Validation of the Postnatal Growth and Retinopathy of Prematurity Screening Criteria

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IMPORTANCE The first Postnatal Growth and Retinopathy of Prematurity Study (G-ROP-1) developed new screening criteria with 100% sensitivity for type 1 retinopathy of prematurity (ROP) and 30% reduction of infants requiring examinations in a retrospective development cohort of 7483 infants from 29 North American hospitals in 2006-2012. Infants meeting 1 or more of the following criteria undergo examinations: gestational age less than 28 weeks or birth weight less than 1051 g; weight gain less than 120 g during age 10 to 19 days, weight gain less than 180 g during age 20 to 29 days, or weight gain less than 170 g during age 30 to 39 days; or hydrocephalus.

OBJECTIVE To evaluate the generalizability of the G-ROP screening criteria in a new cohort of at-risk infants.

DESIGN, SETTING, AND PARTICIPANTS This prospective validation cohort study (G-ROP-2) was conducted at 41 hospitals in the United States and Canada (25 G-ROP-1 hospitals and 16 new hospitals) from September 8, 2015, to June 13, 2017, among 3981 premature infants at risk for ROP and with known ROP outcomes.

MAIN OUTCOMES AND MEASURES Sensitivity for Early Treatment for Retinopathy of Prematurity Study type 1 ROP and potential reduction in infants receiving examinations.

RESULTS Among the 3981 infants in the study (1878 girls and 2103 boys; median gestational age, 28 weeks [range, 22-35 weeks]; median birth weight, 1072 g [range, 350-4080 g]; 1966 white; 942 black; 321 Latino; 122 Native Hawaiian or Pacific Islander; and 25 American Indian or Alaskan Native), the G-ROP criteria correctly predicted 219 of 219 cases of type 1 ROP (sensitivity, 100%; 95% CI, 98.3%-100%), while reducing the number of infants undergoing examinations by 35.6% (n = 1418). In a combined G-ROP-1 and G-ROP-2 cohort of 11 463 infants, the G-ROP criteria predicted 677 of 677 cases of type 1 ROP (sensitivity, 100%; 95% CI, 99.4%-100%), reducing the number of infants receiving examinations by 32.5% (n = 3730), while current criteria (birth weight <1501 g or gestational age <30 weeks 0 days) predicted 674 of 677 type 1 cases (sensitivity, 99.6%; 95% CI, 98.7%-99.8%).

CONCLUSIONS AND RELEVANCE This study found that the G-ROP screening criteria were generalizable on validation and, if used clinically in the United States and Canada, could reduce the number of infants receiving examinations. The large G-ROP cohorts provide evidence-based screening criteria that have higher sensitivity and higher specificity (fewer infants receiving examinations) for type 1 ROP than currently recommended guidelines.

Retinopathy of prematurity (ROP) is a potentially blinding disease of the developing retinal vasculature in premature infants. Those at risk for ROP undergo serial diagnostic retinal examinations to identify severe disease characteristics (type 1 ROP), for which treatment is recommended to reduce the risk of further progression to retinal detachment. Infants at risk for ROP are identified using recommended birth weight (BW) and gestational age at birth (GA) criteria. These BW and GA levels are set high in an attempt to ensure that all infants requiring treatment are examined; in the United States, these levels are currently BW less than 1501 g or GA of 30 weeks 0 days or less. These criteria have low specificity for type 1 ROP, as only about 7% of examined infants receive treatment, and only about half of examined infants develop any ROP. Although the BW and GA criteria have high sensitivity for type 1 ROP, they do not have 100% sensitivity, as infants with higher BW and GA sometimes develop type 1 ROP. Consequently, a third subjective, poorly defined criterion of a poor postnatal course is also used in the United States for infants with higher BW and older GA. Therefore, there is potential to improve both the specificity and sensitivity of the current ROP screening criteria, if additional predictive factors can be incorporated in a systematic and practically implementable manner.

