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Screening for Retinoblastoma: A Systematic Review of Current Strategies

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Purpose: The aim of this study was to review the literature on various screening programs, devices, and applications described for the early detection of retinoblastoma.

Design: Systematic review article.

Methods: A PubMed® search was performed to identify articles published with specific reference to screening of neonates, infants and children for retinoblastoma.

Results: Various devices and mobile phone-based applications based on altered red reflex are finding their way into community screening. Diagnosis of retinoblastoma by newborn eye screening is emphasized in several countries, and red reflex is the most widely employed technique.

Conclusions: Several screening programs for early detection of retinoblastoma are evolving in the developing countries, but the practices are not uniform. Universal newborn screening should be the norm. Newer tools and software can be utilized to screen infants on a community scale. Focussed research on revolutionizing digital imaging for a versatile screening tool holds promise for early diagnosis of retinoblastoma.

Key Words: ArcLight™, cancer, CRADLE, eye, leukocoria, RB, retinoblastoma, screening

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Retinoblastoma (RB) is the most common intraocular cancer of childhood with an incidence ranging from 3.4 to 42.6 cases per million live births across the world.[1] Survival rates in developed countries in the present era have crossed 95% but on the other end of the spectrum, children continue to succumb to the disease in low- and middle-income countries, that is attributed to late presentation.[2–8] This gap can be bridged by the implementation of effective screening strategies.[7–9] Tumors in younger children tend to involve the posterior pole and move towards the periphery with advancing age, although not without exceptions.[10] It is also known that high-risk features such as optic nerve invasion, massive choroidal invasion, and anterior segment invasion are more common with increasing age which translates to increased risk of systemic metastasis and death.[11,12] Therefore, if diagnosed and treated early, the disease can be managed with less radical forms of therapy, allowing salvage of a child's life and the affected eye with the benefit of vision salvage in select cases.[9,12]

Screening protocols for population at risk[13,14] for retinoblastoma are well established, but without universal screening of neonates and infants, this grave disease may not be identified until it reaches an advanced stage. This review attempts to summarize the various screening programs, devices, and strategies employed across the world for early detection of RB and enable the formulation of an effective screening protocol which is universally acceptable.

METHODS

A PubMed® search was performed to identify articles published in MEDLINE® database with specific reference to screening of neonates and infants for retinoblastoma. Search with "retinoblastoma 'AND' early detection", and "retinoblastoma 'AND' screening" produced 4,357 articles of which 59 articles were related to early diagnosis, detection and screening of RB. After checking for duplication and excluding articles on screening of 'at-risk children', screening of 'family members', pre-natal diagnosis of RB, case reports, and commentaries, 15 studies were included, which were on: 1) novel screening devices or tools utilized for early detection of RB; 2) hospital- or community-based prospective studies aimed at detection of RB in neonates and infants; 3) eye screening programs in children as a part of which RB was diagnosed early

Screening devices, applications, and software were evaluated based on the principle, sensitivity, specificity, limitations, and cost. Prospective and retrospective studies were summarized. Details of target population, screening devices, methodology, results, and conclusions were assessed.

RESULTS

Novel Devices with Scope of Utility in Screening for RB

Novel tools (alternative to direct or indirect ophthalmoscopy) utilized in screening for RB are based on either detection of leukocoria or imaging the retina. The devices described in literature include ArcLight™, Portable Eye Examination Kit (PEEK), iCam (Optovue), and RetinaScope. Smartphone-based applications include CRADLE, MDEyeDetector, and soft fusion classifier leukocoria detector (Table 1).[15–27] The ArcLight™ is a handheld diagnostic tool which can be used on ophthalmoscope

