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ORIGINAL ARTICLE - NEUROSURGERY GENERAL

Association between medical academic genealogy and publication outcome: impact of unconscious bias on scientific objectivity

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Abstract

Background Our previous studies suggest that the training history of an investigator, termed "medical academic genealogy", influences the outcomes of that investigator's research. Here, we use meta-analysis and quantitative statistical modeling to determine whether such effects contribute to systematic bias in published conclusions.

Methods A total of 108 articles were identified through a comprehensive search of the high-grade glioma (HGG) surgical resection literature. Analysis was performed on the 70 articles with sufficient data for meta-analysis. Pooled estimates were generated for key academic genealogies. Monte Carlo simulations were performed to determine whether the effects attributed to genealogy alone can arise due to chance alone.

Results Meta-analysis of the HGG literature without consideration for academic medical genealogy revealed that gross total resection (GTR) was associated with a significant decrease in the odds ratio (OR) for the hazard of death after surgery for both anaplastic astrocytoma (AA) and glioblastoma (AA: log [OR] = − 0.04, 95% CI [− 0.07 to − 0.01]; glioblastoma log [OR] = − 0.36, 95% CI [− 0.44 to − 0.29]). For the glioblastoma literature, meta-analysis of articles contributed by members of a genealogy consisting of mostly radiation oncologists revealed no reduction in the hazard of death after GTR [log [OR] = − 0.16, 95% CI [− 0.41 to 0.09]. In contrast, meta-analysis of published articles contributed by members of a genealogy consisting of mostly neurosurgeons revealed that GTR was associated with a significant reduction in the hazard of death [log [OR] = − 0.29, 95% CI [− 0.40 to 0.18]. Monte Carlo simulation revealed that the observed discrepancy between the articles contributed by the members of these two genealogies was unlikely to arise by chance alone ($p < 0.006$).

Conclusions Meta-analysis of articles contributed by authors belonging to the different medical academic genealogies yielded distinct and contradictory pooled point-estimates, suggesting that genealogy contributes to systematic bias in the published literature.

Keywords Medical academic genealogy · Scientific objectivity · Meta-analysis · Brain tumor

This article is part of the Topical Collection on *Neurosurgery general*

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Introduction

"Medical academic genealogy" refers to the linking of physicians based on their residency or fellowship training mentors [1, 13–15, 22, 38]. We previously studied whether members of academic genealogies disproportionately contributed to the published literature. To this end, we examined the literature investigating whether gross total resection (GTR) was associated with survival benefit in high-grade glioma (HGG) patients. We showed that this literature is dominated by publications contributed by members of two medical academic genealogies [6]. HGG include WHO grade III and IV astrocytomas (also known as anaplastic astrocytomas (AA) and glioblastoma, respectively). These tumors are highly infiltrative, rendering total resection of the tumor impossibility in most clinical context. Supporters of maximal resection suggest that tumor cytoreduction improve the clinical efficacy of subsequent chemo-radiation therapy [37, 41]. In contrast, opponents of maximal resection point to the intrinsic resistance of HGGs to chemotherapy and radiation [19, 20]. The efficacy of GTR in HGG remains an unresolved issue in neurosurgery, though a significant literature has emerged to address the matter [3–5, 7–11, 16–19, 21, 23–26, 29, 31–33, 36, 39, 42].

In our analysis of this literature [3–5, 7–11, 16–19, 21, 23–26, 29, 31–33, 36, 39, 42], we showed members belonging to two genealogies disproportionately contributed to the HGG resection literature. One genealogy (termed genealogy A) was founded by a neurosurgeon and consisted mostly of neurosurgeons. The second genealogy (termed genealogy B) was founded by a radiation oncologist and consisted mostly of radiation oncologists. We subsequently reported that select journals are more likely to publish articles from physicians belonging to the same medical academic genealogy [13]. For instance, articles contributed by genealogy A were more likely published in a neurosurgery journal while articles contributed by genealogy B were more likely published in a radiation oncology journal. Here, we used meta-analysis and statistical modeling to determine whether genealogy membership conferred systematic bias in published conclusions. Meta-analysis and Monte Carlo techniques were used to demonstrate an association between genealogy of investigators and publication outcome in the peer-review literature that examined the clinical benefit of surgical resection in malignant brain tumor patients.

