JAMA Ophthalmology
View Article

JAMA Ophthalmol. 2020 Jan; 138(1): 31–37.
Published online 2019 Nov 14.
doi: 10.1001/jamaophthalmol.2019.4517: 10.1001/jamaophthalmol.2019.4517

PMCID: PMC6865315
PMID: 31725856

Validation of the Postnatal Growth and Retinopathy of Prematurity Screening Criteria

Gil Binenbaum, MD, MSCE,[1,2] Lauren A. Tomlinson, BS,[1] Alejandra G. de Alba Campomanes, MD, MPH,[3] Edward F. Bell, MD,[4] Pamela Donohue, ScD,[5] David Morrison, MD,[6] Graham E. Quinn, MD, MSCE,[1,2] Michael X. Repka, MD, MBA,[7] David Rogers, MD,[8] Michael B. Yang, MD,[9,10] Yinxi Yu, MS,[2] and Gui-shuang Ying, PhD[2], for the Postnatal Growth and Retinopathy of Prematurity (G-ROP) Study Group

[1]Division of Ophthalmology, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania
[2]Perelman School of Medicine, Scheie Eye Institute, University of Pennsylvania, Philadelphia
[3]Department of Ophthalmology, University of California, San Francisco
[4]Division of Neonatology, University of Iowa, Iowa City
[5]Division of Neonatology, Johns Hopkins University, Baltimore, Maryland
[6]Department of Ophthalmology, Vanderbilt University, Nashville, Tennessee
[7]Department of Ophthalmology, Johns Hopkins University, Baltimore, Maryland
[8]Department of Ophthalmology, Nationwide Children's Hospital, Columbus, Ohio
[9]Abrahamson Pediatric Eye Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
[10]Department of Ophthalmology, University of Cincinnati College of Medicine, Cincinnati, Ohio
Corresponding author.

Article Information

Group Information: The Postnatal Growth and Retinopathy of Prematurity (G-ROP) Study Group investigators appear at the end of the article.

Accepted for Publication: September 12, 2019.

Published Online: November 14, 2019. doi:10.1001/jamaophthalmol.2019.4517

Correction: This article was corrected on January 9, 2020, to fix errors in the Group Information.

Corresponding Author: Gil Binenbaum, MD, MSCE, Division of Ophthalmology, The Children's Hospital of Philadelphia, 3401 Civic Center Blvd, Ophthalmology 9-MAIN, Philadelphia, PA 19104 (binenbaum@email.chop.edu).

Author Contributions: Dr Binenbaum had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Binenbaum, Bell, Quinn, Yang, Ying.

Acquisition, analysis, or interpretation of data: Binenbaum, Tomlinson, de Alba Campomanes, Bell, Donohue, Morrison, Repka, Rogers, Yang, Yu, Ying.

Drafting of the manuscript: Binenbaum.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Quinn, Yu, Ying.

Obtained funding: Binenbaum.

Administrative, technical, or material support: Tomlinson, de Alba Campomanes, Donohue, Rogers, Yang.

Supervision: Binenbaum, Tomlinson, Donohue, Morrison, Quinn, Rogers, Yang, Ying.

Conflict of Interest Disclosures: All authors reported receiving grants from the National Institutes of Health during the conduct of the study. Dr Repka reported being an American Academy of Ophthalmology consultant on government affairs. Dr Rogers reported receiving grants from the National Eye Institute outside the submitted work. No other disclosures were reported.

Funding/Support: This study was supported by grant R01EY021137 from the National Institutes of Health and by the Richard Shafritz Endowed Chair in Ophthalmology Research at the Children's Hospital of Philadelphia.

