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# Gene Therapies for High-Grade Gliomas and Glioblastomas: A Systematic Review

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## Introduction

Gliomas are the most common primary brain tumours in adults. World Health Organization classification grades gliomas from Grades I–IV based on how aggressively cells divide. Grades I–II (low grade) are slow-growing tumours and more common in children. High-grade gliomas (HGG) are grades III (also known as anaplastic glioma) and IV (known as glioblastoma [GBM])[1].

The incidence of malignant gliomas is approximately 3–5/100,000, with a slightly higher rate in males. The first line of treatment for HGG is surgical resection, radiotherapy and chemotherapy. Despite advances in standard treatments, the prognosis of patients diagnosed with HGGs is very poor with a 5-year survival rate of <10% for GBM[1-3].

Newer technologies have emerged for the treatment of HGG. In oncology, gene therapies aim to treat disease by transferring manipulated genes via engineered vectors to targeted tumour cells, causing oncolysis and tumour regression. Since the first gene therapy trials for GBM in 1992, the number of trials have increased[4-8].

## Objective

The aim of this systematic literature review (SLR) it to provide a comprehensive overview of published clinical trials assessing gene therapies for the treatment of HGG.

## Method

We conducted a SLR following PRISMA guidelines[9], to identify clinical trials with gene therapy interventions for the treatment of high-grade gliomas in adults. Eligibility criteria are shown in Table 1.

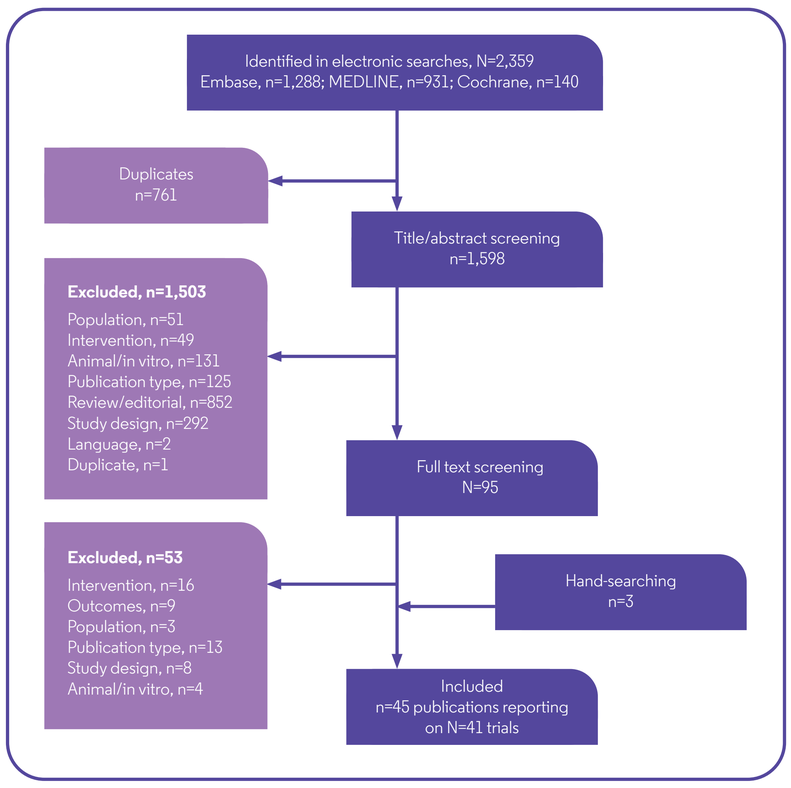
Searches were conducted in Medline (including Epub ahead of print and in-process), Embase and the Cochrane Central Register of Controlled Trials from database inception using the OVID platform. Searches were limited to full publications in the English language. A hand-search of relevant reviews and SLRs was also conducted.

Publications were selected by two independent reviewers.

## Results

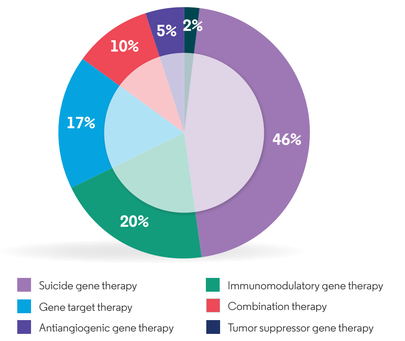
Searches were run on 15 May, 2024. A PRISMA diagram with details of the number of records identified, and selection of publications, is shown in Figure 1.

### Figure 1: PRISMA diagram

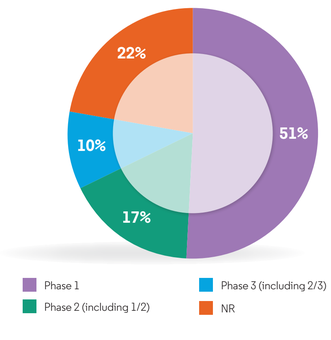



In total, 45 publications reporting on 41 trials were included in the SLR. The most reported gene therapy was suicide gene therapy (SGT; n=19 [46%]), followed by immunomodulatory gene therapy (n=8 [20%]), gene target therapy (n=7 [17%]), antiangiogenic gene therapy (AGT; n=2 [5%]), and tumour suppressor gene therapy (n=1 [2%]). Four trials (10%) assessed combination therapies (SGT and immunomodulatory gene therapies).

