The Economic Model of Retinopathy of Prematurity (EcROP) Screening and Treatment: Mexico and the United States

MICHAEL I. ROTHSCHILD, REBECCA RUSS, KATHRYN A. BRENNAN, CHRISTOPHER J. WILLIAMS, DAVID BERRONES, BHAVESH PATEL, MARIA ANA MARTINEZ-CASTELLANOS, ALCIDES FERNANDES, G. BAKER HUBBARD, III, R.V. PAUL CHAN, ZHOU YANG, AND TIMOTHY W. OLSEN

• PURPOSE: To describe an economic (Ec) model for estimating the impact of screening and treatment for retinopathy of prematurity (ROP).

• DESIGN: EcROP is a cost-effectiveness, cost-utility, and cost-benefit analysis.

• METHODS: We surveyed caregivers of 52 children at schools for the blind or pediatric eye clinics in Atlanta, Georgia and 43 in Mexico City. A decision analytic model with sensitivity analysis determined the incremental cost-effectiveness (primary outcome) and incremental monetary benefit (secondary outcome) of an ideal (100% screening) national ROP program as compared to estimates of current practice. *Direct costs* included screening and treatment expenditures. *Indirect costs* estimated lost productivity of caretaker(s) and blind individuals as determined by face-to-face surveys. Utility and effectiveness were measured in quality-adjusted life years and benefit in US dollars. EcROP includes a sensitivity analysis to assesses the incremental cost-effectiveness and societal impact of ROP screening and treatment within a country or economic region. Estimates are based on evidence-based clinical data and region-specific economic data acquired from direct field survey.

• RESULTS: In both Mexico and the United States, an ideal national ROP screening and treatment program was highly cost-saving. The incremental net benefit of an ideal ROP program over current practice is $5556 per child ($206 574 333 annually) and $3628 per child ($205 906 959 annually) in Mexico and the United States, respectively.

• CONCLUSION: EcROP demonstrates that ROP screening and treatment is highly beneficial for quality of life, cost saving, and cost-effectiveness in the United States and Mexico. EcROP can be applied to any country or region to provide data for informed allocation of limited health care resources. (Am J Ophthalmol 2016;168:110–121. © 2016 Elsevier Inc. All rights reserved.)

RETINOPATHY OF PREMATURITY (ROP) IS A VISION-threatening disorder affecting premature infants resulting from abnormal retinal vascular development.[1] In later stages, fibrovascular proliferation leads to retinal detachment, visual impairment, and blindness.[1] The estimated incidence of any ROP is 68% in premature infants in the United States weighing less than 1251 g.[2]

In the United States, the standard of care is to screen premature infants born at ≤30 weeks' gestational age or weighing ≤1500 g for ROP.[3] Screening guidelines vary internationally, with higher birth-weight thresholds recommended in developing nations. For example, screening is recommended in India and Mexico for infants weighing less than 1750 g or those born at <34 weeks' gestation.[4,5] Effective screening and treatment clearly reduces ROP-related blindness. Nevertheless, ROP represents a major burden and remains a leading cause of childhood blindness worldwide.[6]

In countries where infant mortality rates (IMRs) are <9/1000 live births (United States, Europe, Japan, Australia, South Korea, etc), ROP is less common and is due to lower rates of prematurity and diligent neonatal intensive care unit (NICU) management, along with effective screening and treatment programs delivered by experienced, well-trained professionals. Alternatively, countries with very high IMRs (>60/1000), such as those in sub-Saharan Africa, have low rates of ROP because NICUs are either limited or nonexistent. Thus, most premature infants do not survive. The *third epidemic* of ROP is taking place in middle-income countries with intermediate IMRs ranging from approximately 9/1000 to 60/1000, predominantly located in Latin America, Asia, and Eastern Europe.[7,8] In Mexico, approximately 24% of childhood blindness occurs as a result of ROP.[8]

In Latin America, both low screening penetrance and limited resources contribute to this epidemic. A 2002 multicenter study of 11 NICUs in Latin America indicated

AJO.com Supplemental Material available at AJO.com.

Accepted for publication Apr 20, 2016.

From the Emory Eye Center, Emory University Department of Ophthalmology, and the Global Ophthalmology at Emory (GO-Emory) Program, Atlanta, Georgia (M.I.R., R.R., K.A.B., C.J.W., B.P., A.F., G.B.H., T.W.O.); Rollins School of Public Health, Emory University, Atlanta, Georgia (R.R., Z.Y.); Association to Prevent Blindness in Mexico (APEC), Mexico City, Mexico (D.B., M.A.M.-C.); and University of Illinois at Chicago College of Medicine, Illinois Eye and Ear Infirmary, Department of Ophthalmology and Visual Sciences, Chicago, Illinois (R.V.P.C.).

Inquiries to Timothy W. Olsen, Emory University, 1365B Clifton Road NE, Atlanta, GA 30322; e-mail: tolsen@emory.edu

0002-9394/$36.00
http://dx.doi.org/10.1016/j.ajo.2016.04.014

that there is a 42% rate of ROP among very low birthweight (VLBW) infants, with only 68% screening penetrance.[9] In Brazil, the 2014 screening penetrance was estimated to be approximately 52%[10]; our model assumes similar penetrance in Mexico.

The model we propose in this study is an economic (Ec) methodology for ROP screening and treatment analysis, or "EcROP," that uses decision analytics and cost-utility analysis (CUA). Our cost analysis combines evidence-based data with face-to-face family surveys. Additionally, we interviewed local health care delivery teams to obtain relevant, local, country-specific financial information about labor and supply costs. Therefore, our cost analysis uses local economic data instead of relying on insurance rates that are not generalizable. In addition to cost analysis, EcROP includes quality-adjusted life years (QALYs) to determine the incremental cost-effectiveness of an ideal ROP screening and treatment program (100% penetrance) for a given country or economic region. Next, we expand our model to include a cost-benefit analysis (CBA) that assigns a dollar value to each QALY gained to determine the net savings resulting from implementation of an ideal screening and treatment program.

We tested the EcROP model in both a high- (United States) and middle-income (Mexico) nation. A middle-income nation has a Human Development Index (HDI) ranking of 31–100 (74 in Mexico). At the time of this publication, Mexico is affected by the third epidemic of ROP. By comparison, the United States ranks eigth in HDI, yet the burden of ROP remains significant.[3,11] By applying EcROP in both countries, our analysis is able to estimate the financial impact of effective ROP screening and treatment in these representative middle- and high-income countries.