The incorporation of measures of slow postnatal weight gain into ROP screening criteria based solely on BW and GA improves their specificity. Slow postnatal weight gain is a proposed surrogate measure for low serum insulinlike growth factor 1 and possibly other factors that result in decreased retinal vascular endothelial growth factor activity, poor retinal vessel development, and subsequent ROP. The development of modified ROP screening criteria incorporating measures of slow postnatal weight gain, using data from a retrospective cohort of 7483 infants at 29 hospitals in the United States and Canada in the Postnatal Growth and ROP (G-ROP) Study (Figure) was previously reported. In the G-ROP screening criteria, BW and GA thresholds were lowered to BW less than 1051 g or GA less than 28 weeks; 3 slow weight gain criteria were added to capture infants with higher BW or older GA who developed type 1 ROP; and a sixth criterion, hydrocephalus, was included as a source of nonphysiologic weight gain. Infants meeting any 1 or more of the 6 criteria would receive eye examinations for ROP. The G-ROP criteria had 100% sensitivity for predicting the 459 infants who developed type 1 ROP in the development study cohort, while reducing by 35.6% if only infants meeting screening criteria received examinations.

The criteria would be applied by beginning at the lower left hand of the diagram and proceeding in a clockwise fashion around the 6 criteria. If the gestational age (GA) is younger than 28 weeks, then the infant would receive retinal examinations. If the GA is 28 weeks or older, the next criterion (birth weight [BW]) would be checked, and so forth. If none of the criteria apply, then the infant would not receive retinal examinations.

We sought to evaluate the generalizability of the G-ROP screening criteria in a new cohort of at-risk infants. Although the criteria were developed using a large, diverse cohort, validation is required before the criteria can be recommended for clinical use and widespread implementation.

Methods

We conducted a multicenter prospective cohort study, the G-ROP Validation Study (designated G-ROP-2). We collected data on infants who underwent eye examinations for ROP at 41 hospitals in the United States and Canada: 25 hospitals that had participated in the retrospective G-ROP model development study (now designated G-ROP-1) and 16 new hospitals. Eligible infants were those who underwent ROP examinations between September 8, 2015, and June 13, 2017. Birth weight and GA limits were not used as inclusion criteria, to make the cohort fully representative of all infants undergoing ROP examinations. Infants were deemed evaluable if they had a known ROP outcome. Infants were considered to have a known ROP outcome if (1) either eye had Early Treatment for Retinopathy of Prematurity Study type 1 ROP; type 2 ROP; or treatment; or (2) both eyes had retinal vasculature maturity, immature vasculature extending into zone III without prior disease in zone I or II, or regression of ROP that had not reached criteria for type 1 or 2 ROP. Infants who did not have a known ROP outcome were excluded. Data collectors were trained and certified for the study. They collected detailed ophthalmologic and medical data, which included BW, GA, and daily postnatal weight measurements, from the medical record. These data were entered into a centralized web-based database. Data quality was ensured through data-entry validation rules, data audits, and discrepancy check algorithms. All flagged values were investigated and resolved.
by the data coordinating center in collaboration with local site data collectors who referred back to source documents. Institutional review board approval was obtained from Children’s Hospital of Philadelphia and all study hospitals and waiver of consent based upon 45 CFR 46 was granted at all study hospitals.

In the primary analysis, we applied the screening criteria developed in G-ROP-1. Infants would receive examinations if they met any 1 or more of 6 criteria: BW less than 1051 g; GA less than 28 weeks 0 days; weight gain less than 120 g during the second 10 days after birth (ages, 10-19 days), weight gain less than 180 g during the third 10 days after birth (ages, 20-29 days), or weight gain less than 170 g during the fourth 10 days after birth (ages, 30-39 days); or hydrocephalus diagnosed on results of brain imaging study (ultrasonography, computed tomography, or magnetic resonance imaging) during the first 40 postnatal days.

