies were to be assessed with reference to items included in the CHEERS (Consolidated Health Economic Evaluation Reporting Standards) checklist for reporting (Husereau 2013) and model-based economic evaluations were to be assessed using the NICE methodology checklist (NICE 2014).

Statistical analysis and data synthesis

Statistical analysis and data synthesis for the diagnostic test accuracy review

No diagnostic test is free of errors (Bossuyt 2021); each of the tests can potentially generate false-positive and false-negative results. FISH and PCR-based LOH are the most commonly used tests, so are most familiar to users of the tests. Furthermore, PCR-based LOH is expected to have very high sensitivity (Table 1). We performed three analyses as follows.

- Using FISH as the reference standard.
- Using PCR-based LOH assay as the reference standard.
- Latent class analysis comparing FISH with PCR-based LOH.

For each analysis following the first two strategies, the raw cross-classified test result data from all studies that included the respective reference standard were first relabelled as 'true positive', 'false negative', 'true negative' and 'false negative' (2 × 2 table), based on the reference standard test result. If a study compared more than one test with the reference standard, multiple 2 × 2 tables were derived.

For analysis with each of the respective reference standards, we performed bivariate meta-analyses of the sensitivity and false-positive rate (1 – specificity) of each index test, assuming binomial likelihood for the number of 'true positive' and 'true negative' test results (Chu 2006; Reitsma 2005). This approach allows for heterogeneity in sensitivity and specificity across studies and for between-study correlation in these measures. In our main analyses, we assumed that this between-study correlation and the standard deviation (heterogeneity) parameters were shared (i.e. identical) across tests. This was because there were small numbers of studies

for many of the tests, such that there were few or no data to inform estimation of test-specific correlation and heterogeneity parameters. This unified modelling approach allowed tests to be included in the analysis even if they were only evaluated in a single study: between-study heterogeneity and correlation are allowed for by 'borrowing' these parameters from the data on other tests. The model did not account for within-study correlations arising from a study evaluating two or more tests against the same reference standard.

The bivariate meta-analysis model can be used to produce summary operating points (summary sensitivities and specificities) with 95% confidence or credible regions. Drawing on the equivalence of the bivariate model and the hierarchical summary receiver operating characteristic (HSROC) model (Rutter 2001) in the absence of covariates, the bivariate model can also be used to produce summary receiver operating characteristic curves (Arends 2008; Harbord 2007). We displayed summary operating points for each test with 95% credible intervals (CrIs). By default, we also displayed a 95% credible region (ellipse) and HSROC curve. Plotting of credible ellipses relies on an assumption of approximate bivariate normality of the summary estimates on the logit scale. Where this assumption was clearly violated due to skew, we omitted the summary ellipse and plotted only 95% CrIs. More specifically, ellipses were omitted for tests with summary sensitivity or specificity greater than 99%, which we found to correspond to large skew on the logit scale. HSROC curves are omitted from plots where there was no variability in one of the two accuracy dimensions (sensitivity or specificity) across studies. Prediction ellipses were not plotted.

Because neither FISH nor PCR-based LOH assays are likely to be true 'gold standards', we applied latent class meta-analysis methods to the data for FISH and PCR-based LOH (Chu 2009; Dendukuri 2012; Walter 1999). These methods provide estimates of sensitivity and specificity based on a probabilistic definition of disease state, rather than requiring classification of test results as true positives, false negatives, true negatives and false positives. We assumed multinomial likelihoods for the 2 × 2 table of cross-classified (FISH × PCR-based LOH assay) test results from each study. The four probability parameters are defined as functions of the study-level sensitivity and specificity of each of the two tests and the (unknown) prevalence of 1p/19q codeletion status among people with glioma in the study. We assumed bivariate normal distributions for logit-transformed sensitivity and specificity of each of the two tests across studies.

In latent class analyses, it is important to allow for the possibility that tests are positively correlated within disease states, usually referred to as 'conditional dependence' (Vacek 1985). In addition to 'conditional independence' models, we fitted models that allowed for conditional dependencies through the inclusion of within-study covariance terms (Chu 2009; Dendukuri 2012). These covariance parameters are naturally bound in magnitude by functions of test sensitivity and specificity (Chu 2009; Dendukuri 2012).

The advantage of latent class methods is that they do not make the unrealistic assumption that one of the tests is a gold standard. However, in order to relax this assumption, it is often necessary to make other assumptions. This is to avoid problems with parameter identifiability (Jones 2010), which are introduced by recognising that study-level prevalence and the sensitivity and specificity of the 'reference standard' are all in fact unknown. To reduce the number

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of parameters that need to be estimated, we assumed again that between-study heterogeneity and between-study correlation parameters are shared across tests. We additionally performed an analysis in which we assumed that PCR-based LOH had a sensitivity of at least 95%. PCR-based LOH ought to have a sensitivity close to 100% (no false-negative results) in research contexts. False-negative results on this test can only be obtained if there is excessive contamination of tumour samples with normal tissue. In a research context, we would expect great care to be taken to minimise the risk of contamination with normal tissue. An informative prior distribution (a uniform (0.95, 1.00) prior on sensitivity) was, therefore, used to constrain the sensitivity of this test to be at least 95%.

We had planned to extend the latent class analysis approach to the complex structure of our data (for multiple studies involving different selections of test and different numbers of tests), which would involve novel methodological development of the statistical models. Prioritisation of work in response to the COVID-19 pandemic prevented this development work from happening.

Meta-analysis models were fitted in the Bayesian statistical software WinBUGS (Lunn 2000). For models comparing tests against PCR-based LOH or FISH as a reference standard, vague normal prior distributions were assumed for the mean sensitivity and mean false-positive rate of each test on the logit scale, with a mean of 0 and variance of 100. In latent class models, these were replaced with uniform(0,1) priors on the probability scale, following observed poor mixing of Markov Chain Monte Carlo (MCMC) chains and bimodal posterior distributions with the initial prior distributions.

Standard deviations of logit(sensitivity) and of logit(false-positive rate) across studies were given uniform(0,2) prior distributions. Between-study correlation parameters were given uniform(0,1) priors.

In latent class analyses, each study-specific prevalence parameter was assigned a uniform(0,1) prior. Within-study covariance parameters, representing conditional dependencies between tests, were assumed to be non-negative and were assigned uniform priors across the range zero to their theoretical maximums (Chu 2009; Dendukuri 2012).

In addition to summary operating points, we estimated differences in (summary) sensitivity and in specificity between index tests, which we present with 95% CrIs (Takwoingi 2013).

Investigations of heterogeneity

Investigations of heterogeneity planned for the diagnostic test accuracy review

Where sufficient number of studies assessed the same index test, we planned to investigate the impact of the following index test characteristics and population characteristics.

- Tumour sample type (i.e. FFPE or frozen tissues).
- Region(s) analysed.
- Cut-off/threshold used to determine 1p/19q status.
- Study prevalence of 1p/19q codeletion.
- Tumour subtype and grade.

We did not perform these investigations of heterogeneity due to small numbers of studies for specific tests.

Sensitivity analyses

Sensitivity analyses planned for the diagnostic test accuracy review

For tests evaluated in four or more studies against the same 'reference standard' (FISH or PCR-based LOH), we performed a sensitivity analysis in which accuracy data were meta-analysed separately for each test (i.e. with test-specific between-study heterogeneity and correlation parameters). Prior distributions for these analyses were the same as in the main analysis.

If sufficient data were available, we planned to perform sensitivity analyses by restricting analyses to studies judged not to be at high risk of bias or low applicability.

Assessment of reporting bias

Assessment of reporting bias in the diagnostic test accuracy review

Because of uncertainty about the determinants of publication bias for diagnostic accuracy studies and the inadequacy of tests for detecting funnel plot asymmetry (Deeks 2005), we did not perform tests aimed at detecting publication bias.

Summary of findings for the diagnostic test accuracy review

We presented the summary diagnostic accuracy results for key tests in a summary of findings table, selecting for inclusion the tests that are relevant to current clinical practice (PCR-based LOH, FISH, aCGH, SNP array, NGS, MLPA and real-time PCR). We assessed confidence in each result following the GRADE approach (Guyatt 2008; Schünemann 2008). We rated overall certainty in the evidence for each test as 'high', 'moderate', 'low' or 'very low' considering risk of bias, imprecision, inconsistency, indirectness and publication bias, all of which may lead to downgrading the certainty of the evidence (see Appendix 3).

An issue when using GRADE to rate the certainty of the evidence is that test accuracy is considered a surrogate for outcomes that are important to patients and can only provide indirect evidence of impact on patient-important outcomes (Schünemann 2008). As we described in the Background section, the codeletion has diagnostic, prognostic and predictive abilities in glioma, and all the tests described have the same risk of adverse events associated with the test as they all require some biopsied tumour material. Therefore, we assumed that testing using the most accurate test will improve patient-important outcomes. We used the indirectness domain to downgrade the certainty of the evidence if studies had low applicability to our review question using QUADAS-2. We also considered publication bias, but note that there is uncertainty about the determinants of publication bias for diagnostic accuracy studies and tests for detecting funnel plot asymmetry are inadequate (Deeks 2005).

Full integrated review of economic evidence and economic model

Economic evidence

Characteristics and results of included economic evaluations were to be summarised using additional tables, supplemented by a

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narrative summary to compare and evaluate methods used and principal results between studies. This includes the currency and price year of costs, incremental cost and ICERs. If it were not possible to express costs in this way, then we planned to express these results as the most recent international dollars value using implicit price deflators for gross domestic product (GDP) and GDP Purchasing Power Parities. Where possible, unit cost data were also to be combined and summarised (Shemilt 2019). This review was to be conducted according to current guidance on the use of economics methods in the preparation and maintenance of Cochrane Reviews (Shemilt 2019).

Economic model

We built a decision tree using TreeAge software (TreeAge 2021) to estimate the expected cost of: 1. a true positive diagnosis, 2. a true negative diagnosis and 3. a correct diagnosis for each of the diagnostic tests (Appendix 4). The decision tree was based on the estimated diagnostic accuracies of the testing strategies calculated in the meta-analysis. In terms of cost, the economic model included only those costs associated with carrying out the test. The model adopted a health service perspective and had a very short time horizon covering the diagnostic process only. Thus, the model did not include subsequent patient costs related to further treatment and did not include health outcomes beyond diagnosis.

Estimation of model parameters

Intervention costs were derived from both expert opinion from within the Newcastle upon Tyne Hospitals NHS Foundation Trust based on internal costings and existing literature. This information was provided by G Cuthbert, Consultant Clinical Scientist, Newcastle Genetics Laboratory (21 September 2020). Following advice from clinical expertise in the review team, FISH and CISH costs and real-time PCR and PCR-based costs were grouped due the similarity of the resources involved. This source provided costs for FISH and CISH, real-time PCR and PCR-based LOH, MLPA and SNP array. The overall costs included the staff, consumables, equipment and overheads (heat, power, light, etc.) associated with preparing the sample, running the analysis and feeding back findings. The costs for NGS and aCGH were derived from existing literature. All costs are reported in 2020 pounds sterling, and shown in Appendix 4 (Table A4.1). Where necessary, costs were converted into 2020 pounds sterling using the EPPI-Centre Cost Converter (CCEMG 2019).

No cost for the G-banding, karyotyping, mass spectrometry (MS) and NanoString techniques and CGH were identified. Content experts advised that these tests were not routinely performed in the health system (the UK NHS) that provided the data, and were likely to be used only in research settings. Consequently, these tests are not included in the model.

The model was designed to generate the expected costs per true-positive diagnosis, per true-negative diagnosis and per correct diagnosis. Given the sensitivities and specificities of the different diagnostic tests, and the prevalence rates of glioma in the various studies, we calculated the diagnostic accuracy classifications for the various testing strategies as:

- true positive (TP) rate = prevalence × sensitivity;
- true negative (TN) rate = (1 – prevalence) × specificity;

- correct diagnosis (CD) rate = (prevalence × sensitivity) + ((1 – prevalence) × specificity).

We estimated the prevalence as the proportion of condition-positive individuals across all the studies included in the meta-analysis. This was limited to studies that had low/unclear risk of bias. The true-positive rate can also be thought of as the number of true-positive diagnoses divided by the total number of people in the study. The true-negative rate can be thought of as the true-negative diagnoses divided by the total number people in the study. The correct diagnosis rate is the sum of the true-positive rate and true-negative rate.

Base-case analysis

Once the true-positive, true-negative and correct diagnosis rates were calculated, the diagnostic tests were compared in terms of both their cost and their diagnostic accuracy. Diagnostic tests that were *dominated* and *extendedly dominated* were first removed from the analysis, and the remaining strategies were then compared in terms of their ICERs. A *dominated* strategy is a strategy with both higher costs and worse outcomes than the next less costly strategy. In an incremental analysis, an *extendedly dominated* strategy is a strategy that has an ICER that is higher than the ICER of the next, more effective but more costly, alternative strategy. The ICER shows the estimated additional cost that would be needed for an additional unit of benefit from a strategy. Ranking the diagnostic strategies by cost and comparing the incremental costs and yields between increasingly costly diagnostic strategies allowed for the calculation of incremental costs per additional true positive, true negative and correct diagnosis, and the identification of dominated and extendedly dominated options.

Sensitivity analysis

We carried out a probabilistic sensitivity analysis (PSA) to assess the statistical precision surrounding estimates of cost-effectiveness. Unlike a deterministic sensitivity analysis, a PSA allows uncertainty surrounding the estimates used in the model to be examined simultaneously. In a PSA, uncertain parameters are characterised using appropriate probability distributions around the point estimate for that parameter rather than a single value. Using a Monte Carlo simulation, a set of parameter values is then drawn by randomly sampling from the distribution and cost, and cost-effectiveness is estimated. This process is repeated multiple times so that uncertainty around the model outputs can be presented. In our analysis, we repeated the Monte Carlo simulation process 10,000 times to assess the robustness of the conclusions. We characterised the prevalence and measures of sensitivity and specificity as beta distributions. As there was only one point estimate for the cost of each of the tests, we characterised the cost parameters as triangular distributions, with the minimum and maximum specified as 25% below and 25% above the likeliest value. The specific distributions used for each of the parameters are shown in Appendix 5. We presented results for a range of values (GBP 0 to GBP 10,000) for a decision-maker's willingness to pay for a unit of outcome.

R E S U L T S

Results of the search

Searches of MEDLINE, Embase, BIOSIS, PubMed, Web of Science CPCI-S, ICTRP, OpenGrey, Proquest Dissertations & Theses and

NDLTD identified 5427 records, and one record was identified through other sources. After removal of 2418 duplicate records, we screen the titles and abstracts of 3010 records. We selected 238 records to assess at full text. Fifty-three studies (in 78 publications) met the inclusion criteria for test accuracy studies and were included in the review (Figure 2). We excluded 86 full-text records (Characteristics of excluded studies table). Six studies are awaiting classification (Characteristics of studies awaiting classification table), and five studies are ongoing (Characteristics of ongoing studies table).

Figure 2.   PRISMA flow chart.

Database search results:

- 1399 Ovid MEDLINE (1946 to 31 July 2019)
- 2660 Ovid Embase (1974 to 2019 week 30)
- 984 BIOSIS (1969 to 1 August 2019)
- 59 PubMed not MEDLINE (all years)
- 219 WoS: CPCI-S (1990 to 1 August 2019)
- 54 ICTRP (all available years to 1 August 2019)
- 8 OpenGrey (all available years to 1 August 2019)
- 17 Proquest Dissertations & Theses (all available years to 1 August 2019)
- 27 NDLTD (all years to 30 April 2020)

Total: 5427

1 record identified from other sources

2418 duplicates removed

3010 titles and abstracts screened

2772 records excluded

160 records excluded

86 full-text articles excluded, with reasons

- 5 not a primary study
- 5 single case report
- 40 1p19q not assessed by ≥ 2 DNA techniques
- 21 concordance data only
- 2 participants aged < 18 years
- 1 not a glioma
- 3 recruited based on 1p/19q status
- 9 no results

63 conference abstracts not examined (not listed in review references)

6 awaiting classification

5 ongoing studies

238 full-text records screened

53 studies included in review (78 records)

Figure 2. (Continued)


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Included in quantitative syntheses:

Considering FISH as the reference standard: 41
cross-classified 2 × 2 tables

Considering PCR-based LOH as the reference
standard: 32 cross-classified 2 × 2 tables
```

None of the included studies also met the economic inclusion criteria. There were no studies identified from the NHS EED database and no economic evaluations from grey literature.

We classified the tests used into test categories based on the authors' description of the tests (see Table 1). We also grouped several PCR-based techniques that used some form of real-time PCR-based technology: comparative quantitative PCR (investigated in Chaturbedi 2012), quantitative microsatellite PCR (investigated in Nigro 2001), and semi-quantitative PCR (investigated in Ariza 2010). We included studies that used three additional techniques: MS (investigated in Pesenti 2017), NanoString (Armanious 2017), and G-banding/karyotyping (Dahlback 2009; Dahlback 2011; Ransom 1992a; Ransom 1992b; Schrock 1994).

We initially tried to distinguish PCR-based LOH performed with comparison to normal DNA (extracted from normal tissue or blood from the same patient) from PCR-based LOH performed without this normal DNA sample. One of the studies we included compared assays with and without comparison to normal DNA (Hatanpaa 2003a; Hatanpaa 2003b). However, we found that several studies initially classified as 'PCR-based LOH performed with comparison to normal DNA' stated that, in the absence of normal DNA from the same patient, PCR was performed without the normal DNA sample (e.g. Horbinski 2012 and Clark 2013). Therefore, we combined these two categories.

We included 39 studies that performed two categories of test on the same set of participants (Ariza 2010; Armanious 2017; Bigner 1999; Bouvier 2004; Broholm 2008; Byeon 2014; Chaturbedi 2012; Cieply 2004; Clark 2013; Cowell 2004; D'Haene 2019; Dahlback 2009; Dubbink 2016; Gadji 2009; Ghasimi 2016; Harada 2011; Hinrichs 2016; Horbinski 2012; Jeuken 2006; Jha 2011; Kato 2019; Kolhe 2016; Lass 2013; Lhotska 2015; Na 2019; Natte 2005; Nigro 2001; Park 2019; Paxton 2015; Ransom 1992a; Ransom 1992b; Scheie 2006; Schrock 1994; Sim 2018a (glioblastoma cohort); Sim 2018b (oligodendroglial cohort); Thakur 2012; Thomas 2017; Tsiatis 2010; Wiestler 2014), seven studies performed three categories of test on the same participants (Burger 2001; Dahlback 2011; Hatanpaa 2003a (assay development and non-blinded validation cohort); Hatanpaa 2003b (blinded validation cohort); Mohapatra 2006; Pesenti 2017 (note that in this study four tests were investigated but a maximum of three were applied to the same participants); Smith 1999), and one study performed four test categories on the same participants (Blesa 2009). In addition, several studies performed multiple variants of tests on the same participants (Belaud-Rotureau 2006; Duval 2014; Duval 2015; Hatanpaa 2003a (assay development and non-blinded validation cohort; Hatanpaa 2003b (blinded validation cohort 3); Horbinski 2012; Senetta 2013; Srebotnik-Kirbis 2016; Uchida 2019).

All possible test comparisons from the included studies are shown in Table 3. The studies can be visualised as a network of test comparisons (Figure 3). From Table 2 and Figure 3, it is clear that there is the most information for a comparison between FISH and PCR.

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Figure 3.   Network plot of the included studies. The size of the circles represents the number of test results for a test category. The thickness of the lines is proportional to the number of studies making the comparison. Note that the FISH and PCR circles include comparison within test categories. aCGH: array comparative genomic hybridisation; CGH: comparative genomic hybridisation; CISH: chromogenic in situ hybridisation; FISH: fluorescence in situ hybridisation; LOH: loss of heterozygosity; MLPA: multiplex-ligation-dependent probe amplification; MS; mass spectrometry; NGS: next-generation sequencing; PCR: polymerase chain reaction; RFLP: restriction fragment length polymorphism; RT: real-time; SNP: single nucleotide polymorphism.
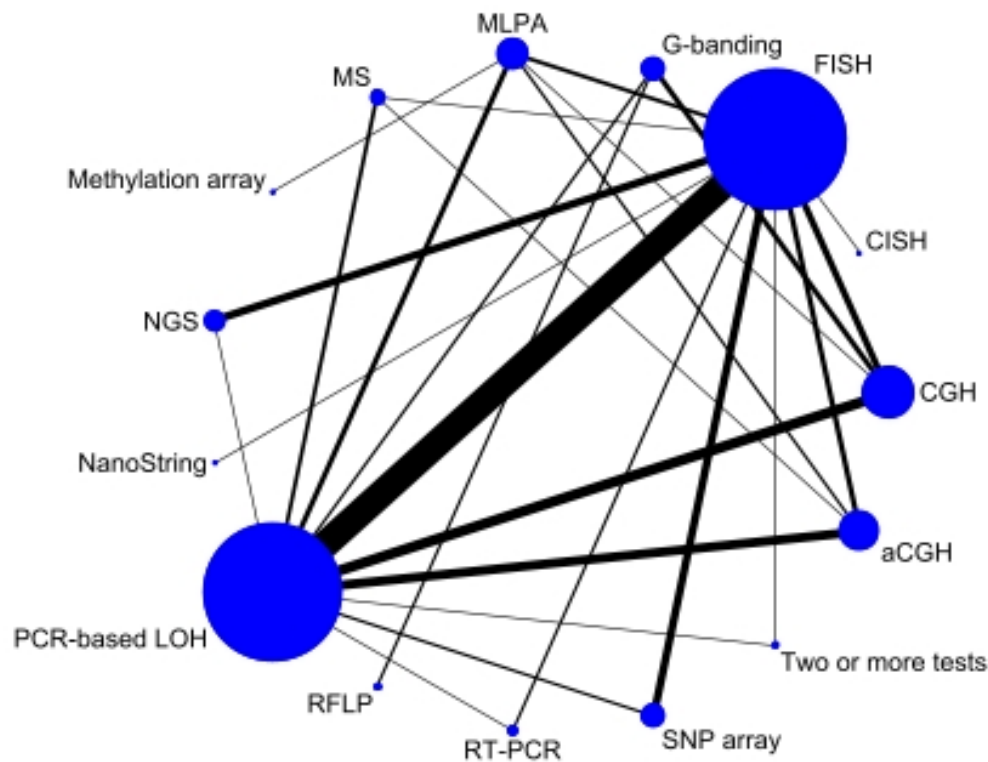
Details of the 53 included studies, including country and population source and setting, inclusion and exclusion criteria, and population characteristics (including age, gender, Karnofsky performance status) and test categories analysed can be found in the Characteristics of included studies table. In most cases, glioma was diagnosed using histopathology.

Raw data from the included studies

Raw data for the included studies extracted as contingency tables of cross-classified test results by tumour subtype (where possible, and as described by the study authors) can be found in Appendix 6. Separate tables are presented for comparisons of four test categories/variants (2 × 2 × 2 × 2 table; Appendix 6, Table A6.1), three test categories/variants (2 × 2 × 2 table; Appendix 6, Table A6.2) and two test categories/variants (2 × 2 table; Appendix 6, Table A6.3). Studies that compared more than two test categories/variants may be found in multiple tables if only a subset of the tests were performed on a proportion of the participants. For example, if a study compared four tests but a subset of participants only

had three tests, the study appears in both the 'three test' and the 'four test' tables. However, each study participant is only included in a single table. Therefore, if interest is in a comparison of two particular tests, it may be necessary to sum across or within (or both) tables, to obtain the relevant 2 × 2 table. Details of the tests used (tumour sample type, region(s) analysed, cut-off used) are also presented in these tables. Details of specific decisions we made during data extraction are provided in Appendix 7 and Appendix 8.

Regions analysed

Where the regions on 1p analysed by the different tests used in the different studies were reported in sufficient detail, we mapped the regions to the regions on 1p. These are shown diagrammatically, where available, in Figure 4 (studies comparing four tests and comparing three tests), Figure 5 (studies comparing two tests) and Figure 6 (comparative listing for FISH and PCR-based LOH). Regions analysed on chromosome 19 are listed in the Characteristics of included studies table. It is to be expected that the more regions are

analysed by a technique, the more reliably a codeletion of whole chromosomal arms will be detected.

Figure 4. Graphical representation of regions analysed in studies comparing four tests (panel A) and studies comparing three tests (panel B), as listed in Appendix 6 (Tables A6.1 and A6.2). The top of the figure indicates a graphical representation of chromosome 1 (adapted from the GRCh38/hg38 assembly). The figure legend indicates the different methods, with different colour codes for FISH, depending on the origin or manufacturer of the probes. In each section, the first author of the study is represented on top, and the techniques on the left of the table. The graphical representation indicates the position of the probe or primer on the chromosome. aCGH: array comparative genomic hybridisation; CGH: comparative genomic hybridisation; CISH: chromogenic in situ hybridisation; FISH: fluorescence in situ hybridisation; LOH: loss of heterozygosity; MLPA: multiplex-ligation-dependent probe amplification; MS; mass spectrometry; NGS: next-generation sequencing; PCR: polymerase chain reaction; RT-PCR: real-time polymerase chain reaction; SNP: single nucleotide polymorphism.

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Figure 5. Graphical representation of regions analysed in studies comparing two tests, as listed in Appendix 6 (Table A6.3). For legend to symbols, see Figure 4. Studies that are already represented in the three- or four-test comparisons are omitted (see footnotes). Studies comparing FISH with FISH used different parameters, see Table A6.3 for details. aCGH: array comparative genomic hybridisation; CGH: comparative genomic hybridisation; CISH: chromogenic in situ hybridisation; FISH: fluorescence in situ hybridisation; MLPA: multiplex-ligation-dependent probe amplification; MS; mass spectrometry; NGS: next-generation sequencing; PCR: polymerase chain reaction; SNP: single nucleotide polymorphism.

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Figure 6.   Comparative listing of all studies using FISH (panel A) and all studies using PCR-based LOH (panel B). Studies appear in alphabetical order of first author. For legend to symbols, see Figure 4. FISH: fluorescence in situ hybridisation; PCR: polymerase chain reaction.

Methodological quality of included studies

Risk of bias

QUADAS-2 risk of bias assessments for studies that performed two or more categories of test are shown in Figure 7, and assessments for studies that performed two or more FISH variants are shown in Appendix 9.

Figure 7.   Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study aCGH: array comparative genomic hybridisation; CGH: comparative genomic hybridisation; CISH: chromogenic in situ hybridisation; FISH: fluorescence in situ hybridisation; LOH: loss of heterozygosity; MLPA: multiplex-ligation-dependent probe amplification; MS; mass spectrometry; NGS: next-generation sequencing; PCR: polymerase chain reaction; RFLP: restriction fragment length polymorphism; SNP: single nucleotide polymorphism. Note: Horbinski 2012 used two FISH variants. The judgements for variant 1 are shown (cut-off: target-ploidy control

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ratio was less than 0.87, with at least 20% of nuclei showing deletion). **Hatanpaa 2003a** and **Hatanpaa 2003b** used two PCR-based LOH variants. The judgements shown are for PCR compared with normal DNA.

Figure 7. (Continued)

Only one study (comparing variants of FISH) was rated at low risk of bias across all domains (Senetta 2013). How patients were selected for inclusion into the study was unclear in most studies. We judged that a consecutive or random series of patients were selected for inclusion for only a minority of studies. It was clear that some studies included a non-random sample of patients, or used a case-control design, and we rated these studies at high risk of bias.

Hatanpaa 2003 selected participants based on them having concordant results on at least two tests investigated in Smith 1999 (majority of participants) or Burger 2001 (one participant). Because of this, we assessed risk of bias due to patient selection to be high in this study. The participants included in Hatanpaa 2003a and Hatanpaa 2003b were removed from the data extraction from Smith 1999 and Burger 2001. However, if the results for the tests investigated in Smith 1999 and Burger 2001 are considered for all three studies together, the risk of bias should be lower, as participants were not selected on the basis of concordant results into Smith 1999 and Burger 2001.

We rated many of the index test methods at unclear or high risk of bias. This was because it was frequently not reported whether the test results were interpreted without the knowledge of the other tests being compared or because the threshold used to classify results was not reported, or both.

Several studies presented raw data but did not classify the results of the test and the authors did not report a cut-off. In these cases, we classified the results using cut-off points we regarded as clinically realistic (see Appendix 2). In such instances, we judged that the lack of prespecification of the cut-off points and the lack of blinding to other test results did not cause bias as our choice of cut-off point was not influenced by the data. However, it should be noted that even in these studies the study authors had frequently made some judgements that we relied upon to determine 1p/19q status, for example whether there was LOH at a particular locus.

We generally assumed that cut-off to determine 1p/19q status for interpretation had been prespecified, provided these thresholds were stated in the methods section of the publication. In some cases, it was clear that the cut-off was not prespecified or that the results of one test were interpreted with full knowledge of the results of at least one other test that was performed. In this situation, we judged the index test domain at high risk of bias.

Many of the studies were rated at high risk of bias on the domain relating to flow and timing of participants. This was always because of missing data. We had predefined a cut-off of 5% of the proportion of the enrolled population being excluded for a study to be rated at high risk of bias, and many studies had missing data for at least 5% of participants. Some studies that compared more than two

tests may have been rated at high risk of bias because of missing data for one or more tests, but the results for some comparisons had no missing data and were at low risk of bias. For example, in Pesenti 2017, all participants had two of the tests investigated (MS and PCR-based LOH). However, this study was rated at high risk of bias because only a small proportion of participants had results for either aCGH or FISH. In Belaud-Rotureau 2006, all participants had results for the comparison of manual versus automatic analysis using the Abbott Vysis probe set. However, fewer than half of the included participants had results for manual analysis using the 1p36.3 (D1Z2)/1q12 (D1Z1) and 19q13.3/19pter probes.

Dubbink 2016 compared NGS with PCR-based LOH and was assessed at low risk of bias on the flow and timing domain. However, participants in Dubbink 2016 were from a randomised trial (EORTC 26951). In this trial, 1p and 19q status was determined by FISH in participants with sufficient tissue. These previously obtained FISH results were not reported for the participants included in Dubbink 2016. Similarly, Wiestler 2014 compared methylation array with MLPA in the biomarker cohort of the NOA-04 trial. In this trial, MLPA was used to detect 1p/19q codeletion, and PCR-based LOH was also used in participants with leukocyte DNA available. There was no comparison of the results of PCR-based LOH with MLPA or methylation array (or both).

Applicability

QUADAS-2 applicability assessments for studies that performed two or more categories of test are shown in Figure 7, and assessments for studies that performed two or more FISH variants are shown in Appendix 9.

We had concerns over the applicability of the included participants for many studies. This is because many of the studies only included participants with specific subtypes of glioma. The results of these studies may not be applicable to all gliomas. We only had low concerns over the applicability of the patient population if the study had included at least patients with both astrocytomas and oligodendrogliomas of several grades, or if the study stated that all gliomas were eligible for inclusion. We had high concerns over the applicability of the included participants in Ransom 1992a and Ransom 1992b. However, these two studies could be considered one larger study: they appeared to have been one study that was then subdivided by subtype of glioma. If they were combined, we would have had low concerns over applicability.

We had low concerns regarding the applicability of the index tests in most studies. We felt that it would be rare that the index tests were conducted or interpreted in a manner that differed from our review question, and, therefore, we had low concerns even in situations where there was minimal detail regarding the index test

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(e.g. in conference abstracts). We had low concerns regarding the applicability of G-banding/karyotyping in studies that performed this test, as results were given for the entire genome, although it should be noted that this technique was rarely used with the expressed purpose of determining 1p/19q status in the studies identified. We had concerns over the index test in a couple of studies. In Sim 2018a (glioblastoma cohort), we had concerns over the aCGH or NGS test (or both). The use of one test or another test (or both) was not applicable to our review question. In Thomas 2017, although we could extract 1p/19q NGS results, there was no attempt to use NGS to determine 1p/19q status in the paper, so it did not appear to represent how the test would be used for this purpose in practice. In Duval 2015, the automated FISH analysis was performed on archival slides that had been stored at −20 °C. The results of the automated analysis were compared with results of the initial manual analysis that had probably been performed when the slides were 'fresh'. Discordances in this study were attributed to degradation of the FISH signals during storage, and this storage is non-standard.

Findings

Results of test accuracy

We report results for analyses of each test using FISH as a reference standard followed by results for each test using PCR-based LOH as a reference standard. We then present results of the latent class analysis comparing FISH with PCR-based LOH and provide a comparison of results based on the two reference standards. Finally, we present the limited data available from studies that did not include FISH or PCR-based LOH, and that compared different variants of FISH and PCR-based LOH.

Using fluorescent in situ hybridisation as the reference standard

From the included studies that performed FISH and at least one other test that was not a FISH variant, we created 41 cross-classified 2 × 2 tables (from 33 studies, 1520 participants) in which FISH was treated as the reference standard. FISH has been compared directly with 10 different test categories: CISH (one comparison), PCR-based LOH (15 comparisons), real-time PCR (two comparisons), MLPA (two comparisons), CGH (four comparisons), aCGH (three comparisons), SNP array (six comparisons), NGS (six comparisons), MS (one comparison) and NanoString (one comparison). Of these 33 studies contributing to the simultaneous analysis, 26 studies compared FISH with one other test category, six studies compared FISH with two other test categories and one study compared FISH with three other test categories.

The main results from the bivariate meta-analysis model are presented in Figure 8 (forest plots) and Figure 9 (summary receiver operating characteristic plots for tests that had been examined in sufficient studies to draw them), and are summarised in Summary of findings 1.

Figure 8. Forest plot of tests: 1 PCR-based LOH (against FISH), 2 SNP array (against FISH), 3 NGS (against FISH), 4 CGH (against FISH), 5 aCGH (against FISH), 6 MLPA (against FISH), 7 real-time PCR (against FISH), 8 CISH (against FISH), 9 MS (against FISH), 10 NanoString (against FISH). aCGH: array comparative genomic hybridisation; CGH: comparative genomic hybridisation; CI: confidence interval; CISH: chromogenic in situ hybridisation; FISH: fluorescence in situ hybridisation; FN: false negative; FP: false positive; LOH: loss of heterozygosity; MLPA:

multiplex-ligation-dependent probe amplification; MS; mass spectrometry; PCR: polymerase chain reaction; SNP: single nucleotide polymorphism; TN: true negative; TP: true positive.

PCR-based LOH (against FISH)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Blesa 2009	9	12	1	25	0.90 [0.55, 1.00]	0.68 [0.50, 0.82]		
Bouvier 2004	4	1	1	8	0.80 [0.28, 0.99]	0.89 [0.52, 1.00]		
Broholm 2008	12	5	4	17	0.75 [0.48, 0.93]	0.77 [0.55, 0.92]		
Burger 2001	6	0	0	11	1.00 [0.54, 1.00]	1.00 [0.72, 1.00]		
Cieply 2004	10	0	0	12	1.00 [0.69, 1.00]	1.00 [0.74, 1.00]		
Clark 2013	1	7	18	420	0.05 [0.00, 0.26]	0.98 [0.97, 0.99]		
Gadji 2009	8	1	0	2	1.00 [0.63, 1.00]	0.67 [0.09, 0.99]		
Hatanpaa 2003a	4	0	0	5	1.00 [0.40, 1.00]	1.00 [0.48, 1.00]		
Hatanpaa 2003b	3	0	0	6	1.00 [0.29, 1.00]	1.00 [0.54, 1.00]		
Horbinski 2012	64	1	20	26	0.76 [0.66, 0.85]	0.96 [0.81, 1.00]		
Jha 2011	15	7	0	18	1.00 [0.78, 1.00]	0.72 [0.51, 0.88]		
Mohapatra 2006	16	1	0	11	1.00 [0.79, 1.00]	0.92 [0.62, 1.00]		
Pesenti 2017	5	0	0	5	1.00 [0.48, 1.00]	1.00 [0.48, 1.00]		
Scheie 2006	20	1	0	19	1.00 [0.83, 1.00]	0.95 [0.75, 1.00]		
Smith 1999	18	0	3	52	0.86 [0.64, 0.97]	1.00 [0.93, 1.00]		

SNP array (against FISH)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Ghasimi 2016	0	0	11	44	0.00 [0.00, 0.28]	1.00 [0.92, 1.00]		
Hinrichs 2016	2	0	0	6	1.00 [0.16, 1.00]	1.00 [0.54, 1.00]		
Kolhe 2016	6	0	0	3	1.00 [0.54, 1.00]	1.00 [0.29, 1.00]		
Lhotska 2015	16	2	0	2	1.00 [0.79, 1.00]	0.50 [0.07, 0.93]		
Paxton 2015	8	0	1	8	0.89 [0.52, 1.00]	1.00 [0.63, 1.00]		
Thakur 2012	2	0	0	0	1.00 [0.16, 1.00]	Not estimable		

NGS (against FISH)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
D'Haene 2019	21	0	1	28	0.95 [0.77, 1.00]	1.00 [0.88, 1.00]		
Kato 2019	3	0	0	6	1.00 [0.29, 1.00]	1.00 [0.54, 1.00]		
Na 2019	12	0	2	121	0.86 [0.57, 0.98]	1.00 [0.97, 1.00]		
Park 2019	19	0	1	0	0.95 [0.75, 1.00]	Not estimable		
Sim 2018b	4	0	1	5	0.80 [0.28, 0.99]	1.00 [0.48, 1.00]		
Thomas 2017	13	0	1	5	0.93 [0.66, 1.00]	1.00 [0.48, 1.00]		

CGH (against FISH)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Burger 2001	6	0	0	11	1.00 [0.54, 1.00]	1.00 [0.72, 1.00]		
Hatanpaa 2003a	1	0	0	4	1.00 [0.03, 1.00]	1.00 [0.40, 1.00]		
Hatanpaa 2003b	2	0	0	5	1.00 [0.16, 1.00]	1.00 [0.48, 1.00]		
Smith 1999	12	1	4	29	0.75 [0.48, 0.93]	0.97 [0.83, 1.00]		

aCGH (against FISH)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Blesa 2009	2	1	0	5	1.00 [0.16, 1.00]	0.83 [0.36, 1.00]		
Byeon 2014	0	0	0	3	Not estimable	1.00 [0.29, 1.00]		
Mohapatra 2006	16	2	0	10	1.00 [0.79, 1.00]	0.83 [0.52, 0.98]		

MLPA (against FISH)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Blesa 2009	2	4	0	8	1.00 [0.16, 1.00]	0.67 [0.35, 0.90]		
Natte 2005	9	3	1	6	0.90 [0.55, 1.00]	0.67 [0.30, 0.93]		

Real-time PCR (against FISH)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Chaturbedi 2012	2	0	2	14	0.50 [0.07, 0.93]	1.00 [0.77, 1.00]		

Figure 8. (Continued)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Chaturbedi 2012	2	0	2	14	0.50 [0.07, 0.93]	1.00 [0.77, 1.00]
Nigro 2001	12	0	1	9	0.92 [0.64, 1.00]	1.00 [0.66, 1.00]

CISH (against FISH)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Lass 2013	19	2	0	17	1.00 [0.82, 1.00]	0.89 [0.67, 0.99]

MS (against FISH)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Pesenti 2017	5	0	0	5	1.00 [0.48, 1.00]	1.00 [0.48, 1.00]

NanoString (against FISH)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Armanious 2017	10	1	2	3	0.83 [0.52, 0.98]	0.75 [0.19, 0.99]

Figure 9. Receiver operating characteristic plots obtained using FISH as the reference standard (panel A) and PCR-based LOH as the reference standard (panel B) for tests with four or more studies and variation in both sensitivity and specificity. Summary estimates of sensitivity and specificity with 95% credible regions are included along with a hierarchical summary receiver operating characteristic (HSROC) line. CGH: comparative genomic hybridisation;

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FISH: fluorescence in situ hybridisation; LOH: loss of heterozygosity; PCR: polymerase chain reaction; SNP: single nucleotide polymorphism.
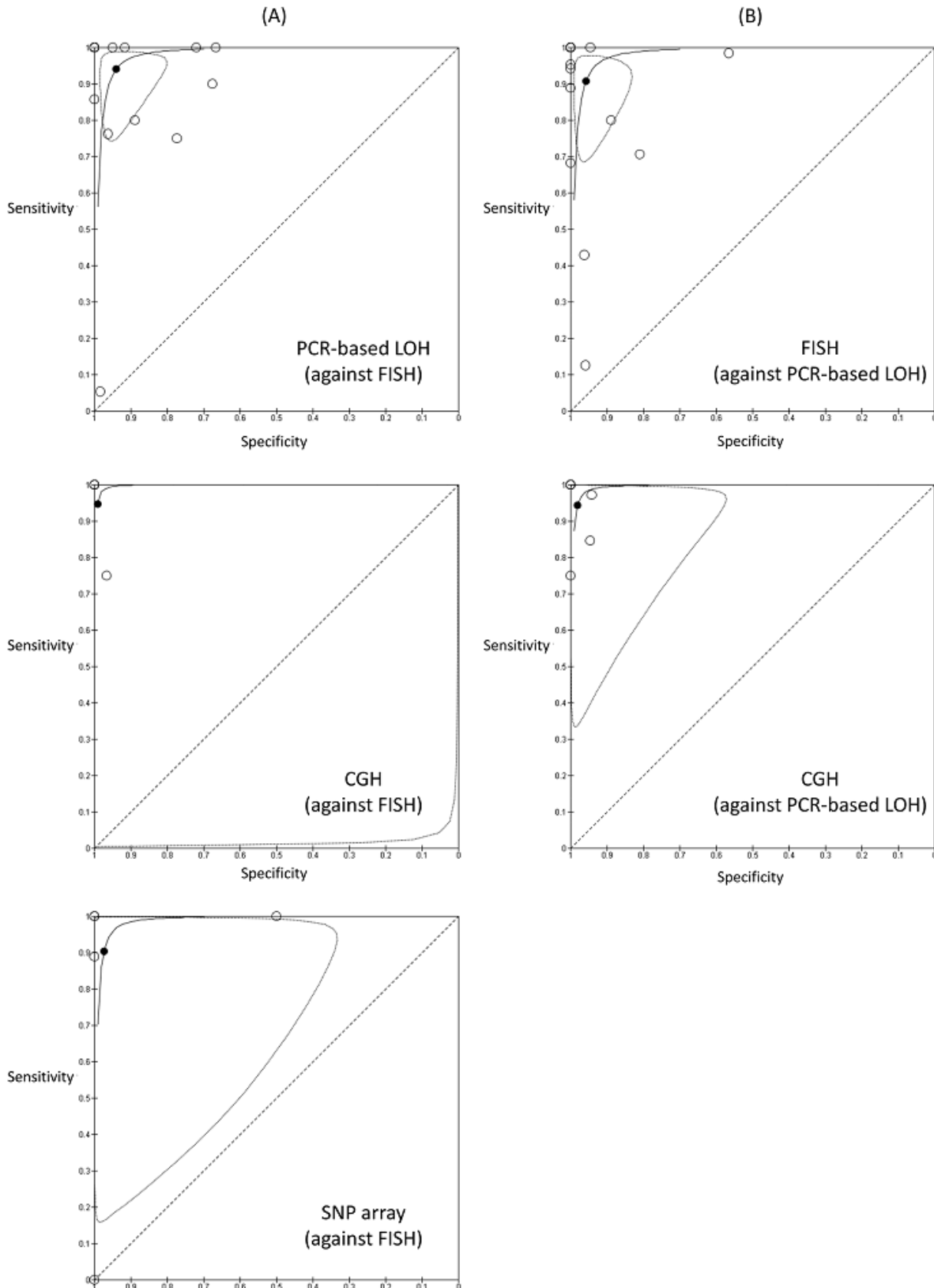
Figure 9. (Continued)
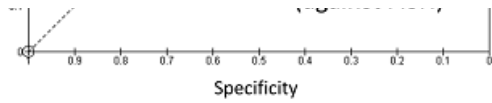
CISH: results using FISH as reference standard. Only one study (with 38 participants) contributed data on CISH against FISH (Data table 1). The estimated sensitivity was 1.00 (95% CrI 0.84 to 1.00) and specificity was 0.92 (95% CrI 0.33 to 1.00). Our GRADE assessment was of low certainty due to high imprecision.

Test 1.   CISH (against FISH)

CISH (against FISH)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Lass 2013	19	2	0	17	1.00 [0.82, 1.00]	0.89 [0.67, 0.99]		

PCR-based LOH: results using FISH as reference standard. 15 studies (915 participants) provided data on PCR-based LOH against FISH (Data table 2), making this the comparison with the strongest evidence base. Central estimates were high with of sensitivity of 0.94 (95% CrI 0.83 to 0.98) and specificity of 0.94 (95% CrI 0.87 to 0.98), indicating high concordance with FISH results.

Our GRADE assessment was of low certainty due to the risk of bias in the individual study results and indirectness. Because we had more than four studies, we included PCR-based LOH in the sensitivity analysis with test-specific between-study heterogeneity and correlation parameters. The results were identical within the level of precision presented (see Table 4).

Test 2.   PCR-based LOH (against FISH)

PCR-based LOH (against FISH)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Blesa 2009	9	12	1	25	0.90 [0.55, 1.00]	0.68 [0.50, 0.82]		
Bouvier 2004	4	1	1	8	0.80 [0.28, 0.99]	0.89 [0.52, 1.00]		
Broholm 2008	12	5	4	17	0.75 [0.48, 0.93]	0.77 [0.55, 0.92]		
Burger 2001	6	0	0	11	1.00 [0.54, 1.00]	1.00 [0.72, 1.00]		
Cieply 2004	10	0	0	12	1.00 [0.69, 1.00]	1.00 [0.74, 1.00]		
Clark 2013	1	7	18	420	0.05 [0.00, 0.26]	0.98 [0.97, 0.99]		
Gadji 2009	8	1	0	2	1.00 [0.63, 1.00]	0.67 [0.09, 0.99]		
Hatanpaa 2003a	4	0	0	5	1.00 [0.40, 1.00]	1.00 [0.48, 1.00]		
Hatanpaa 2003b	3	0	0	6	1.00 [0.29, 1.00]	1.00 [0.54, 1.00]		
Horbinski 2012	64	1	20	26	0.76 [0.66, 0.85]	0.96 [0.81, 1.00]		
Jha 2011	15	7	0	18	1.00 [0.78, 1.00]	0.72 [0.51, 0.88]		
Mohapatra 2006	16	1	0	11	1.00 [0.79, 1.00]	0.92 [0.62, 1.00]		
Pesenti 2017	5	0	0	5	1.00 [0.48, 1.00]	1.00 [0.48, 1.00]		
Scheie 2006	20	1	0	19	1.00 [0.83, 1.00]	0.95 [0.75, 1.00]		
Smith 1999	18	0	3	52	0.86 [0.64, 0.97]	1.00 [0.93, 1.00]		

RFLP: results using FISH as reference standard. No studies compared RFLP with FISH.

Real-time PCR: results using FISH as reference standard. Two comparisons (40 participants) provided data on real-time PCR against FISH (Data table 3). Sensitivity was estimated to be 0.81 (95% CrI 0.20 to 0.99) and specificity to be 1.00 (95% CrI 0.95 to 1.00). Our GRADE assessment was of very low certainty, with low precision for sensitivity as well as risk of bias and indirectness.

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Test 3. Real-time PCR (against FISH)

Real-time PCR (against FISH)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Chaturbedi 2012	2	0	2	14	0.50 [0.07, 0.93]	1.00 [0.77, 1.00]		
Nigro 2001	12	0	1	9	0.92 [0.64, 1.00]	1.00 [0.66, 1.00]		

MLPA: results using FISH as reference standard. Two comparisons (33 participants) provided data on MLPA against FISH (Data table 4). Central estimates of sensitivity was 0.96 (95% CrI 0.44 to 1.00) and specificity was 0.68 (95% CrI 0.20 to 0.95), the latter result arising from seven cases (out of 21) in which MLPA identified a deletion when FISH did not. Our GRADE assessment was of very low certainty.

Test 4. MLPA (against FISH)

MLPA (against FISH)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Blesa 2009	2	4	0	8	1.00 [0.16, 1.00]	0.67 [0.35, 0.90]		
Natte 2005	9	3	1	6	0.90 [0.55, 1.00]	0.67 [0.30, 0.93]		

CGH: results using FISH as reference standard. Four comparisons (75 participants) provided data on CGH against FISH (Data table 5). Central estimates of sensitivity was 0.95 (95% CrI 0.59 to 1.00) and specificity was 0.99 (95% CrI 0.90 to 1.00), providing some evidence of high specificity in relation to FISH. Our GRADE assessment was of low certainty. The sensitivity analysis gave a similar result, although with a slightly different result for sensitivity, perhaps not surprising given that sensitivity was estimated imprecisely in both analyses (see Table 4).

Test 5. CGH (against FISH)

CGH (against FISH)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Burger 2001	6	0	0	11	1.00 [0.54, 1.00]	1.00 [0.72, 1.00]		
Hatanpaa 2003a	1	0	0	4	1.00 [0.03, 1.00]	1.00 [0.40, 1.00]		
Hatanpaa 2003b	2	0	0	5	1.00 [0.16, 1.00]	1.00 [0.48, 1.00]		
Smith 1999	12	1	4	29	0.75 [0.48, 0.93]	0.97 [0.83, 1.00]		

aCGH: results using FISH as reference standard. Three comparisons (39 participants) provided data on aCGH against FISH (Data table 6). Sensitivity was estimated to be high at 1.00 (95% CrI 0.89 to 1.00) although specificity was imprecisely estimated at 0.91 (95% CrI 0.55 to 0.99). Our GRADE assessment was of very low certainty.

Test 6. aCGH (against FISH)

aCGH (against FISH)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Blesa 2009	2	1	0	5	1.00 [0.16, 1.00]	0.83 [0.36, 1.00]		
Byeon 2014	0	0	0	3	Not estimable	1.00 [0.29, 1.00]		
Mohapatra 2006	16	2	0	10	1.00 [0.79, 1.00]	0.83 [0.52, 0.98]		

SNP arrays: results using FISH as reference standard. Six comparisons (111 participants) provided data on SNP arrays against FISH (Data table 7). Central estimates of sensitivity was 0.90 (95% CrI 0.57 to 0.99) and specificity was 0.97 (95% CrI 0.84 to 1.00). Our GRADE assessment was of very low certainty. The sensitivity analysis gave a very similar result (see Table 4).

Test 7. SNP array (against FISH)

SNP array (against FISH)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ghasimi 2016	0	0	11	44	0.00 [0.00, 0.28]	1.00 [0.92, 1.00]
Hinrichs 2016	2	0	0	6	1.00 [0.16, 1.00]	1.00 [0.54, 1.00]
Kolhe 2016	6	0	0	3	1.00 [0.54, 1.00]	1.00 [0.29, 1.00]
Lhotska 2015	16	2	0	2	1.00 [0.79, 1.00]	0.50 [0.07, 0.93]
Paxton 2015	8	0	1	8	0.89 [0.52, 1.00]	1.00 [0.63, 1.00]
Thakur 2012	2	0	0	0	1.00 [0.16, 1.00]	Not estimable

Methylation arrays: results using FISH as reference standard. No studies compared methylation arrays with FISH.

NGS: results using FISH as reference standard. Six comparisons (243 participants) provided data on NGS against FISH (Data table 8).

Central estimates of sensitivity was 0.94 (95% CrI 0.75 to 0.99) and specificity was 1.00 (95% CrI 0.99 to 1.00). Our GRADE assessment was of low certainty. Results of the sensitivity analysis were very similar (Table 4).

Test 8. NGS (against FISH)

NGS (against FISH)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
D'Haene 2019	21	0	1	28	0.95 [0.77, 1.00]	1.00 [0.88, 1.00]
Kato 2019	3	0	0	6	1.00 [0.29, 1.00]	1.00 [0.54, 1.00]
Na 2019	12	0	2	121	0.86 [0.57, 0.98]	1.00 [0.97, 1.00]
Park 2019	19	0	1	0	0.95 [0.75, 1.00]	Not estimable
Sim 2018b	4	0	1	5	0.80 [0.28, 0.99]	1.00 [0.48, 1.00]
Thomas 2017	13	0	1	5	0.93 [0.66, 1.00]	1.00 [0.48, 1.00]

MS: results using FISH as reference standard. Very little information was available for MS against FISH, with just one comparison involving 10 participants (Data table 9), leaving us with very low certainty.

Test 9. MS (against FISH)

MS (against FISH)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Pesenti 2017	5	0	0	5	1.00 [0.48, 1.00]	1.00 [0.48, 1.00]

NanoString: results using FISH as reference standard. Very little information was available for NanoString against FISH, with just one comparison involving 16 participants (Data table 10), leaving us with very low certainty.

Test 10. NanoString (against FISH)

NanoString (against FISH)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Armanious 2017	10	1	2	3	0.83 [0.52, 0.98]	0.75 [0.19, 0.99]

G-banding: results using FISH as reference standard. No studies compared G-banding with FISH.

Overview across tests: using FISH as reference standard. Differences between tests in sensitivity and specificity are shown in Table 5. There are suggestions of differences between tests such that specificity of NGS may be higher than for PCR-based LOH and SNP array, and that real-time PCR may have higher specificity than PCR-based LOH, aCGH and MLPA.

Technical details

The main results above arise from a single, simultaneous analysis in which the same amount of heterogeneity was assumed for all tests, so a small number of studies for a specific test does not adversely affect our ability to estimate heterogeneity in the random-effects model. Estimated between-study standard deviation and correlation parameters from both the main analysis and the sensitivity analysis are shown in Appendix 10 (Table A10.1). Several of these estimates are likely heavily driven by the prior distributions, due to the limited data available. The estimated heterogeneity standard deviation in the main analysis was 1.84 (95% CrI 1.42 to 1.99) on the logit(sensitivity) scale and 1.36 (95% CrI 0.78 to 1.94) on the logit(1 – specificity) scale.

Using polymerase chain reaction-based loss of heterozygosity as the reference standard

From the included studies that performed PCR-based LOH and at least one other test that was not a PCR-based LOH variant, we created 32 cross-classified 2 × 2 tables (from 22 studies, 1304 participants) in which PCR-based LOH was treated as the reference standard. PCR-based LOH has been compared directly with nine different test categories: FISH (15 comparisons, the same as those summarised in 'Using FISH as the reference standard'), real-time PCR (one comparison), MLPA (one comparison), CGH (six comparisons), aCGH (four comparisons), SNP array (two comparisons), NGS (one comparison), G-banding (one comparison), and MS (one comparison). Of these 22 studies contributing to the simultaneous analysis, 14 studies compared PCR-based LOH with one other test category, six studies compared PCR-based LOH with two other test categories, and two studies compared PCR-based LOH with three other test categories.

The main results from the bivariate meta-analysis model are presented in Figure 10 (forest plots) and Figure 9 (summary receiver operating characteristic plots for tests that had been examined in sufficient studies to draw them), and are summarised in Summary of findings 2).

Figure 10. Forest plot of tests: 11 FISH (against PCR-based LOH), 12 CGH (against PCR-based LOH), 13 aCGH (against PCR-based LOH), 14 SNP array (against PCR-based LOH), 15 NGS (against PCR-based LOH), 16 G-banding (against PCR-based LOH), 17 MLPA (against PCR-based LOH), 18 real-time PCR (against PCR-based LOH), 19 MS (against PCR-based LOH). aCGH: array comparative genomic hybridisation; CGH: comparative genomic hybridisation; FISH: fluorescence in situ hybridisation; FN: false negative; FP: false positive; LOH: loss of heterozygosity; MLPA:

multiplex-ligation-dependent probe amplification; MS; mass spectrometry; NGS: next-generation sequencing; PCR: polymerase chain reaction; SNP: single nucleotide polymorphism; TN: true negative; TP: true positive.

FISH (against PCR-based LOH)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Blesa 2009	9	1	12	25	0.43 [0.22, 0.66]	0.96 [0.80, 1.00]
Bouvier 2004	4	1	1	8	0.80 [0.28, 0.99]	0.89 [0.52, 1.00]
Broholm 2008	12	4	5	17	0.71 [0.44, 0.90]	0.81 [0.58, 0.95]
Burger 2001	6	0	0	11	1.00 [0.54, 1.00]	1.00 [0.72, 1.00]
Cieply 2004	10	0	0	12	1.00 [0.69, 1.00]	1.00 [0.74, 1.00]
Clark 2013	1	18	7	420	0.13 [0.00, 0.53]	0.96 [0.94, 0.98]
Gadji 2009	8	0	1	2	0.89 [0.52, 1.00]	1.00 [0.16, 1.00]
Hatanpaa 2003a	4	0	0	5	1.00 [0.40, 1.00]	1.00 [0.48, 1.00]
Hatanpaa 2003b	3	0	0	6	1.00 [0.29, 1.00]	1.00 [0.54, 1.00]
Horbinski 2012	64	20	1	26	0.98 [0.92, 1.00]	0.57 [0.41, 0.71]
Jha 2011	15	0	7	18	0.68 [0.45, 0.86]	1.00 [0.81, 1.00]
Mohapatra 2006	16	0	1	11	0.94 [0.71, 1.00]	1.00 [0.72, 1.00]
Pesenti 2017	5	0	0	5	1.00 [0.48, 1.00]	1.00 [0.48, 1.00]
Scheie 2006	20	0	1	19	0.95 [0.76, 1.00]	1.00 [0.82, 1.00]
Smith 1999	18	3	0	52	1.00 [0.81, 1.00]	0.95 [0.85, 0.99]

CGH (against PCR-based LOH)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bigner 1999	35	1	1	16	0.97 [0.85, 1.00]	0.94 [0.71, 1.00]
Burger 2001	6	0	0	11	1.00 [0.54, 1.00]	1.00 [0.72, 1.00]
Dahlback 2011	9	0	3	7	0.75 [0.43, 0.95]	1.00 [0.59, 1.00]
Hatanpaa 2003a	1	0	0	4	1.00 [0.03, 1.00]	1.00 [0.40, 1.00]
Hatanpaa 2003b	2	0	0	5	1.00 [0.16, 1.00]	1.00 [0.48, 1.00]
Smith 1999	11	2	2	35	0.85 [0.55, 0.98]	0.95 [0.82, 0.99]

aCGH (against PCR-based LOH)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Blesa 2009	3	1	0	7	1.00 [0.29, 1.00]	0.88 [0.47, 1.00]
Cowell 2004	8	0	0	6	1.00 [0.63, 1.00]	1.00 [0.54, 1.00]
Mohapatra 2006	17	1	0	10	1.00 [0.80, 1.00]	0.91 [0.59, 1.00]
Pesenti 2017	2	0	0	2	1.00 [0.16, 1.00]	1.00 [0.16, 1.00]

SNP array (against PCR-based LOH)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Harada 2011	14	0	1	14	0.93 [0.68, 1.00]	1.00 [0.77, 1.00]
Tsiatis 2010	1	0	0	3	1.00 [0.03, 1.00]	1.00 [0.29, 1.00]

NGS (against PCR-based LOH)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Dubbink 2016	18	1	0	30	1.00 [0.81, 1.00]	0.97 [0.83, 1.00]

G-banding (against PCR-based LOH)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Dahlback 2011	0	0	13	8	0.00 [0.00, 0.25]	1.00 [0.63, 1.00]

MLPA (against PCR-based LOH)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Blesa 2009	8	0	0	10	1.00 [0.63, 1.00]	1.00 [0.69, 1.00]

Real-time PCR (against PCR-based LOH)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ariza 2010	10	0	0	0	1.00 [0.69, 1.00]	Not estimable

MS (against PCR-based LOH)

Diagnostic test accuracy and cost-effectiveness of tests for codeletion of chromosomal arms 1p and 19q in people with glioma (Review)

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Figure 10. (Continued)

| Ariza 2010 | 10 | 0 | 0 | 0 | 1.00 [0.69, 1.00] | Not estimable |

MS (against PCR-based LOH)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Pesenti 2017	16	0	0	34	1.00 [0.79, 1.00]	1.00 [0.90, 1.00]
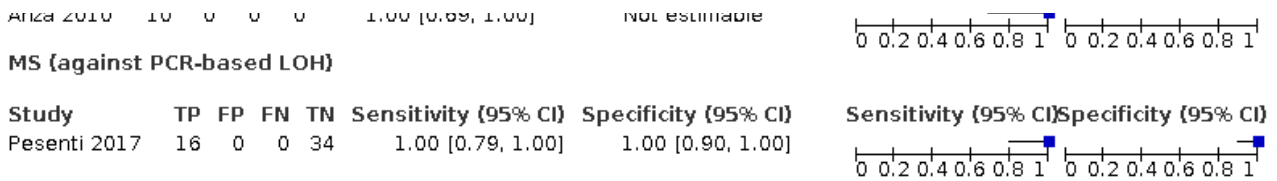
FISH: results using PCR-based LOH as reference standard. Fifteen comparisons (915 participants) provided data on FISH against PCR-based LOH (Data table 11). The central estimate of sensitivity was 0.91 (95% CrI 0.78 to 0.97), which is slightly lower than the sensitivity of PCR-based LOH at detecting deletions determined by FISH (0.94, based on the same data). The central estimate of specificity was 0.96 (95% CrI 0.90 to 0.99), slightly higher than the converse (0.94, again based on the same data). A sensitivity analysis with test-specific between-study heterogeneity and correlation parameters gave the same results (Table 6). Our GRADE assessment was of low certainty due to risk of bias and indirectness.

Test 11. FISH (against PCR-based LOH)

FISH (against PCR-based LOH)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Blesa 2009	9	1	12	25	0.43 [0.22, 0.66]	0.96 [0.80, 1.00]
Bouvier 2004	4	1	1	8	0.80 [0.28, 0.99]	0.89 [0.52, 1.00]
Broholm 2008	12	4	5	17	0.71 [0.44, 0.90]	0.81 [0.58, 0.95]
Burger 2001	6	0	0	11	1.00 [0.54, 1.00]	1.00 [0.72, 1.00]
Cieply 2004	10	0	0	12	1.00 [0.69, 1.00]	1.00 [0.74, 1.00]
Clark 2013	1	18	7	420	0.13 [0.00, 0.53]	0.96 [0.94, 0.98]
Gadji 2009	8	0	1	2	0.89 [0.52, 1.00]	1.00 [0.16, 1.00]
Hatanpaa 2003a	4	0	0	5	1.00 [0.40, 1.00]	1.00 [0.48, 1.00]
Hatanpaa 2003b	3	0	0	6	1.00 [0.29, 1.00]	1.00 [0.54, 1.00]
Horbinski 2012	64	20	1	26	0.98 [0.92, 1.00]	0.57 [0.41, 0.71]
Jha 2011	15	0	7	18	0.68 [0.45, 0.86]	1.00 [0.81, 1.00]
Mohapatra 2006	16	0	1	11	0.94 [0.71, 1.00]	1.00 [0.72, 1.00]
Pesenti 2017	5	0	0	5	1.00 [0.48, 1.00]	1.00 [0.48, 1.00]
Scheie 2006	20	0	1	19	0.95 [0.76, 1.00]	1.00 [0.82, 1.00]
Smith 1999	18	3	0	52	1.00 [0.81, 1.00]	0.95 [0.85, 0.99]

CISH: results using PCR-based LOH as reference standard. No studies compared CISH with PCR-based LOH.

RFLP: results using PCR-based LOH as reference standard. No studies compared RFLP with PCR-based LOH.

Real-time PCR: results using PCR-based LOH as reference standard. One comparison (10 participants) provided data on real-time PCR against PCR-based LOH (Data table 12). The two techniques were completely concordant for the 10 participants, with all participants having positive results by both tests. Sensitivity was estimated to be 1.00 (95% CrI 0.77 to 1.00). Specificity was not estimable (as there were no negative cases by either test). Our GRADE assessment was of very low certainty, due to risk of bias, the small number of participants tested and indirectness.

Test 12. Real-time PCR (against PCR-based LOH)

Real-time PCR (against PCR-based LOH)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ariza 2010	10	0	0	0	1.00 [0.69, 1.00]	Not estimable

MLPA: results using PCR-based LOH as reference standard. One comparison (18 participants) provided data on MLPA against PCR-based LOH (Data table 13). Results were completely concordant for the 18 participants. Central estimates of sensitivity was 1.00 (95% CrI 0.74 to 1.00) and specificity was 1.00 (95% CrI 0.83 to 1.00). Our GRADE assessment was of very low certainty, due to high risk of bias, the small number of participants tested and indirectness.

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Test 13. MLPA (against PCR-based LOH)

MLPA (against PCR-based LOH)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Blesa 2009	8	0	0	10	1.00 [0.63, 1.00]	1.00 [0.69, 1.00]		

CGH: results using PCR-based LOH as reference standard. Six comparisons (151 participants) provided data on CGH against PCR-based LOH (Data table 14). Central estimates of sensitivity was 0.94 (95% CrI 0.74 to 0.99) and specificity was 0.98 (95% CrI 0.91 to 1.00), providing some evidence of high specificity in relation to PCR-based LOH. Our GRADE assessment was of low certainty due to risk of bias and indirectness. The sensitivity analysis gave very similar results (see Table 6).

Test 14. CGH (against PCR-based LOH)

CGH (against PCR-based LOH)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Bigner 1999	35	1	1	16	0.97 [0.85, 1.00]	0.94 [0.71, 1.00]		
Burger 2001	6	0	0	11	1.00 [0.54, 1.00]	1.00 [0.72, 1.00]		
Dahlback 2011	9	0	3	7	0.75 [0.43, 0.95]	1.00 [0.59, 1.00]		
Hatanpaa 2003a	1	0	0	4	1.00 [0.03, 1.00]	1.00 [0.40, 1.00]		
Hatanpaa 2003b	2	0	0	5	1.00 [0.16, 1.00]	1.00 [0.48, 1.00]		
Smith 1999	11	2	2	35	0.85 [0.55, 0.98]	0.95 [0.82, 0.99]		

aCGH: results using PCR-based LOH as reference standard. Four comparisons (57 participants) provided data on aCGH against PCR-based LOH (Data table 15). Sensitivity (1.00, 95% CrI 0.97 to 1.00) and specificity (0.96, 95% CrI 0.75 to 1.00) were estimated to be high. Our GRADE assessment was of low certainty due to high risk of bias. The sensitivity analysis gave very similar results (see Table 6).

Test 15. aCGH (against PCR-based LOH)

aCGH (against PCR-based LOH)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Blesa 2009	3	1	0	7	1.00 [0.29, 1.00]	0.88 [0.47, 1.00]		
Cowell 2004	8	0	0	6	1.00 [0.63, 1.00]	1.00 [0.54, 1.00]		
Mohapatra 2006	17	1	0	10	1.00 [0.80, 1.00]	0.91 [0.59, 1.00]		
Pesenti 2017	2	0	0	2	1.00 [0.16, 1.00]	1.00 [0.16, 1.00]		

SNP arrays: results using PCR-based LOH as reference standard. Two comparisons (33 participants) provided data on SNP arrays against PCR-based LOH (Data table 16). Sensitivity was estimated at 0.97 (95% CrI 0.50 to 1.00) and specificity at 1.00 (95% CrI 0.92 to 1.00). Our GRADE assessment was of very low certainty due to risk of bias and high imprecision in the estimate of sensitivity.

Test 16. SNP array (against PCR-based LOH)

SNP array (against PCR-based LOH)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Harada 2011	14	0	1	14	0.93 [0.68, 1.00]	1.00 [0.77, 1.00]		
Tsiatis 2010	1	0	0	3	1.00 [0.03, 1.00]	1.00 [0.29, 1.00]		

Methylation arrays: results using PCR-based LOH as reference standard. No studies compared methylation arrays with PCR-based LOH.
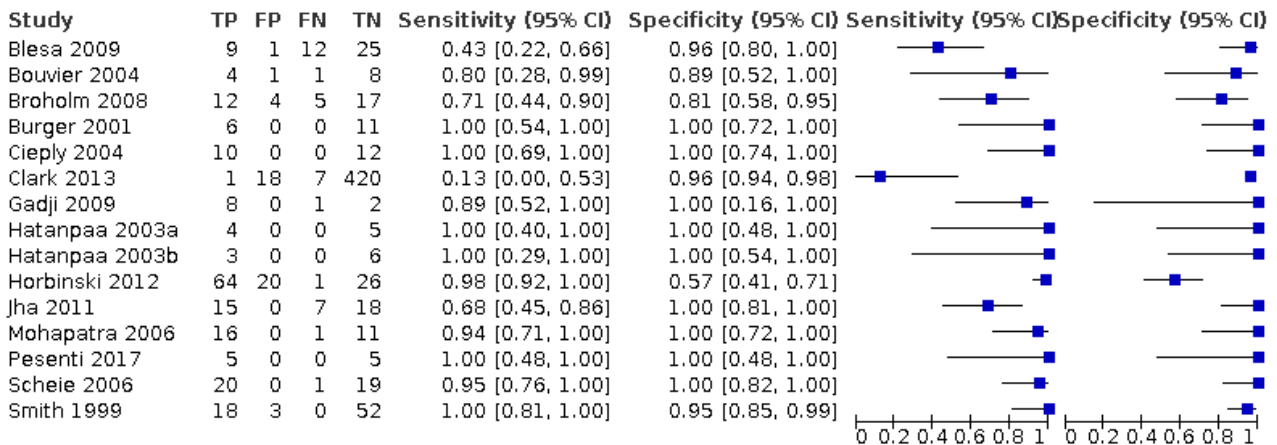
NGS: results using PCR-based LOH as reference standard. One comparison (49 participants) provided data on NGS against PCR-based LOH (Data table 17). Sensitivity was estimated at 1.00 (95% CrI 0.86 to 1.00) and specificity at 0.98 (95% CrI 0.64 to 1.00). Our

GRADE assessment was of very low certainty due to risk of bias, imprecision (of the estimate of specificity) and indirectness.

Test 17. NGS (against PCR-based LOH)

MS: results using PCR-based LOH as reference standard. One comparison (50 participants) provided data on MS against PCR-based LOH (Data table 18). Sensitivity was estimated at 1.00 (95% CrI 0.85 to 1.00) and specificity at 1.00 (95% CrI 0.94 to 1.00). Our GRADE assessment was of very low certainty due to risk of bias and the small number of participants tested.

Test 18. MS (against PCR-based LOH)
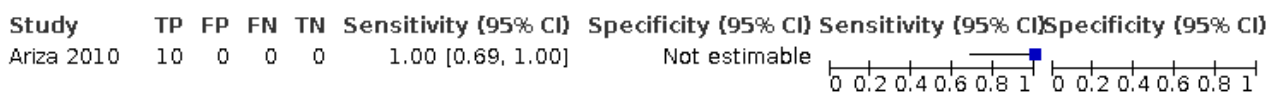

NanoString: results using PCR-based LOH as reference standard. No studies compared NanoString with PCR-based LOH.

G-banding: results using PCR-based LOH as reference standard. One comparison (21 participants) provided data on G-banding against PCR-based LOH (Data table 19). Sensitivity was estimated at 0.00 (95% CrI 0.00 to 0.20) and specificity at 1.00 (95% CrI 0.78 to 1.00). The poor estimate of sensitivity for G-banding/karyotyping is based on a single study in which none of 13 PCR-detected 1p/19q codeletions were identified. Our GRADE assessment was of very low certainty due to high risk of bias, high imprecision and indirectness.

Test 19. G-banding (against PCR-based LOH)

Overview across tests: PCR-based LOH as reference standard. Differences between tests in sensitivity and specificity are shown in Table 7. There is a suggestion of greater sensitivity of aCGH than CGH. Other than differences relating to the poor estimated sensitivity for G-banding/karyotyping, there were no other apparent differences between tests in either sensitivity or specificity.

Technical details

The main results above arose from a single, simultaneous analysis in which the same amount of heterogeneity was assumed for all tests (see Appendix 10, Table A10.2). The estimated heterogeneity standard deviation in the main analysis was 1.66 (95% CrI 1.09 to 1.98) on the logit(sensitivity) scale and 1.27 (95% CrI 0.69 to 1.93) on the logit(1 – specificity) scale. Several of the estimates presented above are likely to be heavily driven by the prior distributions, due to the limited data available. Note that the prior distributions forced correlation parameters to be non-negative and standard deviation parameters to be no greater than 2.

Latent class analysis

A total of 915 participants from 15 studies provided data on both FISH and PCR-based LOH. We present results from three latent class models applied to these data in Table 8. Point estimates of sensitivity were sensitive to the assumptions we made, although CrIs had a large degree of overlap. Our preferred model from a theoretical perspective had been the model allowing for conditional dependencies between FISH and PCR-based LOH test results. However, we observed no improvement in model fit (as measured by residual deviance) between this model and the conditional independence model despite including many more parameters, so we focus on results from the conditional independence model. The results suggest that PCR-based LOH may be slightly more accurate than FISH, consistent with our a priori expectation that PCR-based LOH has near-perfect sensitivity. Sensitivity of PCR-based LOH was estimated as 0.97 (95% CrI 0.90 to 1.00) and sensitivity of FISH as 0.95 (95% CrI 0.83 to 1.00). Specificity of PCR-based LOH was estimated as 0.98 (95% CrI 0.91 to 1.00) and specificity of FISH as 0.97 (95% CrI 0.93 to 0.99). As explained in the methods section, we were unable to include the other tests in the latent class analysis.

Comparison of results obtained when using fluorescent in situ hybridisation or polymerase chain reaction-based loss of heterozygosity as the reference standard

A comparison of the results obtained using FISH as the reference standard and using PCR-based LOH as the reference standard (for test categories that were included in both analyses) is shown in Table 9. Note that different studies contributed to the two analyses for each test category and care is required not to over interpret the results. Apart from a general observation that methods are generally in good agreement with both FISH and PCR-based LOH, there is little to discern between the two sets of analyses. There is a suggestion that MLPA may label more cases as codeletions when FISH does not than when PCR-based LOH does not (specificity 0.68, 95% CI 0.20 to 0.95 when FISH is the reference versus 1.00, 95% CI 0.83 to 1.00 when PCR-based LOH is the reference) and that real-time PCR may miss more cases that FISH detects as codeletions than PCR-based LOH detects as codeletions (sensitivity 0.81, 95%

CI 0.20 to 0.99 when FISH is the reference versus 1.00, 95% CI 0.77 to 1.00 when PCR-based LOH is the reference).

Results for other comparison of tests

Six studies (262 participants) did not include FISH or PCR-based LOH. One study (71 participants) compared CGH with MLPA (Jeuken 2006; Data table 20), finding them to be highly concordant. One study (99 participants) compared methylation array with MLPA (Wiestler 2014; Data table 21), observing seven cases in which MLPA identified a deletion but methylation array did not (specificity 0.85, 95% CrI 0.71 to 0.94). Two studies (65 participants) compared G-banding with CGH (Dahlback 2009; Schrock 1994); we present the results of this comparison, including also a result from a third study that also included PCR-based LOH (Dahlback 2011; included in the analyses above) in Data table 22 (total 75 participants). G-banding found no deletion detections using CGH. Finally, two comparisons (27 participants) were made between G-banding and RFLP (Ransom 1992a; Ransom 1992b; Data table 23). Again G-banding failed to identify any instances in which RFLP detected a deletion.

Test 20. CGH (against MLPA)

CGH (against MLPA)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Jeuken 2006	25	0	1	45	0.96 [0.80, 1.00]	1.00 [0.92, 1.00]		

Test 21. Methylation array (against MLPA)

Methylation array (against MLPA)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Wiestler 2014	39	1	7	52	0.85 [0.71, 0.94]	0.98 [0.90, 1.00]		

Test 22. G-banding (against CGH)

G-banding (against CGH)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Dahlback 2009	0	0	5	52	0.00 [0.00, 0.52]	1.00 [0.93, 1.00]		
Dahlback 2011	0	0	0	10	Not estimable	1.00 [0.69, 1.00]		
Schrock 1994	0	0	0	8	Not estimable	1.00 [0.63, 1.00]		

Test 23. G-banding (against RFLP)

G-banding (against RFLP)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Ransom 1992a	0	0	2	3	0.00 [0.00, 0.84]	1.00 [0.29, 1.00]		
Ransom 1992b	0	0	0	22	Not estimable	1.00 [0.85, 1.00]		

Seven studies compared different versions of FISH. Belaud-Rotureau 2006 performed FISH with manual analysis with the 1p36.3 (D1Z2)/1q12 (D1Z1) and 19q13.3/19pter probe set, manual analysis with the 1p36/1q25 and 19q13/19p13 Abbott Vysis probe set, and automatic analysis (Metafer 4, Metasystems, Althlussheim, Germany) with the 1p36/1q25 and 19q13/19p13 Abbott Vysis probe set. Ten participants were tested with all three FISH variants, and 13 with two FISH variants. For all participants, the results obtained were concordant. Duval 2014 performed FISH and immunoFISH (FISH with immunohistochemistry against Ki67 (MIB-1)), and used two different cut-offs for both: a "combination" cut-off (which was based on the number of cells showing a deletion) and a "ratio" cut-off (based on the ratio of signals for 1p to 1q and 19q and 19p). Twenty participants were positive on all four FISH variants, and 14 negative on all four variants, but one obtained a negative result with ImmunoFISH using the "combination" cut-off despite obtaining positive results with the other variants; and one was positive on FISH (both cut-offs) but negative on ImmunoFISH (both cut-offs). Duval 2015 performed FISH with automated analysis (Metafer 4 software (Metasystem) using the "1p19q tile-sampling classifier") and FISH with manual analysis. There were discordant results for four of the 29 participants, Senetta 2013 performed FISH with two different cut-offs (cut-off ratios 1p of 0.8 or less and 19q of 0.8 or less and cut-off ratios 1p of 0.7 or less and 19q of 0.8 or less). There were discordant results for 16 of the 143 participants. Srebotnik-Kirbis 2016 performed FISH on fresh tissue cytospins and on FFPE sections. Results were concordant for all 12 participants. Uchida 2019 performed FISH with two different criteria for judging whether a deletion was present (signals of 1p or 19q less than signals of 1q or 19p or single signal of 1p or 19q and two signals of 1q or 19p; in both cases the cut-off value was set at 20%). Results were discordant for five of the 141 participants. Horbinski 2012 performed FISH with two different cut-offs (target-ploidy control ratio less than 0.87, with at least 20% of nuclei showing deletion and target-ploidy control ratio less than 0.75, with at least 20% of nuclei showing deletion), in addition to PCR-based LOH. The FISH results using the two different cut-offs were discordant for eight of the 111 participants. Raw results for these studies are presented in Appendix 6; we were unable to include the results of these studies in our statistical analyses.

There were two comparisons (in one publication) that compared different version of PCR-based LOH. The study performed PCR-based LOH with or without comparison to normal DNA (in addition to CGH and FISH). This study developed a cut-off for PCR-based LOH without comparison to normal DNA in one set of participants (Hatanpaa 2003a) and validated it in another set of participants (Hatanpaa 2003b). The results for both variants of PCR-based LOH were concordant. Raw results for these studies are presented in Appendix 6; we were unable to include the results of these studies in our statistical analyses.

Results of model-based economic evaluation

The base-case economic analysis results along with results of the probabilistic sensitivity analyses are shown in Table 10 (for FISH as reference standard) and Table 11 (for PCR-based LOH as reference standard). These were based on the overall prevalence (the proportion of condition positive participants in the population tested) of 0.31 among all the studies included in the meta-analysis, the costs in Appendix 4 and the diagnostic accuracy results in Figure 8 and Figure 10. Many of the results derive from estimates of accuracy that are based on small numbers of studies, so caution

is required in the interpretation of the point estimates of cost-effectiveness from the deterministic analysis.

When FISH was used as the reference standard (Table 10), and if a decision were to be made on cost alone, then MLPA had almost 100% chance of being considered the least costly. With regard to the incremental cost per true positive detected, MLPA had 95% or higher chance of being considered cost-effective given a willingness to pay (WTP) up to GBP 1000 per true positive. As WTP per true positive increases, the probability of other tests being considered cost-effective increases. However, of the seven tests compared, none had a probability of being cost-effective above 50% when WTP per true positive detected was GBP 10,000.

When considering true negatives, the real-time PCR test had the highest probability (54% to 67%) of being cost-effective at a WTP per additional true negative detected of between GBP 500 and GBP 10,000. None of the other tests had a probability of being cost-effective above 30% when WTP per additional true negative detected was between GBP 500 and GBP 10,000.

For a correct diagnosis, real-time PCR had the highest probability of being cost-effective at a WTP of GBP 500 and GBP 1000, and the aCGH had the highest probability of being cost-effective at a WTP of GBP 5000 and GBP 10,000. However, for none of the seven tests compared over the ranges of WTP between GBP 500 and GBP 10,000 was the probability of test being cost-effective over 60%.

When PCR-LOH was used as the reference standard, the results indicated that MLPA had a 100% probability of being considered the least costly of the five tests compared (Table 11). MLPA also had the highest probability of being cost-effective in terms of true positives, true negative and correct diagnoses at a WTP up to GBP 10,000. However, at GBP 5000 and GBP 10,000, no test had a probability of being cost-effective above 55%.

DISCUSSION

Summary of main results

Test accuracy

We found limited evidence about most of the available techniques for detecting 1p/19q codeletions. Most techniques, with the exception of G-banding, provided point estimates indicating very good sensitivity (i.e. produced few false-negative results) for detection of 1p/19q codeletion when either FISH or PCR-based LOH were considered as the reference standard. There was some evidence for differences in specificity (false-positive rate) with some techniques. However, we caution against ranking the tests included in this review based on point estimates of sensitivity and specificity. Our latent class analysis was not conclusive, but suggested that PCR-based LOH may be more accurate than FISH. This concords with our a prior assumption that PCR-based LOH has very high sensitivity.

G-banding had low sensitivity and specificity when PCR-based LOH was the reference standard, suggesting that G-banding may not be a suitable test for 1p/19q analysis. G-banding is not in current routine clinical use for 1p/19q analysis and most of the studies investigating this technique were older, with the last study investigating this technique published in 2011. Although MS had very high sensitivity and specificity when both FISH and PCR-based LOH were considered the reference standard, these results should

be treated with caution because they were based on only one study, which had a small number of participants. MS is not in current clinical use for 1p/19q analysis but further research may be indicated in this area.

Both NGS and SNP array had high specificity when considered against FISH. For both of these, there were six studies including a good number of participants (243 for NGS and 111 for SNP array). NGS and SNP array also had high specificity when PCR-based LOH was considered the reference standard, although the CrIs were much wider as these results were based on fewer studies (just one study with 49 participants for NGS and two studies with 33 participants for SNP array). Real-time PCR also showed high specificity with FISH as a reference standard, although there were only two studies including 40 participants in this analysis. It seems unsurprising that NGS and SNP array had high specificity given that these two techniques are capable of looking at the whole chromosome arm.

