American Academy of Ophthalmology
The Eye M.D. Association

# Prevention of Retinal Detachment in Stickler Syndrome

## *The Cambridge Prophylactic Cryotherapy Protocol*

*Gregory S. Fincham, MRCOphth,[1] Laura Pasea, MSc,[2] Christopher Carroll, PhD,[3] Annie M. McNinch, SRN,[1,4] Arabella V. Poulson, FRCOphth,[1] Allan J. Richards, PhD,[4,5] John D. Scott, FRCOphth,[1] Martin P. Snead, MD, FRCOphth[1,4]*

***Purpose:*** The Stickler syndromes are the most common causes of inherited and childhood retinal detachment; however, no consensus exists regarding the effectiveness of prophylactic intervention. We evaluate the long-term safety and efficacy of the Cambridge prophylactic cryotherapy protocol, a standardized retinal prophylactic treatment developed to prevent retinal detachment arising from giant retinal tears in type 1 Stickler syndrome.

***Design:*** Retrospective comparative case series.

***Participants:*** Four hundred eighty seven patients with type 1 Stickler syndrome.

***Methods:*** Time to retinal detachment was compared between patients who received bilateral prophylaxis and untreated controls, with and without individual patient matching. Patients receiving unilateral prophylaxis (after fellow eye retinal detachment) were similarly compared with an appropriate control subgroup. Individual patient matching ensured equal age and follow-up between groups and that an appropriate control (who had not suffered a retinal detachment before the age at which their individually matched treatment patient underwent prophylactic treatment) was selected. Matching was blinded to outcome events. Individual patient matching protocols purposely weighted bias against the effectiveness of treatment. All treatment side effects are reported.

***Main Outcome Measures:*** Time to retinal detachment and side effects occurring after prophylactic treatment.

***Results:*** The bilateral control group (n = 194) had a 7.4-fold increased risk of retinal detachment compared to the bilateral prophylaxis group (n = 229) (hazard ratio [HR], 7.40; 95% confidence interval [CI], 4.53−12.08; $P<0.001$); the matched bilateral control group (n = 165) had a 5.0-fold increased risk compared to the matched bilateral prophylaxis group (n = 165) (HR, 4.97; 95% CI, 2.82−8.78; $P<0.001$). The unilateral control group (n = 104) had a 10.3-fold increased risk of retinal detachment compared to the unilateral prophylaxis group (n = 64) (HR, 10.29; 95% CI, 4.96−21.36; $P<0.001$); the matched unilateral control group (n = 39) had a 8.4-fold increased risk compared to the matched unilateral prophylaxis group (n = 39) (HR, 8.36; 95% CI, 3.24−21.57; $P<0.001$). No significant long-term side effects occurred.

***Conclusions:*** In the largest global cohort of type 1 Stickler syndrome patients published, all analyses indicate that the Cambridge prophylactic cryotherapy protocol is safe and markedly reduces the risk of retinal detachment. *Ophthalmology 2014;121:1588-1597 © 2014 by the American Academy of Ophthalmology.*

*Supplemental video is available at www.aaojournal.org.*

The Stickler syndromes are among the most frequently inherited connective tissue disorders, with an estimated incidence of 1:7500 live births; they are the most common cause of inherited and childhood retinal detachment.[1,2] Originally considered a single gene disorder, at least 6 subgroups have been characterized according to genetic abnormalities of type II, IX, or XI collagen.[3−10] These structural proteins are principally and collectively expressed in the eye and in articular and hyaline cartilage. Affected patients present with premature arthropathy and classic orofacial, auditory, and ocular features.[1,11−13] More than 80% of affected patients have type 1 Stickler syndrome.[14,15]

To date, no prospective, randomized trial investigating the prevention of nonsyndromic retinal detachment has been conducted.[16] Evidence informing current clinical practice does not support prophylactically treating asymptomatic breaks or lattice degeneration.[17] Prophylactic treatment may prevent tear formation within treated areas but does not preclude or predict tears occurring elsewhere in the retina.[18]

Type 1 Stickler syndrome, however, lends itself as a prime model for retinal prophylaxis because it is genetically defined and identifiable[15,19] and recognized as the subgroup with the highest risk of retinal detachment.[2] Patients typically develop retinal detachments from giant retinal tear formation at the



ISSN 0161-6420/14/$ - see front matter
http://dx.doi.org/10.1016/j.ophtha.2014.02.022

pars plana[5] and this predisposition offers the unique opportunity for a specific prophylactic strategy to prevent such tears from progressing to retinal detachment.

The Cambridge prophylactic cryotherapy protocol was developed with the specific rationale of preventing retinal detachment arising from giant retinal tears. For over 37 years, prophylaxis has been offered to all type 1 Stickler syndrome patients and deployed in a standardized, uniform manner.[20] We report results on the largest global cohort of type 1 Stickler syndrome patients with regard to the efficacy and safety of this standardized protocol in reducing the risk of retinal detachment and blindness.

## Methods

### Patients and Study Design

Patients with type 1 Stickler syndrome (Online Mendelian Inheritance in Man no. 108300) were retrospectively identified from the Vitreoretinal Research Unit database, clinical records, and research pedigree files, the diagnosis being made according to published clinical criteria.[1] All patients who received any form of nonstandardized prophylaxis (including any previous focal laser or cryotherapy to identified retinal breaks or areas of lattice degeneration, previous 360° prophylactic laser retinopexy, previous prophylactic scleral buckling, or previous 360° prophylactic cryotherapy undertaken in other eye units, but completed posterior to the oral retina [equatorially]) were excluded. Only patients with both eyes available for study were included.

Mutation analysis was confirmed in the majority of cases and in every case where vitreous phenotyping was not possible due to previous bilateral vitrectomy.

Patients were divided into 4 groups for analysis. (1) *The bilateral prophylaxis group* comprised patients who had suffered no previous retinal detachment and had undergone the Cambridge prophylactic cryotherapy protocol to both eyes. (2) *The bilateral control group* comprised patients who had not undergone the prophylactic protocol (patients may have suffered unilateral, bilateral, or no previous retinal detachment). (3) *The unilateral prophylaxis group* comprised patients who had undergone the prophylactic protocol after retinal detachment in their fellow eye. (4) *The unilateral control group* comprised patients who had not undergone the prophylactic protocol but suffered previous unilateral or bilateral retinal detachment (control subgroup).

### Primary Outcome Measures

We measured (1) time to retinal detachment (this also included any case requiring further retinopexy after prophylactic cryotherapy but without formal retinal detachment repair) and (2) side effects resulting from prophylactic treatment.