The primary study outcomes were (I) sensitivity for predicting Early Treatment for Retinopathy of Prematurity type 1 ROP (proportion of infants who developed type 1 disease in 1 or both eyes for whom examinations would be indicated by the G-ROP criteria) and (2) the reduction in individual infants receiving examinations, which is a more intuitive measure of the specificity of the criteria. In these analyses, the criteria were used hypothetically to make “all-or-none” ROP screening decisions (ie, infants who met the screening criteria would receive examinations, and the remaining infants would not). Secondary outcomes included sensitivities for Early Treatment for Retinopathy of Prematurity type 2 ROP and infants receiving ROP treatment. The 95% and 99% CIs for sensitivity were calculated using the Wilson method. The performance of the G-ROP criteria was compared with the performance of the currently recommended BW and GA criteria using a combined G-ROP-1 and G-ROP-2 cohort to maximize the precision of the sensitivity estimates for each set of criteria. The G-ROP criteria do not contain a subjective criterion, so such a criterion was not considered in comparing the performance of the criteria with the current BW and GA criteria. An a priori plan was made to update or further adjust the G-ROP criteria using the combined G-ROP-1 and G-ROP-2 data sets if the sensitivity for type 1 ROP was less than 100%, because updating is the recommended approach in that circumstance. However, updating was not necessary. Finally, we considered a post hoc simplification of the G-ROP criteria in which the same weight gain threshold value was used for all 3 growth periods, to make the criteria as user friendly as possible. All statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc).

Table 1. Birth Weight and Gestational Age at Birth of 3981 Infants in the Postnatal Growth and Retinopathy of Prematurity Validation Study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Type 1 ROP (n = 219)*</th>
<th>Type 2 ROP (n = 264)*</th>
<th>Stage 3 Zone III ROP (n = 20)*</th>
<th>Mild ROP (n = 1140)*</th>
<th>No ROP (n = 2338)*</th>
<th>Total (N = 3981)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight, g</td>
<td>Mean (SD)</td>
<td>Median (IQR)</td>
<td>Mean (SD)</td>
<td>Median (IQR)</td>
<td>Mean (SD)</td>
<td>Median (IQR)</td>
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<td>[range]</td>
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<td>[range]</td>
<td>[range]</td>
<td>[range]</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>687 (162)</td>
<td>723 (212)</td>
<td>924 (212)</td>
<td>931 (288)</td>
<td>1243 (309)</td>
<td>1087 (351)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>665 (576-780)</td>
<td>690 (580-820)</td>
<td>845 (771-1110)</td>
<td>890 (720-1100)</td>
<td>1255 (1030-1440)</td>
<td>1072 (800-1340)</td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>Mean (SD)</td>
<td>24.6 (1.5)</td>
<td>24.9 (1.7)</td>
<td>26.8 (2.6)</td>
<td>26.8 (2.3)</td>
<td>29.3 (2.2)</td>
</tr>
<tr>
<td></td>
<td>[range]</td>
<td>[22.0-32.0]</td>
<td>[24.0-32.0]</td>
<td>[22.0-32.0]</td>
<td>[22.0-32.0]</td>
<td>[22.0-32.0]</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>24.0 (24.0-25.0)</td>
<td>25.0 (24.0-26.0)</td>
<td>26.0 (24.5-28.5)</td>
<td>27.0 (25.0-28.0)</td>
<td>29.0 (28.0-31.0)</td>
<td>28.0 (26.0-30.0)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>[22.0-32.0]</td>
<td>[22.0-32.0]</td>
<td>[22.0-32.0]</td>
<td>[22.0-32.0]</td>
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</tr>
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Abbreviations: IQR, interquartile range; ROP, retinopathy of prematurity.

* Infants are categorized by worst ROP diagnosis.

Results

Of 4371 eligible infants in G-ROP-2, 3981 infants had a known ROP outcome and were included in the analysis (Table 1). A total of 390 infants without a known outcome were excluded; reasons included transfer to a nonstudy hospital (98 infants), outpatient follow-up with a nonstudy ophthalmologist (250), and death (42). The median BW was 1072 g (range, 350-4080 g), and the median GA was 28 weeks (range, 22-38 weeks). There were 1878 girls (47.2%), 1966 white infants (49.4%), 942 black infants (23.7%), 321 Latino infants (8.1%), 120 Asian infants (3.0%), 22 Native Hawaiian or Pacific Islander infants (0.6%), and 25 American Indian or Alaskan Native infants (0.6%). Race/ethnicity was not reported for 559 infants (14.0%), and 3047 infants (76.5%) were born at a study hospital.

