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A Randomized Trial of Binocular Dig Rush Game Treatment for Amblyopia in Children Aged 7 to 12 Years

*Pediatric Eye Disease Investigator Group**
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Purpose: To compare visual acuity (VA) improvement in children aged 7 to 12 years with amblyopia treated with a binocular iPad game plus continued spectacle correction vs. continued spectacle correction alone.

Design: Multicenter randomized clinical trial.

Participants: One hundred thirty-eight participants aged 7 to 12 years with amblyopia (33−72 letters, i.e., approximately 20/200 to 20/40) resulting from strabismus, anisometropia, or both. Participants were required to have at least 16 weeks of optical treatment in spectacles if needed or demonstrate no improvement in amblyopic-eye visual acuity (VA) for at least 8 weeks prior to enrollment.

Methods: Eligible participants (mean age 9.6 years, mean baseline VA of 59.6 letters, history of prior amblyopia treatment other than spectacles in 96%) were randomly assigned to treatment for 8 weeks with the dichoptic binocular Dig Rush iPad game (prescribed for 1 hour per day 5 days per week) plus spectacle wear if needed (n = 69) or continued spectacle correction alone if needed (n = 69).

Main Outcome Measures: Change in amblyopic-eye VA from baseline to 4 weeks, assessed by a masked examiner.

Results: At 4 weeks, mean amblyopic-eye VA letter score improved from baseline by 1.3 (2-sided 95% confidence interval [CI]: 0.1−2.6; 0.026 logMAR) with binocular treatment and by 1.7 (2-sided 95% CI: 0.4−3.0; 0.034 logMAR) with continued spectacle correction alone. After adjusment for baseline VA, the letter score difference between groups (binocular minus control) was -0.3 (95% CI: -2.2 to 1.5, $P = 0.71$, difference of -0.006 logMAR). No difference in letter scores was observed between groups when the analysis was repeated after 8 weeks of treatment (adjusted mean: -0.1, 98.3% CI: -2.4 to 2.1). For the binocular group, adherence data from the iPad indicated that slightly more than half of the participants (58% and 56%) completed >75% of prescribed treatment by the 4- and 8-week visits, respectively.

Conclusions: In children aged 7 to 12 years who have received previous treatment for amblyopia other than spectacles, there was no benefit to VA or stereoacuity from 4 or 8 weeks of treatment with the dichoptic binocular Dig Rush iPad game. *Ophthalmology 2018;■:1−11 © 2018 by the American Academy of Ophthalmology*

Supplementary files available at www.aaojournal.org.

Small case series and single-center randomized trials have been supportive of dichoptic binocular treatment for amblyopia (henceforth referred to as "binocular treatment") as an intervention for anisometropic, strabismic, or combined-mechanism amblyopia that does not rely on patching or penalization.[1−3] Binocular treatment may work by a fundamentally different mechanism, and has been reported successful in adults with amblyopia, including those previously treated with patching.[1,2] Nevertheless, results from 2 recent large multicenter randomized clinical trials (RCTs) using a falling-blocks binocular game played on handheld devices found less improvement in amblyopic-eye visual acuity (VA) with binocular treatment than with part-time patching[4] or no greater improvement than a nonbinocular control game treatment.[5] In both of these previous RCTs, poor adherence was blamed for failure to find a greater effect.[4,5] A new binocular game ("Dig Rush") has become available that may be more engaging than the falling-blocks game and for which a pilot study found better adherence and evidence of effectiveness among amblyopic children aged 4 to 9 years.[3] We conducted a multicenter RCT to compare amblyopic-eye VA improvement between treatment with the Dig Rush binocular game plus spectacle wear (if needed) and treatment with continued spectacle wear alone (if needed), in children aged 7 to 12 years.

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Methods

The study was conducted at 41 institution- and community-based clinical sites and approved by the respective institutional review boards. A parent or guardian (referred to subsequently as "parent") of each study participant gave written informed consent, and each participant assented to participation as required. The study is listed on www.clinicaltrials.gov, under identifier NCT02983552 accessed August 7, 2018. The complete study protocol is available on the Pediatric Eye Disease Investigator Group (PEDIG) website (www.pedig.net, accessed August 7, 2018). Major eligibility criteria were as follows: age 7 to <13 years; amblyopia associated with anisometropia, strabismus, or both; VA in the amblyopic eye between 33 and 72 letters inclusive (i.e., approximately 20/200 to 20/40); and an interocular difference of at least 3 logMAR lines. Additional eligibility criteria are listed in Table 1, including the requirement for no more than 4 prism diopters (PD) of tropia at near fixation to allow bifoveal (or almost bifoveal) binocularity. To minimize the impact of improvement with glasses alone, participants were required to have at least 16 weeks of spectacle wear (if needed) before enrollment or to demonstrate no improvement in amblyopic-eye VA (<0.1 logMAR improvement) in current spectacle correction over 2 consecutive visits at least 8 weeks apart.

Randomized Treatment Groups

Participants were randomly assigned via the PEDIG website with equal probability to receive 8 weeks of either binocular treatment with spectacles (if needed) or continued spectacles alone (if needed), subsequently referred to as "binocular treatment" and "control treatment," respectively, using a permutated block design stratified by baseline amblyopic-eye VA (53−72 letters [20/40 to 20/80] vs. 33−52 letters [20/100 to 20/200]).

For participants in both treatment groups, spectacles (if worn) were prescribed for all waking hours. The binocular treatment group was prescribed the binocular Dig Rush iPad game[3] for 1 hour a day 5 days per week, allowing the hour to be divided into shorter sessions.

Children assigned to binocular treatment were loaned an iPad with Dig Rush, an action-oriented adventure game with 42 levels that consists of miners digging for gold.[3] As described by Kelly et al[3] during game play, children wore red-green anaglyphic glasses that separate game elements seen by each eye, with reduced-contrast elements seen by the fellow eye, high-contrast elements seen by the amblyopic eye, and high-contrast background elements seen by both eyes. Both eyes must see their respective game components for successful game play. Amblyopic-eye contrast remained at 100% contrast, while contrast presented to the fellow eye started at 20%. The contrast presented to the fellow eye only changed if the game was played ≥ 15 minutes on the preceding day and either increased by 10% increments with game success or decreased by 5% increments if game play was not successful.[3]

Parents or participants recorded the number of hours of game play and/or spectacle wear each day using study-provided calendars. The iPad automatically recorded the duration of game play and contrast to the fellow eye.