Outcomes between groups receiving the Cambridge prophylactic cryotherapy protocol and their respective controls were retrospectively compared. To account for differences in age and follow-up duration, individual patient matching was undertaken between the bilateral prophylaxis and bilateral control groups, and the unilateral prophylaxis and unilateral control groups (see matching protocols below). To facilitate equal age at last review between matched pairs, a control group follow-up "cropping" step was implemented; any retinal detachment that occurred during this "cropped" period was discarded because it did not occur during the matched follow-up time. Matching created comparison groups exactly equal in number, age, and follow-up duration, and in which patients receiving prophylaxis did so before any potential retinal detachment event in their individually matched control.

### Matching Protocol 1: Bilateral Prophylaxis versus Bilateral Control Group

1. All bilateral prophylaxis group patients with both eyes available for analysis were included for matching.
2. Observers were blinded to prophylactic cryotherapy failure status.
3. All bilateral prophylaxis group patients were arranged in descending order of length of follow-up after prophylactic cryotherapy. Those patients with less than 1 year of follow-up after prophylactic cryotherapy were excluded from further analysis.
4. The bilateral prophylaxis group patient with the longest follow-up after prophylactic cryotherapy was selected for matching. The age at which this patient underwent prophylactic cryotherapy and their age at last review were noted for subsequent control matching.
5. All bilateral control group patients with both eyes available for analysis were included for matching.
6. From the bilateral control group, all patients who had their first retinal detachment at an age equal to or less than the age at which the selected bilateral prophylaxis group patient had their prophylactic cryotherapy were excluded from the current round of matching (but returned to the bilateral control group for subsequent rounds of matching).
7. Observers were blinded to the retinal detachment status in this selected subgroup of bilateral control group patients available for the current round of matching.
8. From this subgroup, the patient with an equal or next closest (but older) age at last review was selected to be matched to the selected bilateral prophylaxis group patient (if no control group patient had an equal or older age at last review, the selected prophylaxis group patient was considered unmatched and excluded from further matching analysis; analysis would then restart from step 4).
9. Once matched, these patients were removed from their respective bilateral prophylaxis and bilateral control groups and made unavailable for further matching.
10. Steps 4 through 9 were repeated, using the bilateral prophylaxis group patient with the next longest post-prophylactic cryotherapy follow-up as the next selected case for matching.
11. Matching continued until all bilateral prophylaxis group patients had been matched to an appropriate bilateral control or were excluded from matching.
12. The matched bilateral prophylaxis and bilateral control group patients were unmasked with regard to prophylactic cryotherapy failure and retinal detachment status, respectively.
13. Individual patient ages at last review in the matched bilateral control group (purposely selected to be equal in age or older) were compared with the individual patient ages at last review in the corresponding matched bilateral prophylaxis group and "cropped" accordingly to equal the age at last review of their match. Any retinal detachment events that occurred in the matched bilateral control group patients during this "cropped" period were excluded from further analysis.
14. Prevalence of retinal detachment was then compared between the matched bilateral prophylaxis and "cropped" matched bilateral control groups.

### Matching Protocol 2: Unilateral Prophylaxis versus Unilateral Control Group

1. All unilateral prophylaxis group patients with both eyes available for analysis were included for matching.

2. Observers were blinded to prophylactic cryotherapy failure status.
3. All unilateral prophylaxis group patients were arranged in descending order of length of follow-up after prophylactic cryotherapy. Those patients with less than 1 year of follow-up after prophylactic cryotherapy were excluded from further analysis.
4. The unilateral prophylaxis group patient with the longest follow-up after prophylactic cryotherapy was selected for matching. The age at which this patient suffered their first retinal detachment (untreated eye), the age at which they underwent prophylactic cryotherapy (treated eye), and their age at last review were noted for subsequent control matching.
5. All unilateral control group patients with both eyes available for analysis were included for matching.
6. Observers were blinded to retinal detachment status in the second eye.
7. The unilateral control group patient with an age of first retinal detachment closest to that of the selected unilateral prophylaxis group patient's age of first retinal detachment was selected for further matching (if there was a difference of greater than 3 years, the selected unilateral prophylaxis group patient was considered unmatched and excluded from further matching analysis; analysis would then restart from step 4).
8. If the selected unilateral control group patient's age at last review was equal to or older than the selected unilateral prophylaxis group patient's age at last review, they were considered for the final matching step (if the age at final review was less than the selected unilateral prophylaxis group patient's age at last review, the matching process returned to step 7, selecting the unilateral control group patient with the next closest age of first retinal detachment).
9. The final matching step involved unmasking the selected unilateral control group patient's retinal detachment status in their second eye. If the selected unilateral control group patient did not have a second retinal detachment event or the age at which they had their second retinal detachment was older than the age at which the selected unilateral prophylaxis group patient had their prophylactic cryotherapy, they were considered an appropriate match (if the selected unilateral control group patient's age at second retinal detachment was the same or younger than the age at which the selected unilateral prophylaxis group patient had their cryotherapy, the match was considered inappropriate and the matching process returned to step 7, selecting the unilateral control group patient with the next closest age of first retinal detachment).
10. Once matched, these patients were removed from their respective unilateral prophylaxis and unilateral control groups and made unavailable for further matching.
11. Steps 4 through 10 were repeated using the unilateral prophylaxis group patient with the next longest follow-up after prophylactic cryotherapy as the next selected case for matching.
12. Matching continued until all unilateral prophylaxis group patients had been matched to an appropriate control or were excluded from matching.
13. The matched unilateral prophylaxis group patients were unmasked with regard to prophylactic cryotherapy failure.
14. Individual patient ages at last review in the matched unilateral control group (purposely selected to be equal in age or older) were compared with the individual patient ages at last review in the corresponding matched unilateral prophylaxis group and "cropped" accordingly to equal the age at last review of their match. Any retinal detachment event that occurred in the matched unilateral control group patients during this "cropped" period were excluded from further analysis.
15. The prevalence of retinal detachment was then compared between the matched unilateral prophylaxis and "cropped" matched unilateral control groups.

### The Cambridge Prophylactic Cryotherapy Protocol[20]

Informed, written consent was obtained from all patients electing to undergo prophylactic treatment. Under general anesthesia, carefully monitored 360° transconjunctival prophylactic cryotherapy was applied in a contiguous ribbon at the junction of the postoral retina with the pars plana (Fig 1; procedure Video available at www.aaojournal.org).

### Side Effects

The occurrence of the following prophylaxis side effects was assessed: change in pre- and postoperative visual acuity, lid and conjunctival inflammation, accommodation insufficiency, discomfort, photophobia, macular pucker, and any perioperative surgical complication. Anesthetic recovery records were reviewed for episodes of nausea or vomiting.