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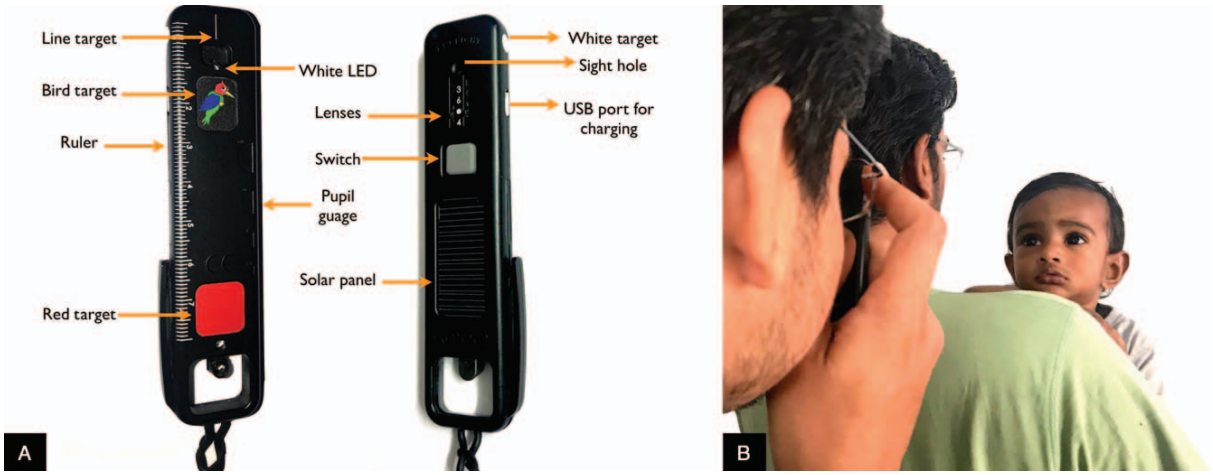

FIGURE 1. Retinoblastoma screening with ArcLight™. A, Screening device ArcLight™. B, Usage of ArcLight to examine red reflex in a child.

(Fig. 1), anterior segment loupe, or an otoscope with attachments. It is low-cost equipment with a solar panel and ergonomic design intended for use in low resource settings.[15,16] PEEK is an adaptor clip which, when combined with a mobile phone, can be used to capture retinal images with minimal training. It has been used widely in Kenya to study disorders of the posterior segment.[18,19] iCAM Optovue, Inc. (Fremont, CA) is a portable fundus camera which utilizes infrared light emitting diode (LED) to capture retinal images which can be viewed on a computer screen.[20] Mndeme et al demonstrated the utility of ArcLight™, PEEK and iCAM in detecting media opacities by trained nurses in ophthalmic as well as pediatric clinics with a sensitivity of 93%, 90%, and 98% respectively for Arclight™, PEEK and iCAM.[15] Trained ophthalmic nurses were capable of using all these devices effectively, hence they can be potential screening tools for screening in children.[15] Patel et al described a widefield smartphone-based retinal imaging system (RetinaScope) for pediatric fundus photography. The device was used to image 6 eyes with retinoblastoma among 43 children with various ocular pathology.[21]

ComputeR-Assisted Detector of LEukocoria (CRADLE), also popular as "White Eye Detector," is a freeware application available for download on a smartphone. It is designed to detect leukocoria by analyzing the digital image (Fig. 2). The application is user-friendly and can be used by parents and caretakers to screen children.[22,23] However, Vagge et al and Khadekar et al have found low sensitivity and detection rates for this application.[24,25] Khadekar et al compared CRADLE with a similar smartphone application MDEyeCare[26] and concluded that with modification in the photography parameters, the latter had superior detection rates for retinoblastoma than CRADLE.[25] MDEyeCare, however, needs subjective interpretation of the image after capture of the pupillary reflex.[25,26] Rivas-Parea designed a software on similar lines for better accuracy using technology of 'soft fusion of classifiers' for improved detection of leukocoria.[27]