A further technology that has gained importance in neuropathology diagnostics is methylation array, combined with algorithmic tumour classification (Capper 2018a; Jaunmuktane 2019; Pickles 2020). The readout of these methylation arrays also returns a copy number assay that has the added benefit of directly demonstrating chromosomal aberrations, including 1p/19q codeletion (Capper 2018b). The estimated costs in clinical practice have been calculated in one of the UK studies (Jaunmuktane 2019).

Complete hemizygous losses of 1p are tightly associated with 19q loss and oligodendroglial phenotype, whereas partial 1p deletions alone are mainly observed in astrocytic tumours, including the IDH-wildtype glioblastoma, and are not associated with 19q loss. As these tumours represent biologically distinct entities, they are associated with a different (in this case poorer) prognosis (Vogazianou 2010). Therefore, false positives in detection of 1p loss caused by partial 1p deletions are of key clinical importance in 1p/19q analysis because they may result in incorrect diagnosis and treatment. See also illustrations of regions analysed on 1p in the different studies in Figure 4; Figure 6; Figure 7; Figure 8; Figure 9; Figure 10; and Figure 11.

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Figure 11. Economic model CISH: chromogenic in situ hybridisation; MLPA: multiplex-ligation-dependent probe amplification; RT-PCR: real-time polymerase chain reaction.
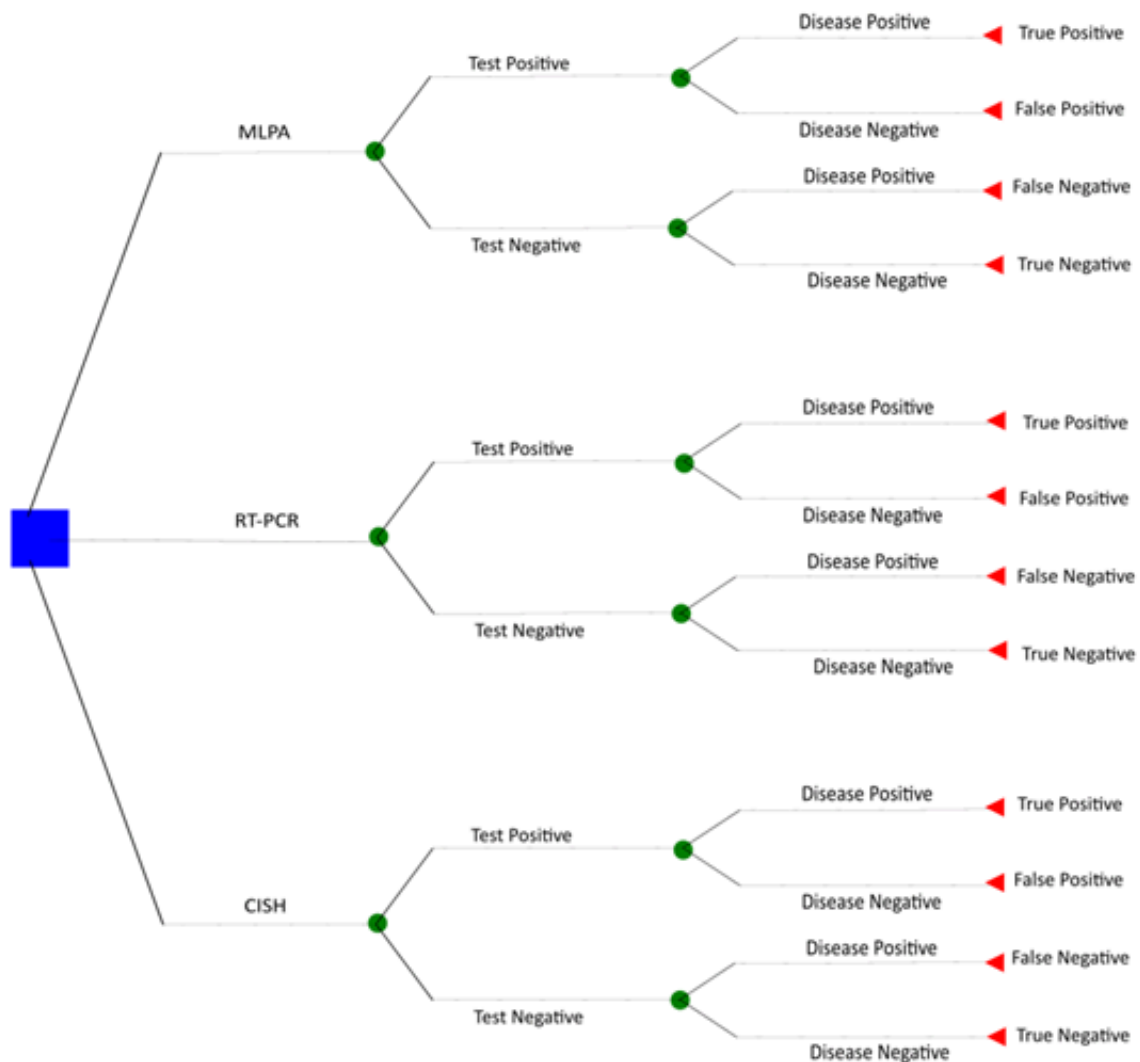
The results for test accuracy are in concordance with Zhao 2014, who found that there was no difference in the HR for overall survival between studies using two different techniques (PCR-based LOH and FISH) to assess the status of chromosomal arms 1p and 19q.

Cost-effectiveness

We identified no economic evaluations relevant to this study question. There is thus a paucity of evidence about the optimum testing strategy for 1p/19q codeletion in the management of glioma.

Results from the economic model extend the DTA results, highlighting which tests appear on average to have lower accuracy (or – for extendedly dominated tests – not sufficiently better test accuracy) and at higher cost. The analysis incorporates the imprecision surrounding diagnostic performance and test costs. Which test appeared most likely to be cost-effective depended on which measure of diagnostic performance was considered and the value placed on a unit change in that measure.

Taking FISH as the reference standard, MLPA was the most likely to be cost-effective if society were willing to pay GBP 1000 per true-positive case detected. At willingness to pay thresholds higher than this, no test was clearly superior. However, if the outcome were true-negative cases detected then providing society were willing to pay over GBP 500, real-time PCR was most likely to be cost-effective.

When PCR-based LOH was the reference standard, MLPA was the most likely to be considered cost-effective if society were willing to pay GBP 5000 for either a true-positive case detected, true-negative case detected or a correct diagnosis. However, at threshold values higher than this, no test was clearly more likely to be considered cost-effective.

Overall, even when accounting for the imprecision in estimates, the results showed that cost-effectiveness is sensitive to the choice of

the reference standard and the decision maker's willingness to pay for additional benefit.

Strengths and weaknesses of the review

To our knowledge this is the first systematic review of the DTA of different techniques for assessing 1p/19q codeletion in glioma. We undertook a thorough search, applied systematic methods and assessed results for risk of bias using the QUADAS-2 tool.

The review has some limitations, however. None of the available tests is perfect, and we undertook analyses assuming either FISH or PCR-based LOH as reference standards. In these analyses, none of the investigated tests was superior to the reference standard assumed. Related to this, we were unable to include the results of studies that did not investigate either FISH or PCR-based LOH in the statistical synthesis.

For most techniques, there was a relatively small number of studies available, most of which had few participants. This meant that some studies produced empty cells in the 2 × 2 comparisons created. Our search was undertaken in July 2019, and further studies may have been reported since then. Furthermore, most studied had risks of bias: only one study was at low risk of bias across all domains of QUADAS-2. Where reported, we used authors' classifications and thresholds, and it is possible that some of the thresholds used did not fully exploit the potential of the investigated technique.

We were unable to distinguish between absolute and relative deletions in most studies. Even when studies used techniques that can, in theory, distinguish between absolute and relative deletions, few did so. Furthermore, loss of 1p and 19q in combination with 1q or 19p (or both) was considered by some studies to count as 1p/19q codeletion, and in others not. When we had to interpret the results of techniques, we did so by looking for the presence/absence of 1p and 19q without consideration of 1q and 19p.

On a technical note, we did not allow for within-study correlations when performing the statistical synthesis. In addition, we did not extract some of the information contained within studies that did not address our objectives. For example, some studies had correlated their test results with prognosis, which provides information about which test results were more likely to be correct in the case of discordant test results.

The structure of the economic model was relatively simple, and we did not allow for the possibility of using multiple tests or sequences of tests in diagnosis. Furthermore, since it is based on the results of the meta-analysis, the economic model has all the same strengths and limitations as that analysis. In particular, cost-effectiveness results are based on a small number of studies, each typically with a small number of participants. For example, the MLPA technique had the highest probability of being cost-effective when the threshold value was GBP 1000 or less when PCR-based LOH was used as the reference standard. This is primarily due to lower costs. However, the sensitivity and specificity values were based on a single study with a sample size of 18. The imprecision associated with this is shown when the threshold was higher (e.g. GBP 10,000). At these higher thresholds, no test was clearly cost-effective.

Another weakness was that we obtained costs from a single hospital provider, supplemented by expert opinion. These are best thought of as illustrative and it is for readers to judge how applicable these

costs are to their own setting. Alternative costs could in principle be derived from a sample of hospitals, and by costing each aspect of resource use needed to provide a test, using micro-costing techniques. However, such costs may vary substantially between hospitals and between countries. Although we accounted for the uncertainty in the costs in the PSA by including the parameters as triangular distributions, other distributions (e.g. gamma) would be preferable if better data were available.

We also considered only the costs of the tests themselves and measures of diagnostic accuracy. We did not include the impact on health and subsequent costs of management (both to health services and the patient and their families) which may occur following the use of the diagnostic test. Specifically, the consequences of false positives, false negatives and correct diagnoses may have different resource implications. The inclusion of longer-term costs and consequences of the diagnosis would be useful for future evaluations of tests for 1p/19q codeletion in people with glioma.

Applicability of findings to the review question

The majority of studies recruited participants with particular types of glioma, rather than a cross-section of all gliomas, meaning that our results may not be applicable to all glioma subtypes. In general, we judged that tests were conducted as we would expect them to be performed in practice, although some tests are probably outdated (G-banding/karyotyping) and others have not yet been put into practice and are probably more experimental in nature (e.g. NanoString and MS).

A U T H O R S '   C O N C L U S I O N S

Implications for practice

Current guidelines recommend that 1p/19q codeletion should be evaluated to support a diagnosis of oligodendroglioma and to predict the chemosensitivity and prognosis of these patients (NICE 2018; Stupp 2014); however, there is no consensus as to the best approach. Our review judged the certainty of evidence for all tests to be low or very low, making it difficult to make recommendations for practice. We found little evidence to support the use of G-banding/karyotyping for 1p/19q analysis. However, all other techniques appeared to have high sensitivity when compared against fluorescent in situ hybridisation (FISH) or polymerase chain reaction (PCR)-based loss of heterozygosity (LOH) (which itself is thought to be highly sensitive) as a reference standard. Among currently considered techniques, next-generation sequencing (NGS) and single nucleotide polymorphism (SNP) array had the strongest evidence of high specificity against FISH and PCR-based LOH, and these two techniques also have the advantage of being able to detect other abnormalities simultaneously.

The various tests differed in costs, but which test would make the best use of resources depends on which measure of diagnostic accuracy is most important. Taking FISH as a reference standard and focusing on the ability to make a correct diagnosis, all the tests except multiplex-ligation-dependent probe amplification (MLPA) and chromogenic in situ hybridisation (CISH) were inefficient. MLPA was less costly and was less able to make a true diagnosis than CISH, based on very limited data, but CISH was estimated to cost an additional GBP 9032 per additional true-positive case diagnosed. When PCR-based LOH was used as the reference standard, MLPA

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was the dominant strategy on average. It is for the decision-maker to judge whether the benefits of a test with potentially better diagnostic performance are worth any extra cost.

Implications for research

For the comparison of most techniques with FISH or PCR-based LOH, we identified a relatively small numbers of studies, most of which had few participants. We were unable to reach conclusions about several techniques with promising results due to a sparsity of data. Further research on promising tests is warranted. For example, mass spectroscopy had high sensitivity and specificity when both FISH and PCR-based LOH were the reference standard, but our results should be treated with caution because they are based on only one study, which had a small number of participants.

Because none of the available tests is perfect, our results are limited by our assumptions about which can be taken as a reference standard. A future analysis of the data would recognise that all tests are imperfect, for example by assuming a latent class model. We plan such an analysis for an update of this review.

Our economic model addresses an evidence gap on the efficiency of genetic testing in the management of people with glioma. However, further evidence is required for a full evaluation of the cost-effectiveness of the different tests. Once more evidence on the diagnostic performance of the techniques is available, a more detailed modelling study will be able to determine the most cost-effective diagnostic testing strategy for this patient group. This analysis should more fully incorporate uncertainties using techniques such as probabilistic sensitivity analysis. A more complete evaluation would also seek to explore how test results are used and the implications of this on patient management and health.

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Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, eds.WHO Classification of Tumours of the Central Nervous System. 4th edition. Lyon (France): International Agency for Research on Cancer (IARC), 2007.

WHO 2016

Louis DN, Ohgaki H, Wiestler OD, Cavenee WK.WHO Classification of Tumours of the Central Nervous System. Revised 4th edition. Lyon (France): International Agency for Research on Cancer (IARC), 2016.

Zhao 2014

Zhao J, Ma W, Zhao H.Loss of heterozygosity 1p/19q and survival in glioma: a meta-analysis. *Neuro-Oncology* 2014;**16**(1):103-12.

References to other published versions of this review

McAleenan 2019

McAleenan A, Jones HE, Kernohan A, Faulkner CL, Palmer A, Dawson S, et al.Diagnostic test accuracy and cost-effectiveness of tests for codeletion of chromosomal arms 1p and 19q in people with glioma. *Cochrane Database of Systematic Reviews* 2019, Issue 8. Art. No: CD013387. [DOI: 10.1002/14651858.CD013387]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Ariza 2010

Study characteristics	
Patient Sampling	**Inclusion/exclusion criteria** Not explicitly reported. Included a series of 69 astrocytomas and 10 oligodendrogliomas (although data could not be extracted for the 69 astrocytomas). **Prior testing**

Ariza 2010 *(Continued)*

	Not explicitly reported but presumably histopathological diagnosis, as a series of 69 astrocytomas and 10 oligodendrogliomas was included.
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 10
	Country: Spain
	Population source and setting: NR
	Age: NR
	Gender: NR
	Karnofsky performance status: NR
	First diagnosis/recurrent disease: NR
Index tests	**2 tests:** PCR-based LOH and real-time PCR
	PCR-based LOH
	Tumour sample type: NR
	Region(s) analysed: NR
	Cut-off: NR
	Real-time PCR
	Tumour sample type: NR
	Region(s) analysed: 1p (SPAG17, ATG4), 19q (DPY19L3, RPS9), 1q (PYGO2 and GREM2), 19p (COPE, FUT3)
	Cut-off: NR
	Additional details: semiquantitative real-time PCR, quote: "Semi-quantitative real-time PCR of telomeric and centromeric sequences on 1 p (SPAG17, ATG4), 19q (DPY19L3, RPS9), 1q (PYGO2 and GREM2), and 19p (COPE, FUT3) … the deltadeltaCt method was used for relative quantification of PCR products".
Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. PCR-based LOH used as reference standard in some of our analyses.
Flow and timing	We presumed that all tests were performed on biopsied tumour material collected on 1 occasion.
Comparative	
Notes	Conference abstract

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		

Ariza 2010 *(Continued)*

Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	Unclear risk
Are there concerns that the included patients and setting do not match the review question?	High

DOMAIN 2: Index Test (NanoString)

DOMAIN 2: Index Test (aCGH)

DOMAIN 2: Index Test (NGS)

DOMAIN 2: Index Test (G-banding)

DOMAIN 2: Index Test (FISH (variant 4))

DOMAIN 2: Index Test (SNP array)

DOMAIN 2: Index Test (PCR (with comparison to normal DNA))

DOMAIN 2: Index Test (PCR (without comparison to normal DNA))

DOMAIN 2: Index Test (CISH)

DOMAIN 2: Index Test (MS)

DOMAIN 2: Index Test (RFLP)

DOMAIN 2: Index Test (PCR-based LOH)

If a threshold was used, was it pre-specified?	Unclear
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

DOMAIN 2: Index Test (NGS or aCGH (or both))

DOMAIN 2: Index Test (Methylation array)

DOMAIN 2: Index Test (FISH)

DOMAIN 2: Index Test (FISH (variant 1))

DOMAIN 2: Index Test (FISH (variant 2))

DOMAIN 2: Index Test (FISH (variant 3))

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Ariza 2010 *(Continued)*

DOMAIN 2: Index Test (Real-time PCR)

If a threshold was used, was it pre-specified?	Unclear
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear

Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

DOMAIN 2: Index Test (MLPA)

DOMAIN 2: Index Test (CGH)

DOMAIN 3: Reference Standard

Is the reference standards likely to correctly classify the target condition?	No

Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk

Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

DOMAIN 4: Flow and Timing

Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Unclear

Could the patient flow have introduced bias?	Unclear risk

Armanious 2017

Study characteristics	
Patient Sampling	**Inclusion/exclusion criteria**
	Inclusion criteria: FFPE specimens with histological diagnosis by a neuropathologist and confirmed FISH results.
	Prior testing
	Histopathological diagnosis and FISH
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 16
	Country: Canada
	Population source and setting: NR

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	Age: NR
	Gender: NR
	Karnofsky performance status: NR
	First diagnosis/recurrent disease: NR
Index tests	**2 tests:** FISH and NanoString
	FISH
	Tumour sample type: NR
	Region(s) analysed: NR
	Cut-off: NR
	NanoString
	Tumour sample type: FFPE
	Region(s) analysed: NR
	Cut-off: NR
	Additional details: quote: "Nanostring nCounter CNV assay … Samples were run on the nCounter CNV assay and analyzed by the nSolver software".
Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. FISH used as reference standard in some of our analyses.
Flow and timing	We presumed that all tests were performed on biopsied tumour material collected on 1 occasion.
Comparative	
Notes	Conference abstract

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (NanoString)			
If a threshold was used, was it pre-specified?	Unclear		

Armanious 2017 *(Continued)*

Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (aCGH)			
DOMAIN 2: Index Test (NGS)			
DOMAIN 2: Index Test (G-banding)			
DOMAIN 2: Index Test (FISH (variant 4))			
DOMAIN 2: Index Test (SNP array)			
DOMAIN 2: Index Test (PCR (with comparison to normal DNA))			
DOMAIN 2: Index Test (PCR (without comparison to normal DNA))			
DOMAIN 2: Index Test (CISH)			
DOMAIN 2: Index Test (MS)			
DOMAIN 2: Index Test (RFLP)			
DOMAIN 2: Index Test (PCR-based LOH)			
DOMAIN 2: Index Test (NGS or aCGH (or both))			
DOMAIN 2: Index Test (Methylation array)			
DOMAIN 2: Index Test (FISH)			
If a threshold was used, was it pre-specified?	Unclear		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (FISH (variant 1))			
DOMAIN 2: Index Test (FISH (variant 2))			
DOMAIN 2: Index Test (FISH (variant 3))			
DOMAIN 2: Index Test (Real-time PCR)			

Armanious 2017 *(Continued)*

DOMAIN 2: Index Test (MLPA)			

DOMAIN 2: Index Test (CGH)			

DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	No		
Could the reference standard, its conduct, or its interpretation have introduced bias?		High risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern

DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Were all patients included in the analysis?	No		
Could the patient flow have introduced bias?		High risk	

Belaud-Rotureau 2006

Study characteristics	

Patient Sampling	**Inclusion/exclusion criteria**
	Inclusion criteria: grade II or III glioma, sufficient frozen material for FISH analysis and histological control of frozen sections performed during the imprint procedure.
	Prior testing
	Examination of haematoxylin and eosin-stained paraffin sections. Glial-fibrillary acid-protein and MIB-1 immunostaining. Classified and graded according to WHO 2000.
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by** ≥ 2**DNA-based tests:** 23
	Country: France
	Population source and setting: Neurosurgery Department of the University Hospital Centre of Bordeaux, France. July 1995 to September 2002
	Age: NR
	Gender: NR
	Karnofsky performance status: NR
	First diagnosis/recurrent disease: unclear. Previously untreated glioma
Index tests	**3 tests:** FISH (variant 1), FISH (variant 2) and FISH (variant 3)
	FISH (variant 1)
	Tumour sample type: touch imprints of frozen tumours

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Belaud-Rotureau 2006 *(Continued)*

Region(s) analysed: 1p36.3 (D1Z2)/1q12 (D1Z1), 19q13.3/19pter

Cut-off: quote: "For each chromosome probe mix, hybridization signals of control and test probes were counted per nucleus, which was classified as follows: (1) In case of deletion, the ratio of control and test probes was 2/1, partially in conjunction with 4/2, 3/1, 4/1 ratios. (2) An imbalance hybridization pattern was associated to a disproportion of the ratio of control and test probes signals (3/2, 4/3, 5/3, etc.). Such pattern does not prove an LOH, which should be further determined by ancillary techniques. (3) A normal pattern (no deletion, no imbalance) was associated to an equal ratio of control and test probes signals (2/2, 4/4). At least 200 tumour cell nuclei were assessed. The cut-off values, i.e. the percentage of deleted patterns required to assess a deletion for each 1p36 or 19q13 probes were determined to be the mean + 3 SD of the percentage of deleted nuclei on control tissues (reactive lymphadenitis, n=5) [45]. A tumour was classified as deleted if the percentage (%) of deleted nuclei exceeded the cut-off value of the probe set. In the other cases, it was classified as (1) normal if the percentage of deleted plus imbalanced nuclei was less than the cutoff or (2) imbalanced if the percentage of imbalanced nuclei or the sum of imbalanced plus deleted nuclei was greater than or equal to the cut-off".

Comment: cut-off determined to be 10%.

Additional details: manual analysis with 1p36.3 (D1Z2)/1q12 (D1Z1) and 19q13.3/19pter probe set

FISH (variant 2)

Tumour sample type: touch imprints of frozen tumours

Region(s) analysed: 1p36/1q25, 19q13/19p13 (Abbott Vysis)

Cut-off: quote: "For each chromosome probe mix, hybridization signals of control and test probes were counted per nucleus, which was classified as follows: (1) In case of deletion, the ratio of control and test probes was 2/1, partially in conjunction with 4/2, 3/1, 4/1 ratios. (2) An imbalance hybridization pattern was associated to a disproportion of the ratio of control and test probes signals (3/2, 4/3, 5/3, etc.). Such pattern does not prove an LOH, which should be further determined by ancillary techniques. (3) A normal pattern (no deletion, no imbalance) was associated to an equal ratio of control and test probes signals (2/2, 4/4). At least 200 tumour cell nuclei were assessed. The cut-off values, i.e. the percentage of deleted patterns required to assess a deletion for each 1p36 or 19q13 probes were determined to be the mean + 3 SD of the percentage of deleted nuclei on control tissues (reactive lymphadenitis, n=5) [45]. A tumour was classified as deleted if the percentage (%) of deleted nuclei exceeded the cut-off value of the probe set. In the other cases, it was classified as (1) normal if the percentage of deleted plus imbalanced nuclei was less than the cut-off or (2) imbalanced if the percentage of imbalanced nuclei or the sum of imbalanced plus deleted nuclei was greater than or equal to the cut-off".

Comment: cut-off determined to be 6%.

Additional details: manual analysis with the 1p36/1q25 and 19q13/19p13 Abbott Vysis probe set.

FISH (variant 3)

Tumour sample type: touch imprints of frozen tumours

Region(s) analysed: 1p36/1q25, 19q13/19p13 (Abbott Vysis)

Cut-off: quote: "For each chromosome probe mix, hybridization signals of control and test probes were counted per nucleus, which was classified as follows: (1) In case of deletion, the ratio of control and test probes was 2/1, partially in conjunction with 4/2, 3/1, 4/1 ratios. (2) An imbalance hybridization pattern was associated to a disproportion of the ratio of control and test probes signals (3/2, 4/3, 5/3, etc.). Such pattern does not prove an LOH, which should be further determined by ancillary techniques. (3) A normal pattern (no deletion, no imbalance) was associated to an equal ratio of control and test probes signals (2/2, 4/4). At least 200 tumour cell nuclei were assessed. The cut-off values, i.e. the percentage of deleted patterns required to assess a deletion for each 1p36 or 19q13 probes were determined to be the mean + 3 SD of the percentage of deleted nuclei on control tissues (reactive lymphadenitis, n=5) [45]. A tumour was classified as deleted if the percentage (%) of deleted nuclei exceeded the cut-off value of the probe set. In the other cases, it was classified as (1) nor-

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Belaud-Rotureau 2006 *(Continued)*

	mal if the percentage of deleted plus imbalanced nuclei was less than the cut-off or (2) imbalanced if the percentage of imbalanced nuclei or the sum of imbalanced plus deleted nuclei was greater than or equal to the cut-off". Comment: cut-off determined to be 6%. Additional details: automatic analysis (Metafer 4, Metasystems, Althlussheim, Germany) with the 1p36/1q25 and 19q13/19p13 Abbott Vysis probe se
Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. No tests used as reference standard in our analyses.
Flow and timing	All tests were performed on frozen tissue samples.
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		High risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (NanoString)			
DOMAIN 2: Index Test (aCGH)			
DOMAIN 2: Index Test (NGS)			
DOMAIN 2: Index Test (G-banding)			
DOMAIN 2: Index Test (FISH (variant 4))			
DOMAIN 2: Index Test (SNP array)			
DOMAIN 2: Index Test (PCR (with comparison to normal DNA))			
DOMAIN 2: Index Test (PCR (without comparison to normal DNA))			

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Belaud-Rotureau 2006 *(Continued)*

DOMAIN 2: Index Test (CISH)		
DOMAIN 2: Index Test (MS)		
DOMAIN 2: Index Test (RFLP)		
DOMAIN 2: Index Test (PCR-based LOH)		
DOMAIN 2: Index Test (NGS or aCGH (or both))		
DOMAIN 2: Index Test (Methylation array)		
DOMAIN 2: Index Test (FISH)		
DOMAIN 2: Index Test (FISH (variant 1))		
If a threshold was used, was it pre-specified?	Yes	
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Yes	
Could the conduct or interpretation of the index test have introduced bias?	Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (FISH (variant 2))		
If a threshold was used, was it pre-specified?	Yes	
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Yes	
Could the conduct or interpretation of the index test have introduced bias?	Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (FISH (variant 3))		
If a threshold was used, was it pre-specified?	Yes	

Belaud-Rotureau 2006 *(Continued)*

Were the index test results interpreted without knowledge of the results of the other tests being compared?	Yes	
Could the conduct or interpretation of the index test have introduced bias?	Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (Real-time PCR)		
DOMAIN 2: Index Test (MLPA)		
DOMAIN 2: Index Test (CGH)		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Were all patients included in the analysis?	No	
Could the patient flow have introduced bias?	High risk	

Bigner 1999

Study characteristics

Patient Sampling	**Inclusion/exclusion criteria**

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Bigner 1999 *(Continued)*

| | Inclusion criteria: tumours composed partially or completely of neoplastic oligodendroglia (only cases on which there was agreement between 2 or 3 of the 3 observers for histological classification were included); frozen tissue and normal peripheral lymphocytes available.

Prior testing

Histopathological classification |
| --- | --- |
| Patient characteristics and setting | **Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 53

Country: USA

Population source and setting: NR

Age: mean: 39.9 years, standard deviation: 11.8 years

Gender: 64.2% male

Karnofsky performance status: NR

First diagnosis/recurrent disease: unclear. We excluded the recurrences for people whose primary tumour was also included in the study. Some additional participants had had prior surgery or RT, unclear if the tumours studied were recurrences. |
| Index tests | **2 tests:** CGH and PCR-based LOH

CGH

Tumour sample type: frozen

Region(s) analysed: genome wide

Cut-off: ratio of 0.85 indicated a loss.

PCR

Tumour sample type: frozen

Region(s) analysed: FGR, MYCL1, AMY2B (1p); D19S217, D19S112, D19S412, STD, D19S596, D19S180, D19S254, D19S218 (19q)

Cut-off: a reduction in intensity > 50% in the tumour lane compared to the corresponding blood lane was scored as LOH. |
Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. PCR-based LOH used as reference standard in some of our analyses.
Flow and timing	Both tests were performed on frozen tumour material.
Comparative	
Notes	
Methodological quality	

Item	Authors' judgement	Risk of bias	Applicability concerns

Bigner 1999 *(Continued)*

DOMAIN 1: Patient Selection

Was a consecutive or random sample of patients enrolled?	Yes	
Was a case-control design avoided?	Yes	
Did the study avoid inappropriate exclusions?	Yes	
Could the selection of patients have introduced bias?	Low risk	
Are there concerns that the included patients and setting do not match the review question?		High

DOMAIN 2: Index Test (NanoString)

DOMAIN 2: Index Test (aCGH)

DOMAIN 2: Index Test (NGS)

DOMAIN 2: Index Test (G-banding)

DOMAIN 2: Index Test (FISH (variant 4))

DOMAIN 2: Index Test (SNP array)

DOMAIN 2: Index Test (PCR (with comparison to normal DNA))

DOMAIN 2: Index Test (PCR (without comparison to normal DNA))

DOMAIN 2: Index Test (CISH)

DOMAIN 2: Index Test (MS)

DOMAIN 2: Index Test (RFLP)

DOMAIN 2: Index Test (PCR-based LOH)

If a threshold was used, was it pre-specified?	Unclear	
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear	
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern

DOMAIN 2: Index Test (NGS or aCGH (or both))

DOMAIN 2: Index Test (Methylation array)

DOMAIN 2: Index Test (FISH)

DOMAIN 2: Index Test (FISH (variant 1))

Bigner 1999 *(Continued)*

DOMAIN 2: Index Test (FISH (variant 2))		
DOMAIN 2: Index Test (FISH (variant 3))		
DOMAIN 2: Index Test (Real-time PCR)		
DOMAIN 2: Index Test (MLPA)		
DOMAIN 2: Index Test (CGH)		
If a threshold was used, was it pre-specified?	Unclear	
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear	
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	Low risk	

Blesa 2009

Study characteristics	
Patient Sampling	**Inclusion/exclusion criteria** Not explicitly reported but only oligodendrogliomas and oligoastrocytomas included. **Prior testing** Histopathological diagnosis according to WHO 2007 classification.
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 52

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Blesa 2009 *(Continued)*

	Country: Spain
	Population source and setting: Virgen de la Salud Hospital (Toledo, Spain), Clinic Hospital (Barcelona, Spain), and Xeral-Cies Hospital (Vigo, Spain). Time period NR
	Age: mean: 45.8 years, standard deviation: 12.5 years
	Gender: 55.8% male
	Karnofsky performance status: NR
	First diagnosis/recurrent disease: NR
Index tests	**4 tests:** aCGH, FISH, MLPA and PCR
	aCGH
	Tumour sample type: fresh-frozen
	Region(s) analysed: whole genome
	Cut-off: quote: "Genomic imbalances were determined on the basis of the log2 of the Cy3/Cy5 ratios of the average of 3 clone replicates, and regions were considered to have a gain or loss of DNA if at least 2 consecutive clones exceeded the +/-0.25 threshold".
	Additional details: used a (quote) "whole human genome CGH array developed in collaboration with Dr. Klaas Kok at the University Medical Centre Groningen (Department of Genetics, Groningen, The Netherlands)".
	FISH
	Tumour sample type: FFPE
	Region(s) analysed: 1p36/1q25, 19p13/19q13 (Vysis Inc., Downers Grove, Illinois, USA)
	Cut-off: quote: "Tumors were considered as having loss when an unbalanced 1p/1q (1 vs 2 signals) or 19p/19q (2 vs 1 signal) was identified in more than 25% of tumor cells. In addition, loss with ploidy was noted when an unbalanced pattern 1p/1q of 2 versus 4 signals or an unbalanced 19p/19q of 4 versus 2 signals was detected".
	MLPA
	Tumour sample type: unclear, either FFPE or frozen
	Region(s) analysed: NR. Salsa kit P088, MRC-Holland, Amsterdam, the Netherlands
	Cut-off: losses scored when ≥ 3 test probes exhibited a ratio < 0.7.
	Additional details: Salsa kit P088, MRC-Holland, Amsterdam, the Netherlands
	PCR
	Tumour sample type: fresh-frozen or FFPE
	Region(s) analysed: 1p: D1S199, D1S186, D1S162, D1S312, D1S226; 19q: D19S918, D19S112, D19S206
	Cut-off: LOH pattern, when the shorter allele presented a relatively high peak and the longer allele a low peak (never > 12% of the height of the

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Blesa 2009 *(Continued)*

	shorter allele), or when the intensity of the shorter allele was less than that of the longer allele. When all markers were homozygous, LOH was scored as positive.
	Additional details: PCR-based LOH (microsatellite) without the need for comparison to normal DNA. References Hatanpaa 2003a.
Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. FISH or PCR-based LOH used as reference standard in some of our analyses.
Flow and timing	We presumed that all tests were performed on biopsied tumour material collected on 1 occasion.
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (NanoString)			
DOMAIN 2: Index Test (aCGH)			
If a threshold was used, was it pre-specified?	Yes		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (NGS)			
DOMAIN 2: Index Test (G-banding)			
DOMAIN 2: Index Test (FISH (variant 4))			

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Blesa 2009 *(Continued)*

DOMAIN 2: Index Test (SNP array)		

DOMAIN 2: Index Test (PCR (with comparison to normal DNA))		

DOMAIN 2: Index Test (PCR (without comparison to normal DNA))		

DOMAIN 2: Index Test (CISH)		

DOMAIN 2: Index Test (MS)		

DOMAIN 2: Index Test (RFLP)		

DOMAIN 2: Index Test (PCR-based LOH)		
If a threshold was used, was it pre-specified?	Yes	
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear	
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern

DOMAIN 2: Index Test (NGS or aCGH (or both))		

DOMAIN 2: Index Test (Methylation array)		

DOMAIN 2: Index Test (FISH)		
If a threshold was used, was it pre-specified?	Yes	
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear	
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern

DOMAIN 2: Index Test (FISH (variant 1))		

DOMAIN 2: Index Test (FISH (variant 2))		

DOMAIN 2: Index Test (FISH (variant 3))		

DOMAIN 2: Index Test (Real-time PCR)		

DOMAIN 2: Index Test (MLPA)		
If a threshold was used, was it pre-specified?	Yes	
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear	

Could the conduct or interpretation of the index test have introduced bias?		Unclear risk
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (CGH)		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?		High risk
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Were all patients included in the analysis?	No	
Could the patient flow have introduced bias?		High risk

Bouvier 2004

Study characteristics	
Patient Sampling	**Inclusion/exclusion criteria** NR. The study included 35 patients operated on or biopsied at the Department of Neurosurgery (la Timone hospital, Marseille) between June and December 2001. This included (quote) "one grade III astrocytoma, 14 glioblastomas, 10 oligodendrogliomas (five grades II and III) and four mixed oligoastrocytomas (three grade II and one grade III). One oligodendroglioma grade II was reclassified as gliomatosis after neuroimaging review. Five cortectomies for epilepsy were used as controls". **Prior testing** Histopathological diagnosis according to the WHO classification (version not specified).
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 14 **Country:** France **Population source and setting:** Department of Neurosurgery, la Timone hospital, Marseille, France. June to December 2001

	Age: NR
	Gender: NR
	Karnofsky performance status: NR
	First diagnosis/recurrent disease: NR
Index tests	**2 tests:** FISH and PCR
	FISH
	Tumour sample type: frozen smear
	Region(s) analysed: 1p36.33 vs 1q12; 19q13.3 vs 19p13.2
	Cut-off: NR
	PCR
	Tumour sample type: frozen
	Region(s) analysed: 1p36.23 (D1S1612), 1p34.2 (D1S447), 1p13.3 (D1S252) and on 19q13.32 (D19S412 and D19S219), 19p13.12 (D19S226).
	Cut-off: LOH was scored when signal intensity was < 0.5 or > 2 in a tumour sample.
Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. FISH or PCR-based LOH used as reference standard in some of our analyses.
Flow and timing	We presumed that all tests were performed on biopsied tumour material collected on 1 occasion.
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (NanoString)			
DOMAIN 2: Index Test (aCGH)			

Bouvier 2004 *(Continued)*

DOMAIN 2: Index Test (NGS)			
DOMAIN 2: Index Test (G-banding)			
DOMAIN 2: Index Test (FISH (variant 4))			
DOMAIN 2: Index Test (SNP array)			
DOMAIN 2: Index Test (PCR (with comparison to normal DNA))			
DOMAIN 2: Index Test (PCR (without comparison to normal DNA))			
DOMAIN 2: Index Test (CISH)			
DOMAIN 2: Index Test (MS)			
DOMAIN 2: Index Test (RFLP)			
DOMAIN 2: Index Test (PCR-based LOH)			
If a threshold was used, was it pre-specified?	Unclear		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (NGS or aCGH (or both))			
DOMAIN 2: Index Test (Methylation array)			
DOMAIN 2: Index Test (FISH)			
If a threshold was used, was it pre-specified?	Unclear		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (FISH (variant 1))			
DOMAIN 2: Index Test (FISH (variant 2))			
DOMAIN 2: Index Test (FISH (variant 3))			
DOMAIN 2: Index Test (Real-time PCR)			

Bouvier 2004 *(Continued)*

DOMAIN 2: Index Test (MLPA)		
DOMAIN 2: Index Test (CGH)		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Were all patients included in the analysis?	No	
Could the patient flow have introduced bias?	High risk	

Broholm 2008

Study characteristics	
Patient Sampling	**Inclusion/exclusion criteria** NR. Quote: "46 patients were included in the study. The material consisted of 10 oligodendrogliomas (5 WHO Grade II (OII) and 5 Grade III (AOIII)), 10 mixed oligoastrocytomas (5 WHO Grade II (OAII) and 5 Grade III (AOAIII)), 10 astrocytomas (5 WHO Grade II (AII) and 5 Grade III (AAIII)) and 11 glioblastomas, WHO Grade IV (GBMIV)". **Prior testing** Histopathological diagnosis according to WHO 2000 classification.
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 38 **Country:** Denmark **Population source and setting:** FFPE tissue from the Laboratory of Neuropathology, Rigshospitalet, Copenhagen, Denmark. Time period NR **Age:** NR **Gender:** NR **Karnofsky performance status:** NR **First diagnosis/recurrent disease:** NR
Index tests	**2 tests:** FISH and PCR

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FISH

Tumour sample type: FFPE

Region(s) analysed: 1p36.33 and 19q13 (Vysis #40218 and #38967, Vysis, Des Plaines, Illinois, USA)

Cut-off: quote: "The FISH-sum in % was calculated (amount of cells with only one or none fluorescence signal for the investigated probe in relation to the total cell count). The conclusion – loss (Pos.) or no loss (N) was noted. For 1p loss the FISH-sum in % had to be higher than the calculated cut-off level at 43.24% and for 19q more than 55.12%".

PCR

Tumour sample type: FFPE

Region(s) analysed: D1S164 (1p34.4), D1S496 (1p34.4), D1S199 (1p36.1), D1S468 (1p36.3), D1S2736 (1p36.3); D19S867 (19q13.3), D19S888 (19q13.4), D19S572 (19q13.4), D19S210 (19q13.4)

Cut-off: allelic ratio < 0.5 or > 1.65

Additional details: PCR-based LOH (microsatellite) without the need for comparison to normal DNA. References Hatanpaa 2003a.

Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. FISH or PCR-based LOH used as reference standard in some of our analyses.
Flow and timing	We presumed that all tests were performed on biopsied tumour material collected on 1 occasion.
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (NanoString)			
DOMAIN 2: Index Test (aCGH)			

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Broholm 2008 *(Continued)*

DOMAIN 2: Index Test (NGS)			
DOMAIN 2: Index Test (G-banding)			
DOMAIN 2: Index Test (FISH (variant 4))			
DOMAIN 2: Index Test (SNP array)			
DOMAIN 2: Index Test (PCR (with comparison to normal DNA))			
DOMAIN 2: Index Test (PCR (without comparison to normal DNA))			
DOMAIN 2: Index Test (CISH)			
DOMAIN 2: Index Test (MS)			
DOMAIN 2: Index Test (RFLP)			
DOMAIN 2: Index Test (PCR-based LOH)			
If a threshold was used, was it pre-specified?	Unclear		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (NGS or aCGH (or both))			
DOMAIN 2: Index Test (Methylation array)			
DOMAIN 2: Index Test (FISH)			
If a threshold was used, was it pre-specified?	Unclear		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (FISH (variant 1))			
DOMAIN 2: Index Test (FISH (variant 2))			
DOMAIN 2: Index Test (FISH (variant 3))			
DOMAIN 2: Index Test (Real-time PCR)			

Broholm 2008 (Continued)

DOMAIN 2: Index Test (MLPA)		

DOMAIN 2: Index Test (CGH)		

DOMAIN 3: Reference Standard		

Is the reference standards likely to correctly classify the target condition?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?		High risk
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern

DOMAIN 4: Flow and Timing		

Was there an appropriate interval between index test and reference standard?	Yes	
Were all patients included in the analysis?	No	
Could the patient flow have introduced bias?		High risk

Burger 2001

Study characteristics	
Patient Sampling	**Inclusion/exclusion criteria**
	NR. The study included 18 cases of classic and borderline examples of infiltrating gliomas of oligodendroglioma, mixed gliomas (oligoastrocytomas), fibrillary astrocytomas of varying grade, and difficult-to-classify intermediate lesions (note, 1 glioma was included in Hatanpaa 2003b and is extracted as part of that study).
	Prior testing
	Initial histopathological diagnosis, followed by review and diagnosis according to WHO 2000 classification (independent of the results of CGH, FISH and LOH microsatellite analysis).
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 17
	Country: USA
	Population source and setting: NR
	Age: mean: 39.5 years, standard deviation: 12.7 years
	Gender: 41.2% male
	Karnofsky performance status: NR
	First diagnosis/recurrent disease: NR

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Burger 2001 *(Continued)*

Index tests	**3 tests:** CGH, FISH and PCR
	CGH
	Tumour sample type: FFPE (apart from 1 case, where fresh tissue was available)
	Region(s) analysed: genome wide
	Cut-off: scored as loss if the relative loss < 0.8
	FISH
	Tumour sample type: FFPE (apart from 1 case, where fresh tissue was available)
	Region(s) analysed: 1p36, 1q24, 19p13.1, 19q13.1-q13.2, 19q13.3
	Cut-off: NR
	PCR
	Tumour sample type: FFPE (apart from 1 case, where fresh tissue was available)
	Region(s) analysed: 1p: D1S226, D1S312, D1S162, D1S186, D1S199, D1S243; 19p: D19S206, D19S412, D19S112, D19S197, D19S400, D19S422, D19S570
	Cut-off: NR. Overall results for 1p and 19q not given. We assumed that if results were homozygous or indeterminant at all loci examined that codeletion was present.
Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. FISH or PCR-based LOH used as reference standard in some of our analyses.
Flow and timing	We presumed that all tests were performed on biopsied tumour material collected on 1 occasion.
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern

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Burger 2001 *(Continued)*

DOMAIN 2: Index Test (NanoString)			
DOMAIN 2: Index Test (aCGH)			
DOMAIN 2: Index Test (NGS)			
DOMAIN 2: Index Test (G-banding)			
DOMAIN 2: Index Test (FISH (variant 4))			
DOMAIN 2: Index Test (SNP array)			
DOMAIN 2: Index Test (PCR (with comparison to normal DNA))			
DOMAIN 2: Index Test (PCR (without comparison to normal DNA))			
DOMAIN 2: Index Test (CISH)			
DOMAIN 2: Index Test (MS)			
DOMAIN 2: Index Test (RFLP)			
DOMAIN 2: Index Test (PCR-based LOH)			
If a threshold was used, was it pre-specified?	No		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (NGS or aCGH (or both))			
DOMAIN 2: Index Test (Methylation array)			
DOMAIN 2: Index Test (FISH)			
If a threshold was used, was it pre-specified?	Unclear		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (FISH (variant 1))			
DOMAIN 2: Index Test (FISH (variant 2))			

Burger 2001 *(Continued)*

DOMAIN 2: Index Test (FISH (variant 3))	
DOMAIN 2: Index Test (Real-time PCR)	
DOMAIN 2: Index Test (MLPA)	
DOMAIN 2: Index Test (CGH)	

If a threshold was used, was it pre-specified?	Yes	
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear	
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern

DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern

DOMAIN 4: Flow and Timing	
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Byeon 2014

Study characteristics	
Patient Sampling	**Inclusion/exclusion criteria**
	Inclusion criteria: treated for rhabdoid glioblastoma
	Prior testing
	Histopathological diagnosis. Electron microscopy
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 3
	Country: Republic of Korea

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Byeon 2014 *(Continued)*

	Population source and setting: Seoul National University Hospital, Yonsei Severance Hospital, and Soon Cheon Yang University Bucheon Hospital, Republic of Korea. 2004–2011
	Age[a]: mean: 35.6 years, standard deviation: NR; range: 20–45 years
	Gender[a]: 20.0% male
	Karnofsky performance status: NR
	[a]For whole population: 5 participants included in the study, only 3 were tested with aCGH and FISH.
Index tests	**2 tests:** aCGH and FISH
	aCGH
	Tumour sample type: FFPE
	Region(s) analysed: genome wide
	Cut-off: NR
	Additional details: used a (quote) "MacArray Karyo (Macrogen, Seoul, South Korea), which consisted of 4365 human bacterial artificial chromosome clones".
	FISH
	Tumour sample type: NR
	Region(s) analysed: Vysis probes (Abbott Laboratories, Abbott Park, Illinois, USA). 1p36 and 19q13 (from DOI: 10.1593/tlo.12328, reference 12 in the paper).
	Cut-off: < 0.8 (from doi.org/10.1111/j.1440-1789.2006.00735.x, which is referenced by reference 12 in the paper).
Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. FISH used as reference standard in some of our analyses.
Flow and timing	We presumed that all tests were performed on biopsied tumour material collected on 1 occasion.
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		

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Byeon 2014 *(Continued)*

Could the selection of patients have introduced bias?	Unclear risk	
Are there concerns that the included patients and setting do not match the review question?		High
DOMAIN 2: Index Test (NanoString)		
DOMAIN 2: Index Test (aCGH)		
If a threshold was used, was it pre-specified?	Unclear	
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear	
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (NGS)		
DOMAIN 2: Index Test (G-banding)		
DOMAIN 2: Index Test (FISH (variant 4))		
DOMAIN 2: Index Test (SNP array)		
DOMAIN 2: Index Test (PCR (with comparison to normal DNA))		
DOMAIN 2: Index Test (PCR (without comparison to normal DNA))		
DOMAIN 2: Index Test (CISH)		
DOMAIN 2: Index Test (MS)		
DOMAIN 2: Index Test (RFLP)		
DOMAIN 2: Index Test (PCR-based LOH)		
DOMAIN 2: Index Test (NGS or aCGH (or both))		
DOMAIN 2: Index Test (Methylation array)		
DOMAIN 2: Index Test (FISH)		
If a threshold was used, was it pre-specified?	Yes	
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear	
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern

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DOMAIN 2: Index Test (FISH (variant 1))	
DOMAIN 2: Index Test (FISH (variant 2))	
DOMAIN 2: Index Test (FISH (variant 3))	
DOMAIN 2: Index Test (Real-time PCR)	
DOMAIN 2: Index Test (MLPA)	
DOMAIN 2: Index Test (CGH)	

DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	No		
Could the reference standard, its conduct, or its interpretation have introduced bias?		High risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Were all patients included in the analysis?	No		
Could the patient flow have introduced bias?		High risk	

Chaturbedi 2012

Study characteristics	
Patient Sampling	**Inclusion/exclusion criteria**
	NR. Quote: "We included DNA samples from 44 OTs, 9 paired blood lymphocytes collected from patients during surgical resection of their gliomas, and 14 glioblastoma multiformes (GBMs) in this study. Breaking down of 44 OT samples included in analysis are 21 WHO grade II oligodendroglioma (OG), 8 WHO Grade II mixed oligo-astrocytoma (OA), 15 either WHO grade III anaplastic oligodendroglioma (AO) or WHO grade III anaplastic mixed oligo-astrocytoma (AOA)".
	Prior testing
	Histopathological diagnosis
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 18
	Country: USA
	Population source and setting: University of California, Irvine, USA and University of Arkansas for Medical Sciences, USA. Time period NR

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Chaturbedi 2012 *(Continued)*

	Age: NR
	Gender: NR
	Karnofsky performance status: NR
	First diagnosis/recurrent disease: NR
Index tests	**2 tests:** FISH and real-time PCR
	FISH
	Tumour sample type: FFPE
	Region(s) analysed: 1p36/1q24, 19q13/19p13
	Cut-off: quote: "A normal ratio is considered 1.0 and any ratio <0.80 is considered deletion of the region of interest"
	Real-time PCR
	Tumour sample type: frozen
	Region(s) analysed: 1p: E2F2 (1p36) and NOTCH2 (1p13-11) (also looked at CAMTA1 (1p36.31-p36.23), but then excluded). 19q: PLAUR (19q13). Reference genes ERC2 (3p14.3), SPAG16 (2q34) and SPOCK1 (5q31). However: (quote) "A ratio of 1:1 between selected marker and reference genes in autosomal chromosomes is expected in normal cells while changes in this ratio in tumor DNA would suggest CNV, either deletion or amplification, in the studied gene of interest. Considering the inherent genome instability of cancer cells, we analyzed the stability of three reference genes in tumor samples and found amplification of SPAG16 in some OT. To mitigate this, we took the average of two ratios of ERC2 and SPOCK1 for most tumors. For other samples, the two reference gene ratios showing the most concordance were used to take a mean and SD. With consideration of 10%–20% variation inherited with real-time PCR, the mean values of the marker and reference ratio was taken for determination of deletion (<0.8) or amplification (>1.2), Shown in Table 1, there was a gain at the 1p marker gene CAMTA1 (1p36.31-23) in both GBM and OT, which were not found in other two 1p marker genes E2F2 (1p36) and NOTCH2 (1p13-p11). Thus average of these two 1p marker genes ratio to reference gene were taken to determine 1p deletion status (value <0.80 is considered 1p deleted)".
	Cut-off: marker/reference < 0.8 per gene. Mean of E2F2 (1p36) and NOTCH2 (1p13-p11) marker genes ratio to reference gene were taken to determine 1p deletion status (value < 0.80 is considered 1p deleted).
	Additional details: comparative quantitative PCR
Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. FISH used as reference standard in some of our analyses.
Flow and timing	We presumed that all tests were performed on samples obtained at the same time.
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			

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Chaturbedi 2012 *(Continued)*

Was a consecutive or random sample of patients enrolled?	Unclear	
Was a case-control design avoided?	Yes	
Did the study avoid inappropriate exclusions?	Unclear	
Could the selection of patients have introduced bias?		Unclear risk
Are there concerns that the included patients and setting do not match the review question?		High
DOMAIN 2: Index Test (NanoString)		
DOMAIN 2: Index Test (aCGH)		
DOMAIN 2: Index Test (NGS)		
DOMAIN 2: Index Test (G-banding)		
DOMAIN 2: Index Test (FISH (variant 4))		
DOMAIN 2: Index Test (SNP array)		
DOMAIN 2: Index Test (PCR (with comparison to normal DNA))		
DOMAIN 2: Index Test (PCR (without comparison to normal DNA))		
DOMAIN 2: Index Test (CISH)		
DOMAIN 2: Index Test (MS)		
DOMAIN 2: Index Test (RFLP)		
DOMAIN 2: Index Test (PCR-based LOH)		
DOMAIN 2: Index Test (NGS or aCGH (or both))		
DOMAIN 2: Index Test (Methylation array)		
DOMAIN 2: Index Test (FISH)		
If a threshold was used, was it pre-specified?	Yes	
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear	
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk

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Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (FISH (variant 1))		
DOMAIN 2: Index Test (FISH (variant 2))		
DOMAIN 2: Index Test (FISH (variant 3))		
DOMAIN 2: Index Test (Real-time PCR)		
If a threshold was used, was it pre-specified?	No	
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear	
Could the conduct or interpretation of the index test have introduced bias?	High risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (MLPA)		
DOMAIN 2: Index Test (CGH)		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Were all patients included in the analysis?	No	
Could the patient flow have introduced bias?	High risk	

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Cieply 2004

Study characteristics

Patient Sampling	**Inclusion/exclusion criteria** NR. 24 cases of gliomas (11 oligodendrogliomas, 5 mixed tumours, 8 astrocytomas) and 10 cases of non-neoplastic tissue were analysed. **Prior testing** Presumably histopathological diagnosis, but not explicitly reported. No other tests reported.
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 22 **Country:** USA **Population source and setting:** NR **Age:** NR **Gender:** NR **Karnofsky performance status:** NR **First diagnosis/recurrent disease:** NR
Index tests	**2 tests:** FISH and PCR **FISH** Tumour sample type: FFPE Region(s) analysed: NR. Quote: "For FISH, the Vysis dual-colour probe sets were utilized with a standard approach". Cut-off: NR **PCR** Tumour sample type: FFPE Region(s) analysed: 1p34-36, 19q13. Quote: "The PCR assay used up to 10 sets of primers for short tandem repeats that localize to 1p34-36 and 19q13". Cut-off: NR
Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. FISH or PCR-based LOH used as reference standard in some of our analyses.
Flow and timing	We presumed that all tests were performed on biopsied tumour material collected on 1 occasion.
Comparative	
Notes	Conference abstract

Methodological quality

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Cieply 2004 *(Continued)*

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (NanoString)			
DOMAIN 2: Index Test (aCGH)			
DOMAIN 2: Index Test (NGS)			
DOMAIN 2: Index Test (G-banding)			
DOMAIN 2: Index Test (FISH (variant 4))			
DOMAIN 2: Index Test (SNP array)			
DOMAIN 2: Index Test (PCR (with comparison to normal DNA))			
DOMAIN 2: Index Test (PCR (without comparison to normal DNA))			
DOMAIN 2: Index Test (CISH)			
DOMAIN 2: Index Test (MS)			
DOMAIN 2: Index Test (RFLP)			
DOMAIN 2: Index Test (PCR-based LOH)			
If a threshold was used, was it pre-specified?	Unclear		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (NGS or aCGH (or both))			
DOMAIN 2: Index Test (Methylation array)			
DOMAIN 2: Index Test (FISH)			

Cieply 2004 *(Continued)*

If a threshold was used, was it pre-specified?	Unclear
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear

Could the conduct or interpretation of the index test have introduced bias?	Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern

DOMAIN 2: Index Test (FISH (variant 1))
DOMAIN 2: Index Test (FISH (variant 2))
DOMAIN 2: Index Test (FISH (variant 3))
DOMAIN 2: Index Test (Real-time PCR)
DOMAIN 2: Index Test (MLPA)
DOMAIN 2: Index Test (CGH)
DOMAIN 3: Reference Standard

Is the reference standards likely to correctly classify the target condition?	No

Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern

DOMAIN 4: Flow and Timing

Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	No

Could the patient flow have introduced bias?	High risk

Clark 2013

Study characteristics	
Patient Sampling	**Inclusion/exclusion criteria**
	Inclusion criteria: glioblastoma cases in the Hillman Cancer registry. Exclusion criteria: cases of recurrent or treated (or both) glioma.
	Prior testing
	Histopathological diagnosis (WHO 2007 classification).

Clark 2013 *(Continued)*

Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 446
	Country: USA
	Population source and setting: Hillman Cancer Registry, University of Pittsburgh, USA. 2002–2010
	Age[a]: median: 63 years, interquartile range: NR; range: 18–89 years
	Gender[a]: 58.5% male
	Karnofsky performance status: NR
	First diagnosis/recurrent disease: 100% first diagnosis. Cases of recurrent glioma were excluded.
	[a]For whole population: there were 532 cases in the complete glioblastoma cohort, 491 had upfront 1p/19q testing, 446 had results for both tests.
Index tests	**2 tests:** FISH and PCR
	FISH
	Tumour sample type: FFPE
	Region(s) analysed: 1p36/1q25, 19q13/19p36 (Abbott Molecular, Des Plaines, Illinois, USA).
	Cut-off: quote: "Codeletion was counted if the 1p36/1q25 and 19q13/19p13 ratios were both below 0.87 and at least 20% of tumour nuclei showed relative deletion".
	PCR
	Tumour sample type: FFPE
	Region(s) analysed: D1S1172, D1S226, D1S162, D1S1161, D1S199, D1S407, D1S171, D19S112, D19S206, D19S559 (from 2007 onwards, comprising 75% of the total cohort)
	Cut-off: quote: "To be considered codeleted the majority of informative microsatellite loci on both 1p and 19q had to show LOH".
Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion.
	FISH or PCR-based LOH used as reference standard in some of our analyses.