### Statistical Analysis

Kaplan–Meier survival curves and log-rank tests were used to compare time-to-event outcomes between patients. For the bilateral prophylaxis versus bilateral control group, the primary outcome was time from birth to first retinal detachment. However, for the matched bilateral prophylaxis versus matched bilateral control group, it was time from cryotherapy (or the corresponding time in the individually matched control) to first retinal detachment. For the unilateral prophylaxis versus unilateral control group, the primary outcome was time from first retinal detachment to second retinal detachment. However, for the matched unilateral prophylaxis versus matched unilateral control group, it was time from cryotherapy (or the corresponding time in the individually matched control) to second retinal detachment. Sex-adjusted hazard ratios for treatment effect and 95% confidence intervals (CIs) were calculated using Cox proportional hazards regression models. All statistical tests were 2-sided and used a 5% significance level. Analyses were completed using SPSS software 21.0 (IBM Corp., Armonk, NY).

## Results

Four hundred eighty-seven patients with type 1 Stickler syndrome from 239 family pedigrees met the inclusion criteria; 229 underwent bilateral prophylaxis, 64 underwent unilateral prophylaxis, and 194 received no prophylactic intervention (104 of whom qualified for the unilateral control subgroup). Of these, 426 patients (87.5%) were tested for *COL2A1* mutations; the mutation detection rate using the Cambridge 2-stage diagnostic screening strategy[19] was 96.9% at the time of study completion. Demographic details are given in Table 1.

### Bilateral Prophylaxis versus Bilateral Control Group

The prevalence of retinal detachment in the bilateral prophylaxis group was 8.3% (19/229), of which 7.9% (18/229) were unilateral

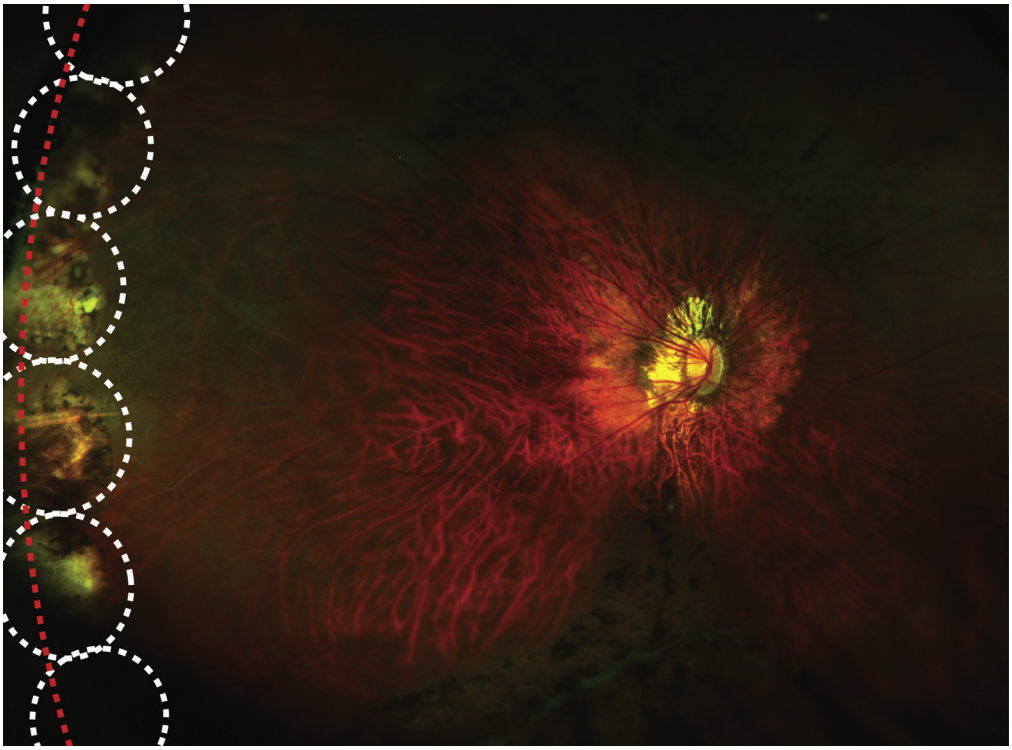

**Figure 1.** Noncontact, high-resolution ultrawide-field fundal photography, annotated to demonstrate the standardized anterior positioning of retinal cryopexy applied during the Cambridge prophylactic cryotherapy protocol. Individual cryotherapy applications (white dotted circles) touch shoulder to shoulder and include the ora serrata (dotted red line).

and 0.4% (1/229) bilateral. The prevalence of retinal detachment in the bilateral control group was 53.6% (104/194), of which 10.3% (20/194) were unilateral and 43.3% (84/194) bilateral (Fig 2). Of the 20 retinal detachment events occurring after prophylaxis, 12 required surgical repair and 8 were managed with additional retinopexy alone; all 188 control group retinal detachments required formal surgical repair.

The median time to first retinal detachment was 18.28 years (95% CI, 14.92−21.63) in the bilateral control group; a median time was not reached in the bilateral prophylaxis group (Fig 3A). The hazard ratio of having a retinal detachment without prophylaxis, based on treatment effect adjusted for sex, was 7.40 (95% CI, 4.53−12.08; $P<0.001$) (Table 2).

## Matched Bilateral Prophylaxis versus Matched Bilateral Control Group

The individual matching protocol resulted in 165 patients with equal age at last review and follow-up duration being paired for comparison. The prevalence of retinal detachment in the matched bilateral prophylaxis group was 9.1% (15/165), of which 8.5% (14/165) were unilateral and 0.6% (1/165) bilateral. The prevalence of retinal detachment in the matched bilateral control group was 37.0% (61/165), of which 16.4% (27/165) were unilateral and 20.6% (34/165) bilateral (Fig 2). Of the 16 retinal detachment events occurring after prophylaxis, 12 required surgical repair and 4 were managed with additional retinopexy alone; all 95 matched control group retinal detachments required formal surgical repair. Before "cropping," the prevalence of retinal detachment in the matched bilateral control group was 61.8% (102/165); 89 retinal detachment events were "cropped" and omitted from analysis.

The median time to retinal detachment was 16.41 years (95% CI, 5.31−27.51) in the matched bilateral control group; a median time was not reached in the matched bilateral prophylaxis group (Fig 3B). The hazard ratio of having a retinal detachment without prophylaxis, based on treatment effect adjusted for sex, was 4.97 (95% CI, 2.82−8.78; $P<0.001$) (Table 2).

