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# Clinical and Molecular Features of Patients with Gliomas Harboring Idh1 Non-Canonical Mutations: A Systematic Review and Meta-Analysis.

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# Abstract

### Purpose

The canonical isocitrate dehydrogenase 1 R132 mutation (IDH1 R132) is the most frequent mutation among IDH mutated gliomas. Non-canonical IDH1 mutations or IDH2 mutations are unusual and their clinical and biological role is still unclear.

### Methods

We performed a systematic review and meta-analysis aimed to assess the clinical role of IDH non-canonical mutations.

### Results

Overall, we selected 13 of 3513 studies reporting data of 4007 patients with a diagnosis of grade 2 and grade 3 including 3091 patients with a molecularly proven IDH1 or IDH2 mutation. Patients with non-canonical IDH1 mutations were younger and presented a higher DNA methylation level as compared to those with canonical IDH1 R132H alteration. The overall incidence of non-canonical IDH1 mutations was 7.9% (95% CI 5.4 – 10.7%) in patients with IDH mutated gliomas. There was no statistical difference in terms of incidence between patients with grade 2 or grade 3 glioma. Patients with non-canonical IDH mutations had a lower rate of 1p19q codeletion (risk difference: 31%, 95% CI 23 -38%) and presented a significantly prolonged survival (pooled-HR 0.47, 95% CI, 0.28-0.81) as compared to those with IDH1 R132H mutation.

### Conclusion

Non-canonical IDH1 mutations occur in 7.9% of IDH mutated gliomas and recognize a specific subgroup of patients with an improved survival despite a lower rate of 1p19q codeletion. Data about the type of IDH mutation should be collected in clinical practice and within interventional trials as this could be a critical variable for an improved patient's stratification and selection.


# Introduction

The diagnosis of gliomas required an integrated histological and molecular assessment [1-3]. In particular, the 2016 World Health Organization (WHO) Classification of Tumors of the Central Nervous System recognized specific tumor subtypes according to different genomic alterations [3].

In this classification, the presence of the Isocitrate dehydrogenases 1 or 2 (IDH1 or 2) gene represents a key point. Indeed, patients with IDH1 or 2 mutations can be diagnosed as WHO grade 2 or 3 astrocytomas (IDH mutant, nuclear ATRX lost, CDKN2A/B retained), WHO grade 4 astrocytomas (ATRX lost, CDKN2A/B retained with necrosis and microvascular proliferation, or ATRX lost and CDKN2A/B hemizygously deleted) or WHO grade 2 or 3 oligodendroglioma (ATRX retained, 1p19q codeletion with/without TERT mutation) [3]. Patients with IDH wild-type gliomas are classified as glioblastoma or diffuse hemispheric glioma (H3.3 G34R/V- mutant tumors) as well as diffuse midline gliomas (H3 K27 M- mutant and loss of H327me3) [3].

The IDH genes are also a critical prognostic factor since that patient harboring IDH mutations have significantly longer survival compared to those with IDH wild type (wt) [4-7].

The R132H (c.395 G>A, exon 4 codon 132) mutation of the IDH1 gene is certainly the most common IDH mutation[4-8]. However, thanks to novel techniques performing fast and deep genome novel and uncommon IDH gene mutations have been identified.

There are an increasing amount of data suggesting that patients harbouring IDH1 mutations different from R132H have specific clinical, radiological, and molecular features[9].

Nonetheless, data about the effective clinical role of non-canonical IDH mutations are still conflicting. Here we investigated the clinical role of IDH non-canonical mutations through a systematic review and meta-analysis. We describe outcomes considering IDH mutations as follows:

1) IDH mutations: all-types of IDH mutation;

2) IDH1 R132H: canonical IDH1 R132H mutation;

3) IDH non-canonical mutation: IDH2 or IDH1 mutation different from R132H;

4) IDH2: mutation of R172 or R140;

5) IDH1 non-canonical mutation: IDH mutation differing from IDH R132H and IDH2.

# Methods

### 2.1 Evidence Acquisition

We adopted the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines to conduct this study.

### 2.2 Searching strategy and data collected

Four distinct authors (AAB, VDN, EF, AT, and LG) searched English-written articles published on PubMed/Medline, Cochrane library, and Scopus until the 1$^{st}$ of May 2021. Keywords adopted for the research were: "IDH" OR "IDH1" OR "IDH2" OR "Isocitrate dehydrogenase" AND "glioma". In addition, we searched also relevant abstracts of the main International oncological and neuro oncological meetings (American Society of Clinical Oncology, European Organisation of Research and Treatment of Cancer, European Association of Neuro-Oncology, European Society for Medical Oncology, Society of Neuro-Oncology).

In the case of multiple publications of the same cohort of patients, we included the most updated version with a longer follow-up. In case of the presence of both abstract and complete published version of the same cohort, we selected the complete publication.

We collected the following data from each study selected: 1) First author's name, 2) Year of publication, 3) the overall number of patients, 4) the overall number of grade 2 and grade 3 tumors, 5) the overall number of IDH mutated grade 2 and grade 3 gliomas, 6) patients with IDH2 and IDH1 non-canonical mutations, 7) patients with 1p19q codeletion and IDH1 non-canonical mutation 8) the survival Hazard Ratio (HR) with 95% Confidence interval.

In addition, we collected data about the modality adopted for IDH assessment and age at diagnosis between subgroups with different IDH mutations. Finally, we recorded also the different grades of MGMT methylation according to the type of IDH mutation.

