

## Online Appendix

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2 The development of the ETDRS DME severity scale is summarized in Appendix Tables 1A  
3 and 1B, from Gangnon, R, et al. IOVS 2005;46:ARVO E-Abstract 3269 (Table 1A is from the final  
4 poster and differs slightly from the table in the E-Abstract, principally because the scale steps were  
5 renumbered). Table 1A presents mean baseline visual acuity score (VA) for both eyes of 3711  
6 ETDRS participants cross-classified by location of retinal thickening and its extent within one disc  
7 diameter of the center of the macula and by degree of retinal thickness at the center. Cells with  
8 similar VA were combined as shown using cluster analysis and clinical judgment. The diagonal  
9 pairing of many of the cells in levels 2 through 5B is as might be expected when two additive risk  
10 factors are cross-classified. The advantage of subdividing the large number of eyes (1363) with  
11 center thickness  $\geq 1X$ ,  $< 2X$  reference thickness by area of thickening within 1 DD of center (the “inner  
12 zone”) is apparent, as mean VA in the subdivisions falls from 81.8 to 64.3 letters as the area of  
13 involvement increases. Table 1B shows the cells of Table 1A pooled to produce the scale.

14 Appendix Table 2A presents median (quartiles) OCT-measured retinal thickness in the  
15 central subfield for the 435 eyes analyzed in this report in each cell of a table cross-classifying the  
16 same photographic variables as those in Table 1A. For the analyses in this report, the ETDRS DME  
17 severity scale was modified in three ways. First, the three lowest levels (1A, 1B, and 1C), which  
18 contain eyes with no retinal thickening at the center of the macula and little ( $< 1$  DA) or no retinal  
19 thickening within 1 DD of center, were combined because the OCT measures to be analyzed in this  
20 report would be expected to differ little between them. Second, levels 3A and 3B, which were similar  
21 in the original scale and had small numbers in our data set, were combined. Finally, the largest  
22 category for inner zone thickening provided by the original scale ( $\geq 2$  DA) was divided into two  
23 parts:  $\geq 2$  DA but  $< 3$  DA and  $\geq 3$  DA. As a result of this modification, separation of the 61 eyes in  
24 row 6, column 4, from the 47 eyes in row 5, column 4, made the scale more suitable for the large  
25 proportion of eyes with very severe DME in this data set. Appendix Table 2B shows the cells of  
26 Table 2A pooled to produce the modified scale.

27           Reproducibility of the photograph gradings underlying the modified ETDRS DME severity  
28 scale was assessed by regrading baseline and 12-month visits of 60 eyes selected to represent all  
29 steps in the scale at baseline but without regard to photo quality. The regradings were carried out  
30 without knowledge of the original gradings but graders were aware that this was a quality control  
31 exercise. Baseline and month 12 gradings were carried out independently of each other. For 2 of  
32 the 120 original gradings, the regrading was cannot grade for one or both of the abnormalities  
33 required for calculation of the scale and these gradings were excluded, leaving 118 replicate  
34 gradings. There was exact agreement in 42%, agreement within one step in 83%, and agreement  
35 within two steps in 93%. The weighted Kappa statistic (1-step disagreements weighed 0.75 and all  
36 other disagreements zero) was 0.58 (SE 0.05). Weighted Kappa statistics for the components of the  
37 scale were similar (0.58 for degree of thickening at the center of the macula and 0.67 for area of  
38 thickening in the inner zone categorized as it was in the ETDRS.

Appendix Table 1A. Mean (standard deviation) baseline visual acuity score\* in ETDRS eyes cross-classified by location and extent of retinal thickening and by thickness of the retina at the center of the macula assessed in stereoscopic color fundus photographs.