## Unilateral Prophylaxis versus Unilateral Control Group

The prevalence of second eye retinal detachment in the unilateral prophylaxis group was 12.5% (8/64) compared with 80.8% (84/104) in the unilateral control group (Fig 2). Of the 8 retinal detachment events occurring after prophylaxis, 6 required surgical repair and 2 were managed with additional retinopexy alone; all 84 second eye retinal detachments in the control group required formal surgical repair.

The median time to second eye retinal detachment was 4.00 years (95% CI, 2.17−5.83) in the unilateral control group compared with 51.60 years (95% CI, 13.29−88.83) in the unilateral prophylaxis group (Fig 3C). The hazard ratio of having a second eye retinal detachment without prophylaxis, based on treatment effect adjusted for sex, was 10.29 (95% CI, 4.96−21.36; $P<0.001$) (Table 2).

## Matched Unilateral Prophylaxis versus Matched Unilateral Control Group

The individual matching protocol resulted in 39 patients with equal age at last review and follow-up duration being paired for comparison. The prevalence of second eye retinal detachment in the matched unilateral prophylaxis group was 15.4% (6/39) compared

Table 1. Matched and Unmatched Prophylactic and Control Group Demographics

| Group | No. of Patients | Sex Ratio (M:F) | Mean Age (SD) at Last Review (yrs) | Mean Age (SD) at First Retinal Detachment (yrs) | Mean Age (SD) at Second Retinal Detachment (yrs) | Mean Age (SD) at Prophylaxis (yrs) | Mean (SD) Follow-up after Prophylaxis (yrs) |
|---|---|---|---|---|---|---|---|
| **Bilateral prophylaxis group** | 229 | 104:125 | 20.8 (16.9) | — | — | 14.5 (15.9) | 6.3 (6.4) |
| No RD | 210 | 92:118 | 19.6 (16.6) | — | — | 13.7 (15.3) | 5.9 (6.0) |
| Unilateral RD | 18 | 11:7 | 34.6 (19.6) | 29.3 (19.4) | — | 24.1 (20.4) | 10.6 (9.0) |
| Bilateral RD | 1 | 1:0 | 10.9 | 4.19 | 4.19 | 4.0 | 6.8 |
| **Bilateral control group** | 194 | 95:99 | 31.3 (21.6) | — | — | — | — |
| No RD | 90 | 38:52 | 18.6 (18.6) | — | — | — | — |
| Unilateral RD | 20 | 9:11 | 37.0 (24.6) | 24.8 (20.4) | — | — | — |
| Bilateral RD | 84 | 48:36 | 43.4 (15.7) | 15.2 (10.4) | 22.0 (13.8) | — | — |
| **Matched bilateral prophylaxis group** | 165 | 78:87 | 19.8 (15.0) | — | — | 11.6 (12.9) | 7.7 (6.2) |
| No RD | 150 | 68:82 | 18.8 (14.3) | — | — | 10.9 (12.3) | 7.8 (6.0) |
| Unilateral RD | 14 | 9:5 | 31.9 (17.5) | 25.5 (16.8) | — | 19.1 (17.0) | 12.8 (9.0) |
| Bilateral RD | 1 | 1:0 | 10.9 | 4.19 | 4.19 | 4.0 | 6.8 |
| **Matched bilateral control group** | 165 | 83:82 | 19.8 (15.0) | — | — | — | — |
| No RD | 104 | 48:56 | 19.5 (15.8) | — | — | — | — |
| Unilateral RD | 34 | 17:10 | 18.4 (13.2) | 15.2 (13.1) | — | — | — |
| Bilateral RD | 27 | 18:16 | 22.0 (14.1) | 14.8 (12.1) | 16.9 (12.0) | — | — |
| **Unilateral prophylaxis group** | 64 | 37:27 | 33.2 (18.0) | 16.9 (13.5) | — | 22.9 (15.7) | 10.1 (10.4) |
| Unilateral RD | 56 | 31:25 | 32.2 (18.3) | 17.4 (13.9) | — | 23.3 (15.6) | 9.0 (9.7) |
| Bilateral RD | 8 | 6:2 | 40.1 (14.2) | 13.1 (10.2) | 27.8 (15.8) | 20.0 (17.6) | 19.2 (11.8) |
| **Unilateral control group** | 104 | 57:47 | 42.2 (17.8) | 17.0 (13.4) | — | — | — |
| Unilateral RD | 20 | 9:11 | 37.0 (24.6) | 24.8 (20.4) | — | — | — |
| Bilateral RD | 84 | 48:36 | 43.4 (15.7) | 15.2 (10.4) | 22.0 (13.8) | — | — |
| **Matched unilateral prophylaxis group** | 39 | 23:16 | 31.4 (16.3) | 14.2 (11.8) | — | 17.8 (13.3) | 13.7 (11.1) |
| Unilateral RD | 33 | 19:14 | 30.7 (17.0) | 14.9 (12.6) | — | 19.0 (14.0) | 11.7 (10.2) |
| Bilateral RD | 6 | 4:2 | 35.5 (12.4) | 10.6 (5.7) | 21.0 (9.6) | 11.1 (5.9) | 24.6 (9.8) |
| **Matched unilateral control group** | 39 | 27:12 | 31.4 (16.3) | 14.4 (11.6) | — | — | — |
| Unilateral RD | 12 | 9:3 | 28.8 (16.7) | 13.8 (13.2) | — | — | — |
| Bilateral RD | 27 | 18:9 | 32.6 (16.31) | 14.7 (11.1) | 23.4 (14.1) | — | — |

M:F = male:female; RD = retinal detachment; SD = standard deviation.

with 69.2% (27/39) in the matched unilateral control group (Fig 2). Of the 6 retinal detachment events occurring after prophylaxis, 5 required surgical repair and 1 was managed with additional retinopexy alone; all 27 matched control group second eye retinal detachments required formal surgical repair. Before "cropping," the incidence of second eye retinal detachment in the matched unilateral control group was 87.2% (34/39); 7 second eye retinal detachments were "cropped" and omitted from analysis.

The median time to second eye retinal detachment was 5.93 years (95% CI, 0.00−13.66) in the matched unilateral control group; a median time was not reached in the matched unilateral prophylaxis group (Fig 3D). The hazard ratio of having a second eye retinal detachment without prophylaxis, based on treatment effect adjusted for sex, was 8.36 (95% CI, 3.24−21.57; $P<0.001$) (Table 2).

## Prophylaxis Failure

Failure of retinal cryotherapy prophylaxis occurred in 9.0% (27/299) of patients receiving treatment. The average age at the time of the cryotherapy procedure in the failed cases was 21.5 years (range, 2.4−59.6 years; standard deviation, 19.2 years) and the average time from treatment to prophylaxis failure was 5.6 years (range, 0.1−22.4 years; standard deviation, 7.2 years).

