A “Weighted” Fluorescence In Situ Hybridization Strengthens the Favorable Prognostic Value of 1p/19q Codeletion in Pure and Mixed Oligodendroglial Tumors

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INTRODUCTION

In recent years, progress in molecular analysis has contributed to recognizing important genetic alterations in brain tumors, some of which are related to patient prognosis (1, 2). The observation of different clinical behavior in gliomas presenting with the same histology and tumor grade has led to the need for a better molecular characterization of these lesions that could identify new useful biomarkers for both tumor classification and patient management (1, 2). Among the molecular markers identified as helpful for neurologic and neuropathologic assessments, 1p/19q status analysis is one of the most important tools with diagnostic, prognostic, and predictive value in oligodendrogial-derived brain tumors (3–21). It is well known that codeletion of chromosome arms 1p and 19q defines a subset of patients with better prognosis most likely because of a higher sensitivity to genotoxic stress (21). Because of the strong association between 1p/19q allelic loss and favorable outcome, 1p/19q status is routinely investigated in pure and mixed oligodendroglial tumors.

Fluorescence in situ hybridization (FISH) is the most widely used technique for investigating 1p/19q status because it allows the assessment of 1p/19q allelic loss on paraffin-embedded tissue samples, thereby permitting matching of cell morphology and genetic alterations (15, 22). To date, the interpretation of FISH results for defining 1p/19q status has not been standardized, and laboratories arbitrarily choose their criteria to interpret FISH data based on ratio evaluation (between 1p/1q and 19q/19p), calculation of the percentage of neoplastic nuclei carrying deletion, or according to guidelines defined by the International Society of Pediatric Oncology (ESIOP Neuroblastoma Study Group) (8, 10–12, 15, 19, 22–29). Furthermore, few authors have attempted to integrate the ratio and percentage of deleted nuclei to determine 1p/19q status (25, 30). The lack of a standard procedure for the interpretation of FISH data has led to interinstitutional disagreement on how to characterize 1p/19q molecular status, thereby creating some confusion among clinicians regarding the prognostic and predictive value of codeletion. This confusion most likely accounts for a “gray prognostic zone,” which includes codeleted patients with an unexpected unfavorable outcome that is probably based on false-positive FISH results.

To optimize the prognostic role of 1p/19p status in pure and mixed oligodendroglial tumors, we have tried to establish
and compare different criteria for interpreting FISH results to reduce the impact of the gray zone. Specifically, in this retrospective series of 161 oligodendrogliomas, we assessed 1p/19q status using FISH according to the following parameters: 1) 2 different ratio values; 2) the percentage of neoplastic nuclei carrying chromosomal deletion; and 3) a novel integrated evaluation based on the ratio corrected by the percentage of neoplastic cells carrying codeletion, weighted differently for 1p or 19q. In addition, we evaluated the prognostic impact of an imbalanced 1p/19q deletion, as observed in the polysomy condition.

**MATERIALS AND METHODS**

**Patients and Follow-up Analysis**

A series of 161 cases of brain tumors with an oligodendroglioma component were tested for 1p/19q status by FISH between January 2004 and March 2012 and were retrospectively retrieved from the pathology files of our department. Hematoxylin and eosin–stained slides were independently reviewed by 2 pathologists (Paola Cassoni and Rebecca Senetta) who were blinded to the patient outcome. The histologic diagnosis was made solely on hematoxylin and eosin–stained slides before determining the FISH status. The tumors were classified according to the World Health Organization Classification of Brain Tumors (31). In biopsy specimens, the diagnosis of high-grade gliomas was made when necrosis, microvascular proliferations, and/or mitotic activity (more than 2 mitoses/biopsy) were present. After revision, 18 (11.2%) of 161 cases were excluded from the study because they were recurrences, brain tumors without an undoubtedly oligodendroglioma component, or cases with diagnostic disagreement between the 2 observers. The histologic diagnoses of the 143 cases included in the study were as follows: 89 (62.2%) of 143 pure oligodendrogliomas (O), 48 of 89 grade II (OII), and 41 of 89 grade III (OIII); 38 (26.6%) of 143 mixed oligoastrocytomas (OA), 18 of 38 OA grade II (OAI; and 20 of 38 grade III (OAIII); and 16 (11.2%) of 143 glioblastomas with an oligodendrogliom component (Table 1).

None of the patients had been previously treated with chemotherapy or radiotherapy. Follow-up data concerning the overall survival (OS) were available for all 143 cases. Overall survival was defined as months from the date of initial surgery to the date of tumor progression/recurrence (defined radiologically or clinically) or last follow-up.

