Parapapillary Gamma Zone and Progression of Myopia in School Children: The Beijing Children Eye Study

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PURPOSE. To assess the development and enlargement of the parapapillary gamma zone in school children.

METHODS. This school-based prospective longitudinal study included Chinese children attending grade 1 in 2011 and returning for yearly follow-up examinations until 2016. These examinations consisted of a comprehensive ocular examination with biometry and color fundus photographs. The parents underwent a standardized interview. The parapapillary gamma zone was defined as the area with visible sclera at the temporal optic disc margin, and the optic disc itself was measured on fundus photographs.

RESULTS. The study included 294 children (mean age in 2016, 11.4 ± 0.5 years [range, 10–13 years]; mean axial length, 24.1 ± 1.1 mm [range, 21.13–27.29 mm]). In multivariate analysis, larger increases in the gamma zone area during the study period were correlated (coefficient of determination for bivariate analysis [r²], r² = 0.69) with larger increases in the vertical-to-horizontal disc diameter ratios (P < 0.001; standardized regression coefficient beta [beta], 0.53; nonstandardized regression coefficient B [B], 4.05; 95% confidence intervals [CI], 3.57–4.73), larger axial elongation (P < 0.001; beta, 0.32; B, 0.37; 95% CI, 0.26–0.47), a larger vertical disc diameter at baseline (P < 0.001; beta, 0.22; B, 0.58; 95% CI, 0.62–1.33), a larger gamma zone area at baseline (P < 0.001; beta, 0.14; B, 0.41; 95% CI, 0.17–0.64), and more time spent indoors studying (P = 0.015; beta, 0.10; B, 0.09; 95% CI, 0.02–0.17).

CONCLUSIONS. The development and enlargement of the gamma zone in the temporal parapapillary region were associated with an optic disc rotation around the vertical disc axis as indicated by an increasing vertical-to-horizontal disc diameter ratio. These morphologic findings fit with the notion of a backward pull of the temporal peripapillary sclera through the optic nerve dura mater in axially elongated eyes.

Keywords: parapapillary gamma zone, optic disc shape, optic disc rotation, parapapillary atrophy, myopia, myopic retinopathy, Bruch’s membrane defects, myopia progression

The parapapillary gamma zone has recently been described as the region located at the optic disc border. It is characterized by the absence of Bruch’s membrane, retinal pigment epithelium, deep retinal layers, choriocapillaris, and Sattler’s layer of medium-sized choroidal vessels.1-15 The sclera in the gamma zone is directly covered by the elongated and thinned peripapillary choroidal border tissue of Jacoby and the retinal nerve fibers.4-10 It has been shown that larger parapapillary gamma zone size is strongly associated with longer ocular axial length, but the etiology of the gamma zone has remained elusive so far.1-11 Therefore, we conducted this longitudinal study to examine the development and enlargement of the parapapillary gamma zone in school children who were repeatedly and regularly examined over a 5-year period. The aim of this study was to determine which eyes developed a parapapillary gamma zone and/or showed an enlargement of the gamma zone and which factors were associated with such changes in the gamma zone.

METHODS

In The Beijing Children Eye Study, children living in a rural region or an urban area of Greater Beijing and attending primary schools in grade 1 in the year 2011 were ophthalmologically examined. The only inclusion criterion was attending the selected schools in grade 1. There were no exclusion criteria. The Human Research Ethics Committee of the TongRen Hospital at the Capital Medical University, Beijing, approved the study design. Informed written consent was obtained from at least one parent per child. The baseline examination of the study was conducted in 2011, and the last follow-up examination was performed in 2016. The two study sites were the urban Beijing Dong Cheng District, which had an average income of ¥30,684 (US $4843) in 2010 (average income across all Beijing, ¥19,640 (US $3100)) and is located in the center of Beijing, and the rural Beijing Huai Rou District, which had an average income of ¥11,012 (US $1738) and is located in the southeast of Beijing 40 km from the city center.
Although the rural Beijing Hual Rou District is more developed than rural regions in western China, it consisted mainly of simple single-family houses with small gardens surrounded by walls. Family life predominantly took place within these compounds. The majority of the roads were not bituminized. In contrast, the urban study region was that Beijing Hual Rou District consisted of multistory houses and had relatively dense vehicle traffic in the streets. The study design and the study population have been described in detail recently.12,13