Retinopathy of prematurity developed in 1643 infants (41.3%), of whom 219 (5.5%) developed type 1 ROP, 264 (6.6%) developed type 2 ROP, and 256 (6.4%) were treated; of the infants who were treated, 217 had type 1 ROP, 31 had type 2 ROP, and 8 had stage 2 or 3, zone III ROP. Application of the G-ROP criteria, without updating, correctly predicted type 1 ROP in 219 of 219 infants (sensitivity, 100%; 95% CI, 98.3%-100%), type 2 ROP in 264 of 264 infants, and treatment for ROP in 253 of 256 infants (sensitivity, 98.8%; 95% CI, 96.6%-99.6%) (Table 2). Of 3981 infants in the study, 1418 (35.6%) did not meet any of the 6 criteria and would not have received examinations if the study hospitals had been using these criteria for ROP screening. Forty-one hospitals participated in G-ROP-2; among the 25 hospitals that had also participated in G-ROP-1, the G-ROP criteria predicted type 1 ROP in 156 of 156 infants (sensitivity, 100%; 95% CI, 97.6%-100.0%), and 954 of 2746 infants (34.7%) would not have received examinations; among the 16 new hospitals that had not participated in G-ROP-1, the G-ROP criteria predicted type 1 ROP in 63 of 63 infants (sensitivity, 100%; 95% CI, 94.3%-100%), and 464 of 1235 infants (37.6%) would not have received examinations.
The study outcomes were further assessed using a combination of the G-ROP-1 and G-ROP-2 study cohorts (Table 3). Among 11,463 infants in the combined cohort, the G-ROP criteria correctly predicted type 1 ROP in 677 of 677 infants (sensitivity, 100%; 95% CI, 99.4%-100.0%), type 2 ROP in 727 of 737 infants (sensitivity, 98.6%; 95% CI, 97.5%-99.3%), and treatment for ROP in 767 of 770 infants (sensitivity, 99.6%; 95% CI, 98.9%-99.9%). There were 3730 infants (32.5%) who did not meet criteria and would not have received examinations. The currently recommended BW and GA guidelines (BW <1501 g or GA ≤30 weeks) correctly predicted type 1 ROP in 674 of 677 infants (sensitivity, 99.6%; 95% CI, 98.7%-99.8%), type 2 ROP in 735 of 737 infants (sensitivity, 99.7%; 95% CI, 99.0%-99.9%), and treatment for ROP in 767 of 770 infants (sensitivity, 99.6%; 95% CI, 98.9%-99.9%). There were 3730 infants (32.5%) who did not meet criteria and would not have received examinations. The currently recommended BW and GA guidelines (BW <1501 g or GA ≤30 weeks) correctly predicted type 1 ROP in 674 of 677 infants (sensitivity, 99.6%; 95% CI, 98.7%-99.8%), type 2 ROP in 735 of 737 infants (sensitivity, 99.7%; 95% CI, 99.0%-99.9%), and treatment for ROP in 767 of 770 infants (sensitivity, 99.6%; 95% CI, 98.9%-99.9%). There were 3730 infants (32.5%) who did not meet criteria and would not have received examinations. The currently recommended BW and GA guidelines (BW <1501 g or GA ≤30 weeks) correctly predicted type 1 ROP in 674 of 677 infants (sensitivity, 99.6%; 95% CI, 98.7%-99.8%), type 2 ROP in 735 of 737 infants (sensitivity, 99.7%; 95% CI, 99.0%-99.9%), and treatment for ROP in 767 of 770 infants (sensitivity, 99.6%; 95% CI, 98.9%-99.9%). There were 3730 infants (32.5%) who did not meet criteria and would not have received examinations. The currently recommended BW and GA guidelines (BW <1501 g or GA ≤30 weeks) correctly predicted type 1 ROP in 674 of 677 infants (sensitivity, 99.6%; 95% CI, 98.7%-99.8%), type 2 ROP in 735 of 737 infants (sensitivity, 99.7%; 95% CI, 99.0%-99.9%), and treatment for ROP in 767 of 770 infants (sensitivity, 99.6%; 95% CI, 98.9%-99.9%). There were 3730 infants (32.5%) who did not meet criteria and would not have received examinations. The currently recommended BW and GA guidelines (BW <1501 g or GA ≤30 weeks) correctly predicted type 1 ROP in 674 of 677 infants (sensitivity, 99.6%; 95% CI, 98.7%-99.8%), type 2 ROP in 735 of 737 infants (sensitivity, 99.7%; 95% CI, 99.0%-99.9%), and treatment for ROP in 767 of 770 infants (sensitivity, 99.6%; 95% CI, 98.9%-99.9%). There were 3730 infants (32.5%) who did not meet criteria and would not have received examinations. The currently recommended BW and GA guidelines (BW <1501 g or GA ≤30 weeks) correctly predicted type 1 ROP in 674 of 677 infants (sensitivity, 99.6%; 95% CI, 98.7%-99.8%), type 2 ROP in 735 of 737 infants (sensitivity, 99.7%; 95% CI, 99.0%-99.9%), and treatment for ROP in 767 of 770 infants (sensitivity, 99.6%; 95% CI, 98.9%-99.9%). There were 3730 infants (32.5%) who did not meet criteria and would not have received examinations. The currently recommended BW and GA guidelines (BW <1501 g or GA ≤30 weeks) correctly predicted type 1 ROP in 674 of 677 infants (sensitivity, 99.6%; 95% CI, 98.7%-99.8%), type 2 ROP in 735 of 737 infants (sensitivity, 99.7%; 95% CI, 99.0%-99.9%), and treatment for ROP in 767 of 770 infants (sensitivity, 99.6%; 95% CI, 98.9%-99.9%). There were 3730 infants (32.5%) who did not meet criteria and would not have received examinations. The currently recommended BW and GA guidelines (BW <1501 g or GA ≤30 weeks) correctly predicted type 1 ROP in 674 of 677 infants (sensitivity, 99.6%; 95% CI, 98.7%-99.8%), type 2 ROP in 735 of 737 infants (sensitivity, 99.7%; 95% CI, 99.0%-99.9%), and treatment for ROP in 767 of 770 infants (sensitivity, 99.6%; 95% CI, 98.9%-99.9%). There were 3730 infants (32.5%) who did not meet criteria and would not have received examinations.}