The study was performed according to the standards of the Institutional Ethical Committee and the Helsinki Declaration of 1975, as revised in 1983, and approved by the institutional review board of our institution. All tissue samples were anonymized by staff members who were not involved in the study according to published procedures (32).

**Fluorescence In Situ Hybridization**

The FISH test was performed using the LSI 1p36/19q13 Dual-Color Probe Sets (Vysis/Abbott, Molecular Europe, Wiesbaden, Germany). The Dual-Color Probe Set consists of 2 separate probe mixtures: 1 probe set contains the LSI 1p36 Spectrum Orange test probe and the LSI 1q25 Spectrum Green control probe; the other probe set contains the LSI 19q13 Spectrum Orange test probe and the LSI 1q25 Spectrum Green control probe. The paraffin sections were deparaffinized, air-dried, incubated in pretreatment solution at 98°C for 15 minutes in Heat Pretreatment Solution (Invitrogen, Carlsbad, CA), and subsequently immersed in purified water. The slides were then treated with Enzyme Reagent (Invitrogen) in a humidified box for 30 to 40 minutes at room temperature and washed in purified water. After air dehydration, 10 μL of probe mixture was applied to each sample. The slides were then coverslipped and sealed with rubber cement. Slides and probes were codenaturated at 74°C for 5 minutes and hybridized at 37°C for 16 hours in the dark using the Vysis HYBrite Denaturation/Hybridization Unit (Vysis). A posthybridization wash was performed in 2× SSC–0.3% NP-40 at 73°C for 3 minutes. Finally, the slides were dehydrated and mounted in antifade with DAPI (4',6-diamidino-2-phenylindole; Abbott Molecular) and stored in the dark before signal evaluation. An automated scanning station, MetaSystems (Carl Zeiss MetaSystems, Thornwood, NY), equipped with an AxioImager-Z1 epifluorescence microscope, was used to determine 1p/19q status. The first step was signal acquisition over 7 to 10 areas that were selected for each slide by a dedicated operator. To choose regions with the most neoplastic cells, areas with a high signal quality and good nuclear preservation were assessed. These areas were automatically scanned, and 13 different consecutive focal planes were made for each FISH signal to form a single bidimensional image. For traditional reading, the automatically acquired images were transferred to Isis software (Zeiss) and stored in dedicated files. The evaluation of hybridization signals was then performed in 200 or more nonoverlapping nuclei, and the

**TABLE 1. Correlation Between Histologic Diagnosis and 1p/19q Status (Ratio Cutoff for 1p ≤ 0.7 or 0.8 and Ratio Cutoff for 19q ≤ 0.8) in 143 Brain Tumors With an Oligodendrogliom Component**

| GBMO   | OII (n = 48) | OIII (n = 41) | OAI (n = 18) | OAIII (n = 20) |
|--------|-------------|---------------|--------------|---------------|
| 1p/19q codeleted | 25 (52.1) | 31 (64.6) | 17 (41.5) | 22 (53.6) |
| 1p deleted | 1 (2.1) | 4 (8.4) | 4 (9.7) | 6 (16.6) |
| 19q deleted | 13 (27.1) | 7 (14.5) | 8 (19.5) | 3 (7.1) |
| 1p/19 not deleted | 9 (18.8) | 6 (12.5) | 12 (29.3) | 10 (24.4) |

GBMO, glioblastoma with an oligodendroglioma component; OII, oligodendroglioma grade II; OIII, oligodendroglioma grade III; OAI, oligoastrocytoma grade II; OAIII, oligoastrocytoma grade III.
nuclei counted displayed at least 2 green signals. The ratio of 1p/1q and 19q/1p was calculated by dividing the number of orange and green signals.

For each case, FISH data were analyzed using criteria as follows: 1) a cutoff ratio of less than or equal to 0.8 was used to define 1p and 19q allelic losses; in addition, for 1p chromosomal arm, we applied a more stringent ratio cutoff equivalent to less than or equal to 0.7, as previously reported (13); and 2) percentage of neoplastic nuclei carrying 1p and 19q deletions using greater than or equal to 50% as the cutoff to define 1p and 19q deletions, as previously reported (24); 3) an integrated evaluation, merging points 1 and 2 with further subcategories, as detailed below. Finally, we investigated the role of codepletion in chromosomal imbalance conditions (polysomy) to determine its possible prognostic value, which is debated in the literature (28).