The eye examination carried out for all study participants consisted of measurement of the refractive error and an assessment of visual acuity, an evaluation of ocular motility, slit lamp-assisted biomicroscopy of the anterior and posterior segments of the eye, and nonmydriatic digital fundus photography (45°; CR-DGI camera; Canon Inc., Tokyo, Japan). By applying optical low-coherence reflectometry (Lenstar 900 optical biometer; Haag-Streit, Koeniz, Switzerland), the ocular biometric parameters of central corneal thickness, corneal curvature radius, anterior chamber depth, lens thickness, and axial length were measured in the right eyes of all children. The axial length:corneal curvature radius (ALCC) ratio was calculated.14 The refractive error was measured in a non-cycloplegic state, first automatically (auto-refractor KR-8900; Topcon, Tokyo, Japan) and then subjectively. In an attempt to prevent accommodation by the young study participants under the noncycloplegic conditions, we routinely started using correcting lenses of about +6 diopters for the assessment of refractive error, followed by slowly decreasing the refractive power of the correcting lens until the children achieved best corrected visual acuity. The interview of the parents consisted of a questionnaire with questions about the children's family history, time spent outdoors, activities performed outdoors, time spent indoors, and activities carried out indoors (supplementary material available online).

The size of the optic disc, optic cup, and parapapillary gamma zone were measured on the optic disc photographs by using Image J software (version 1.43u; developed by Wayne Rasband, National Institutes of Health, Bethesda, MD; available in the public domain at http://rsb.info.nih.gov/ij/index.html). In the region of the parapapillary gamma zone, the large choroidal vessels and the sclera were clearly visible. The parapapillary gamma zone had round borders with the adjacent alpha zone on its peripheral side and with the peripapillary ring of the optic disc on its central side (Fig. 1). The parapapillary gamma zone was differentiated from the parapapillary alpha zone, which had an irregular hypopigmentation and hyperpigmentation and was adjacent to the retina on its outer side.15,16 While studying the fundus photographs collected in the current study, the parapapillary gamma zone could not be clearly differentiated from the parapapillary beta zone, which had previously been defined by visible sclera and visible large choroidal vessels prior to the introduction of optical coherence tomography (OCT) into clinical ophthalmology.17 With the help of the OCT technology, the (old) beta zone could then be differentiated into a (new) beta zone, characterized by the presence of Bruch’s membrane without the retinal pigment epithelium, and into the parapapillary gamma zone without Bruch’s membrane.1,12 Subsequent studies revealed that the new OCT-defined beta zone was associated predominantly with glaucomatous optic neuropathy and to only a minor degree, if at all, with axial elongation.1,12 The gamma zone was strongly correlated with axial elongation, and it was not significantly associated with glaucomatous optic neuropathy.1,12 In our study, the parapapillary area with visible sclera was, therefore, considered to be the parapapillary gamma zone, because none of the study participants had glaucoma. An additional reason was that the newly defined beta zone occurs only rarely in children and adolescents.13,14 Magnification by the optic media of the eye was corrected by applying the method of Littmann and using axial length measurements.16,19 To calculate Littmann’s magnification factor, we applied the formula of (Axial Length [mm] − 1.82)/21.92. It was calculated for each fundus image separately, because axial length was elongated significantly (22.7 ± 0.8 mm versus 24.1 ± 1.1 mm; P < 0.001) during the study period. In contrast, the corneal curvature radius did not change significantly (7.82 ± 0.25 mm versus 7.83 ± 0.25 mm; P = 0.11). Correspondingly, Littmann’s factor increased significantly (from 0.95 ± 0.04 mm to 1.02 ± 0.05 mm; P < 0.001). The measurements were carried out by a trained ophthalmologist (YG) in a masked manner without knowledge of refractive error and axial length, and they were supervised by a panel of glaucoma specialists (LX, JBJ).