Materials and methods

Literature search strategy

The terms used for a comprehensive PubMed search to identify articles that examined whether gross total resection in HGG patients is associated with survival was as previously described [14]. One hundred and eight articles were identified in this search. Training history of the first and last authors for each article was analyzed and genealogy relation constructed using network analysis [6, 35, 40]. Construction of medical academic genealogy has been detailed in our previous publications [12–14]. Two key medical academic genealogies consisting of radiation oncologists and neurosurgeons were identified in our previous study [14].

Statistical analysis

Articles contributed by the members of the two genealogies were included in the meta-analysis. Results were pooled using a random-effect model. Pooled survival benefit estimates associated with GTR as a function of the two previously identified genealogies were calculated. Odds ratio (OR) with 95% confidence interval (CI) were used to estimate the effect size. Separate analyses were performed for the two types of HGG: AA ($n = 10$) and glioblastoma ($n = 60$). There was an insufficient number of studies that were contributed by genealogy members to examine whether genealogy was associated with publication results in the AA literature. We, therefore, examined this question in the glioblastoma literature. Separate pooled meta-analyses of survival benefits associated with GTR of glioblastoma were determined for publications contributed by members of genealogy A (neurosurgeons) and B (radiation oncologists), as well as non-genealogy members. To determine whether the observed disparity was random, we performed χ^2-based Monte Carlo simulations with a p value based on 10,000 simulations [30]. Monte Carlo simulations were executed by randomly selecting 6 and 20 studies from all articles identified in our literature search (matching the number of articles contributed by the radiation oncology genealogy and neurosurgery genealogy, respectively). Pooled estimates of these randomly selected 6 and 20 studies in terms of death hazard reduction attributable to surgical resection were calculated.

All statistical analyses were performed using R V.3.1.2 (R Foundation for Statistical Computing) and p values < 0.05 were considered significant [28].

Results

A meta-analysis of survival benefit in AA patients

We identified ten studies with a focus on the survival benefit associated with GTR of AA that included necessary information for meta-analysis. The individual estimates of each study as well as the pooled meta-analysis for the odds ratio for the hazard of death after GTR are shown in Fig. 1. Five of the ten identified studies yield point-estimates with a confidence interval that suggest that GTR is associated with a reduction in the hazard of death. The pooled estimate (log OR) for the hazard of death after GTR (relative to sub-total resection (or STR)) for AA was −0.04 (95% CI [−0.07 to −0.01]). This result suggests that GTR is associated with improved survival expectation in AA patients. There was an insufficient number of studies that were contributed by genealogy members to examine whether genealogy was associated with publication results in the AA literature.

A meta-analysis of survival benefit in glioblastoma patients

We identified 60 studies with a focus on the survival benefit associated with GTR of glioblastoma that included necessary information for meta-analysis. The individual estimates of each study, as well as the pooled meta-analysis for the odds

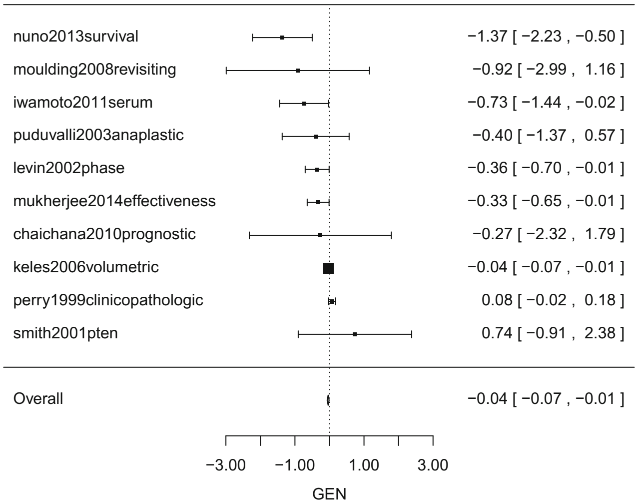

Fig. 1 Forest plot demonstrating odds ratio for hazard of death after gross total resection (GTR) in anaplastic astrocytoma (AA). Squares and horizontal bars indicate point estimate and 95% confidence intervals of odds ratio in each study, respectively. Diamonds indicate the summary estimates that are calculated as per random effects model. All values are in logarithmic scale

ratio for hazard of death after GTR relative to STR, are shown in Fig. 2. Forty-four of the 60 identified studies suggest that GTR is associated with a reduction in the hazard of death. The pooled estimate (log OR) for the hazard of death after surgery for glioblastoma was − 0.36 (95% CI [− 0.44 to − 0.29]). This result suggests that GTR is associated with improved survival expectation in glioblastoma patients.