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Group Information: The Postnatal Growth and Retinopathy of Prematurity (G-ROP) Study Group investigators include the following: Office of Study Chair: The Children's Hospital of Philadelphia: Gil Binenbaum, MD, MSCE (principal investigator [PI]), Lauren A. Tomlinson, BS (Project Manager), Trang B. Duros, Anh Nguyen. Data Coordinating Center: University of Pennsylvania Perelman School of Medicine: Gui-shuang Ying, PhD (PI), Maureen G. Maguire, PhD, Mary Brightwell-Arnold, BA, SCP, James Shaffer, MS, Yinxi Yu, MS, Maria Blanco BS, Trina Brown BS, Christopher P. Helker, MSPH. Clinical Centers: Emory University School of Medicine (Children's Healthcare of Atlanta): Amy Hutchinson, MD (PI), Carrie Young, RN. University of Colorado Denver (University of Colorado Hospital, Children's Hospital Colorado): Emily McCourt, MD (PI), Anne Lynch, MD (coinvestigator), Jennifer Cathcart, MPH, Ashlee Cerda, MPH, Levi Bonnell, MPH, Tamara Thevarajah, MS. Albany Medical College: Gerard P. Barry, MD (PI), Marilyn Fisher, MD, MS (coinvestigator), Maria V. Battaglia, BS, MS, Alex M. Drach, BA, Kevin Hughes, BA. Lehigh Valley Hospital: Nachammai Chinnakaruppan, MD (PI), Andrew Meyer, MD (PI), Christina Gogal, BS, CCRC, Cynthia Beitler, BS, MT, BB(ASCP), CCRC, Lauri Centolanza, BS, MT(ASCP), Keith T. Moyer, MS, Mary Sobotor, CLA-ASCP, CCRC. Johns Hopkins University (Johns Hopkins Hospital): Pamela Donohue, ScD (PI), Michael X. Repka, MD (coinvestigator), Jennifer A. Shepard, CRNP, Megan Doherty, NNP. University at Buffalo (Women & Children's Hospital of Buffalo): James D. Reynolds, MD (PI), Erin Connelly. Medical University of South Carolina: Edward Cheeseman, MD, MBA (PI), Kinsey Shirer, RN, Carol Bradham, COA, CCRC, Allison McAlpine, Sudeep Sunthankar. University of Illinois at Chicago: Javaneh Abbasian, MD (PI), Janet Lim, MD. Cincinnati Children's Hospital Medical Center (Cincinnati Children's Hospital Medical Center, Good Samaritan Hospital, and University of Cincinnati Medical Center): Michael Yang, MD (PI), Patricia Cobb, MS, Elizabeth L. Alfano. Nationwide Children's Hospital (Nationwide Children's Hospital, Riverside Methodist Hospital, Grant Medical Center, Doctors Hospital): David Rogers, MD (PI), Rachel E. Reem, MD, Amanda Schreckengost, MA, Rae R. Fellows, MEd, CCRC, Kaitlyn Loh, Madeline A. McGregor, Thabit Mustafa, Ivy Dean, Rachel Miller, Tess Russell, Rebecca Stattler, Sara Maletic, Theran Jake Selph. Kapi'olani Medical Center for Women and Children: David Young, MD (PI), Andrea Siu, MPH, RAC, Michele Kanemori, George Kingston. University of Texas at Houston (Children's Memorial Hermann Hospital): Megan Geloneck, MD (PI), Robert Feldman (PI), Ted Baker, Laura Baker, Ephrem Melese, MD. Indiana University (Riley Hospital for Children at Indiana University Health): Kathryn Haider, MD (PI), Jingyun Wang, PhD (PI), Elizabeth Hynes, RNC-NIC, CLC. University of Iowa (University of Iowa Stead Family Children's Hospital): Edward F. Bell, MD (PI), Alina V. Dumitrescu, MD (coinvestigator), Jonathan M. Klein, MD (coinvestigator), Gretchen A. Cress, RN, MPH, Avanthi S. Ajjarapu, Kristine Berge, MSN, Eric Boeshart, Morgan Dorsey, Bethany M. Funk, Grace Hach, Claire L. Johnson, Kevin Kurian, Emily Miller, Angela C. Platt. Queen's University (Kingston Health Sciences Center): Christine Law, MD (PI), Andrew Gissing. Loma Linda University (Loma Linda University Children's Hospital): Leila Khazaeni, MD (PI), Jennifer Dunbar, MD