Establishment of Specific Codepletion Criteria

To identify the most prognostically reliable evaluation of codepletion (intended as a favorable indicator), we set different criteria. As a premise, we specified a different ratio cutoff regarding 1p exclusively, whereas the 19q cutoff for deletion remained unchanged at less than or equal to 0.8. The reason for this choice was based on preliminary evidence that 1p is the most relevant chromosome for favorable prognosis, whereas the 19q deletion can bear unfavorable prognostic value (16, 33).

Therefore, we designated our cutoff criteria for codepletion as follows: 1) codepletion determined as ratio value less than or equal to 0.8 for both 1p and 19q; 2) codepletion determined as ratio value less than or equal to 0.7 for 1p and less than 0.8 for 19q; 3) codepletion determined as more than 50% of neoplastic cells carrying both 1p and 19q deletion irrespective of the ratio value; 4) codepletion determined as ratio value less than or equal to 0.8 for both 1p and 19q + more than 50% of cells carrying the 1p deletion (merging points 1 and 3); and 5) codepletion determined as ratio value less than or equal to 0.7 for 1p and 0.8 for 19q and more than 50% of cells carrying the 1p deletion (merging points 2 and 3).

Statistical Analysis

The data were analyzed with SPSS Version 19 (SPSS, Inc., Chicago, IL). A statistically significant probability value was defined as p < 0.05. Univariate survival analysis was performed using the Mantel-Cox test (34) and depicted by the Kaplan-Meier method (35). Multivariate survival analysis was performed using the Cox model.

RESULTS

Clinical and Pathologic Prognostic Variables: Age, Extent of Surgical Resection, and Histologic Grade

The patients included 81 men and 62 women, aged 22 to 81 years (mean, 51.5 years); 60 (42%) of 143 patients were younger than 50 years and 83 (58%) of 143 were older. Thirty-six (60%) of 60 patients younger than 50 years and 30 (37.5%) of 80 patients older than 50 years had a low-grade glioma. By univariate analysis, age significantly correlated with OS (p < 0.0001), identifying a subgroup of younger patients with a more favorable outcome (Fig. 1A). No correlation was found with DFS (p = 0.27) (Fig. 1B). In addition, young age (<50 years) retained its favorable prognostic value.

FIGURE 1. Kaplan-Meier analyses of estimated overall survival OS (A) and disease-free survival (DFS) (B) in relation to patient age in 143 oligodendroglial brain tumors.
not only in the overall series but also within the distinct not-deleted and codeleted subgroups (p < 0.0001 and p = 0.001, respectively).

Data concerning the extent of surgical resection were available in 99 (69.2%) of 143 cases. More precisely, 19 (19.2%) of 99 patients underwent a biopsy; 59 (59.6%) of 99, a partial resection; 14 (14.2%) of 99, a subtotal resection; and 7 (7%) of 99, a radical resection. There was no significant difference in OS and DFS between these groups (OS, p = 0.07). As expected, a histologic low tumor grade was related to better OS (p < 0.0001) (Fig. 2A). Regarding the DFS, there was a significant difference in tumor recurrence and progression between grades II and IV only (p = 0.008) (Fig. 2B).

FISH Data Interpretation

Ratio Cutoff Setting 1p ≤ 0.8/19q ≤ 0.8

We determined 1p/19q status using 2 different ratio cutoff values to validate whether a more severe (≤0.7) deletion criterion for 1p could reduce the gray zone of unfavorable outcome despite codeletion. According to the 1p ≤ 0.8/19q ≤ 0.8 ratio, there were 68 (47.6%) of 143 cases that had both 1p and 19q allelic losses, 21 (14.7%) of 143 and 18 (12.6%) of 143 cases had isolated loss of 1p or 19q, respectively, and 36 (25.1%) of 143 cases did not have codeletions or single deletions (Table 1).

Using the more stringent ratio cutoff (≤0.7) to define 1p allelic loss, 16 (23.5%) of 68 of the prior codeleted cases were redistributed into different subgroups; thus, codeletion was observed in 52 (36.3%) of 143 cases (Table 1). By univariate analysis independent of the 1p ratio cutoff, the subgroup of cases with 1p/19q codeletion showed longer OS and DFS (1p ≤ 0.8/19q ≤ 0.8, OS, p = 0.002 and DFS, p = 0.03; 1p ≤ 0.7/19q ≤ 0.8, OS, p = 0.002 and DFS, p = 0.005) (Fig. 3). For DFS, the use of the 0.7 cutoff for the 1p deletion strengthened the favorable prognostic value of codeletion. However, despite the use of a different cutoff ratio and patient redistribution, the percentages of codeleted patients who died at the end of follow-up (42%) were equivalent (29 of 68 and 22 of 52 patients in 0.8 and 0.7 cutoff, respectively) (Supplemental Digital Content 1, http://links.lww.com/NEN/A447). These results indicate that restricting the cutoff ratio for 1p is not helpful in reducing the gray zone of codeleted patients with poor outcome. In addition, using the 0.8 ratio cutoff, the 19q allelic loss alone identified a subset of patients with the worst prognosis (Fig. 3A–C). The presence of an isolated 19q loss was not closely associated with any specific tumor histologic type.