Flow and timing	We presumed that all tests were performed on biopsied tumour material collected on 1 occasion.
Comparative	
Notes	
Methodological quality	

Item	Authors' judgement	Risk of bias	Applicability concerns

Diagnostic test accuracy and cost-effectiveness of tests for codeletion of chromosomal arms 1p and 19q in people with glioma (Review)   **92**

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DOMAIN 1: Patient Selection

Was a consecutive or random sample of patients enrolled?	Unclear	
Was a case-control design avoided?	Yes	
Did the study avoid inappropriate exclusions?	Yes	
Could the selection of patients have introduced bias?		Unclear risk
Are there concerns that the included patients and setting do not match the review question?		High

DOMAIN 2: Index Test (NanoString)

DOMAIN 2: Index Test (aCGH)

DOMAIN 2: Index Test (NGS)

DOMAIN 2: Index Test (G-banding)

DOMAIN 2: Index Test (FISH (variant 4))

DOMAIN 2: Index Test (SNP array)

DOMAIN 2: Index Test (PCR (with comparison to normal DNA))

DOMAIN 2: Index Test (PCR (without comparison to normal DNA))

DOMAIN 2: Index Test (CISH)

DOMAIN 2: Index Test (MS)

DOMAIN 2: Index Test (RFLP)

DOMAIN 2: Index Test (PCR-based LOH)

If a threshold was used, was it pre-specified?	Yes	
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear	
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern

DOMAIN 2: Index Test (NGS or aCGH (or both))

DOMAIN 2: Index Test (Methylation array)

DOMAIN 2: Index Test (FISH)

If a threshold was used, was it pre-specified?	Yes	

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Clark 2013 *(Continued)*

Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear	
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (FISH (variant 1))		
DOMAIN 2: Index Test (FISH (variant 2))		
DOMAIN 2: Index Test (FISH (variant 3))		
DOMAIN 2: Index Test (Real-time PCR)		
DOMAIN 2: Index Test (MLPA)		
DOMAIN 2: Index Test (CGH)		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Were all patients included in the analysis?	No	
Could the patient flow have introduced bias?	High risk	

Cowell 2004

Study characteristics

Patient Sampling	**Inclusion/exclusion criteria**
	NR. However, (quote) "To assess the usefulness of CGHa for the identification of LOH events in low-grade brain tumors, we used DNA from a series of 3 different tumor subtypes whose LOH status had previously been determined using microsatellite markers (23). The tumors had been grouped according to histopathological diagnosis and divided into low-grade oligodendrogliomas (LGO), anaplastic oligodendrogliomas (AO), and mixed oligoastrocytomas (MOA). From the original series of tumors classified using microsatellite markers, we analyzed representative samples that consisted of 6 LGOs, 5 AOs, and 3 MOAs. In each of these groups were examples of tumors where there was clear presence or absence of LOH for

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at least one of the microsatellite markers on each of the 1p and 19q chromosome arms".

Prior testing

Presumably histopathological diagnosis, although not explicitly reported. To be included in this study LOH status had to have previously been determined using microsatellite markers (PCR-based LOH).

Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 14
	Country: USA
	Population source and setting: Cleveland Clinic Foundation Department of Neurosurgery. Time period NR
	Age: NR
	Gender: NR
	Karnofsky performance status: NR
	First diagnosis/recurrent disease: NR
Index tests	**2 tests:** aCGH and PCR
	aCGH
	Tumour sample type: frozen
	Region(s) analysed: genome wide. Quote: "A genome-wide resource of ~6,000 FISH-mapped, gene/marker content-verified, sequenced BAC clones (22) from the RPCI-11 human BAC library are represented as immobilized DNA targets on glass slides for array-based CGH analysis, as previously described (20). Each clone is spotted in triplicate at 280 µm intervals (see http://genomics.roswellpark.org for a complete list of clones)".
	Cut-off: quote: "In general, background variation was considered to extend between ratios of 1.2 and 0.8 for diploid tumors on the linear scale and hybridization ratios outside of these values were considered losses or gains of genetic material".
	PCR
	Tumour sample type: frozen
	Region(s) analysed: 1p36 (D1S552, D1S1612, D1S468), 1p31 (D1S551, D1S430), 19q13.4 (D19S254, D19S572)
	Cut-off: NR
Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. PCR-based LOH used as reference standard in some of our analyses.
Flow and timing	We presumed that all tests were performed on biopsied tumour material collected on 1 occasion.
Comparative	
Notes	
Methodological quality	

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Cowell 2004 *(Continued)*

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Unclear		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		High risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (NanoString)			
DOMAIN 2: Index Test (aCGH)			
If a threshold was used, was it pre-specified?	Unclear		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (NGS)			
DOMAIN 2: Index Test (G-banding)			
DOMAIN 2: Index Test (FISH (variant 4))			
DOMAIN 2: Index Test (SNP array)			
DOMAIN 2: Index Test (PCR (with comparison to normal DNA))			
DOMAIN 2: Index Test (PCR (without comparison to normal DNA))			
DOMAIN 2: Index Test (CISH)			
DOMAIN 2: Index Test (MS)			
DOMAIN 2: Index Test (RFLP)			
DOMAIN 2: Index Test (PCR-based LOH)			
If a threshold was used, was it pre-specified?	Unclear		

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Cowell 2004 *(Continued)*

Were the index test results interpreted without knowledge of the results of the other tests being compared?	Yes

Could the conduct or interpretation of the index test have introduced bias?	Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern

DOMAIN 2: Index Test (NGS or aCGH (or both))
DOMAIN 2: Index Test (Methylation array)
DOMAIN 2: Index Test (FISH)
DOMAIN 2: Index Test (FISH (variant 1))
DOMAIN 2: Index Test (FISH (variant 2))
DOMAIN 2: Index Test (FISH (variant 3))
DOMAIN 2: Index Test (Real-time PCR)
DOMAIN 2: Index Test (MLPA)
DOMAIN 2: Index Test (CGH)
DOMAIN 3: Reference Standard

Is the reference standards likely to correctly classify the target condition?	No

Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern

DOMAIN 4: Flow and Timing

Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes

Could the patient flow have introduced bias?	Low risk

D'Haene 2019

Study characteristics

Patient Sampling	**Inclusion/exclusion criteria**

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Inclusion criteria: quote: "samples were selected according to the availability of NGS results obtained by the Ion AmpliSeq CHP (v2, Thermo Fisher Scientific, Carlsbad, CA, United States) and the availability of the 1p/19q codeletion status, as determined by FISH". Exclusion criteria: NGS results were excluded if they were low quality.

Prior testing

Presumably histopathological diagnosis (WHO 2016 classification for glioma samples), although not explicitly reported. Had to have NGS and FISH results.

Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 50
	Country: Belgium
	Population source and setting: Department of Pathology, Erasme Hospital, Brussels, Belgium. Time period NR
	Age: NR
	Gender: NR
	Karnofsky performance status: NR
	First diagnosis/recurrent disease: NR
Index tests	**2 tests:** FISH and NGS
	FISH
	Tumour sample type: FFPE
	Region(s) analysed: 1p36/1q25 and 19p13/19q13 (Vysis Inc., Downers Grove, Illinois, USA)
	Cut-off: quote: "The codeletion was considered to be positive in cases where the ratio of red (1p or 19q) versus green (1q or 19p) signals were lower than 0.8 after scoring at least 50 nuclei".
	NGS
	Tumour sample type: FFPE
	Region(s) analysed: 55 SNPs along the full length of chromosomes 1 and 19 (30 on chromosome 1 and 25 on chromosome 19). Quote: "These SNPs were selected based on the high polymorphic value of their minor allele frequency, as reported on the National Center for Biotechnology Information (NCBI) dbSNP database, as well as from previous reports [24,28]. The average distance between SNPs is 5.2 Mb in 1p, 8.0 Mb in 1q, 1.9 Mb in 19p, and 2.1 Mb in 19q". SNPs: 1p: rs7663, rs169957, rs309481, rs159525, rs157208, rs6425953, rs7315, rs7903, rs504816, rs7374, rs87061, rs11811946, rs5680, rs191142, rs54396, rs106075, rs1132, rs8888, rs6604120, rs8128; 1q: rs2275073, rs347303, rs4575136, rs898114, rs1342566, rs12744553, rs2802849, rs1770214, rs6692892, rs16848862, rs2275073, rs347303, rs4575136, rs898114, rs1342566; 19p: rs13345388, rs7256720, rs36115836, rs164020, rs57167556, rs2114724, rs7246440, rs10419689, rs8107776, rs4808732; 19q: rs7283, rs2542297, rs33841, rs12852, rs1291, rs17628, rs166539, rs3817, rs10113, rs8355, rs11573, rs193040, rs3814, rs10217, rs10448.
	Cut-off: quote: "To detect 1p/19q LOH, we firstly applied a quality criterion based on the SNP coverage. The test was considered optimal, suboptimal, or non-informative, according to the number of SNPs that were covered by fewer than 250 reads (Table 3). Secondly, the allelic frequencies (AF) for each SNP (with more than 250×) were annotated. Homozygous SNPs with the same nucleotide as that of the reference genome will have an AF of approximately 100%, while homozygous SNPs with a nucleotide that differs from the reference genome will have an AF of approximately 0%. Heterozygous SNPs will have an AF of approximately 50%. However, because NGS provides a semi-quantitative measure based on the number of reads [19], we established the following confidence intervals: 90–100% or 0–10% for homozygous markers, and 40–60% for heterozygous markers. These confidence intervals were defined based on the analysis of 12 nontumor samples. Imbalances of 1p and 19q markers due to LOH were scored when their AFs were outside the established ranges

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for homozygosity or heterozygosity (i.e., 10–40% or 60–90%) (Figure 1). We defined the criterion for the 1p/19q codeletion as the absence of any heterozygous markers in these chromosomal arms, together with the presence of at least one heterozygous marker in the opposite arm. No codeletion was scored if at least one heterozygous marker was present in 1p or 19q. A whole chromosome arm LOH is observed when there are no heterozygous markers present in either arm".

Additional details: custom-designed glioma NGS-targeted panel. Sequenced using an Ion Torrent Personal Genome Machine (Thermo Fisher).

Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. FISH used as reference standard in some of our analyses.
Flow and timing	We presumed that all tests were performed on biopsied tumour material collected on 1 occasion.
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		High risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (NanoString)			
DOMAIN 2: Index Test (aCGH)			
DOMAIN 2: Index Test (NGS)			
If a threshold was used, was it pre-specified?	Yes		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	

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Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

DOMAIN 2: Index Test (G-banding)

DOMAIN 2: Index Test (FISH (variant 4))

DOMAIN 2: Index Test (SNP array)

DOMAIN 2: Index Test (PCR (with comparison to normal DNA))

DOMAIN 2: Index Test (PCR (without comparison to normal DNA))

DOMAIN 2: Index Test (CISH)

DOMAIN 2: Index Test (MS)

DOMAIN 2: Index Test (RFLP)

DOMAIN 2: Index Test (PCR-based LOH)

DOMAIN 2: Index Test (NGS or aCGH (or both))

DOMAIN 2: Index Test (Methylation array)

DOMAIN 2: Index Test (FISH)

If a threshold was used, was it pre-specified?	Yes

Were the index test results interpreted without knowledge of the results of the other tests being compared?	Yes

Could the conduct or interpretation of the index test have introduced bias?	Low risk	

Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern

DOMAIN 2: Index Test (FISH (variant 1))

DOMAIN 2: Index Test (FISH (variant 2))

DOMAIN 2: Index Test (FISH (variant 3))

DOMAIN 2: Index Test (Real-time PCR)

DOMAIN 2: Index Test (MLPA)

DOMAIN 2: Index Test (CGH)

D'Haene 2019 *(Continued)*

DOMAIN 3: Reference Standard

Is the reference standards likely to correctly classify the target condition?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?		High risk
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern

DOMAIN 4: Flow and Timing

Was there an appropriate interval between index test and reference standard?	Yes	
Were all patients included in the analysis?	No	
Could the patient flow have introduced bias?		High risk

Dahlback 2009

Study characteristics

Patient Sampling	**Inclusion/exclusion criteria** Inclusion criteria: primary GBM (including GBM, multifocal GBM, gliosarcoma, giant cell GBM, GBM with granular cell component, GBM with oligodendroglial component). Aged ≥ 16 years at time of surgery. **Prior testing** Histopathological diagnosis according to the WHO 2007 classification.
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 57 **Country:** Norway **Population source and setting:** Department of Neurosurgery, Rikshospitalet, Oslo, Norway. January 2005 to January 2008 **Age:** mean: 61.7 years, standard deviation: 9.4 years **Gender:** 57.9% male **Karnofsky performance status:** NR **First diagnosis/recurrent disease:** NR

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Index tests	**2 tests:** CGH and G-banding
	CGH
	Tumour sample type: fresh-frozen
	Region(s) analysed: genome wide
	Cut-off: quote: "Aberrations were scored whenever the case profile and the reference profile did not overlap with a significance level of 99%".
	Additional details: high-resolution CGH. Quote: "CGH was performed on DNA from these samples according to the manufacturer's protocol and analyzed according to Kallioniemi et al., (1992) with the modifications described by Kraggerud et al., (2000) and Teixeira et al. (2004). Final evaluations of the CGH results used dynamic standard reference intervals (D-SRI) as described by Ribeiro et al. (2006)".
	G-banding
	Tumour sample type: fresh
	Region(s) analysed: genome wide
	Cut-off: N/A
	Additional details: quote: "Chromosome preparations were G-banded using Wright stain and karyotyped according to the ISCN (2005) guidelines".
Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. No tests used as reference standard in our analyses.
Flow and timing	We presumed that all tests were performed on biopsied tumour material collected on 1 occasion.
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (NanoString)			

Dahlback 2009 *(Continued)*

DOMAIN 2: Index Test (aCGH)		
DOMAIN 2: Index Test (NGS)		
DOMAIN 2: Index Test (G-banding)		
If a threshold was used, was it pre-specified?	Yes	
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Yes	
Could the conduct or interpretation of the index test have introduced bias?	Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (FISH (variant 4))		
DOMAIN 2: Index Test (SNP array)		
DOMAIN 2: Index Test (PCR (with comparison to normal DNA))		
DOMAIN 2: Index Test (PCR (without comparison to normal DNA))		
DOMAIN 2: Index Test (CISH)		
DOMAIN 2: Index Test (MS)		
DOMAIN 2: Index Test (RFLP)		
DOMAIN 2: Index Test (PCR-based LOH)		
DOMAIN 2: Index Test (NGS or aCGH (or both))		
DOMAIN 2: Index Test (Methylation array)		
DOMAIN 2: Index Test (FISH)		
DOMAIN 2: Index Test (FISH (variant 1))		
DOMAIN 2: Index Test (FISH (variant 2))		
DOMAIN 2: Index Test (FISH (variant 3))		
DOMAIN 2: Index Test (Real-time PCR)		
DOMAIN 2: Index Test (MLPA)		
DOMAIN 2: Index Test (CGH)		
If a threshold was used, was it pre-specified?	Unclear	
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear	

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Could the conduct or interpretation of the index test have introduced bias?	Unclear risk
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern
DOMAIN 3: Reference Standard	
Is the reference standards likely to correctly classify the target condition?	No
Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern
DOMAIN 4: Flow and Timing	
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	High risk

Dahlback 2011

Study characteristics	
Patient Sampling	**Inclusion/exclusion criteria**
	Inclusion criteria: Grade II glioma; aged ≥ 16 years at time of surgery
	Prior testing
	Histopathological diagnosis according to the WHO 2007 classification.
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 32
	Country: Norway
	Population source and setting: The Department of Neurosurgery, Oslo University Hospital, Rikshospitalet, Oslo, Norway. January 2005 to October 2008
	Age: mean: 38.4 years, standard deviation: 8.7 years
	Gender: 65.6% male
	Karnofsky performance status: NR
	First diagnosis/recurrent disease: 78.1% primary (25/32 participants with results on ≥ 2 tests), 21.9% recurrent (7/32 participants)
Index tests	**3 tests:** CGH, G-banding and PCR

Dahlback 2011 *(Continued)*

CGH

Tumour sample type: fresh-frozen

Region(s) analysed: genome wide

Cut-off: from Dahlback 2009: quote "Aberrations were scored whenever the case profile and the reference profile did not overlap with a significance level of 99%".

Additional details: quote: "HR-CGH [high-resolution CGH] was performed according to the manufacturer's protocol and analyzed as previously described (Dahlback et al., 2009)". Dahlback 2009: quote: "CGH was performed on DNA from these samples according to the manufacturer's protocol and analyzed according to Kallioniemi et al., (1992) with the modifications described by Kraggerud et al., (2000) and Teixeira et al. (2004). Final evaluations of the CGH results used dynamic standard reference intervals (D-SRI) as described by Ribeiro et al. (2006)".

G-banding

Tumour sample type: fresh

Region(s) analysed: whole genome

Cut-off: not applicable

Additional details: quote: "Chromosome preparations were G-banded using Wright stain and karyotyped according to the ISCN (2009)".

PCR

Tumour sample type: fresh-frozen

Region(s) analysed: at least 4 of 6 microsatellite markers on 1p35-36 (D1S2660, D1S507, D1S199, D1S2734, D1S1676, D1S247) and 19q13 (D19S918, D19S219, D19S112, D19S412, D19S596, D19S206) used.

Cut-off: As described in Scheie D, Cvancarova M, Mork S, Skullerud K, Andresen PA, Benestad I, Helseth E, Meling T, Beiske K. 2008. Can morphology predict 1p/19q loss in oligodendroglial tumors? *Histopathology* 53:578-87: results were defined as LOH-positive when the peak areas of fluorescent intensity curves, corresponding to PCR products from individual primer sets, showed a relative reduction of ≥ 40% when the products from tumour DNA were compared with those from normal DNA. Unclear how many markers had to display LOH.

Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. PCR-based LOH used as reference standard in some of our analyses.
Flow and timing	We presumed that all tests were performed on biopsied tumour material collected on 1 occasion.
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			

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Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (NanoString)			
DOMAIN 2: Index Test (aCGH)			
DOMAIN 2: Index Test (NGS)			
DOMAIN 2: Index Test (G-banding)			
If a threshold was used, was it pre-specified?	Yes		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (FISH (variant 4))			
DOMAIN 2: Index Test (SNP array)			
DOMAIN 2: Index Test (PCR (with comparison to normal DNA))			
DOMAIN 2: Index Test (PCR (without comparison to normal DNA))			
DOMAIN 2: Index Test (CISH)			
DOMAIN 2: Index Test (MS)			
DOMAIN 2: Index Test (RFLP)			
DOMAIN 2: Index Test (PCR-based LOH)			
If a threshold was used, was it pre-specified?	Unclear		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear		

Dahlback 2011 *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (NGS or aCGH (or both))			
DOMAIN 2: Index Test (Methylation array)			
DOMAIN 2: Index Test (FISH)			
DOMAIN 2: Index Test (FISH (variant 1))			
DOMAIN 2: Index Test (FISH (variant 2))			
DOMAIN 2: Index Test (FISH (variant 3))			
DOMAIN 2: Index Test (Real-time PCR)			
DOMAIN 2: Index Test (MLPA)			
DOMAIN 2: Index Test (CGH)			
If a threshold was used, was it pre-specified?	Unclear		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	No		
Could the reference standard, its conduct, or its interpretation have introduced bias?		High risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Were all patients included in the analysis?	No		

Could the patient flow have introduced bias?	High risk

Dubbink 2016

Study characteristics

Patient Sampling	**Inclusion/exclusion criteria** Inclusion criteria for EORTC 26951: quote: "Patients were eligible for this study if they had been diagnosed by the local pathologist with an anaplastic oligodendroglioma or anaplastic mixed oligoastrocytoma with at least 25% oligodendroglial elements; had at least three of five anaplastic characteristics (high cellularity, mitosis, nuclear abnormalities, endothelial proliferation, and necrosis); were between 16 and 70 years old; had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2; had provided written informed consent; had not undergone prior chemotherapy or RT to the skull; had no diseases interfering with follow-up; and had adequate hematologic, renal, and hepatic function (WBC [white blood cell] count ≥ 3.0 × 10^9/L, platelets ≥ 100 × 10^9/L, serum creatinine < 120 μmol/L, and serum bilirubin < 25 μmol/L)". How participants were selected for this study was NR. **Prior testing** Histopathological diagnosis. For participants with sufficient tissue to assess 1p and 19q status, this was performed by FISH in EORTC 26951. FISH results for the participants included in this study were NR.
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 49 **Country:** Austria, Belgium, Finland, France, Germany, Hungary, Italy, the Netherlands, Sweden, UK **Population source and setting:** quote "Forty-nine glioma tissues were collected between 1997 and 2003 during the European Organization of Research and Treatment of Cancer study 26951 on adjuvant procarbazine, lomustine, and vincristine chemotherapy of anaplastic oligodendrogliomas and anaplastic oligoastrocytomas". **Age^a*:** median: 48.6 years in the RT plus PCV arm; 49.8 years in the RT arm, interquartile range: NR; range: 18.6–68.7 years in the RT plus PCV arm; 19.2–68.7 years in the RT only arm. **Gender^a:** 57.6% male **Karnofsky performance status:** NR **First diagnosis/recurrent disease:** unclear. Patients with "newly diagnosed" anaplastic oligodendrogliomas or anaplastic oligoastrocytomas recruited into the trial. However, some had had previous resections for lower-grade tumours. ^{a}For whole population: results are for the 368 patients included in EORTC 26951, only 49 samples included in this study.
Index tests	**2 tests:** NGS and PCR-based LOH **NGS** Tumour sample type: FFPE Region(s) analysed: chromosome 1p: SNP rs7663, position 16112795; SNP rs169957, position 19683301; SNP rs169885, position 21628545; SNP rs742358, position 22459170; SNP rs309481, position 23210600; SNP rs189882, position 24868045; SNP rs9259, position 25168124; SNP rs7491, position 25895238; SNP rs159525, position 26213991; SNP rs7504, position 27238150; SNP rs6564, position 28212975; SNP rs157208, position 29245406; SNP rs6425953, position 36168038; SNP rs7686, position 38268918; SNP rs7315, position 40306898; SNP rs7903, position 45976472; SNP rs504816, position 53307957; SNP rs7374, position 55316322; SNP rs87061, position 60594980; SNP rs11811946, position 65952428; SNP rs5680, position 71477315; SNP rs191142, position 76990862; SNP rs12754569, position 85462971; SNP rs54396, po-

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sition 88776278; SNP rs106075, position 91604522, SNP rs1132, position 95394352; SNP rs8888, position 101338324; SNP rs6604120, position 109289487; SNP rs8128, position 115110683; Chromosome 19q: SNP rs7283, position 30106659, SNP rs2542297, position 31883906; SNP rs33841, position 34011248; SNP rs12852, position 35615179; SNP rs1291, position 38229378; SNP rs17628, position 39926509; SNP rs166539, position 40931717; SNP rs3817, position 44090195; SNP rs10113, position 47112648; SNP rs8355, position 48833800; SNP rs6521, position 49519873; SNP rs11573, position 51359497; SNP rs193040, position 53073605; SNP rs3814, position 53611187; SNP rs10217, position 56030428; SNP rs10448, position 59093239

Cut-off: quote: "A SNP was considered to be imbalanced or relatively lost when the variant B-allele frequency of a heterozygous SNP was either higher than 55% or lower than 45%. All variant frequencies between 45% and 55% were considered not to be aberrant. Similarly, cut-off lines were indicated at 5% and 95%, if not otherwise stated … Typical oligodendroglial co-deletion of 1p and 19q was defined as equivalent of all informative SNP on both chromosomal arms".

Additional details: quote: "A custom primer panel was designed that includes SNPs on chromosomes 1p and 19q using the Ion AmpliSeq Designer 2.0 (ThermoFisher Scientific Inc.).23 Highly polymorphic SNPs on both chromosomes were selected via the NCBI SNP database (http://www.ncbi.nlm.nih.gov/SNP, last accessed September 17, 2013) with a global minor allele frequency of at least 45% to obtain a high number of informative SNPs in each assay. The mean SNP density for chromosomes 1p and 19q was set arbitrarily to approximately 1SNP per 3.5Mb and 1 SNP per 2 Mb, respectively, yielding a total of 29 SNPs on chromosome 1p and 16 SNPs on chromosome 19q that covered the entire chromosomal arms (Figure 1A). Selected SNPs and their chromosomal localization (SNP database 138) are shown in Table 2. Next-generation targeted sequencing was performed by semiconductor sequencing with the Ion Torrent Personal Genome Machine".

PCR

Tumour sample type: FFPE

Region(s) analysed: D1S199 (locus: 1p36.13), D1S513 (1p35.2), D1S197 (1p32.3), D1S2806 (1p31.3), D1S495 (1p21.1), D19S875 (19q12), D19S198 (19q13.2), D19S412 (19q13.32), D19S606 (19q13.32), D19S572 (19q13.42)

Cut-off: quote: "Allelic losses were assessed based on the analysis of multiple informative markers, as described elsewhere.10 Typical oligodendroglial co-deletion of 1p and 19q was defined as equivalent imbalance of all informative SNPs on both chromosomal arms. If not all informative markers were lost, a chromosome was considered partially lost".

Additional details: PCR without the need for comparison to normal DNA: reference Hatanpaa 2003a, and state no normal tissue available.

Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. PCR-based LOH used as reference standard in some of our analyses.
Flow and timing	We presumed that all tests were performed on biopsied tumour material collected on 1 occasion.
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		

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Was a case-control design avoided?	Unclear		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (NanoString)			
DOMAIN 2: Index Test (aCGH)			
DOMAIN 2: Index Test (NGS)			
If a threshold was used, was it pre-specified?	Yes		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (G-banding)			
DOMAIN 2: Index Test (FISH (variant 4))			
DOMAIN 2: Index Test (SNP array)			
DOMAIN 2: Index Test (PCR (with comparison to normal DNA))			
DOMAIN 2: Index Test (PCR (without comparison to normal DNA))			
DOMAIN 2: Index Test (CISH)			
DOMAIN 2: Index Test (MS)			

Dubbink 2016 *(Continued)*

DOMAIN 2: Index Test (RFLP)		
DOMAIN 2: Index Test (PCR-based LOH)		
If a threshold was used, was it pre-specified?	Yes	
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear	
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (NGS or aCGH (or both))		
DOMAIN 2: Index Test (Methylation array)		
DOMAIN 2: Index Test (FISH)		
DOMAIN 2: Index Test (FISH (variant 1))		
DOMAIN 2: Index Test (FISH (variant 2))		
DOMAIN 2: Index Test (FISH (variant 3))		
DOMAIN 2: Index Test (Real-time PCR)		
DOMAIN 2: Index Test (MLPA)		
DOMAIN 2: Index Test (CGH)		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?		High risk
Are there concerns that the target condi-		Low concern

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tion as defined by the reference standard does not match the question?

DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Low risk

Duval 2014

Study characteristics	
Patient Sampling	**Inclusion/exclusion criteria**
	Inclusion criteria: oligodendrogliomas with FFPE tissue with previously established 1p/19q status by FISH.
	Prior testing
	Histopathological diagnosis according to WHO 2007 classification. Previously established 1p/19q status by FISH.
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 36
	Country: Canada
	Population source and setting: NR
	Age: median: 55 years, interquartile range: NR; range: 26–82 years
	Gender: 38.9% male
	Karnofsky performance status: NR
	First diagnosis/recurrent disease: 16.7% recurrent tumours
Index tests	**4 tests:** FISH (variant 1), FISH (variant 2), FISH (variant 3) and FISH (variant 4)
	FISH (variant 1)
	Tumour sample type: FFPE
	Region(s) analysed: 1p36/19q13 Dual-Color Probe kit (Abbott Molecular, Abbott Park, Illinois, USA)
	Cut-off: combination cut-off: quote: "The cut-off of nuclei that had to show deletion was calculated on a series of 10 non-neoplastic brain tissue sam-

Duval 2014 *(Continued)*

ples (from epilepsy surgery cases and autopsy brains). This cut-off was calculated using mean +3 SD and was set at 50% for both 1p and 19q. Cases above the cutoff were considered deleted and those under the cut-off were considered normal or imbalanced according to the literature guidelines [43,44]".

FISH (variant 2)

Tumour sample type: FFPE

Region(s) analysed: 1p36/19q13 Dual-Color Probe kit (Abbott Molecular, Abbott Park, Illinois, USA)

Cut-off: ratio cut-off: ratio ≤ 0.8 was considered to indicate a deletion; quote: "For each case the signal ratio of red signals to green signals per cell was also established. A ratio ≤0.8 was considered to indicate a deletion whereas a ratio between 0.8 and 1.1 was considered to indicate a normal status on the chromosomal arm. A ratio over 1.1 was considered to indicate polysomy and was classified in the imbalanced status subgroup [2,30]".

FISH (variant 3)

Tumour sample type: FFPE

Region(s) analysed: 1p36/19q13 Dual-Color Probe kit (Abbott Molecular, Abbott Park, Illinois, USA)

Cut-off: combination cut-off: quote: "cut-off at the median value of our tumor series which corresponds to a value of 65% for both 1p and 19q".

Additional details: ImmunoFISH. IHC performed against Ki67 (MIB-1).

FISH (variant 4)

Tumour sample type: FFPE

Region(s) analysed: 1p36/19q13 Dual-Color Probe kit (Abbott Molecular, Abbott Park, Illinois, USA)

Cut-off: ratio cut-off: ratio ≤ 0.8 was considered to indicate a deletion; quote: "For the ratio method, established values were the same as for the FISH".

Additional details: ImmunoFISH. IHC performed against Ki67 (MIB-1).

Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. No tests used as reference standard in our analyses.
Flow and timing	We presumed that all tests were performed on biopsied tumour material collected on 1 occasion.
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			

Duval 2014 *(Continued)*

Was a consecutive or random sample of patients enrolled?	No	
Was a case-control design avoided?	Yes	
Did the study avoid inappropriate exclusions?	Unclear	
Could the selection of patients have introduced bias?		High risk
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (NanoString)		
DOMAIN 2: Index Test (aCGH)		
DOMAIN 2: Index Test (NGS)		
DOMAIN 2: Index Test (G-banding)		
DOMAIN 2: Index Test (FISH (variant 4))		
If a threshold was used, was it pre-specified?	Yes	
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (SNP array)		
DOMAIN 2: Index Test (PCR (with comparison to normal DNA))		
DOMAIN 2: Index Test (PCR (without comparison to normal DNA))		
DOMAIN 2: Index Test (CISH)		
DOMAIN 2: Index Test (MS)		
DOMAIN 2: Index Test (RFLP)		
DOMAIN 2: Index Test (PCR-based LOH)		
DOMAIN 2: Index Test (NGS or aCGH (or both))		
DOMAIN 2: Index Test (Methylation array)		
DOMAIN 2: Index Test (FISH)		
DOMAIN 2: Index Test (FISH (variant 1))		

Duval 2014 *(Continued)*

If a threshold was used, was it pre-specified?	Yes		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (FISH (variant 2))			
If a threshold was used, was it pre-specified?	Yes		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (FISH (variant 3))			
If a threshold was used, was it pre-specified?	Yes		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Real-time PCR)			
DOMAIN 2: Index Test (MLPA)			
DOMAIN 2: Index Test (CGH)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	No		
Could the reference standard, its conduct, or its interpretation have introduced bias?		High risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			

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Duval 2014 *(Continued)*

Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Duval 2015

Study characteristics	
Patient Sampling	**Inclusion/exclusion criteria**
	NR
	Prior testing
	Not explicitly reported but presumably histopathological diagnosis
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 29
	Country: France
	Population source and setting: Centre Hospitalier Universitaire de Rennes (France). 2010–2015
	Age: NR
	Gender: NR
	Karnofsky performance status: NR
	First diagnosis/recurrent disease: NR
Index tests	**2 tests:** FISH (variant 1) and FISH (variant 2)
	FISH (variant 1)
	Tumour sample type: FFPE
	Region(s) analysed: 1p36/1q25 and 19q13/19p13 (Dual Color Probe kit, Abbott Molecular, Abbott Park, Illinois, USA).
	Cut-off: combination + ratio method. Cases deleted in 1 method and normal in the other were considered deleted.
	Combination method: deletion status combinations (for 1p and 19q, control/test): 2/0, 2/1, 3/0, 3/1, 4/1, 4/2, 5/2, 6/2, 6/3. Normal status combinations 2/2, 1/2. (Imbalance status combinations 1/3, 1/4, 2/3, 2/4, 2/5, 3/3, 3/4, 4/3, 4/4, 4/5, 5/4, 5/5, 5/6.) The cut-off value for the number of nuclei that had to show deletion was 55% for both 1p and 19q for deletion status (and 20% for imbalance status). Ratio method: the signal ratio of test:control probes ≤ 0.8 was considered to indicate a deletion.
	Additional details: automated analysis using the Metafer 4 software (Metasystem) using the "1p19q tile-sampling classifier".
	FISH (variant 2)
	Tumour sample type: FFPE

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Duval 2015 *(Continued)*

| | Region(s) analysed: 1p36/1q25 and 19q13/19p13 (Dual Color Probe kit, Abbott Molecular, Abbott Park, Illinois, USA).

Cut-off: combination + ratio method. Cases deleted in 1 method and normal in the other were considered deleted.

Combination method: deletion status combinations (for 1p and 19q, control/test): 2/0, 2/1, 3/0, 3/1, 4/1, 4/2, 5/2, 6/2, 6/3. Normal status combinations 2/2, 1/2. (Imbalance status combinations 1/3, 1/4, 2/3, 2/4, 2/5, 3/3, 3/4, 4/3, 4/4, 4/5, 5/4, 5/5, 5/6.) The cut-off value for the number of nuclei that had to show deletion was 55% for both 1p and 19q for deletion status (and 20% for imbalance status). Ratio method: the signal ratio of test:control probes ≤ 0.8 was considered to indicate a deletion.

Additional details: manual analysis |

Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. No tests used as reference standard in our analyses.
Flow and timing	We presumed that all tests were performed on biopsied tumour material collected on 1 occasion.
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (NanoString)			
DOMAIN 2: Index Test (aCGH)			
DOMAIN 2: Index Test (NGS)			
DOMAIN 2: Index Test (G-banding)			
DOMAIN 2: Index Test (FISH (variant 4))			
DOMAIN 2: Index Test (SNP array)			

Duval 2015 *(Continued)*

DOMAIN 2: Index Test (PCR (with comparison to normal DNA))

DOMAIN 2: Index Test (PCR (without comparison to normal DNA))

DOMAIN 2: Index Test (CISH)

DOMAIN 2: Index Test (MS)

DOMAIN 2: Index Test (RFLP)

DOMAIN 2: Index Test (PCR-based LOH)

DOMAIN 2: Index Test (NGS or aCGH (or both))

DOMAIN 2: Index Test (Methylation array)

DOMAIN 2: Index Test (FISH)

DOMAIN 2: Index Test (FISH (variant 1))

If a threshold was used, was it pre-specified?	Yes		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			High

DOMAIN 2: Index Test (FISH (variant 2))

If a threshold was used, was it pre-specified?	Unclear		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Unclear

DOMAIN 2: Index Test (FISH (variant 3))

DOMAIN 2: Index Test (Real-time PCR)

DOMAIN 2: Index Test (MLPA)

DOMAIN 2: Index Test (CGH)

DOMAIN 3: Reference Standard

Duval 2015 *(Continued)*

Is the reference standards likely to correctly classify the target condition?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Were all patients included in the analysis?	No	
Could the patient flow have introduced bias?	High risk	

Gadji 2009

Study characteristics	
Patient Sampling	**Inclusion/exclusion criteria**
	Inclusion criteria: initially diagnosed oligodendroglial or oligoastrocytomal brain tumour
	Prior testing
	Histopathological diagnosis: tumours were reviewed and classified according to the WHO 2007 classification.
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 11
	Country: Canada
	Population source and setting: Sherbrooke University hospital, Canada. 1993–2007
	Age: mean: 38.8 years, standard deviation: 8.3 years
	Gender*: 35.1% male
	Karnofsky performance status: NR
	First diagnosis/recurrent disease: NR
	*For whole population: 37 participants were included, but only 11 had both tests.
Index tests	**2 tests:** FISH and PCR
	FISH
	Tumour sample type: FFPE or fresh (touch-preparation smear)

Gadji 2009 *(Continued)*

Region(s) analysed: 1p36/1q25, 19p13/19q13 (Vysis LSI; Abbott Molecular, Des Plaines, Illinois, USA)

Cut-off: quote: "A case was considered deleted with 1p, 19q, or both when the scored nuclei displayed an imbalance between green and red signals".

PCR

Tumour sample type: NR

Region(s) analysed: chromosome 1 (8 test markers on the short arm and 2 control markers on the long arm): D1S2795 (1p36.31), D1S2666 (1p36.23), D1S244 (1p36.22), D1S2676 (1p34.3), D1S2729 (1p34.3), D1S2722 (1p34.2), D1S508 (1p36.31~p36.21), D1S2734 (1p35.36), D1S252 (1q21), D1S2346 (1q22); chromosome 19 (9 test markers on the long arm and 1 control marker on the short arm): D19S412 (19q13.32), D19S559 (19q13.32), D19S200 (19q13.2), D19S397 (19q13.14), D19S422 (19q13.13), D19S425 (19q13.12), D19S416 (19q13.11), D19S112 (19q13.3), D19S556 (19p13.13). All markers were obtained from IDT (Coralville, Iowa, USA).

Cut-off: quote: "An absence or a significant reduction in intensity of >50% in the tumor lane compared with the corresponding blood and saliva lanes was scored as LOH".

Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. FISH or PCR-based LOH used as reference standard in some of our analyses.
Flow and timing	We presumed that all tests were performed on biopsied tumour material collected on 1 occasion.
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (NanoString)			
DOMAIN 2: Index Test (aCGH)			
DOMAIN 2: Index Test (NGS)			

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DOMAIN 2: Index Test (G-banding)

DOMAIN 2: Index Test (FISH (variant 4))

DOMAIN 2: Index Test (SNP array)

DOMAIN 2: Index Test (PCR (with comparison to normal DNA))

DOMAIN 2: Index Test (PCR (without comparison to normal DNA))

DOMAIN 2: Index Test (CISH)

DOMAIN 2: Index Test (MS)

DOMAIN 2: Index Test (RFLP)

DOMAIN 2: Index Test (PCR-based LOH)

If a threshold was used, was it pre-specified?	Unclear		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern

DOMAIN 2: Index Test (NGS or aCGH (or both))

DOMAIN 2: Index Test (Methylation array)

DOMAIN 2: Index Test (FISH)

If a threshold was used, was it pre-specified?	Unclear		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern

DOMAIN 2: Index Test (FISH (variant 1))

DOMAIN 2: Index Test (FISH (variant 2))

DOMAIN 2: Index Test (FISH (variant 3))

DOMAIN 2: Index Test (Real-time PCR)

Gadji 2009 *(Continued)*

DOMAIN 2: Index Test (MLPA)		
DOMAIN 2: Index Test (CGH)		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?		High risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Were all patients included in the analysis?	Unclear	
Could the patient flow have introduced bias?		Unclear risk

Ghasimi 2016

Study characteristics		
Patient Sampling	**Inclusion/exclusion criteria**	
	Inclusion criteria: availability of FFPE tissue. No other criteria were reported. This study included 33 grade II–III gliomas and 58 glioblastomas.	
	Prior testing	
	Presumably histopathological diagnosis, although not explicitly reported.	
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 55	
	Country: Sweden	
	Population source and setting: Umeå University Hospital, Sweden. Time period NR	
	Age[a]: median: 58 years, interquartile range: NR; range: 15–80 years	
	Gender[a]: 59.3% male	
	Karnofsky performance status: NR	
	First diagnosis/recurrent disease: NR	
	[a]For whole population: the data are for the 59 participants who had SNP array data, of whom 55 also had FISH data.	
Index tests	**2 tests:** FISH and SNP array	

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Ghasimi 2016 *(Continued)*

	FISH
	Tumour sample type: FFPE
	Region(s) analysed: 1p36/1q13, 19p13/19q13 (Vysis, Illinois, USA)
	Cut-off: 1p36/1q25 ratios < 0.88 and 19q13/19p13 ratios < 0.74 in > 12% of the cells were considered as deleted.
	SNP array
	Tumour sample type: FFPE
	Region(s) analysed: regions corresponding to the location of the FISH probes
	Cut-off: quote: "For comparison between FISH and ASCAT, we extracted the median total copy number from the ASCAT profiles for the genomic regions corresponding to the FISH probes. These copy number data were subsequently used to mimic the sample classification based on FISH data, by calculating the same ratios and using the same cutoff values that had been used for classification by FISH".
	Additional details: "Illumina HumanOmni1-Quad BeadChips. The ASCAT algorithm [26] (version 2.0) was used to calculate somatic whole-genome allele-specific copy number profiles (ASCAT-profiles), as well as estimates of tumor cell content and tumor cell ploidy".
Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. FISH used as reference standard in some of our analyses.
Flow and timing	We presumed that all tests were performed on biopsied tumour material collected on 1 occasion.
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (NanoString)			
DOMAIN 2: Index Test (aCGH)			

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DOMAIN 2: Index Test (NGS)			
DOMAIN 2: Index Test (G-banding)			
DOMAIN 2: Index Test (FISH (variant 4))			
DOMAIN 2: Index Test (SNP array)			
If a threshold was used, was it pre-specified?	Yes		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (PCR (with comparison to normal DNA))			
DOMAIN 2: Index Test (PCR (without comparison to normal DNA))			
DOMAIN 2: Index Test (CISH)			
DOMAIN 2: Index Test (MS)			
DOMAIN 2: Index Test (RFLP)			
DOMAIN 2: Index Test (PCR-based LOH)			
DOMAIN 2: Index Test (NGS or aCGH (or both))			
DOMAIN 2: Index Test (Methylation array)			
DOMAIN 2: Index Test (FISH)			
If a threshold was used, was it pre-specified?	Yes		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (FISH (variant 1))			
DOMAIN 2: Index Test (FISH (variant 2))			
DOMAIN 2: Index Test (FISH (variant 3))			
DOMAIN 2: Index Test (Real-time PCR)			

Ghasimi 2016 *(Continued)*

DOMAIN 2: Index Test (MLPA)		
DOMAIN 2: Index Test (CGH)		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Were all patients included in the analysis?	No	
Could the patient flow have introduced bias?	High risk	

Harada 2011

Study characteristics	
Patient Sampling	**Inclusion/exclusion criteria**
	Inclusion criteria: samples submitted for routine clinical analysis of 1p/19q loss.
	Prior testing
	Not explicitly reported, but presumably histopathological diagnosis.
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 29
	Country: USA
	Population source and setting: Johns Hopkins Medical Institutions. 2010
	Age[a]: mean: 42.7 years (48.3 years in participants with oligodendrogliomas, 37.7 years in participants with non-oligodendrioglioma tumours, standard deviation: 15.3 years[b]; range: 14–82 years
	Gender[a]: 53.3% male
	Karnofsky performance status: NR
	First diagnosis/recurrent disease: NR
	[a]Included 1 participant with pineal parenchymal tumour of intermediate differentiation, who was excluded.

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Harada 2011 *(Continued)*

ᵇThe standard error of the mean was 4.47 years in participants with oligo-dendrogliomas and 3.35 years in participants with non-oligodendroglioma tumours. The standard deviation was calculated from these figures.

Index tests	**2 tests:** PCR and SNP array
	PCR
	Tumour sample type: FFPE
	Region(s) analysed: chromosome 1: D1S199, D1S186, D1S162, D1S312, D1S226; chromosome 19: D19S918, D19S112, D19S206
	Cut-off: NR
	Additional details: Multiplex PCR (as described in Hatanpaa 2003a and Hatanpaa 2003b). Fluorescent labelled PCR products were detected by capillary electrophoresis with use of the ABI 3130 Genetic Analyzer and GeneMapper software version 4 (Applied Biosystems, Carlsbad, California, USA).
	SNP array
	Tumour sample type: FFPE
	Region(s) analysed: genome wide
	Cut-off: NR
	Additional details: quote: "Illumina Infinium II SNP array with 300K markers (HumanCytoSNP-12, Illumina Inc., San Diego, CA)".
Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. PCR-based LOH used as reference standard in some of our analyses.
Flow and timing	We presumed that all tests were performed on biopsied tumour material collected on 1 occasion.
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Unclear risk	

Are there concerns that the included patients and setting do not match the review question?	Low concern

DOMAIN 2: Index Test (NanoString)

DOMAIN 2: Index Test (aCGH)

DOMAIN 2: Index Test (NGS)

DOMAIN 2: Index Test (G-banding)

DOMAIN 2: Index Test (FISH (variant 4))

DOMAIN 2: Index Test (SNP array)

If a threshold was used, was it pre-specified?	Unclear
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear

Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

DOMAIN 2: Index Test (PCR (with comparison to normal DNA))

DOMAIN 2: Index Test (PCR (without comparison to normal DNA))

DOMAIN 2: Index Test (CISH)

DOMAIN 2: Index Test (MS)

DOMAIN 2: Index Test (RFLP)

DOMAIN 2: Index Test (PCR-based LOH)

If a threshold was used, was it pre-specified?	Unclear
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear

Could the conduct or interpretation of the index test have introduced bias?	Unclear risk

Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

DOMAIN 2: Index Test (NGS or aCGH (or both))

DOMAIN 2: Index Test (Methylation array)

DOMAIN 2: Index Test (FISH)

DOMAIN 2: Index Test (FISH (variant 1))

DOMAIN 2: Index Test (FISH (variant 2))		
DOMAIN 2: Index Test (FISH (variant 3))		
DOMAIN 2: Index Test (Real-time PCR)		
DOMAIN 2: Index Test (MLPA)		
DOMAIN 2: Index Test (CGH)		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	Low risk	

Hatanpaa 2003a

Study characteristics	
Patient Sampling	**Inclusion/exclusion criteria**
	Inclusion criteria: tested for 1p/19q codeletion by ≥ 2 of the following 3 reference methods with concordant results: CGH, FISH and PCR-based microsatellite analysis with comparison to normal DNA from the same participant.
	Prior testing
	Tested for 1p/19q codeletion by ≥ 2 of the following 3 reference methods with concordant results: CGH, FISH and PCR-based microsatellite analysis with comparison to normal DNA from the same participant. Appeared that histopathological grading was redone from the original studies.
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 10
	Country: USA
	Population source and setting: FFPE glioma specimens with concordant results in Smith 1999 or Burger 2001 (note: we could not match 1 tumour, T117, to tumours described in either study)

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Age: NR

Gender: NR

Karnofsky performance status: NR

First diagnosis/recurrent disease: NR in this publication. Smith 1999 included both primary and recurrent tumour specimens.

Index tests	**4 tests:** CGH, FISH, PCR (with comparison to normal DNA) and PCR (without comparison to normal DNA)

CGH

Tumour sample type: NR

Region(s) analysed: NR

Cut-off: Smith 1999 references Mohapatra G, Kim DH, Feuerstein BG. Detection of multiple gains and losses of genetic material in ten glioma cell lines by comparative genomic hybridization. *Genes, Chromosomes & Cancer* 1995;13;86-93. In this publication: quote: "Definition of CGH ratio thresholds to define ratios that were indicative of changes in DNA copy number, we performed 21 CGH experiments using normal control DNA. We calculated average ratio changes and standard deviations by using the software program cghprofstats. new (Piper et al., 1994). The average ratio for all 21 hybridizations was 0.99 (range 0.9-1.1). The average standard deviation was 0.04 (range 0.02-0.06). Taking these findings into consideration, we chose upper and lower ratio thresholds of 1.2 and 0.8, respectively. Any change in ratio in excess of these thresholds was interpreted as indicative of DNA copy number changes only if found in both forward and reverse experiments. Amplifications were defined both by a ratio >2.0 and by visual inspection". Piper J, Rutovitz D, Sudar D, Kallioniemi A, Kallioniemi O, Waldman FM, et al. Computer image analysis of comparative genomic hybridization. *Cytometry* 1995;19:10-26 also cited.

FISH

Tumour sample type: NR

Region(s) analysed: from Smith 1999: 1p36, 1q24, 19p13.1, 19q13.1-q13.2, 19q13.3

Cut-off: for Smith 1999 we defined codeletion defined as hemizygous deletion of 1p36, 1q13.1-q13.2 and 19q13.3. What defined hemizygous deletion NR. Also cited Qian J, Bostwick DG, Takahashi S, Borell TJ, Herath JF, Lieber MM et al. Chromosomal anomalies in prostatic intraepithelial neoplasia and carcinoma detected by fluorescence in situ hybridization. *Cancer Research* 1995;55:5408-14. In this paper (quote) "abnormal autosomal loss required ≥55% nuclei with zero or one signal". Unclear if this threshold was used.

PCR (with comparison to normal DNA) (referred to as PCR-based LOH below. Note: the risk of bias and applicability judgements for this PCR variant appear in Figure 7)

Tumour sample type: NR

Region(s) analysed: 1p: D1S468, D1S1612, D1S1597, D1S199, D1S1665, D1S1728, D1S1588, D1S1675, D1S187; 19q: D19S213, D19S569, D19S422. D19S219, SM, S19S112, S19S412, D19S596, HRC, D19S589, D19S218
Cut-off: For Smith 1999 we defined codeletion as all markers showing confirmed allelic loss, presumed allelic loss, were homozygous or were indeterminant.

Additional details: PCR with comparison to normal DNA

PCR (without comparison to normal DNA)

Tumour sample type: FFPE

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	Region(s) analysed: chromosome 1: D1S162, D1S226, D1S199, D1S186, D1S312; chromosome 19: D19S112, D19S918, D19S206. Cut-off: presence of 1 allele or LOH pattern A or B at all loci ("LOH pattern A, consisted of a shorter allele (the allele measuring fewer nucleotides in length) with a relatively high peak and a longer allele with a diminutive peak (Fig. 6). The height of the longer allele was never more than 12% of the height of the shorter allele … LOH pattern B, the intensity of the shorter allele was less than that of the longer allele"). Additional details: PCR-based LOH (microsatellite) without the need for comparison to normal DNA. Quote: "Multiplex PCR amplification of microsatellite loci followed by high-resolution PCR product sizing by capillary electrophoresis on formalin-fixed, paraffin-embedded tissue".
Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. FISH or PCR-based LOH used as reference standard in some of our analyses.
Flow and timing	We presumed that all tests were performed on biopsied tumour material collected on 1 occasion.
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
Could the selection of patients have introduced bias?		High risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (NanoString)			
DOMAIN 2: Index Test (aCGH)			
DOMAIN 2: Index Test (NGS)			
DOMAIN 2: Index Test (G-banding)			
DOMAIN 2: Index Test (FISH (variant 4))			
DOMAIN 2: Index Test (SNP array)			
DOMAIN 2: Index Test (PCR (with comparison to normal DNA))			

Hatanpaa 2003a *(Continued)*

DOMAIN 2: Index Test (PCR (without comparison to normal DNA))

If a threshold was used, was it pre-specified?	No

Were the index test results interpreted without knowledge of the results of the other tests being compared?	No

Could the conduct or interpretation of the index test have introduced bias?	High risk	

Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern

DOMAIN 2: Index Test (CISH)

DOMAIN 2: Index Test (MS)

DOMAIN 2: Index Test (RFLP)

DOMAIN 2: Index Test (PCR-based LOH)

If a threshold was used, was it pre-specified?	Unclear

Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear

Could the conduct or interpretation of the index test have introduced bias?	Low risk	

Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern

DOMAIN 2: Index Test (NGS or aCGH (or both))

DOMAIN 2: Index Test (Methylation array)

DOMAIN 2: Index Test (FISH)

If a threshold was used, was it pre-specified?	Unclear

Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear

Could the conduct or interpretation of the index test have introduced bias?	Low risk	

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Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (FISH (variant 1))		
DOMAIN 2: Index Test (FISH (variant 2))		
DOMAIN 2: Index Test (FISH (variant 3))		
DOMAIN 2: Index Test (Real-time PCR)		
DOMAIN 2: Index Test (MLPA)		
DOMAIN 2: Index Test (CGH)		
If a threshold was used, was it pre-specified?	Unclear	
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear	
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?		High risk
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Low risk

Diagnostic test accuracy and cost-effectiveness of tests for codeletion of chromosomal arms 1p and 19q in people with glioma (Review) **132**

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Hatanpaa 2003b *(Continued)*

Study characteristics

Patient Sampling	**Inclusion/exclusion criteria** Inclusion criteria: tested for 1p/19q codeletion by ≥ 2 of the following 3 reference methods with concordant results: CGH, FISH and PCR-based microsatellite analysis with comparison to normal DNA from the same participant. **Prior testing** Tested for 1p/19q codeletion by ≥ 2 of the following 3 reference methods with concordant results: CGH, FISH and PCR-based microsatellite analysis with comparison to normal DNA from the same participant. Appeared that histopathological grading was redone from the original studies.
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 9 **Country:** USA **Population source and setting:** FFPE glioma specimens with concordant results in Smith 1999 or Burger 2001 (note: we could not match 1 tumour, T117, to tumours described in either study) **Age:** NR **Gender:** NR **Karnofsky performance status:** NR **First diagnosis/recurrent disease:** NR in this publication. Smith 1999 included both primary and recurrent tumour specimens.
Index tests	**4 tests:** CGH, FISH, PCR (with comparison to normal DNA) and PCR (without comparison to normal DNA) **CGH** Tumour sample type: NR Region(s) analysed: NR Cut-off: Smith 1999 references Mohapatra G, Kim DH, Feuerstein BG. Detection of multiple gains and losses of genetic material in ten glioma cell lines by comparative genomic hybridization. *Genes, Chromosomes & Cancer* 1995;13;86-93. In this publication: "Definition of CGH ratio thresholds to define ratios that were indicative of changes in DNA copy number, we performed 21 CGH experiments using normal control DNA. We calculated average ratio changes and standard deviations by using the software program cghprofstats.new (Piper et al., 1994). The average ratio for all 21 hybridizations was 0.99 (range 0.9-1.1). The average standard deviation was 0.04 (range 0.02-0.06). Taking these findings into consideration, we chose upper and lower ratio thresholds of 1.2 and 0.8, respectively. Any change in ratio in excess of these thresholds was interpreted as indicative of DNA copy number changes only if found in both forward and reverse experiments. Amplifications were defined both by a ratio >2.0 and by visual inspection". Piper J, Rutovitz D, Sudar D, Kallioniemi A, Kallioniemi O, Waldman FM, et al. Computer image analysis of comparative genomic hybridization. *Cytometry* 1995;19:10-26 also cited. **FISH** Tumour sample type: NR

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Region(s) analysed: from Smith 1999: 1p36, 1q24, 19p13.1, 19q13.1-q13.2, 19q13.3

Cut-off: for Smith 1999 we defined codeletion defined as hemizygous deletion of 1p36, 1q13.1-q13.2 and 19q13.3. What defined hemizygous deletion NR. Also cited Qian J, Bostwick DG, Takahashi S, Borell TJ, Herath JF, Lieber MM et al. Chromosomal anomalies in prostatic intraepithelial neoplasia and carcinoma detected by fluorescence in situ hybridization. *Cancer Research* 1995;55:5408-14. In this paper (quote) "abnormal autosomal loss required ≥55% nuclei with zero or one signal". Unclear if this threshold was used.

PCR (with comparison to normal DNA) (referred to as PCR-based LOH below. Note: the risk of bias and applicability judgements for this PCR variant appear in Figure 7 **)**

Tumour sample type: NR