METHODS

WE PERFORMED A COST-UTILITY AND COST-BENEFIT ANALysis for implementation of an ideal ROP screening and treatment program in both the United States and Mexico. We incorporated sensitivity analysis and measured for the relative impact of this intervention by using commonly accepted parameters for cost-effectiveness.

In addition to using published data, EcROP gathered country-specific economic data using local care standard-of-care clinical protocols combined with economic data from face-to-face family interviews of those affected. This approach differed from traditional insurance or social service (ie, Medicaid)-based analyses. While insurance-based financial references may allow for an assessment of direct costs and opportunity costs, they often are not generalizable between countries and do not fully assess productivity costs. By using a more direct survey instrument and incorporating productivity losses, EcROP could provide a more complete analysis of the utility and cost-effectiveness of ROP screening and intervention.

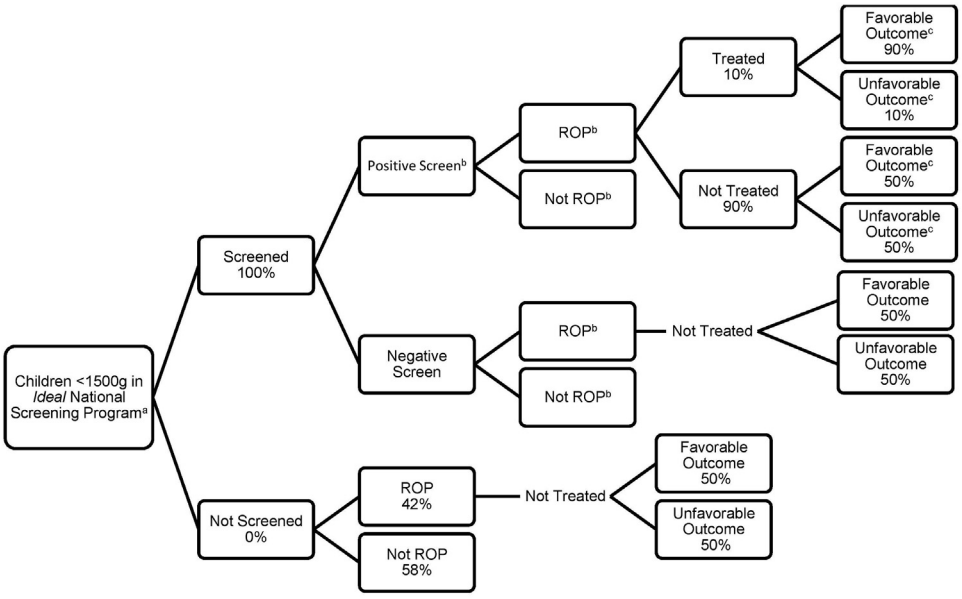
The surveys conducted in this study had prospective Institutional Review Board approval from Emory University along with regional hospital approval from Asociación para Evitar la Ceguera en México (APEC; The Association to Prevent Blindness in Mexico). Informed parental consent was obtained for each interview. The study was in full compliance with all federal and state laws of Mexico and the United States, was in full compliance with HIPAA regulations, and adhered to the tenets of the Declaration of Helsinki.

• **DECISION ANALYTIC MODEL:** The CUA and CBA were created considering a societal perspective and were based on a decision analytic model using a software program (TreeAge Pro, Williamstown, Massachusetts, USA). A decision analytic model uses a decision tree to show all possible event pathways, the probabilities that each event will occur, and the consequences of these events in terms of cost and effect on utility.

Our analysis compared 2 branches. For each country, we compared (1) *current* levels of screening and treatment of ROP to (2) an *ideal* national program with 100% screening coverage and appropriate management and treatment of all infants with ROP. Figure 1 shows a partial version of the decision tree that was constructed; only the branch for the ideal national program is shown in full. In the complete version of the decision tree, the branch for the current program uses the exact same decision pathway as the branch shown for the ideal national program, though the probabilities, costs, and utility values differ.

The specific probabilities, costs, utility values, and assumptions used in the decision tree are discussed in the sections below and data and details are found in Table 1. Regionally collected data were extrapolated to estimate a national impact by using population data from each nation. The intervention timeframe was focused on the first year of life for a premature infant, when most direct costs are incurred. The analytic horizon was the lifetime of the affected individual. Assumptions were labeled as "Best Case" or "Worst Case" from the best and worst outcome in the EcROP model, as opposed to from the neonate or the disease perspective.

• **ASSUMPTIONS AND PROBABILITY INPUTS:** Both current and ideal national programs assume screening and treatment of infants weighing ≤1500 g in both countries. We assume 100% screening coverage in an *ideal* national program. There is a paucity of data regarding *current* ROP screening coverage in the United States and Mexico. Our best estimate of *current* screening coverage is 80% and 52% in the United States and Mexico, respectively.[10] We also assumed that all infants who qualified, received treatment; no infant deaths occurred after ROP screening; and the sensitivity and specificity of ROP screening was 100%.



[a] This figure represents part of the complete decision model: the branch representing an ideal national screening program. The complete tree includes a structurally similar branch for children <1500g screened in current practice, except that screening coverage is 52% in Mexico[10] and 80% in the U.S.
[b] Calculated based on sensitivity, specificity, and prevalence values[2,12].
[c] Cost and effective outcomes are entered at the terminal nodes. Favorable structural outcomes are associated with QALYs calculated for normal-seeing individuals, whereas unfavorable structural outcomes are associated with QALYs calculated for blind individuals.

FIGURE 1. Retinopathy of prematurity (ROP) decision tree. This is a partial and representative version of a decision tree detailing possible outcomes for a given child born < 1500 g, with each branch representing a possible endpoint and each node representing a probability. Of note, this tree is not to be confused with a clinical decision-making flow chart. The decision tree for a child born weighing < 1500 g under current screening practices would be identical, with the exception of screening penetrance (probabilities at first branch point, listed in this figure as either 0%, Not Screened, or 100%, Screened for an ideal program). We estimate screening penetrance to be 52% in Mexico and 80% in the United States.[10]

The decision tree incorporated published natural history data and the known effectiveness of current treatments. In order to populate the decision tree using appropriate probabilities, the natural history of ROP (without treatment) from the control arm of the Cryotherapy for ROP (CRYO-ROP) study[12] was compared to the current standards of successful treatment, using the evidence-based care from the laser treatment arm of the Early Treatment for Retinopathy of Prematurity (ETROP) study.[2] Other probability inputs were determined from either the peer-reviewed, published literature or expert opinion, as cited in Table 1.