Study Visits and Testing Procedures

After randomization (subsequently referred to as "baseline"), follow-up visits were scheduled at 4 and 8 weeks (±1 week), with the primary outcome visit at 4 weeks. After the 8-week visit, participants initially randomized to control treatment were offered 8 weeks of binocular treatment, and they returned for a final visit at 16 weeks (±1 week) postrandomization. At each visit, VA was measured in each eye with optimal refractive correction (if applicable) and without cycloplegia, by a study-certified examiner, using the Electronic Early Treatment Diabetic Retinopathy Study protocol.[6,7] Ocular alignment was measured using the simultaneous prism and cover test and the prism and alternate cover test, and stereoacuity was measured using the Randot Butterfly and Randot Preschool stereoacuity tests (Stereo Optical Co., Chicago, IL). Visual acuity and stereoacuity testing were performed at 4 and 8 weeks by an examiner masked to the participant's randomized treatment. Before clinical testing, parents completed questionnaires regarding their child's symptoms and diplopia while participants completed a separate set of questions about diplopia.

Statistical Analyses

A sample size of 84 participants was selected to have 90% power with a 2-sided type I error of 5% to detect a treatment group difference at 4 weeks if the true difference in mean VA letter score change was 3.75, assuming a standard deviation (SD) of change of 5 letters based on a prior PEDIG study[8] and no more than 5% loss to follow-up (the final observed SD of change [pooled across the 2 treatment groups] in amblyopic-eye VA from baseline to 4 weeks was 5.4 letters, adjusting for baseline acuity). A preplanned sample size re-estimation was conducted using masked and pooled 4-week data from 42 participants (54% of original sample size) and was reviewed by the Data and Safety Monitoring Committee. Based on the observed SD of change of 6 letters, the Data and Safety Monitoring Committee recommended increasing the sample size to 116 participants.

The primary outcome measure was the change in amblyopic-eye VA letter score from baseline to 4 weeks (21 to <49 days). A modified intent-to-treat analysis of covariance, only including participants completing the 4-week outcome, was performed to estimate the treatment group difference in mean change in VA at 4 weeks and a 2-sided 95% confidence interval (CI), adjusted for baseline VA. Alternative approaches to this analysis are specified in Table S2 (available at www.aaojournal.org).

Statistical methods for additional analyses are described in the relevant Tables and Figures. Analyses for secondary outcomes of VA (3 prespecified analyses) and stereoacuity (4 prespecified analyses) were adjusted for multiple testing using the Bonferroni method such that the overall type I error rate was 5% within the 2 sets of secondary outcomes. Statistical significance for safety analyses was tested using a 2-sided type I error rate of 1%. Exploratory analyses were conducted for secondary outcomes and adherence measures for participants assigned to control treatment who later received 8 weeks of binocular treatment. Log file data at 4 weeks (binocular treatment group) and 8 weeks (pooled across both original treatment groups) were used to quantify measures of adherence (treatment duration and change in contrast presented to the fellow eye) and to examine the relationship between these adherence measures and treatment response. For each participant, the total hours of completed and prescribed game play were calculated from the date the iPad was received until the study visit (inclusive), and the percentage of prescribed treatment completed (adherence) was computed using the ratio of the completed and prescribed hours of game play for that interval. Analyses were conducted using SAS version 9.4 (SAS Inc, Cary, NC). All *P* values are 2-sided.

Results

Baseline Characteristics

Between March 2017 and February 2018, 138 participants were randomly assigned to binocular treatment (n = 69) or control (continued optical treatment) (n = 69). An additional 22

Table 1. Study Inclusion and Exclusion Criteria

Eligibility Criteria

The following criteria must be met for the patient to be enrolled in the study:

1. Age 7 to <13 years
2. Amblyopia associated with strabismus, anisometropia, or both (previously treated or untreated)

a. Criteria for strabismus: At least **1** of the following must be met:
- Presence of a heterotropia on examination at distance or near fixation (with or without optical correction), must be no more than 4 PD by SPCT at near fixation.
- Documented history of strabismus that is no longer present

b. Criteria for anisometropia: At least **1** of the following criteria must be met:
- ≥1.00 D difference between eyes in spherical equivalent
- ≥1.50 D difference in astigmatism between corresponding meridians in the 2 eyes

c. Criteria for combined-mechanism amblyopia: **Both** of the following criteria must be met:
- Criteria for strabismus are met (see above)
- ≥1.00 D difference between eyes in spherical equivalent
  OR
  ≥1.50 D difference in astigmatism between corresponding meridians in the 2 eyes

3. No amblyopia treatment in the past 2 weeks (patching, atropine, Bangerter, vision therapy, binocular treatment)
4. Requirements for required refractive error correction (*based on a CR within the last 7 months):*
- Hypermetropia of 2.50 D or more by SE
- Myopia of amblyopic eye of 0.50 D or more SE
- Astigmatism of 1.00 D or more
- Anisometropia of more than 0.50D SE

Note: Subjects with cycloplegic refractive errors that do not fall within the requirements above for spectacle correction may be given spectacles at investigator discretion but must follow the study-specified prescribing guidelines, as detailed below.

a. Spectacle prescribing instructions referenced to the CR completed within the last 7 months:
- SE must be within 0.50 D of fully correcting the anisometropia.
- SE must not be undercorrected by more than 1.50 D SE, and reduction in plus sphere must be symmetrical in the 2 eyes.
- Cylinder power in both eyes must be within 0.50 D of fully correcting the astigmatism.
- Cylinder axis must be within ±10 degrees if cylinder power is ≤1.00 D, and within ±5 degrees if cylinder power is >1.00 D.
- Myopia must not be undercorrected by more than 0.25 D or overcorrected by more than 0.50 D SE, and any change must be symmetrical in the 2 eyes.

b. Spectacle correction meeting the above criteria must be worn:
- 16 weeks
  OR
  until VA stability is documented (defined as <0.1 logMAR change by the same testing method measured on 2 consecutive examinations at least 8 weeks apart).
- Determining visual acuity stability (nonimprovement):
  - The first of 2 measurements may be made (1) in current correction, or (2) in trial frames with or without cycloplegia, or (3) without correction (if new correction is prescribed).
  - The second measurement must be made without cycloplegia in the correct spectacles that have been worn for at least 8 weeks.
  - Note: Since this determination is a prestudy procedure, the method of measuring visual acuity is not mandated.