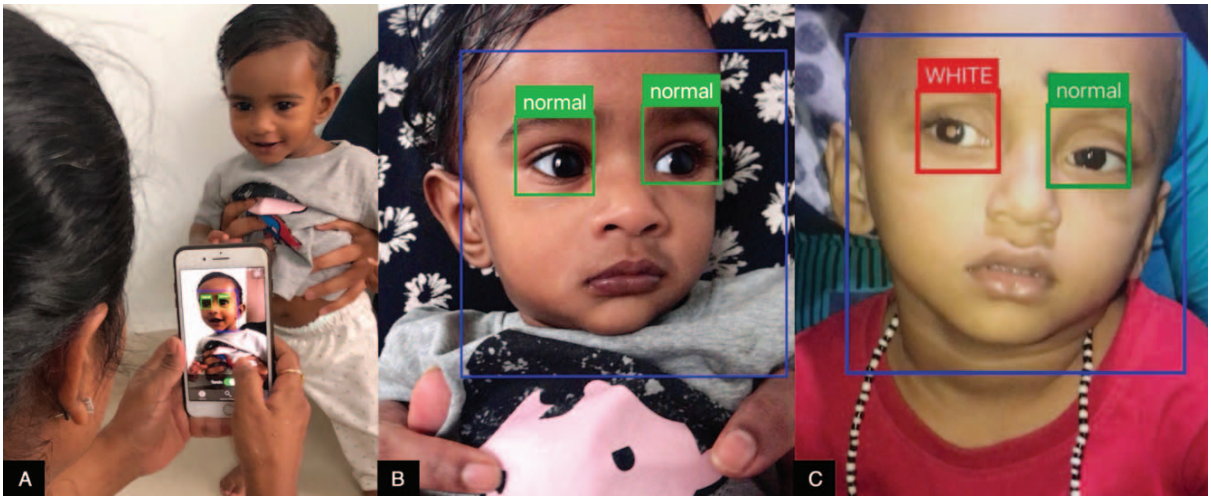

FIGURE 2. Retinoblastoma screening in children. A, Photograph showing usage of the CRADLE application on a smartphone by the parent of the toddler. B, Normal reflex in both eyes as seen on the CRADLE application. C, White reflex detected by the CRADLE application in a child with right eye retinoblastoma. CRADLE, ComputeR-Assisted Detector of LEukocoria.

TABLE 1. Novel Devices and Softwares Employed for Early Detection of Leukocoria and Retinoblastoma

Device/Software	Principle	User	Input	Output	Validation in Literature (Leukocoria)	Advantages	Limitations
ArcLight	Miniature direct ophthalmoscope	Ophthalmologist/ trained pediatrician/ technician/ nurse	Direct ophthalmoscopic examination	Interpretation of red reflex by the examiner	Sensitivity 93% [10]	Cheap Portable Solar and battery powered	Requires hardware and trained personnel with knowledge of interpretation
PEEK	Clip-on smartphone attachment for image acquisition	Ophthalmologist/ trained / technician/ nurse	Analogous to capturing fundus photograph	Captured image, to be interpreted by the user	Sensitivity 90%[10]	Portable	Requires hardware and trained personnel. Captured images need interpretation May not be suitable for young children
iCam (Optovue)	Portable fundus camera	Ophthalmologist/ trained technician/ nurse	Analogous to capturing fundus photograph	Captured image	Sensitivity: 98%[10]	Portable	Expensive Requires hardware, trained personnel for image capture and interpretation
CRADLE	Application for leukocoria detection	Anyone acquainted with smartphone usage	Photograph captured through camera or saved on device	Automated: "Normal" or "White"	Munson et al[18]: Sensitivity 90% Specificity 20% Accuracy 55% Khadekar et al[20]: Percentage of detection (%): 0,0,0,0,100% in Group A to Group E RB respectively Vagge et al[19] Sensitivity 15.4% Specificity 100% Negative likelihood ratio 1%	Free software available for download on iOS and Google Play Utility established in non-standard-setting, hence can be extrapolated to screening in community Interpretation not user-dependent	Requires access to and knowledge of usage of smart phone Low detection rates for early disease (Group A and B)
MDEye Detector	Application for leukocoria detection	Anyone (requires knowledge of smartphone usage)	Photograph captured through camera or saved on device	Photograph needs to be interpreted by the user	Percentage of detection (%)[20]: 0,0,83,100,100 in Group A to Group E RB respectively	Free software available for download on iOS and Google Play	Interpretation of image is subjective
Soft fusion of classifiers for leukocoria detection	Detection of leukocoria from recreational photographs by soft fusion of classifiers	-	-	-	Riva-Perea P et al[22]: Accuracy 92% True positive 89% False positive 11%	Interpretation not user dependent Soft fusion is better than other methods of combining classifiers used in image processing	Not commercially available
RetinaScope	Clip-on smartphone attachment for fundus imaging	Ophthalmologist/ trained technician/ nurse	Analogous to capturing dilated fundus photograph	Captured image	Patel et al[16]: Detection rate of pathology (93–100% with interobserver variation)	Portable	Requires dilatation and subject cooperation Interpretation of image is subjective

RB indicates Retinoblastoma.