(coinvestigator), Kelley Hawkins, Sharon Lee, RN, Lily Sung, Carly Leggitt. University of Louisville (Norton Children's Hospital): Aparna Ramasubramanian, MD (PI), Rahul Bhola, MD (PI), Michelle Bottorff, COA, CCRC, Neviana Dimova, MD, MS, Rachel Keith, PhD, MSN, NP-C, Laura Thomas RN, BSN, CCRN. University of Minnesota (Masonic Children's Hospital, formerly University of Minnesota–Amplatz Children's Hospital): Jill Anderson, MD (PI), Raymond G. Areaux Jr, MD (coinvestigator), Ann Marie Holleschau, BA, CCRP, Jordan Gross, Andrea Kramer. Vanderbilt Eye Institute and Vanderbilt University Medical Center: (Monroe Carell Jr Children's Hospital at Vanderbilt): David Morrison, MD (PI), Sean Donahue, MD, PhD (coinvestigator), Carsyn Saige Wilkins, Neva Fukuda, CO, Sandy Owings, COA, CCRP, Scott Ruark. University of Oklahoma (The Children's Hospital at OU Medical Center/The University of Oklahoma Health Sciences Center): R. Michael Siatkowski, MD (PI), Faizah Bhatti, MD (coinvestigator), Vanessa Bergman, COT, CCRC, Karen Corff, APRN, NNP, Kari Harkey, RNC-NIC, Amy Manfredo, APRN-CNP, Ashley Helmbrecht, DNP, APRN-CNP, Shrenik Talsania, MBBS, MPH, CPH, Terri Whisenhunt, MS, RN. University of Nebraska (Nebraska Medicine): Donny Suh, MD, FAAP (PI), Ann Anderson Berry, MD, PhD (coinvestigator), Denise Lynes APRN-CNS, MSN, Kelly C. Erikson, MPH. The Children's Hospital of Philadelphia (The Children's Hospital of Philadelphia, Hospital of the University of Pennsylvania, Pennsylvania Hospital): Gil Binenbaum, MD, MSCE (PI), Soraya Abbasi, MD (PI), Haresh Kirpalani, MD, MSc, Graham E. Quinn, MD, MSCE, Lindsay Dawson, MD, Lauren A. Tomlinson, BS. University of Pittsburgh (Children's Hospital of Pittsburgh, Magee Women Hospital of UPMC): Christin Sylvester, MD (PI), Kanwal Nischal, MD (PI), Lauren Runkel, MA. Rhode Island Hospital (Women and Infants Hospital of Rhode Island): Wendy S. Chen, MD, PhD (PI), Deidrya Jackson. St Louis University (Cardinal Glennon Children's Hospital): Bradley Davitt, MD (PI), Dawn Govreau, COT, Linda Breuer, LPN, September Noonan, RN. University of Utah (Primary Children's Hospital and University of Utah Hospital): Robert Hoffman, MD (PI), Joanna Beachy, MD, PhD, Kelliann Farnsworth, COT, Katie Jo Farnsworth, CRC, Deborah Harrison, MS, Ashlie Bernhisel, Bonnie Carlstrom. University of California, San Francisco (UCSF Benioff Children's Hospital and Zuckerberg San Francisco General Hospital, formerly San Francisco General Hospital): Alejandra G. de Alba Campomanes, MD, MPH (PI), Yizhuo Bastea-Forte, Lucia Rivera Sanchez, Jacquelyn Kemmer, Alexandra Neiman, Sarah Sitati-Ng'Anda MD. Seattle Children's Hospital (Seattle Children's Hospital, University of Washington Medical Center): Kristina Tarczy-Hornoch, MD, DPhil (PI), Francine Baran, MD (PI), Lauren Eaton. The Hospital for Sick Children (Sick Kids), Toronto: Nasrin Najm-Tehrani, MBBCh, MSc, FRCS Ed(Ophth), FRCSC (PI), Tanya Grossi, Maram Isaac, Robin Knighton. Los Angeles Biomedical Research Institute (Harbor-UCLA Medical Center): Monica Ralli Khitri, MD (PI), Madeline Del Signore, RN. Crozer-Chester Medical Center (Crozer Chester Medical Center, Delaware County Memorial Hospital): Cynthia Dembofsky, MD (PI), Andrew Meyer, MD (PI), Karen Flaherty, Tracey Harris, Jamie Heeneke. Nemours/Alfred I. duPont Hospital for Children: Dorothy Hendricks, MD (PI), Christopher M. Fecarotta, MD (PI), Alicia Olivant Fisher, MS, Mark Paullin, MS. Cost-Effectiveness Component: Beth Israel Deaconess Medical Center: John Zupancic, MD, MS, ScD (PI). Executive/Editorial Committee: Alejandra de Alba Campomanes, MD, MPH, Edward F. Bell, MD, Gil Binenbaum, MD, MSCE, Pamela Donohue, ScD, David Morrison, MD, Graham E. Quinn, MD, MSCE, Michael X. Repka, MD, David L. Rogers, MD, Lauren A. Tomlinson, BS, Michael Yang, MD, Gui-shuang Ying, PhD.