Eighteen eyes required formal surgical retinal detachment repair. Six of these cases were due to retinal breaks identified posteriorly and 5 cases were attributed to treated anterior breaks being lifted off or extending through the cryotherapy treatment barrier. There was a single case treated for a break that developed at the junction of the posterior edge of the cryotherapy treatment and untreated retina. No data were available for 6 cases requiring surgical retinal detachment repair, 2 of which presented with associated proliferative vitreoretinopathy owing to delayed presentation after retinal detachment.

Of the 10 cases of prophylaxis classed as "failure" but managed with additional retinopexy alone, 7 cases were for retinal breaks occurring posteriorly (3 of which had associated subretinal fluid), 2 cases were for localized retinal detachments that were being held by the cryotherapy treatment (but a further retinopexy barrier was applied for additional security), and 1 case was for a suspected break at the junction of the posterior edge of the cryotherapy-treated and untreated retina.

All failure cases were unilateral except one bilateral case, which developed in a 4-year-old child with a coexisting diagnosis of Down syndrome; the operation record documented concerns regarding the appearance of the peripheral retina at the time of cryotherapy. Bilateral prophylactic cryotherapy failure was diagnosed 51 days after treatment; the right retinal detachment had

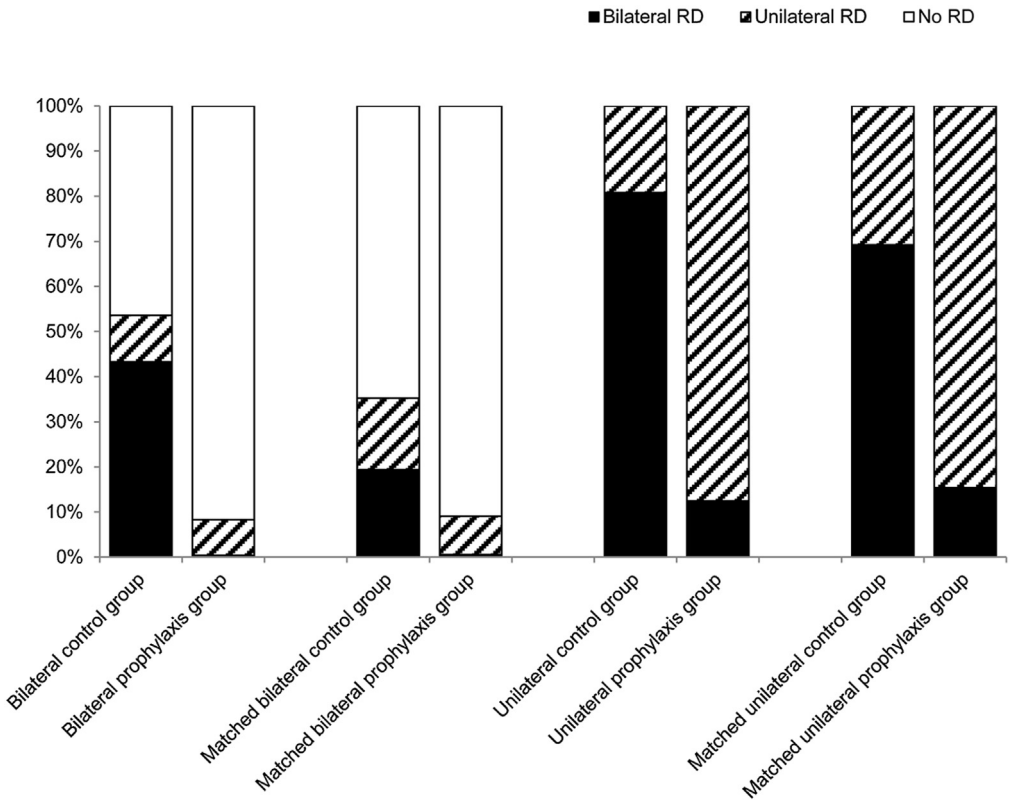


**Figure 2.** Prevalence of unilateral and bilateral retinal detachments (RDs) in matched and unmatched prophylactic and control groups.

associated proliferative vitreoretinopathy and the left retinal detachment was secondary to an inferior horseshoe tear located posteriorly to the treatment barrier.

### Side Effects

The Cambridge prophylactic cryotherapy protocol caused no reported significant long-term side effects in any of the 293 patients who underwent treatment. In particular, no cases of choroidal hemorrhage, macular pucker, or unexplained visual loss occurred.

The mean logarithm of the minimum angle of resolution visual acuity before and after prophylaxis, recorded in 414 eyes (182 bilateral prophylactic and 50 unilateral prophylactic group patients), was 0.29 (range, -0.18−1.80; standard deviation, 0.29) and 0.25 (range, -0.18−1.30; standard deviation, 0.24), respectively. At review, visual acuity was the same or better than preoperative acuity readings in all patients, except for a single 38.4-year-old patient with a previously diagnosed Foster Fuch's spot and progressive macular atrophy, who did not regain unilateral preoperative vision. Table 3 summarizes all reported side effects.

## Discussion

The risk of retinal detachment in patients with type 1 Stickler syndrome is very high.[20−23] The oldest patient in the current series to suffer their first retinal detachment was 78.5 years. The median survival time to first retinal detachment in the bilateral control group was 18.3 years, and the median survival time from first to second retinal detachment in the unilateral control group was 4.0 years. The most disturbing cases, however, are the late presentations of preverbal children with inoperable bilateral retinal detachments. Severe visual loss, compounded by the hearing, speech, and mobility problems associated with this disorder, results in a significant, life-long impact on the future of these young people.

Recent development and provision of 2-stage diagnostic screening[19] means that type 1 Stickler syndrome can now be accurately identified and confirmed in over 90% of cases.[15] Further refinement with specialized minigene and multiplex ligation-dependent probe amplification analysis has resulted in a mutation detection rate of 96.9% at the time of completion of this study (Department of Health National Specialist Commissioning Team [NSCT], Stickler Diagnostic Service, unpublished data, June 2011).

Our current practice algorithm for managing patients with Stickler syndrome commences with multidisciplinary team phenotyping to direct which collagen gene is to be sequenced. Identification of a *COL2A1* mutation confirms the clinical diagnosis of type 1 Stickler syndrome and patients are offered genetic counseling. The risk of retinal detachment versus the risks of retinal prophylaxis is discussed with patients and families. Should prophylactic intervention be sought, patients are routinely wait-listed for surgery.