Guidelines, Programmes, and Policies for Screening of RB

According to the World Health Organization (WHO) Guide for Effective Programmes in Cancer Control, programs are recommended for 'early diagnosis' (target population being children with white reflex and convergent strabismus, as these are the most common symptoms) but not for 'screening'.[28] However, ocular examination of neonates, infants and children is recommended as a part of various policies and governing bodies in several countries have formulated guidelines for the same. Ocular examination in neonatal period and infancy is crucial for detection of various ocular pathologies including RB. Guidelines for neonate and infant eye examinations could be retrieved only for select countries and notably most of them emphasize the importance of red reflex examination by trained personnel as a mandate. (Table 2).[29–37] However, maintenance of a database for RB including details of cases referred from screening programs is not practised worldwide.[31]

Studies Aimed at Detection of RB or Other Ocular Pathologies in Neonates, Infants, and Children

Vagge et al and Khadekar et al explored the utility of smartphone-based applications for detection of leukocoria to determine sensitivity and specificity. Both these studies showed low detection rates in early disease, both in small as well as a larger cohort of patients.[24,25] Khadekar et al suggested a modification in MDEyeCare application to improve detection rates.[25]

Several studies across the world have shown the benefit of ocular examination in neonates by testing for red reflex and retinal imaging. Various ocular pathologies were detected in asymptomatic children including RB. Prevalence of any form of ocular anomaly ranged from 5% to 24% in several studies.[21,38–45] The details of the same are summarized in Table 3.

DISCUSSION

American Academy of Ophthalmic Oncologists and Pathologists has formulated clear guidelines for detection of RB in children 'at risk' for retinoblastoma and these are practised widely.[13] However, about 90% of patients diagnosed with RB, who do not have a positive family history, are sporadic, thus may not be diagnosed early, often leading to worse outcomes. Proven risk factors for poor survival rates with RB in developing countries include delay in diagnosis and treatment abandonment.[7–9] Although the latter revolves around the socio-economic status, cultural, and literary background, the former can be tackled by increasing awareness and implementation of effective screening programs.[7,9]

TABLE 2. Policies and Guidelines on Screening for Retinoblastoma in Different Countries

Geographic Location	Organization	Screening Guidelines for Newborns, Infants and Children Relevant to Detection of Retinoblastoma
-	WHO Guide for Effective Programmes: Cancer Control	Programmes recommended for early diagnosis (target population being children with white reflex an convergent strabismus) but not for screening.
Canada	Canadian Task Force on Preventive Health Care, Community Pediatric Society, National Retinoblastoma Strategy Canadian guidelines for Cancer Care	Red reflex examination from birth to three months of age; failure to visualize a normal red reflex warrants immediate referral to ophthalmologist Ophthalmic examinations from 6–12 months, 3–5 years and 6–18 years
USA	American Academy of Pediatrics: Policy Statement	Mandatory red reflex examination of all infants within first 2 months of life by pediatrician or by a trained primary care ophthalmic clinician
Mexico	Official Gazette of the Federation, General Health Law	Neonatal eye examination 4 weeks after birth (no technical guidelines)
Latin and South America	AHOPCA RetMex GALOP	Treatment guidelines defined, but no screening protocol/ guidelines
United Kingdom	NIPE screening programme UK National Retinoblastoma Service	Red reflex examination within 72 hours of birth and at 6–8 weeks of age Dim or absent red reflex referred to ophthalmology service
Kenya	Kenya National Screening Guidelines	Ocular examination and genetic testing for children "at risk" for RB
India	Rashtriya Bal Swasthya Karyakram	Identification of at-risk newborns (family history of retinoblastoma) Ophthalmic examination including red reflex testing using an ophthalmoscope Referral of infants at risk or with abnormal red reflex to ophthalmologists. Responsibility delegated to: Pediatricians/medical officers of special newborn care unit, staff nurse, optometrist of the district hospital and the ophthalmologist of district hospital/ private hospital
Australia	National Children's Vision Screening Project	Proposed screening programs for universal red reflex examination in newborn by trained personnel and staged screening approach all pre-school children (<4 years) starting with assessment of visual acuity
New Zealand	Ministry of Health	Red reflex examination within first week and at 6 weeks of birth by lead maternity care, general practitioner or pediatrician

AHOPCA indicates Asociación Hemato- Oncológica Pediátrica de Centro America; GALOP, Grupo de America Latina de Oncologia Pediatrica; NIPE, Newborn and infant physical examination; WHO, World Health Organization.