|  | Retinal Thickness at Center of the Macula |      |      |              |      |     |                 |      |     |                |      |      |           |      |     | Total |      |      |           |
|--|---|------|------|--------------|------|-----|-----------------|------|-----|----------------|------|------|-----------|------|-----|-------|------|------|-----------|
|  | None                                      |      |      | Questionable |      |     | <1X Reference † |      |     | ≥1X, <2X Ref † |      |      | ≥2X Ref † |      |     |       |      |      |           |
| Extent of Retinal Thickening   | Mean                                      | SD   | N    | Mean         | SD   | N   | Mean            | SD   | N   | Mean           | SD   | N    | Mean      | SD   | N   | Mean  | SD   | N    |           |
| None in Field 2  | 86.8                                      | 5.8  | 2463 |              |      |     |                 |      |     |                |      |      |           |      |     | 86.8  | 5.8  | 2463 | Level 1A  |
| None within 1 DD of center   | 86.2                                      | 6.2  | 761  |              |      |     |                 |      |     |                |      |      |           |      |     | 86.2  | 6.2  | 761  | Level 1B  |
| Questionable within 1 DD of center   | 85.0                                      | 7.1  | 401  | 82.2         | 8.5  | 216 |                 |      |     |                |      |      |           |      |     | 84.0  | 7.7  | 617  | Level 1C  |
| Definite, <1/2 DA within 1 DD of center  | 85.2                                      | 6.7  | 522  | 82.5         | 8.9  | 315 | 81.2            | 8.5  | 175 | 81.8           | 8.2  | 102  | 75.0      | NA   | 1   | 83.5  | 8.0  | 1115 | Level 2   |
| ≥1/2 DA, <1 DA within 1 DD of center   | 83.2                                      | 8.2  | 145  | 81.1         | 10.2 | 216 | 78.9            | 9.6  | 235 | 77.2           | 10.9 | 223  | 72.5      | 14.1 | 6   | 79.8  | 10.1 | 825  | Level 3A  |
| ≥1 DA, < 2 DA within 1 DD of center  | 82.2                                      | 9.0  | 30   | 79.6         | 11.9 | 90  | 75.1            | 12.3 | 282 | 72.8           | 12.4 | 571  | 66.7      | 15.0 | 34  | 74.1  | 12.7 | 1007 | Level 3B  |
| ≥2 DA within 1 DD of center  | 60.7                                      | 13.9 | 3    | 87.0         | 8.5  | 7   | 72.1            | 13.3 | 58  | 64.3           | 14.6 | 467  | 59.8      | 13.6 | 99  | 64.5  | 14.7 | 634  | Level 4   |
| Total  | 86.2                                      | 6.3  | 4325 | 81.8         | 9.5  | 844 | 77.5            | 11.1 | 750 | 71.3           | 13.9 | 1363 | 62.2      | 14.4 | 140 | 81.6  | 11.2 | 7422 | Level 5 A |
| DD, disc diameter; DA, disc area   |   |      |      |              |      |     |                 |      |     |                |      |      |           |      |     |       |      |      |           |
| *Sneller equivalents: 100 = 20/10, 85 = 20/20, 70 = 20/40, 65 = 20/50, 60 = 20/63                                      |   |      |      |              |      |     |                 |      |     |                |      |      |           |      |     |       |      |      |           |
| †Reference thickness is the maximum thickness of normal retina 0.5 to 1.0 disc diameter from the center of the macula. |   |      |      |              |      |     |                 |      |     |                |      |      |           |      |     |       |      |      |           |

| <b>Appendix Table 1B. Mean (standard deviation) baseline VA score by level on ETDRS DME severity scale</b> |             |             |             |
|--|-------------|-------------|-------------|
|  | <b>Mean</b> | <b>SD</b>   | <b>N</b>    |
| <b>Level 1A</b>  | <b>86.8</b> | <b>5.8</b>  | <b>2463</b> |
| <b>Level 1B</b>  | <b>86.2</b> | <b>6.2</b>  | <b>761</b>  |
| <b>Level 1C</b>  | <b>84.8</b> | <b>7.1</b>  | <b>1068</b> |
| <b>Level 2</b>   | <b>81.9</b> | <b>9.0</b>  | <b>1055</b> |
| <b>Level 3A</b>  | <b>79.1</b> | <b>10.4</b> | <b>335</b>  |
| <b>Level 3B</b>  | <b>76.1</b> | <b>11.8</b> | <b>505</b>  |
| <b>Level 4</b>   | <b>72.7</b> | <b>12.5</b> | <b>635</b>  |
| <b>Level 5A</b>  | <b>64.5</b> | <b>14.6</b> | <b>501</b>  |
| <b>Level 5B</b>  | <b>59.8</b> | <b>13.6</b> | <b>99</b>   |