Contribution of genealogy members to the glioblastoma literature

Of the 60 meta-analysis compatible glioblastoma articles, 20 studies were contributed by genealogy A and six studies were contributed by genealogy B. The median survival of each of these studies is plotted in Fig. 3. Plotted on the *Y*-axis are the median months of survival after GTR. The median months of survival after STR were plotted on *X*-axis. The diagonal line indicates the situations where median survivals after GTR and STR were equivalent. Studies contributed by members of genealogy A are indicated in red while studies contributed by members of genealogy B are indicated in blue. Studies contributed by non-genealogy members were plotted in black. The size of the study is indicated by the size of the data point (i.e., larger dot denotes bigger sample size). As can be visually appreciated, nearly all studies lie above the diagonal line indicating no survival difference between GTR and STR. Also notable in this plot is the over-representation of articles contributed by genealogy B in studies located near or below the GTR = STR line. These results suggest that the pooled hazard of death estimate derived from articles contributed by genealogy B significantly differs from that derived from genealogy A or from non-genealogy members.

Pooled meta-analysis of articles contributed by genealogy members

To test the above hypothesis, we calculated the pooled estimates of OR for hazard of death in glioblastoma patients who underwent GTR relative to those who underwent STR. The results are shown in Fig. 4. The studies contributed by members of genealogy A are indicated in red while studies contributed by members of genealogy B are indicated in blue. The pooled estimates for the articles contributed by the neurosurgery genealogy indicate that glioblastoma GTR is associated with a 29.3% reduction in the hazard for death (range 0.09 to 0.97) (CI: 38.9 to 19.7%, $p < 0.001$). In contrast, meta-analysis of studies contributed by members of genealogy B suggests that GTR of glioblastoma did not significantly affect the hazard of death (OR 29.6%, CI: 60.9% to − 1.6%, $p > 0.062$). The pooled estimates for the studies contributed by the other independent groups **(**Fig. 4, black) suggested a significant decrease in the hazard of death after gross total resection in patients with malignant brain tumor (range 0.05 to 2.57) (log [OR] = − 0.34, 95% CI [− 0.45 to − 0.23].

We next tested whether the observed discrepancy in survival benefit attributable to surgery reported by articles of the radiation oncology genealogy and of the neurosurgery genealogy arose by chance. To this end, we performed Monte Carlo simulations by randomly selecting 6 and 20 studies from all articles identified in our literature search (matching the number of articles contributed by the radiation oncology genealogy and neurosurgery genealogy, respectively). We then calculated the pooled estimates of these randomly selected 6 and 20 studies in terms of death hazard reduction attributable to surgical resection. We determined if these pooled estimates recapitulated the observed difference in death hazard reduction. We repeated this simulation 10,000 times and found that 55 of the 10,000 simulations ($p < 0.006$) recapitulated the observed difference. These results suggest that the observed discrepancy in the pool-estimates of articles contributed by genealogies A and B unlikely arose from chance alone.

Discussion

We previously demonstrated the clinical investigators who share academic genealogy disproportionately contribute to the literature that examined the survival benefit of extended surgical resection in patients afflicted with malignant brain cancer [14]. Using mixed logistic regression models, we further demonstrated that articles contributed by the neurosurgery genealogy were more likely to support the efficacy of gross total resection. In contrast, manuscripts published by the radiation oncology genealogy were less likely to support the efficacy of gross total resection [14]. In this study, we took