TABLE 3. Comprehensive Review of Neonatal and Childhood Eye Screening Programs for Early Detection of Childhood Eye Disorders Including Retinoblastoma

Author, year	Population	Intervention (Methods)	Comparison	Outcome	Study Type
Vagge et al[19], 2019	122 children (244 eyes)	Screened with CRADLE for detection of leukocoria	Cycloplegic fundus examination	Sensitivity-15.4% Specificity-100% Negative likelihood ratio-0.85%	Qualitative
Khedekar et al[20], 2019	34 eyes of 23 RB patients and 4 normal children	Screened with MDEyeCare (modified) and CRADLE for detection of leucocoria	Clinical (fundus) examination	Percentage of detection (%) MDEyeCare: 0,0,83,100,100 in Group A to Group E RB respectively CRADLE: 0,0,0,0,100 in Group A to Group E RB respectively	Qualitative
Hussain et al[33], 2019	Staged screening of 33,549 children (<16 years) for ocular anomalies	Phase 1: Screening by trained community health workers Phase 2: Comprehensive ophthalmologist Phase 3: Pediatric ophthalmologist	Referred children evaluated by pediatric ophthalmologists	3 cases (0.008%) of retinoblastoma identified, prevalence of 0.09 per 1000 screened was noted	Quantitative
Simkin et al[34], 2019	All infants born between (350) June 2015 and December 2016	Dilated WFDRI using RetCam Shuttle (Clarity MSI USA) at a community birth centre, New Zealand	Images reviewed by ophthalmologist through telemedicine	Various ocular abnormalities (15.9%) detected including retinal hemorrhages, congenital cataract and optic nerve hypoplasia. No casess of retinoblastoma were diagnosed	Quantitative
Mndeme et al[10], 2018	a) 1152 children (<5 years) b) 41 cases and 60 controls c) 2728 children	Torchlight exam, red reflex assessment in Reproductive and Child Health Clinics I-Cam, ArcLight, Portable Eye Examination Kit, torchlight use in Hospital setting Reproductive and Child Health Clinics	Indirect ophthalmoscopy Indirect ophthalmoscopy Indirect ophthalmoscopy for referred children	Red reflex testing more sensitive than torchlight in detecting ocular media disorders, 94.7% versus 42% (p=0.0005) Sensitivity: I- Cam 97.56%, Arclight 92.68%, Portable Eye Examination Kit 90.2%, torchlight 7.3% Arclight was easy to use initial learning curve was easier	Qualitative
Goyal et al[35], 2018	1152 neonates from March 2014 to Oct 2015	Dilated fundus examination of apparently healthy neonates a civil hospital in Eastern India	None	Significant ocular findings in 172 babies (14.9%) including retinal hemorrhages, congenital glaucoma, cystic fovea, uveal coloboma, albinotic fundus, fundal jaundice	Quantitative
Cagini et al[36], 2017	22,272 children born in Umbria, Italy between January 2012 to December 2013	Red reflex was tested and labelled as positive or equivocal; later referred to ophthalmologist	Ophthalmoscopy for referred children	3/ 461 (0.013% of total) neonates with equivocal reflex had ocular pathology, 1 (0.004%) of which was retinoblastoma	Quantitative
Jayadev et al[37], 2015	1450 preterm infants from January 2011 to December 2011	WFDRI captured over multiple sessions using RetCam Shuttle (Clarity MSI USA)	All images analyzed by pediatric retinal specialists	2 eyes (0.14%) with retinoblastoma diagnosed early	Quantitative
Vinekar et al[38], 2015	1021 term infants	WFDRI over multiple sessions using RetCam Shuttle (Clarity MSI USA)	Children with abnormal images examined clinically	4.7% had ocular anomalies 1 child with retinoblastoma detected	Quantitative
Luo et al[39], 2014	779 preterm and term infants	WFDRI	Images analyzed	1 retinoblastoma detected amongst 69 children with abnormal fundus findings	Quantitative
Li LH et al [40], 2013	3573 healthy neonates within 42 days of birth	Flash light, Retinoscope, WFDRI	None	871 (24.1%) abnormal cases 2 cases (0.06) of retinoblastoma	Quantitative