Ratio and Tumor Histology/Grade

Subdividing all cases according to the histologic type, 1p/19q codeletion (independently of the ratio applied [0.7 or 0.8]) retained prognostic significance only in pure oligodendrogial tumors, identifying oligodendrogliomas with prolonged overall and progression-free survival (1p ≤ 0.8/19q ≤ 0.8, OS, p = 0.005 and DFS, p < 0.0001; 1p ≤ 0.7/19q ≤ 0.8, OS, p = 0.006 and DFS, p < 0.0001) (Table 1). No correlation was found in mixed oligodendrogial tumors of any histologic grade.

Similarly, grouping all cases according to the histologic grade, regardless of tumor histotype, 1p/19q codeletion (with any ratio) identified a subset of patients with a better prognosis within grade II tumors only (1p ≤ 0.8/19q ≤ 0.8, OS, p = 0.03; 1p ≤ 0.7/19q ≤ 0.8, OS, p = 0.01). In addition, we observed...
a trend for correlation between codeletion and OS in grade IV tumors only when applying the ratio cutoff $1p \leq 0.7/19q \leq 0.8$ (OS, $p = 0.05$).

Merging the previously reported data, we analyzed the prognostic impact of $1p/19q$ status in pure oligodendrogliomas according to histologic grade (grade II vs grade III). Applying the ratio cutoff $1p \leq 0.8/19q \leq 0.8$, codeletion identified a subset of lesions with better outcome in both OII and OIII (OS, $p = 0.04$ and $p = 0.05$, respectively). Conversely, no correlation was found using the more severe cutoff (OS, $p = 0.1$ and $p = 0.2$, respectively), although there was a detectable trend toward significance. In terms of DFS, with both ratios,

![Graphs showing Kaplan-Meier analyses of estimated OS (A, B) and DFS (C, D) in relation to 1p/19q status, as assessed by applying a 1p $\leq 0.8/19q \leq 0.8$ ratio cutoff (A-C) and 1p $\leq 0.7/19q \leq 0.8$ ratio cutoff (B-D).](https://example.com/graphs.png)
codeletion was found to be significant only in OII (1p ≤ 0.8/19q ≤ 0.8 and 1p ≤ 0.7/19q ≤ 0.8, p < 0.0001).

**Percentage of Neoplastic Nuclei Deletion**

For the second setting, we defined the 1p/19q molecular status according to the “rough” percentage of neoplastic nuclei carrying the deletion, independent of the ratio (in 11 of 143 cases, the data concerning the percentage of deleted nuclei were not available). The cutoff for codeletion was greater than or equal to 50% of nuclei carrying loss of chromosomal material from both arms (24). Forty-two (31.8%) of 132 cases showed combined 1p and 19q loss; 24 (18.18%) of 132 and 18 (13.6%) of 132 cases showed single 1p or 19q allelic loss, respectively; and 48 (36.3%) of 132 cases displayed 1p/19q maintenance. The subgroup of codeleted lesions showed a better prognosis both in terms of OS and DFS (OS, p = 0.01; DFS, p = 0.02) (Fig. 4). The percentage of codeleted patients who died at the end of follow-up was 31.1% (16 of 42 cases) (Supplemental Digital Content 1, http://links.lww.com/NEN/A447).