Statistical analysis was performed using a statistical software package (SPSS for Windows, version 22.0; SPSS, Chicago, IL, USA). Data from the right eyes were analyzed. The parameters were presented as the mean ± standard deviation. After conducting univariate linear regression analysis of associations between the size of the gamma zone and other variables, we performed a stepwise multivariate regression analysis with the size of gamma zone as the dependent variable and all independent variables, all those parameters which had shown a significant association with the gamma zone in the univariate analysis. The univariate analyses were not corrected when performing multiple statistical comparisons, because the results of the univariate analysis served only as the basis for the multivariate analysis. In the latter, all independent parameters that either showed an unacceptably high collinearity or that were no longer significantly associated with the dependent parameter (i.e., increase in the gamma zone area during the study period) were dropped step by step. The standardized regression coefficient beta and the nonstandardized regression coefficient B and its 95% CIs were calculated. All P values were 2-sided and were considered statistically significant when the values were less than 0.05.

RESULTS

Out of 387 eligible students, 382 (98.7%) children participated in the study at baseline. Out of these 382 grade 1 children examined at the baseline of this study in 2011, 294 (77.0%) children returned to be examined in 2016 and had sequential fundus photographs of sufficient quality to be assessed. Among them, 179 (60.9%) students were living in the urban region and the remaining 115 (39.1%) children came from the rural region. The mean age in 2016 was 11.4 ± 0.5 years (median, 11 years; range, 10–13 years), the mean refractive error was −1.57 ± 1.96 diopters (median, −1.13 diopters; range, −8.25 to +5.50 diopters), and the mean axial length was 24.1 ± 1.1 mm (median, 24.1 mm; range, 21.13 to 27.29 mm) (Table 1). Out of the original 382 children examined at baseline of this study, 88 (23%) children dropped out of the follow-up examination. The children participating in this study were slightly but significantly older (6.4 ± 0.5 years versus 6.2 ± 0.5 years; P = 0.006) compared to the children who dropped out, and the group of children participating in the study included relatively more girls than boys (46.6% versus 31.0%; P = 0.008) compared to the group of children who dropped out. Both groups did not differ significantly in axial length in 2011 (P = 0.25) or in refractive error (P = 0.95).

The prevalence of the gamma zone increased from 94/294 (32%; 95% CI, 26.6–37.3) in 2011 to 203/294 (69%; 95% CI, 65.7–74.4) in 2016 (Fig. 1). The maximal width of the gamma zone increased from 0.30 ± 0.11 mm in 2011 to 0.35 ± 0.35 mm in 2016 (Table 1). The cumulative incidence of the gamma...
zone was 109/294 or 37.1%. In the same period, the prevalence of myopia defined as a refractive error of \( \leq -0.50 \) diopters increased from 35.3% (95% CI, 30.4-40.2) in 2011 to 68.4% (95% CI, 63.2–73.6) in 2016. The prevalence of myopia defined as a refractive error of \( \leq -1.00 \) diopters increased from 15.2% (95% CI, 11.6–18.9) in 2011 to 56.7% (95% CI, 51.1-62.3) in 2016. The prevalence of myopia defined as a refractive error of \( \leq -1.50 \) diopters increased from 7.0% (95% CI, 4.4–9.5) in 2011 to 43.6% (95% CI, 38.1–49.2) in 2016. The prevalence of myopia defined as a refractive error of \( \leq -2.00 \) diopters

**FIGURE 1.** Optic disc photographs of an axially elongated eye in an adolescent individual, taken at baseline in 2011 (A, B) and in yearly follow-up examinations (C–J). *White arrow and yellow stars:* outer border of parapapillary gamma zone; *black arrow and black stars:* peripapillary ring of the optic disc.
increased from 1.9% (95% CI, 0.5–3.3) in 2011 to 35.2% (95% CI, 29.8–40.6) in 2016.

In univariate analysis, a larger increase in the parapapillary gamma zone area during the study period was significantly associated with the following ocular parameters: rural region of habitation, more myopic refractive error and longer axial length in 2011, larger increases in myopia and axial length over the study period, a higher ALCC ratio and larger increase in the ALCC ratio, larger horizontal optic disc diameter and smaller change in the horizontal disc diameter, larger increase in the vertical-to-horizontal disc diameter ratio (Fig. 2), and larger increase in the parapapillary gamma zone at baseline (Table 2). A larger increase in the parapapillary gamma zone area was significantly correlated with the following systemic parameters: less time spent outdoors with leisure (including walking, having a picnic, and playing games) \( (P = 0.006) \), a larger increase in the parameter of time spent outdoors with leisure during the study period \( (P = 0.04) \), less time spent outdoors with activities (including outdoors sports and riding a bicycle) \( (P = 0.03) \), more time spent indoors studying \( (P < 0.001) \), less time spent indoors watching television \( (P < 0.001) \), higher level of parental education \( (P = 0.01) \), higher level of parental profession (father, \( P < 0.001 \); mother, \( P = 0.001 \)), and higher prevalence of maternal myopia \( (P = 0.009) \) (Table 2).