Disclaimer: The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources or the National Institutes of Health.

Meeting Presentation: This paper was presented at the Annual Meeting of the American Association for Pediatric Ophthalmology and Strabismus; March 30, 2019; San Diego, California.

Received 2019 Apr 29; Accepted 2019 Sep 12.

Key Points

Question

Are the Postnatal Growth and Retinopathy of Prematurity modified screening criteria generalizable?

Findings

In a cohort study of 3981 premature infants, the Postnatal Growth and Retinopathy of Prematurity criteria correctly predicted type 1 retinopathy of prematurity in 219 of 219 infants, while reducing the number of infants receiving examinations by 35.6% if only infants meeting screening criteria received examinations.

Meaning

The modified screening criteria were validated and could be used clinically to reduce the number of infants receiving examinations while consistently identifying retinopathy of prematurity requiring treatment.

Abstract

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; 120 Asian; 22 Native Hawaian 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.

Introduction

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.[1] Infants at risk for ROP are identified using recommended birth weight (BW) and gestational age at birth (GA) criteria.[2] 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.[2] 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.[3,4] 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.[2] 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.[5,6,7,8,9,10] 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.[11,12,13] 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.[4,9] 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 30% the number of infants who would otherwise have received diagnostic retinal examinations.[9]

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,[4,9] validation is required before the criteria can be recommended for clinical use and widespread implementation.[14]

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,[1] type 2 ROP,[1] or ROP 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.[4] 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.[9] 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 (1) 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.[15] 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[4,9] 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.[14,16] 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).

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,[9] without updating, correctly predicted type 1 ROP in 219 of 219 infants (sensitivity, 100%; 95% CI, 98.3%-100%), type 2 ROP in 260 of 264 infants (sensitivity, 98.5%; 95% CI, 96.2%-99.4%), 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%), 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%); 3730 infants (32.5%) 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 766 of 770 infants treated for ROP (sensitivity, 99.5%; 95% CI, 98.7%-99.8%); 1060 infants (9.2%) did not meet either of the current BW or GA criteria and would not have received examinations. The latter 1060 infants were examined as a result of the subjective third criterion; 3 of these infants had type 1 ROP and 12 had type 2 ROP. In contrast, 294 infants with BW and GA above the current BW and GA criteria met the G-ROP criteria, which do not include a subjective criterion. When the 3 G-ROP weight gain time periods all had the same slow weight gain threshold of less than 180 g, sensitivity did not change and the reduction in infants requiring examinations was 27.3% (Table 3).

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.[16,17] 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.[4,14] In contrast, prior models incorporating measures of slow postnatal weight gain, such as the WINROP (Weight, IGF-1, Neonatal Retinopathy of Prematurity),[5] CHOP ROP (Children’s Hospital of Philadelphia Retinopathy of Prematurity),[6] and CO-ROP (Colorado-Retinopathy of Prematurity)[7] models, were developed using small cohorts and had less than 100% sensitivity in validation studies[8,18,19,20] 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, which is forthcoming. The G-ROP criteria and the currently recommended criteria both missed a small percentage of infants who developed type 2 ROP (G-ROP criteria, 1.3%; and current criteria, 0.3%). Retinopathy of prematurity regressed spontaneously in all of those infants, and treatment is not currently recommended for eyes with type 2 ROP.[1] Therefore, missing a small percentage of cases of type 2 ROP may be acceptable to greatly reduce the number of infants receiving examinations. Currently, premature infants in most practices receive ophthalmologic examinations later during infancy to monitor visual development; assuming this current practice will continue, it provides an opportunity to capture any missed outlier cases of type 2 ROP. When such follow-up occurs currently, it is typically arranged when an ophthalmologist discharges an infant from acute ROP screening. Therefore, recommendations for such follow-up might need to be formulated to standardize follow-up for premature infants below a certain GA, even if they did not meet the G-ROP criteria. Another approach might be inclusion of a subjective criterion, as discussed below.