5. Visual acuity, measured in each eye without cycloplegia incurrent spectacle correction (if applicable) within 7 days prior to randomization using the E-ETDRS VA protocol for children ≥7 years on a study-approved device displaying single surrounded optotypes, as follows:

a. VA in the amblyopic eye 33 to 72 letters (E-ETDRS)

b. Best-corrected fellow-eye VA meeting the following criteria:
- Age 7 or older, 20/25 or better by E-ETDRS (>78 letters)

c. IOD ≥ 3 logMAR lines or ≥15 letters (E- ETDRS)

6. Heterotropia with a near deviation of <5PD (measured by SPCT) in habitual correction
7. Subject is able to play the Dig Rush game (at least level 3) on the study iPad under binocular conditions (with red-green glasses). Subject must be able to see both the red "diggers" and blue "gold carts" when contrast is at 20% for the nonamblyopic eye.
8. Investigator is willing to prescribe computer game play, or continue spectacle wear per protocol
9. Parent understands the protocol and is willing to accept randomization
10. Parent has phone (or access to phone) and is willing to be contacted by Jaeb Center staff or other study staff
11. Relocation outside of area of an active PEDIG site for this study within the next 8 weeks is not anticipated.

Exclusion Criteria

1. Prism in the spectacle correction at time of enrollment (eligible only if prism is discontinued 2 weeks prior to enrollment)
2. Myopia greater than -6.00 D spherical equivalent in either eye
3. Previous intraocular or refractive surgery
4. Any treatment for amblyopia (patching, atropine, Bangerter filter, or previous binocular treatment) during the past 2 weeks. Previous amblyopia therapy is allowed regardless of type, but must have been discontinued at least 2 weeks prior to enrollment.
5. Ocular comorbidity that may reduce VA determined by an ocular examination performed within the past 7 months (*note: nystagmus per se does not exclude the subject if the above visual acuity criteria are met*)
6. Down syndrome or cerebral palsy
7. Severe developmental delay that would interfere with treatment or evaluation (in the opinion of the investigator). Subjects with mild speech delay or reading and/or learning disabilities are not excluded.
8. Subject has demonstrated previous low compliance with binocular treatment and/or spectacle treatment (as assessed by investigator)

CR = cycloplegic refraction; D = diopter; E-ETDRS = Electronic Early Treatment Diabetic Retinopathy Study; IOD = interocular difference; PD = prism diopter; PEDIG = Pediatric Eye Disease Investigator Group; SE = spherical equivalent; SPCT = simultaneous prism and cover test; VA = visual acuity.

Table 3. Baseline Characteristics for Randomized Participants by Treatment Group

	Binocular Treatment (n = 69)*		Control Treatment (n = 69)	
	N	%	N	%
Sex: female	30	43	35	51
Age (years)				
7 to <10	45	65	45	65
10 to <13	24	35	24	35
Mean (SD)	9.6 (1.6)		9.6 (1.5)	
Race/ethnicity				
White	50	72	55	80
Black/African American	3	4	2	3
Hispanic	9	13	8	12
Asian	6	9	1	1
More than 1 race	1	1	2	3
Unknown/not reported	0	0	1	1
Prior amblyopia treatment†				
None	4	6	2	3
Patching	34	49	36	52
Atropine	0	0	1	1
Patching/atropine	26	38	21	30
Patching/other	3	4	2	3
Patching/atropine/other	2	3	7	10
Prior binocular treatment	1	1	4	6
Distance amblyopic-eye VA (letter score)				
20/160 (38–42)	2	3	2	3
20/125 (43–47)	3	4	3	4
20/100 (48–52)	8	12	8	12
20/80 (53–57)	10	14	17	25
20/63 (58–62)	19	28	14	20
20/50 (63–67)	11	16	10	14
20/40 (68–72)	16	23	15	22
Mean (SD)	60.0 (7.8)		59.1 (8.2)	
Distance fellow-eye VA (letter score): mean (SD)	87.9 (4.0)		87.9 (3.7)	
Interocular difference (letter score): mean (SD)	27.9 (9.2)		28.8 (9.3)	
Stereoacuity: nil	33	48	33	48
Stereoacuity seconds of arc): median (range)	2000 (40 to nil)		2000 (40 to nil)	
Amblyopia cause				
Strabismus	15	22	11	16
Anisometropia	27	39	39	57
Combined mechanism	27	39	19	28
Distance SPCT: maximum angle of deviation (Δ)				
Orthotropic	47	68	50	72
1 to 4	18	26	15	22
5 to 9	2	3	2	3
≥10	2	3	2	3
Near SPCT: maximum angle of deviation (Δ)				
Orthotropic	44	64	47	68
1 to 4	25	36	22	32
Amblyopic-eye spherical equivalent (D)				
Mean (SD)	+4.35 (2.42)		+4.40 (2.28)	
Fellow-eye spherical equivalent (D)				
Mean (SD)	+2.10 (2.12)		+2.22 (1.99)	
Spherical equivalent anisometropia (D)				
Mean (SD)	+2.29 (1.79)		+2.27 (1.62)	

D = diopter; SD = standard deviation; SPCT = simultaneous prism and cover test; VA = visual acuity.
*Two participants in the binocular treatment group were subsequently found to be ineligible for the study. For 1 participant, different testing methods were used to document stability in glasses prior to enrollment; for the other participant, patching was discontinued <2 weeks prior to enrollment.
†Other treatment includes plano (or reduced plus) lens wear, fogging (Bangerter filter, tape, optical), vision therapy (home or office), orthoptics/binocular therapy, or binocular treatment from a previous PEDIG study of binocular treatment.[4,8]

participants were enrolled over the planned sample size, prior to the recruitment end date, set at the end of the final month, to ensure that the recruitment goal would be met. Baseline characteristics were similar (Table 3), with the exception of somewhat more participants with strabismic or combined amblyopia in the binocular treatment group, but a sensitivity analysis adjusting for cause of amblyopia yielded results consistent with the primary analysis (Table S2).