The multivariate regression analysis included enlargement of the parapapillary gamma zone area as the dependent variable and all parameters that were significantly \( (P < 0.05) \) correlated with the change in gamma size were independent variables in the univariate analysis. Due to collinearity, we first dropped the parameters of time spent outdoors with leisure in 2011 (variance inflation factor [VIF], 74), time spent with outdoor activity in 2011 (VIF 6.8), change in refractive error (VIF 6.5), region of habitation (VIF 4.1), change in the ALCC ratio (VIF 7.0), horizontal disc diameter in 2011 (VIF 3.1), change in horizontal disc diameter (VIF 3.6), and maternal occupation (VIF 2.9). Due to the lack of statistical significance, we then dropped, step by step, the parameters of change in the amount of time spent outdoors with leisure \( (P = 0.91) \), maternal myopia \( (P = 0.71) \), paternal education \( (P = 0.66) \), paternal occupation \( (P = 0.60) \), refractive error in 2011 \( (P = 0.52) \), ALCC ratio in 2011 \( (P = 0.55) \), axial length in 2011 \( (P = 0.11) \) and amount of time spent watching television in 2011 \( (P = 0.09) \). In the final model, a larger increase in the gamma zone area during the study period was correlated \( (r^2 = 0.65) \) with a larger increase in the vertical-to-horizontal disc diameter ratio, a larger axial elongation during the study period, a larger vertical disc diameter in 2011, a larger gamma zone area in 2011, and more time spent indoors studying in 2011 (Table 3).
DISCUSSION

In this longitudinal school-based study on Chinese children with incident and progressing axial myopia, we found that the development and enlargement of the parapapillary gamma zone was associated with an increase in the vertical-to-horizontal disc diameter ratio in the multivariate analysis, which adjusted for axial elongation during the study period, vertical disc diameter in 2011, gamma zone area in 2011, and time spent indoors studying in 2011. An increase in the vertical-to-horizontal disc diameter ratio reflected a rotation of the optic disc around the vertical disc axis with backward movement of the temporal disc border. Causing an alteration in the ophthalmoscopic view of the optic disc, the vertical optic disc rotation led to a change in the ophthalmoscopically perceived optic disc shape, which changed from a more circular form to a more vertically oval form (Fig. 1). Other parameters associated with an increase in the size of the

![Image](http://arvojournals.org/)

**Figure 2.** Scattergram showing the distribution of the change in the vertical-to-horizontal optic disc diameter ratio versus the change gamma zone area in 2016 versus 2011.