### 2.3 Outcomes of the meta-analysis

We were interested to investigate multiple issues (see below). In particular, all these outcomes were focused on patients with WHO grade 2 or grade 3 gliomas excluding all patients with Glioblastoma.

The main outcomes of the present analysis were:

1) The overall incidence of non-canonical mutations among patients with gliomas.

In particular, we were interested to assess the overall incidence of IDH non-canonical mutations and IDH1 non-canonical mutations among all Grade 2 and 3 gliomas and IDH mutated gliomas. To assess these issues, we selected studies reporting retrospective and prospective cohorts of patients with complete data of incidence. Thus, we did not include case-control studies for this outcome;

2) Incidence of IDH1 non-canonical mutations according to WHO tumor grade among patients with gliomas. For this outcome, we selected only studies reporting complete incidence data according to different tumor grades. For the risk-difference analysis (adopted to estimate the different incidence between patients with grade 2 and grade 3 tumors) we included also case-control studies.

3) Survival comparison between patients with IDH and IDH1 non-canonical mutations.

For this outcome, we selected only studies reporting complete data about survival. The preferred summarizing tool was Hazard Ratio (HR) with 95% Confidence Interval. When available we used the HR provided by the multivariate Cox regression model instead of that provided by the univariate log-rank test. Studies performing a survival comparison but not showing an HR were also reported in the text but not included in the analysis.

4) Difference between 1p19q codeletion incidence among patients with canonical IDH1 mutation or non-canonical IDH one.

5) For this outcome, we selected only studies reporting complete incidence data according to the different 1p19q incidence rates. Since we were interested in an incidence ratio between 1p19q patients and patients with IDH1 canonical/non-canonical mutations we included also case-control studies.

6) DNA methylation levels, localization of tumors on CNS, and age of diagnosis difference between patients with/without non-canonical mutations.

Studies reporting a comparison of methylation grade and age of diagnosis have been selected for this outcome.

### 2.3 Statistical Methods

All analyses have been performed through R statistical software. Packages adopted for the analysis were: tidyverse, dplyr, meta, and metaphor.

In survival analysis, we applied the inverse variance technique for HR assessment reporting both random and fixed effects models.

For incidence analysis, we used the Freeman-Tukey double arcsine transformation of proportions while inverse variance with the Der Simonian-Laird method adopted to estimate between-study variance has been employed.

Finally, the difference between proportions has been performed through a risk difference comparison. The inverse variance weighting has been used for pooling results.

### 2.4 Risk of Bias

We employed the Newcastle-Ottawa Scale (NOS) to assess the risk of bias of studies included in the meta-analysis. Four authors independently reviewed all studies (VDN, EF, AT, LG) rating each selected study. Studies with a score of 7 or more, 4–6, and lower than 4 were considered to have a low, moderate, and high risk of bias, respectively [10].

## Results

### 3.1 Study selection

We selected 13 of 3513 studies reporting data of 4007 patients with a diagnosis of grade 2 and grade 3 including 3091 patients with a molecular proven IDH1 or IDH2 mutations (figure 1) [7, 9, 11-19].

The two main reasons for study exclusion were: 1) review or case reports, 2) lack of distinction between the type of IDH mutations.

We reported a summary of each study selected in table 1. Of note, one of the studies selected [9] reported the clinical outcome of 3 different cohorts of patients with gliomas (CATNON, TAVAREC, and TGCA) [20-22]

### 3.1 Incidence

For overall incidence assessment, we employed 12 of 13 publications excluding the case-control study [7, 9, 12-19].

The estimated incidence proportion of patients with IDH non-canonical among patients with G2 and G3 gliomas is 9.3% (95% CI, 5.4 – 14%, $I^2$ 94%. Figure 2 A). Nine of 13 [7, 12-19] studies performed a clear distinction between IDH2 and IDH1 non-canonical mutations. The incidence of IDH1 non-canonical mutations was estimated to be 5.4% (95% CI, 2.5 – 9.2%, $I^2$ 94%, Figure 2B) between patients with grade 2 grade 3 gliomas population with and without IDH mutation. This same incidence increased to 7.9% (95% CI 5.4 – 10.7%, $I^2$ 72%, Figure 2C) among patients with IDH mutated gliomas [7, 12-19].

### 3.2 Grade

We investigated the overall incidence of non-canonical mutations according to tumor grade in IDH mutated gliomas. Five of 13 studies [12-15, 17] reported complete data about the incidence of patients with IDH1 non-canonical mutations while 4 studies described non-canonical IDH1 mutations incidence among patients with grade 3 IDH mutated gliomas [11, 13-15]. The pooled incidence resulted from analysis was 8.2% (95%CI 4.9% - 12.0% $I^2$ 57%, Figure 3A) and 6.7% (95% CI, 5.0 – 8.7%, $I^2$0%, Figure 3B) for patients with grade 2 and grade 3 IDH mutated gliomas respectively.

No differences in terms of risk difference emerged on the pooled analysis between patients with grade 2 and grade 3 IDH mutated gliomas (Figure 3C). These results did not change also adding the case-control study included in our study (Figure 3D).

### 3.3 1p19q

Only 3 of 13 studies [11, 14, 15] were considered the incidence of IDH1 non-canonical mutations according to the 1p19q.