### Discussion

The G-ROP criteria were validated in a new cohort of at-risk infants, both “externally” at new hospitals that had not participated in the G-ROP-1 study, and “temporally” during a later study period at hospitals that had participated in the G-ROP-1 study. The G-ROP criteria, without updating, correctly predicted all infants with type 1 ROP, and the number of infants receiving ROP examinations would have been reduced by more than one-third if the criteria had been used to make screening decisions. These criteria are the first weight gain-based model to maintain 100% sensitivity on validation, likely because of the large cohort in the first G-ROP study. The large number of cases of severe ROP in that study helped to minimize overfitting to the data. In contrast, prior models incorporating measures of slow postnatal weight gain, such as the WINROP (Weight, IGF-1, Neonatal Retinopathy of Prematurity), CHOP ROP (Children’s Hospital of Philadelphia Retinopathy of Prematurity), and CO-ROP (Colorado Retinopathy of Prematurity) models, were developed using small cohorts and had less than 100% sensitivity in validation studies and thus were not sufficiently generalizable on validation to be used clinically for all or none screening decisions. The absence of a need to update the G-ROP criteria to accurately predict all infants developing type 1 ROP in the validation cohort provides additional confidence in the robustness of the criteria.

The G-ROP criteria demonstrated higher sensitivity than the current BW and GA criteria for type 1 ROP (100% vs 99.6%) and a greater reduction in the number of infants requiring examinations (32.5% vs 9.2%) (Table 3). These findings suggest that the G-ROP criteria would be a dominant strategy with respect to both clinical effectiveness and cost-effectiveness; the latter may be confirmed with a formal cost-effectiveness analysis.
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The G-ROP criteria did not require a subjective criterion to accurately predict all infants who developed type 1 ROP. However, the use of a subjective criterion alongside the G-ROP criteria might provide an additional safety measure. It could facilitate capture of some otherwise missed cases of type 2 ROP, as it does now for the current BW and GA guidelines; enable ophthalmologists to consider additional sources of nonphysiologic weight gain, such as excessive whole-body edema; and make use of the new criteria more palatable to neonatologists, who would retain an ability to apply clinical judgment by requesting ROP examinations for infants they perceive to be at high risk. Finally, it would enable the G-ROP criteria to perform as well as current guidelines but with the benefit of a significantly reduced screening burden.