**TABLE 1.** Characteristics of the Study Population at Baseline and at the Last Follow-up in 2016, Stratified by Region of Habitation (Mean ± Standard Deviation)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Year</th>
<th>Whole Study Population</th>
<th>Urban Region</th>
<th>Rural Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>2016</td>
<td>11.4 ± 0.5</td>
<td>11.4 ± 0.5</td>
<td>11.4 ± 0.5</td>
</tr>
<tr>
<td>Male/female (total)</td>
<td>2011</td>
<td>157/137 (¼294)</td>
<td>100/79 (¼179)</td>
<td>57/58 (¼115)</td>
</tr>
<tr>
<td>Refractive error, D</td>
<td>2011</td>
<td>−0.16 ± 0.90</td>
<td>−0.42 ± 0.90</td>
<td>+0.24 ± 0.74</td>
</tr>
<tr>
<td></td>
<td>2016</td>
<td>−1.57 ± 1.96</td>
<td>−2.09 ± 2.00</td>
<td>−0.78 ± 1.61</td>
</tr>
<tr>
<td>Axial length, mm</td>
<td>2011</td>
<td>22.7 ± 0.8</td>
<td>22.8 ± 0.8</td>
<td>22.4 ± 0.8</td>
</tr>
<tr>
<td></td>
<td>2016</td>
<td>24.1 ± 1.1</td>
<td>24.5 ± 1.0</td>
<td>23.5 ± 1.0</td>
</tr>
<tr>
<td>ALCC</td>
<td>2011</td>
<td>2.90 ± 0.08</td>
<td>2.91 ± 0.08</td>
<td>2.88 ± 0.07</td>
</tr>
<tr>
<td></td>
<td>2016</td>
<td>3.08 ± 0.14</td>
<td>3.12 ± 0.13</td>
<td>3.01 ± 0.11</td>
</tr>
<tr>
<td>Optic disc, horizontal diameter, mm</td>
<td>2011</td>
<td>1.68 ± 0.19</td>
<td>1.68 ± 0.19</td>
<td>1.68 ± 0.19</td>
</tr>
<tr>
<td></td>
<td>2016</td>
<td>1.91 ± 0.24</td>
<td>1.90 ± 0.24</td>
<td>1.92 ± 0.24</td>
</tr>
<tr>
<td>Optic disc, vertical diameter, mm</td>
<td>2011</td>
<td>1.90 ± 0.19</td>
<td>1.89 ± 0.18</td>
<td>1.92 ± 0.20</td>
</tr>
<tr>
<td></td>
<td>2016</td>
<td>2.25 ± 0.25</td>
<td>2.26 ± 0.23</td>
<td>2.19 ± 0.29</td>
</tr>
<tr>
<td>Optic disc, vertical-to-horizontal diameter ratio</td>
<td>2011</td>
<td>1.14 ± 0.09</td>
<td>1.13 ± 0.08</td>
<td>1.15 ± 0.09</td>
</tr>
<tr>
<td></td>
<td>2016</td>
<td>1.18 ± 0.13</td>
<td>1.20 ± 0.13</td>
<td>1.15 ± 0.13</td>
</tr>
<tr>
<td>Optic cup, horizontal diameter, mm</td>
<td>2011</td>
<td>0.67 ± 0.24</td>
<td>0.64 ± 0.24</td>
<td>0.71 ± 0.21</td>
</tr>
<tr>
<td></td>
<td>2016</td>
<td>0.74 ± 0.26</td>
<td>0.73 ± 0.25</td>
<td>0.76 ± 0.27</td>
</tr>
<tr>
<td>Optic cup, vertical diameter, mm</td>
<td>2011</td>
<td>0.72 ± 0.23</td>
<td>0.67 ± 0.23</td>
<td>0.80 ± 0.20</td>
</tr>
<tr>
<td></td>
<td>2016</td>
<td>0.84 ± 0.23</td>
<td>0.83 ± 0.22</td>
<td>0.85 ± 0.24</td>
</tr>
<tr>
<td>Gamma zone, widest width, mm</td>
<td>2011</td>
<td>0.07 ± 0.11</td>
<td>0.08 ± 0.17</td>
<td>0.16 ± 0.34</td>
</tr>
<tr>
<td></td>
<td>2016</td>
<td>0.35 ± 0.35</td>
<td>0.99 ± 0.98</td>
<td>0.50 ± 0.64</td>
</tr>
<tr>
<td>Gamma zone, area, mm²</td>
<td>2011</td>
<td>0.11 ± 0.25</td>
<td>0.06 ± 0.10</td>
<td>0.08 ± 0.12</td>
</tr>
<tr>
<td></td>
<td>2016</td>
<td>0.80 ± 0.89</td>
<td>0.43 ± 0.34</td>
<td>0.24 ± 0.27</td>
</tr>
</tbody>
</table>
gamma zone were the amount of axial elongation during the study period, the disc size at baseline (expressed as the vertical disc diameter), the size of gamma zone at baseline, and the amount of time spent indoors studying (Table 3). These findings confirmed the results obtained in a recent cross-sectional investigation of the population-based Beijing Eye Study.20 In that study, a wider parapapillary gamma zone was associated with a marked vertical optic disc rotation after adjusting for a marked horizontal optic disc rotation, a longer axial length, a longer horizontal optic disc diameter, a longer disc-fovea distance, a higher degree of fundus tessellation, and a thinner subfoveal choroidal thickness.20 The results of this study are also in agreement with a cross-sectional assessment of a larger study population of school children in which a higher optic disc ovality (similar to an increased vertical-to-horizontal disc diameter ratio in our study) was significantly associated with a larger parapapillary gamma zone in a multivariate analysis.21 The findings of our study also fit with the description of the appearance of the optic nerve head in highly myopic eyes, which were characterized by a large parapapillary gamma zone and a markedly vertically oval optic disc shape on fundus photographs.22,23 Our study agrees with a previous retrospective study on 118 Korean children with an age of 7.3 years (range, 1–17 years) at baseline and a mean follow-up period of 38 months (range, 12–88 months).24 In that study, progressive tilting of the optic nerve head (i.e., optic disc rotation around the vertical axis) was associated with the development and enlargement of parapapillary atrophy in children who showed progression of myopia. The novelties of our study included the following: a multivariate analysis of the associations of the parapapillary gamma zone was performed to decrease the risk of potentially confounding effects, our
study population was considerably larger than in previous investigations, study participants were recruited on the basis of school attendance and not hospital attendance, and participants were prospectively evaluated over a relatively long follow-up period of 5 years.