| Appendix Table 2A. Median (quartiles) OCT-measured retinal thickness at baseline in the central subfield of 435 DRCR network eyes cross-classified by area of retinal thickening and thickness of the retina at the center of the macula assessed in stereoscopic color fundus photographs, within each of the cells that are combined to produce in the modified ETDRS DME severity scale. |                         |                       |     |              |                       |    |                |                       |    |                |                       |     |           |                       |    |                       |     |
|---|-------------------------|-----------------------|-----|--------------|-----------------------|----|----------------|-----------------------|----|----------------|-----------------------|-----|-----------|-----------------------|----|-----------------------|-----|
| Retinal Thickness at the Center of the Macula   |                         |                       |     |              |                       |    |                |                       |    |                |                       |     |           |                       |    |                       |     |
| RT area<br>inner zone<br>disc areas   | None                    |                       |     | Questionable |                       |    | <1X Reference* |                       |    | >=1X, <2X Ref* |                       |     | >=2X Ref* |                       |    | Total                 |     |
|   | Level                   | Median<br>(Quartiles) | N   | Level        | Median<br>(Quartiles) | N  | Level          | Median<br>(Quartiles) | N  | Level          | Median<br>(Quartiles) | N   | Level     | Median<br>(Quartiles) | N  | Median<br>(Quartiles) | N   |
| 0   | 1A &<br>1B <sup>‡</sup> | 235<br>(210, 269)     | 74  |              |                       |    |                |                       |    |                |                       |     |           |                       |    | 235<br>(210, 269)     | 74  |
| <0.5  | 1C                      | 237<br>(214, 262)     | 63  | 2            | 250<br>(202, 268)     | 11 | 2              | 239<br>(210, 267)     | 3  | 2              | 289<br>(277, 300)     | 2   | 2         |                       | 0  | 239<br>(214, 267)     | 79  |
| 0.5 - <1.0  | 1C                      | 244<br>(217, 263)     | 23  | 2            | 237<br>(217, 261)     | 15 | 3A             | 296<br>(258, 363)     | 8  | 3B             | 306<br>(298, 355)     | 8   | 4         |                       | 0  | 252<br>(225, 293)     | 54  |
| 1.0 - <2.0  | 2                       | 214<br>(204, 258)     | 7   | 3A           | 268<br>(238, 341)     | 14 | 3B             | 265<br>(244, 304)     | 25 | 4              | 334<br>(287, 401)     | 46  | 5A        |                       | 0  | 290<br>(253, 359)     | 92  |
| 2.0 - <3.0  | 3A                      | 281                   | 1   | 3A           | 191                   | 1  | 4              | 290<br>(263, 324)     | 10 | 5A             | 363<br>(282, 424)     | 47  | 5B        | 430<br>(373,486)      | 2  | 343<br>(278, 419)     | 61  |
| >= 3.0  | 3A                      |                       | 0   | 4            | 259                   | 1  | 5A             | 323<br>(187, 404)     | 3  | 5B             | 436<br>(298, 545)     | 61  | 5C        | 517<br>(455, 598)     | 10 | 445<br>(318, 545)     | 75  |
| <b>Total</b>  |                         | 236<br>(214, 264)     | 168 |              | 244<br>(225, 271)     | 42 |                | 272<br>(244, 315)     | 49 |                | 365<br>(290, 451)     | 164 |           | 503<br>(451, 570)     | 12 | 273<br>(233, 364)     | 435 |

RT, retinal thickening; inner zone, area within 1 disc diameter of the center of the macula (total = 4 disc areas).

\*Reference thickness is the maximum thickness of normal retina 0.5 to 1.0 disc diameter from the center of the macula.

<sup>‡</sup>Level 1A=no RT in photographic field 2; 1B=RT in field 2, but none in the inner zone.

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| <b>Appendix Table 2B. Median (quartiles) OCT-measured retinal thickness in the central subfield in each level of the modified ETDRS DME severity scale.</b> |                           |            |
|---|---------------------------|------------|
|   | <b>Median (Quartiles)</b> | <b>N</b>   |
| <b>Level 1</b>  | <b>236</b> (214, 264)     | <b>160</b> |
| <b>Level 2</b>  | <b>238</b> (214, 267)     | <b>38</b>  |
| <b>Level 3</b>  | <b>274</b> (244, 315)     | <b>57</b>  |
| <b>Level 4</b>  | <b>327</b> (283, 394)     | <b>57</b>  |
| <b>Level 5A</b>   | <b>355</b> (282, 420)     | <b>50</b>  |
| <b>Level 5B</b>   | <b>436</b> (298, 545)     | <b>63</b>  |
| <b>Level 5C</b>   | <b>517</b> (455, 598)     | <b>10</b>  |

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