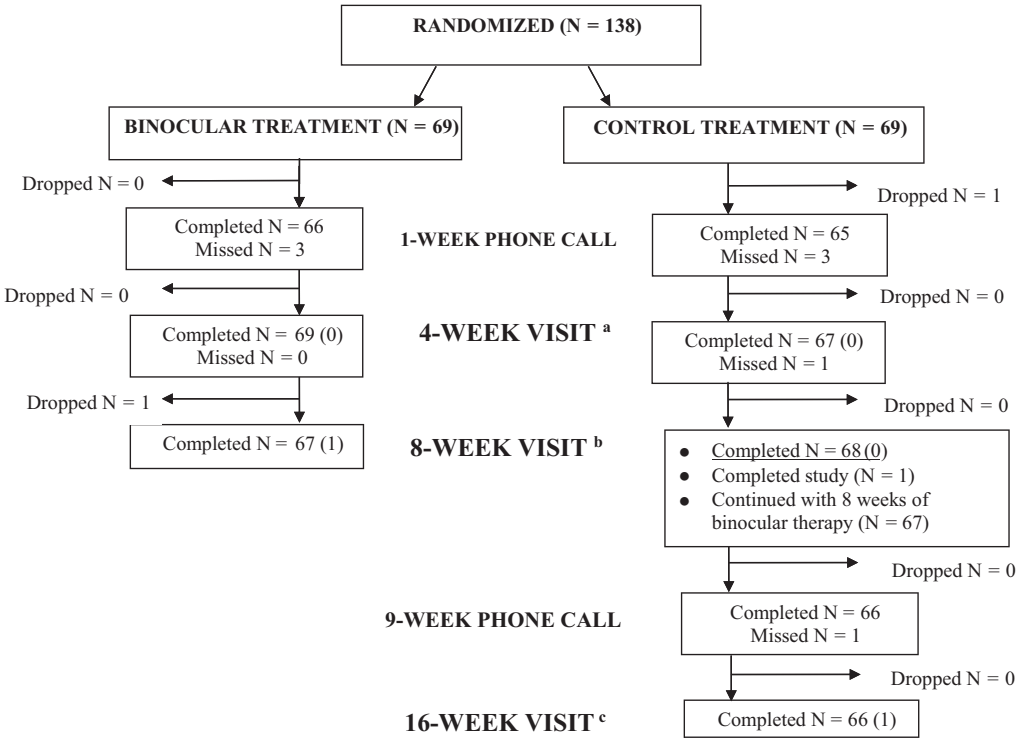

Figure 1. Visit completion by treatment. The 4-week primary outcome visits were classified as being within the analysis window if completed between 21 and <49 days from randomization (a). The 8-week visits were classified as being within the analysis window if completed between 49 and <105 days from randomization (b). The 16-week visits were classified as being within the analysis window if completed between 105 and <161 days from randomization (c). Numbers in parentheses indicate visits completed outside of the analysis window.

Visit Completion

The 4-week primary outcome visit and the subsequent 8-week visits were completed by 69 (100%) and 67 (97%) participants in the binocular treatment group, respectively, and 67 (97%) and 68 (99%) in the control group, respectively (Fig 1). Masking of the VA/stereoacuity testers was maintained at 100% of visits for both groups.

Adherence

Parent-reported adherence with spectacle wear (excluding participants with reported compliance of "not applicable") for the initial 4 weeks was >75% for 57 (86%) and 57 (95%) participants in the binocular treatment and control groups, respectively, and averaged >75% across 8 weeks for 61 (90%) and 62 (98%) participants in the binocular treatment and control groups, respectively. For the binocular treatment group, parent-reported adherence to prescribed game play (1 hour a day, 5 days per week) was >75% for 47 (68%) participants during the initial 4 weeks and 51 (75%) participants throughout 8 weeks. Slightly poorer adherence was indicated by the log file data than by parental report: 40 (58%) and 38 (56%) participants completed >75% of prescribed game play during the initial 4 weeks (median = 80%, range 2%−133%) and throughout 8 weeks (median = 80%, range 1%−133%), respectively. The median total hours of game play was 13 hours of the intended 20 hours (range: 1−40 hours) at 4 weeks and 31 hours of the intended 40 hours (range: 1−52 hours) at 8 weeks.

No participant in either treatment group was prescribed treatment other than the randomly assigned treatment during the study.

Contrast Level of the Binocular Treatment over the Course of the Randomized Study

For binocular treatment, contrast presented to the fellow eye increased from 20% to 100% by the 4-week visit for 30 (43%) participants and by the 8-week visit for 59 (87%) participants (Fig S2, available at www.aaojournal.org). Only 1 participant had contrast presented to the fellow eye of 20% or lower at the 4- and 8-week visits.

Amblyopic-Eye Visual Acuity

At 4 weeks, after adjusting for baseline VA, mean amblyopic-eye VA letter score improved from baseline by 1.3 (95% CI: 0.1−2.6; equivalent to 0.026 logMAR) in the binocular treatment group and 1.7 (95% CI: 0.4−3.0; equivalent to 0.034 logMAR) in the control group (Table 4, Fig S3A and S3B, available at www.aaojournal.org). The difference between binocular and control treatment letter scores was -0.3 (95% CI: -2.2 to 1.5, $P = 0.71$; equivalent to -0.006 logMAR). Sensitivity analyses yielded similar results (Table S2).

When possible differential treatment effect was analyzed by baseline characteristics (Table S5, available at www.aaojournal.org), no factors were found to be statistically significant. In particular, there was no suggestion of effect modification by baseline stereoacuity; binocular treatment seemed similarly ineffective in those with or without measurable baseline stereoacuity, but the study was not powered for this comparison.

At 8 weeks, the difference between the adjusted mean amblyopic-eye VA letter score improvement for the binocular

Table 4. Distribution of Amblyopic-Eye Visual Acuity Outcomes by Treatment Group at Randomization and Follow-up Visits*