Presently, infants diagnosed by clinicians with type 1 or type 2 ROP but who had BW and GA greater than current screening thresholds are first identified for screening through the subjective criterion of a poor postnatal course in the judgment of the neonatologist.[2] 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 neonatologists 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 increased,[21] 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.[22,23,24] 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.

References

1. Early Treatment for Retinopathy of Prematurity Cooperative Group Revised indications for the treatment of retinopathy of prematurity: results of the Early Treatment for Retinopathy of Prematurity randomized trial. *Arch Ophthalmol*. 2003;121(12):1684-1694. doi:10.1001/archopht.121.12.1684 [PubMed: 14662586] [CrossRef: 10.1001/archopht.121.12.1684]

2. Fierson WM; American Academy of Pediatrics Section on Ophthalmology; American Academy of Ophthalmology; American Association for Pediatric Ophthalmology and Strabismus; American Association of Certified Orthoptists . Screening examination of premature infants for retinopathy of prematurity. *Pediatrics*. 2013;131(1):189-195. doi:10.1542/peds.2012-2996 [PubMed: 23277315] [CrossRef: 10.1542/peds.2012-2996]

3. Quinn GE, Ying GS, Bell EF, et al. ; G-ROP Study Group . Incidence and early course of retinopathy of prematurity: secondary analysis of the Postnatal Growth and Retinopathy of Prematurity (G-ROP) Study. *JAMA Ophthalmol*. 2018;136(12):1383-1389. doi:10.1001/jamaophthalmol.2018.4290 [PMCID: PMC6583045] [PubMed: 30326046] [CrossRef: 10.1001/jamaophthalmol.2018.4290]

4. Binenbaum G, Tomlinson LA. Postnatal Growth and Retinopathy of Prematurity Study: rationale, design, and subject characteristics. *Ophthalmic Epidemiol*. 2017;24(1):36-47. doi:10.1080/09286586.2016.1255765 [PMCID: PMC6499901] [PubMed: 27996334] [CrossRef:

10.1080/09286586.2016.1255765]

5. Hellström A, Hård AL, Engström E, et al. . Early weight gain predicts retinopathy in preterm infants: new, simple, efficient approach to screening. *Pediatrics*. 2009;123(4):e638-e645. doi:10.1542/peds.2008-2697 [PubMed: 19289449] [CrossRef: 10.1542/peds.2008-2697]

6. Binenbaum G, Ying GS, Quinn GE, et al. . The CHOP postnatal weight gain, birth weight, and gestational age retinopathy of prematurity risk model. *Arch Ophthalmol*. 2012;130(12):1560-1565. doi:10.1001/archophthalmol.2012.2524 [PubMed: 23229697] [CrossRef: 10.1001/archophthalmol.2012.2524]

7. Cao JH, Wagner BD, McCourt EA, et al. . The Colorado-Retinopathy of Prematurity model (CO-ROP): postnatal weight gain screening algorithm. *J AAPOS*. 2016;20(1):19-24. doi:10.1016/j.jaapos.2015.10.017 [PubMed: 26917066] [CrossRef: 10.1016/j.jaapos.2015.10.017]

8. Binenbaum G, Ying GS, Tomlinson LA; Postnatal Growth and Retinopathy of Prematurity (G-ROP) Study Group . Validation of the Children's Hospital of Philadelphia Retinopathy of Prematurity (CHOP ROP) model. *JAMA Ophthalmol*. 2017;135(8):871-877. doi:10.1001/jamaophthalmol.2017.2295 [PMCID: PMC5710287] [PubMed: 28715553] [CrossRef: 10.1001/jamaophthalmol.2017.2295]

9. Binenbaum G, Bell EF, Donohue P, et al. ; G-ROP Study Group . Development of modified screening criteria for retinopathy of prematurity: primary results from the Postnatal Growth and Retinopathy of Prematurity Study. *JAMA Ophthalmol*. 2018;136(9):1034-1040. doi:10.1001/jamaophthalmol.2018.2753 [PMCID: PMC6142979] [PubMed: 30003216] [CrossRef: 10.1001/jamaophthalmol.2018.2753]

10. Eckert GU, Fortes Filho JB, Maia M, Procianoy RS. A predictive score for retinopathy of prematurity in very low birth weight preterm infants. *Eye (Lond)*. 2012;26(3):400-406. doi:10.1038/eye.2011.334 [PMCID: PMC3298990] [PubMed: 22193874] [CrossRef: 10.1038/eye.2011.334]