Overall, of 683 patients with the IDH1 canonical mutation, the co-deletion was identified on 306 patients while the 1p19q co-deletion was present on 29 of 164 patients with IDH1non-canonical mutations. The pooled risk difference estimated was 31% (95% CI 23 -38%, $I^2$ 6%, Figure 4) showing a significantly higher possibility to found a 1p19q codeletion among patients with canonical IDH1 mutations compared to those with non-canonical IDH1 mutations [11, 14, 15].

### 3.4 Survival

Four of 13 studies reported complete survival data for patients with IDH non-canonical (n= 160) and canonical mutations (n= 1019) [9, 15, 20-22]. The pooled HR of these studies was 0.47 (95% CI, 0.28-0.81, $I^2$ 74%, Figure 5) confirming a possible positive prognostic role for IDH non-canonical mutations. One study reported a prolonged survival for patients with IDH1 non-canonical mutations as compared to IDH canonical one[15]. Two studies reported a lack of impact in terms of survival for the presence of IDH1 non-canonical mutations without reporting HR with the confidence interval[11, 14].

### 3.5 Age

Three of 13 [11, 13, 15] selected studies reported a significant difference in IDH1 non-canonical mutations according to age. One study reported a significantly younger age only for patients with IDH1 R132C non-canonical mutations (median age of 34.9 vs 42.9 years) [13]. The remaining two studies reported a younger age for patients harboring all types of IDH1 non-canonical mutations as compared to the IDH1 canonical one (median age of 35 versus 43 years and 29 versus 39 years) [11, 15]. All studies reported the range between younger and older instead of standard deviance as dispersion index thus a formal comparison with meta-analysis was not possible.

### 3.6 Methylation

Only one study assessed the level of DNA methylation between patients with non-canonical mutation among three cohorts of patients enrolled on CATNON, TCGA, and TAVAREC studies [9, 20-22]. In all these cohorts the grade of methylation was significantly higher on patients with IDH non-canonical glioma as compared to patients with IDH1 canonical mutation.

### 3.7 Familiar risk of cancer

Only one of the 13 studies selected reported a possible correlation between the incidence of non-canonical IDH1 mutations and familiar risk of cancer [11]. In particular, the familiar incidence of the tumor was significantly higher as compared to those patients harboring an IDH1R132H mutation (22.2% vs 5.1%).

### 3.8 Localization of tumors on the CNS

Only one of the 13 studies reported differences in localization of tumors with IDH1 non-canonical mutations as compared to those with IDH1 R132H mutated gliomas. This study reported that gliomas with IDH1 non-canonical mutations are more frequently localized on the infratentorial region (5.5% vs 0%) and are more frequently multicentric (4.8% vs 0.9%) as compared to tumors with IDH1 R132H mutation.

## Discussion

We carried out a systematic review and meta-analysis aimed to assess clinical and biological features of patients with IDH1 non-canonical [7, 9, 11-19].

After the selection of 13 relevant studies, we identified an overall incidence of 7.9% (95%CI 5.4 – 10.7%, $I^2$ 72%) of IDH1 non-canonical mutations in IDH mutated grade 2 and grade 3 gliomas. We did not identify an incidence difference according to the tumor grade within all IDH mutated gliomas. The survival of patients with IDH non-canonical mutations was significantly prolonged as compared to those observed in patients with IDH1 canonical mutations (HR 0.47, 95% CI, 0.28-0.81, $I^2$ 74%) and this assumes particular interest also considering the lower rate of 1p19q codeletion detected in these patients (Risk difference of 31%, 95% CI 23 -38%, $I^2$ 6%). We were not able to perform a comparison for age and levels of DNA methylation however available data suggest that patients with IDH non-canonical mutations are younger and have a higher methylation level compared to those patients with IDH1 canonical mutations. We also reported that one study identified a strong correlation between IDH1 non-canonical mutations and familiar risk of cancer.

There are some limitations of our study.

The incidence rate of IDH1 non-canonical mutations can be underestimated due to different techniques of genomic sequencing and molecular assessment adopted [23]. Studies selected are mainly retrospective cohort studies, with only one paper assessing three different cohorts of patients (including 2 randomized controlled trials) and one case-control study [7, 9, 11-22]. These studies were not generally focused to assess clinical outcomes of patients with non-canonical mutations. To reduce this potentially confounding factor, we assessed each study for the specific risk of bias adopting the NOS scale. We identified a low risk of bias for all studies included. Nonetheless, it should be highlighted that the NOS scale could present some limitations [10, 24].

On the survival analysis, we did not include 2 studies with a negative result on survival comparison. The study of Poetsch L et al [11] did not find a survival advantage for non-canonical mutations. However, the median OS was not reached and only 16% of deaths were observed on patients with IDH1 non-canonical mutations suggesting a still immature number of events. Gravendeel L et al [14] failed to show a survival improvement for patients with IDH1 non-canonical mutations in both univariate and multivariate analysis. However, the authors did not report the median follow-up and the number of events that occurred. We did not include these two negative studies since HR (the summary measure selected) was not available [11, 14].

It should be noted that survival data reported for CATNON, TAVAREG, and TCGA) reported a survival comparison between IDH1 canonical and IDH non-canonical mutations[9, 20-22]. It has been reported that IDH2 mutations are associated with a higher

rate of 1p19q codeletion compared to patients with IDH1 mutations. The positive prognostic role of 1p19q codeletion could partially explain the prolonged survival observed in the subgroup with IDH2 alterations [8]. Nonetheless, one study [15] reported a clear survival benefit for patients harboring no IDH1 non-canonical mutations suggesting that these mutations alone can be associated with prolonged survival.