### Figure 2: Gene therapies for high-grade glioma or glioblastoma assessed in published trials




### Figure 3: Trial phase in published trials on gene therapies for high-grade glioma or glioblastoma




**Abbreviations:** NR- Not reported

Most trials were Phase 1 (n=21 [51%]). Seven (17%) trials were Phase 2, and four (10%) were Phase 3. The trial phase was not reported in 9 (22%) trials.

Median (range) sample size was 13 (3, 403).

Twenty trials (49%) were single-arm trials, 15 (36%) were dose-escalation trials and only six (15%) were randomised controlled trials (RCTs)[10-15]. Of these, five reported on SGTs in patients with recurrent HGGs (n=3)[11-13] or in newly diagnosed GBM (n=2)[14, 15], with a sample size ranging from 53 to 403. One RCT focused on AGT in patients with recurrent glioblastoma, with a sample size of 256[10]. Details of the RCTs are presented in Table 2, and the results in these RCTs are summarised in Table 3.

Three RCTs found no improvement in overall survival (OS) with SGT compared with the standard of care (SOC)[11, 14, 15], whereas two reported a statistically significant increase [12, 13]. In three trials there was a higher incidence of serious adverse events (SAEs)[(14)], treatment-related adverse events [15] and grade 3–5 adverse events [11] in SGT compared with SOC. In the two remaining trials, SGT was well tolerated [12, 13].

One RCT focused on AGT in patients with recurrent glioblastoma, with a sample size of 256 [10]. In this trial, AGT did not improve OS compared with SOC and the rates of adverse events were similar in both groups.

### Table 1: Eligibility criteria for the SLR

| Criteria | Include | Exclude |
|---|---|---|
| **Population** | • Adults (≥18 years) diagnosed with HGG or glioblastoma<br>• Any disease stage, treatment naïve or previously treated | Patients with any other disease |
| **Intervention / Comparator** | • Gene therapy including:<br>  • SGT Tumour suppressor gene therapy<br>  • Immunomodulatory gene therapy<br>  • Gene target therapy<br>  • Gene editing<br>• Any clinical trial where gene therapy has been used as intervention (monotherapy, in combination with other treatments or as adjuvant therapy) | Oncolytic virotherapy |
| **Outcomes** | • Safety<br>• Clinical efficacy including OS, PFS, and ORR | Any outcomes not of interest |
| **Study design/ publication type** | • RCTs<br>• Controlled and single-arm trials (Phase 1–3)<br>• Full publications | • Animal/*in vitro* studies<br>• Editorials<br>• Reviews<br>• Letters<br>• Case studies<br>• Case reports<br>• Observational studies<br>• Conference abstracts |
| **Date of publication** | No restriction | |
| **Language of publication** | English language only | Other non-English studies |

**Abbreviations:** HGG, High-grade glioma; ORR, objective response rate; OS, overall survival; PFS, progression free survival; RCT, randomised controlled trial; SGT, suicide gene therapy.

### Table 2: RCTs in gene therapy for high-grade gliomas and glioblastomas – Study details

| Author, year | Study phase | Interventions received | Population description | Sample size |
|---|---|---|---|---|
| **Suicide gene therapy** | | | | |
| Rainov 2000 (14) | 3 | • Intervention: tumor resection plus HSV-tk VPCs into the wall of the resection cavity plus GCV iv<br>• Control: tumor resection | Adults diagnosed with GBM and previously untreated | 248 |
| Immonen 2004 (12) | NR | • Intervention: tumor resection plus AdvHSV-tk into the wound bed after tumor resection plus GCV iv.<br>Control: tumor resection | Adults with operable primary or recurrent high-grade glioma | 36 |
| Westphal_2013 (ASPECT) (15) | 3 | • Intervention: tumor resection plus HSV-tk (sitimagene ceradenovec) into the wall of the resection cavity plus GCV iv<br>• Control: tumor resection | Adults with newly diagnosed GBM | 250 |
| Ji 2016 (13) | 2 | • Intervention: ADV-tk via intra-arterial cerebral infusion plus GCV iv<br>• Control: surgery or systemic chemotherapy or palliative care | Adults with high-grade recurrent malignant glioma | 53 |
| Cloughesy 2020 (11) | 2/3 | • Intervention: tumor resection plus Toca 511 into the resection cavity wall plus oral Toca FC<br>• Control: tumor resection plus SOC (investigator's choice of single agent chemotherapy (lomustine or temozolomide) or bevacizumab | Adult patients with recurrent glioblastoma or AA | 403 |
| **Antiangiogenic gene therapy** | | | | |
| Cloughesy 2020 (GLOBE) (10) | 3 | • Intervention: VB-111 iv plus bevacizumab iv<br>• Control: Bevacizumab iv | Adult patients with recurrent GBM | 256 |