Region(s) analysed: 1p: D1S468, D1S1612, D1S1597, D1S199, D1S1665, D1S1728, D1S1588, D1S1675, D1S187; 19q: D19S213, D19S569, D19S422. D19S219, SM, S19S112, S19S412, D19S596, HRC, D19S589, D19S218

Cut-off: for Smith 1999 we defined codeletion as all markers showing confirmed allelic loss, presumed allelic loss, were homozygous or were indeterminant.

Additional details: PCR with comparison to normal DNA

PCR (without comparison to normal DNA)

Tumour sample type: FFPE

Region(s) analysed: chromosome 1: D1S162, D1S226, D1S199, D1S186, D1S312; chromosome 19: D19S112, D19S918, D19S206.

Cut-off: presence of 1 allele or LOH pattern A or B at all loci ("LOH pattern A, consisted of a shorter allele (the allele measuring fewer nucleotides in length) with a relatively high peak and a longer allele with a diminutive peak (Fig. 6). The height of the longer allele was never more than 12% of the height of the shorter allele … LOH pattern B, the intensity of the shorter allele was less than that of the longer allele").

Additional details: PCR-based LOH (microsatellite) without the need for comparison to normal DNA. Quote: "Multiplex PCR amplification of microsatellite loci followed by high-resolution PCR product sizing by capillary electrophoresis on formalin-fixed, paraffin-embedded tissue".

Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. FISH or PCR-based LOH used as reference standard in some of our analyses.
Flow and timing	We presumed that all tests were performed on biopsied tumour material collected on 1 occasion.
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		

Hatanpaa 2003b *(Continued)*

Did the study avoid inappropriate exclusions?	No		
Could the selection of patients have introduced bias?		High risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (NanoString)			
DOMAIN 2: Index Test (aCGH)			
DOMAIN 2: Index Test (NGS)			
DOMAIN 2: Index Test (G-banding)			
DOMAIN 2: Index Test (FISH (variant 4))			
DOMAIN 2: Index Test (SNP array)			
DOMAIN 2: Index Test (PCR (with comparison to normal DNA))			
DOMAIN 2: Index Test (PCR (without comparison to normal DNA))			
If a threshold was used, was it pre-specified?	Yes		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (CISH)			
DOMAIN 2: Index Test (MS)			
DOMAIN 2: Index Test (RFLP)			
DOMAIN 2: Index Test (PCR-based LOH)			
If a threshold was used, was it pre-specified?	Unclear		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear		

Hatanpaa 2003b *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?	Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (NGS or aCGH (or both))		
DOMAIN 2: Index Test (Methylation array)		
DOMAIN 2: Index Test (FISH)		
If a threshold was used, was it pre-specified?	Unclear	
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear	
Could the conduct or interpretation of the index test have introduced bias?	Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (FISH (variant 1))		
DOMAIN 2: Index Test (FISH (variant 2))		
DOMAIN 2: Index Test (FISH (variant 3))		
DOMAIN 2: Index Test (Real-time PCR)		
DOMAIN 2: Index Test (MLPA)		
DOMAIN 2: Index Test (CGH)		
If a threshold was used, was it pre-specified?	Unclear	
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear	
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 3: Reference Standard		

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Hatanpaa 2003b *(Continued)*

Is the reference standards likely to correctly classify the target condition?	No

Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk

Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

DOMAIN 4: Flow and Timing

Was there an appropriate interval between index test and reference standard?	Yes

Were all patients included in the analysis?	Yes

Could the patient flow have introduced bias?	Low risk

Hinrichs 2016

Study characteristics	

Patient Sampling	**Inclusion/exclusion criteria**
	Inclusion criteria: GBM-O. Cases were selected from the 28 diagnosed cases (quote) "based on availability of tissue and diversity of clinical diagnostic markers".
	Prior testing
	Histopathological diagnosis using WHO 2007 classification. FISH for EGFR and 1p/19q. Immunohistochemistry for IDH1.

Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 8
	Country: USA
	Population source and setting: Emory University Hospitals, USA. 2007–2011
	Age: mean: 55.0 years, standard deviation: 17.3 years
	Gender: 75% male
	Karnofsky performance status: NR
	First diagnosis/recurrent disease: 87.5% (7/8) primary tumours, 12.5% (1/8) secondary tumours

Index tests	**2 tests:** FISH and SNP array
	FISH

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Hinrichs 2016 *(Continued)*

	Tumour sample type: FFPE
	Region(s) analysed: 1p36/1q25, 19p13/19q13 (Vysis LSI probe sets, Abbott Molecular). From Appin CL, Gao J, Chisolm C, Torian M, Alexis D, Vincentelli C, et al. Glioblastoma with oligodendroglioma component (GBM-O): molecular genetic and clinical characteristics. *Brain Pathology* 2013;23:454-61 (reference 2 in this study).
	Cut-off: quote: "1p and 19q deletions were considered present if ≥10% of cells contained the respective deletions". From Appin CL, Gao J, Chisolm C, Torian M, Alexis D, Vincentelli C, et al. Glioblastoma with oligodendroglioma component (GBM-O): molecular genetic and clinical characteristics. *Brain Pathology* 2013;23:454-61 (reference 2 in this study).
	SNP array
	Tumour sample type: FFPE
	Region(s) analysed: genome wide
	Cut-off: segmented log2 ratio of −0.135 for losses and −0.45 for homozygous deletions
	Additional details: quote: "Illumina HumanCytoSNP-12v2.1-FFPE SNP arrays … Data were processed and analyzed with BioDiscovery Nexus software (Hawthorne, CA) using SNPRank segmentation".
Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. FISH used as reference standard in some of our analyses.
Flow and timing	
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Unclear		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		High risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (NanoString)			
DOMAIN 2: Index Test (aCGH)			

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Hinrichs 2016 *(Continued)*

DOMAIN 2: Index Test (NGS)			
DOMAIN 2: Index Test (G-banding)			
DOMAIN 2: Index Test (FISH (variant 4))			
DOMAIN 2: Index Test (SNP array)			
If a threshold was used, was it pre-specified?	Yes		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (PCR (with comparison to normal DNA))			
DOMAIN 2: Index Test (PCR (without comparison to normal DNA))			
DOMAIN 2: Index Test (CISH)			
DOMAIN 2: Index Test (MS)			
DOMAIN 2: Index Test (RFLP)			
DOMAIN 2: Index Test (PCR-based LOH)			
DOMAIN 2: Index Test (NGS or aCGH (or both))			
DOMAIN 2: Index Test (Methylation array)			
DOMAIN 2: Index Test (FISH)			
If a threshold was used, was it pre-specified?	Yes		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (FISH (variant 1))			
DOMAIN 2: Index Test (FISH (variant 2))			
DOMAIN 2: Index Test (FISH (variant 3))			
DOMAIN 2: Index Test (Real-time PCR)			

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Hinrichs 2016 *(Continued)*

DOMAIN 2: Index Test (MLPA)		
DOMAIN 2: Index Test (CGH)		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	Low risk	

Horbinski 2012

Study characteristics	
Patient Sampling	**Inclusion/exclusion criteria**
	Inclusion criteria: oligodendrogliomas. Exclusion criteria: recurrent or treated (or both) gliomas; children aged < 18 years
	Prior testing
	Histopathological diagnosis according to WHO criteria at the time of initial biopsy.
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 111
	Country: USA
	Population source and setting: University of Pittsburgh. 2002–2010
	Age: median: Grade II oligodendroglioma: 42 years. Grade III oligodendroglioma: 49 years. Interquartile range: NR; range: 19–80 years (Grade II oligodendroglioma 19–79 years; Grade III oligodendroglioma 25–80 years)
	Gender: 56.8% male
	Karnofsky performance status: NR
	First diagnosis/recurrent disease: first diagnosis (cases of recurrent glioma were excluded)
Index tests	**3 tests:** FISH (variant 1), FISH (variant 2) and PCR

FISH (variant 1) (referred to as FISH below. Note: the risk of bias and applicability judgements for this FISH variant appear in Figure 7 **)**

Tumour sample type: FFPE

Region(s) analysed: 1p36/1q25 19q13 /19p13 (Abbott Molecular, Des Plaines, Illinois, USA)

Cut-off: target-ploidy control ratio was < 0.87, with ≥ 20% of nuclei showing deletion

FISH (variant 2)

Tumour sample type: FFPE

Region(s) analysed: 1p36/1q25 19q13 /19p13 (Abbott Molecular, Des Plaines, Illinois)

Cut-off: target-ploidy control ratio was < 0.75, with ≥ 20% of nuclei showing deletion

PCR

Tumour sample type: FFPE

Region(s) analysed: chromosome 1: D1S1172, D1S226, D1S162, D1S1161, D1S199, D1S407, D1S171; chromosome 19: D19S112, D19S206

Cut-off: at least half of all informative microsatellite loci on both 1p and 19q had to show LOH to be designated as having 1p/19q codeletion. Quote: "When available, patient-matched germline DNA from a peripheral blood sample was used as a control. When normal tissue was not available, peak height ratios falling outside 2 SDs beyond the mean of previously validated normal values for each polymorphic allele paring were assessed as showing LOH".

Additional details: from Horbinski C, Hamilton RL, Nikiforov Y, Pollack IF. Association of molecular alterations, including BRAF, with biology and outcome in pilocytic astrocytomas. Acta Neuropathologica 2010;119:641-49) "Polymerase chain reaction was performed, and the products were analyzed using capillary gel electrophoresis on GeneMapper ABI 3730 (Applied Biosystems, Foster City, CA)".

Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. FISH or PCR-based LOH used as reference standard in some of our analyses.
Flow and timing	We presumed that all tests were performed on biopsied tumour material collected on 1 occasion.
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		

Horbinski 2012 *(Continued)*

Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (NanoString)			
DOMAIN 2: Index Test (aCGH)			
DOMAIN 2: Index Test (NGS)			
DOMAIN 2: Index Test (G-banding)			
DOMAIN 2: Index Test (FISH (variant 4))			
DOMAIN 2: Index Test (SNP array)			
DOMAIN 2: Index Test (PCR (with comparison to normal DNA))			
DOMAIN 2: Index Test (PCR (without comparison to normal DNA))			
DOMAIN 2: Index Test (CISH)			
DOMAIN 2: Index Test (MS)			
DOMAIN 2: Index Test (RFLP)			
DOMAIN 2: Index Test (PCR-based LOH)			
If a threshold was used, was it pre-specified?	Yes		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (NGS or aCGH (or both))			
DOMAIN 2: Index Test (Methylation array)			
DOMAIN 2: Index Test (FISH)			
If a threshold was used, was it pre-specified?	Yes		

Horbinski 2012 *(Continued)*

Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (FISH (variant 1))			
DOMAIN 2: Index Test (FISH (variant 2))			
If a threshold was used, was it pre-specified?	No		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		High risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (FISH (variant 3))			
DOMAIN 2: Index Test (Real-time PCR)			
DOMAIN 2: Index Test (MLPA)			
DOMAIN 2: Index Test (CGH)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	No		
Could the reference standard, its conduct, or its interpretation have introduced bias?		High risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

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Jeuken 2006 *(Continued)*

Study characteristics

Patient Sampling	**Inclusion/exclusion criteria**
	NR. Quote: "Eighty-eight specimens obtained from glioma patients treated in the Department of Neurosurgery of the Radboud University Nijmegen Medical Centre, The Netherlands, were selected".
	Prior testing
	Histopathological diagnosis (WHO 2000 classification). 79/88 participants were previously analysed by conventional CGH.
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 71
	Country: the Netherlands
	Population source and setting: Department of Neurosurgery of the Radboud University Nijmegen Medical Center, the Netherlands. Time period NR
	Age: NR
	Gender: NR
	Karnofsky performance status: NR
	First diagnosis/recurrent disease: NR
Index tests	**2 tests:** CGH and MLPA
	CGH
	Tumour sample type: snap-frozen
	Region(s) analysed: genome wide
	Cut-off: 0.8 for losses and 1.2 for gains
	MLPA
	Tumour sample type: snap frozen or FFPE
	Region(s) analysed: 1p: TNFRSF4, GB1, SKII, TP72, PARK7, EPHA8, RUNX3, PTAFR, STK22C, MYCL1, FAF1, PPAP2B, CYP2J2, LPHN2, SOYS, NARS, NOTCH2; 19q: CCNE1, PDCD5, UPK1A, TGFB1, ZNF342, PPP1R15A, BAX, BC-2 (kit P088; MRC-Holland, Amsterdam, the Netherlands)
	Cut-off: ratio ≤ 0.8 per probe. Overall results for 1p and 19q not given. We assumed that if all probes were lost, or the majority were lost and those that were not lost were flanked by probes that were that lost that loss had occurred (stated in paper: "ratios of adjacent probes should be taken into consideration for the assessment of the presence of gains or losses"). We ignored the results for the most centromeric 1p probe (NOTCH2).
Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. No tests used as reference standard in our analyses.

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Jeuken 2006 *(Continued)*

Flow and timing	We presumed that both tests were performed on samples obtained at the same time.
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (NanoString)			
DOMAIN 2: Index Test (aCGH)			
DOMAIN 2: Index Test (NGS)			
DOMAIN 2: Index Test (G-banding)			
DOMAIN 2: Index Test (FISH (variant 4))			
DOMAIN 2: Index Test (SNP array)			
DOMAIN 2: Index Test (PCR (with comparison to normal DNA))			
DOMAIN 2: Index Test (PCR (without comparison to normal DNA))			
DOMAIN 2: Index Test (CISH)			
DOMAIN 2: Index Test (MS)			
DOMAIN 2: Index Test (RFLP)			
DOMAIN 2: Index Test (PCR-based LOH)			
DOMAIN 2: Index Test (NGS or aCGH (or both))			
DOMAIN 2: Index Test (Methylation array)			
DOMAIN 2: Index Test (FISH)			

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Jeuken 2006 *(Continued)*

DOMAIN 2: Index Test (FISH (variant 1))			

DOMAIN 2: Index Test (FISH (variant 2))			

DOMAIN 2: Index Test (FISH (variant 3))			

DOMAIN 2: Index Test (Real-time PCR)			

DOMAIN 2: Index Test (MLPA)			
If a threshold was used, was it pre-specified?	Yes		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern

DOMAIN 2: Index Test (CGH)			
If a threshold was used, was it pre-specified?	Yes		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern

DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	No		
Could the reference standard, its conduct, or its interpretation have introduced bias?		High risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern

DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Were all patients included in the analysis?	No		
Could the patient flow have introduced bias?		High risk	

Jha 2011

Study characteristics

Patient Sampling	**Inclusion/exclusion criteria** NR. 40 gliomas including 16 oligodendrogliomas grade-II (O-II), 14 oligodendrogliomas grade III (AO-III) and 10 GBMs were selected for this study. **Prior testing** Histopathological diagnosis according to the WHO 2007 classification.
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 40 **Country:** India **Population source and setting:** Neurosurgery Department of All India Institute of Medical Sciences, New Delhi, India. Time period NR **Age:** mean: 37.3 years, standard deviation: 10.8 years **Gender:** 80% male **Karnofsky performance status:** NR **First diagnosis/recurrent disease:** NR
Index tests	**2 tests:** FISH and PCR **FISH** Tumour sample type: FFPE Region(s) analysed: 1p36/1q25, 19q13/1p36 (using a locus-specific probe for 1p36 and 19q13) (Vysis, Downers Grove, Illinois, USA). Cut-off: an interpretation of deletion or imbalance was made if > 20% of the nuclei showed test to reference ratio of 1/2 or 0/2. **PCR** Tumour sample type: fresh-frozen Region(s) analysed: 1p: D1S1184 (1P31.1), D1S1592 (1P36.13), D1S548 (1P36.23), D1S1608 (1P36.32); 19q: D19S431 (19q12), D19S718 (19q13.2), D19S559 (19q13.32), D19S601 (19q13.41) Cut-off: a complete loss of band or reduction in intensity of > 50% in the tumour lane in comparison with the corresponding blood lane was scored as LOH.
Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. FISH or PCR-based LOH used as reference standard in some of our analyses.
Flow and timing	We presumed that all tests were performed on biopsied tumour material collected on 1 occasion.
Comparative	
Notes	

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Jha 2011 (Continued)

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (NanoString)			
DOMAIN 2: Index Test (aCGH)			
DOMAIN 2: Index Test (NGS)			
DOMAIN 2: Index Test (G-banding)			
DOMAIN 2: Index Test (FISH (variant 4))			
DOMAIN 2: Index Test (SNP array)			
DOMAIN 2: Index Test (PCR (with comparison to normal DNA))			
DOMAIN 2: Index Test (PCR (without comparison to normal DNA))			
DOMAIN 2: Index Test (CISH)			
DOMAIN 2: Index Test (MS)			
DOMAIN 2: Index Test (RFLP)			
DOMAIN 2: Index Test (PCR-based LOH)			
If a threshold was used, was it pre-specified?	Unclear		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (NGS or aCGH (or both))			
DOMAIN 2: Index Test (Methylation array)			

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Jha 2011 *(Continued)*

DOMAIN 2: Index Test (FISH)		
If a threshold was used, was it pre-specified?	Yes	
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear	
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (FISH (variant 1))		
DOMAIN 2: Index Test (FISH (variant 2))		
DOMAIN 2: Index Test (FISH (variant 3))		
DOMAIN 2: Index Test (Real-time PCR)		
DOMAIN 2: Index Test (MLPA)		
DOMAIN 2: Index Test (CGH)		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?		High risk
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Low risk

Kato 2019

Study characteristics

Patient Sampling	**Inclusion/exclusion criteria**
	NR. 9 "grade II–IV gliomas" seem to have been studied.
	Prior testing

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	Presumably tumour grading, but this was not reported explicitly.		
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 9 **Country:** Japan **Population source and setting:** NR **Age:** NR **Gender:** NR **Karnofsky performance status:** NR **First diagnosis/recurrent disease:** NR		
Index tests	**2 tests:** FISH and NGS **FISH** Tumour sample type: NR Region(s) analysed: NR Cut-off: NR **NGS** Tumour sample type: FFPE or PAXgene-fixed paraffin-embedded Region(s) analysed: NR Cut-off: NR Additional details: MiSeq (Illumina) processed by Genome Jack (Mitsubishi Space Software Inc.)		
Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. FISH used as reference standard in some of our analyses.		
Flow and timing	We presumed that all tests were performed on biopsied tumour material collected on 1 occasion.		
Comparative			
Notes	Conference abstract		

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Unclear risk	

Kato 2019 *(Continued)*

Are there concerns that the included patients and setting do not match the review question?	Unclear
DOMAIN 2: Index Test (NanoString)	
DOMAIN 2: Index Test (aCGH)	
DOMAIN 2: Index Test (NGS)	
If a threshold was used, was it pre-specified?	Unclear
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern
DOMAIN 2: Index Test (G-banding)	
DOMAIN 2: Index Test (FISH (variant 4))	
DOMAIN 2: Index Test (SNP array)	
DOMAIN 2: Index Test (PCR (with comparison to normal DNA))	
DOMAIN 2: Index Test (PCR (without comparison to normal DNA))	
DOMAIN 2: Index Test (CISH)	
DOMAIN 2: Index Test (MS)	
DOMAIN 2: Index Test (RFLP)	
DOMAIN 2: Index Test (PCR-based LOH)	
DOMAIN 2: Index Test (NGS or aCGH (or both))	
DOMAIN 2: Index Test (Methylation array)	
DOMAIN 2: Index Test (FISH)	
If a threshold was used, was it pre-specified?	Unclear
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern
DOMAIN 2: Index Test (FISH (variant 1))	

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Kato 2019 *(Continued)*

DOMAIN 2: Index Test (FISH (variant 2))		
DOMAIN 2: Index Test (FISH (variant 3))		
DOMAIN 2: Index Test (Real-time PCR)		
DOMAIN 2: Index Test (MLPA)		
DOMAIN 2: Index Test (CGH)		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Were all patients included in the analysis?	Unclear	
Could the patient flow have introduced bias?	Unclear risk	

Kolhe 2016

Study characteristics	
Patient Sampling	**Inclusion/exclusion criteria** NR. Quote: "Adult brain tumors". **Prior testing** Histopathological diagnosis
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 9 **Country:** USA **Population source and setting:** NR **Age:** NR **Gender:** NR **Karnofsky performance status:** NR **First diagnosis/recurrent disease:** NR
Index tests	**2 tests:** FISH and SNP array

Kolhe 2016 *(Continued)*

	FISH
	Tumour sample type: NR
	Region(s) analysed: NR
	Cut-off: NR
	SNP array
	Tumour sample type: FFPE
	Region(s) analysed: genome wide
	Cut-off: NR
	Additional details: OncoScan assay, Affymetrix, Inc.
Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. FISH used as reference standard in some of our analyses.
Flow and timing	We presumed that all tests were performed on biopsied tumour material collected on 1 occasion.
Comparative	
Notes	Conference abstract

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (NanoString)			
DOMAIN 2: Index Test (aCGH)			
DOMAIN 2: Index Test (NGS)			
DOMAIN 2: Index Test (G-banding)			
DOMAIN 2: Index Test (FISH (variant 4))			
DOMAIN 2: Index Test (SNP array)			
If a threshold was used, was it pre-specified?	Unclear		

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Kolhe 2016 *(Continued)*

Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (PCR (with comparison to normal DNA))			
DOMAIN 2: Index Test (PCR (without comparison to normal DNA))			
DOMAIN 2: Index Test (CISH)			
DOMAIN 2: Index Test (MS)			
DOMAIN 2: Index Test (RFLP)			
DOMAIN 2: Index Test (PCR-based LOH)			
DOMAIN 2: Index Test (NGS or aCGH (or both))			
DOMAIN 2: Index Test (Methylation array)			
DOMAIN 2: Index Test (FISH)			
If a threshold was used, was it pre-specified?	Unclear		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (FISH (variant 1))			
DOMAIN 2: Index Test (FISH (variant 2))			
DOMAIN 2: Index Test (FISH (variant 3))			
DOMAIN 2: Index Test (Real-time PCR)			
DOMAIN 2: Index Test (MLPA)			
DOMAIN 2: Index Test (CGH)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	No		

Kolhe 2016 *(Continued)*

Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern
DOMAIN 4: Flow and Timing	
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	Unclear risk

Lass 2013

Study characteristics	
Patient Sampling	**Inclusion/exclusion criteria**
	Not explicitly reported. Quote: "Formalin fixed paraffin-embedded (FFPE) tissue of 42 consecutive brain tumor biopsies with previously established 1p/19q status by FISH was available for a comparative analysis of CISH … FISH analysis of 1p/19q was initiated in all cases during diagnostic work-up and based on morphological features resembling oligodendroglioma".
	Prior testing
	Histopathological diagnosis according to WHO 2007 classification. All tumours had previously established 1p/19q status by FISH.
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 38
	Country: Germany
	Population source and setting: NR
	Age: mean: 43.2 years, standard deviation: 14.8 years
	Gender: 52.6% male
	Karnofsky performance status: NR
	First diagnosis/recurrent disease: NR
Index tests	**2 tests:** CISH and FISH
	CISH
	Tumour sample type: FFPE
	Region(s) analysed: 1p36/1q25, 19q13/19p13
	Cut-off: 50% of cells had to show deletion
	FISH

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Lass 2013 *(Continued)*

	Tumour sample type: FFPE
	Region(s) analysed: 1p36/1q25, 19q13/19p13 (ZytoVision)
	Cut-off: 50% of cells had to show deletion
Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. FISH used as reference standard in some of our analyses.
Flow and timing	We presumed that all tests were performed on biopsied tumour material collected on 1 occasion.
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (NanoString)			
DOMAIN 2: Index Test (aCGH)			
DOMAIN 2: Index Test (NGS)			
DOMAIN 2: Index Test (G-banding)			
DOMAIN 2: Index Test (FISH (variant 4))			
DOMAIN 2: Index Test (SNP array)			
DOMAIN 2: Index Test (PCR (with comparison to normal DNA))			
DOMAIN 2: Index Test (PCR (without comparison to normal DNA))			
DOMAIN 2: Index Test (CISH)			
If a threshold was used, was it pre-specified?	Yes		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Yes		

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Lass 2013 *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?	Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (MS)		
DOMAIN 2: Index Test (RFLP)		
DOMAIN 2: Index Test (PCR-based LOH)		
DOMAIN 2: Index Test (NGS or aCGH (or both))		
DOMAIN 2: Index Test (Methylation array)		
DOMAIN 2: Index Test (FISH)		
If a threshold was used, was it pre-specified?	Yes	
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Yes	
Could the conduct or interpretation of the index test have introduced bias?	Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (FISH (variant 1))		
DOMAIN 2: Index Test (FISH (variant 2))		
DOMAIN 2: Index Test (FISH (variant 3))		
DOMAIN 2: Index Test (Real-time PCR)		
DOMAIN 2: Index Test (MLPA)		
DOMAIN 2: Index Test (CGH)		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	

Lass 2013 *(Continued)*

Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Lhotska 2015

Study characteristics	
Patient Sampling	**Inclusion/exclusion criteria**
	Inclusion criteria: low grade (WHO grade II) oligodendroglioma and oligoastrocytoma
	Prior testing
	Not explicitly reported but presumably histopathological diagnosis
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 20
	Country: Czech Republic
	Population source and setting: Department of Neurosurgery, Central Military Hospital and 1st Faculty of Medicine, Charles University, Prague, Czech Republic and the Department of Neurosurgery, Regional Hospital, Liberec, Czech Republic. 2005–2014
	Age[a]: 56.5% aged ≤ 50 years (median age 34.5 years); 43.5% aged > 50 years (median age 57 years)
	Gender[b]: 55.6% male
	Karnofsky performance status: NR
	First diagnosis/recurrent disease: NR
	[a]For whole population: the study included 23 participants with oligodendroglioma or oligoastrocytoma, results for both tests available for 20.
	[b]For whole population: this result included participants with astrocytoma (1p/19q status not investigated). 23 participants with oligodendroglioma or oligoastrocytoma. Results for both tests available for 20.
Index tests	**2 tests:** FISH and SNP array
	FISH
	Tumour sample type: fresh
	Region(s) analysed: 1p36/1q25, 19q13/19p13 (Vysis probes; Abbott Molecular, Des Plaines, Illinois, USA)
	Cut-off: 5% for deletion
	SNP array
	Tumour sample type: fresh
	Region(s) analysed: genome wide

Lhotska 2015 *(Continued)*

	Cut-off: NR and participants not classified. We set the criteria for codeletion as 1 copy of (or homozygous for) 1p36.33p11.2 or 1p31.1p12 or 1p31.3p31.1 AND 1 copy of (or homozygous for) 19q12q13.43 or 19q13.2q13.43 or 19q13.32q13.43. Additional details: human CytoSNP-12 BeadChip (Illumina, San Diego, California)
Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. FISH used as reference standard in some of our analyses.
Flow and timing	All tests performed with tumour tissues taken during routine neurosurgical procedures and peripheral blood taken after the procedures.
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (NanoString)			
DOMAIN 2: Index Test (aCGH)			
DOMAIN 2: Index Test (NGS)			
DOMAIN 2: Index Test (G-banding)			
DOMAIN 2: Index Test (FISH (variant 4))			
DOMAIN 2: Index Test (SNP array)			
If a threshold was used, was it pre-specified?	No		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	No		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	

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Lhotska 2015 *(Continued)*

Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

DOMAIN 2: Index Test (PCR (with comparison to normal DNA))

DOMAIN 2: Index Test (PCR (without comparison to normal DNA))

DOMAIN 2: Index Test (CISH)

DOMAIN 2: Index Test (MS)

DOMAIN 2: Index Test (RFLP)

DOMAIN 2: Index Test (PCR-based LOH)

DOMAIN 2: Index Test (NGS or aCGH (or both))

DOMAIN 2: Index Test (Methylation array)

DOMAIN 2: Index Test (FISH)

If a threshold was used, was it pre-specified?	Yes	
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear	
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern

DOMAIN 2: Index Test (FISH (variant 1))

DOMAIN 2: Index Test (FISH (variant 2))

DOMAIN 2: Index Test (FISH (variant 3))

DOMAIN 2: Index Test (Real-time PCR)

DOMAIN 2: Index Test (MLPA)

DOMAIN 2: Index Test (CGH)

DOMAIN 3: Reference Standard

Is the reference standards likely to correctly classify the target condition?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?		High risk
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern

Lhotska 2015 *(Continued)*

DOMAIN 4: Flow and Timing

Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	High risk

Mohapatra 2006

Study characteristics	
Patient Sampling	**Inclusion/exclusion criteria**
	Not explicitly reported, but all glioma samples had oligodendroglial features on histopathological examination.
	Prior testing
	Not explicitly reported, but presumably histopathological diagnosis.
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 28
	Country: USA
	Population source and setting: Massachusetts General Hospital. 1999–2004
	Age: NR
	Gender: NR
	Karnofsky performance status: NR
	First diagnosis/recurrent disease: NR
Index tests	**3 tests:** aCGH, FISH and PCR
	aCGH
	Tumour sample type: FFPE
	Region(s) analysed: not explicitly reported but 100 BACs (bacterial artificial chromosome) over chromosome 1, 50 BACs over chromosome 19
	Cut-off: quote: "Segments were considered to represent true losses or gains according to whether their associated absolute mean log2 ratio levels were greater than $(2 \times \sigma/\sqrt{n})$ With σ estimated to be 0.58, the empirical estimate of the SD of the standardized segment means for 1q, and n equal to the number of clones in the given segment. For example, a 19q segment that contains 26 clones was considered to represent loss if its estimated mean level was less than −0.23. A 1p segment that contains 57 clones was considered to represent loss if its estimated mean level was less than −0.16. A 1p segment that contains 30 clones was considered to represent loss if its estimated mean level was less than −0.22".

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Mohapatra 2006 *(Continued)*

	Additional details: a BAC array was constructed containing 200 targets that represented chromosomes 1, 7, 19, and X.
	FISH
	Tumour sample type: FFPE
	Region(s) analysed: 1p36.2/1q21, 19q13.3/19p13.3
	Cut-off: quote: "Relative copy numbers for 1p/1q and 19q/19p were counted, and a ratio of 0.7 or less for 1p:1q and/or 19q:19p was considered a loss".
	PCR
	Tumour sample type: FFPE
	Region(s) analysed: 1p: D1S508, D1S199, D1S2734; 19q: D19S219, D19S112, D19S412.
	Cut-off: NR
Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. FISH or PCR-based LOH used as reference standard in some of our analyses.
Flow and timing	All tests were performed on the same FFPE tissue.
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (NanoString)			
DOMAIN 2: Index Test (aCGH)			
If a threshold was used, was it pre-specified?	Yes		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	

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Mohapatra 2006 *(Continued)*

Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (NGS)		
DOMAIN 2: Index Test (G-banding)		
DOMAIN 2: Index Test (FISH (variant 4))		
DOMAIN 2: Index Test (SNP array)		
DOMAIN 2: Index Test (PCR (with comparison to normal DNA))		
DOMAIN 2: Index Test (PCR (without comparison to normal DNA))		
DOMAIN 2: Index Test (CISH)		
DOMAIN 2: Index Test (MS)		
DOMAIN 2: Index Test (RFLP)		
DOMAIN 2: Index Test (PCR-based LOH)		
If a threshold was used, was it pre-specified?	Unclear	
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (NGS or aCGH (or both))		
DOMAIN 2: Index Test (Methylation array)		
DOMAIN 2: Index Test (FISH)		
If a threshold was used, was it pre-specified?	Yes	
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (FISH (variant 1))		
DOMAIN 2: Index Test (FISH (variant 2))		
DOMAIN 2: Index Test (FISH (variant 3))		

Mohapatra 2006 *(Continued)*

DOMAIN 2: Index Test (Real-time PCR)		
DOMAIN 2: Index Test (MLPA)		
DOMAIN 2: Index Test (CGH)		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?		High risk
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Were all patients included in the analysis?	No	
Could the patient flow have introduced bias?		High risk

Na 2019

Study characteristics	
Patient Sampling	**Inclusion/exclusion criteria** Inclusion criteria: FFPE specimens of primary diffuse glioma **Prior testing** Histopathological diagnosis according to WHO 2016 classification and the update series of the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy-Not Official WHO (cIMPACT-NOW). Quote: "Ancillary tests used in initial diagnosis included IDH1 (R132H), p53, and ATRX immunostaining and fluorescence in situ hybridization (FISH)-based detection of 1p/19q-codeletion. Select cases were immunostained by BRAF (VE1) or by paired set of H3.3K27M and H3K27me3 (midline location). After diagnosis, most representative FFPE specimens were tested for TERT mutation, MGMT methylation, and analyzed by NGS".
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 135 **Country:** Republic of Korea **Population source and setting:** Severance Hospital, Republic of Korea. March 2017 to May 2018 **Age[a]:** mean: 51.0 years, standard deviation: 16.3 years **Gender:** 59.3% male **Karnofsky performance status:** NR

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Na 2019 *(Continued)*

	First diagnosis/recurrent disease: unclear. Described as "primary" diffuse gliomas.
	aThere are 5 participants aged < 18 years in this analysis. We have not excluded them as we are unable to link their individual patient data to the 1p/19q result for all of the tumours.
Index tests	**2 tests:** FISH and NGS
	FISH
	Tumour sample type: FFPE
	Region(s) analysed: 1p36/1q25, 19q13/19p13 (Vysis, Abbott Molecular, Illinois, USA)
	Cut-off: deletion was defined as signal ratios of > 50% for region of interest to control probe.
	NGS
	Tumour sample type: FFPE
	Region(s) analysed: 1p: NRAS, MYCL1; 19q: ERCC1, ERCC2, AKT2
	Cut-off: quote: "The genes with lower than 0.7-fold change relative to average levels were considered to exhibit significant copy number loss".
	Additional details: Illumina TruSight Tumor 170 (TST-170) panel
Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. FISH used as reference standard in some of our analyses.
Flow and timing	We presumed that both tests were performed on the same sample for each case.
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (NanoString)			

DOMAIN 2: Index Test (aCGH)

DOMAIN 2: Index Test (NGS)

If a threshold was used, was it pre-specified?	Unclear
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear

Could the conduct or interpretation of the index test have introduced bias?	High risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern

DOMAIN 2: Index Test (G-banding)

DOMAIN 2: Index Test (FISH (variant 4))

DOMAIN 2: Index Test (SNP array)

DOMAIN 2: Index Test (PCR (with comparison to normal DNA))

DOMAIN 2: Index Test (PCR (without comparison to normal DNA))

DOMAIN 2: Index Test (CISH)

DOMAIN 2: Index Test (MS)

DOMAIN 2: Index Test (RFLP)

DOMAIN 2: Index Test (PCR-based LOH)

DOMAIN 2: Index Test (NGS or aCGH (or both))

DOMAIN 2: Index Test (Methylation array)

DOMAIN 2: Index Test (FISH)

If a threshold was used, was it pre-specified?	Yes
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Yes

Could the conduct or interpretation of the index test have introduced bias?	Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern

DOMAIN 2: Index Test (FISH (variant 1))

DOMAIN 2: Index Test (FISH (variant 2))

Na 2019 *(Continued)*

DOMAIN 2: Index Test (FISH (variant 3))		
DOMAIN 2: Index Test (Real-time PCR)		
DOMAIN 2: Index Test (MLPA)		
DOMAIN 2: Index Test (CGH)		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?		High risk
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Low risk

Natte 2005

Study characteristics	
Patient Sampling	**Inclusion/exclusion criteria**
	NR. 19 oligodendroglial tumours from 19 participants were analysed.
	Prior testing
	Histopathological diagnosis according to WHO classification. Quote: "From all tumors FISH data were available".
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 19
	Country: the Netherlands
	Population source and setting: NR
	Age: NR
	Gender: NR
	Karnofsky performance status: NR
	First diagnosis/recurrent disease: NR

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Natte 2005 *(Continued)*

Index tests	**2 tests:** FISH and MLPA
	FISH
	Tumour sample type: FFPE
	Region(s) analysed: 1p36(D1S32)/1cen(PUC 1.77) and 19q13(BAC127F23)/19p13(BAC2310A1)
	Cut-off: 0.8
	MLPA
	Tumour sample type: FFPE
	Region(s) analysed: 1p36.33, 1p36, 1p36.3,1p34.3-1p32.1, 1p13.2, 1p22-21, 1p13.3, 19q13.3, 19q13.3, 19q13, 19q13.43. Quote: "The MLPA kit was assembled by MRC-Holland (Amsterdam, The Netherlands). Details of MLPA and probes can be found at http://www.mlpa.com".
	Cut-off: the principal decision rule for a deletion was that for 1p ≥ 4 probes (of 7?) and for 19q ≥ 2 focus probes (of 4?) had normalised peak heights ≥ 0.25 below the median normalised peak height of the reference probes.
Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. FISH used as reference standard in some of our analyses.
Flow and timing	We presumed that all tests were performed on biopsied tumour material collected on 1 occasion.
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Unclear		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (NanoString)			
DOMAIN 2: Index Test (aCGH)			
DOMAIN 2: Index Test (NGS)			

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Natte 2005 *(Continued)*

DOMAIN 2: Index Test (G-banding)			
DOMAIN 2: Index Test (FISH (variant 4))			
DOMAIN 2: Index Test (SNP array)			
DOMAIN 2: Index Test (PCR (with comparison to normal DNA))			
DOMAIN 2: Index Test (PCR (without comparison to normal DNA))			
DOMAIN 2: Index Test (CISH)			
DOMAIN 2: Index Test (MS)			
DOMAIN 2: Index Test (RFLP)			
DOMAIN 2: Index Test (PCR-based LOH)			
DOMAIN 2: Index Test (NGS or aCGH (or both))			
DOMAIN 2: Index Test (Methylation array)			
DOMAIN 2: Index Test (FISH)			
If a threshold was used, was it pre-specified?	Yes		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (FISH (variant 1))			
DOMAIN 2: Index Test (FISH (variant 2))			
DOMAIN 2: Index Test (FISH (variant 3))			
DOMAIN 2: Index Test (Real-time PCR)			
DOMAIN 2: Index Test (MLPA)			
If a threshold was used, was it pre-specified?	Yes		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern

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Natte 2005 *(Continued)*

DOMAIN 2: Index Test (CGH)	

DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?		High risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern

DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Low risk

Nigro 2001

Study characteristics	
Patient Sampling	**Inclusion/exclusion criteria**
	Inclusion criteria: oligodendrogliomas and oligoastrocytomas
	Prior testing
	Histopathological diagnosis
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 22
	Country: USA
	Population source and setting: University of California, San Francisco. Time period NR
	Age: NR
	Gender: NR
	Karnofsky performance status: NR
	First diagnosis/recurrent disease: NR
Index tests	**2 tests:** FISH and real-time PCR
	FISH
	Tumour sample type: FFPE
	Region(s) analysed: 1p36/1q24, 19p13/19q13.3
	Cut-off: ratio of target to control probes of ≤ 0.85 scored as a loss

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Nigro 2001 *(Continued)*

	Real-time PCR
	Tumour sample type: FFPE
	Region(s) analysed: D1S468, D1S214, D1S2736, D1S2783, D1S514, D19S408, D19S596, D19S867, D19S418, D19S926. Not all primers run for all samples.
	Cut-off: copy numbers < 1.58 in ≥ 2 sequential loci (requirement for loss at ≥ 2 sequential loci at least for 1p).
	Additional details: real-time quantitative PCR, quantitative microsatellite analysis. Utilises a probe designed to bind to CA repeats.
Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. FISH used as reference standard in some of our analyses.
Flow and timing	We presumed that all tests were performed on biopsied tumour material collected on 1 occasion.
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (NanoString)			
DOMAIN 2: Index Test (aCGH)			
DOMAIN 2: Index Test (NGS)			
DOMAIN 2: Index Test (G-banding)			
DOMAIN 2: Index Test (FISH (variant 4))			
DOMAIN 2: Index Test (SNP array)			
DOMAIN 2: Index Test (PCR (with comparison to normal DNA))			
DOMAIN 2: Index Test (PCR (without comparison to normal DNA))			

Nigro 2001 *(Continued)*

DOMAIN 2: Index Test (CISH)		
DOMAIN 2: Index Test (MS)		
DOMAIN 2: Index Test (RFLP)		
DOMAIN 2: Index Test (PCR-based LOH)		
DOMAIN 2: Index Test (NGS or aCGH (or both))		
DOMAIN 2: Index Test (Methylation array)		
DOMAIN 2: Index Test (FISH)		
If a threshold was used, was it pre-specified?	Yes	
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear	
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (FISH (variant 1))		
DOMAIN 2: Index Test (FISH (variant 2))		
DOMAIN 2: Index Test (FISH (variant 3))		
DOMAIN 2: Index Test (Real-time PCR)		
If a threshold was used, was it pre-specified?	Unclear	
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (MLPA)		
DOMAIN 2: Index Test (CGH)		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?		High risk

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Nigro 2001 (Continued)

Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

DOMAIN 4: Flow and Timing	
Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	High risk

Park 2019

Study characteristics	
Patient Sampling	**Inclusion/exclusion criteria**
	Inclusion criteria: oligodendroglial tumours (oligodendroglioma or anaplastic oligodendroglioma) with 1p/19q FISH results available
	Prior testing
	Presumably histopathological diagnosis, although not explicitly stated. FISH
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 20
	Country: Republic of Korea
	Population source and setting: Asan Medical Center, Seoul, Korea. January 2015 to December 2016
	Age: mean: 51.7 years, standard deviation: 11.6 years
	Gender: 45% male
	Karnofsky performance status: NR
	First diagnosis/recurrent disease: NR
Index tests	**2 tests:** FISH and NGS
	FISH
	Tumour sample type: FFPE
	Region(s) analysed: 1p36 and 19q13 (Vysis, Downers Grove, Illinois, USA)
	Cut-off: combined target-to-control signal ratio < 0.75 or cut-off of a nucleus with a 1 or 0 target signal > 50%.
	NGS
	Tumour sample type: FFPE
	Region(s) analysed: whole genome. 1p and 19q specific: chr1:1- 125000000 and chr19:26500001-59128983

Park 2019 *(Continued)*

	Cut-off: quote: "The targeted NGS panel did not cover the whole chromosome; therefore, chromosome 1p deletion and 19q deletion were defined as complete segmental loss covered by NGS panel within chr1:1- 125000000 and chr19:26500001-59128983, respectively, based on the hg19 human reference genome. Partial segmental loss within regions was classified as negative". CNV plots obtained using the log 2 ratio were reviewed manually by 2 pathologists.
	Additional details: "MiSeq (Illumina, Inc., San Diego, CA, USA) with OncoPanel AMCv3 (OP-AMCv3, developed in-house by Asan-CCGD) to include the exons of 199 genes (575,147 bp) and partial introns from 8 genes often rearranged in cancer (209,397 bp) to detect fusion genes and additional small (10,534 bp) specific single nucleotide polymorphism loci for CNV analysis. Overall, the panel covered 823,971 bp".
Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. FISH used as reference standard in some of our analyses.
Flow and timing	We presumed that all tests were performed on biopsied tumour material collected on 1 occasion.
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (NanoString)			
DOMAIN 2: Index Test (aCGH)			
DOMAIN 2: Index Test (NGS)			
If a threshold was used, was it pre-specified?	Yes		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	

Park 2019 *(Continued)*

Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (G-banding)		
DOMAIN 2: Index Test (FISH (variant 4))		
DOMAIN 2: Index Test (SNP array)		
DOMAIN 2: Index Test (PCR (with comparison to normal DNA))		
DOMAIN 2: Index Test (PCR (without comparison to normal DNA))		
DOMAIN 2: Index Test (CISH)		
DOMAIN 2: Index Test (MS)		
DOMAIN 2: Index Test (RFLP)		
DOMAIN 2: Index Test (PCR-based LOH)		
DOMAIN 2: Index Test (NGS or aCGH (or both))		
DOMAIN 2: Index Test (Methylation array)		
DOMAIN 2: Index Test (FISH)		
If a threshold was used, was it pre-specified?	Yes	
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Yes	
Could the conduct or interpretation of the index test have introduced bias?	Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (FISH (variant 1))		
DOMAIN 2: Index Test (FISH (variant 2))		
DOMAIN 2: Index Test (FISH (variant 3))		
DOMAIN 2: Index Test (Real-time PCR)		
DOMAIN 2: Index Test (MLPA)		
DOMAIN 2: Index Test (CGH)		
DOMAIN 3: Reference Standard		

Park 2019 *(Continued)*

Is the reference standards likely to correctly classify the target condition?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?		High risk
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Low risk

Paxton 2015

Study characteristics

Patient Sampling	**Inclusion/exclusion criteria** Inclusion criteria: cases were selected retrospectively from confirmed glioma diagnoses based on positive FISH results for either 1p/19q codeletions (9) or EGFR amplification (8). **Prior testing** FISH (to determine 1p/19q status). Presumably histopathological diagnosis, although not explicitly reported.
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 17 **Country:** USA **Population source and setting:** NR **Age:** NR **Gender:** NR **Karnofsky performance status:** NR **First diagnosis/recurrent disease:** NR
Index tests	**2 tests:** FISH and SNP array **FISH** Tumour sample type: NR Region(s) analysed: NR Cut-off: NR

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Paxton 2015 *(Continued)*

	SNP array Tumour sample type: FFPE Region(s) analysed: whole genome Cut-off: NR Additional details: OncoScan array
Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. FISH used as reference standard in some of our analyses.
Flow and timing	We presumed that both tests were performed on the same archival sample for each participant.
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	No		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		High risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (NanoString)			
DOMAIN 2: Index Test (aCGH)			
DOMAIN 2: Index Test (NGS)			
DOMAIN 2: Index Test (G-banding)			
DOMAIN 2: Index Test (FISH (variant 4))			
DOMAIN 2: Index Test (SNP array)			
If a threshold was used, was it pre-specified?	Unclear		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	

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Paxton 2015 *(Continued)*

Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

DOMAIN 2: Index Test (PCR (with comparison to normal DNA))

DOMAIN 2: Index Test (PCR (without comparison to normal DNA))

DOMAIN 2: Index Test (CISH)

DOMAIN 2: Index Test (MS)

DOMAIN 2: Index Test (RFLP)

DOMAIN 2: Index Test (PCR-based LOH)

DOMAIN 2: Index Test (NGS or aCGH (or both))

DOMAIN 2: Index Test (Methylation array)

DOMAIN 2: Index Test (FISH)

If a threshold was used, was it pre-specified?	Unclear	
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern

DOMAIN 2: Index Test (FISH (variant 1))

DOMAIN 2: Index Test (FISH (variant 2))

DOMAIN 2: Index Test (FISH (variant 3))

DOMAIN 2: Index Test (Real-time PCR)

DOMAIN 2: Index Test (MLPA)

DOMAIN 2: Index Test (CGH)

DOMAIN 3: Reference Standard

Is the reference standards likely to correctly classify the target condition?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?		High risk
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern

DOMAIN 4: Flow and Timing

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Paxton 2015 *(Continued)*

Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Pesenti 2017

Study characteristics

Patient Sampling	**Inclusion/exclusion criteria** Inclusion criteria: diffuse glioma; availability of tumour and peripheral blood specimens **Prior testing** Presumably histopathological diagnosis
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 50 **Country:** Italy **Population source and setting:** Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico di Milano, Italy. December 2013 to November 2016 **Age[a]:** median: 53 years, interquartile range: NR; range: 21–81 years **Gender:** 56.0% male **Karnofsky performance status:** NR **First diagnosis/recurrent disease:** NR [a]For whole population: all 50 participants had 1 tests (MS and PCR-based LOH), only a subset had aCGH or FISH.
Index tests	**4 tests:** aCGH, FISH, MS and PCR-based LOH **aCGH** Tumour sample type: FFPE Region(s) analysed: genome wide Cut-off: quote: "The aberration filter was set to detect a minimum of five consecutive probes/region, and the minimum absolute average log ratio (MAALR) was ± 0.25. A second analysis was run with a MAALR of ± 0.15 (again with a minimum number of five probes/region), to detect low level mosaicism". Additional details: SurePrint G3 Human CGH 4 × 180K, Agilent Technologies, Santa Clara, California, USA **MS** Tumour sample type: FFPE Region(s) analysed: rs3737577 (1p21.2), rs59317557 (1p21.2), rs2038366 (1p21.2), rs859104 (1p21.3), rs17378384 (1p31.3), rs2455638 (1p32.1), rs550663 (1p33), rs586057 (1p34.3), rs624971 (1p34.3), rs16866144 (1p35.2), rs11247639 (1p36.11), rs2473287 (1p36.12),

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rs7512426 (1p36.21), rs809972 (1p36.22), rs4908744 (1p36.23), rs6426368 (1p36.32), rs28503746 (19q13.2), rs67421541 (19q13.2), rs12611404 (19q13.2), rs6070 (19q13.33), rs1674139 (19q13.33), rs1807277 (19q13.33), rs186585 (19q13.41), rs28702875 (19q13.41), rs11666952 (19q13.42), rs36629 (19q13.42) and rs437229 (19q13.43)

Cut-off: the following equation was used to quantitatively define the LOH status: (N2/N1)/((N2/N1) + (T2/T1)) where N1 and N2 were the frequencies of Allele 1 and Allele 2 found in peripheral blood lymphocyte DNA and T1 and T2 were those of the corresponding alleles in tumour DNA. LOH was defined as detected with the value obtained using this formula was < 0.3 or > 0.7. LOH/NO LOH status was defined by the presence of ≥ 2 informative SNPs per chromosome arm with concordant results, 1 of which was located in a centromeric region and the other at a telomeric locus.

Additional details: MassARRAY iPLEX platform (Agena Bioscience, San Diego, California, USA), based on MALDI-TOF MS. PCR performed as a first step.

PCR

Tumour sample type: FFPE

Region(s) analysed: D1S1592 (1p36.13), D1S548 (1p36.23), D1S2694 (1p36.23), D1S2666 (1p36.23), D1S1612 (1p36.23), D1S468 (1p36.32), D19S412 (19q13.32), D19S596 (19q13.33) and D19S206 (19q13.41)

Cut-off: the peak height derived from each allele amplified from both tumor and corresponding normal DNA was compared. The formula (T1/T2)/(N1/N2) was applied, where T1 and T2 were the peak heights of the alleles detected in tumor DNA, and N1 and N2 were the peak heights produced from peripheral blood lymphocyte DNA. LOH was considered present when the result of the calculation was < 0.50. For values > 1.00, the ratio was converted to 1/[(T1/T2)/(N1/N2)] and, again, LOH was considered present if the resulting value was < 0.50.

Additional details: analysed by capillary gel electrophoresis using Gene Mapper software on an ABI 3130XL system

FISH

Tumour sample type: FFPE

Region(s) analysed: p36/1q25 and 19q13/19p13 (ZytoVision, Bremerhaven, Germany)

Cut-off: quote: "Interpretation of FISH images was performed accordingly to Ambros et al, 2001 [37]: normal pattern was defined by the presence of an equal number of control/green and target/red signals (i.e. control/target ratio: 2/2, 3/3, 4/4, etc), deletion pattern was characterized by the presence of at least two control/green signals but only one or zero target/red signals (i.e. control/target ratio: 2/1, 2/0, 3/1, etc); finally imbalance pattern was identified by the presence of more than 1 target/red signal (i.e. control/target ratio: 3/2, 4/2, 4/3, etc). A sample was considered positive for 1p/19q codeletion when more than 50% of nuclei per chromosome arm displayed a typical deletion pattern".

Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. FISH or PCR-based LOH used as reference standard in some of our analyses.
Flow and timing	We presumed that all tests were performed on biopsied tumour material collected on 1 occasion.
Comparative	
Notes	
Methodological quality	

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Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (NanoString)			
DOMAIN 2: Index Test (aCGH)			
If a threshold was used, was it pre-specified?	Yes		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (NGS)			
DOMAIN 2: Index Test (G-banding)			
DOMAIN 2: Index Test (FISH (variant 4))			
DOMAIN 2: Index Test (SNP array)			
DOMAIN 2: Index Test (PCR (with comparison to normal DNA))			
DOMAIN 2: Index Test (PCR (without comparison to normal DNA))			
DOMAIN 2: Index Test (CISH)			
DOMAIN 2: Index Test (MS)			
If a threshold was used, was it pre-specified?	Yes		

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Were the index test results interpreted without knowledge of the results of the other tests being compared?	Yes

Could the conduct or interpretation of the index test have introduced bias?	Low risk	

Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern

DOMAIN 2: Index Test (RFLP)

DOMAIN 2: Index Test (PCR-based LOH)

If a threshold was used, was it pre-specified?	Unclear

Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear

Could the conduct or interpretation of the index test have introduced bias?	Unclear risk	

Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern

DOMAIN 2: Index Test (NGS or aCGH (or both))

DOMAIN 2: Index Test (Methylation array)

DOMAIN 2: Index Test (FISH)

If a threshold was used, was it pre-specified?	Yes

Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear

Could the conduct or interpretation of the index test have introduced bias?	Unclear risk	

Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern

DOMAIN 2: Index Test (FISH (variant 1))

DOMAIN 2: Index Test (FISH (variant 2))

DOMAIN 2: Index Test (FISH (variant 3))

Pesenti 2017 *(Continued)*

DOMAIN 2: Index Test (Real-time PCR)		
DOMAIN 2: Index Test (MLPA)		
DOMAIN 2: Index Test (CGH)		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?		High risk
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Were all patients included in the analysis?	No	
Could the patient flow have introduced bias?		High risk

Ransom 1992a

Study characteristics	
Patient Sampling	**Inclusion/exclusion criteria**
	Inclusion criteria: participants with oligodendroglioma, pilocytic astrocytoma, or ependymoma
	Prior testing
	Tumours were classified morphologically according to the WHO 1993 classification and were graded by the St Anne/Mayo method (Daumas-Duport 1988).
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 5
	Country: USA
	Population source and setting: location NR. May 1988 to June 1990
	Age: mean: 45.0 years, standard deviation: 17.0 years
	Gender: 80% male
	Karnofsky performance status: NR

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Ransom 1992a *(Continued)*

First diagnosis/recurrent disease: 80% (4/5) first diagnosis, 20% (1/5) recurrent disease

Index tests	**2 tests:** G-banding and RFLP
	G-banding
	Tumour sample type: NR
	Region(s) analysed: genome wide
	Cut-off: N/A
	Additional details: from Ransom 1992b: "cytogenetically analyzed using previously described methods (Jenkins et al., 1989)".
	RFLP
	Tumour sample type: frozen
	Region(s) analysed: 1p: DIZ2 (1p36.3), AMY (1p21), NGFB (1p22.1); 19q D19S8 (19q13.2), S19S7 (19cen-q12)
	Cut-off: NR
	Additional details: from Ransom 1992b: "Paired blood and tumor DNA specimens were digested with various restriction enzymes and electrophoresed on agarose gels. Southern blotting was performed, and nylon membranes were hybridized under high stringency to a series of probes detecting RFLPs on all human chromosomes (Feinberg and Vogelstein, 1984; Southern, 1975). The resulting autoradiographs were then examined for signal intensity. Quantitative densitometry was applied to autoradiographs in cases were subjective interpretation was not immediately obvious. A normal range for relative tumor/leukocyte DNA allele intensity was established using the 3'HVR probe, which detects multiple alleles on chromosome 16 and is frequently heterozygous. The probe 3'HVR was chosen because of its high PIC score and because chromosome 16 is rarely lost in gliomas (James et al., 1988; this report). Quantitative results were then objectively classified into the categories of loss, no loss, or indeterminate, as determined by comparison to normal range values".
Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. No tests used as reference standard in our analyses.
Flow and timing	We presumed that all tests were performed on biopsied tumour material collected on 1 occasion.