The positive survival impact observed in our analysis could reflect an overall high grade of DNA methylation[25] as compared to patients with IDH1 canonical mutations.

The DNA-methylation reflects the enzymatic activity of IDH. Indeed, IDH mutant dimers shifted the metabolism of the isocitrate to the production of D-2-hydroxyglutarate (D-2-HG) instead of theα-ketoglutarate (which is the usual product of non-mutated IDH enzyme) [6]. The variable intracellular levels of D-2-HG obtained according to IDH mutations could reflect a different methylation status of DNA however this should be still demonstrated[26, 27]. An increased level of DNA methylation has been demonstrated in patients with IDH non-canonical mutations as compared to those with IDH canonical ones. Nonetheless, when survival analysis was adjusted also for methylation grade the type of IDH mutation maintained a positive effect on survival suggesting an independent role as a prognostic factor without confounding effect mediated by methylation grade [9].

Another still unknown issue is the sensitivity of non-canonical IDH1 mutations to IDH inhibitors which are currently under investigation on patients with IDH mutated primary brain tumors [28].

In conclusion, the results of our meta-analysis identify a new class of gliomas with rare non-canonical IDH1 mutation characterized by young age at diagnosis, high level of DNA methylation, and a possible association with a family history of cancer. Furthermore, Compared to gliomas with IDH1 canonical mutations, patients with IDH1 non-canonical mutations have a lower rate of 1p19q codeletion and improved survival. These same gliomas are generally diagnosed at a younger age.

## Conclusion

In this systematic review and meta-analysis, we found that patients with IDH1 non-canonical mutations have an overall incidence of 7.9% among patients with IDH mutated gliomas. These patients are generally younger, with a lower rate of 1p19q codeletion, and present an increased survival as compared to gliomas with IDH1 canonical mutation.

Our results suggest that gliomas with IDH1 non-canonical mutations are a distinct class of gliomas with their own clinical and molecular behaviors that should be distinguished from oligodendroglioma and astrocytoma with IDH1 canonical mutation.

## Declarations

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Availability of data and material: data adopted for analysis is available upon request to the corresponding author.

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**Author contributions:** EF, VDN, AAB conceptualization. EF, VDN, AT, LG, IM, SB, DA writing, software and data curation. VDN, EF statistical analyses. AAB and RL supervision, visualization and investigation. All authors helped in review and editing.

## References


1. Louis DN, Perry A, Reifenberger G, et al (2016). The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol 131(6): 803-820 DOI: 10.1007/s00401-016-1545-1.
2. Ostrom QT, Cioffi G, Gittleman H, et al (2019). CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2012-2016. Neuro Oncol 21(Suppl 5): v1-v100 DOI: 10.1093/neuonc/noz150.
3. Weller M, van den Bent M, Preusser M, et al (2021). EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood. Nat Rev Clin Oncol 18(3): 170-186 DOI: 10.1038/s41571-020-00447-z.
4. Brat DJ, Verhaak RG, Aldape KD, et al (2015). Comprehensive, Integrative Genomic Analysis of Diffuse Lower-Grade Gliomas. N Engl J Med 372(26): 2481-2498 DOI: 10.1056/NEJMoa1402121.
5. Mair MJ, Geurts M, van den Bent MJ, and Berghoff AS (2021). A basic review on systemic treatment options in WHO grade II-III gliomas. Cancer Treat Rev 92: 102124 DOI: 10.1016/j.ctrv.2020.102124.
6. Sanson M, Marie Y, Paris S, et al (2009). Isocitrate dehydrogenase 1 codon 132 mutation is an important prognostic biomarker in gliomas. J Clin Oncol 27(25): 4150-4154 DOI: 10.1200/jco.2009.21.9832.
7. Yan H, Parsons DW, Jin G, et al (2009). IDH1 and IDH2 mutations in gliomas. N Engl J Med 360(8): 765-773 DOI: 10.1056/NEJMoa0808710.
8. Wang HY, Tang K, Liang TY, et al (2016). The comparison of clinical and biological characteristics between IDH1 and IDH2 mutations in gliomas. J Exp Clin Cancer Res 35: 86 DOI: 10.1186/s13046-016-0362-7.
9. Tesileanu CMS, Vallentgoed WR, Sanson M, et al (2021). Non-IDH1-R132H IDH1/2 mutations are associated with increased DNA methylation and improved survival in astrocytomas, compared to IDH1-R132H mutations. Acta Neuropathol 141(6): 945-957 DOI: 10.1007/s00401-021-02291-6.
10. Stang A (2010). Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 25(9): 603-605 DOI: 10.1007/s10654-010-9491-z.
11. Poetsch L, Bronnimann C, Loiseau H, et al (2021). Characteristics of IDH-mutant gliomas with non-canonical IDH mutation. J Neurooncol 151(2): 279-286 DOI: 10.1007/s11060-020-03662-x.
12. Metellus P, Coulibaly B, Colin C, et al (2010). Absence of IDH mutation identifies a novel radiologic and molecular subtype of WHO grade II gliomas with dismal prognosis. Acta Neuropathol 120(6): 719-729 DOI: 10.1007/s00401-010-0777-8.
13. Hartmann C, Meyer J, Balss J, et al (2009). Type and frequency of IDH1 and IDH2 mutations are related to astrocytic and oligodendroglial differentiation and age: a study of 1,010 diffuse gliomas. Acta Neuropathol 118(4): 469-474 DOI: 10.1007/s00401-009-0561-9.
14. Gravendeel LA, Kloosterhof NK, Bralten LB, et al (2010). Segregation of non-p.R132H mutations in IDH1 in distinct molecular subtypes of glioma.Hum Mutat 31(3): E1186-1199 DOI: 10.1002/humu.21201.
15. Franceschi E, De Biase D, Di Nunno V, et al (2021). IDH1 Non-Canonical Mutations and Survival in Patients with Glioma. Diagnostics (Basel) 11(2) DOI: 10.3390/diagnostics11020342.
16. Chen N, Yu T, Gong J, et al (2016). IDH1/2 gene hotspot mutations in central nervous system tumours: analysis of 922 Chinese patients. Pathology 48(7): 675-683 DOI: 10.1016/j.pathol.2016.07.010.
17. Camelo-Piragua S, Jansen M, Ganguly A, et al (2011). A sensitive and specific diagnostic panel to distinguish diffuse astrocytoma from astrocytosis: chromosome 7 gain with mutant isocitrate dehydrogenase 1 and p53. J Neuropathol Exp Neurol 70(2): 110-115 DOI: 10.1097/NEN.0b013e31820565f9.
18. Bell EH, Zhang P, Shaw EG, et al (2020). Comprehensive Genomic Analysis in NRG Oncology/RTOG 9802: A Phase III Trial of Radiation Versus Radiation Plus Procarbazine, Lomustine (CCNU), and Vincristine in High-Risk Low-Grade Glioma. J Clin Oncol 38(29): 3407-3417 DOI: 10.1200/jco.19.02983.