CRADLE indicates ComputeR-Assisted Detector of LEukocoria; RB, retinoblastoma; WFDRI, Widefield digital fundus imaging.

Indirect ophthalmoscopic examination with scleral indentation under general anesthesia is the gold standard for establishing or ruling out the diagnosis RB in children.[46] However, it cannot be employed as a screening tool for detection of RB due to various constraints, such as need for pupillary dilatation, general anesthesia or sedation, and technical expertise. Research for better screening tools has paved way to the development of numerous devices for retinal imaging and detection of media opacities.[20] Some of these have shown potential use in screening for RB as well.[18–20] Screening for retinoblastoma can be performed by 2 basic techniques: 1) red reflex assessment and 2) wide-field digital retinal imaging (WFDRI).[16–27] Red reflex is a simple test, which is easy to perform with adequate training.[47] However, it is not fool proof and has a sensitivity of about 85% and specificity of 39%, which further varies with pupillary dilatation.[48] For RB, the location & size of intraocular tumors can affect the degree of distortion of red reflex. WFDRI overcomes these limitations by providing a wider field of view to detect peripheral lesions as well.[20] However, lack of portability and high cost limit the use of WFDRI, giving rise to development of various compact devices such as PEEK and iCAM.[18–20] One inherent disadvantage with any of these methods includes the subjectivity and need for interpretation by expert personnel. Teleconsultation by sharing the images captured is a feasible option to ensure accurate interpretation.[19] Smartphone-based applications for detection of leukocoria came into existence when parents of a child with RB noticed a white reflex in his eyes in serial photographs and they offered these images to be analyzed which heralded the development of CRADLE and MDEyeCare.[22,23,26] Being freewares, these applications can be used widely on a larger scale. CRADLE also displays the result as a "normal" or "white" eye, thereby eliminating the need for interpretation. CRADLE has been shown to have a lead time of 284 ± 547 days and 50 ± 103 days from the diagnosis of unilateral and bilateral retinoblastoma respectively.[23] Further, artificial intelligence and deep learning have enormous potential in this field with scope for interpretation of pupillary reflex as well as retinal imaging for diagnosis.[49]

For the formulation of policies on establishment of screening programs, the WHO defines criteria for 'early diagnosis' and 'screening' of a disease and the choice between the two is determined by weighing the proven benefit of screening, on disease outcomes, and availability of resources. Establishing a 'screening program' is more complex than an 'early detection program' (which targets at-risk populations) and WHO at present does not recommend a screening programme for RB even in high-resource setting. However, such programmes can be taken up as research projects with clear objectives in terms of effectiveness. Accountability and documentation after implementation play a major role in both early detection and screening programmes to propose changes in program methodology or introduce new programs.[28] Guidelines of several nations reflect significant heterogeneity in terms of timing of examination, number of visits and the personnel involved in screening (Table 2). Notably, maintaining a national registry for RB is not uniformly practised and the importance of the same needs to emphasize.[31] Further, although there are specific guidelines for examination of children with RB and screening of at-risk children, technical guidelines on mandatory infant eye examination including red reflex testing are detailed only by few organizations.[28–37] There is a need to compose uniform guidelines across the world and ensure compliance to the same. The methodology for screening can be customized according to the resources available. Red reflex examination is current standard of care for screening. Policies do not recommend WFDRI as yet for universal ocular examination in children, and researchers have demonstrated its utility in neonatal eye examinations.[28–37]