Type 1 Stickler syndrome carries a life-long risk of retinal detachment and prophylaxis is offered to patients of any age. Historically, prophylaxis was only given after the age of 5, when children were considered cooperative enough to accurately phenotype the vitreous on slit-lamp biomicroscopic examination. Currently, predictive molecular

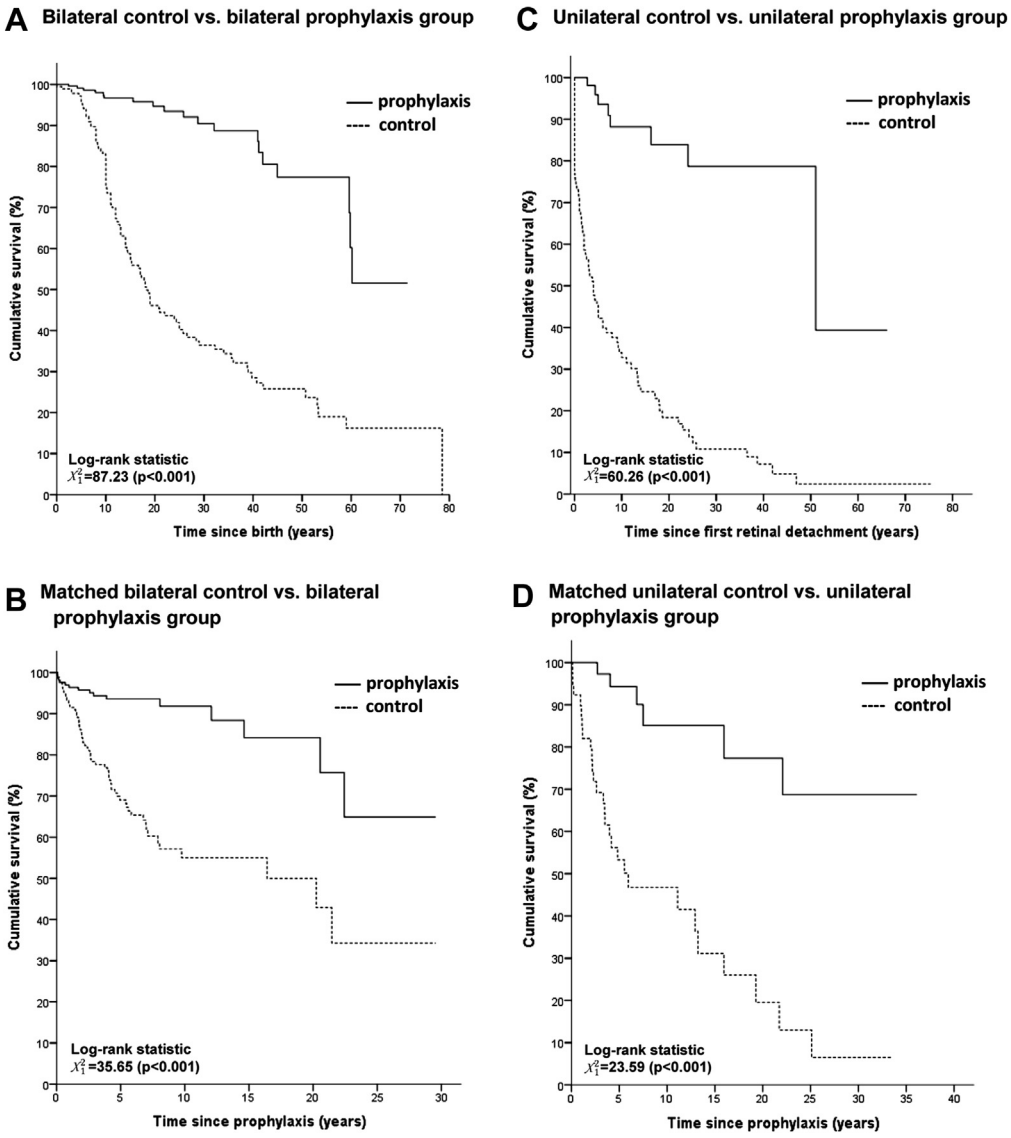


**Figure 3.** Kaplan–Meier survival curves and log-rank test outcomes for matched and unmatched prophylactic and control groups. **A**, Time from birth to first retinal detachment for the bilateral prophylaxis versus bilateral control group. **B**, Time from cryotherapy (or the corresponding time in the individually matched control) to first retinal detachment for the matched bilateral prophylaxis versus matched bilateral control group. **C**, Time from first retinal detachment to second retinal detachment for the unilateral prophylaxis versus unilateral control group. **D**, Time from cryotherapy (or the corresponding time in the individually matched control) to second retinal detachment for the matched unilateral prophylaxis versus matched unilateral control group.

testing in family pedigrees with known mutations allows confirmation of the subtype of the Stickler syndrome at any age, facilitating earlier prophylaxis. Early, accurate diagnosis is essential if prophylaxis is to be offered before retinal detachment occurs. Although rare before 1.5 years of age, the youngest child seen with bilateral retinal detachments was 6 weeks of age; the youngest patient to receive prophylaxis in our series was 10.8 months.

The rationale of the Cambridge prophylactic cryotherapy protocol is to prevent retinal detachment secondary to giant retinal tears; prevention of "conventional" posterior breaks would not be expected or intended. This limitation needs to be clarified to patients consenting to treatment, explaining that the expectation is to substantially reduce (but not eliminate) the risk of retinal detachment.

Cryotherapy rather than prophylactic laser retinopexy was used for every treated patient in this series as past experience has shown it to be safe when deployed according to this specific protocol[20] and to avoid introducing a further confounding variable of a different treatment modality. The results provide the first benchmark against which future treatment modalities or strategies could be compared.