Questions remain regarding which factors might have been responsible for development of the parapapillary gamma zone in general and for the association between the gamma zone and the vertical optic disc rotation in particular. Recent studies by Wang and colleagues and by Demer have suggested that adduction movements of the eye cause pronounced strain on the optic nerve head and that these strains are stronger in axially elongated eyes than in short eyes. Based on biomechanical models of the optic nerve head and magnetic resonance images of the orbit in different gaze positions, it has been suggested that the backward pull of the optic nerve on the peripapillary structures of the optic disc during adduction, greater on the temporal side, is transferred by the optic nerve dura mater to the merging line of the optic nerve dura mater with the posterior sclera in the temporal parapapillary region. This pull of the optic nerve dura mater on the sclera in the temporal parapapillary region during the adduction movements may lead to local expansion (or stretching) of the sclera, parallel to vertical optic disc rotation. Interestingly, the size of the parapapillary gamma zone was associated with the amount of time spent indoors studying. This finding supports the notion of a backward pull of the temporal optic nerve head in the etiology of gamma zone, because studying is associated with adductive gaze movements during reading.

Interestingly, a larger increase in the gamma zone area was strongly correlated with a larger gamma zone area and a larger vertical disc diameter at baseline, after adjusting for parameters such as baseline axial length. The association may suggest that a given axial length in children, the probability of an increase in gamma zone was higher in eyes with a larger gamma zone area at baseline. This association may have clinical importance, because in a recent study on 810 eyes (432 patients) with a mean age of 42.3 ± 16.8 years, a mean axial length of 28.8 ± 1.9 mm at baseline, and a follow-up of 18.7 ± 7.1 years, the main risk factors for progression of myopic maculopathy were the development or enlargement of parapapillary atrophy (i.e. parapapillary gamma zone) besides older age and longer axial length.

The potential limitations of our study need to be discussed. First, the parapapillary gamma zone and optic disc dimensions and shape were measured on fundus photographs. If OCT images of the optic disc and the peripapillary region had been available, it would have been easier to distinguish the parapapillary gamma zone from the parapapillary beta zone, as most recently defined. Second, the availability of OCT images of the optic disc would also have allowed three-dimensional assessment of the optic disc shape in contrast to the two-dimensional assessment based on fundus photographs. Third, the validity of the questionnaires in capturing the activities of the children was not assessed. Fourth, because the study participants were recruited based on their school attendance, an inclusion bias might have occurred. Because this study did not focus on the prevalence of the parapapillary gamma zone but instead focused on associations of the gamma zone, it was unlikely that a potential inclusion bias markedly influenced the results and conclusions of our study.

In conclusion, the development and enlargement of a parapapillary gamma zone was associated with greater axial elongation, optic disc rotation around the vertical disc axis, and with more time spent indoors studying. The findings fit with the notion of a backward pull of the temporal peripapillary sclera through the optic nerve dura mater in axially elongated eyes.

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Jost B. Jonas holds a patent with Bio Compatibility Ltd. (Farnham, Surrey, UK; patent number 20120263794) and a patent application with the University of Heidelberg (Heidelberg, Germany; patent number 3070101).

Disclosure: Y. Guo, None; L.J. Liu, None; P. Tang, None; Y. Feng, None; Y.Y. Lv, None; M. Wu, None; L. Xu, None; J.B. Jonas, P.

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