• **EFFECTIVENESS MEASURES:** A QALY is the measurement unit of utility (0 = death and 1 = perfect health). We calculated the cost per QALY saved by screening and treating ROP. Studies have found the utility factor for blindness ranging between 0.39 and 0.80, with a mean of 0.61, and a utility factor for sight ranging between 0.69 and 1.0, with a mean of 0.89.[13] These QALYs were discounted at a 3% annual rate over the lifetime of the child.[14] Discounting adjusts the future value of the QALY and is based on the concept that the benefit is better now than in the future (positive time preference).

• **COSTS:** In this study, EcROP included both direct and indirect costs that were discounted at an annual rate of 3% and reported in 2014 US dollars ($). Two cost values, the direct cost of raising a blind child and the productivity loss of a caregiver, were derived from our country-specific survey data. The variability in survey data was calculated using a 95% confidence interval (CI).

Direct Costs. *Direct costs* are defined as the required expenses specifically related to disease management and include all disease-related expense for the individual. Direct costs of raising a blind child included the family and societal expenses for the individual and also the individualized EcROP survey that assessed the educational costs per child and other family-incurred expenditures that result from child blindness. Examples included transportation, Braille equipment and supplies, and white canes. Clearly, these expenses would not be incurred for a sighted child. The average Supplemental Security income received by each child was also included. We estimated that the total direct cost of raising a blind child from birth to age 18 is $24 413 in Mexico and $84 586 in the United States (Supplemental Table 1, available at AJO.com).

TABLE 1. Retinopathy of Prematurity Estimates of Probability Parameters and Effectiveness Inputs

Parameter	Mexico			United States		
	Base Case	Best Case for EcROP	Worst Case	Base Case	Best Case for EcROP	Worst Case
Prevalence of ROP in infants weighing <1500 g (%)	42[9]	99	1	42[a]	99	1
Screening penetrance under current practice (%)	52[10]	0	68	80[a]	50	90
Screening penetrance under ideal national program (%)	100[e]	100	69	100[a]	100	91
Probability of a favorable structural outcome in a treated child (%) (±10%)[b]	90[2]	99	81	90[2]	99	81
Probability of a favorable structural outcome in an untreated child (%) (±10%)[b]	50[12,37]	45	55	50[12,36]	45	55
Probability that a child who screens positive will be treated (%) (±10%)[b]	10[38]	20	0	10[37]	20	0
Sensitivity of screening (%)	100[e]			100[e]		
Specificity of screening (%)	100[e]			100[e]		
Discount rate (%)	3[14]	0	5	3[14]	0	5
Effectiveness input						
QALY of a blind person	0.61[13]	0.39	0.80	0.61	0.39	0.80
QALYs of being blind discounted/ lifetime[d]	18.1	11.7	23.8	18.2	11.7	23.9
QALY of a normal-seeing person	0.89[13]	1.00	0.69	0.89	1.00	0.69
QALYs normal-seeing discounted/ lifetime[d]	26.43	29.70	20.49	26.62	29.91	20.64
Main costs[c]						
Screening (±30%)[b]	3228	2260	4197	9821	6874	12 767
Treatment (±30%)[b]	504	353	655	4037	2826	5249
Follow-up (±30%)[b]	2214	1550	2878	1538	1076	1999
Raising a blind child (0, upper limit 95% CI)[b]	24 413	67 803	0	84 586	239 307	0
Productivity loss, caregivers (0, upper limit 95% CI)[b]	305 584	926 331	0	817 996	2 329 654	0
Productivity loss, blind individuals (±30%)[b]	142 172	99 521	184 824	357 019	249 913	464 124

CI = confidence interval; EcROP = economic model of retinopathy of prematurity; QALY = quality-adjusted life year; ROP = retinopathy of prematurity.

[a]Assumptions of EcROP model.

[b]Range used for sensitivity analysis, including best-case and worst-case analysis.

[c]Costs are discounted at 3% per year and adjusted for inflation in 2014 US dollars.

[d]QALYs were discounted at a rate of 3% over the expected lifespan (75 years in Mexico and 77 years in the United States).[26]

[e]Assuming ideal screening.

The direct cost of ROP screening included all equipment and labor expenses associated with evidence-based ROP screening, treatment, and follow-up. The data outlined below were used to calculate the final cost of treating each ROP neonate that met criteria. The equipment necessary to treat included a solid-state diode laser with an indirect delivery system (eg, the Iridex IQ-810; Iridex Corp, Mountain View, California, USA), an indirect ophthalmoscope, a condensing lens, and dilating drops, equipment fees, maintenance contracts, and applicable import taxes. Assuming that 15 neonates are treated per year, 10 are screened for every neonate treated, and equipment costs depreciate over 8 years, the cost *per-neonate treated* in Mexico was $3228 and in the United States was $9821 (Supplemental Table 2, available at AJO.com).

The direct costs for US labor including ophthalmology, nursing, and anesthesia salaries were determined for the time spent on both screening and treatment. Physician salary labor costs were estimated using data from a 2012 report published by the Medical Group Management Association (MGMA).[15] Nursing salaries were reported from the Bureau of Labor Statistics.[16] Facility and operating

room costs included the estimated space and time allocation with institutional overhead applied and the related major equipment costs depreciated over 8 years. In the United States, the standard of care for treatment of ROP includes the use of an indirect diode laser–delivered panretinal photocoagulation.[17] The cost of laser treatment for ROP in the United States, as outlined in Supplemental Table 3 (Supplemental Material available at AJO.com), was $4037. The costs of pharmacologic, intravitreal injections using either bevacizumab or ranibizumab in the United States are $603 and $2572, respectively (Supplemental Table 4, available at AJO.com).

The direct treatment costs in Mexico were calculated using country-specific labor, medication, and equipment costs. In order to best represent the direct costs of screening and treatment in Mexico, calculations were based on current clinical practices at the study site, APEC in Mexico City, using identical data collection methodologies as performed in the United States. However, in Mexico, local care practices are more reliant on low-dose bevacizumab as compared to laser-based US treatment. The costs associated with treatment failure for bevacizumab is difficult to determine because there is limited outcome data from this treatment for prethreshold ROP. Therefore, we conservatively estimate a $123 treatment failure cost based on 2 of 70 infants treated with bevacizumab who would require additional laser treatment.[18] The total cost per neonate for treatment with bevacizumab in Mexico was $504, as outlined in Supplemental Table 4.