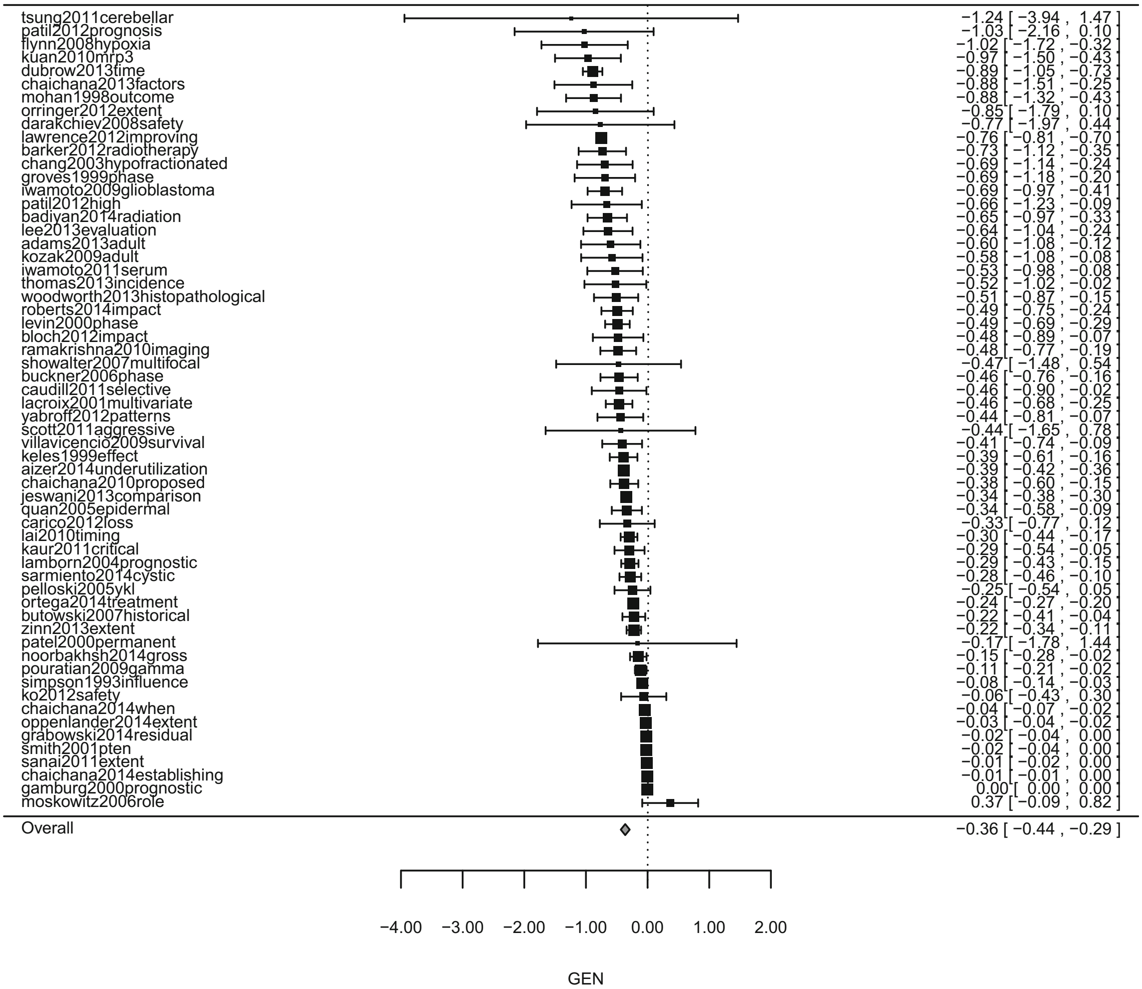

Fig. 2 Forest plot demonstrating odds ratio for hazard of death after GTR in glioblastoma. All values are in logarithmic scale

the analysis one step further to determine how much these articles differed in their conclusions using meta-analysis. Here, we demonstrate that the meta-analysis of published articles from select genealogies yields point-estimates that differ significantly from those derived by other genealogies or non-genealogy members. Using rigorous statistical methods, we further demonstrated that the patterns observed were unlikely to arise by random chance. It is striking that the results