	Randomization		4-Week Visit		8-Week Visit†	
	Binocular Treatment N (%)	*Control Treatment N (%)*	*Binocular Treatment N (%)*	*Control Treatment N (%)*	*Binocular Treatment N (%)*	*Control Treatment N (%)*
Per group (N)	69	69	69	67	67	67
Amblyopic-eye VA (letter score)						
20/320 (23–27)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
20/250 (28–32)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
20/200 (33–37)	0 (0)	0 (0)	0 (0)	2 (3)	0 (0)	1 (1)
20/160 (38–42)	2 (3)	2 (3)	1 (1)	0 (0)	1 (1)	1 (1)
20/125 (43–47)	3 (4)	3 (4)	2 (3)	2 (3)	2 (3)	2 (3)
20/100 (48–52)	8 (12)	8 (12)	10 (14)	9 (13)	8 (12)	8 (12)
20/80 (53–57)	10 (14)	17 (25)	5 (7)	7 (10)	7 (10)	8 (12)
20/63 (58–62)	19 (28)	14 (20)	20 (29)	13 (19)	12 (18)	12 (18)
20/50 (63–67)	11 (16)	10 (14)	16 (23)	14 (21)	16 (24)	13 (19)
20/40 (68–72)	16 (23)	15 (22)	9 (13)	12 (18)	15 (22)	11 (16)
20/32 (73–77)	0 (0)	0 (0)	6 (9)	5 (7)	5 (7)	10 (15)
20/25 (78–82)	0 (0)	0 (0)	0 (0)	2 (3)	1 (1)	0 (0)
Mean (SD) letter score	60.0 (7.8)	59.1 (8.2)	61.4 (8.2)	61.0 (10.6)	62.5 (8.3)	61.7 (10.2)
Mean IOD (SD) letters	27.9 (9.2)	28.8 (9.3)	26.6 (10.5)	28.0 (10.7)	25.9 (9.9)	27.7 (10.4)
Change in amblyopic-eye VA from randomization (letters)						
≥15 letters (≥3 lines) better			1 (1)	2 (3)	2 (3)	1 (1)
10–14 letters (2 lines) better			1 (1)	1 (1)	3 (4)	5 (7)
5–9 letters (1 line) better			13 (19)	14 (21)	11 (16)	17 (25)
Within 4 letters (0 line)			48 (70)	42 (63)	45 (67)	42 (63)
5–9 letters (1 line) worse			4 (6)	5 (7)	4 (6)	1 (1)
10–14 letters (2 lines) worse			2 (3)	3 (4)	2 (3)	0 (0)
≥15 letters (≥3 lines) worse			0 (0)	0 (0)	0 (0)	1 (1)
Mean (95% CI) at 4 weeks‡ / mean (98.3% CI) at 8 weeks‡						
Unadjusted			1.3 (0.1, 2.6)	1.7 (0.4, 3.0)	2.3 (0.6, 4.0)	2.4 (0.9, 4.0)
Adjusted§			1.3 (0.1, 2.6)	1.7 (0.4, 3.0)	2.3 (0.7, 3.9)	2.4 (0.8, 4.0)
Adjusted mean difference (95% CI) at 4 weeks‖			-0.3 (-2.2, 1.5)			
Adjusted mean difference (98.3% CI) at 8 weeks‖					-0.1 (-2.4, 2.1)	
Improvement of ≥10 letters from randomization			2 (3)	3 (4)	5 (7)	6 (9)
Mean difference (98.3% CI)‖			-2% (-13%, 9%)		-1% (-15%, 12%)	

CI = confidence interval; IOD = interocular difference; SD = standard deviation; VA = visual acuity.
*Limited to follow-up visits completed within the prespecified analysis window.
†Two participants (1 per group) were not included with the 8-week VA data. One participant in the control treatment group had VA tested using a nonprotocol method and another participant in the binocular treatment group completed the 8-week examination outside of the analysis window (49 to <105 days from randomization).
‡Positive values indicate improvement in amblyopic-eye visual acuity.
§Adjusted for amblyopic-eye visual acuity at randomization.
‖Positive values favor the binocular treatment group. For secondary visual acuity outcomes, which included the 8-week treatment group comparison, a Bonferroni adjustment was used to control for multiple testing (3 outcomes tested) to preserve the overall type I error rate at 5% (2-sided alpha = 0.017 per test).

group (2.3, 98.3% CI: 0.7–3.9) compared with the control group (2.4, 98.3% CI: 0.8–4.0) was -0.1 (98.3% CI: -2.4 to 2.1) (Table 4, Fig S3A and S3B). Amblyopic-eye VA improved ≥2 lines (letter score of 10) from baseline at 4 weeks for 2 (3%) and 3 (4%) participants in the binocular treatment and control groups, respectively, and at 8 weeks for 5 (7%) and 6 (9%) participants in the binocular treatment and control groups, respectively.

For the binocular treatment group, there was no indication of a dose–response relationship between hours of treatment or change in contrast presented to the fellow eye (objectively recorded on the iPad) and improvement in amblyopic-eye VA at 4 or 8 weeks (Fig 4A–C, upper panels).

Stereoacuity

Change in stereoacuity from baseline did not differ significantly between groups at the 4- and 8-week visits (median change 0 and 0 seconds of arc, and 0 and 0 seconds of arc), or for participants with no history of strabismus at baseline (Table S6, and Table S7, available at www.aaojournal.org).

For the binocular group, improvement in stereoacuity was not associated with either total hours of treatment or change in contrast presented to the fellow eye (Fig 4A–C, lower panels).

Adverse Events

After adjustment for baseline VA, mean fellow-eye VA was found to improve similarly for both the binocular and control treatments at 4 weeks (0.1 letter vs. 1.1 letters, respectively, difference: -1.1 letters, 99% CI: -2.5 to 0.4 letters) and at 8 weeks (0.5 letter vs. 1.5 letters, respectively, difference: -1.0 letters, 99% CI: -2.4 to 0.3 letters, Table S8, available at www.aaojournal.org).

The number of participants with a new heterotropia and/or worsening of a pre-existing tropia of ≥10 PD (by simultaneous