The direct costs related to follow-up care after treatment are calculated in Supplemental Table 5 (Supplemental Material available at AJO.com). We considered the nursing and physician labor, and estimated loss of productivity owing to the time required of the caregiver(s). Panretinal laser photocoagulation, as performed in the United States, requires an average of 4 follow-up visits. The number of follow-up appointments required by neonates treated with bevacizumab is not known.[18,19] Since longer-term monitoring is required, until the retina is vascularized, we conservatively estimated that infants may require up to 20 follow-up visits and multiplied this by the cost per each follow-up in Mexico. The follow-up cost per neonate treated in Mexico was estimated to be $2214 while the cost per follow-up visit for laser treatment in the United States (4 visits) was $1538 (Supplemental Table 5).

Combining all direct costs for the United States and Mexico, we estimated the total cost of treatment per neonate to be $15 396 and $5946, respectively (Supplemental Table 6, available at AJO.com).

Indirect Costs. *Indirect costs* are defined as the cost to society related to disease-specific morbidity. These include costs of loss in productivity from caregivers and affected individuals as a result of ROP-related blindness.

Our survey data were derived from each family's expenses for raising a blind or visually impaired child, as opposed to a sighted child, and included the societal costs of a caretaker's lost productivity. We administered the EcROP survey in person to the parents and/or guardians of 52 children at schools for the blind and pediatric eye clinics in Atlanta and of 43 children in Mexico City (APEC). After informed consent was obtained, surveys were administered in private, one-on-one interviews with a study author (M.I.R., R.R., B.P., or D.B.). Data collected included demographic information, parental income, time missed from work, and other expenses associated with raising a blind child.

We calculated the overall cost to society by considering the demands of a caregiver raising a blind child. Each caregiver's lost wages were multiplied by their average hours of work missed per week by a country-specific national average of contribution to gross domestic product (GDP) per hour of work.[20] In Mexico, cost data were gender-adjusted by multiplying the parent's lost GDP by a country-specific factor for income distribution.[21] In the United States, the costs were adjusted by the relative participation in workforce by gender.[22]

The costs to caregivers of blind children do not end when the child reaches adulthood. Blind individuals often require additional care over their entire lifetime. In the United States, blind adults require 15 days more informal care per year than average adult children.[23] This marginal cost of 15 days per year (after age 20) was gender-adjusted to account for the documented predominance of female caregivers in the United States.[24] Similar data do not exists in Mexico. Therefore, we inquired with known experts and combined the EcROP survey data collected from parents who continued to care for blind children into their adulthood. We found an increased likelihood of multigenerational cohabitation among the Latin American population,[25] and we found that annual caretaker expenditures for teenage blind children are similar for adults. Therefore, over 44 years from birth to retirement, we found a combined parental indirect cost of $305 584 in Mexico and $817 996 in the United States (Supplemental Table 7, available at AJO.com).

GDP per capita was used to calculate the societal cost due to loss in productivity by blind individuals.[26] The annual loss of productivity from blindness was calculated by multiplying the country's annual GDP per capita by the difference in job participation rates between vision-impaired and fully sighted individuals.[27] This number was then multiplied by the average years spent in the workplace in order to estimate the labor-related loss of the individual's productivity over a work-lifetime.[28] We found that the lifetime loss of productivity resulting from a blind individual was $142 172 in Mexico and $357 019 in the United States (Supplemental Table 8, available at AJO.com). We acknowledge that there may be variation in visual impairment.

• **ANALYSIS:** A CUA was used to determine the incremental cost-effectiveness ratio (ICER), our primary outcome. ICER reflects the ratio of the change in costs to incremental benefits of a given therapeutic intervention or treatment. The benefit in our analysis was defined as QALYs gained as a result of the intervention. We then performed a CBA that calculated the net monetary benefit of an intervention with respect to willingness to pay (WTP). Incremental net monetary benefit, our secondary outcome, was calculated using the following equation: (additional QALYs gained × WTP/QALY) − additional cost.

• **VARIABILITY AND UNCERTAINTY:** We accounted for variability and assessed uncertainty in the model by performing both probabilistic and deterministic sensitivity analyses. Sensitivity analyses use a range for each input to test sensitivity of the model to variability. The ranges used for each cost, probability, and utility value are shown in Table 1. Cost of raising a blind child and productivity loss of a caregiver were derived from survey data. Therefore, the range used in sensitivity analysis for these 2 variables was zero to the upper limit 95% CI. All other costs were varied ±30%. Other input ranges were determined from published data or varied ±10%, as indicated.

For probabilistic analysis, we used the decision tree (Figure 1) to perform a Monte Carlo simulation on the base case, with subsequent best- and worst-case analysis. This simulation incorporated a triangular probability distribution for the variables with the highest uncertainty. The simulation ran 10 000 random samples to determine the probability of different ICERs and net benefits.

Deterministic analysis was performed to consider the possible variation in the ICER and incremental net monetary benefit by using a 1-way sensitivity analysis of direct costs with variation in the base case inputs. Threshold analysis was performed to determine the value for different variables at a point when the national program becomes the dominant strategy as compared to the current program.

RESULTS

WE REPORT THE RESULTS IN 2014 US DOLLARS, DISCOUNTED at 3%. Labor and caregiver data are gender adjusted when possible. The base case analysis of our model revealed that ideal national screening and treatment programs in Mexico and the United States would be extremely cost-effective and have a substantially greater net monetary benefit when compared to current practice (Table 2). The ICER of a national program over current practice calculates to a negative value for both Mexico and the United States. The negative ICER value indicates that universal screening dominates current screening and is cost saving in both countries. Per child, the incremental net monetary benefit of a national program over current practice was

TABLE 2. Retinopathy of Prematurity Base Case Analysis of Cost-Effectiveness and Net Health Benefits for Mexico and United States

	Incremental Cost ($Cost_{national} - Cost_{current\ practice}$)[a]	Incremental Effectiveness ($QALY_{national} - QALY_{current\ practice}$)[a]	ICER[a]	Net Monetary Benefit, National Program[a]	Net Monetary Benefit, Current Practice[a]	Incremental Net Monetary Benefit of National Program[a]	Incremental Net Monetary Benefit, Scaled to Population at Risk Over 1 Year[b]
Mexico							
National program	−$2203	0.067	Cost-saving	$1 146 829		$5556	$206 574 333
Current practice					$1 141 272		
United States							
National program	−$2221	0.028	Cost-saving	$996 699		$3628	$205 906 959
Current practice					$993 071		

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year.
Dollar values represent US dollars.
[a]Analyses performed per child.
[b]Population analysis performed by multiplying the incremental net monetary benefit per child by the estimated number of children <1500 g in the nation in 1 year.