19. Balss J, Meyer J, Mueller W, Korshunov A, Hartmann C, and von Deimling A (2008). Analysis of the IDH1 codon 132 mutation in brain tumors. Acta Neuropathol 116(6): 597-602 DOI: 10.1007/s00401-008-0455-2.
20. Ceccarelli M, Barthel FP, Malta TM, et al (2016). Molecular Profiling Reveals Biologically Discrete Subsets and Pathways of Progression in Diffuse Glioma. Cell 164(3): 550-563 DOI: 10.1016/j.cell.2015.12.028.
21. van den Bent MJ, Baumert B, Erridge SC, et al (2017). Interim results from the CATNON trial (EORTC study 26053-22054) of treatment with concurrent and adjuvant temozolomide for 1p/19q non-co-deleted anaplastic glioma: a phase 3, randomised, open-label intergroup study. Lancet 390(10103): 1645-1653 DOI: 10.1016/s0140-6736(17)31442-31443.
22. van den Bent MJ, Klein M, Smits M, et al (2018). Bevacizumab and temozolomide in patients with first recurrence of WHO grade II and III glioma, without 1p/19q co-deletion (TAVAREC): a randomised controlled phase 2 EORTC trial. Lancet Oncol 19(9): 1170-1179 DOI: 10.1016/s1470-2045(18)30362-0.
23. Han S, Liu Y, Cai SJ, et al (2020). IDH mutation in glioma: molecular mechanisms and potential therapeutic targets. Br J Cancer 122(11): 1580-1589 DOI: 10.1038/s41416-020-0814-x.
24. Lo CK, Mertz D, and Loeb M (2014). Newcastle-Ottawa Scale: comparing reviewers' to authors' assessments. BMC Med Res Methodol 14: 45 DOI: 10.1186/1471-2288-14-45.
25. Visani M, de Biase D, Marucci G, et al (2014). Expression of 19 microRNAs in glioblastoma and comparison with other brain neoplasia of grades I-III. Mol Oncol 8(2): 417-430 DOI: 10.1016/j.molonc.2013.12.010.
26. Ferreyra Vega S, Olsson Bontell T, Corell A, Smits A, Jakola AS, and Carén H (2021). DNA methylation profiling for molecular classification of adult diffuse lower-grade gliomas. Clin Epigenetics 13(1): 102 DOI: 10.1186/s13148-021-01085-7.
27. Pirozzi CJ and Yan H (2021). The implications of IDH mutations for cancer development and therapy.Nat Rev Clin Oncol DOI: 10.1038/s41571-021-00521-0.
28. Gatto L, Franceschi E, Tosoni A, et al (2021). IDH Inhibitors and Beyond: The Cornerstone of Targeted Glioma Treatment. Mol Diagn Ther DOI: 10.1007/s40291-021-00537-3.

# Tables

### Table 1

Summary of the studies included in the meta-analysis. FISH: fluorescence in situ hybridization, IDH: isocitrate dehydrogenase, IHC: immunohistochemistry, NGS: Next-generation sequencing, PCR: *polymerase chain reaction*