**“Weighted” Ratio: Ratio + ≥50% of Neoplastic Nuclei Carrying 1p Deletion in Codeleted Tumors**

As previously reported, there was a statistical correlation between codeletion and better patient outcome established by using both the ratio and the rough percentage as independent criteria. Thus, we tried to combine them to optimize the prognostic value of FISH. We identified a subgroup of codeleted tumors according to both previously reported ratio cutoff values and then considered only codeleted cases with greater than or equal to 50% of cells carrying 1p loss. The presence on 1p deletion in greater than or equal to 50% of neoplastic nuclei in codeleted cases identified a subset of patients with better outcome (1p ≤ 0.8/19q ≤ 0.8, OS, p = 0.03 and DFS, p = 0.04; 1p ≤ 0.7/19q ≤ 0.8, OS, p = 0.001) (Fig. 5) (Supplemental Digital Content 1, http://links.lww.com/NEN/A447). Specifically, in the 1p ≤ 0.8/19q ≤ 0.8 codeleted group (63 patients), 9 (56.2%) of 16 patients who had less than 50% of 1p deleted cells died (Fig. 6). Strikingly, in the 1p ≤ 0.7/19q ≤ 0.8 codeleted group (47 patients), all patients (100%) with less than 50% of 1p deleted nuclei died (Fig. 6). In addition, among 8 (12.7%) of 63 and 7 (14.9%) of 47 codeleted patients showing 1p greater than or equal to 50% and a concomitant 19q loss in less than 50% of neoplastic cells, 7 (87.5%, using 1p ≥ 0.8) of 8 and 6 (85.7%, using 1p ≥ 0.7) of 7 respectively, were still living. These data highlight the favorable effect of 1p deletion and the unfavorable effect that 19q loss can have on patient prognosis.

**Multivariate Analysis**

By multivariate Cox regression analysis, among all the clinical, histologic, and molecular variables considered, the age at diagnosis, histologic tumor grade, and 1p/19q deletion status assessed using any reported criteria were independent prognostic factors (Table 2). The combined (weighted) criteria based on ratio plus cell percentage significantly strengthened the favorable prognostic value of FISH, as assessed by codeletion (Table 2).

**Concurrent 1p/19q Loss and Polysomy: Evaluation of Prognostic Significance**

Among the codeleted cases that were identified according to the ratio criteria, 5 lesions showed polysomy (≥30% of...
neoplastic nuclei carrying 3 or more green signals for both arms) (28). We identified 5 (7.9%) of 63 and 5 (10.6%) of 47 cases using the ratio cutoff of $1p^{e_0.8}/19q^{e_0.8}$ or $1p^{e_0.7}/19q^{e_0.8}$, respectively. Two (40%) of 5 were grade II and 3 (60%) of 5 were grade III tumors. We did not observe any significant difference in terms of OS or DFS among the subgroups with and without polysomy (OS, $p = 0.9$ and DFS, $p = 0.7$ for both ratio values).

**DISCUSSION**

To date, the 1p/19q codeletion remains the major favorable prognostic/predictive indicator for oligodendrogial
Co-deletion according to ratio

**Cut-off**
- **1p≤0.8 and 19q≤0.8**
  - 63 co-deleted patients

- **50% of 1p deleted nuclei**
  - ≥50% of 1p deleted nuclei
  - 47 patients
  - 31/47 alive (66%)
  - 16/47 dead (34%)

- <50% of 1p deleted nuclei
  - 16 patients
  - 7/16 alive (44%)
  - 9/16 dead (56%)

**Cut-off**
- **1p≤0.7 and 19q≤0.8**
  - 47 co-deleted patients

- **50% of 1p deleted nuclei**
  - ≥50% of 1p deleted nuclei
  - 42 patients
  - 29/42 alive (69%)
  - 13/42 dead (31%)

- <50% of 1p deleted nuclei
  - 5 patients
  - 0/5 alive (0%)
  - 5/5 dead (100%)

**FIGURE 6.** Stratification of follow-up according to ratio cutoff values and percentage of neoplastic nuclei carrying a 1p loss.

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tumors (3, 4, 6, 9, 16, 19, 21), but its efficacy may be impaired because of the heterogeneity of methods used for its determination and to the lack of uniform reading criteria within the specific techniques. A good concordance between FISH and polymerase chain reaction-based loss of heterozygosity has been previously reported, and a recent study highlighted that modulation of FISH interpretation criteria and additional determination of 10q status could increase its predictive reliability (25). The need for standardized protocols for FISH is indicated by the relevant percentage of poor outcomes of patients with codeleted tumors, suggesting that interpretation of data could be optimized. To achieve a significant reduction of this gray zone of unexpected unfavorable outcomes in codeleted oligodendrogliomas, we created a weighted/scored FISH interpretation that proved helpful in increasing the prognostic stratification and that is easy to use in the daily diagnostic assessment of 1p/19q status.