Early detection of RB has been reported from universal eye screening programs in the pediatric age group.[15,39,41–45] With a reported prevalence of ocular pathology of nearly 25% in some studies, universal ocular examination for neonates certainly needs consideration.[45] Although WFDRI is ideal, cost constraints limit its use. Goyal et al noted ocular pathology in 15% in a study of 1152 apparently healthy neonates, but analyzing the cost involved, and they concluded that the 'inexpensive' red reflex examination is a more viable alternative for universal screening and recommended that WFDRI should be limited to children at risk of development of ocular disease.[40] Vinekar et al, on the other hand, extrapolated their results of WFDRI in 1021 term infants to national scenario (India), and estimated that about 226,950 infants requiring treatment may go undiagnosed if routine WFDRI is not performed.[43] For translation of screening strategies to programs, it is important to take into account the 'number needed to screen'.[50] Defined as 'the number of people that need to be screened to prevent one death or adverse event', the number needed to screen can be calculated from clinical trials on screening or estimated from studies on prevalence of unrecognized disease and clinical trials on treatment.[50] For RB, this would involve estimating the population with early disease (ie, earlier than the most common group at presentation for a given population), adverse events being as vision loss, eye removal, metastasis, or death from the disease. The cost of resources for its implementation needs to be weighed against a benefit of reduction in the adverse events, which may vary in developed countries and developing countries, to determine the feasibility.

In a setting of limited resources with a large disease burden, red reflex testing would be a feasible option with focus on reducing the mortality first and subsequently improvise. Till WFDRI is widely available for screening, smartphone-based cost-effective strategies and smartphone-based screening applications hold promise and are currently under-utilized. The responsibility lies on the shoulders of health care professions in pursuing research on novel screening techniques.

Summarizing all the above facts, though disease burden and challenges vary across the world (Table 4), universal guidelines for retinoblastoma screening are the need of the hour, allowing leeway for modifications subject to availability of resources in the form of screening devices, manpower, and logistics. Maintenance of an interconnected nationwide database is invaluable from an epidemiological perspective and formulation of health policies; hence strongly recommended. Novel devices and applications need large scale trials for validation and research for an ideal screening tool should be pursued upfront. Till wide-field retinal imaging can be made available for all neonates and infants, no child should be deprived of the benefit of a red reflex examination. Every child should undergo red reflex testing at birth and within first few years of life by trained social workers or pediatricians, if not an ophthalmologist.

TABLE 4. Worldwide Disease Burden, Clinical Profile, Outcomes, Challenges, and Directions for Screening in Various Regions

Region (N)[8]	Disease Burden(n)[8]	IRSS Stage at Presentation[8]	Predominant Socioeconomic Status[3]	Survival Rates Mean (Range)	Current Challenges[7,8]	Considerations for Additional Screening Tools and Strategies
North America (2)	200	**0: 59.5%; I: 39.0%** II: 0.5% III: 0.5% IV:0.5% NA:0.5%	High-income	>99% survival rate[2–4] >90% retain vision in one eye[2–4]	Leading cause of mortality: second non-ocular cancers	Timely diagnosis and of second cancers
Europe (40)	522	**0: 53.6% I: 42.9%** II: 1.1% III: 0.6% IV: 1.1% NA:0.6%				
Oceania (3)	17	**0: 29.4% I: 64.7%** IV: 5.9%				
Latin and Caribbean (23)	312	**0: 23.4% I: 50.0%** II: 7.7% III: 4.8% IV:8.3% NA:5.8%	Upper-middle income	79% (54–93%)[5]	Delay in diagnosis leading to development of extraocular or metastatic disease	Improve life salvage and attempt to preserve vision through: Collaborative screening programs (Malaysia, South Africa): universal screening with fundus imaging may be feasible (iCAM)
Asia (42)	2276	**0: 37.5% I: 39.6%** II: 4.0% III: 8.2% IV: 5.8% NA:4.9%	Lower-middle income	77% (60–92%)[5,6]	Delay in diagnosis and refusal to treatment	Improve life salvage through: community level screening (PEEK/ CRADLE/ ArcLight) Emphasis on socioeconomic factors
Africa (43)	1024	0: 15.1% **I: 35.6%** II: 9.5% **III: 19.1%** IV: 15.6% NA:5.2%	Low-income	40% (23–70%)[5]		

* IRSS indicates International Retinoblastoma Staging System: N, number of countries; n, number of cases of retinoblastoma over an 18-month-period.

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