TABLE 3. One-way, Deterministic Sensitivity Analysis of Direct Costs in Retinopathy of Prematurity Management

Direct Cost Inputs, per Child	Mexico		United States	
	Incremental Net Benefit per Child of National vs Current Program	Incremental Net Benefit in Nation Over 1 Year	Incremental Net Benefit per Child of National vs Current Program	Incremental Net Benefit in Nation Over 1 Year
Base case	$5556	$206 574 333	$3628	$205 906 959
Screening				
Increased 30%	$5092	$189 278 289	$3039	$172 478 293
Decreased 30%	$6021	$223 854 759	$4218	$239 392 379
Treatment				
Increased 30%	$5553	$206 454 987	$3618	$205 339 409
Decreased 30%	$5559	$206 678 061	$3639	$206 531 263
Follow-up				
Increased 30%	$5543	$206 083 197	$3624	$205 679 939
Decreased 30%	$5567	$206 975 493	$3641	$206 644 773

The incremental net monetary benefits are shown when the different components of a national retinopathy of prematurity screening program are varied ±30%. All figures are in US dollars.

$5556 in Mexico and $3628 in the United States. The incremental net monetary benefit of a national program, scaled to the population of babies at risk (≤1500 g) born in 1 year (37 179 and 56 754 babies in Mexico and the United States, respectively), was $206 574 333 in Mexico and $205 906 959 in the United States (Table 2).[29–31]

We also examined the results for the United States if the care delivered was an injection with bevacizumab or ranibizumab rather than laser. We calculated that each was cost saving, with incremental net monetary benefits of $3615 and $3598 per infant treated with bevacizumab and ranibizumab, respectively.

• **DETERMINISTIC SENSITIVITY ANALYSIS:** Deterministic sensitivity analysis was performed on direct costs, to better inform health care policymakers of the effects of variation in the direct costs (increase or decrease of 30%) of an ROP screening and treatment program (Table 3). Thus, deterministic sensitivity analysis is a way to generate a reasonable estimate of variation with uncertainty externalized to our model.

Threshold analysis was also performed for each country to determine variable values when the national strategy would become the dominant strategy. In Mexico, 2 threshold values were found. When the prevalence of those at risk, based on ROP screening criteria (birth weight <1500 g), was >9%, or when the probability that a child who needs treatment was treated is >2%, the national strategy was dominant. In the United States, when the prevalence of babies at risk (birth weight <1500 g) was >15%, or when the probability that a child who needs treatment was treated is >4%, the national strategy was dominant. In the United States, when there was a screening sensitivity of >35%, the national strategy was dominant, whereas no similar screening threshold was found for Mexico.

• **PROBABILISTIC SENSITIVITY ANALYSIS:** Probabilistic sensitivity analysis, using Monte Carlo simulation, was performed using best-case and worst-case analysis. The following 9 variables cumulatively accounted for over 99.9% of the uncertainty in the model: (1) prevalence of ROP, (2) discount rate, (3) probability that a child who screened positive for any ROP would end up receiving treatment, (4) probability that a child not treated would have a favorable structural outcome, (5) cost of productivity loss of the caregiver, (6) direct cost of raising a blind child, (7) cost of productivity loss of a blind individual, (8) QALYs of a blind individual, and (9) QALYs of a normal-seeing individual. Because these 9 variables accounted for the greatest uncertainty, a triangular probability distribution (Figure 2) was created for each and was incorporated into the simulation. Thus, the probabilistic sensitivity analysis is a way to generate uncertainty into the analysis and considers uncertainty as a distribution and the output also appears as a distribution (Figure 2).

Base Case Scenario. The results of the simulation are represented as a scatterplot based on comparing incremental cost-effectiveness to QALYs (Figure 2). Every data point on the graph represents an iteration from the simulation and of a random combination of values for each input selected from the probability distribution. The results demonstrate that in Mexico, there is a 91% chance that a national screening program would be cost-saving or cost-effective (below $50 000/QALY). There is a 73% chance that an iteration of EcROP will fall in the lower right (southeast) quadrant, meaning the national program would result in an increase in QALYs while simultaneously resulting in cost savings. There is an 18% chance that an iteration will fall in the upper right (northeast) quadrant, but below the dashed line; or that a national program will increase QALYs at an increased

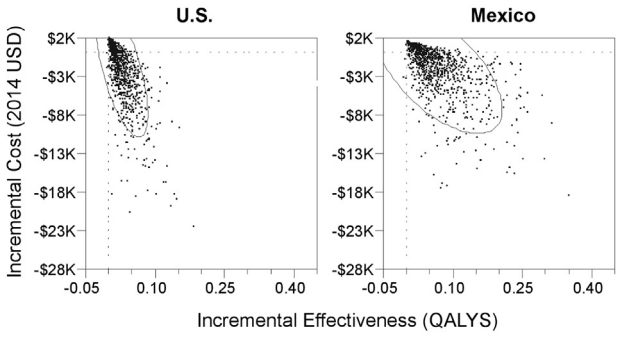


FIGURE 2. Incremental cost-effectiveness scatterplot of national retinopathy of prematurity program vs current practice. Each point represents an iteration from a random combination of values for each input as derived from the probabilistic sensitivity analysis. The more cost-effective possibilities are located in the southeast quadrant. The dashed line is the cost-effectiveness threshold of $50 000/quality-adjusted life year (QALY). The ellipse represents the boundary in which 95% of the iterations fell. These data indicate a high likelihood distribution that a national program would be cost-effective.