Our search for a gold standard in FISH data analysis was organized through consecutive steps within a series of 143 tumors with an oligodendroglial component, either pure (grade II and III oligodendrogliomas) or mixed (grade II and III oligoastrocytomas and glioblastomas with an oligodendrogliial component). First, we compared 2 ratio cutoff values for 1p (0.8 and 0.7, respectively) in the presence of a fixed FIGURE 6. Stratification of follow-up according to ratio cutoff values and percentage of neoplastic nuclei carrying a 1p loss.

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**TABLE 2.** Multivariate Analysis of OS Based on Patient Age, Histologic Tumor Grade, and 1p/19q Codeletion Assessed Using Different Criteria in 143 Brain Tumors With an Oligodendroglial Component

| Variable         | Ratio 1p ≤ 0.8 | Ratio 1p ≤ 0.7 | ≥50% of Neoplastic Cells Carrying 1p and 19q Deletion | Ratio 1p ≤ 0.8 | 19q ≤ 0.8 | ≥50% of 1p Deleted Nuclei | Ratio 1p ≤ 0.7 | 19q ≤ 0.8 | ≥50% of 1p Deleted Nuclei |
|------------------|---------------|---------------|-----------------------------------------------------|---------------|----------|---------------------------|---------------|----------|---------------------------|
| Age <50 years    | 0.330 0.1–0.5 | <0.001        | 0.354 0.2–0.6                                        | <0.001        | 0.375    | 0.2–0.6                   | 0.001         | 0.390    | 0.2–0.6                   |
| Histologic grade | 0.512 0.3–0.7 | <0.001        | 0.501 0.3–0.7                                        | <0.001        | 0.462    | 0.3–0.6                   | <0.001        | 0.486    | 0.3–0.7                   |
| 1p/19q codeletion| 0.468 0.2–0.7 | 0.002         | 0.465 0.2–0.7                                        | 0.003         | 0.440    | 0.2–0.7                   | 0.005         | 0.381    | 0.2–0.6                   |

95% CI, 95% confidence interval; RR, relative risk.
0.8 cutoff for 19q and then weighted this analysis by setting a further correction within the codeleted cases, linked to the percentage of neoplastic cells carrying 1p deletion. Specifically, we selected the 0.8 ratio cutoff as the most commonly used and the 0.7 cutoff as the lowest reported in literature (10, 11, 13, 15, 30). This allowed us to identify and compare the variation of relative risk among different subclasses of codeleted tumors. The 2 ratio cutoff values, as well as the cell percentage "restriction criteria," have been applied within codeleted gliomas to tumors with 1p chromosome loss only because its prognostic weight seems to be greater than 19q (33). Furthermore, there are conflicting results in the literature on the prognostic weight seems to be greater than 19q (33). Furthermore, there are conflicting results in the literature on the prognostic weight seems to be greater than 19q (33). Furthermore, there are conflicting results in the literature on the prognostic weight seems to be greater than 19q (33). Furthermore, there are conflicting results in the literature on the prognostic weight seems to be greater than 19q (33). Furthermore, there are conflicting results in the literature on the prognostic weight seems to be greater than 19q (33). Furthermore, there are conflicting results in the literature on the prognostic weight seems to be greater than 19q (33). Furthermore, there are conflicting results in the literature on the prognostic weight seems to be greater than 19q (33). Furthermore, there are conflicting results in the literature on the prognostic weight seems to be greater than 19q (33). Furthermore, there are conflicting results in the literature on the prognostic weight seems to be greater than 19q (33). Furthermore, there are conflicting results in the literature on the prognostic weight seems to be greater than 19q (33). Furthermore, there are conflicting results in the literature on the prognostic weight seems to be greater than 19q (33). Furthermore, there are conflicting results in the literature on the prognostic weight seems to be greater than 19q (33). Furthermore, there are conflicting results in the literature on the prognostic weight seems to be greater than 19q (33). Furthermore, there are conflicting results in the literature on the prognostic weight seems to be greater than 19q (33). Furthermore, there are conflicting results in the literature on the prognostic weight seems to be greater than 19q (33). Furthermore, there are conflicting results in the literature on the prognostic weight seems to be greater than 19q (33). Furthermore, there are conflicting results in the literature on the prognostic weight seems to be greater than 19q (33). Furthermore, there are conflicting results in the literature on the prognostic weight seems to be greater than 19q (33). Furthermore, there are conflicting results in the literature on the prognostic weight seems to be greater than 19q (33). Furthermore, there are conflicting results in the literature on the prognostic weight seems to be greater than 19q (33). Furthermore, there are conflicting results in the literature on the prognostic weight seems to be greater than 19q (33). Further...
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