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		

Ransom 1992a *(Continued)*

Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (NanoString)			
DOMAIN 2: Index Test (aCGH)			
DOMAIN 2: Index Test (NGS)			
DOMAIN 2: Index Test (G-banding)			
If a threshold was used, was it pre-specified?	Yes		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (FISH (variant 4))			
DOMAIN 2: Index Test (SNP array)			
DOMAIN 2: Index Test (PCR (with comparison to normal DNA))			
DOMAIN 2: Index Test (PCR (without comparison to normal DNA))			
DOMAIN 2: Index Test (CISH)			
DOMAIN 2: Index Test (MS)			
DOMAIN 2: Index Test (RFLP)			
If a threshold was used, was it pre-specified?	Unclear		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern

DOMAIN 2: Index Test (PCR-based LOH)

DOMAIN 2: Index Test (NGS or aCGH (or both))

DOMAIN 2: Index Test (Methylation array)

DOMAIN 2: Index Test (FISH)

DOMAIN 2: Index Test (FISH (variant 1))

DOMAIN 2: Index Test (FISH (variant 2))

DOMAIN 2: Index Test (FISH (variant 3))

DOMAIN 2: Index Test (Real-time PCR)

DOMAIN 2: Index Test (MLPA)

DOMAIN 2: Index Test (CGH)

DOMAIN 3: Reference Standard

Is the reference standards likely to correctly classify the target condition?	No		
Could the reference standard, its conduct, or its interpretation have introduced bias?		High risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern

DOMAIN 4: Flow and Timing

Was there an appropriate interval between index test and reference standard?	Yes		
Were all patients included in the analysis?	No		
Could the patient flow have introduced bias?		High risk	

Ransom 1992b

Study characteristics

Patient Sampling	**Inclusion/exclusion criteria**
	Inclusion criteria: diffuse astrocytomas of gemistocytic, fibrillary and protoplasmic type; astroblastomas; mixed oligoastrocytomas.
	Exclusion criteria: pure oligodendrogliomas, pilocytic astrocytomas, subependymal giant cell astrocytomas and ependymomas.
	Prior testing

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Ransom 1992b *(Continued)*

	Tumours were morphologically classified using the WHO 1993 classification and were graded by the St Anne/Mayo method (Daumas-Duport 1988).
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 22 **Country:** USA **Population source and setting:** source and setting NR. Collected between May 1988 and June 1990 **Age:** mean: 53.5 years, standard deviation: 14.3 years **Gender:** 63.6% male **Karnofsky performance status:** NR **First diagnosis/recurrent disease:** first diagnosis 86.4% (19/22); 13.6% recurrent (3/22)
Index tests	**2 tests:** G-banding and RFLP **G-banding** Tumour sample type: NR Region(s) analysed: genome wide Cut-off: NA Additional details: quote: "cytogenetically analyzed using previously described methods (Jenkins et al., 1989)". **RFLP** Tumour sample type: frozen Region(s) analysed: 1p: DIZ2 (1p36.3), AMY (1p21), NGFB (1p22.1); 19q D19S8 (19q13.2) and S19S7 (19cen-q12) Cut-off: NR Additional details: quote: "Paired blood and tumor DNA specimens were digested with various restriction enzymes and electrophoresed on agarose gels. Southern blotting was performed, and nylon membranes were hybridized under high stringency to a series of probes detecting RFLPs on all human chromosomes (Feinberg and Vogelstein, 1984; Southern, 1975). The resulting autoradiographs were then examined for signal intensity. Quantitative densitometry was applied to autoradiographs in cases were subjective interpretation was not immediately obvious. A normal range for relative tumor/leukocyte DNA allele intensity was established using the 3'HVR probe, which detects multiple alleles on chromosome 16 and is frequently heterozygous. The probe 3'HVR was chosen because of its high PIC score and because chromosome 16 is rarely lost in gliomas (James et al., 1988; this report). Quantitative results were then objectively classified into the categories of loss, no loss, or indeterminate, as determined by comparison to normal range values".
Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. No tests used as reference standard in our analyses.
Flow and timing	We presumed that all tests were performed on biopsied tumour material collected on 1 occasion.

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Ransom 1992b *(Continued)*

Comparative			
Notes			

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (NanoString)			
DOMAIN 2: Index Test (aCGH)			
DOMAIN 2: Index Test (NGS)			
DOMAIN 2: Index Test (G-banding)			
If a threshold was used, was it pre-specified?	Yes		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (FISH (variant 4))			
DOMAIN 2: Index Test (SNP array)			
DOMAIN 2: Index Test (PCR (with comparison to normal DNA))			
DOMAIN 2: Index Test (PCR (without comparison to normal DNA))			
DOMAIN 2: Index Test (CISH)			
DOMAIN 2: Index Test (MS)			

Ransom 1992b *(Continued)*

DOMAIN 2: Index Test (RFLP)

If a threshold was used, was it pre-specified?	Unclear		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern

DOMAIN 2: Index Test (PCR-based LOH)

DOMAIN 2: Index Test (NGS or aCGH (or both))

DOMAIN 2: Index Test (Methylation array)

DOMAIN 2: Index Test (FISH)

DOMAIN 2: Index Test (FISH (variant 1))

DOMAIN 2: Index Test (FISH (variant 2))

DOMAIN 2: Index Test (FISH (variant 3))

DOMAIN 2: Index Test (Real-time PCR)

DOMAIN 2: Index Test (MLPA)

DOMAIN 2: Index Test (CGH)

DOMAIN 3: Reference Standard

Is the reference standards likely to correctly classify the target condition?	No		
Could the reference standard, its conduct, or its interpretation have introduced bias?		High risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern

DOMAIN 4: Flow and Timing

Was there an appropriate interval between index test and reference standard?	Yes		
Were all patients included in the analysis?	No		
Could the patient flow have introduced bias?		High risk	

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Scheie 2006 *(Continued)*

Study characteristics

Patient Sampling	**Inclusion/exclusion criteria** Inclusion criteria: people with a supratentorial oligodendroglial tumour **Prior testing** Histopathological diagnosis according to WHO 2000 classification.
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 40 **Country:** Norway **Population source and setting:** Rikshospitalet-Radiumhospitalet Medical Center (Oslo, Norway). 2000–2004. **Age:** mean: 43.1 years, standard deviation: NR; range: 19–66 years **Gender:** NR **Karnofsky performance status:** NR **First diagnosis/recurrent disease:** 95% first diagnosis (38/40); 5% recurrent disease (2/40)
Index tests	**2 tests:** FISH and PCR **FISH** Tumour sample type: fresh or fresh-frozen Region(s) analysed: 1p36.3 (D1Z2)/D1Z hybridising to the pericentric region (Q-biogene, Heidelberg, Germany), 19q (D19S238E)/telomeric region on chromosome 19p (Vysis Inc, Downers Grove, Illinois, USA). Cut-off: a tumour was defined as FISH positive when FISH-sum (proportion of cells with FISH-LOH and FISH-imbalance) exceeded the mean plus 3 standard deviations value in control specimens from non-neoplastic brain tissue. The presence of 0 or 1 1p36- or 19q- signal was reported as FISH-LOH. Losses with any disproportion (signal ratios 3/2, 4/3, 4/2, 5/3, etc. were defined as FISH-imbalance. Cut-offs: 27.7% for 1p and 33.2% for 19q Additional details: FISH on touch preparations **PCR** Tumour sample type: fresh-frozen or FFPE Region(s) analysed: ≥ 4 of the following for chromosome 1 and 19: chromosome 1: D1S2660, D1S507, D1S199, D1S2734, D1S1676, D1S247; chromosome 19: D19S918, D19S219, D19S112, D19S412, D19S596, D19S206 Cut-off: results were defined as LOH-positive when the peak areas of fluorescent intensity curves, corresponding to PCR products from individual primer sets, showed a relative reduction of ≥ 40% when the products from tumour DNA were compared with those from normal DNA. Unclear how many markers had to display LOH.

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Scheie 2006 *(Continued)*

Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. FISH or PCR-based LOH used as reference standard in some of our analyses.
Flow and timing	We presumed that both tests were performed on the same sample for each participant.
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (NanoString)			
DOMAIN 2: Index Test (aCGH)			
DOMAIN 2: Index Test (NGS)			
DOMAIN 2: Index Test (G-banding)			
DOMAIN 2: Index Test (FISH (variant 4))			
DOMAIN 2: Index Test (SNP array)			
DOMAIN 2: Index Test (PCR (with comparison to normal DNA))			
DOMAIN 2: Index Test (PCR (without comparison to normal DNA))			
DOMAIN 2: Index Test (CISH)			
DOMAIN 2: Index Test (MS)			
DOMAIN 2: Index Test (RFLP)			
DOMAIN 2: Index Test (PCR-based LOH)			
If a threshold was used, was it pre-specified?	Yes		

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Scheie 2006 *(Continued)*

Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (NGS or aCGH (or both))			
DOMAIN 2: Index Test (Methylation array)			
DOMAIN 2: Index Test (FISH)			
If a threshold was used, was it pre-specified?	Yes		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (FISH (variant 1))			
DOMAIN 2: Index Test (FISH (variant 2))			
DOMAIN 2: Index Test (FISH (variant 3))			
DOMAIN 2: Index Test (Real-time PCR)			
DOMAIN 2: Index Test (MLPA)			
DOMAIN 2: Index Test (CGH)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	No		
Could the reference standard, its conduct, or its interpretation have introduced bias?		High risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			

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Scheie 2006 *(Continued)*

Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Schrock 1994

Study characteristics

Patient Sampling	**Inclusion/exclusion criteria** NR. Quote: "Nine human malignant gliomas" studied. **Prior testing** Histopathological diagnosis according to WHO 1993 classification.
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 8 **Country:** Germany **Population source and setting:** NR **Age:** mean: 57.5 years, standard deviation: 12.8 years **Gender:** 62.5% male **Karnofsky performance status:** NR **First diagnosis/recurrent disease:** 87.5% (7/8) primary tumours, 12.5% (1/8) recurrent tumour
Index tests	**2 tests:** CGH and G-banding **CGH** Tumour sample type: frozen Region(s) analysed: genome wide Cut-off: quote: "For each case evaluation of chromosomal imbalances and amplification sites in gliomas was performed both by visual inspection and calculation of fluorescence ratio profiles. For visual inspection digitized FITC and TRITC images of 10 reference metaphase spreads and the corresponding ratio images were analyzed.29 A five color lookup table was established according to the results of CGH with test DNAs from cell populations with specific monosomies and trisomies (S. du Manoir et al, manuscript in preparation). Chromosomes were identified using DAPI banding patterns. Photographs were taken from the screen with Agfa RS 50 color slide film. For fluorescence ratio profiles computer programs were developed on the basis of TCL-Image (TNO Institute of Applied Physics, Delft, The Netherlands) running on a Macintosh Quadra 950. After determination of the chromosomal axis, individual FITC/TRITC profiles were calculated for each chromosome. Mean ratio profiles were determined from 10 metaphases. The central line in the profiles (Figures 2 and 5) represents the most frequently measured fluorescence ratio for each reference metaphase spread. The left and right vertical lines define threshold values for

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Schrock 1994 *(Continued)*

underrepresentation and overrepresentation of chromosome material (S. du Manoir et al, manuscript in preparation)".

G-banding

Tumour sample type: fresh

Region(s) analysed: genome wide

Cut-off: not applicable

Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. No tests used as reference standard in our analyses.
Flow and timing	We presumed that all tests were performed on biopsied tumour material collected on 1 occasion.
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (NanoString)			
DOMAIN 2: Index Test (aCGH)			
DOMAIN 2: Index Test (NGS)			
DOMAIN 2: Index Test (G-banding)			
If a threshold was used, was it pre-specified?	Yes		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	

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Schrock 1994 *(Continued)*

Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (FISH (variant 4))		
DOMAIN 2: Index Test (SNP array)		
DOMAIN 2: Index Test (PCR (with comparison to normal DNA))		
DOMAIN 2: Index Test (PCR (without comparison to normal DNA))		
DOMAIN 2: Index Test (CISH)		
DOMAIN 2: Index Test (MS)		
DOMAIN 2: Index Test (RFLP)		
DOMAIN 2: Index Test (PCR-based LOH)		
DOMAIN 2: Index Test (NGS or aCGH (or both))		
DOMAIN 2: Index Test (Methylation array)		
DOMAIN 2: Index Test (FISH)		
DOMAIN 2: Index Test (FISH (variant 1))		
DOMAIN 2: Index Test (FISH (variant 2))		
DOMAIN 2: Index Test (FISH (variant 3))		
DOMAIN 2: Index Test (Real-time PCR)		
DOMAIN 2: Index Test (MLPA)		
DOMAIN 2: Index Test (CGH)		
If a threshold was used, was it pre-specified?	Yes	
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	No	

Schrock 1994 *(Continued)*

Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	Low risk	

Senetta 2013

Study characteristics	
Patient Sampling	**Inclusion/exclusion criteria**
	Brain tumours with an oligodendroglial component with diagnostic agreement between 2 observers. Recurrences were excluded.
	Prior testing
	Histopathological diagnosis using the WHO 2007 classification.
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 143
	Country: Italy
	Population source and setting: Department of Medical Sciences, University of Turin. January 2004 to March 2012
	Age: mean: 51.5 years, standard deviation: NR; range: 22–81 years
	Gender: 56.6% male
	Karnofsky performance status: NR
	First diagnosis/recurrent disease: 100% first diagnosis
Index tests	**2 tests:** FISH (variant 1) and FISH (variant 2)
	FISH (variant 1)
	Tumour sample type: FFPE
	Region(s) analysed: 1p36/1q25 and 19q13/19p13 (Vysis, Abbott Molecular Europe, Wiesbaden, Germany)
	Cut-off: ratios 1p ≤ 0.8 and 19q ≤ 0.8
	FISH (variant 2)
	Tumour sample type: FFPE

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	Region(s) analysed: 1p36/1q25 and 19q13/19p13 (Vysis, Abbott Molecular Europe, Wiesbaden, Germany)		
	Cut-off: ratios 1p ≤ 0.7 and 19q ≤ 0.8		
Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. No tests used as reference standard in our analyses.		
Flow and timing	The same FISH preparations were used, and 2 different thresholds were applied.		
Comparative			
Notes			

Methodological quality

Item	Authors' judge-ment	Risk of bias	Applicability con-cerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (NanoString)			
DOMAIN 2: Index Test (aCGH)			
DOMAIN 2: Index Test (NGS)			
DOMAIN 2: Index Test (G-banding)			
DOMAIN 2: Index Test (FISH (variant 4))			
DOMAIN 2: Index Test (SNP array)			
DOMAIN 2: Index Test (PCR (with comparison to normal DNA))			
DOMAIN 2: Index Test (PCR (without comparison to normal DNA))			
DOMAIN 2: Index Test (CISH)			
DOMAIN 2: Index Test (MS)			
DOMAIN 2: Index Test (RFLP)			
DOMAIN 2: Index Test (PCR-based LOH)			

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Senetta 2013 *(Continued)*

DOMAIN 2: Index Test (NGS or aCGH (or both))		

DOMAIN 2: Index Test (Methylation array)		

DOMAIN 2: Index Test (FISH)		

DOMAIN 2: Index Test (FISH (variant 1))		
If a threshold was used, was it pre-specified?	Yes	
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Yes	
Could the conduct or interpretation of the index test have introduced bias?	Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern

DOMAIN 2: Index Test (FISH (variant 2))		
If a threshold was used, was it pre-specified?	Yes	
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Yes	
Could the conduct or interpretation of the index test have introduced bias?	Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern

DOMAIN 2: Index Test (FISH (variant 3))		

DOMAIN 2: Index Test (Real-time PCR)		

DOMAIN 2: Index Test (MLPA)		

DOMAIN 2: Index Test (CGH)		

DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern

DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Were all patients included in the analysis?	Yes	

Senetta 2013 *(Continued)*

Could the patient flow have introduced bias?	Low risk

Sim 2018a

Study characteristics	
Patient Sampling	**Inclusion/exclusion criteria**
	Inclusion criteria: glioblastoma
	Prior testing
	Histopathological diagnosis (WHO 2007 classification)
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 75
	Country: Republic of Korea
	Population source and setting: Samsung Medical Center, Seoul, Korea. 2011–2014
	Age: mean: 52.8 years, standard deviation: NR; range: 21–76 years
	Gender: 53.3% male
	Karnofsky performance status: NR
	First diagnosis/recurrent disease: not clear. We excluded recurrent samples from participants who also contributed samples from their primary tumour.
Index tests	**2 tests:** FISH and NGS or aCGH (or both)
	FISH
	Tumour sample type: FFPE
	Region(s) analysed: 1p36 and 19q13 (Vysis, Downers Grove, Illinois, USA)
	Cut-off: 1p deletion as a combined target-to-control signal ratio < 0.75 or cut-off of a nucleus with a 1 or 0 target signal > 50%. 19q deletion as a combined target-to-control signal ratio < 0.8 and a nucleus cut-off with a 1 or 0 target signal > 30%
	NGS or aCGH (or both)
	Tumour sample type: fresh frozen
	Region(s) analysed: genome wide
	Cut-off: whole arm losses
	Additional details: aCGH (Afilent SurePrint G3 Human CGH 4x180k array) or whole exome sequencing (Illumina TruSeq Exome capture kit or the Agilent SureSelect kit and either the Illumina HiSeq 2000 or HiSeq 2500) (or both)

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Sim 2018a *(Continued)*

Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. FISH used as reference standard in some of our analyses.
Flow and timing	We presumed that all tests were performed on biopsied tumour material collected on 1 occasion.
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (NanoString)			
DOMAIN 2: Index Test (aCGH)			
DOMAIN 2: Index Test (NGS)			
DOMAIN 2: Index Test (G-banding)			
DOMAIN 2: Index Test (FISH (variant 4))			
DOMAIN 2: Index Test (SNP array)			
DOMAIN 2: Index Test (PCR (with comparison to normal DNA))			
DOMAIN 2: Index Test (PCR (without comparison to normal DNA))			
DOMAIN 2: Index Test (CISH)			
DOMAIN 2: Index Test (MS)			
DOMAIN 2: Index Test (RFLP)			
DOMAIN 2: Index Test (PCR-based LOH)			
DOMAIN 2: Index Test (NGS or aCGH (or both))			
If a threshold was used, was it pre-specified?	Yes		

Sim 2018a *(Continued)*

Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear	
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Unclear
DOMAIN 2: Index Test (Methylation array)		
DOMAIN 2: Index Test (FISH)		
If a threshold was used, was it pre-specified?	Unclear	
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear	
Could the conduct or interpretation of the index test have introduced bias?	High risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (FISH (variant 1))		
DOMAIN 2: Index Test (FISH (variant 2))		
DOMAIN 2: Index Test (FISH (variant 3))		
DOMAIN 2: Index Test (Real-time PCR)		
DOMAIN 2: Index Test (MLPA)		
DOMAIN 2: Index Test (CGH)		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Were all patients included in the analysis?	Unclear	
Could the patient flow have introduced bias?	Unclear risk	

Sim 2018b

Study characteristics

Patient Sampling	**Inclusion/exclusion criteria**
	Inclusion: oligodendroglial tumour
	Prior testing
	Presumably histopathological diagnosis, although not explicitly reported
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 10
	Country: Republic of Korea
	Population source and setting: NR
	Age: mean: 45.7 years, standard deviation: 13.5 years
	Gender: 60% male
	Karnofsky performance status: NR
	First diagnosis/recurrent disease: NR
Index tests	**2 tests:** FISH and NGS
	FISH
	Tumour sample type: FFPE
	Region(s) analysed: 1p36 and 19q13 (Vysis, Downers Grove, Illinois, USA)
	Cut-off: 1p deletion as a combined target-to-control signal ratio < 0.75 or cut-off of a nucleus with a 1 or 0 target signal > 50%. 19q deletion as a combined target-to-control signal ratio < 0.8 and a nucleus cut-off with a 1 or 0 target signal > 30%
	NGS
	Tumour sample type: fresh frozen
	Region(s) analysed: genome wide
	Cut-off: whole arm losses
	Additional details: whole exome sequencing (Illumina TruSeq Exome capture kit or the Agilent SureSelect kit and either the Illumina HiSeq 2000 or HiSeq 2500)
Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. FISH used as reference standard in some of our analyses.
Flow and timing	We presumed that both tests were performed on tumour material harvested at the same time point.
Comparative	

Sim 2018b *(Continued)*

Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (NanoString)			
DOMAIN 2: Index Test (aCGH)			
DOMAIN 2: Index Test (NGS)			
If a threshold was used, was it pre-specified?	Yes		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (G-banding)			
DOMAIN 2: Index Test (FISH (variant 4))			
DOMAIN 2: Index Test (SNP array)			
DOMAIN 2: Index Test (PCR (with comparison to normal DNA))			
DOMAIN 2: Index Test (PCR (without comparison to normal DNA))			
DOMAIN 2: Index Test (CISH)			
DOMAIN 2: Index Test (MS)			
DOMAIN 2: Index Test (RFLP)			
DOMAIN 2: Index Test (PCR-based LOH)			
DOMAIN 2: Index Test (NGS or aCGH (or both))			

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DOMAIN 2: Index Test (Methylation array)		
DOMAIN 2: Index Test (FISH)		
If a threshold was used, was it pre-specified?	Unclear	
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear	
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (FISH (variant 1))		
DOMAIN 2: Index Test (FISH (variant 2))		
DOMAIN 2: Index Test (FISH (variant 3))		
DOMAIN 2: Index Test (Real-time PCR)		
DOMAIN 2: Index Test (MLPA)		
DOMAIN 2: Index Test (CGH)		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?		High risk
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Low risk

Smith 1999

Study characteristics

Patient Sampling	**Inclusion/exclusion criteria**
	Inclusion criteria: diffuse gliomas
	Prior testing

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Smith 1999 *(Continued)*

	Histopathological diagnosis according to WHO 1993 classification.
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 79
	Country: USA
	Population source and setting: Mayo Clinic in Rochester, MN, Johns Hopkins Hospital in Baltimore, Maryland, USA, and the University of California at San Francisco, USA. Time period NR. Cases subsequently included in Hatanpaa 2003a and Hatanpaa 2003b were removed.
	Age: NR
	Gender: NR
	Karnofsky performance status: NR
	First diagnosis/recurrent disease: 72.2% (57/79) primary glioma specimens; 27.8% (22/79) recurrent glioma specimens
Index tests	**3 tests:** CGH, FISH and PCR
	CGH
	Tumour sample type: NR
	Region(s) analysed: NR
	Cut-off: reference Mohapatra G, Kim DH, Feuerstein BG. Detection of multiple gains and losses of genetic material in ten glioma cell lines by comparative genomic hybridization. *Genes, Chromosomes & Cancer* 1995;13;86-93. In this publication: "Definition of CGH ratio thresholds to define ratios that were indicative of changes in DNA copy number, we performed 21 CGH experiments using normal control DNA. We calculated average ratio changes and standard deviations by using the software program cghprofstats.new (Piper et al., 1994). The average ratio for all 21 hybridizations was 0.99 (range 0.9-1.1). The average standard deviation was 0.04 (range 0.02-0.06). Taking these findings into consideration, we chose upper and lower ratio thresholds of 1.2 and 0.8, respectively. Any change in ratio in excess of these thresholds was interpreted as indicative of DNA copy number changes only if found in both forward and reverse experiments. Amplifications were defined both by a ratio >2.0 and by visual inspection". Piper J, Rutovitz D, Sudar D, Kallioniemi A, Kallioniemi O, Waldman FM, et al. Computer image analysis of comparative genomic hybridization. *Cytometry* 1995;19:10-26 also cited.
	FISH
	Tumour sample type: NR
	Region(s) analysed: 1p36, 1q24, 19p13.1, 19q13.1-q13.2 and 19q13.3.
	Cut-off: we defined codeletion as hemizygous deletion of 1p36, 1q13.1-q13.2 and 19q13.3. What defined hemizygous deletion NR. Also cited Qian J, Bostwick DG, Takahashi S, Borell TJ, Herath JF, Lieber MM et al. Chromosomal anomalies in prostatic intraepithelial neoplasia and carcinoma detected by fluorescence in situ hybridization. *Cancer Research* 1995;55:5408-14. In this paper (quote) "abnormal autosomal loss required ≥55% nuclei with zero or one signal". Unclear if this threshold was used.
	PCR
	Tumour sample type: NR

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Region(s) analysed: 1p: D1S468, D1S1612, D1S1597, D1S199, D1S1665, D1S1728, D1S1588, D1S1675, D1S187; 19q: D19S213, D19S569, D19S422. D19S219, SM, S19S112, S19S412, D19S596, HRC, D19S589, D19S218

Cut-off: we defined codeletion as all markers showing confirmed allelic loss, presumed allelic loss, were homozygous or were indeterminant.

Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. FISH or PCR-based LOH used as reference standard in some of our analyses.
Flow and timing	We presumed that all tests were performed on biopsied tumour material collected on 1 occasion.
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (NanoString)			
DOMAIN 2: Index Test (aCGH)			
DOMAIN 2: Index Test (NGS)			
DOMAIN 2: Index Test (G-banding)			
DOMAIN 2: Index Test (FISH (variant 4))			
DOMAIN 2: Index Test (SNP array)			
DOMAIN 2: Index Test (PCR (with comparison to normal DNA))			
DOMAIN 2: Index Test (PCR (without comparison to normal DNA))			
DOMAIN 2: Index Test (CISH)			
DOMAIN 2: Index Test (MS)			

Smith 1999 *(Continued)*

DOMAIN 2: Index Test (RFLP)			
DOMAIN 2: Index Test (PCR-based LOH)			
If a threshold was used, was it pre-specified?	Unclear		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (NGS or aCGH (or both))			
DOMAIN 2: Index Test (Methylation array)			
DOMAIN 2: Index Test (FISH)			
If a threshold was used, was it pre-specified?	Unclear		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (FISH (variant 1))			
DOMAIN 2: Index Test (FISH (variant 2))			
DOMAIN 2: Index Test (FISH (variant 3))			
DOMAIN 2: Index Test (Real-time PCR)			
DOMAIN 2: Index Test (MLPA)			
DOMAIN 2: Index Test (CGH)			
If a threshold was used, was it pre-specified?	Unclear		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	

Smith 1999 (Continued)

Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Were all patients included in the analysis?	No	
Could the patient flow have introduced bias?	High risk	

Srebotnik-Kirbis 2016

Study characteristics	
Patient Sampling	**Inclusion/exclusion criteria** No further details reported. Included an oligodendroglial tumour and non-oligodendroglial tumour cohort. We have only extracted data for the oligodendroglial tumour cohort. **Prior testing** Histopathological diagnosis, according to the WHO 2007 classification.
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 12 **Country:** Slovenia **Population source and setting:** tissue samples from non-consecutive patients who underwent surgical resection or biopsy to the Institute of Pathology, Faculty of Medicine, University of Ljubljana. December 2011 to November 2015. **Age:** mean: 47.8 years, standard deviation: 10.5 years **Gender:** 50% male **Karnofsky performance status:** NR **First diagnosis/recurrent disease:** NR

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Srebotnik-Kirbis 2016 *(Continued)*

Index tests	**2 tests:** FISH (variant 1) and FISH (variant 2)
	FISH (variant 1)
	Tumour sample type: fresh tissue cytospins
	Region(s) analysed: 1p36/1q25 and 19q13/19p13 (Vysis paired probes, Abbott Laboratories, Abbott Park, Illinois, USA)
	Cut-off: quote: "Deletion was defined as a nucleus showing none or one target signal, and 2 or more control signals (ex. 1/2, 0/2, 1/3 etc.) … A tumour sample was considered positive for 1p or 19q deletion when it displayed a percentage of nuclei with deletion above the cut-off value for that probe, specifically … 30% for 1p and 19% for 19q on cytospins".
	FISH (variant 2)
	Tumour sample type: FFPE tissue section
	Region(s) analysed: 1p36/1q25 and 19q13/19p13 (Vysis paired probes, Abbott Laboratories, Abbott Park, Illinois, USA)
	Cut-off: quote: "Deletion was defined as a nucleus showing none or one target signal, and 2 or more control signals (ex. 1/2, 0/2, 1/3 etc.) … A tumour sample was considered positive for 1p or 19q deletion when it displayed a percentage of nuclei with deletion above the cut-off value for that probe, specifically, 43% for 1p and 33% for 19q in tissue sections" and "the cut-off value of 50 %, which is often reported in the literature, was also included in the analysis of FISH results for FFPE sections".
Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. No tests used as reference standard in our analyses.
Flow and timing	We presumed that all tests were performed on biopsied tumour material collected on 1 occasion.
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		High risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (NanoString)			

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Srebotnik-Kirbis 2016 *(Continued)*

DOMAIN 2: Index Test (aCGH)			
DOMAIN 2: Index Test (NGS)			
DOMAIN 2: Index Test (G-banding)			
DOMAIN 2: Index Test (FISH (variant 4))			
DOMAIN 2: Index Test (SNP array)			
DOMAIN 2: Index Test (PCR (with comparison to normal DNA))			
DOMAIN 2: Index Test (PCR (without comparison to normal DNA))			
DOMAIN 2: Index Test (CISH)			
DOMAIN 2: Index Test (MS)			
DOMAIN 2: Index Test (RFLP)			
DOMAIN 2: Index Test (PCR-based LOH)			
DOMAIN 2: Index Test (NGS or aCGH (or both))			
DOMAIN 2: Index Test (Methylation array)			
DOMAIN 2: Index Test (FISH)			
DOMAIN 2: Index Test (FISH (variant 1))			
If a threshold was used, was it pre-specified?	Yes		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (FISH (variant 2))			
If a threshold was used, was it pre-specified?	Yes		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern

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Srebotnik-Kirbis 2016 *(Continued)*

DOMAIN 2: Index Test (FISH (variant 3))		
DOMAIN 2: Index Test (Real-time PCR)		
DOMAIN 2: Index Test (MLPA)		
DOMAIN 2: Index Test (CGH)		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?		High risk
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Were all patients included in the analysis?	No	
Could the patient flow have introduced bias?		High risk

Thakur 2012

Study characteristics	
Patient Sampling	**Inclusion/exclusion criteria**
	NR
	Prior testing
	NR
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 2
	Country: USA
	Population source and setting: NR
	Age: NR
	Gender: NR
	Karnofsky performance status: NR
	First diagnosis/recurrent disease: NR
Index tests	**2 tests:** FISH and SNP array

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Thakur 2012 *(Continued)*

	FISH
	Tumour sample type: NR
	Region(s) analysed: NR
	Cut-off: NR
	SNP array
	Tumour sample type: FFPE
	Region(s) analysed: genome wide
	Cut-off: NR
	Additional details: quote: "Affymetrix GeneChip human mapping 250L Nsp I array".
Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. FISH used as reference standard in some of our analyses.
Flow and timing	We presumed that all tests were performed on biopsied tumour material collected on 1 occasion.
Comparative	
Notes	Conference abstract

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (NanoString)			
DOMAIN 2: Index Test (aCGH)			
DOMAIN 2: Index Test (NGS)			
DOMAIN 2: Index Test (G-banding)			
DOMAIN 2: Index Test (FISH (variant 4))			
DOMAIN 2: Index Test (SNP array)			

Thakur 2012 *(Continued)*

If a threshold was used, was it pre-specified?	Unclear		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (PCR (with comparison to normal DNA))			
DOMAIN 2: Index Test (PCR (without comparison to normal DNA))			
DOMAIN 2: Index Test (CISH)			
DOMAIN 2: Index Test (MS)			
DOMAIN 2: Index Test (RFLP)			
DOMAIN 2: Index Test (PCR-based LOH)			
DOMAIN 2: Index Test (NGS or aCGH (or both))			
DOMAIN 2: Index Test (Methylation array)			
DOMAIN 2: Index Test (FISH)			
If a threshold was used, was it pre-specified?	Unclear		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (FISH (variant 1))			
DOMAIN 2: Index Test (FISH (variant 2))			
DOMAIN 2: Index Test (FISH (variant 3))			
DOMAIN 2: Index Test (Real-time PCR)			
DOMAIN 2: Index Test (MLPA)			
DOMAIN 2: Index Test (CGH)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	No		

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Could the reference standard, its conduct, or its interpretation have introduced bias?		High risk
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Were all patients included in the analysis?	Unclear	
Could the patient flow have introduced bias?		Unclear risk

Thomas 2017

Study characteristics	
Patient Sampling	**Inclusion/exclusion criteria**
	Nested in a phase II study.
	Inclusion criteria: diagnosis of anaplastic oligodendroglioma or anaplastic oligoastrocytoma according to the WHO 2000 classification (mixed tumours should have a minimum of 25% oligodendroglial elements); aged ≥18 years; Karnofsky performance status ≥ 60; adequate organ and bone marrow function including a granulocyte count ≥ 1.5×10^9/L, platelet count of ≥ 100×10^9/L, aspartate aminotransferase ≤ 2× UNL, serum creatinine ≤1.5 × UNL and bilirubin ≤ 1.5 × UNL.
	Exclusion criteria: systemic or non-contiguous leptomeningeal metastases; prior cranial RT or systemic chemotherapy; other concurrent malignancy with the exception of cervical carcinoma in situ or basal cell carcinoma of the skin; serious illness that would interfere with the prescribed treatment; pregnancy or lactation; refusal to use effective contraception.
	Prior testing
	Histopathological diagnosis according to the WHO 2000. Quote: "Within 2 weeks of starting treatment, all patients were evaluated with a complete history, physical and neurological examination, contrast enhanced MRI [magnetic resonance imaging], a biochemistry panel, and complete blood count and underwent screening for hepatitis B and C and HIV".
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 19
	Country: USA
	Population source and setting: phase II study
	Age[a]: median: 44 years, interquartile range: NR; range: 30–66 years
	Gender: 65.9% male
	Karnofsky performance status: median 90, range 70–100

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Thomas 2017 *(Continued)*

First diagnosis/recurrent disease: unclear. Quote: "Patients with newly diagnosed AO [anaplastic oligodendroglioma] or AOA [anaplastic oligoastrocytoma] were eligible to participate in this prospective multicenter phase II study".

aFor whole population: 41 people in the phase II study, only 19 had available tissue with adequate DNA quality and quantity for NGS.

Index tests	**2 tests:** FISH and NGS
	FISH
	Tumour sample type: NR
	Region(s) analysed: NR
	Cut-off: NR
	NGS
	Tumour sample type: NR
	Region(s) analysed: genome wide
	Cut-off: NR
	Additional details: MSK-IMPACT: a hybridisation capture-based sequencing assay utilising an Illumina HiSeq 2500 platform.
Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. FISH used as reference standard in some of our analyses.
Flow and timing	We presumed that all tests were performed on biopsied tumour material collected on 1 occasion.
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (NanoString)			

Thomas 2017 *(Continued)*

DOMAIN 2: Index Test (aCGH)			
DOMAIN 2: Index Test (NGS)			
If a threshold was used, was it pre-specified?	Unclear		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	No		
Could the conduct or interpretation of the index test have introduced bias?		High risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			High
DOMAIN 2: Index Test (G-banding)			
DOMAIN 2: Index Test (FISH (variant 4))			
DOMAIN 2: Index Test (SNP array)			
DOMAIN 2: Index Test (PCR (with comparison to normal DNA))			
DOMAIN 2: Index Test (PCR (without comparison to normal DNA))			
DOMAIN 2: Index Test (CISH)			
DOMAIN 2: Index Test (MS)			
DOMAIN 2: Index Test (RFLP)			
DOMAIN 2: Index Test (PCR-based LOH)			
DOMAIN 2: Index Test (NGS or aCGH (or both))			
DOMAIN 2: Index Test (Methylation array)			
DOMAIN 2: Index Test (FISH)			
If a threshold was used, was it pre-specified?	Unclear		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (FISH (variant 1))			
DOMAIN 2: Index Test (FISH (variant 2))			

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DOMAIN 2: Index Test (FISH (variant 3))		
DOMAIN 2: Index Test (Real-time PCR)		
DOMAIN 2: Index Test (MLPA)		
DOMAIN 2: Index Test (CGH)		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?		High risk
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Were all patients included in the analysis?	No	
Could the patient flow have introduced bias?		High risk

Tsiatis 2010

Study characteristics	
Patient Sampling	**Inclusion/exclusion criteria** NR **Prior testing** NR, but presumably histopathological diagnosis.
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 4 **Country:** USA **Population source and setting:** NR **Age:** mean: 43.3 years, standard deviation: 8.2 years **Gender:** 25% male **Karnofsky performance status:** NR **First diagnosis/recurrent disease:** NR
Index tests	**2 tests:** PCR and SNP array

Tsiatis 2010 *(Continued)*

	PCR
	Tumour sample type: FFPE
	Region(s) analysed: D1S199, D1S186, D1S162, D1S312, D1S226, D19S918, D19S112, D19S206
	Cut-off: NR
	Additional details: quote: "Samples were run on an ABI 3100 following multiplex PCR amplification of 5 STRs on chromosome 1p (D1S199, D1S186, D1S162, D1S312, D1S226) and 3 STRs on chromosome 19q (D19S918, D19S112, D19S206)".
	SNP array
	Tumour sample type: FFPE
	Region(s) analysed: genome wide
	Cut-off: NR
	Additional details: quote: "Array analysis was performed using the Affymetrix genome-wide human SNP array 6.0 platform (906,600 SNPs) according to protocol. Data were analyzed with Partek Genomics Suite".
Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. PCR-based LOH used as reference standard in some of our analyses.
Flow and timing	We presumed that all tests were performed on biopsied tumour material collected on 1 occasion.
Comparative	
Notes	Conference abstract

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (NanoString)			
DOMAIN 2: Index Test (aCGH)			
DOMAIN 2: Index Test (NGS)			

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Tsiatis 2010 *(Continued)*

DOMAIN 2: Index Test (G-banding)		
DOMAIN 2: Index Test (FISH (variant 4))		
DOMAIN 2: Index Test (SNP array)		
If a threshold was used, was it pre-specified?	Unclear	
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear	
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (PCR (with comparison to normal DNA))		
DOMAIN 2: Index Test (PCR (without comparison to normal DNA))		
DOMAIN 2: Index Test (CISH)		
DOMAIN 2: Index Test (MS)		
DOMAIN 2: Index Test (RFLP)		
DOMAIN 2: Index Test (PCR-based LOH)		
If a threshold was used, was it pre-specified?	Unclear	
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear	
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (NGS or aCGH (or both))		
DOMAIN 2: Index Test (Methylation array)		
DOMAIN 2: Index Test (FISH)		
DOMAIN 2: Index Test (FISH (variant 1))		
DOMAIN 2: Index Test (FISH (variant 2))		
DOMAIN 2: Index Test (FISH (variant 3))		
DOMAIN 2: Index Test (Real-time PCR)		
DOMAIN 2: Index Test (MLPA)		

Tsiatis 2010 *(Continued)*

DOMAIN 2: Index Test (CGH)		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Were all patients included in the analysis?	Unclear	
Could the patient flow have introduced bias?	Unclear risk	

Uchida 2019

Study characteristics	
Patient Sampling	**Inclusion/exclusion criteria** Inclusion criteria: primary glioblastoma. Tested by FISH **Prior testing** Presumably histopathological diagnosis, although this was not explicitly reported.
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 141 **Country:** Japan **Population source and setting:** The Department of Neurosurgery, University of Kagoshima. 2009–2016 **Age:** NR **Gender:** NR **Karnofsky performance status:** NR **First diagnosis/recurrent disease:** unclear. Primary GBM
Index tests	**2 tests:** FISH (variant 1) and FISH (variant 2) **FISH (variant 1)** Tumour sample type: NR Region(s) analysed: 1p36/1q25, 19p13/19q13 (Vysis LSI DNA probes)

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	Cut-off: 20%. Criteria for judging whether a deletion was present: signals of 1p or 19q < signals of 1q or 19p.
	FISH (variant 2)
	Tumour sample type: NR
	Region(s) analysed: 1p36/1q25, 19p13/19q13 (Vysis LSI DNA probes)
	Cut-off: 20%. Criteria for judging whether a deletion was present: single signal of 1p or 19q and 2 signals of 1q or 19p.
Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. No tests used as reference standard in our analyses.
Flow and timing	This was 1 test analysed with 2 different cut-offs.
Comparative	
Notes	Conference abstract

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (NanoString)			
DOMAIN 2: Index Test (aCGH)			
DOMAIN 2: Index Test (NGS)			
DOMAIN 2: Index Test (G-banding)			
DOMAIN 2: Index Test (FISH (variant 4))			
DOMAIN 2: Index Test (SNP array)			
DOMAIN 2: Index Test (PCR (with comparison to normal DNA))			
DOMAIN 2: Index Test (PCR (without comparison to normal DNA))			
DOMAIN 2: Index Test (CISH)			

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Uchida 2019 *(Continued)*

DOMAIN 2: Index Test (MS)			
DOMAIN 2: Index Test (RFLP)			
DOMAIN 2: Index Test (PCR-based LOH)			
DOMAIN 2: Index Test (NGS or aCGH (or both))			
DOMAIN 2: Index Test (Methylation array)			
DOMAIN 2: Index Test (FISH)			
DOMAIN 2: Index Test (FISH (variant 1))			
If a threshold was used, was it pre-specified?	No		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		High risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (FISH (variant 2))			
If a threshold was used, was it pre-specified?	No		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		High risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (FISH (variant 3))			
DOMAIN 2: Index Test (Real-time PCR)			
DOMAIN 2: Index Test (MLPA)			
DOMAIN 2: Index Test (CGH)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	No		
Could the reference standard, its conduct, or its interpretation have introduced bias?		High risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern

DOMAIN 4: Flow and Timing

Was there an appropriate interval between index test and reference standard?	Yes
Were all patients included in the analysis?	Unclear
Could the patient flow have introduced bias?	Unclear risk

Wiestler 2014

Study characteristics	
Patient Sampling	**Inclusion/exclusion criteria**
	Inclusion criteria for NOA-04: adults with centrally confirmed diagnosis of a WHO grade III anaplastic glioma, Karnofsky performance score ≥ 70, no prior systemic chemotherapy or RT to the brain, and adequate bone marrow reserve, liver and renal functions, and stable or decreasing corticosteroid dose within 14 days before random assignment.
	Prior testing
	Histopathological diagnosis according to WHO 1993 and WHO 2000 classifications.
Patient characteristics and setting	**Number of participants/tumours with results for 1p/19q status by ≥ 2 DNA-based tests:** 99
	Country: Germany
	Population source and setting: people enrolled in the NOA-04 trial from 39 sites in Germany. Time period NR
	Age[a]: median: 42 years in the RT arm and 41.5 years in the procarbazine, lomustine and vincristine/temozolomide arm, interquartile range: NR; range: 23–74 years
	Gender[b]: 57.7% male
	Karnofsky performance status**: median 90, range 70–100
	First diagnosis/recurrent disease: NR, although presumably first diagnosis.
	[a]For whole population: these data were for the biomarker cohort (the 115 participants with sufficient amount and quantity of tumour DNA). Methylation array and MLPA data was only available for 99 participants.
	[b]For whole population: these data were for the modified intention-to-treat population of NOA-04. This included 274 participants, we had data on both tests for 99 participants.
Index tests	**2 tests:** methylation array and MLPA
	Methylation array
	Tumour sample type: FFPE
	Region(s) analysed: genome wide

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Cut-off: quote: "Copy number aberrations were detected from the HM450 data as described.20,22 Copy number plots were manually analysed for 1p/19q codeletion".

Additional details: HM450 BeadChip (Illumina, San Diego, California, USA)

MLPA

Tumour sample type: FFPE

Region(s) analysed: used Salsa MLPA P088, MRC Holland, Amsterdam, the Netherlands

Cut-off: quote: "Chromosomal regions were scored as under- or overrepresented if two or more loci on 1p or 19q adjacent to each other exhibited a gene dosage ratio less than 70% or more than 130% relative to the reference value".

Additional details: Salsa MLPA, P088 lots 0305 and 0706, MRC Holland, Amsterdam, the Netherlands

Target condition and reference standard(s)	Target condition was absolute 1p/19q deletion. No tests used as reference standard in our analyses.
Flow and timing	We presumed that all tests were performed on biopsied tumour material collected on 1 occasion.
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (NanoString)			
DOMAIN 2: Index Test (aCGH)			
DOMAIN 2: Index Test (NGS)			
DOMAIN 2: Index Test (G-banding)			
DOMAIN 2: Index Test (FISH (variant 4))			

Wiestler 2014 *(Continued)*

DOMAIN 2: Index Test (SNP array)

DOMAIN 2: Index Test (PCR (with comparison to normal DNA))

DOMAIN 2: Index Test (PCR (without comparison to normal DNA))

DOMAIN 2: Index Test (CISH)

DOMAIN 2: Index Test (MS)

DOMAIN 2: Index Test (RFLP)

DOMAIN 2: Index Test (PCR-based LOH)

DOMAIN 2: Index Test (NGS or aCGH (or both))

DOMAIN 2: Index Test (Methylation array)

If a threshold was used, was it pre-specified?	Unclear		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern

DOMAIN 2: Index Test (FISH)

DOMAIN 2: Index Test (FISH (variant 1))

DOMAIN 2: Index Test (FISH (variant 2))

DOMAIN 2: Index Test (FISH (variant 3))

DOMAIN 2: Index Test (Real-time PCR)

DOMAIN 2: Index Test (MLPA)

If a threshold was used, was it pre-specified?	Yes		
Were the index test results interpreted without knowledge of the results of the other tests being compared?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern

DOMAIN 2: Index Test (CGH)

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Wiestler 2014 *(Continued)*

DOMAIN 3: Reference Standard

Is the reference standards likely to correctly classify the target condition?	No	
Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern

DOMAIN 4: Flow and Timing

Was there an appropriate interval between index test and reference standard?	Yes	
Were all patients included in the analysis?	No	
Could the patient flow have introduced bias?	High risk	

aCGH: array comparative genomic hybridisation; CGH: comparative genomic hybridisation; CI: confidence interval; CISH: chromogenic in situ hybridisation; DNA: deoxyribonucleic acid; EORTC: European Organisation for Research and Treatment of Cancer; FFPE: formalin-fixed, paraffin-embedded; FISH: fluorescent in situ hybridisation; IDH: isocitrate dehydrogenase; LOH: loss of heterozygosity; MLPA: multiplex-ligation-dependent probe amplification; MS: mass spectrometry; NGS: next-generation sequencing; NR: not reported; PCR: polymerase chain reaction; RFLP: restriction fragment length polymorphism; RT: radiotherapy; SNP: single nucleotide polymorphism; WHO: World Health Organization.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Afyounian 2017	1p19q not assessed by ≥ 2 DNA techniques.
Alentorn 2014	Concordance only data.
Aoki 2015a	1p19q not assessed by ≥ 2 DNA techniques.
Aoki 2015b	1p19q not assessed by ≥ 2 DNA techniques.
Assem 2009	1p19q not assessed by ≥ 2 DNA techniques.
Assem 2012	No results.
Bady 2013	1p19q not assessed by ≥ 2 DNA techniques.
Ballester 2017	Single case report.
Becker 2017	1p19q not assessed by ≥ 2 DNA techniques.
Bienkowski 2018	No results.
Boudreau 2004	Not a primary study.
Brat 2015	1p19q not assessed by ≥ 2 DNA techniques.

Study	Reason for exclusion
Buckley 2011	Concordance only data.
Burgenske 2017	1p19q not assessed by ≥ 2 DNA techniques.
Bystricka 2011	Concordance only data.
Carrato 2006	Concordance only data.
Carrato 2010	Recruited based on 1p/19q status.
Carter 2016	Concordance only data.
Castilla 2003	1p19q not assessed by ≥ 2 DNA techniques.
Chernova 2003	1p19q not assessed by ≥ 2 DNA techniques.
Cieply 2005	Concordance only data.
Durand 2010	1p19q not assessed by ≥ 2 DNA techniques.
Eckel-Passow 2017	Concordance only data.
Fontaine 2007	Concordance only data.
Franco-Hernandez 2009a	Concordance only data.
Franco-Hernandez 2009b	1p19q not assessed by ≥ 2 DNA techniques.
French 2005	1p19q not assessed by ≥ 2 DNA techniques.
Garber 2016	1p19q not assessed by ≥ 2 DNA techniques.
Hartmann 2005	Not a primary study.
Hashimoto 2002	1p19q not assessed by ≥ 2 DNA techniques.
Hench 2018	Concordance only data.
Horbinski 2008	Single case report.
Horbinski 2011	Concordance only data.
Ida 2018	Participants aged < 18 years.
Idbaih 2008	1p19q not assessed by ≥ 2 DNA techniques.
Joo 2013	Single case report.
Juratli 2012	No results.
Kamoun 2015	1p19q not assessed by ≥ 2 DNA techniques.
Kashofer 2018	1p19q not assessed by ≥ 2 DNA techniques.
Kim 2016	1p19q not assessed by ≥ 2 DNA techniques.

Study	Reason for exclusion
Kitange 2004	1p19q not assessed by ≥ 2 DNA techniques.
Kitange 2005	No results.
Klink 2010	No results.
Klink 2011	No results
Kouwenhoven 2009	1p19q not assessed by ≥ 2 DNA techniques.
Kuo 2009	1p19q not assessed by ≥ 2 DNA techniques.
Kuo 2013	1p19q not assessed by ≥ 2 DNA techniques.
Kwon 2019	1p19q not assessed by ≥ 2 DNA techniques.
Lautenschlaeger 2013	1p19q not assessed by ≥ 2 DNA techniques.
Levine 2018	1p19q not assessed by ≥ 2 DNA techniques.
Liu 2014	1p19q not assessed by ≥ 2 DNA techniques.
Magnani 2003	1p19q not assessed by ≥ 2 DNA techniques.
Martinez 2005	Single case report.
Marucci 2012	1p19q not assessed by ≥ 2 DNA techniques.
McDonald 2005	1p19q not assessed by ≥ 2 DNA techniques.
Mohapatra 2011	No results.
Molinari 2010	Concordance only data.
Mrachek 2018	Recruited based on 1p/19q status.
Mur 2013	1p19q not assessed by ≥ 2 DNA techniques.
Myung 2011	Not a glioma.
Narasimhaiah 2010	Concordance only data.
Neill 2015	Single case report.
Nielsen 2007	Not a primary study.
Parizi-Robinson 2004	Concordance only data.
Payne 2008	1p19q not assessed by ≥ 2 DNA techniques.
Pekmezci 2016	1p19q not assessed by ≥ 2 DNA techniques.
Pietsch 2015	Participants aged < 18 years.
Pina-Oviedo 2012	Concordance only data.

Study	Reason for exclusion
Pinkham 2015	Not a primary study.
Pinto 2008	No results.
Ramkissoon 2015	No results.
Rolston 2002	1p19q not assessed by ≥ 2 DNA techniques.
Roy 2012	Concordance only data.
Satomi 2018	Concordance only data.
Satomi 2019	Concordance only data.
Scheinin 2014	1p19q not assessed by ≥ 2 DNA techniques.
Schiavo 2009	1p19q not assessed by ≥ 2 DNA techniques.
Serrano 2015	Concordance only data.
Tauziede-Espariat 2018	1p19q not assessed by ≥ 2 DNA techniques.
Walker 2000	1p19q not assessed by ≥ 2 DNA techniques.
Woehrer 2015	Not a primary study.
Xiu 2015	1p19q not assessed by ≥ 2 DNA techniques.
Yokogami 2018	Concordance only data.
Yoshimoto 2002	1p19q not assessed by ≥ 2 DNA techniques.
Zacher 2017	Recruited based on 1p/19q status.
Zheng 2019	Concordance only data.

DNA: deoxyribonucleic acid.

Characteristics of studies awaiting classification [ordered by study ID]

Ducray 2011

Patient Sampling
Patient characteristics and setting
Index tests
Target condition and reference standard(s)
Flow and timing
Comparative

Ducray 2011 *(Continued)*

Notes	No full-text

Hazra 2006

Patient Sampling	
Patient characteristics and setting	
Index tests	
Target condition and reference standard(s)	
Flow and timing	
Comparative	
Notes	No full-text

McDonald 2003

Patient Sampling	
Patient characteristics and setting	
Index tests	
Target condition and reference standard(s)	
Flow and timing	
Comparative	
Notes	No full-text

Meunier 2005

Patient Sampling	
Patient characteristics and setting	
Index tests	
Target condition and reference standard(s)	
Flow and timing	
Comparative	
Notes	No full-text

Monnot 2007

Patient Sampling	
Patient characteristics and setting	
Index tests	
Target condition and reference standard(s)	
Flow and timing	
Comparative	
Notes	No full-text

Sebastian 2003

Patient Sampling	
Patient characteristics and setting	
Index tests	
Target condition and reference standard(s)	
Flow and timing	
Comparative	
Notes	No full-text

Characteristics of ongoing studies *[ordered by study ID]*

ACTRN12618000006246

Study name	Access to innovative molecular diagnostic PROfiling for paediatric brain tumours (application of innovative molecular profiling techniques to improve diagnosis of paediatric central nervous system tumours and develop an accredited Australasian molecular profiling service)
Target condition and reference standard(s)	
Index and comparator tests	
Starting date	
Contact information	
Notes	

JPRN-UMIN000003196

Study name	Genetic analysis of prognosis-related factors in gliomas: methylation of MGMT, LOH of 1p/19q, and mutation of IDH1/2
Target condition and reference standard(s)	
Index and comparator tests	
Starting date	
Contact information	
Notes	

NCT00031538

Study name	Genetic analysis of brain tumors (a prospective national study to molecularly and genetically characterize human gliomas: the Glioma Molecular Diagnostic Initiative)
Target condition and reference standard(s)	
Index and comparator tests	
Starting date	
Contact information	
Notes	

NCT01004887

Study name	Study of tissue and blood samples from patients with high-grade glioma (diagnostic and prognostic markers in high-grade glioma)
Target condition and reference standard(s)	
Index and comparator tests	
Starting date	
Contact information	
Notes	

NCT03336931

Study name	Precision medicine for children with cancer (a multicenter prospective study of the feasibility and clinical value of a diagnostic service for identifying therapeutic targets and recommending personalised treatment for children and adolescents with high-risk cancer)
Target condition and reference standard(s)	
Index and comparator tests	
Starting date	
Contact information	
Notes	

D A T A

Presented below are all the data for all of the tests entered into the review.

Table Tests. Data tables by test

Test	No. of studies	No. of participants
1 CISH (against FISH)	1	38
2 PCR-based LOH (against FISH)	15	915
3 Real-time PCR (against FISH)	2	40
4 MLPA (against FISH)	2	33
5 CGH (against FISH)	4	75
6 aCGH (against FISH)	3	39
7 SNP array (against FISH)	6	111
8 NGS (against FISH)	6	243
9 MS (against FISH)	1	10
10 NanoString (against FISH)	1	16
11 FISH (against PCR-based LOH)	15	915
12 Real-time PCR (against PCR-based LOH)	1	10
13 MLPA (against PCR-based LOH)	1	18
14 CGH (against PCR-based LOH)	6	151
15 aCGH (against PCR-based LOH)	4	57

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Test	No. of studies	No. of participants
16 SNP array (against PCR-based LOH)	2	33
17 NGS (against PCR-based LOH)	1	49
18 MS (against PCR-based LOH)	1	50
19 G-banding (against PCR-based LOH)	1	21
20 CGH (against MLPA)	1	71
21 Methylation array (against MLPA)	1	99
22 G-banding (against CGH)	3	75
23 G-banding (against RFLP)	2	27

ADDITIONAL TABLES

Table 1. Techniques that can be used to detect 1p/19q codeletion

Technique	Brief description
FISH	FISH testing uses fluorescently labelled probes that are designed to hybridise to specific chromosomal locations. It can be performed on FFPE, and on fresh or frozen tissue. In this technique tissue architecture is preserved. To test for chromosome 1p/19q codeletion, chromosomes 1 and 19 are analysed on separate slides. FISH probes corresponding to regions of 1p or 19q labelled using 1 colour, and control probes on 1q or 19p labelled in another colour (as 1q and 19p seem to remain unaffected) are used. Many commercially available probes hybridise to loci at 1p36 and 19q13, although the FISH probes used at different centres may not target exactly the same loci (Pinkham 2015). Normal nuclei show a diploid signal ratio of 2/2 (2 signals from 1p or 19q and 2 signals from 1q or 19p). Absolute deletions will theoretically result in 1 signal from 1p or 19q in the presence of 2 signals from the control loci. There is no consensus on cut-offs to diagnose codeletion. This is demonstrated by the fact that the EORTC study 26951 and the RTOG study 9402 used slightly different criteria (Pinkham 2015). Some laboratories define cut-offs based on the percentage of cells with deleted and imbalanced signals, some define cut-offs based on ratios calculated by dividing the total number of test probes by the total number of control probes, and some combine percentage and ratio cut-offs.
CISH	This is a very similar technique to FISH, but instead of using fluorescent labelling, the probes are labelled with a marker such as biotin, digoxigenin or dinitrophenyl, and then this marker is detected using antibodies or streptavidin (that binds biotin) that is conjugated to enzymes such as horseradish peroxidase or alkaline phosphatase. The presence of the probe can then be visualised in the presence of a substrate that undergoes a colour change in the presence of the enzyme. The advantages of CISH is that it does not require a fluorescence microscope and staining is permanent.