11. Hellstrom A, Perruzzi C, Ju M, et al. . Low IGF-I suppresses VEGF-survival signaling in retinal endothelial cells: direct correlation with clinical retinopathy of prematurity. *Proc Natl Acad Sci U S A*. 2001;98(10):5804-5808. doi:10.1073/pnas.101113998 [PMCID: PMC33294] [PubMed: 11331770] [CrossRef: 10.1073/pnas.101113998]

12. Hellström A, Engström E, Hård AL, et al. . Postnatal serum insulin-like growth factor I deficiency is associated with retinopathy of prematurity and other complications of premature birth. *Pediatrics*. 2003;112(5):1016-1020. doi:10.1542/peds.112.5.1016 [PubMed: 14595040] [CrossRef: 10.1542/peds.112.5.1016]

13. Jensen AK, Ying GS, Huang J, Quinn GE, Binenbaum G. Postnatal serum insulin-like growth factor I and retinopathy of prematurity. *Retina*. 2017;37(5):867-872. doi:10.1097/IAE.0000000000001247 [PMCID: PMC5303693] [PubMed: 27529840] [CrossRef: 10.1097/IAE.0000000000001247]

14. Moons KG, Royston P, Vergouwe Y, Grobbee DE, Altman DG. Prognosis and prognostic research: what, why, and how? *BMJ*. 2009;338:b375. doi:10.1136/bmj.b375 [PubMed: 19237405] [CrossRef: 10.1136/bmj.b375]

15. Wilson EB. Probable inference, the law of succession, and statistical inference. *J Am Stat Assoc*. 1927;22:209-212. doi:10.1080/01621459.1927.10502953 [CrossRef: 10.1080/01621459.1927.10502953]

16. Altman DG, Vergouwe Y, Royston P, Moons KG. Prognosis and prognostic research: validating a prognostic model. *BMJ*. 2009;338:b605. doi:10.1136/bmj.b605 [PubMed: 19477892] [CrossRef: 10.1136/bmj.b605]

17. Moons KG, Altman DG, Vergouwe Y, Royston P. Prognosis and prognostic research: application and

impact of prognostic models in clinical practice. *BMJ*. 2009;338:b606. doi:10.1136/bmj.b606 [PubMed: 19502216] [CrossRef: 10.1136/bmj.b606]

18. McCourt EA, Ying GS, Lynch AM, et al. ; G-ROP Study Group . Validation of the Colorado Retinopathy of Prematurity screening model. *JAMA Ophthalmol*. 2018;136(4):409-416. doi:10.1001/jamaophthalmol.2018.0376 [PMCID: PMC5876910] [PubMed: 29543944] [CrossRef: 10.1001/jamaophthalmol.2018.0376]

19. Cao JH, Wagner BD, Cerda A, et al. . Colorado Retinopathy of Prematurity model: a multi-institutional validation study. *J AAPOS*. 2016;20(3):220-225. doi:10.1016/j.jaapos.2016.01.017 [PubMed: 27166790] [CrossRef: 10.1016/j.jaapos.2016.01.017]

20. Wu C, Löfqvist C, Smith LE, VanderVeen DK, Hellström A; WINROP Consortium . Importance of early postnatal weight gain for normal retinal angiogenesis in very preterm infants: a multicenter study analyzing weight velocity deviations for the prediction of retinopathy of prematurity. *Arch Ophthalmol*. 2012;130(8):992-999. doi:10.1001/archophthalmol.2012.243 [PMCID: PMC4059056] [PubMed: 22491391] [CrossRef: 10.1001/archophthalmol.2012.243]

21. Yang LL, Lambert SR, Drews-Botsch C, Stulting RD. Long-term visual outcome of penetrating keratoplasty in infants and children with Peters anomaly. *J AAPOS*. 2009;13(2):175-180. doi:10.1016/j.jaapos.2008.10.007 [PubMed: 19393517] [CrossRef: 10.1016/j.jaapos.2008.10.007]

22. Zin AA, Moreira ME, Bunce C, Darlow BA, Gilbert CE. Retinopathy of prematurity in 7 neonatal units in Rio de Janeiro: screening criteria and workload implications. *Pediatrics*. 2010;126(2):e410-e417. doi:10.1542/peds.2010-0090 [PubMed: 20660549] [CrossRef: 10.1542/peds.2010-0090]