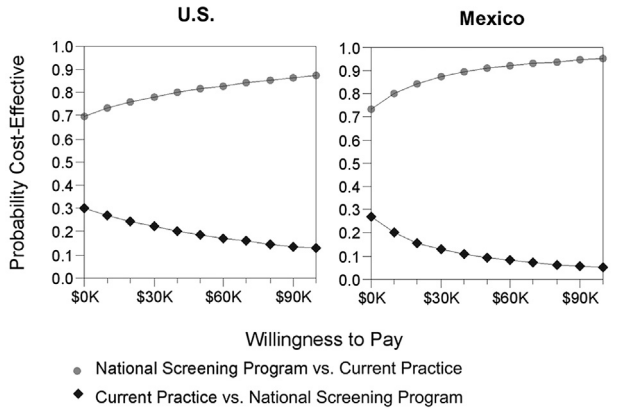


FIGURE 3. Acceptability curves of cost-effectiveness for national retinopathy of prematurity program vs current practice. Willingness to pay (WTP) per quality-adjusted life year (QALY) is varied on the x-axis and the probability of cost-effectiveness at each WTP is reflected on the y-axis. This illustrates the cost-effectiveness of the programs at a willingness to pay varying from the typically used $50 000/QALY.

cost, but the ICER will be less than the WTP threshold. For Mexico, only 9% fell in the northeast quadrant above the dashed line, indicating an ICER of greater than the WTP threshold. The results demonstrate that in the United States, there is an 82% probability that an ideal national screening program would be cost-saving or cost-effective and below the WTP threshold. A national program in the United States is 70% likely to incur a cost savings. There is only an 18% chance that the incremental cost will be too high for a national program to be cost-effective.

Figure 3 graphically represents an acceptability curve for a national ROP program as compared with current practice. Because societal WTP/QALY may vary in different countries, we plotted the range from $0/QALY to $100 000/QALY. The acceptability curves show the probability that a national strategy will be cost-effective when compared with current practice, given a threshold WTP. In Mexico, the probability that the national program would have a positive economic benefit (ie, either cost-saving *or cost-effective)* compared to the current program is 73%–95%, from $0 to $100 000 WTP, respectively. In the United States, the probability that the national program would have a positive economic benefit compared to the current program is 70%–90%, from $0 to $100 000 WTP, respectively.

Best-Case and Worst-Case Scenarios. Probabilistic sensitivity analysis was also used to determine the scenarios in which a national program is most or least favorable. The best-case scenario was performed by changing inputs to values that increased the favorability of the national program. For example, the lowest-range costs of screening and treatment were used, whereas the highest range in productivity losses were used. In Mexico, the best-case scenario yielded a 98% chance that a national screening program would have a positive economic benefit based on a WTP of $50 000/QALY and an 87% chance that the national program would yield cost savings. Probabilistic sensitivity analysis of the worst-case scenario was performed by changing inputs to values that decreased the favorability of the national program. For Mexico, the worst-case scenario yielded an 80% chance that a national screening program would have an economic benefit and a 52% chance to be cost-effective.

In the United States, the best-case scenario yielded a 92% chance that a national screening program would be economically beneficial and an 85% chance it would yield a cost savings. In the worst-case scenario, the national program had a 63% chance of being economically beneficial, with a 47% chance of yielding a cost savings.

Cost-Benefit Outcomes. The simulation calculated a probabilistic sensitivity analysis of net monetary benefits. Through the simulation, the incremental net monetary benefits of the national program over current practice were determined for each country, while simultaneously varying the value for WTP (Table 4). In Mexico, the incremental net monetary benefit per child from an ideal national program ranged from $2203 to $8910 at a WTP of $0/QALY to $100 000/QALY, respectively. In the United States, the incremental net monetary benefit per child from an ideal national program ranged from $2221 to $5053 at a WTP of $0/QALY to $100 000/QALY, respectively (Table 4).

TABLE 4. Incremental Net Monetary Benefit of a National Retinopathy of Prematurity Program Over Current Practice, per Child, Varied by Willingness to Pay

	Mexico		United States	
Willingness to Pay, $/QALY	Incremental Net Monetary Benefit per Child	Incremental Net Monetary Benefit per Year	Incremental Net Monetary Benefit	Incremental Net Monetary Benefit per Year
0	$2203	$81 906 439	$2221	$126 052 744
1000	$2270	$84 397 465	$2249	$127 641 883
10 000	$2874	$106 853 883	$2503	$142 057 640
50 000	$5556	$206 569 302	$3628	$205 906 959
100 000	$8910	$331 269 345	$5035	$285 761 173

QALY = quality-adjusted life year.
All figures are in US dollars.
The incremental net benefit per child and per year varies as the willingness to pay per QALY varies from the typical $50 000/QALY.

DISCUSSION

THE ECROP MODEL ANALYZES THE ECONOMIC IMPACT OF ROP screening and treatment at a national and societal level for the designated country or economic region. The EcROP face-to-face interviews and fieldwork gathered relevant data and included a sensitivity analysis that provides socioeconomic information about both direct and indirect cost data for the regions studied. Information from both the United States (an example of a developed nation) and Mexico (an example of a middle-income developing nation) clearly demonstrate that screening and treatment of ROP is both highly cost-effective and also cost-saving. EcROP also calculates a high likelihood that a positive incremental net monetary benefit for both the United States and Mexico would result from implementing an ideal program. Thus, implementation of a national ROP program would be strongly beneficial, yielding both meaningful improvements in quality of life and overall financial savings.

Currently, the most commonly cited acceptable cost-effectiveness ratio is the $50 000/QALY. Though this figure may vary, we scaled the WTP ($/QALY) and discovered cost savings at *all* levels, even levels over $100 000/QALY.[32] The sensitivity analysis performed suggests that there is a very high likelihood that these parameters will be realized, even with extremely conservative estimates of variation. Sensitivity analysis is implemented to shield against flaws in our data collection or errors in assumptions. Caregivers' productivity loss and the cost of raising a blind child were calculated from our survey data to measure the time missed from work for parents of blind children and the expenses of child rearing. We used sensitivity analysis with wide intervals (0, upper 95% CI) and wide ranges for variation in other costs to account for value fluctuations that are certain to be present both when surveying families and estimating disease incidence. We conclude that effective screening and treatment programs for ROP in both the United States and Mexico would be highly cost-effective. Furthermore, EcROP is readily applicable to other developed and developing nations.[33] Other area or regional analysis would require further support and investigation, as societal factors in different geographies will vary. As a general call to action from the EcROP findings, failure to implement an ROP screening and treatment program is likely to result in meaningful loss of QALYs and also have profoundly negative financial implications for countries and areas where these results are ignored.

The role for anti–vascular endothelial growth factor agents in ROP management remains unclear. Our analysis looked at each treatment method available in the United States and Mexico (laser, bevacizumab, ranibizumab), because the evidence-based care may change over time. Nevertheless, any treatment method selected has a minimal overall impact on either the ICER or net incremental benefit calculations. A positive effect from broad ranges in treatment cost is corroborated by the results of our sensitivity analysis. Because the direct costs vary, we found consistent cost-effectiveness and cost savings. Thus, we conclude that the cost of any available ROP intervention is negligible when compared to the cost of blindness that begins in infancy.