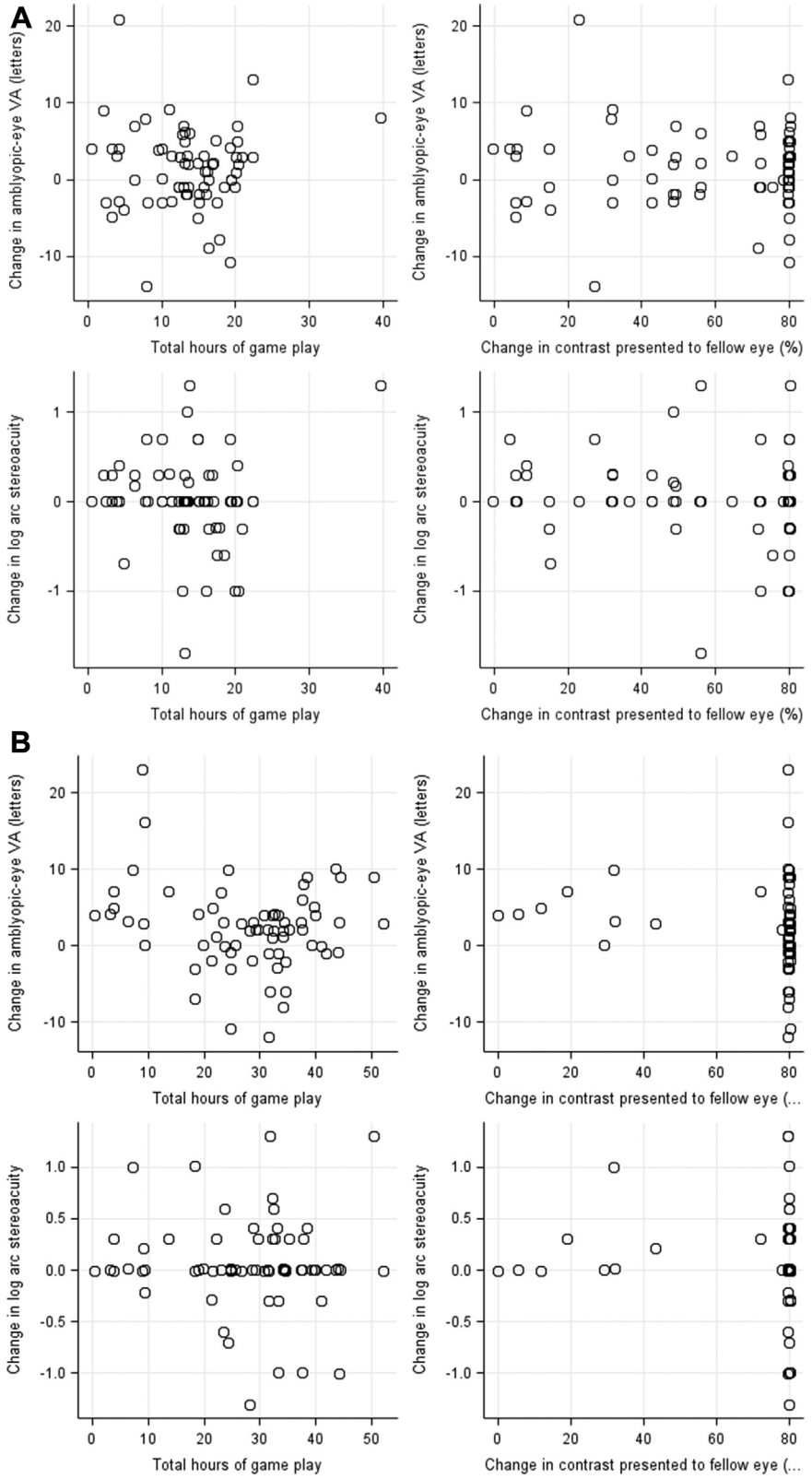

Figure 4. A, Relationship between hours played and contrast settings (from the log files) with treatment response for visual acuity (VA) and stereoacuity after 4 weeks of binocular therapy (binocular treatment group) for those who completed the 4-week visit within the predefined analysis window. Change in amblyopic-eye visual acuity from baseline (letters) versus total hours of binocular treatment (**A,** Top left, Pearson correlation coefficient, $r = 0.01$) and versus percent change in contrast presented to the fellow eye (maximum 80%) from baseline to 4 weeks (**A,** Top right, $r = -0.04$). Change in stereoacuity

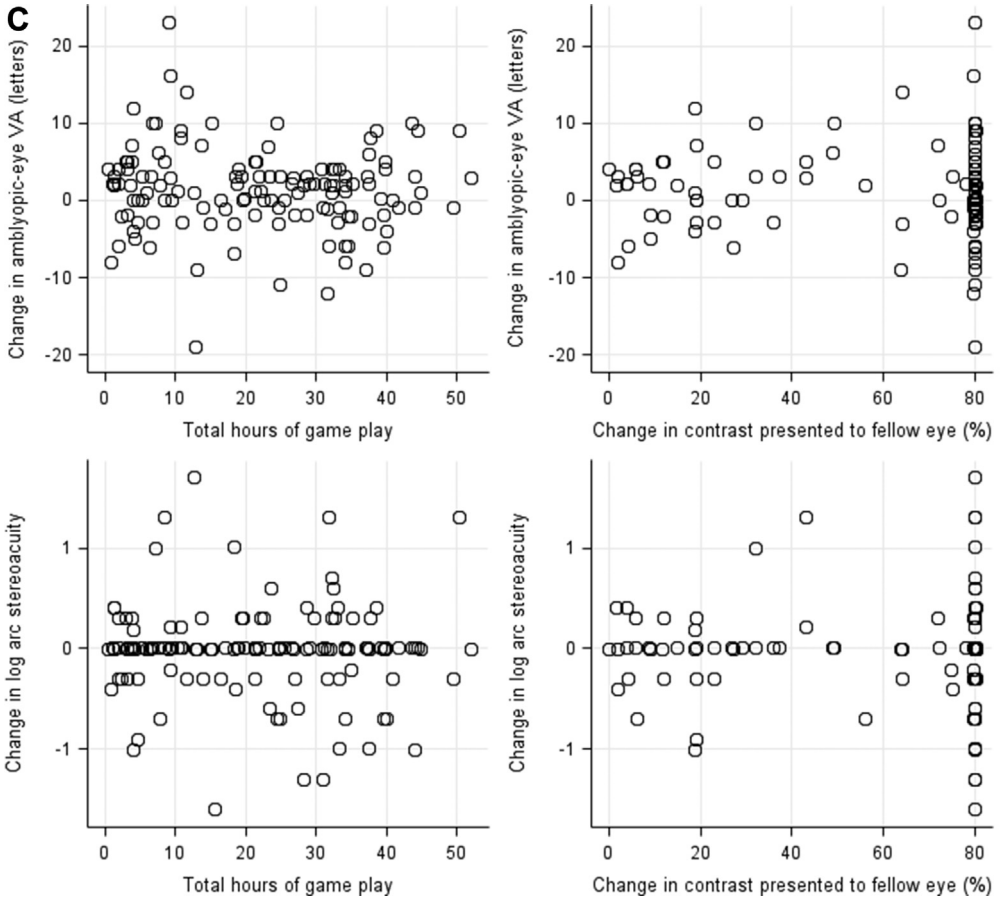

Figure 4. (*continued*).

prism and cover test) was 10 (14%) and 6 (9%) at 4 weeks ($P = 0.37$) for the binocular and control treatments, respectively, and 9 (13%) in each group at 8 weeks ($P > 0.99$). A similar number of participants with 1 to 4 PD at the time of randomization were orthotropic at the 4-week (15%) and 8-week (18%) examinations. There were only a few cases of diplopia in each group, and only 2 participants (both in the binocular treatment group) reported diplopia frequency of more than once per week at the 4-week visit, but neither of these participants reported diplopia at 8 weeks (Table S9, Table S10 available at www.aaojournal.org). Very few participants had worsening of symptoms (Table S10-S12, available at www.aaojournal.org).