23. Gilbert C, Fielder A, Gordillo L, et al. ; International NO-ROP Group . Characteristics of infants with severe retinopathy of prematurity in countries with low, moderate, and high levels of development: implications for screening programs. *Pediatrics*. 2005;115(5):e518-e525. doi:10.1542/peds.2004-1180 [PubMed: 15805336] [CrossRef: 10.1542/peds.2004-1180]

24. Zepeda-Romero LC, Hård AL, Gomez-Ruiz LM, et al. . Prediction of retinopathy of prematurity using the screening algorithm WINROP in a Mexican population of preterm infants. *Arch Ophthalmol*. 2012;130(6):720-723. doi:10.1001/archophthalmol.2012.215 [PubMed: 22801831] [CrossRef: 10.1001/archophthalmol.2012.215]

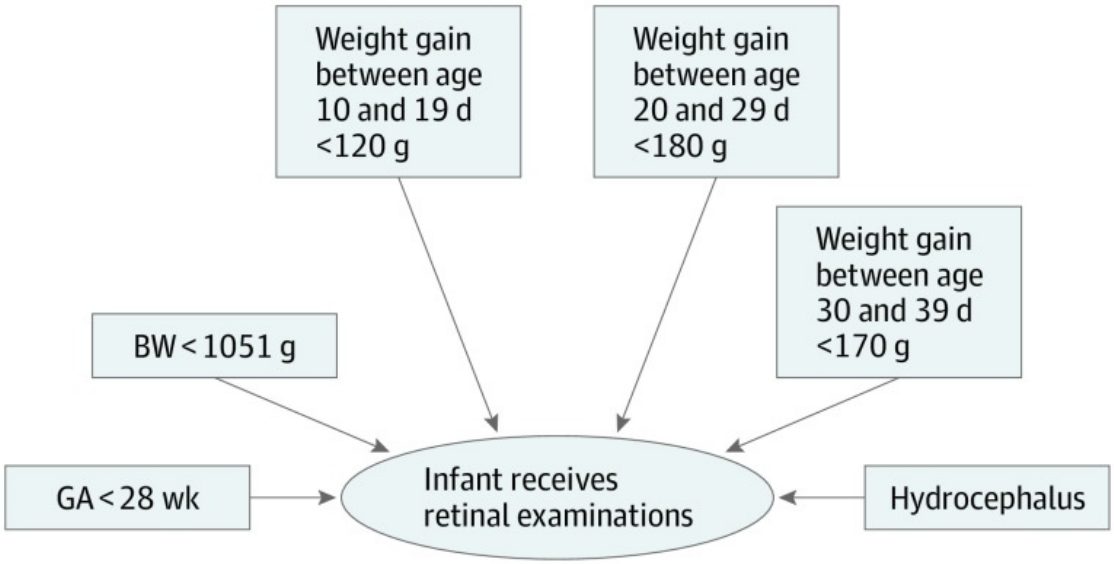
25. Shiraki A, Fukushima Y, Kawasaki R, et al. . Retrospective validation of the Postnatal Growth and Retinopathy of Prematurity (G-ROP) criteria in a Japanese cohort. *Am J Ophthalmol*. 2019;205:50-53. doi:10.1016/j.ajo.2019.03.027 [PubMed: 30954468] [CrossRef: 10.1016/j.ajo.2019.03.027]

26. Saugstad OD, Aune D. Optimal oxygenation of extremely low birth weight infants: a meta-analysis and systematic review of the oxygen saturation target studies. *Neonatology*. 2014;105(1):55-63. doi:10.1159/000356561 [PubMed: 24247112] [CrossRef: 10.1159/000356561]

27. Askie LM, Brocklehurst P, Darlow BA, Finer N, Schmidt B, Tarnow-Mordi W; NeOProM Collaborative Group . NeOProM: Neonatal Oxygenation Prospective Meta-analysis Collaboration study protocol. *BMC Pediatr*. 2011;11:6. doi:10.1186/1471-2431-11-6 [PMCID: PMC3025869] [PubMed: 21235822] [CrossRef: 10.1186/1471-2431-11-6]

Figures and Tables

Figure.