**Abbreviations:** AA: anaplastic astrocytoma; Adv: Adenovirus; ADV-tk: adenovirus mutant thymidine kinase; GBM: glioblastoma; GCV: glancicovir; HSV-tk: herpes simplex virus thymidine kinase; iv:intravenous; SOC: standard of care; VPC: vector-producing cells

### Table 3-RCTs in gene therapy for high-grade gliomas and glioblastomas – Results

| Author, year | Primary outcome | Efficacy results | Safety results |
|---|---|---|---|
| **Suicide gene therapy** | | | |
| Rainov 2000 (14) | Time to progression (recurrence-free time) and time to death (OS) | Median (95% CI) time to tumor progression, days:<br>• Intervention: 180 (174, 220)<br>• Control: 183 (174, 226)<br>Median (95% CI) OS, days:<br>• Intervention: 365 (334, 416)<br>• Control: 354 (315, 372)<br>NS difference for any of the outcomes evaluated | SAEs, gene therapy vs control:<br>• Incidence of cranial hematomas: 8 vs 1<br>• Incidence of thromboembolic events: 16 vs 13 |
| Immonen 2004 (12) | Survival from the date of operation as defined by death or surgery for recurrence | Median survival, weeks:<br>• Intervention: 62.4<br>• Control: 37.7<br>• p=0.0095<br>Median OS (all cause mortality), weeks:<br>• Intervention: 62.4<br>• Control: 45<br>• p=0.0256 | AdvHSV-tk treatment was well tolerated |
| Westphal_2013 (ASPECT) (15) | Time to death or re-intervention | Median (95% CI) time to death or re-intervention, days:<br>• Intervention: 308 (283, 373)<br>• Control: 268 (210, 313)<br>• p=0.0057<br>Median (95% CI) OS (all cause mortality), days:<br>Intervention: 497 (369, 574)<br>Control: 452 (437, 558)<br>p=0.31 | Rate of treatment-related adverse events intervention vs control: 71% vs 41% |
| Ji 2016 (13) | 6-month PFS | 6-month PFS rate:<br>• Intervention: 54%<br>• Control: 13.6%<br>• p=0.001<br>Median OS, weeks:<br>• Intervention: 45.4<br>• Control: 14.3<br>• p <0.001 | ADV-TK was well tolerated. No treatment-related severe adverse events were noted |
| Cloughesy 2020 (11) | OS | Median (95% CI) OS, months:<br>• Intervention: 6.8 (5.7, 7.9)<br>• Control: 7.9 (7.0, 9.7)<br>• p=0.19 | Rate of grades 3–5 adverse events, intervention vs control: 67% vs 40%events: 16 vs 13 |
| **Antiangiogenic gene therapy** | | | |
| Cloughesy 2020 (GLOBE) (10) | OS | Median OS, months:<br>• Intervention: 11.1<br>• Control: 12.22<br>• p=0.62 | The rates of adverse events were similar in the intervention and control groups |

**Abbreviations:** CI, confidence interval; NS, non-significant; OS, overall survival; PFS, progression free survival; SAE, serious adverse events; vs, versus.

## Discussion

We conducted a SLR following PRISMA guidelines to identify clinicaltrials of gene therapy interventions for the treatment of HGGs. The most reported gene therapy was SGT (46%), 51% of the trials were Phase 1, and only 6 trials (15%) were RCTs. The median (range) sample size was 13 (3, 403). The number of published RCTs identified was very limited and therefore no conclusion can be drawn regarding the efficacy of gene therapies from these trials.

This SLR provides a comprehensive overview of the published clinical trials assessing gene therapies for the treatment of HGGs. One limitation of this SLR is that it does not include unpublished data (conference abstracts were not included) or a search for on-going trials. New clinical trials evaluating gene therapies in HGGs are on-going and the overall view of the type of gene therapies being conducted may differ from the trials that have resulted in publications.

Over the last thirty years there has been a considerable increase in the number of clinical trials on gene therapies for GBMs. The fist trials were conducted in 1992 and were predominantly Phase 1 trials. Phase 3 trials emerged from 2015 reaching a peak in 2018 and while there was a subsequent decline probably due to the COVID-19 pandemic, current statistics are promising. Including a search for unpublished and on-going trials would provide further data from an increasing number of emerging clinical trials in the pipeline.

## Conclusion

The majority of the published trials included in this SLR reported on SGT. Only 15% of studies were RCTs and, in most cases, OS did not differ between gene therapies and SOC. The evidence from RCTs is very limited and therefore no conclusion can be drawn regarding the efficacy of gene therapies from these trials, highlighting the need for additional RCTs to evaluate the efficacy of gene therapies in HGGs.



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