our experience, this might potentially delay the progression of conjunctivalization and scarring but cannot totally prevent it. Aniridic keratopathy has a variable phenotype; we have seen patients with stable AAK for long periods of medical management and other patients with faster progression, so it is difficult to measure the effect of autologous serum.

All in all, management of AAK is challenging. Although we have tried to provide evidence-based data and algorithms for the management of AAK,[6] there are many questions and controversies that need to be resolved with future studies.

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## Comment on: Racial, Ethnic, and Socioeconomic Disparities in Retinoblastoma Enucleation: A Population-Based Study, SEER 18 2000–2014

EDITOR:

I READ WITH INTEREST THE ARTICLE BY RAJESHUNI AND associates[1] on socioeconomic disparities in retinoblastoma (RB) treatment. The authors reported that the rate of enucleation was higher in children of nonwhite race and lower socioeconomic status (SES). They concluded that "these disparities appear unrelated to delayed diagnosis." The implication is that a nonpoor nonminority child would receive advanced globe-saving therapies such as intravitreal or intra-arterial chemotherapy, and a poor minority child with an identical tumor burden would be enucleated.

The International Classification of Retinoblastoma (ICRB) was published in 2005[2] and superseded the Reese-Ellsworth classification. The ICRB classifies tumor burden into 5 groups (A–E), which are defined by the size and location of the tumor(s) within the eye relative to the optic disc and foveola; presence and extent of subretinal fluid; location and extent of vitreous or subretinal seeding; and additional findings such as anterior segment invasion. The ICRB predicts chemoreduction success.[3] Tumor group is the strongest predictor of the need for primary or secondary enucleation. A delay in detection or referral allows for tumor growth and the development of vitreous and subretinal seeding, leading to a higher group at diagnosis.

Rajeshuni and associates used data from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program. SEER's Extent of Disease (EOD) database codes fit poorly with the ICRB (https://staging.seer.cancer.gov/eod_public/input/1.0/retinoblastoma/eod_primary_tumor). There appears to be no code consistent with Group A. Group B tumors are ≤1.5 mm from the optic disc or ≤3 mm from the center of the foveola, but the EOD codes use only 1.5 mm from both anatomic landmarks. Two codes include vitreous or subretinal seeding but not extent or location, therefore the database cannot distinguish between Group C (seeding ≤3 mm from tumor margin) and Group D (seeding >3 mm from tumor margin). Globe salvage is much higher in Group C eyes.[3] Conversely, there are 5 codes that apply to Group E. Since most unilateral RB Group E eyes are primarily enucleated, splitting them into 5 separate codes is of minimal predictive utility. Further, pathologic staging takes precedence over clinical staging in the EOD system; however, pathologic staging has no effect on the clinical decision to enucleate, since it is unknown. Finally, the start of the study period precedes the introduction of the ICRB by 5 years, and the old Reese-Ellsworth RB classification system is entirely different from the ICRB.[3] Given these contradictions and limitations, it is unlikely that the EOD has been accurately and consistently reported to the SEER database over the entire study period.

The authors admit that statistical significance between rates of enucleation and SES groups was "largely not met." When combined with the questionable validity of the primary data on disease burden, I believe the authors have over-reached in their conclusion that children of low SES are more likely to be enucleated for reasons other

than a delay in diagnosis and greater tumor burden at presentation.

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# Reply to Comment on: Racial, Ethnic, and Socioeconomic Disparities in Retinoblastoma Enucleation: A Population-Based Study, SEER 18 2000–2014

REPLY

WE ARE THANKFUL FOR THE OPPORTUNITY TO RESPOND TO the issues raised in Dr Brown's letter. We would also like to thank Dr Brown for these comments and for expressing interest in our work.[1]

Dr Brown raises concerns regarding the validity of SEER stage data. Dr Brown notes SEER Extent of Disease (EOD) does not fully correspond with the International Classification of Retinoblastoma (ICRB). SEER historic stage, used in our study, is based on EOD and categorized as localized, regional, or distant. Therefore, Dr Brown's point further implies SEER staging may be insufficiently granular, as all ICRB categories will correspond primarily to "localized" SEER staging. In such case, one would expect SEER stage to not statistically qualify as a confounder in regression modeling. However, in our analysis, SEER stage not only met criteria, but subsequent adjustment showed an independently significant association between race, ethnicity, socioeconomic status (SES), and enucleation.

When discussing the validity of SEER stage data, Dr Brown notes that pathologic staging takes precedence over clinical staging in the EOD system. However, SEER historic stage used in our study combines EOD data with clinical data, representing a more wholistic perspective.

We appreciate and acknowledge that differences between ICRB and SEER staging is a limitation of our study, particularly when evaluating delayed diagnosis as an etiology of racial, ethnic, and socioeconomic disparities. However, the primary objective of our study was first and foremost to examine whether disparities are present at all, which both our descriptive and regression results confirm. To evaluate delayed diagnosis as an etiology, we examined for effect modification between stage and race, ethnicity, and SES but observed none. Granted, specific staging, chemotherapy, and primary vs secondary enucleation data are integral to fully understanding treatment courses. These are important limitations, which we acknowledge in our manuscript.[1] Therefore, though it is difficult to definitively exclude delayed diagnosis as a driver of treatment disparities, factors like geographic practice patterns and healthcare access should not be overlooked.

Of note, SEER is an epidemiologic registry aimed at capturing oncologic data across various institutions,[2,3] some of which lack expertise in ocular oncology and retinoblastoma and therefore may not use ICRB. With this context, the racial, ethnic, and socioeconomic differences in SEER become even more meaningful.

Dr Brown finally comments that statistical significance between enucleation and racial, ethnic, and socioeconomic groups was described as "largely not met." However, the statement Dr Brown is referring to specifically addresses treatment trends over time. Enucleation differences in both descriptive and regression analyses were statistically significant. Furthermore, although statistical significance was not met in our treatment trend analysis, nonwhite, Hispanic, and socioeconomically disadvantaged children were consistently enucleated in greater proportions from 2000 to 2014, despite overall decreases in enucleation rates.

Overall, we believe the strengths of our study outweigh the limitations. Although further research is certainly required to better delineate why racial, ethnic, and socioeconomic disparities in treatment patterns occur, our manuscript is an important start, highlighting that other factors beyond delayed diagnosis should be considered and addressed.

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