Postnatal Growth and Retinopathy of Prematurity (G-ROP) Study Screening Criteria

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.[9]

Table 1.

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

Characteristic	Type 1 ROP (n = 219)[a]	Type 2 ROP (n = 264)[a]	Stage 3 Zone III ROP (n = 20)[a]	Mild ROP (n = 1140)[a]	No ROP (n = 2338)[a]	Total (N = 3981)[a]
Birth weight, g						
Mean (SD)	687 (162)	723 (212)	924 (212)	931 (288)	1243 (309)	1087 (351)
Median (IQR) [range]	665 (576-780) [380-1273]	690 (580-820) [350-2030]	845 (771-1110) [593-1347]	890 (720-1100) [360-2600]	1255 (1030-1440) [470-4080]	1072 (800-1340) [350-4080]
Gestational age, wk						
Mean (SD)	24.6 (1.5)	24.9 (1.7)	26.8 (2.6)	26.8 (2.3)	29.3 (2.2)	28.0 (2.7)
Median (IQR) [range]	24.0 (24.0-25.0) [22.0-32.0]	25.0 (24.0-26.0) [22.0-32.0]	26.0 (24.5-28.5) [24.0-32.0]	27.0 (25.0-28.0) [22.0-36.0]	29.0 (28.0-31.0) [22.0-38.0]	28.0 (26.0-30.0) [22.0-38.0]

Abbreviations: IQR, interquartile range; ROP, retinopathy of prematurity.

[a]Infants are categorized by worst ROP diagnosis.

Table 2.

Prediction of ROP by the G-ROP Screening Criteria, Among 3981 Infants in the Postnatal Growth and Retinopathy of Prematurity Validation Study

Met G-ROP Criteria	Infants, No. (%)					
	Type 1 ROP[a]	Type 2 ROP[a]	Not Type 1 or 2 ROP[a]	No ROP[a]	Total	Treated for ROP
No	0	4 (1.5)	184 (15.9)	1230 (52.6)	1418 (35.6)	3 (1.2)
Yes	219 (100.0)	260 (98.5)	976 (84.1)	1108 (47.4)	2563 (64.4)	253 (98.8)
Total, No.	219	264	1160	2338	3981	256

Abbreviations: G-ROP, Growth and Retinopathy of Prematurity; ROP, retinopathy of prematurity.

[a]Infants are categorized by worst ROP diagnosis. Sensitivity for type 1 ROP, 100.0% (95% CI, 98.3%-100.0%); sensitivity for type 2 ROP, 98.5% (95% CI, 96.2%-99.4%); sensitivity for treated ROP, 98.8% (95% CI, 96.6%-99.6%); number of infants who would not receive examinations, 1418 (35.6%).

Table 3.

Prediction of ROP by Currently Recommended BW and GA Screening Criteria and G-ROP Screening Criteria, Among 11 464 Infants in the G-ROP-1 and G-ROP-2 Studies

Whole Cohorts	BW <1501 g or GA ≤30 wk	G-ROP Criteria	G-ROP 180 g
Type 1 ROP (n = 677)			
Sensitivity, % (95% CI)	99.6 (98.7-99.8)	100 (99.4-100.0)	100 (99.4-100.0)
99% CI	98.3-99.9	99.0-100.0	99.0-100.0
Type 2 ROP (n = 737)			
Sensitivity, % (95% CI)	99.7 (99.0-99.9)	98.6 (97.5-99.3)	98.8 (97.7-99.4)
99% CI	98.6-99.9	97.0-99.4	97.2-99.5
Treated ROP (n = 770)			
Sensitivity, % (95% CI)	99.5 (98.7-99.8)	99.6 (98.9-99.9)	99.6 (98.9-99.9)
99% CI	98.3-99.8	98.5-99.9	98.5-99.9
Reduction in infants receiving examinations			
% (95% CI)	9.2 (8.7-9.8)	32.5 (31.7-33.4)	27.3 (26.5-28.1)
99% CI	8.6-10.0	31.4-33.7	26.2-28.4

Abbreviations: BW, birth weight; GA, gestational age; G-ROP, Growth and Retinopathy of Prematurity; G-ROP 180 g, G-ROP screening criteria in which all 3 weight gain thresholds are set at <180 g; ROP, retinopathy of prematurity.