| Study | year | Type of study | Patientsoverall | G2/G3 gliomas | IDH1 Assessmentmodality | Studydescription | Risk of Bias |
|---|---|---|---|---|---|---|---|
| Blass J. et al. [19] | 2008 | Molecular analysis (IDH1 direct sequencing) | 685 | 685 | NGS | Molecular study showing a higher incidence of IDH1 mutations on astrocytoma and oligodendroglioma as compared to glioblastoma. | Low |
| Gravendeel et al. [14] | 2009 | Molecular and clinical assessment of patients with IDH NCM | 496 | 496 | NGS | IDH1 type of mutations did not affect the patient's survival. IDH1 non-canonical mutation occurred more frequently in patients with 1p19qcodeletion. | Low |
| Yan H et al. [7] | 2009 | Molecular IDH1 assessment of patients with CNS and non-CNS tumor | 445 | 186 | NGS + assessment of enzymatic activity. | Mutations of IDH1 and IDH2 occur in the majority of malignant glioma. | Low |
| Hartmann C et al. [13] | 2009 | The molecular analysis aimed to assess IDH1/2 mutation types and frequencies | 1010 | 1010 | NGS | IDH2 mutations occurred more frequently on oligodendrogliomas, IDH1 and IDH2 were inversely associated | Low |
| Metellus P. et al. [12] | 2010 | Molecular analysis assessing genomic and clinical features of IDH wt G2 | 47 | 47 | NGS | The absence of IDH mutations in G2 gliomas recognized a novel entity of low grade gliomas with infiltrative behaviors. | Low |
| Camelo-Piragua S. et al. [17] | 2011 | The molecular assessment aimed to determine the most useful panel to distinguish astrocytoma from astrocytosis | 21 | 21 | IHC + FISH + SNaPshotGenotyping | Higher sensitivity by combining fluorescence in situ hybridization for chromosome 7 and the p-53 IDH1 IHC panel | Low |
| Chen N[16] | 2016 | Molecular assessment of IDH mutations on Chinese patients | 922 | 570 | IHC + PCR-based direct sequencing | lower expression of p53 and ki-67 correlated with IDH1 mutation status. IDH1 correlated with PFS and disease-free survival. | Low |
| Poetsch L. et al. [11] | 2020 | Case controlateral | 321 | 302 | IHC + Sanger | No survival advantages | Low |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | comparing clinical behaviors of patients with NCM to patients with standard IDH1 mutation | | | | emerged, however, follow-up is still immature as only 16 and 38 events (deaths) occurred in patients with IDH1 non-canonical mutation and canonical IDH mutation respectively. Compared to canonical mutations IDH1 non-canonical mutations are frequently found in the infratentorial region and multicentric. Patients with IDH1 non-canonical mutation had more frequently a younger age and family history of cancer. | |
| Bell E.H. et al. [18] | 2020 | Molecular analysis on the population of the phase III interventional trial: RTOG 9802 | 106 | 106 | IHC and/or NGS | Post hoc analysis assessing the predictive value of molecular classification in patients with low-grade glioma within the RTOG9802 interventional clinical trial | Low |
| Franceschi et al. [15] | 2021 | Prognostic assessment of patients with IDH non-canonical mutations | 431 | 431 | NGS | Association between rare mutation and improved prognosis. Patients with NCM less often host 1p19q codeletion | Low |
| Tesileanu C. et al[9, 20-22] | 2021 | Clinical comparison between patients with canonical and non-canonical mutations. | TCGA | 438 | NGS | Patients with NCM had increased DNA methylation and improved survival. | Low |
| | | | CATNON | 214 | | | |
| | | | TAVAREC | 94 | | | |