There are additional practical considerations. The criteria are easy to use (Figure). Infants who meet either of the first 2 of the G-ROP criteria (the BW or the GA criteria) do not require any growth calculations.9 For other infants, weight measurements are routinely collected in the neonatal intensive care unit and therefore are readily available. However, the 3 weight gain criteria could be simplified further if a single value is applied to all 3 periods. Using the conservative threshold of weight gain less than 180 g for each 10-day period, the sensitivity for type 1 ROP is maintained at 100% and still achieves a 27.3% reduction in infants requiring examinations (Table 3). To apply the G-ROP criteria, clinicians would need some additional guidance as to which infants the growth and hydrocephalus criteria should be applied. One approach is to set an upper limit for GA; for example, the criteria would be applied to infants with GA less than 33 weeks, because type 1 and type 2 ROP did not develop in infants with older GA in either G-ROP-1 or G-ROP-2. Finally, the G-ROP criteria could be used for all or none screening decisions or to modify examination schedules. Infants who do not meet the G-ROP criteria would be considered at low risk for ROP. Low-risk infants might undergo no examinations to detect acute phase ROP, as was simulated in the G-ROP-1 and G-ROP-2 studies. To be used in this fashion, the modified criteria likely would need to be incorporated into published ROP guidelines for clinicians to feel comfortable changing their practice. Alternatively, one might envision low-risk infants receiving fewer examinations. For example, their examinations may start later, the interval between examinations may be increased21, or their examinations may be ended sooner, such as at a specific postmenstrual age or on hospital discharge so that outpatient follow-up would not be necessary. These possibilities require further analysis before application.

Limitations

There are limitations of the G-ROP studies to consider. The criteria should not be generalized to countries in which excessive oxygen supplementation is the primary cause of ROP and postnatal weight gain is not reliably predictive of ROP.22-24 The criteria may prove to be robust in countries with highly developed neonatal care systems, but formal validation studies should be performed in those other populations before clinical use. For example, the G-ROP criteria were recently reported to have 100% sensitivity in a cohort of 692 Japanese infants, of whom 81 were treated.25 The study data in both G-ROP studies were obtained during the normal course of clinical care. Retinopathy of prematurity examinations were not standardized with regard to method or timing; however, the ophthalmologists had expertise in ROP and used standard classification terms. The weight measurements were also not regimented, but these data incorporate the variability seen for this routinely collected clinical measurement. More generally, the use of real-world data for these studies arguably provides the best simulated clinical application of the criteria.

An important limitation of the first study was the potential for subsequent changes in neonatal care to decrease the generalizability of the criteria. However, the criteria performed well despite potential changes in care that likely occurred in the years between G-ROP-1 (retrospective data from 2006 to 2012) and G-ROP-2 (prospective data from 2015 to 2017). For example, during this intervening period, the results of multiple harmonized randomized trials (the NeOProM [Neonatal Oxygenation Prospective Meta-analysis Collaboration] studies) comparing lower (85%-89%) with higher (91%-95%) oxygen saturation target ranges suggested an increase in mortality for infants in the lower oxygen range.26,27 As a result, some hospitals shifted their oxygen saturation targets to a higher level, so some change in the characteristics of infants developing ROP might be expected.

Conclusions

The G-ROP screening criteria were developed and successfully validated in 2 successive, diverse cohorts representative...
of infants undergoing ROP examinations in North America. The 2 large cohorts studied provide evidence-based screening criteria with higher sensitivity and higher specificity than the currently recommended ROP screening guidelines. The criteria can be used clinically to potentially reduce the number of infants receiving examinations. We recommend incorporation of the G-ROP screening criteria into national ROP screening guidelines.

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Validation of the Postnatal Growth and Retinopathy of Prematurity Screening Criteria

**Original Investigation**

**Research**

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**REFERENCES**