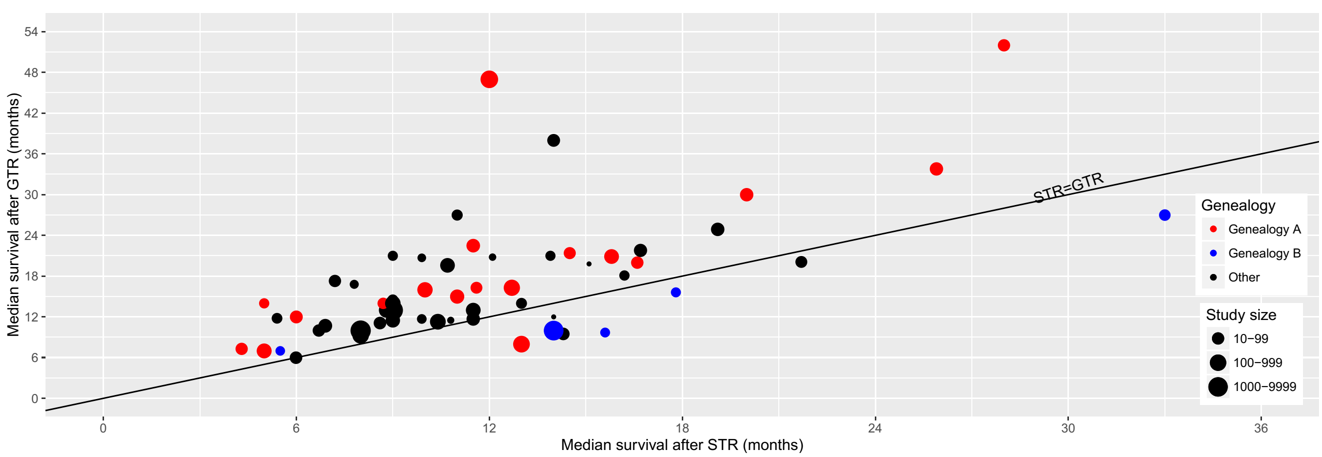

Fig. 3 Studies demonstrating extent of surgical resection of malignant brain tumors and median survival benefit (in months).GTR: gross total resection; STR: subtotal resection. Genealogy A (studies contributed by the neurosurgeon genealogy); genealogy B (studies contributed by the radiation oncology genealogy)