PCR-based LOH assays	This technique analyses polymorphic microsatellites that are dispersed throughout the genome. Different alleles have different numbers of repeats. PCR amplification of regions containing polymorphic microsatellites can therefore result in different length PCR products. If an individual is heterozygous (has 2 different alleles) for a microsatellite, PCR of this region will result in 2 differ-

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Table 1.   Techniques that can be used to detect 1p/19q codeletion *(Continued)*

	ent length products. If heterozygosity is lost, only 1 length product will be obtained. An individual must be heterozygous for a microsatellite for it to be informative, and DNA from normal tissue is required to determine this. LOH can be determined by comparing the ratio of PCR products of different lengths obtained from normal and tumour tissue. Primers that amplify regions containing microsatellites on 1p and 19q can be used to determine whether 1p and 19q are codeleted. However, there is no consensus on location or number of microsatellites analysed.
RFLP analysis	LOH can also be detected using RFLP analysis. In RFLP, restriction enzymes that recognise specific sequences are used to cut DNA, resulting in fragments of specific sizes. Different alleles may contain cut sites, or the DNA fragment that the restriction enzyme produces after digestion may be expected to differ due to different numbers of repeats in different alleles. Therefore, in a similar manner to PCR, LOH can be detected through loss of fragments of a specific size from informative loci (where an individual is heterozygous in normal tissue).
Comparative quantitative PCR	Comparative quantitative PCR compares the amount of PCR product obtained from 1p/19q with PCR product obtained from other chromosomal regions. If a deletion is present, less PCR product will be obtained. This technique has the advantages that heterozygosity at loci is not required, neither is a sample of normal tissue.
MLPA	MLPA uses probes designed to hybridise to specific regions of the genome that have been split into 2. Each probe 'half' also contains sequences corresponding to universal forward and reverse binding sites for PCR primers, and 1 'half' contains a region of varying length to help identify the probe later. The primers are hybridised to denatured sample DNA (e.g. from a tumour). The next step is ligation. Only probe halves that are hybridised to adjacent sequences on the sample DNA will be ligated together. PCR, using primers corresponding to the universal binding sides contained in the probes, is used to amplify the probes. Only those probe halves that were ligated together will be amplified to any extent, as it is only these products that contain the binding sites for both the forward and reverse PCR primers. The PCR products can then be separated by length, and quantified. The results are then normalised internally (by comparing reference probes with target probes), and then compared with reference samples. Heterozygous deletions can be identified as a probe ratio of 0.5 will be observed, and heterozygous duplications from a probe ratio of 1.5. Usually, probe ratios < 0.7 or > 1.3 are regarded as indicative of a heterozygous deletion (copy number change from 2 to 1 allele) or duplication (copy number change from 2 to 3 alleles), respectively ([Eijk-Van Os 2011](#)).
CGH	In CGH, differentially labelled genomes from the tumour (the test genome) and normal tissue (the control genome, which does not need to be from the same person) are simultaneously hybridised to normal metaphase chromosomes. Changes in copy number, caused for example by loss or gain of regions, will alter the ratio of the 2 genomes. If 2 different fluorochromes are used to mark the genomes (or detect the labels), changes in copy number can be revealed from the relative intensities of fluorochromes used to detect the 2 genomes. CGH detects DNA sequence copy number changes relative to the mean copy number in the entire tumour sample. However, signals can be normalised using the sex chromosomes, which may help if a tumour is known to be normal for these chromosomes.
aCGH	aCGH follow the same principles as CGH, but instead of the 2 genomes being competitively hybridised to metaphase chromosomes, they are hybridised to a microarray. The theoretical resolution of aCGH is greater than that of traditional CGH.
SNP arrays	An SNP array is a type of DNA microarray. SNP arrays allow both copy number status and genotype to be determined, allowing detection of both losses and copy-neutral LOH. SNPs are variations at a single position in a DNA sequence. Since individuals usually inherit 1 copy of each SNP position from each parent, the individual's genotype at a SNP site is typically either *AA*, *AB* or *BB*.

Table 1. Techniques that can be used to detect 1p/19q codeletion *(Continued)*

	To detect abnormalities using SNP arrays, sample DNA is fragmented, labelled and hybridised to an array containing immobilised allele-specific oligonucleotide probes (1 probe for each allele). The signal intensity associated with each probe is then measured. Copy number changes can be detected from the intensity of signal. By comparing the result for each SNP with those from normal tissue, or by using a hidden Markov model, LOH can be detected.
	In the rare case of 2:2 tetraploidy, it is possible that SNP arrays will not be able to distinguish absolute from relative deletions.
Methylation arrays	Genome-wide DNA methylation array data can also be used to detect 1p/19q status, as reported in Capper 2018b.
	In methylation arrays, specific regions of the genome that may be modified by methylation are investigated. The array has 2 probes for each region, 1 for the methylated and 1 for the unmethylated. To detect copy number variations, the signal from both probes (the methylated and unmethylated) for a specific region are added together and compared with a reference genome.
NGS	NGS refers to post-Sanger sequencing technologies including sequencing-by-synthesis, sequencing-by-ligation and ion semiconductor sequencing. While traditional Sanger sequencing sequences a single DNA sequence, NGS is capable of sequencing multiple sequences simultaneously.
	Techniques have been developed to detect LOH and copy number variations using NGS. Deletions can be detected by relative perturbations in the read depth.
	LOH can be detected when the ratio of alleles at a heterozygous SNP site is perturbed.

aCGH: array comparative genomic hybridisation; CGH: comparative genomic hybridisation; CISH: chromogenic in situ hybridisation; DNA: deoxyribonucleic acid; EORTC: European Organisation for Research and Treatment of Cancer; FFPE: formalin-fixed, paraffin-embedded tissue; FISH: fluorescence in situ hybridisation; LOH: loss of heterozygosity; MLPA: multiplex-ligation-dependent probe amplification; NGS: next-generation sequencing; PCR: polymerase chain reaction; RFLP: restriction fragment length polymorphism; RTOG: Radiation Therapy Oncology Group; SNP: single nucleotide polymorphism.

Table 2. Theoretical ways in which false-positive and false-negative results could be obtained from the various techniques

Technique	Potential ways false-positive results could be obtained	Potential ways false-negative results could be obtained
FISH	Focal deletions at regions that the target probes hybridise could lead to false-positive results as these cannot be distinguished from whole arm deletions (as only 1 probe per chromosome arm is normally used).	False-negative results could be obtained if there has been a loss of heterozygosity without copy number reduction.
	Depending on the way that deletions are diagnosed (i.e. the cut-off used and whether it depends on the ratio of test probes to control probes), aberrations that lead to disproportionate gain in control probe loci (i.e. 1q and 19p) could lead to false-positive results.	False-negative results could be obtained if non-neoplastic nuclei are assessed.
	The way that the tumour tissue is sectioned to prepare it for FISH could lead to 'truncation artefact'. Nuclei may be transected, which may lead to them containing incomplete genetic material. False-positive results may be obtained from normal tissue in the presence of excessive truncation artefact.	Excessive truncation artefact in neoplastic tissue could lead to false-negative results.
CISH	As for FISH.	As for FISH.

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Table 2. Theoretical ways in which false-positive and false-negative results could be obtained from the various techniques *(Continued)*

PCR-based LOH assays	PCR cannot distinguish between relative and absolute deletions, so people with relative deletions will be given false-positive results.	If tumour samples are heavily contaminated with normal tissue, PCR products for both alleles will be obtained in a ratio that would give a false-negative result.
	Depending on primer spacing and the number of informative loci, the technique may detect focal rather than whole arm deletions.	
	Imbalanced polysomy, e.g. gain of 1 copy of chromosome 1 and 19, may result in allelic imbalance and be interpreted as loss of heterozygosity.	
RFLP analysis	Cannot distinguish between relative and absolute deletions, so people with relative deletions will be given false-positive results.	If tumour samples are heavily contaminated with normal tissue, digestion products for both alleles will be obtained in a ratio that would give a false-negative result.
	Depending on the regions analysed, it is possible that this technique may detect focal rather than whole arm deletions.	
	Imbalanced polysomy, e.g. gain of 1 copy of chromosome 1 and 19, may result in allelic imbalance and be interpreted as loss of heterozygosity.	
Comparative quantitative PCR	PCR cannot distinguish between absolute deletion and relative deletions in the presence of polyploidy (i.e. those deletions that would give a 2:4 ratio/equivalent with FISH).	If tumour samples are heavily contaminated with normal tissue the amount of PCR product obtained would result in a false-negative result.
	Polysomy which causes the PCR product from control regions to increase could result in false-positive results.	False-negative results could be obtained if there has been an LOH without copy number reduction.
		Aneuploidy which causes the PCR product from control regions to decrease could result in false-negative results.
MLPA	Cannot distinguish between absolute deletion and relative deletions in the presence of polyploidy (i.e. those deletions that would give a 2:4 ratio/equivalent with FISH).	If tumour samples are heavily contaminated with normal tissue, a false-negative result may arise.
	SNPs at primer binding sites, as single mismatches at ligation sites can inhibit ligation.	False-negative results could be obtained if there has been an LOH without copy number reduction.
CGH	Cannot distinguish between absolute deletion and relative deletions in the presence of polyploidy (i.e. those deletions that would give a 2:4 ratio/equivalent with FISH).	If tumour samples are heavily contaminated with normal tissue, a false-negative result may arise.
		False-negative results could be obtained if there has been an LOH without copy number reduction.
aCGH	As for CGH.	As for CGH.

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Table 2. Theoretical ways in which false-positive and false-negative results could be obtained from the various techniques *(Continued)*

SNP arrays	Cannot distinguish between absolute deletion and relative deletions in the presence of polyploidy arising from whole genome duplication after the codeletion event (i.e. those deletions that would give a 2:4 ratio/equivalent with FISH).	If tumour samples are heavily contaminated with normal tissue, a false-negative result may arise.
Methylation arrays	Cannot distinguish between absolute deletion and relative deletions in the presence of polyploidy arising from whole genome duplication after the codeletion event (i.e. those deletions that would give a 2:4 ratio/equivalent with FISH).	If tumour samples are heavily contaminated with normal tissue, a false-negative result may arise.
		False-negative results could be obtained if there has been an LOH without copy number reduction.
NGS	Cannot distinguish between absolute deletion and relative deletions in the presence of polyploidy arising from whole genome duplication after the codeletion event (i.e. those deletions that would give a 2:4 ratio/equivalent with FISH).	If tumour samples are heavily contaminated with normal tissue, a false-negative result may arise.

aCGH: array comparative genomic hybridisation; CGH: comparative genomic hybridisation; CISH: chromogenic in situ hybridisation; FFPE: formalin-fixed, paraffin-embedded tissue; FISH: fluorescence in situ hybridisation; LOH: loss of heterozygosity; MLPA: multiplex-ligation-dependent probe amplification; NGS: next-generation sequencing; PCR: polymerase chain reaction; RFLP: restriction fragment length polymorphism; SNP: single nucleotide polymorphism.

Table 3.   All possible 2 × 2 test comparisons from the included studies

Test categories	aCGH	CGH	CISH	FISH	G-banding	Methylation array	MLPA	MS	NanoString	NGS	PCR-based LOH	RFLP	Real-time PCR	SNP array
aCGH	—	—	—	Blesa 2009; Byeon 2014; Mohapatra 2006; Pesenti 2017	—	—	Blesa 2009	Pesenti 2017	—	—	Blesa 2009; Cowell 2004; Mohapatra 2006	—	—	—
CGH	—	—	—	Burger 2001; Hatanpaa 2003a (assay development and non-blinded validation cohort); Hatanpaa 2003b (blinded validation cohort); Smith 1999	Dahlback 2009; Dahlback 2011; Schrock 1994	—	Jeuken 2006	—	—	—	Bigner 1999; Burger 2001; Dahlback 2011; Hatanpaa 2003a (assay development and non-blinded validation cohort); Hatanpaa 2003b (blinded validation cohort); Smith 1999	—	—	—
CISH	—	—	—	Lass 2013	—	—	—	—	—	—	—	—	—	—
FISH	—	—	—	Belaud-Rotureau 2006 [a]; Duval 2014[b]; Duval 2015[c]; Horbinski 2012[d]; Senetta 2013[e]; Srebotnik-Kir	—	—	Blesa 2009; Natte 2005	Pesenti 2017	Armanious 2017	D'Haene 2019; Kato 2019; Na 2019; Park 2019; Sim 2018a (glioblastoma co-	Blesa 2009; Bouvier 2004; Broholm 2008; Burger 2001; Cieply 2004; Clark 2013; Gadji 2009; Hatanpaa 2003a (assay development and non-blinded validation cohort); Hatanpaa 2003b (blinded validation cohort); Horbinski 2012; Jha 2011; Mohapatra	—	Chaturbedi 2012; Nigro 2001	Ghasimi 2016; Hinrichs 2016; Kolhe 2016; Lhotska 2015; Paxton 2015;

Table 3. All possible 2 × 2 test comparisons from the included studies *(Continued)*

			bis 2016[f]; Uchida 2019[g]							hort)[h]; Sim 2018b (oligodendroglial cohort); Thomas 2017	2006; Pesenti 2017; Scheie 2006; Smith 1999			Thakur 2012
G-banding	—	—	—	—	—	—	—	—	—	—	Dahlback 2011	Ransom 1992a; Ransom 1992b	—	—
Methylation array	—	—	—	—	—	—	—	Wiestler 2014	—	—	—	—	—	—
MLPA	—	—	—	—	—	—	—	—	—	—	Blesa 2009	—	—	—
MS	—	—	—	—	—	—	—	—	—	—	Pesenti 2017	—	—	—
NanoString	—	—	—	—	—	—	—	—	—	—	—	—	—	—
NGS	—	—	—	—	—	—	—	—	—	—	Dubbink 2016	—	—	—
PCR-based LOH	—	—	—	—	—	—	—	—	—	—	Hatanpaa 2003a (assay development and non-blinded validation cohort[i]); Hatanpaa 2003b (blinded validation cohort[i])	—	Ariza 2010	Harada 2011; Tsiatis 2010
RFLP	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Real time PCR	—	—	—	—	—	—	—	—	—	—	—	—	—	—

SNP array	—	—	—	—	—	—	—	—	—	—	—	—	—

aCGH: array comparative genomic hybridisation; CGH: comparative genomic hybridisation; CISH: chromogenic in situ hybridisation; FISH: fluorescence in situ hybridisation; LOH: loss of heterozygosity; MLPA: multiplex-ligation-dependent probe amplification; NGS: next-generation sequencing; PCR: polymerase chain reaction; RFLP: restriction fragment length polymorphism; SNP: single nucleotide polymorphism.

[a] Belaud-Rotureau 2006 performed FISH with manual analysis with the 1p36.3 (D1Z2)/1q12 (D1Z1) and 19q13.3/19pter probe set, manual analysis with the 1p36/1q25 and 19q13/19p13 Abbott Vysis probe set, and automatic analysis (Metafer 4, Metasystems, Althlussheim, Germany) with the 1p36/1q25 and 19q13/19p13 Abbott Vysis probe set.

[b] Duval 2014 performed FISH and immunoFISH (FISH with immunohistochemistry against Ki67 (MIB-1)), and used two different cut-offs for both – a "combination" cut-off (which was based on the number of cells showing a deletion) and a "ratio" cut-off (based on the ratio of signals for 1p to 1q and 19q and 19p).

[c] Duval 2015 performed FISH with automated analysis (Metafer 4 software (Metasystem) using the "1p19q tile-sampling classifier") and FISH with manual analysis.

[d] Horbinski 2012 performed FISH with two different cut-offs in addition to PCR-based LOH (target-ploidy control ratio < 0.87, with ≥ 20% of nuclei showing deletion and target-ploidy control ratio < 0.75, with ≥ 20% of nuclei showing deletion).

[e] Senetta 2013 performed FISH with two different cut-offs (cut-off ratios 1p ≤ 0.8 and 19q ≤ 0.8 and cut-off ratios 1p ≤ 0.7 and 19q ≤ 0.8).

[f] Srebotnik-Kirbis 2016 FISH variants on fresh tissue cytospins and on FFPE sections.

[g] Uchida 2019 performed FISH with two different criteria for judging whether a deletion was present (signals of 1p or 19q < signals of 1q or 19p or single signal of 1q or 19q and two signals of 1q or 19p; in both cases the cut-off value was set at 20%).

[h] In Sim 2018a and Sim 2018b, glioblastoma cohort FISH was compared to NGS or aCGH (or both). We categorised NGS or aCGH (or both) as NGS for the purposes of this table.

[i] Hatanpaa 2003a and Hatanpaa 2003b performed PCR-based LOH with or without comparison to normal DNA (in addition to CGH and FISH). This study developed a cut-off for PCR-based LOH without comparison to normal DNA in one set of participants (Hatanpaa 2003a assay development and non-blinded validation cohort) and validated it in another set of participants (Hatanpaa 2003b blinded validation cohort).

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Table 4. Results of the main analysis (simultaneous analysis of all tests against FISH), with results of the sensitivity analysis (separate analyses for each test with four or more studies) using FISH as the reference standard

Test	Number of studies	Main analysis		Sensitivity analysis	
		Sensitivity (95% CrI)	Specificity (95% CrI)	*Sensitivity (95% CrI)*	*Specificity (95% CrI)*
CISH	1	1.00 (0.84 to 1.00)	0.92 (0.33 to 1.00)	*Insufficient studies*	
PCR-based LOH	15	0.94 (0.83 to 0.98)	0.94 (0.87 to 0.98)	*0.94 (0.83 to 0.98)*	*0.94 (0.87 to 0.98)*
Real-time PCR	2	0.81 (0.20 to 0.99)	1.00 (0.95 to 1.00)	*Insufficient studies*	
MLPA	2	0.96 (0.44 to 1.00)	0.68 (0.20 to 0.95)	*Insufficient studies*	
CGH	4	0.95 (0.59 to 1.00)	0.99 (0.90 to 1.00)	*0.90 (0.64 to 0.99)*	*0.99 (0.91 to 1.00)*
aCGH	3	1.00 (0.89 to 1.00)	0.91 (0.55 to 0.99)	*Insufficient studies*	
SNP array	6	0.90 (0.57 to 0.99)	0.97 (0.84 to 1.00)	*0.90 (0.57 to 0.99)*	*0.97 (0.84 to 1.00)*
NGS	6	0.94 (0.75 to 0.99)	1.00 (0.99 to 1.00)	*0.93 (0.83 to 0.98)*	*1.00 (0.99 to 1.00)*
MS	1	1.00 (0.60 to 1.00)	1.00 (0.70 to 1.00)	*Insufficient studies*	
NanoString	1	0.85 (0.11 to 1.00)	0.80 (0.10 to 1.00)	*Insufficient studies*	

aCGH: array comparative genomic hybridisation; CGH: comparative genomic hybridisation; CISH: chromogenic in situ hybridisation; CrI: credible interval; FISH: fluorescence in situ hybridisation; LOH: loss of heterozygosity; MLPA: multiplex-ligation-dependent probe amplification; MS; mass spectrometry; NGS: next-generation sequencing; PCR: polymerase chain reaction; SNP: single nucleotide polymorphism.

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Table 5. Differences in sensitivity (upper right triangle) and specificity (bottom left triangle) from analyses using FISH as the reference standard. Values are test in column minus test in row (95% credible interval). Positive values favour the test defining the column, negative values favour the test defining the row

Test	PCR-based LOH	SNP array	NGS	CGH	aCGH	MLPA	Real-time PCR	CISH	MS	NanoString
PCR-based LOH	—	−0.03 (−0.37 to 0.1)	0 (−0.19 to 0.12)	0.01 (−0.35 to 0.13)	0.05 (−0.05 to 0.16)	0.02 (−0.5 to 0.14)	−0.12 (−0.74 to 0.09)	0.05 (−0.1 to 0.16)	0.05 (−0.34 to 0.16)	−0.08 (−0.82 to 0.11)
SNP array	−0.03 (−0.11 to 0.1)	—	0.04 (−0.17 to 0.37)	0.03 (−0.31 to 0.37)	0.09 (−0.03 to 0.42)	0.04 (−0.46 to 0.38)	−0.08 (−0.7 to 0.29)	0.09 (−0.07 to 0.42)	0.08 (−0.29 to 0.42)	−0.04 (−0.79 to 0.32)
NGS	−0.06 (−0.13 to −0.02)	−0.03 (−0.16 to 0)	—	0 (−0.35 to 0.2)	0.05 (−0.05 to 0.25)	0.01 (−0.5 to 0.21)	−0.12 (−0.74 to 0.14)	0.05 (−0.1 to 0.24)	0.04 (−0.33 to 0.24)	−0.08 (−0.82 to 0.16)
CGH	−0.05 (−0.12 to 0.04)	−0.01 (−0.14 to 0.07)	0.01 (0 to 0.1)	—	0.05 (−0.06 to 0.4)	0.01 (−0.49 to 0.35)	−0.11 (−0.74 to 0.26)	0.05 (−0.1 to 0.4)	0.04 (−0.32 to 0.4)	−0.07 (−0.82 to 0.29)
aCGH	0.03 (−0.08 to 0.4)	0.06 (−0.09 to 0.42)	0.09 (0.01 to 0.45)	0.08 (−0.03 to 0.44)	—	−0.03 (−0.56 to 0.06)	−0.18 (−0.8 to 0)	0 (−0.16 to 0.1)	0 (−0.39 to 0.1)	−0.14 (−0.88 to 0.02)
MLPA	0.25 (−0.02 to 0.75)	0.28 (0 to 0.77)	0.32 (0.05 to 0.8)	0.3 (0.03 to 0.79)	0.2 (−0.22 to 0.71)	—	−0.11 (−0.74 to 0.39)	0.03 (−0.11 to 0.55)	0.03 (−0.32 to 0.55)	−0.08 (−0.83 to 0.41)
Real-time PCR	−0.06 (−0.13 to 0)	−0.02 (−0.16 to 0.03)	0 (−0.01 to 0.05)	−0.01 (−0.09 to 0.04)	−0.09 (−0.45 to 0)	−0.31 (−0.8 to −0.04)	—	0.18 (−0.03 to 0.8)	0.17 (−0.2 to 0.79)	0.02 (−0.73 to 0.68)
CISH	0.02 (−0.09 to 0.62)	0.05 (−0.1 to 0.64)	0.08 (0 to 0.67)	0.07 (−0.05 to 0.66)	−0.01 (−0.36 to 0.57)	−0.19 (−0.72 to 0.4)	0.08 (−0.01 to 0.67)	—	0 (−0.39 to 0.15)	−0.14 (−0.88 to 0.05)
MS	−0.05 (−0.13 to 0.24)	−0.02 (−0.15 to 0.26)	0 (−0.01 to 0.3)	−0.01 (−0.09 to 0.28)	−0.08 (−0.44 to 0.19)	−0.3 (−0.79 to 0.04)	0 (−0.04 to 0.29)	−0.07 (−0.66 to 0.19)	—	−0.13 (−0.87 to 0.23)
NanoString	0.14	0.16	0.2 (0 to 0.9)	0.18	0.09	−0.09	0.2 (0 to 0.9)	0.08	0.18	—

| (−0.08 to 0.84) | (−0.07 to 0.87) | | (−0.03 to 0.88) | (−0.31 to 0.81) | (−0.67 to 0.66) | | (−0.5 to 0.81) | (−0.13 to 0.89) |

aCGH: array comparative genomic hybridisation; CGH: comparative genomic hybridisation; CISH: chromogenic in situ hybridisation; FISH: fluorescence in situ hybridisation; LOH: loss of heterozygosity; MLPA: multiplex-ligation-dependent probe amplification; MS: mass spectrometry; NGS: next-generation sequencing; PCR: polymerase chain reaction; SNP: single nucleotide polymorphism.

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Table 6.   Results of the main analysis (simultaneous analysis of all tests against PCR-based LOH), with results of the sensitivity analysis (separate analyses for each test with four or more studies) using PCR-based LOH as the reference standard

Test	Number of studies	Main analysis		Sensitivity analysis	
		Sensitivity (95% CrI)	Specificity (95% CrI)	Sensitivity (95% CrI)	Specificity (95% CrI)
FISH	15	0.91 (0.78 to 0.97)	0.96 (0.90 to 0.99)	*0.91 (0.78 to 0.97)*	*0.96 (0.90 to 0.99)*
Real-time PCR	1	1.00 (0.77 to 1.00)	No data	*Insufficient studies*	
MLPA	1	1.00 (0.74 to 1.00)	1.00 (0.83 to 1.00)	*Insufficient studies*	
CGH	6	0.94 (0.74 to 0.99)	0.98 (0.91 to 1.00)	*0.93 (0.78 to 0.99)*	*0.97 (0.91 to 1.00)*
aCGH	4	1.00 (0.97 to 1.00)	0.96 (0.75 to 1.00)	*1.00 (0.97 to 1.00)*	*0.95 (0.78 to 1.00)*
SNP array	2	0.97 (0.50 to 1.00)	1.00 (0.92 to 1.00)	*Insufficient studies*	
NGS	1	1.00 (0.86 to 1.00)	0.98 (0.64 to 1.00)	*Insufficient studies*	
MS	1	1.00 (0.85 to 1.00)	1.00 (0.94 to 1.00)	*Insufficient studies*	
G-banding	1	0.00 (0.00 to 0.20)	1.00 (0.78 to 1.00)	*Insufficient studies*	

aCGH: array comparative genomic hybridisation; CGH: comparative genomic hybridisation; CrI: credible interval; FISH: fluorescence in situ hybridisation; LOH: loss of heterozygosity; MLPA: multiplex-ligation-dependent probe amplification; MS: mass spectrometry; NGS: next-generation sequencing; PCR: polymerase chain reaction; SNP: single nucleotide polymorphism.

Table 7. Differences in sensitivity (upper right triangle) and specificity (bottom left triangle) from analyses using PCR-based LOH as the reference standard. Values are test in column minus test in row (95% credible interval). Positive values favour the test defining the column, negative values favour the test defining the row

Test	FISH	CGH	aCGH	SNP array	NGS	G-banding	MLPA	Real-time PCR	MS
FISH	—	0.03 (−0.17 to 0.17)	0.09 (0.03 to 0.22)	0.05 (−0.41 to 0.19)	0.09 (−0.05 to 0.21)	−0.9 (−0.97 to −0.68)	0.08 (−0.17 to 0.21)	0.08 (−0.14 to 0.21)	0.09 (−0.06 to 0.21)
CGH	−0.02 (−0.08 to 0.05)	—	0.05 (0 to 0.25)	0.02 (−0.44 to 0.22)	0.05 (−0.08 to 0.25)	−0.93 (−0.99 to −0.65)	0.05 (−0.2 to 0.25)	0.05 (−0.16 to 0.25)	0.05 (−0.09 to 0.25)
aCGH	0 (−0.07 to 0.2)	0.02 (−0.06 to 0.22)	—	−0.03 (−0.5 to 0.01)	0 (−0.14 to 0.03)	−1 (−1 to −0.79)	0 (−0.26 to 0.03)	0 (−0.23 to 0.03)	0 (−0.15 to 0.03)
SNP array	−0.04 (−0.1 to 0.04)	−0.02 (−0.09 to 0.06)	−0.04 (−0.24 to 0.04)	—	0.03 (−0.09 to 0.49)	−0.95 (−1 to −0.43)	0.03 (−0.2 to 0.49)	0.03 (−0.17 to 0.49)	0.03 (−0.1 to 0.49)
NGS	−0.02 (−0.08 to 0.32)	0 (−0.07 to 0.34)	−0.02 (−0.21 to 0.31)	0.02 (−0.05 to 0.36)	—	−1 (−1 to −0.69)	0 (−0.25 to 0.13)	0 (−0.22 to 0.13)	0 (−0.14 to 0.13)
G-band-ing	−0.04 (−0.1 to 0.17)	−0.01 (−0.09 to 0.19)	−0.04 (−0.24 to 0.16)	0 (−0.07 to 0.21)	−0.02 (−0.35 to 0.18)	—	1 (0.6 to 1)	1 (0.63 to 1)	1 (0.69 to 1)
MLPA	−0.04 (−0.1 to 0.12)	−0.02 (−0.09 to 0.14)	−0.04 (−0.24 to 0.12)	0 (−0.07 to 0.16)	−0.02 (−0.35 to 0.13)	0 (−0.21 to 0.15)	—	0 (−0.21 to 0.25)	0 (−0.14 to 0.25)
Real-time PCR	0.45 (−0.08 to 0.98)	0.47 (−0.06 to 1)	0.43 (−0.17 to 0.99)	0.49 (−0.03 to 1)	0.42 (−0.22 to 1)	0.47 (−0.09 to 1)	0.48 (−0.06 to 1)	—	0 (−0.14 to 0.22)
MS	−0.04 (−0.1 to 0.02)	−0.02 (−0.09 to 0.04)	−0.04 (−0.24 to 0.02)	0 (−0.08 to 0.05)	−0.02 (−0.36 to 0.03)	0 (−0.21 to 0.05)	0 (−0.16 to 0.05)	−0.49 (−1 to 0.02)	—

aCGH: array comparative genomic hybridisation; CGH: comparative genomic hybridisation; FISH: fluorescence in situ hybridisation; LOH: loss of heterozygosity; MLPA: multiplex-ligation-dependent probe amplification; MS: mass spectrometry; NGS: next-generation sequencing; PCR: polymerase chain reaction; SNP: single nucleotide polymorphism.

Table 8.   Results from latent class analyses of FISH and PCR-based LOH

Analysis	Sensitivity of FISH (95% CrI)	Specificity of FISH (95% CrI)	Sensitivity of PCR-based LOH (95% CrI)	Specificity of PCR-based LOH (95% CrI)
Assuming conditional independence	0.95 (0.83 to 1.00)	0.97 (0.93 to 0.99)	0.97 (0.90 to 1.00)	0.98 (0.91 to 1.00)
Allowing for conditional dependencies	0.90 (0.74 to 0.99)	0.96 (0.91 to 0.99)	0.94 (0.80 to 0.99)	0.98 (0.89 to 1.00)
With an informative prior distribution forcing sensitivity of PCR-based LOH to be ≥ 95%	0.92 (0.78 to 0.99)	0.96 (0.90 to 0.99)	0.97 (0.95 to 1.00)	0.98 (0.88 to 1.00)

These results are derived from 910 participants from 16 studies for whom test results were available for both FISH and PCR-based LOH.
CrI: credible interval; FISH: fluorescence in situ hybridisation; LOH: loss of heterozygosity; PCR: polymerase chain reaction.

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Table 9.   Comparison of results obtained when using FISH or PCR-based LOH as the reference standard

Test	Reference standard	Number of studies	Number people with disease	Number people without disease	Total people in meta-analysis	Sensitivity (95% CrI)	Specificity (95% CrI)
Real-time PCR	FISH	2	17	23	40	0.81 (0.20 to 0.99)	1.00 (0.95 to 1.00)
	PCR-based LOH	1	10	0	10	1.00 (0.77 to 1.00)	N/A
MLPA	FISH	2	12	21	33	0.96 (0.44 to 1.00)	0.68 (0.20 to 0.95)
	PCR-based LOH	1	8	10	18	1.00 (0.74 to 1.00)	1.00 (0.83 to 1.00)
CGH	FISH	4	25	50	75	0.95 (0.59 to 1.00)	0.99 (0.90 to 1.00)
	PCR-based LOH	6	70	81	151	0.94 (0.74 to 0.99)	0.98 (0.91 to 1.00)
aCGH	FISH	3	18	21	39	1.00 (0.89 to 1.00)	0.91 (0.55 to 0.99)
	PCR-based LOH	4	30	27	57	1.00 (0.97 to 1.00)	0.96 (0.75 to 1.00)
SNP array	FISH	6	46	65	111	0.90 (0.57 to 0.99)	0.97 (0.84 to 1.00)
	PCR-based LOH	2	16	17	33	0.97 (0.50 to 1.00)	1.00 (0.92 to 1.00)
NGS	FISH	6	78	165	243	0.94 (0.75 to 0.99)	1.00 (0.99 to 1.00)
	PCR-based LOH	1	18	31	49	1.00 (0.86 to 1.00)	0.98 (0.64 to 1.00)
MS	FISH	1	5	5	10	1.00 (0.60 to 1.00)	1.00 (0.70 to 1.00)
	PCR-based LOH	1	16	34	50	1.00 (0.85 to 1.00)	1.00 (0.94 to 1.00)

aCGH: array comparative genomic hybridisation; CGH: comparative genomic hybridisation; CrI: credible interval; FISH: fluorescence in situ hybridisation; LOH: loss of heterozygosity; MLPA: multiplex-ligation-dependent probe amplification; MS; mass spectrometry; N/A: not applicable; NGS: next-generation sequencing; PCR: polymerase chain reaction; SNP: single nucleotide polymorphism.

Table 10.   Costs and diagnostic accuracy of diagnostic tests to evaluate 1p/19q status codeletion (FISH as reference standard)

Inputs	Deterministic analysis	Probabilistic sensitivity analysis
Incremental cost per TP detected		

Diagnostic test	Cost (GBP)	Effect (TP rate)	Incremental cost (GBP)	Incremental effect	ICER (GBP)	Prob of being CE at WTP of GBP 0 per TP	Prob of being CE at WTP of GBP 500 per TP	Prob of being CE at WTP of GBP 1000 per TP	Prob of being CE at WTP of GBP 5000 per TP	Prob of being CE at WTP of GBP 10,000 per TP
MLPA	73	0.27	—	—	—	100%	100%	95%	46%	26%
PCR-based LOH	142	0.25	—	—	Dominated	0%	0%	0%	0%	0%
Real-time PCR	142	0.24	—	—	Dominated	0%	0%	2%	2%	1%
CISH	186	0.30	113	0.03	3827	0%	0%	3%	39%	48%
aCGH	233	0.29	—	—	Dominated	0%	0%	0%	13%	25%
SNP array	257	0.23	—	—	Dominated	0%	0%	0%	0%	0%
NGS	571	0.28	—	—	Dominated	0%	0%	0%	0%	0%

Incremental cost per TN detected

Diagnostic test	Cost (GBP)	Effect (TN rate)	Incremental cost (GBP)	Incremental effect	ICER (GBP)	Prob of being CE at WTP of GBP 0 per TN	Prob of being CE at WTP of GBP 500 per TN	Prob of being CE at WTP of GBP 1000 per TN	Prob of being CE at WTP of GBP 5000 per TN	Prob of being CE at WTP of GBP 10,000 per TN
MLPA	73	0.45	—	—	—	100%	16%	1%	0%	0%
PCR-based LOH	142	0.65	—	—	Dominated	0%	30%	28%	13%	7%
Real-time PCR	142	0.66	69	0.22	326	0%	54%	71%	73%	67%
CISH	186	0.59	—	—	Dominated	0%	0%	0%	2%	2%
aCGH	233	0.66	—	—	Dominated	0%	0%	0%	9%	15%
SNP array	257	0.66	—	—	Dominated	0%	0%	0%	3%	5%
NGS	571	0.69	498	0.24	2111	0%	0%	0%	0%	4%

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Table 10.   Costs and diagnostic accuracy of diagnostic tests to evaluate 1p/19q status codeletion (FISH as reference standard) *(Continued)*

Incremental cost per CD

Diagnostic test	Cost (GBP)	Effect (CD rate)	Incremental cost (GBP)	Incremental effect	ICER (GBP)	Prob of being CE at WTP of GBP 0 per CD	Prob of being CE at WTP of GBP 500 per CD	Prob of being CE at WTP of GBP 1000 per CD	Prob of being CE at WTP of GBP 5000 per CD	Prob of being CE at WTP of GBP 10,000 per CD
MLPA	73	0.72	—	—	—	100%	23%	4%	0%	0%
PCR-based LOH	142	0.90	—	—	Dominated	0%	27%	24%	2%	0%
Real-time PCR	142	0.91	69	0.19	362	0%	47%	54%	27%	18%
CISH	186	0.89	—	—	Dominated	0%	3%	10%	12%	9%
aCGH	233	0.95	160	0.24	673	0%	0%	8	58%	60%
SNP array	257	0.89	—	—	Dominated	0%	0%	0%	0%	0%
NGS	571	0.97	498	0.25	1968	0%	0%	0%	1%	13%

Tests ordered by cost. Diagnostic accuracy figures rounded to 3 decimal places. ICERs based upon exact values for incremental outcomes and costs.

aCGH: array comparative genomic hybridisation; CD: correct diagnosis; CE: cost-effective; CISH: chromogenic in situ hybridisation; FISH: fluorescence in situ hybridisation; ICER: incremental cost-effectiveness ratio; LOH: loss of heterozygosity; NGS: next-generation sequencing; PCR: polymerase chain reaction; SNP: single nucleotide polymorphism; TN: true negative; TP: true positive; WTP: willingness to pay.

Table 11.   Costs and diagnostic accuracy of diagnostic tests to evaluate 1p/19q status codeletion (PCR-based LOH as reference standard)

Inputs			Deterministic analysis			Probabilistic sensitivity analysis				
Incremental cost per true positive detected										
Diagnostic test	Cost (GBP)	Effect (true positive rate)	Incremental cost (GBP)	Incremental effect	ICER (GBP)	Prob of being CE at WTP of GBP 0 per TP	Prob of being CE at WTP of GBP 500 per TP	Prob of being CE at WTP of GBP 1000 per TP	Prob of being CE at WTP of GBP 5000 per TP	Prob of being CE at WTP of GBP 10,000 per TP
MLPA	73	0.28	—	—	—	100%	99%	94%	61%	45%

Table 11. Costs and diagnostic accuracy of diagnostic tests to evaluate 1p/19q status codeletion (PCR-based LOH as reference standard) *(Continued)*

Diagnostic test	Cost	Effect	Incremental cost	Incremental effect	ICER	Prob CE at WTP 0	500	1000	5000	10,000
Real-time PCR	142	0.28	—	—	Dominated	0%	1%	6%	27%	29%
FISH	186	0.26	—	—	Dominated	0%	0%	0%	0%	0%
aCGH	233	0.30	160	0.02	7507	0%	0%	0%	12%	24%
SNP array	257	0.28	—	—	Dominated	0%	0%	0%	0%	2%
NGS	571	0.29	—	—	Dominated	0%	0%	0%	0%	0%

Incremental cost per true negative detected

Diagnostic test	Cost (GBP)	Effect (true negative rate)	Incremental cost (GBP)	Incremental effect	ICER (GBP)	Prob of being CE at WTP of GBP 0 per TN	Prob of being CE at WTP of GBP 500 per TN	Prob of being CE at WTP of GBP 1000 per TN	Prob of being CE at WTP of GBP 5000 per TN	Prob of being CE at WTP of GBP 10,000 per TN
MLPA	73	0.63	—	—	—	100%	99%	94%	61%	49%
FISH	186	0.64	—	—	Extendedly dominated	0%	1%	6%	10%	9%
aCGH	233	0.62	—	—	Dominated	0%	0%	0%	5%	6%
SNP array	257	0.65	184	0.02	8686	0%	0%	0%	24%	35%
NGS	571	0.65	—	—	Dominated	0%	0%	0%	0%	1%

Incremental cost per correct diagnosis

Diagnostic test	Cost (GBP)	Effect (correct diagnosis rate)	Incremental cost (GBP)	Incremental effect	ICER (GBP)	Prob of being CE at WTP of GBP 0 per CD	Prob of being CE at WTP of GBP 500 per CD	Prob of being CE at WTP of GBP 1000 per CD	Prob of being CE at WTP of GBP 5000 per CD	Prob of being CE at WTP of GBP 10,000 per CD
MLPA	73	0.91	—	—	—	100%	99%	93%	55%	42%
FISH	186	0.90	—	—	Dominated	0%	1%	4%	3%	2%
aCGH	233	0.92	—	—	Extendedly dominated	0%	0%	2%	18%	20%

SNP array	257	0.93	0.02	184	10,372	0%	0%	1%	24%	29%
NGS	571	0.94	0.03	498	15,971	0%	0%	0%	0%	7%

Tests ordered by cost. Diagnostic accuracy figures rounded to 3 decimal places. True Negative and Correct Diagnosis rates could be calculated for real-time PCR because a specificity value could not be calculated for this test.

aCGH: array comparative genomic hybridisation; CD: correct diagnosis; CE: cost-effective; FISH: fluorescence in situ hybridisation; ICER: incremental cost-effectiveness ratio; LOH: loss of heterozygosity; MLPA: multiplex-ligation-dependent probe amplification; NGS: next-generation sequencing; PCR: polymerase chain reaction; SNP: single nucleotide polymorphism; TN: true negative; TP: true positive; WTP: willingness to pay.

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APPENDICES

Appendix 1. Database search strategies

In this review, we aimed to include all tests for 1p/19q codeletion that have been studied comparatively, and consequently did not have a predefined list of eligible index tests. Therefore, decided to focus the search strategy based on the population (people with glioma) and the target condition (codeletion of chromosomes 1 and 19).

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1. exp glioma/

2. (glioma* or astrocytoma* or astroblastoma* or ependymoma* or subependymoma* or oligodendroglioma* or oligoastrocytoma* or pleomorphic xanthoastrocytoma* or glioblastoma* or GBM* or ganglioglioma* or gliosarcoma* or gangliocytoma* or ((glial* or glioneuronal* or brain*) and (tumor* or tumour* or cancer* or neoplasm*))).mp.

3. 1 or 2

4. Chromosomes, Human, Pair 1/ or (chromosome 1 or 1p).mp.

5. Chromosomes, Human, Pair 19/ or (chromosome 19 or 19q).mp.

6. (1p?19q* or "1p/19q" or (1p* adj3 19q*)).mp.

7. 4 and 5

8. 6 or 7

9. 3 and 8

Ovid Embase <1974 onwards>

1. exp glioma/

2. (glioma* or astrocytoma* or astroblastoma* or ependymoma* or subependymoma* or oligodendroglioma* or oligoastrocytoma* or pleomorphic xanthoastrocytoma* or glioblastoma* or GBM* or ganglioglioma* or gliosarcoma* or gangliocytoma* or ((glial* or glioneuronal* or brain*) and (tumor* or tumour* or cancer* or neoplasm*))).mp.

3. 1 or 2

4. Chromosome 1/ or chromosome 1p/ or (chromosome 1 or 1p).mp.

5. chromosome 19/ or chromosome 19q/ or (chromosome 19 or 19q).mp.

6. 4 and 5

7. (1p?19q* or "1p/19q" or (1p* adj3 19q*)).mp.

8. 6 or 7

9. 3 and 8

BIOSIS Citation Index <1969 onwards>

#1 TS=(glioma* or astrocytoma* or astroblastoma* or ependymoma* or subependymoma* or oligodendroglioma* or oligoastrocytoma* or pleomorphic xanthoastrocytoma* or glioblastoma* or GBM* or ganglioglioma* or gliosarcoma* or gangliocytoma* or ((glial* or glioneuronal* or brain*) and (tumor* or tumour* or cancer* or neoplasm*)))

#2 TS=(1p*19q* OR "1p/19q")

#3 TS=(("chromosome 1" OR 1p) AND ("chromosome 19" OR 19q))

#4 #2 or #3

#5 #1 and #4

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WHO International Clinical Trials Registry Platform (ICTRP)

Results from each of the following search lines were downloaded and deduplicated in EndNote.

Search 1: *1p* and 19q**

Search 2: *1p19q or 1p/19q*

Search 3: *glioma* and diagnostic test or astrocytoma* and diagnostic test or astroblastoma* and diagnostic test or ependymoma* and diagnostic test or subependymoma* and diagnostic test or oligodendroglioma* and diagnostic test or oligoastrocytoma* and diagnostic test or pleomorphic xanthoastrocytoma* and diagnostic test or glioblastoma* and diagnostic test or GBM* and diagnostic test or ganglioglioma* and diagnostic test or gliosarcoma* and diagnostic test or gangliocytoma* and diagnostic test or glial tumor* and diagnostic test or glial tumour* and diagnostic test or glial cancer* and diagnostic test or glial neoplasm* and diagnostic test or glioneuronal tumor* and diagnostic test or glioneuronal tumour* and diagnostic test or glioneuronal cancer* and diagnostic test or glioneuronal neoplasm* and diagnostic test or brain tumor* and diagnostic test or brain tumour* and diagnostic test or brain cancer* and diagnostic test or brain neoplasm* and diagnostic test*

Search 4: *glioma* and diagnostic assessment or astrocytoma* and diagnostic assessment or astroblastoma* and diagnostic assessment or ependymoma* and diagnostic assessment or subependymoma* and diagnostic assessment or oligodendroglioma* and diagnostic assessment or oligoastrocytoma* and diagnostic assessment or pleomorphic xanthoastrocytoma* and diagnostic assessment or glioblastoma* and diagnostic assessment or GBM* and diagnostic assessment or ganglioglioma* and diagnostic assessment or gliosarcoma* and diagnostic assessment or gangliocytoma* and diagnostic assessment or glial tumor* and diagnostic assessment or glial tumour* and diagnostic assessment or glial cancer* and diagnostic assessment or glial neoplasm* and diagnostic assessment or glioneuronal tumor* and diagnostic assessment or glioneuronal tumour* and diagnostic assessment or glioneuronal cancer* and diagnostic assessment or glioneuronal neoplasm* and diagnostic assessment or brain tumor* and diagnostic assessment or brain tumour* and diagnostic assessment or brain cancer* and diagnostic assessment or brain neoplasm* and diagnostic assessment or brainstem tumor* and diagnostic assessment or brainstem tumour* and diagnostic assessment or brainstem cancer* and diagnostic assessment or brainstem neoplasm* and diagnostic assessment*

Search 5: *glioma* and DTA or astrocytoma* and DTA or astroblastoma* and DTA or ependymoma* and DTA or subependymoma* and DTA or oligodendroglioma* and DTA or oligoastrocytoma* and DTA or pleomorphic xanthoastrocytoma* and DTA or glioblastoma* and DTA or GBM* and DTA or ganglioglioma* and DTA or gliosarcoma* and DTA or gangliocytoma* and DTA or glial tumor* and DTA or glial tumour* and DTA or glial cancer* and DTA or glial neoplasm* and DTA or glioneuronal tumor* and DTA or glioneuronal tumour* and DTA or glioneuronal cancer* and DTA or glioneuronal neoplasm* and DTA or brain tumor* and DTA or brain tumour* and DTA or brain cancer* and DTA or brain neoplasm* and DTA or brainstem tumor* and DTA or brainstem tumour* and DTA or brainstem cancer* and DTA or brainstem neoplasm* and DTA*

Appendix 2. Review-specific tailoring of QUADAS-2

Domain 1: patient selection

Risk of bias

Was a consecutive or random sample of patients enrolled?

- Yes: if a consecutive sample or a random sample of eligible participants was included in the study.
- No: if a non-consecutive sample or a non-random sample of eligible participants was included in the study.
- Unclear: if it was not clear whether a consecutive sample or a random sample of eligible participants was included in the study.

Was a case-control (or 'two-gate') design avoided?

- Yes: if the study had a single set of inclusion criteria.
- No: if the study had more than one set of inclusion criteria.
- Unclear: if the inclusion criteria for the study are not clear.

Did the study avoid inappropriate exclusions?

- Yes: if all patients with glioma were included.
- No: if a subset of patients with glioma were excluded due to subclassification/severity of glioma.
- Unclear: if the inclusion criteria for the study were not clear.

Overall: could the selection of patients have introduced bias?

We took highest concern from any individual signalling question as our overall judgement (i.e. risk of bias was classified as low if the response to all three questions was 'yes'; high if the response to any question was 'no'; and unclear if the response to any question was 'unclear' and the criteria for high risk of bias were not fulfilled).

Applicability

Were there concerns that the included patients do not match the review question?

- High: if the study population included patients who would not have undergone testing in real practice, for example healthy controls.
- Low: if the study included only a clinically relevant population that would have undergone testing in real practice.
- Unclear: if the inclusion criteria for the study are not clear.

Domain 2: index test

Risk of bias

Were the index test results interpreted without knowledge of the results of the other tests being compared?

- Yes: if the index test was objective or if subjective was interpreted without the knowledge of the results of other tests for 1p/19q codeletion. The first test to be interpreted was judged to be interpreted without knowledge of the results of the other tests even if it was not explicitly reported that it was interpreted 'blind' or without the knowledge of other test results.
- No: if test was subjective and interpreted with the knowledge of the results of other tests for 1p/19q codeletion.
- Unclear: if the test was subjective and it was unclear whether it was interpreted with the knowledge of other tests for 1p/19q codeletion.

If a threshold was used, was it prespecified?

- Yes: if the definition of what was considered to be a positive test result was defined before testing was performed (we judged that if a threshold was reported in the methods section that it was prespecified).
- No: if the definition of what was considered to be a positive test result was defined after testing was performed and based on the results.
- Unclear: if it was unclear whether the definition of what was considered to be a positive test result was defined before testing was performed or if the threshold used was not reported.

Overall: could the conduct or interpretation of the index test have introduced bias?

We took highest concern from any individual signalling question as our overall judgement.

If the threshold was not prespecified and patients were not classified, and if we applied our own classification, we judged this domain as low risk of bias because we were not trying to maximise concordance between tests.

Applicability: were there concerns that the index test, its conduct or its interpretation differ from the review question?

- High: if there were concerns that the index test, its conduct or its interpretation differed from the review question.
- Low: if there were no concerns that the index test, its conduct or its interpretation differed from the review question.
- Unclear: if the description of the index test was inadequate.

Domain 3: reference standard

We envisaged that many studies would have compared two or more tests without necessarily designating a reference standard.

In addition, as we planned a latent class analysis, which allows for an imperfect reference standard, the risk of bias signalling question regarding whether the reference standard was likely to correctly classify the target condition was omitted.

For similar reasons, we decided that the applicability question was not relevant.

We completed domain 2 for each test that was compared.

Domain 4: flow and timing

We modified some of the wording of the signalling questions to reflect the fact that studies may not have designated a reference standard.

Risk of bias

Was there an appropriate interval between the tests being compared?

We envisaged that most tests would be performed on biopsied material.

- Yes: if all tests were performed on biopsied tumour material collected on one occasion.
- No: if tests were performed on tumour material collected at different time points.
- Unclear: if it was unclear whether the tests were performed on the same material.

Were all patients included in the analysis?

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- Yes: if all participants were included in the analysis, or if participants were excluded because they did not meet inclusion criteria or if withdrawals were less than 5% of the enrolled population (arbitrarily selected cut-off).
- No: if any participants were excluded from the analysis because of uninterpretable results, because of inability to undergo index test or reference standard or for unclear reasons.

Overall: could the patient flow have introduced bias?

We took the highest concern from any individual signalling question as our overall judgement.

Appendix 3. Domains to be considered when judging the strength of the body of evidence

Domains to be considered when judging the strength of the body of evidence, based on GRADE.

Domain	Explanation
Risk of bias	Based on results of risk of bias assessments. Certainty in the evidence base was downgraded if most of the evidence was from studies not judged to be at low risk of bias.
Imprecision	Certainty in the evidence base was downgraded if the estimate of the effect size from a meta-analysis was not precise. We downgraded by 2 levels if (i) the upper 95% confidence limit for either sensitivity or specificity was more than 2 times the lower limit or (ii) the total sample size was 50 or less; and by 1 level if an upper limit was more than 1.4 times the lower limit.
Inconsistency	Certainty in the evidence base was downgraded if there was unexplained heterogeneity or variability in results across studies.
Indirectness	Based on QUADAS-2 assessments of applicability. Certainty in the evidence base was downgraded if most of the evidence was from studies judged to have low applicability to the review question.
Publication bias	Certainty in the evidence base was downgraded if we uncovered evidence of publication bias.

Appendix 4. Economic model and estimated costs of diagnostic tests

Figure 11 provides the basic model structure for the model-based economic analysis. The model illustrates a choice between three alternatives: the multiplex-ligation-dependent probe (MLPA), real-time polymerase chain reaction (PCR) and chromogenic in situ hybridisation (CISH) tests only. In the analysis, all available tests for each reference standard were included in the model. The blue square is a decision node, which represents a point of choice between the different tests. The green circles are chance nodes, which represent chance events characterised by probabilities (the chance nodes to the left indicate the chance of positive and negative test results, the green chance nodes to the right indicate true disease status). The red triangles are terminal nodes, which represent the final outcomes in terms of diagnosis from the alternative decision tree pathways.

Table A4.1 provides the estimated costs of diagnostic tests.

Table A4.1. Estimated costs of diagnostic tests

Cost Item	Unit cost (GBP)	Source
FISH	185.95	The Newcastle upon Tyne Hospitals NHS Foundation Trust (2020)
CISH	185.95	The Newcastle upon Tyne Hospitals NHS Foundation Trust (2020)
PCR-based LOH	142.21	The Newcastle upon Tyne Hospitals NHS Foundation Trust (2020)
Real-time PCR	142.21	The Newcastle upon Tyne Hospitals NHS Foundation Trust (2020)

(Continued)

MLPA	73.08	The Newcastle upon Tyne Hospitals NHS Foundation Trust (2020)
aCGH	233.47	Sagoo GS, Mohammed S, Barton G, Norbury G, Ahn JW, Ogilvie CM, et al. Cost effectiveness of using array-CGH for diagnosing learning disability. *Applied Health Economic and Health Policy* 2015;13:421-32.
SNP array	256.80	The Newcastle upon Tyne Hospitals NHS Foundation Trust (2020)
NGS	570.87	Marino P, Touzani R, Perrier L, Rouleau E, Kossi DS, Zhaomin Z, et al. Cost of cancer diagnosis using next-generation sequencing targeted gene panels in routine practice: a nationwide French study. *European Journal of Human Genetics* 2018;26:314-23.

aCGH: array comparative genomic hybridisation; CISH: chromogenic in situ hybridisation; FISH: fluorescent in situ hybridisation; LOH: loss of heterozygosity; MLPA: multiplex-ligation-dependent probe amplification; NGS: next-generation sequencing; PCR: polymerase chain reaction; SNP: single nucleotide polymorphism.

Appendix 5. Distributions used in the probabilistic sensitivity analyses

Abbreviations used: aCGH: array comparative genomic hybridisation; CISH: chromogenic in situ hybridisation; FISH: fluorescence in situ hybridisation; LOH: loss of heterozygosity; MLPA: multiplex-ligation-dependent probe amplification; MS; mass spectrometry; N/A: not applicable; NGS: next-generation sequencing; PCR: polymerase chain reaction; RFLP: restriction fragment length polymorphism; SD: standard deviation; SNP: single nucleotide polymorphism.

Table A5.1. Analysis using PCR-based LOH as reference standard

Parameter description	Probability distribution
Prevalence	Beta (mean = 0.31, SD = 0.13)
Sensitivity of MLPA	Beta (α = 9, β = 1)
Specificity of MLPA	Beta (α = 11, β = 1)
Cost of MLPA	Triangular (minimum 55.35, likeliest 73.08, maximum 93.35)
Sensitivity of real-time PCR	Beta (α = 11, β = 1)
Specificity of real-time PCR	N/A
Cost of real-time PCR	Triangular (minimum 106.66, likeliest 142.21, maximum 177.76)
Sensitivity of FISH	Beta (α = 196, β = 37)
Specificity of FISH	Beta (α = 638, β = 48)
Cost of FISH	Triangular (minimum 139.46, likeliest 185.95, maximum 232.44)
Sensitivity of aCGH	Beta (α = 31, β = 1)
Specificity of aCGH	Beta (α = 26, β = 3)
Cost of aCGH	Triangular (minimum 175.10, likeliest 233.47, maximum 291.84)

Sensitivity of SNP array	Beta (α = 16, β = 2)
Specificity of SNP array	Beta (α = 18, β = 1)
Cost of SNP array	Triangular (minimum 192.60, likeliest 256.80, maximum 321.00)
Sensitivity of NGS	Beta (α = 19, β = 1)
Specificity of NGS	Beta (α = 31, β = 2)
Cost of NGS	Triangular (minimum 428.15, likeliest 570.87, maximum 713.59)

Table A5.2. Analysis using FISH as reference standard

Parameter description	Probability distribution
Prevalence	Beta (mean = 0.31, SD = 0.13)
Sensitivity of MLPA	Beta (α = 12, β = 2)
Specificity of MLPA	Beta (α = 15, β = 8)
Cost of MLPA	Triangular (minimum 55.35, likeliest 73.08, maximum 93.35)
Sensitivity of real-time PCR	Beta (α = 15, β = 4)
Specificity of real-time PCR	Beta (α = 24, β = 1)
Cost of real-time PCR	Triangular (minimum 106.66, likeliest 142.21, maximum 177.76)
Sensitivity of PCR-based LOH	Beta (α = 196, β = 48)
Specificity of PCR-based LOH	Beta (α = 633, β = 42)
Cost of PCR-based LOH	Triangular (minimum 106.66, likeliest 142.21, maximum 177.76)
Sensitivity of CISH	Beta (α = 20, β = 1)
Specificity of CISH	Beta (α = 18, β = 3)
Cost of CISH	Triangular (minimum 139.46, likeliest 185.95, maximum 232.44)
Sensitivity of aCGH	Beta (α = 19, β = 1)
Specificity of aCGH	Beta (α = 19, β = 4)
Cost of aCGH	Triangular (minimum 175.10, likeliest 233.47, maximum 291.84)
Sensitivity of SNP array	Beta (α = 35, β = 13)
Specificity of SNP array	Beta (α = 64, β = 3)

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Cost of SNP array	Triangular (minimum 192.60, likeliest 256.80, maximum 321.00)
Sensitivity of NGS	Beta (α = 73, β = 7)
Specificity of NGS	Beta (α = 166, β = 1)
Cost of NGS	Triangular (minimum 428.15, likeliest 570.87, maximum 713.59)

Appendix 6. Raw data from included studies

Table A6.1. Raw results for comparisons of four test categories or variants within categories

Study	Tests included	Tumour type	Tumour grade	++++	+++-	++-+	+-++	-+++	++--	+--+	--++	-++-	-+-+	+-+-	+---	-+--	--+-	---+	----	Total with test results	Notes
Blesa 2009	A: aCGH B: FISH C: MLPA D: PCR	Anaplastic oligodendroglioma	III	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	2	Some differences between Table 2 in text and the Supplementary Table. Since the Supplementary Table had more information, we extracted from this.
		Oligodendroglioma	II	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	
		Anaplastic oligoastrocytoma	III	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	2	Relative deletions on FISH were classified as a negative result as they were not absolute deletions.
Duval 2014	A: FISH (combination cut-off based on number of cells showing a deletion) B: FISH (ratio cut-off based	Oligodendroglioma	II	6	0	1	0	0	0	0	0	0	0	0	0	0	0	0	4	11	FISH assessments were made independently by 2 observers. In 1 case, a participant was classified as having the codeletion by 1 observer but not the other when using the ratio method to interpret the results of ImmunoFISH. Raw data were available from the 2 observers, and we averaged the raw data and applied the reported cut-off to
		Anaplastic oligodendroglioma	III	13	0	0	0	0	1	0	0	0	0	0	0	0	0	0	8	22	
		Glioblastoma with oligodendroglioma component	IV	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	3	

(Continued)

	on the ratio of signals for 1p to 1q and 19q and 19p) C: FISH (immunoFISH with combination cut-off) D: FISH (immunoFISH with ratio cut-off)																				come to a consensus classification.
Hatanpaa 2003a (assay development and non-blinded validation cohort)	A: CGH B: FISH C: PCR (comparison to normal DNA) D: PCR (microsatellite)	Astrocytoma	II	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	2	Participants from Smith 1999. We removed D1S534 from the regions analysed by PCR with comparison to normal DNA as this was not used to assess 1p/19q status. We used the histological diagnosis from this paper (rather than from Smith 1999).
		Astrocytoma	III	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	
		Oligodendroglioma	II	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2	
Hatanpaa	A: CGH	Astro-	II	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	Participants from Smith 1999.

2003b (blinded validation cohort)	B: FISH	cytoma																		
	C: PCR (comparison to normal DNA)	Mixed	II	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	2
		Oligodendroglioma	II	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	3
	D: PCR (microsatellite)																			

We removed D1S534 from the regions analysed by PCR with comparison to normal DNA as this was not used to assess 1p/19q status.

We used the histological diagnosis from this paper (rather than from Smith 1999).

Note: 1 of the ++++ tumours (T246, oligodendroglioma) (quote) "was found to have partial LOH on 1p, a finding confirmed by comparison with the allelic pattern derived from normal tissue dissected from this case (Table 2). In this tumor, heterozygosity was only preserved at one locus of eight assessed on 1p and 19q. In light of previous studies (Bello et al, 2000; Bigner et al, 1999; Smith et al, 1999), this tumor may represent a rare aberration from the usual extent of LOH on 1p in oligodendrogliomas. Although the clinical

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significance of this finding of partial LOH is not known, the tumor is probably best classified as having a high likelihood of clinically relevant LOH on 1p, considering that heterozygosity was preserved at only one locus and that the tumor was histologically an oligodendroglioma".

Hatanpaa 2003b (blinded validation cohort)	A: CGH B: FISH C: PCR (comparison to normal DNA) D: PCR (microsatellite)	Mixed	III	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	Participant from Burger 2001. We have used the histological diagnosis from this paper (rather than from Burger 2001).

++++: number of people positive on all tests (meaning that 1p19q codeletion found with all tests); +++-: positive on test A, positive on test B, positive on test C, negative on test D; ++-+: positive on test A, positive on test B, negative on test C, positive on test D; +-++: positive on test A, negative on test B, positive on test C, positive on test D; -+++: negative on test A; positive on test B; positive on test C; positive on test D; ++--: positive on test A; positive on test B; negative on test C, negative on test D; +--+: positive on test A, negative on test B; negative on test C, positive on test D; --++: negative on test A, negative on test B, positive on test C, positive on test D; -++-: negative on test A, positive on test B, positive on test C, negative on test D; -+-+: Negative on test A, positive on test B, negative on test C, positive on test D; +-+-: Positive on test A, negative on test B, positive on test C, negative on test D; +---: positive on test A, negative on test B, negative on test C, negative on test D; -+--: negative on test A, positive on test B, negative on test C, negative on test D; --+-: negative on test A, negative on test B, positive on test C, negative on test D; ---+: negative on test A, negative on test B, negative on test C, positive on test D; ----: negative on all tests.