# Figures

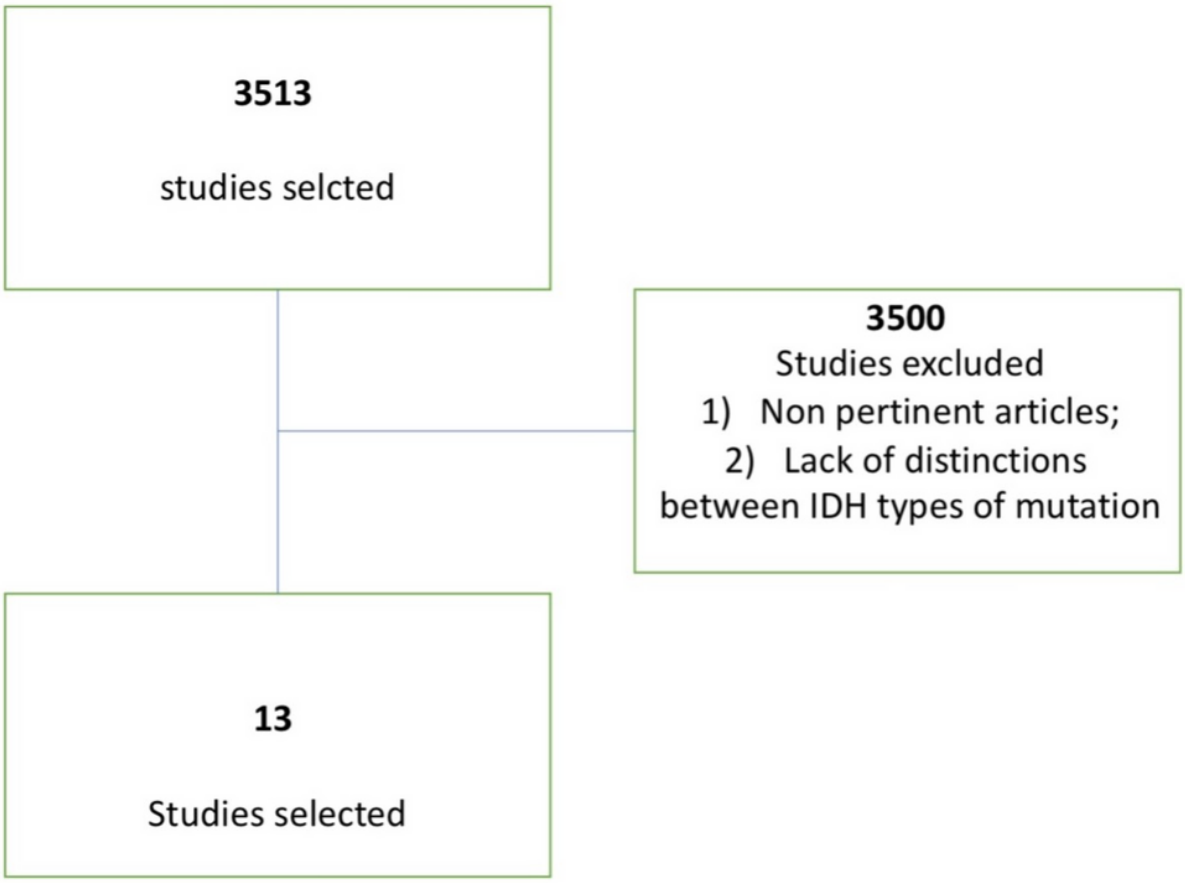
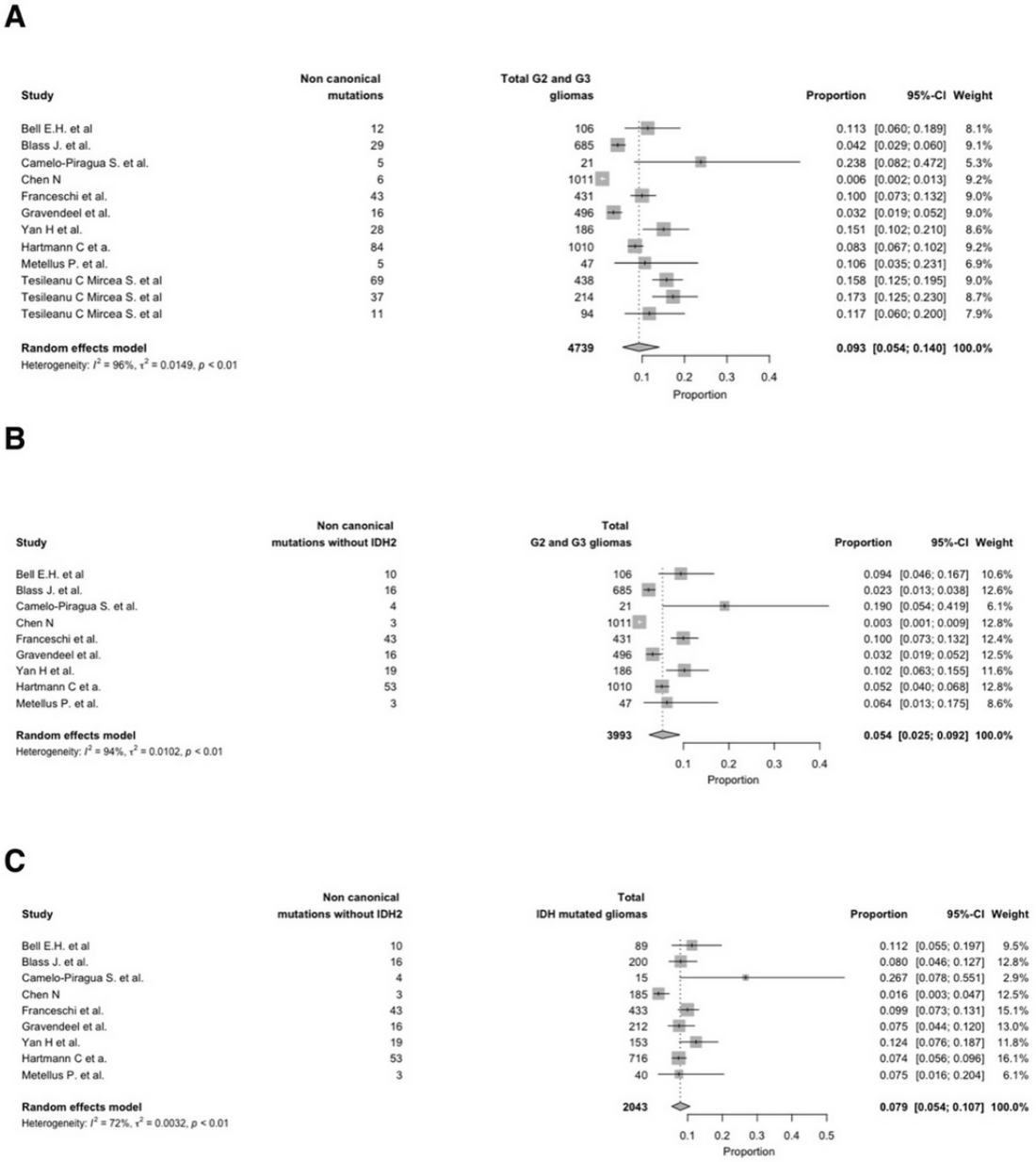