It is accepted that the results of any form of retrospective analysis should be interpreted with caution because they may be more prone to bias; previous studies of prophylaxis in Stickler syndrome are no exception.[20,24,25] Although patients and

Table 2. Unadjusted and Sex-adjusted Hazard Ratios with 95% Confidence Intervals for Matched and Unmatched Prophylactic and Control Groups

| Group | Hazard Ratio* | 95% CI |
|---|---|---|
| Bilateral control vs bilateral prophylaxis (unadjusted) | 7.27* | 4.47–11.87 |
| Bilateral control vs bilateral prophylaxis (sex adjusted) | 7.40* | 4.53–12.08 |
| Matched bilateral control vs matched bilateral prophylaxis (unadjusted) | 4.77* | 2.71–8.40 |
| Matched bilateral control vs matched bilateral prophylaxis (sex adjusted) | 4.97* | 2.82–8.78 |
| Unilateral control vs unilateral prophylaxis (unadjusted) | 10.06* | 4.86–20.84 |
| Unilateral control vs unilateral prophylaxis (sex adjusted) | 10.29* | 4.96–21.36 |
| Matched unilateral control vs matched unilateral prophylaxis (unadjusted) | 6.85* | 2.80–16.75 |
| Matched unilateral control vs matched unilateral prophylaxis (sex adjusted) | 8.36* | 3.24–21.57 |

CI = confidence interval.
*$P<0.001$.

anesthetic records were reviewed on the first postoperative day and 1 month after prophylaxis to evaluate individual responses to treatment and enquire about side effects, it is accepted that because of the retrospective nature of the current study, side effects may be underreported. However, when thoughtfully designed, retrospective studies, such as Lane-Claypon's 1926 seminal investigations into breast cancer risk factors,[26] can contribute vital information that is impossible, impractical, or unethical to ascertain prospectively.[27] Given the inevitable constraints when studying rare genetic disorders, and the results of the current study, it is unlikely a prospective, randomized trial could ever be commissioned to assess the efficacy of retinal prophylaxis in Stickler syndrome.

The observed treatment effect of the current retrospective study is so large it is highly unlikely to be completely due to biases and confounding factors. In fact, the study has been deliberately designed to weight against the benefit of treatment to ensure true treatment effect is underestimated. For example, the outcome measure of retinal detachment in the prophylaxis groups was defined to include retinopexy without surgical repair (any postprophylactic event requiring intervention, however minor), but only included retinal detachment requiring formal surgical repair in the control groups. Although there may be some uncertainty over the precise estimate of treatment effect, outcomes show a clear benefit of prophylactic cryotherapy in reducing the risk of retinal detachment in type 1 Stickler syndrome.

A criticism of previous studies has been appropriate control group selection, with the suggestion that the majority of patients without retinal detachment receive prophylaxis, leaving the major source of control patients as those who have already suffered retinal detachment and incurred the outcome event.[28] This potential bias has been addressed in the current study by creating comparable intervention and control groups; individual patient matching protocols ensured that patients receiving prophylaxis did so before any potential retinal detachment event in their individually matched control. In addition, the prevalence of retinal detachment in the control group for this study (53.6% [104/194]) was lower than published prevalence estimations from Stickler syndrome support group surveys (59.8% [189/316], where not all patients were type 1 and many had undergone previous cryotherapy) and large family pedigree studies (57.6% [95/165] to 65.2% [43/66]).[21–23] Our conservative estimate is due to the Vitreoretinal Research Unit's algorithm of tracing undiagnosed family members from presenting probands and the study exclusion criteria. Furthermore, matching protocols allowed for all retinal detachment events (including post-prophylaxis retinopexy) and follow-up time to be included for prophylaxis patients, but "cropped" follow-up time resulted in lost retinal detachment events in the control groups. These measures intentionally weight bias against the efficacy of treatment, thereby reinforcing any demonstrated protective result. The current findings support the previous study conducted using a sample of the current cohort population.[20]

In summary, this retrospective study compares 293 patients receiving prophylaxis (and up to 36.1 years of follow-

Table 3. Recorded and Reported Side Effects occuring after Prophylactic Cryotherapy

| Side Effect | Affected, n/N (%) | Mean (SD) Age (yrs) | Mean (SD) Time to Resolution (wks) |
|---|---|---|---|
| Lid/conjunctival inflammation | | | |
| Mild | 75/293 (25.6) | 10.7 (9.9) | <4 |
| Moderate | 40/293 (13.7) | 17.4 (18.3) | <4 |
| Marked | 20/293 (6.8) | 14.8 (16.0) | <4 |
| Nausea and/or vomiting | 35/293 (11.9) | 15.8 (12.5) | <1 |
| Accommodation insufficiency | 28/293 (9.6) | 25.8 (14.2) | 5.3 (2.5) |
| Ocular discomfort | 7/293 (2.4) | 21.2 (18) | <1 |
| Anisocoria/mydriasis | 6/293 (2.0) | 30.2 (23.1) | 6.8 (2.9) |
| Photophobia | 3/293 (1.0) | 25.1 (24.6) | 2.7 (1.2) |
| Itchy eyes | 2/293 (0.7) | 9.2 (2.5) | <1 |
| New floater | 1/293 (0.3) | 18.3 | 6 |

SD = standard deviation.

up) with 194 untreated control patients. The results definitively demonstrate that the Cambridge prophylactic cryotherapy protocol is safe and significantly reduces the risk of retinal detachment in type 1 Stickler syndrome.

**Acknowledgments.** The authors thank Professor Allan Hackshaw (statistical analysis and scientific review, Department of Epidemiology and Medical Statistics, Cancer Research UK & UCL Cancer Trials Centre, University College London); Professor Douglas Easton (methodology and scientific discussion, Department of Oncology and Public Health and Primary Care, University of Cambridge); Professor Richard Samworth (statistical analysis, Department of Pure Mathematics and Mathematical Statistics, The University of Cambridge Statistics Clinic); Dr Carl Spickett (scientific review and discussion, Department of Pathology, University of Cambridge); Wieslawa Johnson (essential materials, Department of Medical Genetics, Addenbrooke's Hospital); and C.K. Patel (essential materials, Imaging Department, Oxford Eye Hospital). The Vitreoretinal service at Cambridge University Hospitals NHS Trust Foundation Trust is commissioned by the Department of Health National Specialist Commissioning Team (NSCT) to provide the National Stickler syndrome Diagnostic Service.