Previous studies of the cost utility of ROP screening and treatment in the United States have noted ROP screening to be cost-effective.[34,35] However, these studies report a positive ICER, indicating that dollars would have to be invested in return for QALYs gained.[34,35] On the contrary, EcROP data report a cost savings (based on the negative value of the ICER) in both the United States and Mexico. These are societal impacts from certain and now verified loss in parental or caregiver productivity plus the loss in future earnings of blind individuals. Such societal costs are relevant, are important, and underscore the need for a more detailed analysis as outlined in the

EcROP. Indirect costs may vary in different societies and regions and may change over time. They are also influenced by geopolitical as well as other unpredictable economic and societal forces. The impact of considering indirect cost should clarify the decision to intervene in ROP, as this has a measurable, sustainable, lifetime economic benefit for the child, the family, and society. The performance of a face-to-face family interview that gathers detailed data about costs related to ROP care within the context of the society is an important advantage of the EcROP. The survey considers the region-specific practice patterns as well as supply and labor costs, rather than basing costs on a singular social system or insurance reimbursement. As such, the EcROP assesses both the financial and societal factors of any specific country or region.

In both the United States and Mexico, care guidelines for premature infants at risk for ROP already exist.[3] ROP management guidelines were published by the Mexican Secretary of Health in 2008.[4,36] However, many of the protocols for ROP management are based on criteria developed in countries with excellent perinatal care, and this infrastructure is often unavailable in countries where the ROP burden is higher.[36] Access to prenatal, perinatal, and ophthalmic care is variable in many countries, including Mexico. Mexico City is the economic and geopolitical center where national and medical resources are concentrated. In the schools for the blind, we found many families raising children blind from ROP who reportedly did not have the opportunity of ROP screening. Access to care in more rural areas of the country is considerably more challenging and the burden of disease is greater. Our data predict that an effective national program with high penetrance would include reasonable access to care in all areas in order to optimize the financial and societal gain. Clearly, the capability to screen and treat ROP exists in Mexico. The challenge will be expanding the current systems to increase the penetrance to include the entire population.

In the United States, we have made several assumptions owing to the lack of published data that include the prevalence of ROP among infants <1500 g and the penetrance of current screening patterns. We relied on expert opinion for many variables and accounted for uncertainty using sensitivity analysis. Even in our calculated worst-case scenarios, we still found a high likelihood of cost savings and cost-effectiveness for implementation of effective screening and treatment programs. An area that also lacks published data is the long-term survival for infants affected by ROP. We assumed 100% survival after screening and treatment. This is certainly not the case, and therefore EcROP assumes payment for neonates who will not live. Such an assumption will overestimate the favorability of a national ROP program. An assumption of 100% sensitivity and specificity of screening also likely overestimates the calculated benefit.

In summary, we believe that EcROP and the detailed results from applying the model in both the United States and Mexico should strongly encourage the implementation and maintenance of robust screening and treatment programs with high population penetrance. The EcROP model predicts that investing in viable programs will be extremely cost-beneficial for the countries that implement them effectively. In essence, these programs pay for themselves by reducing the lifelong burden of blindness and visual impairment. Importantly, the EcROP data support a cost savings and QALY improvement, plus societal benefits from implementation of effective ROP management. The window for treating ROP is brief, yet the impact is lifelong and imparts a multigenerational direct benefit to individuals, families, societies, and national economies. We predict that such programs represent one of the most cost-effective uses of health care resources in all of medicine, especially in developing nations. On the other hand, failure to implement, according to these recommendations, will likely lead to a significant financial and societal burden on those countries or regions that fail to recognize the extreme demands of childhood blindness. The time to implement is immediate and urgent, and will have measureable long-term implications. We are confident that the EcROP findings will empower ministers of health to wisely direct necessary resources toward the development and implementation of effective, high-penetrance ROP screening, treatment, and prevention programs.

FUNDING/SUPPORT: THIS WORK WAS SUPPORTED BY AN UNRESTRICTED DEPARTMENTAL GRANT FROM RESEARCH TO PREvent Blindness (New York, NY); a departmental core grant, NEI P30 EY 006360, and Financial Support: Emory Eye Center's GO-Emory, and a portion of the travel expenses were from the Emory University School of Medicine. Also, the teachers and staff at the Center for the Visually Impaired facilitated support of the interviews in Atlanta, GA and at several schools for the blind in Mexico City. Financial disclosures: Timothy W. Olsen: Genentec-Roche (site-PI on Lampalizumab study GX29176; salary support only through Emory University, no outside fees other than meeting travel as required). The following authors have no financial disclosures: Michael I. Rothschild, Rebecca Russ, Kathryn A. Brennan, Christopher J. Williams, David Berrones, Bhavesh Patel, Maria Ana Martinez-Castellanos, Alcides Fernandes, G. Baker Hubbard III, R.V. Paul Chan, and Zhou Yang. All authors attest that they meet the current ICMJE criteria for authorship.