Post–8-Week Phase

At the 8-week visit, 67 (99%) participants in the control group elected to be treated with 8 weeks of binocular therapy and 66 (99%) of those participants completed the 16-week visit (Fig 1). Log file data from this 8-week period indicated that 10 (15%) participants completed >75% of prescribed game play (median = 11 total hours, range: 1–50 hours), and 30 (45%) participants achieved 100% contrast in the fellow eye. The 16-week mean amblyopic-eye VA was 61.9 letters with a mean change of 0.4 letter (95% CI: -0.9 to 1.7 letters) from the 8-week visit. The median change in stereoacuity between the 8- and 16-week visits was 0.

from baseline (log seconds of arc) versus total hours of binocular treatment (**A**, Bottom left, $r = 0.02$) and versus percent change in contrast presented to the fellow eye from baseline to 4 weeks (**A,** Bottom right, $r = -0.14$). Positive values indicate improvement for change in visual acuity and stereoacuity from baseline. **B,** Relationships after 8 weeks of binocular therapy in binocular treatment group for those who completed the 8-week visit within the predefined analysis window. Change in amblyopic-eye visual acuity from baseline versus total hours of binocular treatment (**B**, Top left, $r = -0.17$) and versus change in contrast presented to the fellow eye from baseline (**B,** Top right, $r = -0.15$). Change in stereoacuity from baseline versus total hours of binocular treatment (**B,** Bottom left, $r = -0.06$) and versus percent change in contrast presented to the fellow eye (**B,** Bottom right, $r = -0.09$). **C,** Relationships after 8 weeks of binocular therapy for participants in both treatment groups. Change in amblyopic-eye visual acuity from baseline versus total hours of binocular treatment (**C,** Top left, $r = -0.08$) and versus percent change in contrast presented to the fellow eye from baseline (**C,** Top right, $r = -0.001$). Change in stereoacuity from baseline versus total hours of binocular treatment (**C**, Bottom left, $r = -0.05$) and versus percent change in contrast presented to the fellow eye from baseline (**C,** Bottom right, $r = -0.001$). Plots and analyses excluded data from participants who did not complete the final examination (8-week and 16-week examination for the binocular treatment and control treatment groups, respectively) within the predefined analysis window.

Based on pooled data from all participants who were prescribed 8 weeks of binocular treatment (participants initially randomized to binocular treatment, combined with those who subsequently chose to switch from spectacles alone to binocular therapy at 8 weeks), there was no indication of a treatment dose−response relationship (Fig 4C).

Discussion

In a multicenter RCT, there was no greater improvement in amblyopic-eye VA for 7- to 12-year-old children who were treated with the binocular Dig Rush game prescribed 1 hour a day for 5 days a week along with full-time optical treatment when compared with continued optical treatment alone. In comparison with previous multicenter trials of home-based binocular treatment,[4,5] adherence with Dig Rush binocular treatment was better (although still suboptimal), and therefore it is less likely that poor adherence was the reason for failure to find an effect in our current study.

There are few studies with which we can compare our results. Kelly et al[3] used the same Dig Rush binocular game and reported a mean improvement of 0.15±0.08 logMAR with 2 weeks of binocular treatment in children aged 4 to 10 years, which was greater than the improvement in controls treated with part-time patching (0.07±0.08 logMAR). In addition, they found that children who switched from patching to binocular treatment at 2 weeks also had a total improvement of 0.16±0.12 logMAR at 4 weeks, compared with a total improvement of 0.17±0.10 logMAR with 4 weeks of binocular treatment. Differing from the present study, Kelly et al[3] enrolled children aged 4 to 10 years, which included younger children (aged 4−6 years) who may have been more responsive to amblyopia treatment and more children with no prior amblyopia treatment. Kelly et al[3] also had a greater degree of adherence, which may reflect a higher interest level of younger children in this specific game. Although not incorporating masking of VA testers, Kelly et al[3] did use a standardized method of measuring VA on the electronic VA tester.[9,10] Two previous multicenter randomized trials used the falling-blocks home-based binocular game, which incremented contrast after 30 minutes of successful game play and therefore cannot be directly compared with our study.[4,5]

It has been suggested[11] that failure to find any dose−response relationship between duration of game play, or increment of contrast, and improvement in VA casts doubt on the efficacy of binocular treatment per se. Even if there was a problem of adherence in previous studies, we expected a greater response in those participants who played the game for longer periods and/or were successful in playing the game. Such a dose−response relationship was not found in the 2 previous multicenter randomized trials[4,5] and was also absent in the current study. Although individual response to binocular treatment is likely to be variable,[11] analogous to individual variability in response to patching treatment,[12] the lack of any evidence of a dose−response relationship in previous independent multicenter studies of home-based binocular treatment is perplexing, and leaves unanswered questions regarding the physiological basis of binocular treatment.[11] One possible reason for not seeing a dose−response relationship is the limited time that the binocular treatment is presented at differential contrast. It is possible that, after a child reaches 100% contrast, there is no further treatment effect, and this question should be studied further.

Previous studies have reported the value of optical treatment of amblyopia.[12−14] Some previous studies[4,15] have required only 4 weeks of optical treatment with stability of VA between examinations or at least 16 weeks of optical treatment, whereas our current study required at least 8 weeks of optical treatment with stability of VA or at least 16 weeks of optical treatment. Our more stringent requirement had the advantages of reducing expected improvement with continued optical treatment and reducing the variability of our VA outcome measure. Indeed, our control group of continued optical treatment only improved 1.4 letters (95% CI: 0.1−2.8) at 4 weeks and 2.3 (98.3% CI: 0.5−4.2) at 8 weeks.