## References

1. Snead MP, Yates JR. Clinical and molecular genetics of Stickler syndrome. J Med Genet 1999;36:353–9.
2. Carroll C, Papaioannou D, Rees A, Kaltenthaler E. The clinical effectiveness and safety of prophylactic retinal interventions to reduce the risk of retinal detachment and subsequent vision loss in adults and children with Stickler syndrome: a systematic review. Health Technol Assess 2011;15. iii-xiv, 1–62.
3. Ahmad NN, Ala-Kokko L, Knowlton RG, et al. Stop codon in the procollagen II gene (COL2A1) in a family with the Stickler syndrome (arthro-ophthalmopathy). Proc Natl Acad Sci U S A 1991;88:6624–7.
4. Williams CJ, Ganguly A, Considine E, et al. A-2–>G transition at the 3' acceptor splice site of IVS17 characterizes the COL2A1 gene mutation in the original Stickler syndrome kindred. Am J Med Genet 1996;63:461–7.
5. Snead MP. Retinal detachment in childhood. In: Hoyt CS, Taylor D, eds. Pediatric Ophthalmology and Strabismus. 4th ed. Edinburgh: Saunders/Elsevier; 2013:530–42.
6. Snead MP, McNinch AM, Poulson AV, et al. Stickler syndrome, ocular-only variants and a key diagnostic role for the ophthalmologist. Eye (Lond) 2011;25:1389–400.
7. Richards AJ, Yates JR, Williams R, et al. A family with Stickler syndrome type 2 has a mutation in the COL11A1 gene resulting in the substitution of glycine 97 by valine in alpha 1 (XI) collagen. Hum Mol Genet 1996;5:1339–43.
8. Brunner HG, Van Beersum SE, Warman ML, et al. A Stickler syndrome gene is linked to chromosome 6 near the COL11A2 gene. Hum Mol Genet 1994;3:1561–4.
9. Van Camp G, Snoeckx RL, Hilgert N, et al. A new autosomal recessive form of Stickler syndrome is caused by a mutation in the COL9A1 gene. Am J Hum Genet 2006;79:449–57.
10. Baker S, Booth C, Fillman C, et al. A loss of function mutation in the COL9A2 gene causes autosomal recessive Stickler syndrome. Am J Med Genet A 2011;155A:1668–72.
11. Stickler GB, Belau PG, Farrell FJ, et al. Hereditary progressive arthro-ophthalmopathy. Mayo Clin Proc 1965;40:433–55.
12. Stickler GB, Pugh DG. Hereditary progressive arthro-ophthalmopathy II. Additional observations on vertebral abnormalities, a hearing defect, and a report of a similar case. Mayo Clinic Proc 1967;42:495–500.
13. Poulson AV, Hooymans JM, Richards AJ, et al. Clinical features of type 2 Stickler syndrome [report online]. J Med Genet 2004;41:e107.
14. Robin NH, Moran RT, Warman M, Ala-Kokko L. Stickler syndrome. In: Pagon RA, Adam MP, Bird TD, et al, eds. GeneReviews [database online]. Seattle: University of Washington, Seattle; Updated November 3, 2011. Available at: http://www.ncbi.nlm.nih.gov/books/NBK1302/. Accessed January 13, 2014.
15. Richards AJ, McNinch A, Martin H, et al. Stickler syndrome and the vitreous phenotype: mutations in COL2A1 and COL11A1 [report online]. Hum Mutat 2010;31:E1461–71.
16. Wilkinson CP. Interventions for asymptomatic retinal breaks and lattice degeneration for preventing retinal detachment. Cochrane Database Syst Rev 2012;3:CD003170.
17. American Academy of Ophthalmology Retina/Vitreous Panel. Preferred Practice Pattern Guidelines. Posterior vitreous detachment, retinal breaks and lattice degeneration. San Francisco: American Academy of Ophthalmology; 2013. Available at: http://one.aao.org/guidelines-browse?filter=preferredpracticepatterns. Accessed January 15, 2014.
18. Chauhan DS, Downie JA, Eckstein M, Aylward GW. Failure of prophylactic retinopexy in fellow eyes without a posterior vitreous detachment. Arch Ophthalmol 2006;124:968–71.
19. Richards AJ, Laidlaw M, Whittaker J, et al. High efficiency of mutation detection in type 1 Stickler syndrome using a two-stage approach: vitreoretinal assessment coupled with exon sequencing for screening COL2A1. Hum Mutat 2006;27:696–704.
20. Ang A, Poulson AV, Goodburn SF, et al. Retinal detachment and prophylaxis in type 1 Stickler syndrome. Ophthalmology 2008;115:164–8.
21. Stickler GB, Hughes W, Houchin P. Clinical features of hereditary progressive arthro-ophthalmopathy (Stickler syndrome): a survey. Genet Med 2001;3:192–6.
22. Donoso LA, Edwards AO, Frost AT, et al. Identification of a stop codon mutation in exon 2 of the collagen 2A1 gene in a large Stickler syndrome family. Am J Ophthalmol 2002;134:720–7.
23. Parma ES, Körkkö J, Hagler WS, Ala-Kokko L. Radial perivascular retinal degeneration: a key to the clinical diagnosis of an ocular variant of Stickler syndrome with minimal or no systemic manifestations. Am J Ophthalmol 2002;134:728–34.
24. Leiba H, Oliver M, Pollack A. Prophylactic laser photocoagulation in Stickler syndrome. Eye (Lond) 1996;10:701–8.
25. Monin C, Van Effenterre G, Andre-Sereys P, Haut J. Prevention of retinal detachment in Wagner-Stickler disease. Comparative study of different methods. Apropos of 22 cases [in French]. J Fr Ophtalmol 1994;17:167–74.
26. Lane-Claypon J. A further report on cancer of the breast with special reference to its antecedent conditions. Reports on Public Health and Medical Subjects No. 32. London: H. M. Stationery Office; 1926.
27. Mann CJ. Observational research methods. Research design II: cohort, cross sectional, and case-control studies. Emerg Med J 2003;20:54–60.
28. Aylward B, daCruz L, Ezra E, et al. Stickler syndrome [letter]. Ophthalmology 2008;115:1636–7; author reply 1637–8.

## Footnotes and Financial Disclosures

Originally received: September 18, 2013.
Final revision: February 14, 2014.
Accepted: February 20, 2014.
Available online: May 1, 2014. Manuscript no. 2013-1583.

[1] Vitreoretinal Service, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom.

[2] Centre for Applied Medical Statistics (CAMS), University of Cambridge, Cambridge, United Kingdom.

[3] School of Health and Related Research (ScHARR), University of Sheffield, Sheffield, United Kingdom.

[4] Department of Pathology, University of Cambridge, Cambridge, United Kingdom.

[5] Regional Molecular Genetics Laboratory, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom.

Presented at: The Oxford Ophthalmological Congress, July 2013 (Ian Fraser Cup winner); The Royal Society of Medicine (RSM), June 2013 (Dermot Pierse Prize winner); The Association for Research in Vision and Ophthalmology (ARVO), May 2013 (poster presentation); The East of England Deanery, December 2012 (John Cairns Prize winner).

Financial Disclosures:
The authors have no proprietary or commercial interest in any materials discussed in this article.

Supported by University of Cambridge Retinal Research Fund and in part by Department of Health National Specialist Commissioning Team (NSCT).

Abbreviations and Acronyms:
**CI** = confidence interval; **HR** = hazard ratio; **RD** = retinal detachment.

Correspondence:
Martin P. Snead, MD, FRCOphth, Vitreoretinal Service, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Box 41, Addenbrooke's Hospital, Hills Road, Cambridge, CB2 0QQ, United Kingdom. E-mail: mps34@cam.ac.uk.