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Table A6.2. Raw results for comparisons of three test categories or variants within categories

Study	Tests included	Tumour type	Grade	+++	++-	+-+	-++	+--	--+	-+-	---	Total with test results	Notes
Be-laud-Ro-tureau 2006	A: FISH (1p36.3 (D1Z2)/1q12 (D1Z1) and 19q13.3/19pter probes and manual analysis) B: FISH (1p36/1q25 and 19q13/19p13 Abbott Vysis probe set and manual analysis) C: FISH (1p36/1q25 and 19q13/19p13 Abbott Vysis probe set and auto-mated analysis)	Oligo-den-droglioma	III	1	0	0	0	0	0	0	0	1	—
		Oligoas-trocy-toma	II	1	0	0	0	0	0	0	1	2	
		Oligoas-trocy-toma	III	1	0	0	0	0	0	0	6	7	
Blesa 2009 (aCGH vs	A: aCGH B: FISH C: PCR	Anaplas-tic oligoas-	III	0	0	0	0	0	0	0	1	1	Some differences between Table 2 in text and the Sup-plementary Table. Since the Supplementary Table had

													Notes
		trocy-toma											more information, we extract-ed from this.
		Oligo-den-droglioma	II	1	1	0	0	0	0	0	0	2	Relative deletions on FISH were classified as a negative result as they were not ab-solute deletions.
Blesa 2009 (FISH vs MLPA vs PCR)	A: FISH B: MLPA C: PCR	Anaplas-tic oligo-den-droglioma	III	1	0	0	0	0	0	0	1	2	Some differences between Table 2 in text and the Sup-plementary Table. Since the Supplementary Table had more information, we extract-ed from this.
		Oligo-den-droglioma	II	1	0	0	3	0	0	0	2	6	Relative deletions on FISH were classified as a negative result as they were not ab-solute deletions.
		Anaplas-tic oligoas-trocy-toma	III	0	0	0	0	0	0	0	1	1	
Blesa 2009 (aCGH vs MLPA vs PCR)	A: aCGH B: MLPA C: PCR	Oligo-den-droglioma	II	1	0	0	0	0	0	0	1	2	Some differences between Table 2 in text and the Sup-plementary Table. Since the Supplementary Table had more information, we extract-ed from this. Relative deletions on FISH were classified as a negative result as they were not ab-solute deletions.
Burger 2001	A: CGH B: FISH C: PCR	Oligo-den-droglioma	II	5	0	0	0	0	0	0	0	5	We used the "review" diagno-sis (still done without knowl-edge of the results of the tests).
		Malig-nant oligo-den-droglioma	III	1	0	0	0	0	0	0	0	1	Overall results for PCR-based LOH for 1p and 19q not giv-en. We assumed that if results were homozygous or indeter-

(Continued)

Study	Test	Tumour type	Grade										Notes
		Astrocy-toma	II	0	0	0	0	0	0	0	2	2	minant at all loci examined that codeletion was present.
		Astrocy-toma	III	0	0	0	0	0	0	0	6	6	We excluded the second sample for participant T276.
		Malig-nant mixed glioma	III	0	0	0	0	0	0	0	1	1	We removed participant T272 because they were included in Hatanpaa 2003b.
		Glioblas-toma	IV	0	0	0	0	0	0	0	2	2	
Dahlback 2011	A: CGH B: G-banding C: PCR	Oligoas-trocy-toma	II	0	0	4	0	0	3	0	6	13	We excluded people with failure results.
		Oligo-den-droglioma	II	0	0	4	0	0	0	0	1	5	We could not make the numbers that we derived from Table 1 correspond to what was reported in the text.
Hatan-paa 2003a (assay development and non-blinded validation cohort) (FISH vs PCR with comparison to normal DNA vs PCR without comparison to	A: FISH B: PCR (comparison to normal DNA) C: PCR (microsatellite)	Astrocy-toma	II	0	0	0	0	0	0	0	1	1	Participants from Smith 1999.
		Oligo-den-droglioma	II	1	0	0	0	0	0	0	0	1	We removed D1S534 from the regions analysed by PCR with comparison to normal DNA as this was not used to assess 1p/19q status.
		Oligo-den-droglioma	III	2	0	0	0	0	0	0	0	2	We used the histological diagnosis from this paper (rather than from Smith 1999).

normal DNA)													
Hatan-paa 2003b (blind-ed vali-dation cohort) (FISH vs PCR with com-parison to nor-mal DNA vs PCR without compar-ison to normal DNA)	A: FISH B: PCR (com-pari-son to normal DNA) C: PCR (mi-crosatel-lite)	Astrocy-toma	IV	0	0	0	0	0	0	0	1	1	Participants from Smith 1999. We removed D1S534 from the regions analysed by PCR with comparison to normal DNA as this was not used to assess 1p/19q status. We used the histological diag-nosis from this paper (rather than from Smith 1999).
		Oligo-den-droglioma	II	1	0	0	0	0	0	0	0	1	
Horbins-ki 2012	A: FISH (cut-off < 0.87) B: FISH (cut-off < 0.75) C: PCR	Oligo-den-droglioma	II, III	61	15	3	0	5	1	0	26	111	Discrepancy between text (and what they calculated in Table 2) and Table 1 – we used text and Table 2.
Mohapa-tra 2006 a	A: aCGH B: FISH C: PCR	"Oligo-den-droglial tu-mours"	II, III	16	0	1	0	1	0	0	10	28	32 tumours included in the study, had results for 28 and results not broken down by tumour subtype, apart for the discordant cases.
Pesen-ti 2017 (aCGH vs MS vs PCR)	A: aCGH B: MS C: PCR	Oligo-den-droglioma	II	1	0	0	0	0	0	0	0	1	—
		Anaplas-tic oligo-	III	1	0	0	0	0	0	0	0	1	

Study	Tests	Histology	Grade										Notes
		den-droglioma											
		Glioblas-toma	IV	0	0	0	0	0	0	0	2	2	
Pesenti 2017 (FISH vs MS vs PCR)	A: FISH B: MS C: PCR	Oligo-den-droglioma	II	3	0	0	0	0	0	0	0	3	—
		Anaplas-tic oligo-den-droglioma	III	2	0	0	0	0	0	0	0	2	
		Astrocy-toma	II	0	0	0	0	0	0	0	1	1	
		Glioblas-toma	IV	0	0	0	0	0	0	0	4	4	
Smith 1999	A: CGH B: FISH C: PCR	Astrocy-toma	III	0	0	0	0	0	0	0	3	3	Quote: "LOH, FISH, and CGH were performed as previously described (Cliby et al., 1993; Ritland et al., 1995; Qian et al., 1995; Mohapatra et al., 1995, 1998; Piper et al., 1995)". Overall results for 1p and 19q for PCR not given. We assumed that if results were confirmed allelic loss/presumed allelic loss/homozygous at all loci on 1p except the most centromeric (D1S534- removed from list of loci examined) and all loci on 19q examined that codeletion was present. Overall results for FISH also not reported. We defined codeletion as hemizygous deletion of 1p36, 1q13.1-q13.2 and 19q13.3.
		Astrocy-toma	IV	0	0	0	1	0	0	0	17	18	
		Mixed	II	2	0	0	0	0	0	0	0	2	
		Mixed	III	0	1	0	0	0	0	0	2	3	
		Mixed	IV	0	0	0	1	0	0	1	1	3	
		Oligo-den-droglioma	II	4	0	0	0	0	0	1	4	9	
		Oligo-den-droglioma	III	5	0	0	0	0	0	0	1	6	

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Oligodendroglioma	IV	0	0	0	0	1	0	0	0	1

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+++: number of people (or tumours (ᵃ: studies where we consider the unit of analysis was a tumour)) positive on all tests (meaning that 1p19q codeletion found with all tests); ++-: positive on test A, positive on test B, negative on test C; +-+: positive on test A, negative on test B, positive on test C; -++: negative on test A, positive on test B, positive on test C; +--: positive on test A, negative on test B, negative on test C; --+: negative on test A, negative on test B, positive on test C; -+-: negative on test A, positive on test B, negative on test C; ---: negative on all tests.

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Table A6.3. Raw results for comparisons of two test categories or variants within categories

Study	Tests included	Tumour sub-type	Tumour grade	++	+-	-+	--	Total with test results	Notes
Ariza 2010 [a]	A: PCR B: re-al-time PCR	Oligoden-drogliomas	NR	10	0	0	0	10	69 astrocytomas also studied but information that we could extract not reported.
Armanious 2017 [a]	A: FISH B: NanoString	Oligoden-droglioma, glioblastoma and oligoas-trocytoma	NR	10	2	1	3	16	—
Be-laud-Ro-tureau 2006 (manu-al vs au-tomatic analysis with the 1p36/1q25 and 19q13/19p13 Abbott Vy-sis probe set)	A: FISH (1p36/1q25 and 19q13/19p13 Abbott Vy-sis probe set and manual analysis) B: FISH (1p36/1q25 and 19q13/19p13 Abbott Vy-sis probe set and automat-ed analy-sis)	Astrocytoma	II	0	0	0	6	6	—
		Oligoden-droglioma	III	1	0	0	0	1	—
		Oligoastrocy-toma	II	1	0	0	5	6	—
Bigner 1999	A: CGH B: PCR	Oligoden-droglioma	II	15	0	1	5	21	By CGH, some participants had (quote) "Copy number changes of partial chromo-some arms". It was unclear what the au-thors meant by this – whether the chro-mosome arm was only partial and then there was copy number loss or whether this should be considered partial (i.e.
		Oligoastrocy-toma	II	1	0	0	0	1	

Study	Test	Tumour type	Grade						Notes
		Anaplastic oligodendroglioma	III	16	1	0	3	20	not complete) arm loss. However, from the text it was clear that the authors considered that when this had occurred on 1p/19q that this was considered a codeletion.
		Anaplastic oligoastrocytoma	III	2	0	0	4	6	We excluded recurrent tumours and tumours from participants who were aged < 18 years.
		Glioblastoma	IV	1	0	0	3	4	
		Astrocytoma	II	0	0	0	1	1	
Blesa 2009 (aCGH vs PCR)	A: aCGH B: PCR	Anaplastic oligoastrocytoma	III	0	0	0	1	1	Some differences between Table 2 in text and the Supplementary Table. Since the Supplementary Table had more information, we extracted from this.
Blesa 2009 (FISH vs PCR)	A: FISH B: PCR	Oligodendroglioma	II	2	0	1	4	7	Some differences between Table 2 in text and the Supplementary Table. Since the Supplementary Table had more information, we extracted from this.
		Oligoastrocytoma	II	1	0	0	7	8	Relative deletions on FISH were classified as a negative result as they were not absolute deletions.
		Anaplastic oligodendroglioma	III	3	0	6	0	9	
		Anaplastic oligoastrocytoma	III	0	0	1	5	6	
Blesa 2009 (MLPA vs PCR)	A: MLPA B: PCR	Oligodendroglioma	II	1	0	0	1	2	Some differences between Table 2 in text and the Supplementary Table. Since the Supplementary Table had more information, we extracted from this.
Bouvier 2004	A: FISH B: PCR	Glioblastoma	IV	0	1	0	2	3	2 oligodendroglioma grade II participants and 2 oligodendroglioma grade III participants who were classified as having the codeletion by PCR (concordant with FISH) were then described as having (quote) "a partial deletion on 19q for the 19q13.32 and not for the 19q13.12".
		Oligodendroglioma	II	2	0	1	1	4	
		Oligodendroglioma	III	2	0	0	1	3	

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Study	Test	Histology	Grade						Notes
		Oligoastrocytoma	II	0	0	0	3	3	
		Oligoastrocytoma	III	0	0	0	1	1	
Broholm 2008	A: FISH B: PCR	Oligodendroglioma	II	3	0	1	0	4	—
		Anaplastic oligodendroglioma	III	4	0	0	1	5	
		Oligoastrocytoma	II	2	0	1	2	5	
		Anaplastic oligoastrocytoma	III	2	0	1	2	5	
		Astrocytoma	II	1	0	0	4	5	
		Anaplastic astrocytoma	III	0	2	1	1	4	
		Glioblastoma	IV	0	2	1	7	10	
Byeon 2014	A: aCGH B: FISH	Rhabdoid glioblastoma	NR	0	0	0	3	3	—
Cieply 2004	A: FISH B: PCR	Gliomas (oligodendroglioma, mixed tumours, astrocytoma)	NR	10	0	0	12	22	2 cases (not included) had borderline results for deletion by FISH, and indeterminate results by PCR.
Chaturbedi 2012 [a]	A: FISH B: real-time PCR	Anaplastic oligodendroglioma	III	0	2	0	5	7	Comparative quantitative PCR cut-offs were determined post hoc. Eventually they did use all the prespecified marker or reference genes. We could not recreate their numbers for concordance for 1p and 19q.

Study	Test	Tumour type	Grade						Comments
		Mixed oligoas-trocytoma	II	0	0	0	2	2	
		Oligoden-droglioma	II	2	0	0	7	9	
Clark 2013	A: FISH B: PCR	Glioblastoma	IV	1	18	7	420	446	Another cut-off for FISH mentioned in discussion.
Cowell 2004	A: aCGH B: PCR	Low-grade oligoden-droglioma	NR	4	0	0	2	6	Unclear if all the PCR regions were used to inform the PCR result.
		Anaplastic oligoden-droglioma	NR	3	0	0	2	5	
		Mixed oligoas-trocytoma	NR	1	0	0	2	3	
D'Haene 2019 [a]	A: FISH B: NGS	Gliomas	I–IV	21	1	0	28	50	Results likely to include > 1 sample from the same patient: quote: "A retrospective collection of samples, which consisted of 52 glioma samples from 47 patients". (Presume there is an error and it should read 53 glioma samples.) Excluded 3 with non-informative results on the NGS panel. Note: these results have required a lot of interpretation. Distinguishing glioma from non-glioma samples was difficult, and is based on the text in section 2.3 (quote) "concordant positive results were obtained for 21 of the 22 glioma samples (95.4% sensitivity) … Among the 31 gliomas that did not show a 1p/19q codeletion by FISH, 28 showed neither patterns of 1p/19q loss of heterozygosity (LOH) by NGS, as defined by our criteria (three were non-informative)".
Dahlback 2009	A: CGH B: G-band-ing	Glioblastoma	IV	0	3	0	40	43	—

Study	Test	Tumour type	Grade						Notes
		Glioblastoma – multifocal	IV	0	0	0	1	1	
		Glioblastoma with granular cell component	IV	0	0	0	1	1	
		Glioblastoma with oligodendroglial component	IV	0	1	0	4	5	
		Giant cell glioblastoma	IV	0	0	0	1	1	
		Gliosarcoma	IV	0	1	0	5	6	
Dahlback 2011 (CGH vs G-banding)	A: CGH B: G-banding	Fibrillary astrocytoma	II	0	0	0	8	8	Excluded 5 participants with fibrillary astrocytoma without high resolution-CGH results and 1 participant with a failed result. 1 participant with fibrillary astrocytoma had loss of 1p36 and monosomy 19. In the text, they implied that this does not count as 1p19q codeletion. Quote: "None of the astrocytic tumors displayed the complete 1p/19q codeletion (i.e., loss of both arms 1p and 19q). However, one fibrillary astrocytoma showed partial loss of 1p, one showed partial loss of 19q, and one tumor sample showed loss of 1p36 and monosomy 19".
		Gemistocytic astrocytoma	II	0	0	0	2	2	
Dahlback 2011 (CGH vs PCR)	A: CGH B: PCR	Oligodendroglioma	II	1	0	0	0	1	—
Dahlback 2011 (G-banding vs PCR)	A: G-banding B: PCR	Oligoastrocytoma	II	0	0	0	1	1	—
		Oligodendroglioma	II	0	0	2	0	2	

(Continued)

Study	Test	Tumour	Grade						Comments
Dubbink 2016	A: NGS B: PCR	Anaplastic oligoden-drogliomas and anaplastic oligoastro-cytomas	NR	18	1	0	30	49	—
Duval 2015	A: FISH (automated analysis) B: FISH (manual analysis)	Pilocytic astrocytoma	I	0	0	0	1	1	Quote: "In this control series, two cases were incomplete for 19q (broken slides) and 5 cases were non interpretable for 1p because of a total lack of telomeric fluorescent signal ("R" signal)". Automated method on archival slides that had been stored at −20 °C. We assumed from the discussion that the cut-off used the combination + ratio method.
		Astrocytoma	III	0	0	0	1	1	
		Oligoden-droglioma	II	4	0	0	0	4	
		Oligoden-droglioma	III	0	0	1	0	1	
		Oligoastrocy-toma	II	1	0	0	3	4	
		Oligoastrocy-toma	III	3	1	2	5	11	
		Oligoastrocy-toma	IV	0	0	0	2	2	
		Glioblastoma with oligo-dendroglial component	NR	0	0	0	4	4	
		Dysembry-oplastic neu-roepithelial tumour	I	0	0	0	1	1	
Gadji 2009	A: FISH B: PCR	Anaplastic oligoastrocy-toma	NR	1	0	0	1	2	We extracted the WHO 2007 classification of tumours.

Study	Test	Histology	Grade					Total	Notes
		Anaplastic oligoden-droglioma	NR	6	0	1	0	7	
		Oligoden-droglioma	NR	1	0	0	0	1	
		Gliosarcoma	NR	0	0	0	1	1	
Ghasimi 2016	A: FISH B: SNP array	Mixed (grade II–IV gliomas)	II–IV	0	11	0	44	55	Potential error in paper: is the 1q control probe for FISH 1q25? Results have required intense interpretation. Text stated that 55 people had results from both techniques. Then stated that FISH detected 14 samples with codeletion. From Supplementary Table 3 it appeared that only 11 of these had data from both techniques. We assumed that the phrase (quote) "none was detected by SNP array data" to mean that none was found to have a codeletion by SNP array (not just the 14 with FISH results). Some participants aged < 18 years.
Harada 2011	A: PCR B: SNP array	Oligoden-droglioma	NR	9	0	0	0	9	Have classified the papers' "partial deletions" with no LOH (as not full loss). Within the cohort some participants aged < 18 years (age range 14–82 years). The participant with pineal parenchymal tumour was excluded (not a glioma).
		Anaplastic oligoden-droglioma	NR	4	1	0	0	5	
		Oligoden-droglioma + oligosarcoma	NR	1	0	0	0	1	
		Fibrillary as-trocytoma	NR	0	0	0	3	3	
		Astrocytoma	NR	0	0	0	2	2	
		Anaplastic as-trocytoma	NR	0	0	0	7	7	

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		Glioblastoma	NR	0	0	0	2	2	
Hatanpaa 2003a (assay development and non-blinded validation cohort) (PCR vs ≥ 2 tests)	A: PCR B: ≥ 2 of CGH, FISH and PCR	Astrocytoma	II	0	0	0	1	1	This was a participant we could not match to those included in Smith 1999 or Burger 2001.
Hinrichs 2016	A: FISH B: SNP array	Glioblastoma with an oligodendroglial component (GBM-O)	IV	2	0	0	6	8	Figures based on our interpretation of SNP array results in figure 3 of the paper.
Jeuken 2006 [a]	A: CGH B: MLPA	Oligodendroglioma	II	8	0	0	0	8	Overall results for 1p and 19q not given using MLPA, and threshold to do so not reported. We assumed that if all probes were lost, or the majority were lost and those that were not lost were flanked on both sides by probes that were lost, that loss had occurred (stated in paper: "ratios of adjacent probes should be taken into consideration for the assessment of the presence of gains or losses". We ignored the results for the most centromeric 1p probe (NOTCH2). CGH: references 3 papers. Reference 25 (Jeuken et al. *Journal of Neuropathology & Experimental Neurology* 1999;58:606-12): "Detection thresholds for losses and gains of chromosomal regions (19, 20) were set at 0.8 and 1.2 respectively. Aberrations with a ratio of 0.6 or 1.4 were called clear copy number changes and a ratio larger than 1.6 were called high-copy number gains. CGH only detects copy number changes of chromosomal regions larger than 2Mb (20, 36, 37)". Reference 26 (Jeuken et al. *Journal of Pathology*
		Anaplastic oligodendroglioma	III	12	0	0	2	14	
		Oligoastrocytoma	II	2	0	0	4	6	
		Anaplastic oligoastrocytoma	III	3	0	0	12	15	
		Pilocytic astrocytoma	I	0	0	0	1	1	
		Astrocytoma	II	0	0	1	4	5	
		Anaplastic astrocytoma	III	0	0	0	1	1	
		Ependymoma	II	0	0	0	3	3	

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Study	Test	Histology	Grade						Notes
		Anaplastic ependymoma	III	0	0	0	1	1	2001;194:81-7) References the reference above. "Analysis was performed using QUIPS CGH software (Applied Imaging, UK) and the standard thresholds for gains (1.2) and losses (0.8) were used. Aberrations with a ratio less than 0.6 or more than 1.4 were called clear copy number changes, whereas a ratio larger than 1.6 was called a high copy number gain". Reference 27 (Jeuken et al. *Journal of Neurosurgery* 2002, 96:559-64) – not located.
		Glioblastoma	IV	0	0	0	17	17	
Jha 2011	A: FISH B: PCR	Oligodendroglioma	II	10	0	3	3	16	Although cut-off for number of loci that needed to have LOH not explicitly reported, it was reported how many cases had combined loss of 1p and 19q by PCR and from that it seems that LOH of 1 marker on each of the chromosome arms was sufficient to count as codeletion.
		Anaplastic oligodendroglioma	III	5	0	4	5	14	
		Glioblastoma	IV	0	0	0	10	10	
Kato 2019 a	A: FISH B: NGS	Glioma	II–IV	3	0	0	6	9	We assumed that (quote) "Our sequence pipeline and also FISH identified 1p19q codeletion only in these 3 cases" means that neither test found any other codeletions.
Kolhe 2016	A: FISH B: SNP array	Glioblastoma	IV	1	0	0	1	2	Table very small in the conference abstract. We assumed '+' meant codeleted. We used histological diagnoses.
		Infiltrating mixed glioma, oligoastrocytoma	NR	1	0	0	0	1	
		Anaplastic oligoastrocytoma	III	0	0	0	1	1	
		Anaplastic astrocytoma	III	1	0	0	1	2	

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Study	Tests	Histology	Grade						Comments
		Anaplastic oligodendroglioma	III	2	0	0	0	2	
		Malignant mixed oligoastrocytoma	IV	1	0	0	0	1	
Lass 2013	A: CISH B: FISH	Astrocytoma	II	0	0	0	4	4	Astrocytoma: could not include participant 24 (ID 56240) as no 19q CISH result (however, as 1p retained, and no 1p19q codeletion on FISH, this participant could be classified as negative on both tests). Excluded participant 25 as aged < 18 years.
		Anaplastic astrocytoma	III	0	1	0	9	10	
		GBM	IV	0	0	0	1	1	Anaplastic astrocytoma: CISH result correct – FISH was repeated and tumour was codeleted.
		Oligodendroglioma	II	8	1	0	1	10	Oligodendroglioma: CISH result correct – confirmed by microsatellite PCR and FISH was repeated and tumour was codeleted.
		Anaplastic oligodendroglioma	III	5	0	0	0	5	
		Oligoastrocytoma	II	5	0	0	1	6	Anaplastic oligodendroglioma: we excluded participant 16 (ID56604) because no results on initial FISH, and on investigation it seemed the results depended on where the tumour sample was from.
		Anaplastic oligoastrocytoma	III	1	0	0	0	1	
		Pilocytic astrocytoma	I	0	0	0	1	1	
Lhotska 2015	A: FISH B: SNP array	Oligodendroglioma and oligoastrocytoma	II	16	0	2	2	20	Cut-off to interpret SNP array results not reported, and participants not classified. We set the criteria for codeletion as 1 copy of (or homozygous for) 1p36.33p11.2 or 1p31.1p12 or 1p31.3p31.1 AND 1 copy of/homozygous for 19q12q13.43 or 19q13.2q13.43 or 19q13.32q13.43.
Na 2019	A: FISH B: NGS	Astrocytoma and anaplas-	II/III	0	0	0	23	23	The study also looked at CCNE1 on 19q. But this did not seem to have been considered when calculating concordance.

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Study	Tests	Histology	Grade						Notes
		tic astrocytoma							Quote: "The copy number loss of 1p/19q genes detected in NGS was compared with FISH and the results were concordant in all cases of ODs [oligodendroglioma]. Given that about 20% of ODs are related to incomplete 1p/19q-codeletion [15], some mismatches between the copy number loss of CCNE1 gene (NGS) and 19q deletion (FISH) can be explained by the distant genomic loci of CCNE1 and the FISH-probe target region". Some participants aged < 18 years.
		Oligodendroglioma and anaplastic oligodendroglioma	II/III	12	0	0	4	16	
		Glioblastoma	IV	0	1	0	85	86	
		Diffuse midline glioma	IV	0	1	0	9	10	
Natte 2005	A: FISH B: MLPA	Oligodendroglioma	NR	0	1	0	0	1	—
		Anaplastic oligodendroglioma	NR	9	0	3	3	15	
		Oligoastrocytoma	NR	0	0	0	2	2	
		Anaplastic oligoastrocytoma	NR	0	0	0	1	1	
Nigro 2001 a	A: FISH B: Real-time PCR	Oligodendroglioma	NR	3	0	0	4	7	Figure 5 in the paper implies that some samples were tetraploid. It is not clear how this was detected (i.e. by which technique). In addition, they show an image of the FISH results for 1 case (8758) which they describe as tetraploid. This showed a 1 red: 2 green dot pattern so it was unclear how this case could be tetraploid. Therefore, we assumed that none of the tumours actually were tetraploid.
		Anaplastic oligodendroglioma	NR	5	1	0	4	10	
		Oligoastrocytoma	NR	4	0	0	1	5	
Park 2019	A: FISH B: NGS	Oligodendroglioma	NR	10	0	0	0	10	—

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Study	Tests	Histology	Grade						Notes
		Anaplastic oligodendroglioma	NR	9	1	0	0	10	
Paxton 2015	A: FISH B: SNP array	Oligodendroglioma	NR	8	1	0	0	9	Selected because positive on FISH assay. Quote: "One case (1p19q-03), with diploid copy number along 1p and 19q arms, was tetraploid across the remainder of the genome (Fig. 1a). Genotyping data from the array indicate that 1p and 19q were co deleted prior to a doubling of the genome, so that although diploid in number, the 1p and 19q arms are still deleted in the context of the entire genome". This is a relative rather than an absolute deletion.
		Glioblastoma	NR	0	0	0	8	8	Selected because negative on FISH assay
Pesenti 2017	A: MS B: PCR	Astrocytoma	II	0	0	0	4	4	—
		Anaplastic astrocytoma	III	0	0	0	3	3	
		Oligodendroglioma	II	8	0	0	0	8	
		Anaplastic oligodendroglioma	III	1	0	0	0	1	
		Glioblastoma	IV	0	0	0	20	20	
Ransom 1992a	A: G-banding B: RFLP	Juvenile pilocytic astrocytoma	II	0	0	0	1	1	We removed participants with no growth (G-banding/karyotyping), and those who we thought had no results for RFLP because 1p/19q not listed in the informative arms retained, lost or gained; we also removed participants aged < 18 years. Details of tests taken from Ransom 1992b.
		Oligodendroglioma	II	0	0	1	1	2	
		Oligodendroglioma	III	0	0	1	0	1	
		Ependymoma	I	0	0	0	1	1	

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Study	Test	Tumour type	Grade						Notes
Ransom 1992b	A: G-banding B: RFLP	Astrocytoma	III	0	0	0	1	1	We removed participants with no growth (G-banding/karyotyping), and those who we thought had no results for RFLP because 1p/19q not listed in the informative arms retained, lost or gained.
		Astrocytoma	IV	0	0	0	18	18	
		Mixed oligoastrocytoma	III	0	0	0	2	2	
		Mixed oligoastrocytoma	IV	0	0	0	1	1	
Scheie 2006	A: FISH B: PCR	Oligodendroglioma	II	7	0	0	4	11	Another cut-off for FISH mentioned.
		Oligodendroglioma	III	4	0	0	1	5	
		Oligoastrocytoma	II	8	0	0	6	14	
		Oligoastrocytoma	III	1	0	1	8	10	
Schrock 1994	A: CGH B: G-banding	Anaplastic astrocytoma	III	0	0	0	2	2	Participants aged < 18 years excluded.
		Glioblastoma	IV	0	0	0	6	6	
Senetta 2013 [b]	A: FISH (cut-off ratios 1p ≤ 0.8 and 19q ≤ 0.8) B: FISH (cut-off ratios 1p ≤ 0.7 and 19q ≤ 0.8)	Oligodendroglioma	II	25	6	0	17	48	—
		Oligodendroglioma	III	17	5	0	19	41	
		Oligoastrocytoma	II	5	1	0	12	18	
		Oligoastrocytoma	III	2	1	0	17	20	
		Glioblastoma with an oligodendroglial	IV	3	3	0	10	16	

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		component (GBM-O)							
Sim 2018a (glioblastoma cohort)	A: FISH B: NGS or aCGH (or both)	Glioblastoma	NR	0	2	0	73	75	Excluded the 5 recurrent samples from 4 participants. These were negative on both tests. Quote: "Primary and recurrent tumors from three patients revealed intact 1p or 19q by either technique. Three tumor samples (two recurrent and one primary tumor) from one patient showed partial deletion of 1p36 by aCGH and/or WES [whole exome sequencing], but FISH revealed no deletion of 1p or 19q in the primary or secondary recurrent tumors and no 1p deletion in the first recurrence".
Sim 2018b (oligodendroglial cohort[a])	A: FISH B: NGS	Anaplastic oligodendroglioma	NR	4	1	0	1	6	We used the original diagnoses.
		Anaplastic oligoastrocytoma	NR	0	0	0	3	3	
		Oligoastrocytoma	NR	0	0	0	1	1	
Smith 1999 (CGH vs FISH)	A: CGH B: FISH	Astrocytoma	IV	0	0	0	1	1	Quote: "LOH, FISH, and CGH were performed as previously described (Cliby et al., 1993; Ritland et al., 1995; Qian et al., 1995; Mohapatra et al., 1995, 1998; Piper et al., 1995)". Overall results for FISH not reported. We defined codeletion as hemizygous deletion of 1p36, 1q13.1-q13.2 and 19q13.3.
Smith 1999 (CGH vs PCR)	A: CGH B: PCR	Astrocytoma	III	0	0	0	1	1	Quote: "LOH, FISH, and CGH were performed as previously described (Cliby et al., 1993; Ritland et al., 1995; Qian et al., 1995; Mohapatra et al., 1995, 1998; Piper et al., 1995)". Overall results for 1p and 19q for PCR not given. We assumed that if results were
		Astrocytoma	IV	0	0	0	4	4	

confirmed allelic loss/presumed allelic loss/homozygous at all loci on 1p except the most centromeric (D1S534 – removed from list of loci examined) and all loci on 19q examined that codeletion was present.

Study	Tests	Histology	Grade						Notes
Smith 1999 (FISH vs PCR)	A: FISH B: PCR	Astrocytoma	II	0	0	0	1	1	Quote: "LOH, FISH, and CGH were performed as previously described (Cliby et al., 1993; Ritland et al., 1995; Qian et al., 1995; Mohapatra et al., 1995, 1998; Piper et al., 1995)". Overall results for 1p and 19q for PCR not given. We assumed that if results were confirmed allelic loss/presumed allelic loss/homozygous at all loci on 1p except the most centromeric (D1S534 – removed from list of loci examined) and all loci on 19q examined that codeletion was present. Overall results for FISH also not reported. We defined codeletion as hemizygous deletion of 1p36, 1q13.1-q13.2 and 19q13.3.
		Astrocytoma	III	0	0	0	1	1	
		Astrocytoma	IV	1	0	0	15	16	
		Mixed	II	0	0	0	1	1	
		Mixed	III	0	0	0	3	3	
		Oligodendroglioma	II	3	0	0	2	5	
		Oligodendroglioma	III	1	0	0	0	1	
Srebotnik-Kirbis 2016	A: FISH (cytospins) B: FISH (FFPE)	Oligodendroglioma	II	5	0	0	0	5	Excluded participants with uninterpretable test results. Participants with 1p/19q imbalance were counted as not having the deletion (quote: "Imbalance was defined as a relative loss of target signals in comparison with controls, with target signals >1 (ex. 2/3, 2/4, 3/4, etc.)". Also tested a group of 19 non-oligodendroglial tumours. Could not extract results for these as 7/19 were not gliomas and results just for the participants with glioma were not presented.
		Anaplastic oligodendroglioma	III	1	0	0	0	1	
		Anaplastic oligoastrocytoma	III	1	0	0	5	6	
Thakur 2012 [a]	A: FISH B: SNP array	Oligodendroglioma	NR	2	0	0	0	2	FISH was presumably also on FFPE samples.

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(Continued)

Study	Test	Tumour type	Grade						Notes
Thomas 2017	A: FISH B: NGS	Anaplastic oligodendroglioma, anaplastic oligoastrocytoma	NR	13	1	0	5	19	We assumed only 1 participant with a false-positive result and all other results concordant. Quote: "A total of 19 patients had available tissue with adequate DNA quality and quantity for gene sequencing analysis, including 14 patients with confirmed 1p/19q codeletion and 5 with 1p/19q intact … One patient thought to have 1p/19q codeletion on FISH had a glioblastoma-like signature with PTEN, CDKN2B, CDKN2AP16INK4A, and CDKN2AP14ARF with no evidence of 1p/19q loss or IDH1 or 2 mutation on gene sequencing, suggesting a false-positive 1p/19q codeletion on FISH".
Tsiatis 2010	A: PCR B: SNP array	Anaplastic mixed oligoastrocytoma	NR	0	0	0	1	1	We excluded case n5 as aged < 18 years.
		Anaplastic oligodendroglioma	NR	1	0	0	0	1	
		Astrocytoma	NR	0	0	0	1	1	
		Low-grade glioneural tumour	NR	0	0	0	1	1	
Uchida 2019	A: FISH (deletion criterion of 1p or 19q signals < signals of 1q or 19p) B: FISH (deletion criterion of single signal of	Glioblastoma	IV	1	5	0	135	141	—

	1p or 19q and 2 signals of 1q or 19p)								
Wiestler 2014	A: Methylation array B: MLPA	Anaplastic astrocytoma, Anaplastic oligoastrocytoma, Anaplastic oligodendroglioma	III	39	1	7	52	99	Reference 12 in this paper: Wick et al. (2009) "Detection of chromosome arms 1p and 19q deletions was performed by a multiplex ligation-dependent probe assay (Salsa MLPA, P088 lots 0305 and 0706, MRC Holland, Amsterdam, the Netherlands).16 Chromosomal regions were scored as under- or overrepresented if two or more loci on 1p or 19q adjacent to each other exhibited a gene dosage ratio less than 70% or more than 130% relative to the reference value. In the 59 patients from whom leukocyte DNA was available, we additionally performed microsatellite-based loss of heterozygosity analyses for allelic losses on 1p and 19q. At least five microsatellite loci on each arm were analyzed.17,18". No comparison of the results from these 2 techniques. MLPA methods from this reference. Quote: "In the few discordant 1p/19q cases (1p/19q codeleted based on MLPA, 1p/19q intact as per HM450), the clinical course and pathological characteristics tended to accord to the HM450 data … This may be explained by the rather low threshold chosen in the initial MLPA assessment where two adjacent gene loci with a gene dosage ratio of less than 70% were considered as evidence of chromosome arm deletion".

++: number of people (or tumours (ᵃstudies where we consider the unit of analysis was a tumour)) positive on both tests (meaning that 1p19q codeletion found with both tests); +-: positive on test A, negative on test B; -+: negative on test A, positive on Test B; --: negative on both tests; aCGH: array comparative genomic hybridisation; CGH: comparative genomic hybridisation; CISH: chromogenic in situ hybridisation; FISH: fluorescent in situ hybridisation; LOH: loss of heterozygosity; MLPA: multiplex-ligation-dependent probe amplification; NGS: next-generation sequencing; NR: not reported; PCR: polymerase chain reaction; RFLP: restriction fragment length polymorphism; SNP: single nucleotide polymorphism. ᵇSenetta 2013 had data on other FISH criteria, and comparisons could be made for subsets of participants. These are shown in Appendix 8.

Appendix 7. Data extraction details

We attempted to include participants only once, that is, we extracted one result per person, as 1p/19q codeletion status is thought to be stable. Where it was not clear if results were per person, we extracted data once per tumour. This meant that where possible if it was clear that the same participant contributed multiple samples, we extracted results for only one sample and excluded results for the other samples. It was generally the case that if a study included multiple samples from the same participant, then primary and recurrent tumours were included, and, in this scenario, we used the result for the primary tumour. For example, we excluded recurrent cases from Bigner 1999 and Sim 2018a Glioblastoma cohort, and the second tumour sample from the same participant in Burger 2001. However, in some cases it was not possible to extract just one result per participant despite it being clear that some participants must have contributed more than one sample, because sufficient individual participant data were not presented (e.g. D'Haene 2019).

In some cases the same participants were included in multiple studies. In this situation, we tried to include participants only once in the analyses. For example, Hatanpaa 2003a and Hatanpaa 2003b studied the performance of multiplex microsatellite polymerase chain reaction (PCR) and capillary electrophoresis interpreted without comparison to normal DNA (from normal tissue or blood) in tumour samples that had produced concordant results after being tested with at least of two of the following methods: comparative genomic hybridisation (CGH), fluorescent in situ hybridisation (FISH) and PCR-based microsatellite analysis with comparison to normal deoxyribonucleic acid (DNA) from the same participant. They report using tumour samples from Johns Hopkins Hospital that had been investigated in Smith 1999, and one sample from Burger 2001. We attempted to match the tumour samples up using case numbers, although this required some interpretation as it appeared that histological diagnoses may have altered between publications. However, we were unable to match one participant (T117 in Hatanpaa 2003a; Hatanpaa 2003b) to any of the included participants in Smith 1999. We excluded the matched participants from data sets for Smith 1999 and Burger 2001. During this analysis, the possibility of further overlap in participants between these publications arose as two of the participants in Burger 2001 had the same case numbers as those in Hatanpaa 2003b that were linked to participants in Smith 1999. All three studies used samples from Johns Hopkins Hospital. However, as Burger 2001 made no mention of using samples that had already been tested in Smith 1999, we decided that we could not conclude that these were the same participants.

Where possible, we excluded results for participants aged less than 18 years. However, again in some cases it was clear that some participants were aged less than 18 years (e.g. because the lower bound of the age range was less than 18 years) but it was not possible to exclude results for participants aged less than 18 years as individual participant data with all relevant characteristics were not presented (e.g. Ghasimi 2016; Harada 2011; Na 2019).

We excluded participants without some form of glioma. For example, we excluded one participant with pineal parenchymal tumour from Harada 2011.

If 1p/19q codeletion status was not reported, we examined the status of 1p and 19q, in combination with any reported polysomy to classify participants as having 1p/19q codeletion. However, we did not examine the status of 1q or 19p. This means that some of the participants/tumours that were assessed as having 1p/19q codeletion may have additionally lost 1q or 19p. There were some studies that judged 1p/19q codeletion not to be present if 1q or 19p was lost; if this was the case, we extracted the authors' classifications.

There were several instances where we had to classify the results of at least one test in a study. For example, Smith 1999 compared PCR-based LOH assay with FISH and CGH. Although not explicitly reported in this publication, CGH presumably looked genome wide; there were a number of PCR markers examined along 1p (D1S468, D1S1612, D1S1597, D1S199, D1S1665, D1S1728, D1S1588, D1S1675, D1S187, D1S534) and 19q (D19S213, D19S569, D19S422, D19S219, DM, D19S112, D19S412, D19S596, HRC, D19S589, D19S218); and target FISH probes were used that hybridise to 1p36 and to both 19q13.2-q13.2 (AKT2) and 19q13.3. Cut-offs were not prespecified or explicitly reported, but the paper defined "minimal deletion regions" on 1p36 (D1S468-D1S1612) and 19q13.3 (D19S412-D19S596). It was unclear if these were to be taken as the criteria for judging deletion of 1p or 19q, and classification of participants based on the results of FISH and PCR-based LOH was not reported in the paper (CGH results were classified), although it must have occurred as the paper reported concordances and correlations among PCR-based LOH, FISH and CGH by chromosome arm. Instead, individual participant data for each PCR marker and FISH probe were presented. We assumed that the aim of this paper was to identify the localisation of common deletion regions on 1p and 19q in gliomas, and, given the individual participant data presented, we decided to classify the FISH and PCR results ourselves. 1p was considered lost by PCR if all markers on 1p, with the exception of D1S534, showed either confirmed allelic loss, presumed allelic loss, were homozygous or were indeterminant; and by FISH if there was a hemizygous deletion in the 1p36 probe. 19q was considered lost by PCR if all markers on 19q showed either confirmed allelic loss, presumed allelic loss, were homozygous or were indeterminant; and by FISH if there was a hemizygous deletion in both the 19q13.2-q13.2 (AKT2) and 19q13.3 probe. 1p/19q codeletion was present if both 1p and 19q were lost.

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Burger 2001 also did not classify results for PCR-based LOH, although it did state that some results strongly suggested loss of a chromosome arm. We classified the results with the threshold that all informative markers needed to be homozygous.

Lhotska 2015 did not specify a threshold for determining whether the 1p/19q codeletion was present by single nucleotide polymorphism (SNP) array, and did not classify. We set the criteria for codeletion as one copy of (or homozygous for, suggestive of copy neutral LOH) 1p36.33p11.2 or 1p31.1p12 or 1p31.3p31.1 AND one copy of/homozygous for 19q12q13.43 or 19q13.2q13.43 or 19q13.32q13.43.

Jeuken 2006 prespecified cut-off for particular MLPA probes (probe ratio 0.8 or less) but not for deletion of a chromosome arm. Again, we classified the results. We assumed that if all probes were lost, or the majority were lost and those that were not lost were flanked by probes that were lost, that loss had occurred, ignoring the results for the most centromeric 1p probe (NOTCH2).

We also interpreted the results for the SNP array in Hinrichs 2016.

There were other situations where we had to make judgements regarding 1p/19q status based on reported cytogenetic abnormalities or the presence, loss or gain of chromosomal regions (e.g. Ransom 1992a; Ransom 1992b; Schrock 1994).

In other papers, even though classifications had been made, we had to interpret the results. For example, in Bigner 1999, some participants had the CGH result (quote) "copy number changes of partial chromosome arms". We derived from the text that the authors considered that when this had occurred on 1p/19q that a codeletion was present. In Dahlback 2009 and Dahlback 2011, the criteria for 1p/19q codeletion based on the results of CGH were not reported (high-resolution CGH (HR-CGH), was used in these studies). There were some classifications made in the text, and raw results were also presented. We attempted to identify participants with classifications of 1p/19q codeletion to confirm that they had results from other tests, but we had difficulty identifying which participants would have been classified as having the codeletion. The data extraction for Dahlback 2009 was mainly based on the following text: "Combined 1p/19q loss was not observed by G-banding analysis. The HR-CGH data revealed 1p/19q loss in only five tumours (3 GB, 1 GS, and 1 GB-OD)". In Dahlback 2011, it was reported that "HR-CGH could be performed in 18 of the 22 tumours where LOH-PCR results were available. Both methods found the complete 1p/19q codeletion in nine samples. The PCR-based method detected a codeletion in a sample where HR-CGH showed loss of 19q, but only partial loss of 1p. Two tumours that were normal by LOH-PCR showed partial loss of 19q by HR-CGH and one displayed partial loss of 1p where no aberrations were found by the former method". Numbers with positive results for HR-CGH and PCR by histological diagnosis were also reported. However, not all the numbers tallied. PCR results were categorised in a table. We used these, and the raw HR-CGH results and the text to try and interpret the CGH results. In Duval 2014, FISH assessments were made independently by two observers. In one case, a participant was classified as having the codeletion by one observer but not the other when using the ratio method to interpret the results of ImmunoFISH (FISH with immunohistochemistry against Ki67 (MIB-1)). Raw data were available from the two observers, and we averaged the raw data and applied the reported cut-off to come to a consensus classification. The results in Ghasimi 2016 required careful interpretation. In the text it stated that 55 people had results from both techniques, and that FISH detected 14 people with codeletion. From their Supplementary Table 3 it appeared that only 11 of these people had results also from SNP array. We assumed that the phrase "none was detected by SNP array" to mean that no one had the codeletion by SNP array (and not those with positive FISH results). Thomas 2017 made no direct comparison between the results obtained by FISH and next-generation sequencing (NGS). A discrepant result is described in detail, we have, therefore, assumed that all other cases were concordant. We attempted to extract results for just gliomas from D'Haene 2019. The results we extracted were based on the text "concordant positive results were obtained for 21 of the 22 glioma samples (95.4% sensitivity)." and "Among the 31 gliomas that did not show a 1p/19q codeletion by FISH, 28 showed neither patterns of 1p/19q loss of heterozygosity (LOH) by NGS, as defined by our criteria (three were non-informative)". Kato 2019 was reported as a conference abstract only. We assumed that the sentence "our sequence pipeline and also FISH identified 1p19q codeletion only in these 3 cases" meant that neither test found any other codeletions.

In Blesa 2009, there were some differences between Table 2 in their text and their Supplementary Table. Since their Supplementary Table had more information, we extracted from this. In Horbinski 2012, there were discrepancies between text (and what they calculated in their Table 2) and Table 1; we used the text and their Table 2.

In some cases, results were classified for 1p and 19q separately. We only extracted participants who had results for both 1p and 19q from at least two tests, and classified all other participants as having missing results. In some cases, results would have been deducible: for example if 1p or 19q was retained then the participant could not have the codeletion. However, the result is not deducible in the inverse situation (i.e. if 1p or 19q is deleted but a result is not available for the other chromosome arm).

As described in the introduction, copy neutral loss of heterozygosity was classified as a loss.

Also as described in the introduction, we were interested in diagnosing absolute 1p/19q codeletions (rather than relative codeletions). Some studies classified participants/tumours as have relative codeletions or as having imbalance. We grouped these participants/tumours with participants/tumours without a codeletion. In addition, we made any exception to our rule of extracting the researchers' classifications of test results if it was clear that some of the participants or tumours classified as having a 1p/19q codeletion had a relative codeletion that was detectable by the technique used.

Cut-offs/thresholds used

The cut-offs/thresholds used to classify 1p/19q status were often not described or incompletely reported.

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As stated previously, where available, we extracted the researchers' classifications of test results (i.e. we did not attempt to reclassify test results even if raw data were available if the researchers had made classifications). In some studies, it appeared that the cut-offs/thresholds used to classify codeletion would classify both partial deletions of 1p/19q and full arm deletions of 1p/19q as codeletions or that the cut-offs/thresholds used did not fully exploit the potential of a particular test, or both.

In studies investigating PCR-based LOH, it was sometimes clear that although participants were classified as having the codeletion, it was more likely that they had partial deletions. For example, in Bouvier 2004, codeletion was investigated using three microsatellite markers on 1p and three on 19q (1p36.23 (D1S1612), 1p34.2 (D1S447), 1p13.3 (D1S252) and on 19q13.32 (D19S412 and D19S219), 19p13.12 (D19S226)). Criteria for LOH were prespecified ("LOH was scored when signal intensity was <0.5 or >2 in a tumor sample") but it was unclear how many of the microsatellite markers needed to show LOH to be classified as a codeletion. Four participants classified by the authors as having the codeletion were then described as having "partial deletion on 19q for the 19q13.32 and not for the 19q13.12". Clark 2013 stated that "to be considered codeleted the majority of informative microsatellite loci on both 1p and 19q had to show LOH". Eight glioblastomas tested positive for the codeletion by PCR. However, in the discussion, they stated that "in the 8 cases in this subset that met our initial LOH codeletion criteria, usually only a single 1p or 19q microsatellite remained intact. For there to be true whole-arm codeletion, all microsatellites should be lost on 1p and 19q. Because none of the tumours in this cohort showed complete loss of microsatellites on both arms". In Gadji 2009, it was unclear how many markers needed to show LOH, and some participants who were classified as having 1p/19q codeletion appeared to be heterozygous at numerous markers. In the discussion they stated "additionally, across our population the 1p-/19q- codeletion was located in different regions of chromosome arms 1 and 19, from comprising the whole chromosomal arm deletion to partial terminal chromosomal arm or interstitial chromosomal deletion" implying that not all participants classified as having the codeletion had it. In Jha 2011, although the cut-off for number of loci that needed to have LOH was not explicitly reported, it seemed that LOH of one marker on each of the chromosome arms was sufficient to count as codeletion.

Other tests also had issues. For example, 1p loss by real-time PCR in Nigro 2001 was defined by copy number less than 1.58 in two or more sequential loci (rather than along the whole arm). In Wiestler 2014, the criteria for arm deletion on MLPA was initially two adjacent loci with a gene dosage ratio less than 70% (again, rather than along the whole arm). In Ghasimi 2016, although the SNP array used could look along the whole of 1p and 19q, they chose to only look at the results for regions corresponding to the location of the FISH probes, meaning that the full potential of the SNP array was not exploited.

'Perfect' tests

We extracted results without regard to whether any of the tests was assumed to be a perfect test.

However, several of the included studies predefined the reference standard test and calculated sensitivity and specificity for the other test based on this. For example, Scheie 2006 designated PCR-based LOH as the reference standard when comparing FISH and PCR-based LOH and Nigro 2001 designated FISH as the reference standard for the comparison of real-time PCR with FISH.

Some studies repeated analyses or tested discordant cases using a third technique. For example, Lass 2013 repeated FISH analysis or performed PCR-based LOH (or both) for cases with discordant FISH and CISH results.

Other studies looked at the clinical course/prognosis of participants with discordant results to determine which test was more likely to be correct, for example Wiestler 2014 and Senetta 2013. We did not systematically extract this information as it was outside the scope of this review.

Appendix 8. Extra comparisons in Senetta 2013

Senetta 2013 assessed 1p/19q status using different fluorescent in situ hybridisation (FISH) criteria:

- two different ratio cut-offs (a cut-off ratio of 0.8 or less was used to define 1p and 19q allelic losses; in addition for 1p a more stringent ratio cut-off of 0.7 or less was applied);
- percentage of neoplastic nuclei carrying 1p and 19q deletions of 50% or greater; and
- combination of the ratio cut-offs and percentage of neoplastic nuclei carrying 1p deletions of 50% or greater.

They also considered polysomy (30% or greater of nuclei carrying three or more control signals for both arms).

We extracted into our main outcomes table the comparison between the two different ratio cut-offs (FISH ratio cut-offs of 0.8 or less for 1p and 19q; and 0.7 or less for 1p and 0.8 or less for 19q) as this comparison included all participants.

We could not compare the results of the second set of criteria (percentage of neoplastic nuclei carrying 1p and 19q deletions of 50% or less) with any of the other sets of criteria.

For the third set of criteria, we could make some comparisons with the ratio cut-off alone for the 132 of the 143 cases with data on the percentage of deleted nuclei, as shown below.

Cut-off A	Cut-off B	++	+-	-+	--
Ratio cut-off 1p ≤ 0.8 and 19q ≤ 0.8	Ratio cut-off 1p ≤ 0.8 and 19q ≤ 0.8 **plus** ≥ 50% of 1p deleted nuclei	47	16	0	69
Ratio cut-off 1p ≤ 0.7 and 19q ≤ 0.8	Ratio cut-off 1p ≤ 0.7 and 19q ≤ 0.8 **plus** ≥ 50% of 1p deleted nuclei	42	5	0	85

++: positive using both cut-offs (meaning that 1p19q codeletion found with both cut-offs); +-: positive with cut-off A, negative with cut-off B; -+: negative on cut-off A, positive on cut-off B; --: negative with both cut-offs.

If we considered the relative deletions (deletions in the presence of 30% or greater of nuclei carrying three or more control signals for both arms) as being negative we could calculate the following numbers (assuming that we had data for 132 cases):

Cut-off A	Cut-off B	++	+-	-+	--
Ratio cut-off 1p ≤ 0.8 and 19q ≤ 0.8	Ratio cut-off 1p ≤ 0.8 and 19q ≤ 0.8 **plus** < 30% nuclei carrying 3 or more control signals for both arms	58	5	0	69
Ratio cut-off 1p ≤ 0.7 and 19q ≤ 0.8	Ratio cut-off 1p ≤ 0.7 and 19q ≤ 0.8 **plus** < 30% nuclei carrying 3 or more control signals for both arms	42	5	0	85

++: positive using both cut-offs (meaning that 1p19q codeletion found with both cut-offs); +-: positive with cut-off A, negative with cut-off B; -+: negative on cut-off A, positive on cut-off B; --: negative with both cut-offs.

Appendix 9. QUADAS-2 risk of bias assessments for studies that performed two or more FISH variants

QUADAS-2 risk of bias and applicability assessments for studies that assessed at least two fluorescence in situ hybridisation (FISH) variants are shown in Figure 12.

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Figure 12. Risk of bias and applicability concerns summary for studies that assessed at least two FISH variants: review authors' judgements about each domain for each included study. Note: the judgements for FISH variant 1 for Horbinski 2012 are shown in Figure 7. FISH: fluorescence in situ hybridisation.

The tests were as follows.

- Belaud-Rotureau 2006: FISH variant 1 was FISH with the 1p36.3 (D1Z2)/1q12 (D1Z1) and 19q13.3/19pter probes and manual analysis, FISH variant 2 was FISH with the 1p36/1q25 and 19q13/19p13 Abbott Vysis probe set and manual analysis and FISH variant 3 was FISH with 1p36/1q25 and 19q13/19p13 Abbott Vysis probe set and automated analysis.
- Duval 2014: FISH variant 1 was a combination cut-off (based on number of cells showing a deletion), FISH variant 2 was a ratio cut-off (based on the ratio of signals for 1p to 1q and 19q and 19p), FISH variant 3 was immunoFISH with a combination cut-off, FISH variant 4 was immunoFISH with a ratio cut-off.
- Duval 2015: FISH variant 1 was automated FISH analysis, FISH variant 2 was manual FISH analysis.
- Horbinski 2012: FISH variant 1 was a cut-off of a target-ploidy control ratio of less than 0.87, FISH variant 2 was a cut-off of a target-ploidy control ratio of less than 0.75; in both cases at least 20% of nuclei needed to show deletion. This study is also in Figure 7.
- Senetta 2013: FISH variant 1 was FISH with cut-off ratios 1p of 0.8 or less and 19q of 0.8 or less, FISH variant 2 was cut-off ratios 1p of 0.7 or less and 19q of 0.8 or less.
- Srebotnik-Kirbis 2016: FISH variant 1 was FISH performed on cytospins, FISH variant 2 was FISH performed on FFPE sections.
- Uchida 2019: FISH variant 1 was deletion criterion of 1p or 19q signals < signals of 1q or 19p, FISH variant 2 was deletion criterion of single signal of 1p or 19q and two signals of 1q or 19p; in both cases the cut-off value was set at 20%.

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Appendix 10. Standard deviations and between-study correlations

Table A10.1. Standard deviations and between-study correlation from analyses using FISH as the reference standard

		Standard deviation of logit(sensitivity) (95% CrI)	Standard deviation of logit(1−specificity) (95% CrI)	Between-study correlation (95% CrI)
Main analysis (shared parameters)		1.84 (1.42 to 1.99)	1.36 (0.78 to 1.94)	0.36 (0.03 to 0.78)
Sensitivity analysis	**PCR-based LOH**	1.80 (1.27 to 1.99)	1.39 (0.79 to 1.95)	0.29 (0.02 to 0.73)
	SNP array	1.80 (1.22 to 1.99)	1.55 (0.46 to 1.98)	0.66 (0.07 to 0.98)
	NGS	0.54 (0.03 to 1.78)	0.96 (0.05 to 1.95)	0.50 (0.03 to 0.98)
	CGH	1.11 (0.07 to 1.96)	0.83 (0.05 to 1.93)	0.45 (0.02 to 0.97)

CGH: comparative genomic hybridisation; CrI: credible interval; LOH: loss of heterozygosity; NGS: next-generation sequencing; PCR: polymerase chain reaction; SNP: single nucleotide polymorphism.

Table A10.2. Standard deviations and between-study correlation from analyses using PCR as the reference standard

		Standard deviation of logit(sensitivity) (95% CrI)	Standard deviation of logit(1−specificity) (95% CrI)	Between-study correlation (95% CrI)
Main analysis (shared parameters)		1.66 (1.09 to 1.98)	1.27 (0.69 to 1.93)	0.23 (0.01 to 0.66)
Sensitivity analysis	**FISH**	1.71 (1.14 to 1.99)	1.43 (0.78 to 1.97)	0.22 (0.01 to 0.65)
	CGH	1.01 (0.08 to 1.94)	0.73 (0.03 to 1.91)	0.49 (0.02 to 0.97)
	aCGH	0.97 (0.04 to 1.95)	0.81 (0.04 to 1.92)	0.50 (0.03 to 0.98)

aCGH: array comparative genomic hybridisation; CGH: comparative genomic hybridisation; CrI: credible interval; FISH: fluorescence in situ hybridisation.

H I S T O R Y

Protocol first published: Issue 8, 2019

C O N T R I B U T I O N S   O F   A U T H O R S

SD undertook the searches.
AM, LS, SD, ESL and CF performed title/abstract screening.
AM, LS, ESL and JPTH performed full-text screening.
AM, LS, CK, ESL, AP, JPTH and KMK performed data extraction.
AM, LS, CK, JPTH and KMK undertook QUADAS-2 assessments.
HEJ performed statistical analyses.
AK and TR performed the economic analyses.
JPTH performed GRADE assessments.
AMM managed the project.
JPTH, LV and HEJ provided methodological expertise.

DECLARATIONS OF INTEREST

SOURCES OF SUPPORT

Internal sources

External sources

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made the following changes from the protocol (McAleenan 2019).

Criteria for considering studies for this review

We excluded studies with data for just one person.

We had planned to contact authors of studies where only concordance data were reported rather than contingency tables of cross-classified results, and of studies where it was clear that at least two tests were applied but results were not reported. However, due to resource constraints and a larger than anticipated number of included studies, we were unable to do this.

We added a clarification that studies were only eligible if participants had not been recruited based on their 1p/19q status (i.e. if all participants were 1p/19q positive or if all participants were 1p/19q negative on one test).

Selection of studies

We had planned to retrieve full texts of all titles and abstracts that had been deemed relevant by at least one review author. However, we changed this due to the very large number of papers this would have produced, and used a third review author to arbitrate in cases of disagreement.

Diagnostic test accuracy and cost-effectiveness of tests for codeletion of chromosomal arms 1p and 19q in people with glioma (Review)

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Data extraction and management

In situations where classifications were not made, raw data were presented, and the threshold to be used to interpret the raw data were not specified, we had planned to contact study authors to enquire regarding the threshold to be used, and only to apply our own threshold based on our own expertise if we did not receive a response. However, we applied our own thresholds to interpret the data in all cases.

Assessment of methodological quality

We made some refinements to our tailoring of QUADAS-2.

Statistical analysis and data synthesis

We had planned to investigate whether the index characteristics such as tumour sample type (i.e. FFPE or frozen tissues), region(s) analysed and cut-off/threshold used to determine 1p/19q status, and population characteristics such as prevalence of 1p/19q codeletion and tumour subtype and grade contributed to heterogeneity. We had planned to perform sensitivity analyses restricting to direct comparative studies and by restricting analyses to studies judged not to be at high risk of bias or low applicability. Due limited amounts of data and resource constraints, we did not complete these analyses.

Economic model

As well as reporting the incremental cost per additional true-positive diagnosis (as stated in the protocol), we also reported the incremental cost per additional true-negative diagnosis and incremental cost per correct diagnosis.

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