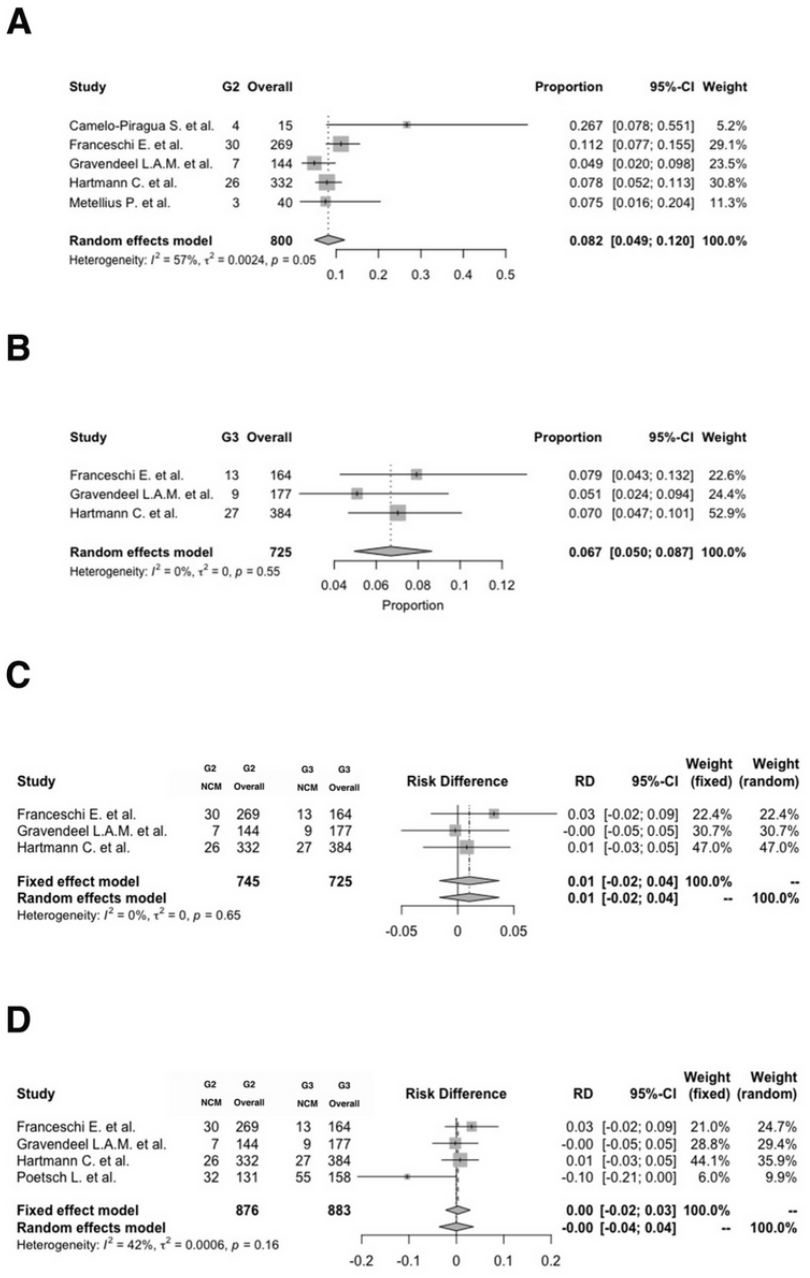

**Figure 1**

Studies selection



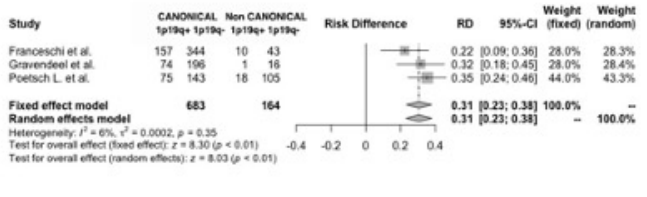

## Figure 2

Panel A Overall incidence of IDH non-canonical mutations on the overall cohort of gliomas; Panel B Overall incidence of IDH1 non-canonical mutations on the overall cohort of gliomas; Panel C Overall incidence of IDH1 non-canonical mutations on the overall cohort of IDH mutated gliomas;




## Figure 3

Panel A: Incidence of IDH1 non-canonical mutations among IDH mutated grade 2 gliomas; Panel B: Incidence of IDH1 non-canonical mutations among IDH mutated grade 3gliomas; Panel C: Risk difference between the incidence of IDH1 non-canonical mutations on grade 2 and grade 3 gliomas; Panel D: Risk difference between the incidence of IDH1 non-canonical mutations on grade 2 and grade 3 gliomas with the addiction of the case-control control.




## Figure 4

Risk difference between patients with canonical and non-canonical mutations harbouring also a 1p19q codeletion.

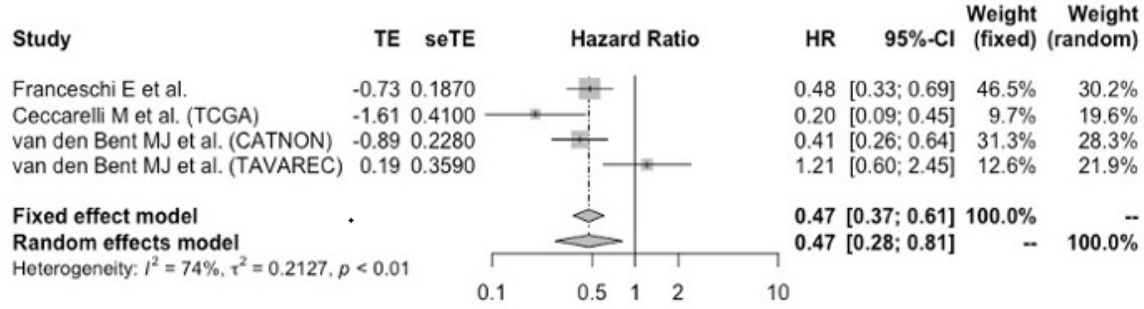



**Figure 5**

Survival comparison in patients with IDH non-canonical mutations.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PRISMAchecklist.docx