REFERENCES

1. Hartnett ME, Penn JS. Mechanisms and management of retinopathy of prematurity. *N Engl J Med* 2012;367(26):2515–2526.
2. Good WV, Hardy RJ, Dodson V, et al. The incidence and course of retinopathy of prematurity: findings from the Early Treatment for Retinopathy of Prematurity Study. *Pediatrics* 2005;116(1):15–23.
3. Section on Ophthalmology American Academy of Pediatrics: American Academy of Ophthalmology: American Association for Pediatric Ophthalmology and Strabismus. Screening examination of premature infants for retinopathy of prematurity. *Pediatrics* 2006;117(2):572–576.
4. Secretaria de Salud, Centro Nacional de Equidad de Genero y Salud Reproductiva. Manejo de la retinopatia del recien nacido prematuro. 2007. Available at: http://www.v2020la.org/docs/lineamiento/Lineamiento-ROP-SSA-2007.pdf. Accessed January 4, 2015.
5. Pejaver RK, Bilagi AP, Vinekar A, Deorari AK, Jalali S. National Neonatology Forum of India (NNF) Clinical Practice Guidelines: Retinopathy of Prematurity. 2010. Available at: http://aimaonline.org/iap-neochap-2013/uploads/acd-corner/nnf_guidelines-2011.pdf. Accessed November 23, 2015.
6. Blencowe H, Lawn JE, Vazquez T, Fielder A, Gilbert C. Beyond newborn survival paper 3. Preterm-associated visual impairment and estimates of retinopathy of prematurity at regional and global levels for 2010. *Pediatr Res* 2013;74(Suppl 1):35–49.
7. Gilbert C, Fielder A, Gordillo L, et al. 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:e518–e525.
8. Gilbert C. Retinopathy of prematurity: a global perspective of the epidemics, population of babies at risk and implications for control. *Early Hum Dev* 2008;84(2):77–82.
9. Neocosur GC. Very-low-birth-weight infant outcomes in 11 South American NICUS. *J Perinatol* 2002;22(1):2–7.
10. Zin AA, Magluta C, Pinto MF, et al. Retinopathy of prematurity screening and treatment cost in Brazil. *Rev Panam Salud Publica* 2014;36(1):37–43.
11. United Nations Development Programme (UNDP). Human Development Report, 2015. Oxford, United Kingdom: Oxford University Press; 2015.
12. Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity: ophthalmological outcomes at 10 years. *Arch Ophthalmol* 2001;119(8):1110–1118.
13. Prevent Blindness America. The Cost of Blindness: QALYs. Available at: http://costofvision.preventblindness.org/costs/loss-of-wellbeing/quality-adjusted-life-years-qalys. Accessed December 4, 2014.
14. Siegel JE, Weinstein MC, Russell LB, Gold MR. Recommendations for reporting cost-effectiveness analyses. Panel on Cost-Effectiveness in Health and Medicine. *JAMA* 1996;276(16):1339–1341.
15. MGMA Physician Compensation and Production Survey: 2012 Report Based on 2011 Data, and Physician Placement Starting Salary Survery: 2012 Report Based on 2011 Data. *Careers in Medicine*: American Association of Medical Colleges. Available at: http://www.mgma.com/industry-data/mgma-surveys-reports. Accessed December 4, 2014.
16. Occupational Employment and Wages- May 2011. US Department of Labor BoLS. Available at: http://www.bls.gov/news.release/archives/ocwage_03272012.pdf. Accessed November 2, 2014.
17. 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;12(12):1684–1694.
18. Mintz-Hittner HA, Kennedy KA, Chuang AZ. BEAT-ROP Cooperative Group. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. *N Engl J Med* 2011;364(7):603–615.
19. Micieli JA, Surkont M, Smith AF. A systematic analysis of the off-label use of bevacizumab for severe retinopathy of prematurity. *Am J Ophthalmol* 2009;148(4):536–543.e2.
20. OECD: The Organisation for Economic Co-operation and Development. Stats Extracts: Level of GDP per capita and productivity. Available at: http://stats.oecd.org/Index.aspx?DataSetCode=PDB_LV. Accessed November 17, 2014.
21. Socio-Economic Database for Latin America and the Caribbean (CEDLAS and the World Bank). Statistics by Gender. Available at: http://sedlac.econo.unlp.edu.ar/eng/statistics-by-gender.php. Accessed November 17, 2014.
22. The World Bank. Databank, indicator: Gender. Available at: http://data.worldbank.org/indicator/SL.TLF.CACT.MA.ZS/countries. Accessed November 17, 2014.
23. Frick KD, Foster A. The magnitude and cost of global blindness: an increasing problem that can be alleviated. *Am J Ophthalmol* 2003;135(4):471–476.
24. Navaie-Waliser M, Spriggs A, Feldman PH. Informal caregiving: differential experiences by gender. *Med Care* 2002;40(12):1249–1259.
25. Taylor P, Passel J, Fry R, et al. The return of the multi-generational family household 2010. Washington D.C.: Pew Research Center. Available at: http://www.pewsocialtrends.org/files/2010/10/752-multi-generational-families.pdf. Accessed November 12, 2014.
26. Central Intelligence Agency WD. The World Factbook 2014. Available at: https://www.cia.gov/library/publications/the-world-factbook/geos/mx.html. Accessed November 10, 2014.
27. The World Bank. Databank, indicator: Labor force participation rate, total. Available at: http://data.worldbank.org/indicator/SL.TLF.CACT.ZS/countries. Accessed November 17, 2014.
28. OECD: The Organisation for Economic Co-operation and Development. Pensions at a glance: retirement-income systems in OECD countries: Mexico. Available at: http://www.oecd.org/els/public-pensions/43021548.pdf. Accessed November 18, 2014.
29. Villanueva Egan LA, Contreras Gutierrez AK, Pichardo Cuevas M, Rosales Lucio J. Perfil epidemiologico del parto prematuro. *Ginecol Obstet Mex* 2008;76(9):542–548.
30. The World Bank. Databank, indicator: Birth rate (crude)/1000 people. Available at: http://data.worldbank.org/indicator/SP.DYN.CBRT.IN. Accessed December 4, 2014.
31. CDC National Vital Statistics Reports. Births: Final Data for 2011. 2013; 62(1). Available at: http://www.cdc.gov/nchs/data/nvsr/nvsr62/nvsr62_01_tables.pdf. Accessed December 4, 2014.

32. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness—the curious resilience of the $50,000-per-QALY threshold. *N Engl J Med* 2014;371(9):796–797.
33. Dave HB, Gordillo L, Yang Z, Zhang MS, Hubbard GB III, Olsen TW. The societal burden of blindness secondary to retinopathy of prematurity in Lima, Peru. *Am J Ophthalmol* 2012;154(4):750–755.
34. Kamholz KL, Cole CH, Gray JE, Zupancic JA. Cost-effectiveness of early treatment for retinopathy of prematurity. *Pediatrics* 2009;123(1):262–270.
35. Dunbar JA, Hsu V, Christensen M, Black B, Williams P, Beauchamp G. Cost-utility analysis of screening and laser treatment of retinopathy of prematurity. *J AAPOS* 2009;13(2):186–190.
36. Carrion JZ, Fortes Filho JB, Tartarella MB, Zin A, Jornada ID Jr. Prevalence of retinopathy of prematurity in Latin America. *Clin Ophthalmol* 2011;5:1687–1695.
37. Palmer EA, Hardy RJ, Dobson V, et al. 15-year outcomes following threshold retinopathy of prematurity: final results from the multicenter trial of cryotherapy for retinopathy of prematurity. *Arch Ophthalmol* 2005;123(3):311–318.
38. Chen J, Stahl A, Hellstrom A, Smith LE. Current update on retinopathy of prematurity: screening and treatment. *Curr Opin Pediatr* 2011;23(2):173–178.