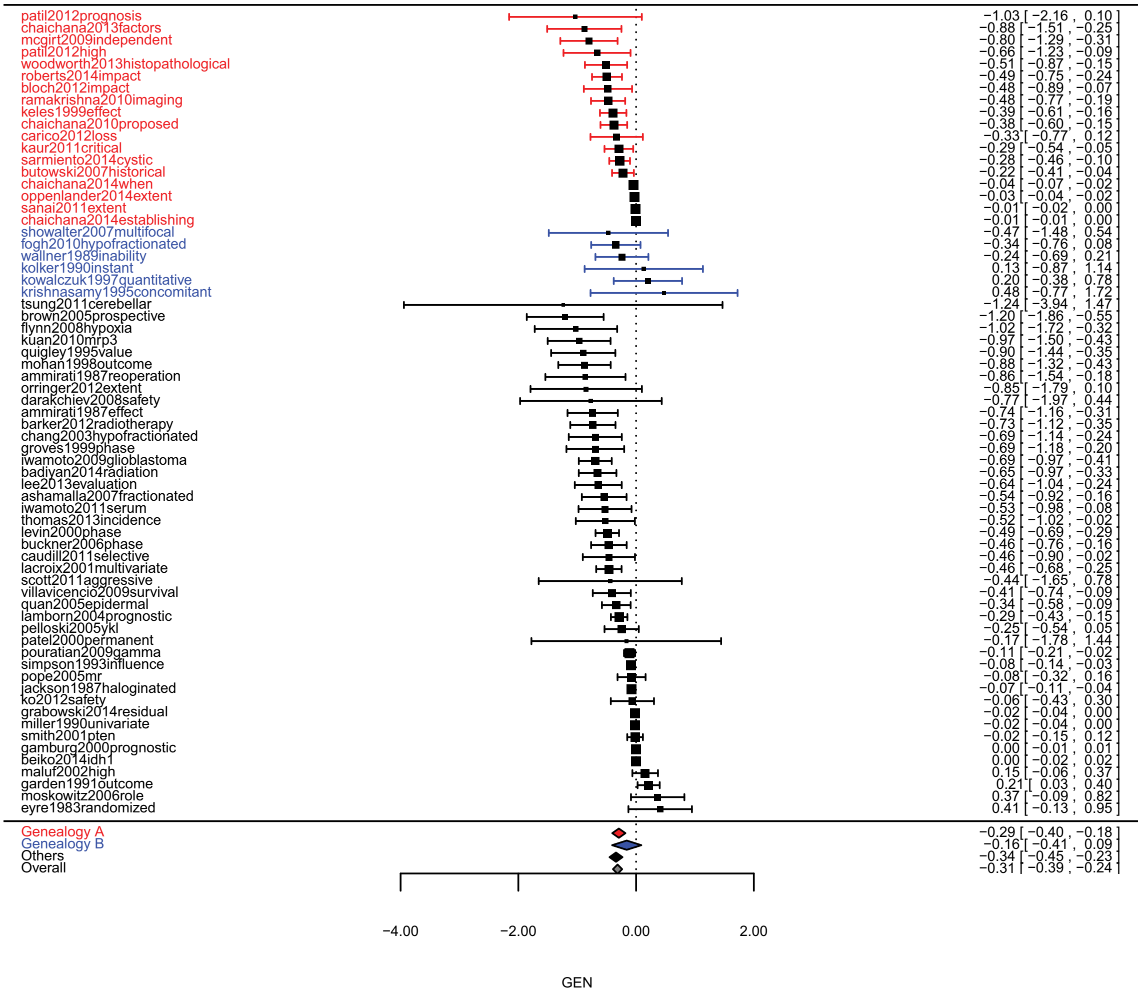

Fig. 4 Forest plot demonstrating OR for hazard of death in glioblastoma patients who underwent GTR relative to those who underwent STR. Red: studies from the members of neurosurgeon genealogy; blue: studies from the members of radiation oncology genealogy; black: studies contributed by other independent groups. All values are in logarithmic scale

published by the neurosurgery and the radiation oncology genealogies differed so much that meta-analysis of articles from each genealogies yield opposite conclusions. The consistency of the results between our previous [14] and current study builds a strong case for the influence of genealogy on published literature.

The notion that one's intellectual efforts may be influenced by mentors is well-appreciated in art, music, and philosophy [2, 27, 34]. Our results suggest that the research efforts in medicine may be similarly influenced. While medical investigations are generally conceptualized with objectivity as the ultimate goal, it is important to recognize that these investigations are fundamentally and profoundly human endeavors, subject to pitfalls related to the intrinsic nature of the human psyche. For instance, membership in a genealogy may predispose a trainee, whether consciously or unconsciously, to adopt the mentor's preferences for particular views, study design, or methods. If these elements affect study outcome, then genealogy may impact publication of certain conclusions, independent of their validity. We propose the term "genealogy bias" to describe this phenomenon. Such bias may confound the peer-reviewed literature that collectively guides clinical decision making. Understanding the influences of genealogy on the landscape of medical literature represents the first step toward mitigating these influences and a stride toward objectivism, to the extent that objectivism is possible in human endeavors.

There are several limitations to the interpretation of our study. First, our study was designed to examine the association between genealogy and publication results. As associations do not necessarily imply causation, we cannot make definitive statements on whether genealogy is contaminating or contributing to publication effects. Further, our study does not make definitive statements about the underlying efficacy of gross total resection. Since analysis would require a careful assessment of the quality of the various studies (i.e., correct distinctions made between STR and GTR, correct inclusion criteria for neurosurgical vs. radio-oncological studies, so as to not compare apples with oranges), which was not performed in our study.

Conclusion

Meta-analysis of articles contributed by authors belonging to different medical academic genealogies yielded distinct and contradictory pooled point-estimates, suggesting a form of "genealogy bias" that influences the landscape of the peer-reviewed literature. Understanding and accounting for this form of bias is essential in our strides toward an objective assessment of the scientific literature.

Compliance with ethical standards

Informed consent For this type of study, formal consent is not required.

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval A formal approval by the institutional ethics committee was not required for this study since all articles, journals, and author data were collected from publicly available sources.

Animal experiments Ethical approval: This article does not contain any studies with animals performed by any of the authors.

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