We are unaware of any sources of bias that may have influenced our results. It is possible that participants were not playing the game for the entire time that the handheld device recorded game play, but the software ended sessions automatically after approximately 1 minute of inactivity, and so it is unlikely that we overestimated the duration of treatment. It is possible that other friends or family played the game, or that the participant did not wear the red-green glasses, and the participant received credit when not being treated; however, we gave clear instructions to try to avoid these scenarios. Our results can only be generalized to children similar to those we enrolled in our study. Our participants were aged 7 to 12 years and nearly all had a history of previous patching and/or atropine treatment for their amblyopia, and as such might be expected to be less responsive than younger children and/or had already reached a treatment plateau where further improvement might be limited because the effect of sequential novel treatments might not be additive. Nevertheless, children with moderate amblyopia aged 7 to 12 years often do respond to treatment, albeit over a longer period of treatment (adjusted mean 1.65 logMAR lines [95% CI 1.31−1.99 lines]), in a meta-analysis of trials of patching, atropine, or Bangerter filters,[16] and 50% improved 2 or more logMAR lines with patching plus atropine plus optical treatment.[17] In addition, many children with amblyopia presenting at such older age have already been treated, and therefore our participants are likely representative. It is possible that our failure to find improvement in stereoacuity was owing to a large proportion of our participants being enrolled with nil stereoacuity, and the absence of a commonly accepted clinical test that measures random dot stereoacuity between nil and 2000 seconds of arc. Alternative binocular treatment protocols incorporating longer periods of game play before contrast increment, slower contrast increment, and additional alternative binocular games might yield greater improvements in VA and stereoacuity, and are currently being studied (NCT03288948).

In conclusion, for children aged 7 to 12 years who have received previous treatment for amblyopia, there is no apparent benefit of treatment with the binocular Dig Rush iPad game when prescribed as home therapy over a 4- to

8-week period. Although we found no benefit to VA or stereoacuity from binocular treatment for 7- to 12-year-old children, there is evidence that such treatment may be more beneficial in younger children,[3,18] particularly those who have not been previously treated. This possibility is being evaluated in an ongoing PEDIG randomized trial (NCT02983552) enrolling children aged 4 to 6 years.

References

1. Hess RF, Mansouri B, Thompson B. A new binocular approach to the treatment of amblyopia in adults well beyond the critical period of visual development. *Restor Neurol Neurosci*. 2010;28(6):793–802.
2. Li J, Thompson B, Deng D, et al. Dichoptic training enables the adult amblyopic brain to learn. *Curr Biol*. 2013;23(8):R308–R309.
3. Kelly KR, Jost RM, Dao L, et al. Binocular iPad game vs patching for treatment of amblyopia in children: a randomized clinical trial. *JAMA Ophthalmol*. 2016;134(12):1402–1408.
4. Holmes JM, Manh VM, Lazar EL, et al. Effect of a binocular iPad game vs part-time patching in children aged 5 to 12 years with amblyopia: a randomized clinical trial. *JAMA Ophthalmol*. 2016;134(12):1391–1400.
5. Gao TY, Guo CX, Babu RJ, et al. Effectiveness of a binocular video game vs placebo video game for improving visual functions in older children, teenagers, and adults with amblyopia: a randomized clinical trial. *JAMA Ophthalmol*. 2018;136(2):172–181.
6. Beck RW, Moke PS, Turpin AH, et al. A computerized method of visual acuity testing: adaptation of the Early Treatment of Diabetic Retinopathy Study testing protocol. *Am J Ophthalmol*. 2003;135(2):194–205.
7. Cotter SA, Chu RH, Chandler DL, et al. Reliability of the Electronic Early Treatment Diabetic Retinopathy Study testing protocol in children 7 to <13 years old. *Am J Ophthalmol*. 2003;136(4):655–661.
8. Manh VM, Holmes JM, Lazar EL, et al. A randomized trial of a binocular iPad game versus part-time patching in children aged 13 to 16 years with amblyopia. *Am J Ophthalmol*. 2018;186:104–115.
9. Holmes JM, Beck RW, Repka MX, et al. The Amblyopia Treatment Study visual acuity testing protocol. *Arch Ophthalmol*. 2001;119(9):1345–1353.
10. Moke PS, Turpin AH, Beck RW, et al. Computerized method of visual acuity testing: adaptation of the amblyopia treatment study visual acuity testing protocol. *Am J Ophthalmol*. 2001;132(6):903–909.
11. Holmes JM. Lessons from recent randomized clinical trials of binocular treatment for amblyopia. *JAMA Ophthalmol*. 2018;136(2):181–183.
12. Stewart CE, Stephens DA, Fielder AR, et al. Objectively monitored patching regimens for treatment of amblyopia: randomised trial. *BMJ*. 2007;335(7622):707–713.
13. Pediatric Eye Disease Investigator Group. Treatment of anisometropic amblyopia in children with refractive correction. *Ophthalmology*. 2006;113(6):895–903.
14. Pediatric Eye Disease Investigator Group, Cotter SA, Foster NC, et al. Optical treatment of strabismic and combined strabismic-anisometropic amblyopia. *Ophthalmology*. 2012;119(1):150–158.
15. Pediatric Eye Disease Investigator Group. A randomized trial of near versus distance activities while patching for amblyopia in children aged 3 to less than 7 years. *Ophthalmology*. 2008;115(11):2071–2078.
16. Holmes JM, Lazar EL, Melia BM, et al. Effect of age on response to amblyopia treatment in children. *Arch Ophthalmol*. 2011;129(11):1451–1457.
17. Pediatric Eye Disease Investigator Group. Randomized trial of treatment of amblyopia in children aged 7 to 17 years. *Arch Ophthalmol*. 2005;123(4):437–447.
18. Kelly KR, Jost RM, Wang YZ, et al. Improved binocular outcomes following binocular treatment for childhood amblyopia. *Invest Ophthalmol Vis Sci*. 2018;59(3):1221–1228.

Footnotes and Financial Disclosures

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HUMAN SUBJECTS: Human subjects were included in this study. The study was conducted at 41 institution- and community-based clinical sites and approved by the respective institutional review boards. All research adhered to the tenets of the Declaration of Helsinki. A parent or guardian (referred to subsequently as "parent") of each study participant gave written informed consent, and each participant assented to participation as required. The study is listed on www.clinicaltrials.gov, under identifier NCT02983552, accessed August 7, 2018. The complete study protocol is available on the PEDIG website (www.pedig.net, accessed August 7, 2018).

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Abbreviations and Acronyms:
CI = confidence interval; **PEDIG** = Pediatric Eye Disease Investigator Group; **RCT** = randomized clinical trial; **SD** = standard deviation; **VA** = visual acuity.

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