REVIEW ARTICLE

Screening Methods for Early Identification of Retinoblastoma: A Systematic Review of Clinical and Genetic Approaches

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Abstract

Purpose: The present systematic review examined the diagnostic efficacy and clinical applicability of modern retinoblastoma screening and early detection methods, including wide-field digital imaging, red reflex examination, smartphone-based tools, ultrasonography, MRI, and RB1 genetic testing. **Methods:** A thorough search of PubMed, Google Scholar, and ResearchGate yielded 2,338 records. 22 papers from 2015–2025 were included after removing duplicates and applying inclusion and exclusion criteria. Data from various healthcare settings were evaluated by screening mode, diagnostic effectiveness, feasibility, and clinical relevance. The QUADAS-2 instrument examined bias. An OSF Registration done. **Results:** The red reflex test was the most used universal screening approach, however it was insensitive to small or posterior cancers. Indirect ophthalmoscopy, ultrasonography, and MRI were mostly confirmatory, with MRI revealing optic nerve and brain extension insights. Wide-field digital retinal imaging was most sensitive for early, asymptomatic tumours, especially in new-born screening. Smartphone imaging and automated leukocoria apps improve early detection in resource-constrained contexts. While access was limited in low- and middle-income countries, genetic testing showed hereditary cases and helped plan surveillance. **Conclusion:** Wide-field imagery was the most effective early detection method, however smartphone-based solutions worked in underserved areas. For paediatric retinoblastoma patients, a stratified, resource-optimized screening strategy that integrates clinical assessment, imaging, and genetic analysis could improve early detection, treatment efficacy, and survival. This study emphasises the need to improve screening techniques and expand diagnostic technology internationally.

Key words: Retinoblastoma, Early detection, Intervention, Screening methods, Genetic testing

INTRODUCTION

Retinoblastoma (RB) is a rare but a most severe retinal neoplasm that attacks one or both eyes of children during their infancy and early childhood. Most of the cases are diagnosed under the age of 5 years, with a median of 23.2 months of age on diagnosis, which is correlated with low survival rates.[1-4] Low-to-middle-income countries (LMICs) patients usually present a high level of disease, which is linked with lower survival rates. On the other hand, the high-income countries patients and those with better socioeconomic status generally report at an earlier stage and have a better access to adequate healthcare, thus, a higher survival rate, globe salvage, better visual function, and greatly reduced risk of spread.[5,6] Early identification is also critically important since it allows adequate intervention to be initiated, enhances the chances of globe salvage, retains visual functionality, and significantly lowers the risk of metastatic extension. Conversely, late presentation is related to severe intraocular disease, extra-ocular extension, enucleation, and low survival rates.

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It is estimated that about half of all cases of RB have a genetic predisposition because it is caused by a germline pathogenic mutation in the RB1 tumor-suppressor gene.[7,8] The presence of mutation carriers can be used to perform targeted monitoring of the RB-affected child at birth, and to detect tumors at an early symptomatic or pre-symptomatic stage (such as in the case of siblings, a potential offspring, and parents).[9] Seeing that hereditary RB constitutes about 40% of all cases, the RB1 mutation analysis has become an essential element of modern screening techniques. The American Academy of Pediatrics suggests age-specific evaluation of visual issues, including a symmetric red reflex, at every health-supervision encounter between birth and the age of five.[10]

RB is, by definition, a neoplasm occurring in young children, with the age at presentation correlating with the chance of bilateral involvement. Patients with bilateral RB typically present at an earlier age (generally before 1 year) compared to those with unilateral disorder.[9] Leukocoria is the most frequent manifestation in over half of cases, and can sometimes be detected after a flash image. The second most common presenting symptom is Strabismus which is normally associated with macular involvement. Advanced intraocular tumors might induce pain due to secondary glaucoma.[10] In underdeveloped nations, limited access to specialist care contributes to diagnostic delays, causing children to exhibit extraocular illness.[11] This not only diminishes the rates of visual retention and ocular preservation but also substantially elevates the morbidity and mortality associated with the disease in affected children.[12]

The last decades have seen a significant improvement in the management of RB, with a greater focus on the maintenance of the eye and vision. Red reflex test is commonly used as a simple, low-cost, and non-invasive screening method that is appropriate with infants and newborn babies. Despite its acceptance in most national screening programs, its sensitivity is inconsistent and significantly influenced by the examiner's proficiency and the characteristics of the tumor. Innovations in pediatric ocular imaging, especially wide-field digital fundus imaging systems like RetCam, have enhanced the capacity to see the posterior segment in non-compliant newborns and identify minor, peripheral, or posterior pole tumors that may be clinically overlooked.[13] Smartphone-based solutions, including RetinaScope for fundus imaging and applications like CRADLE or MDEyeDetector for automated leukocoria detection, also offer scalable options for early identification, although their effectiveness in detecting very early tumors remains variable.[14-16] One major initiative is the National Ophthalmic Disease Genotyping and Phenotyping Network (eyeGENE®), launched by the National Eye Institute in 2006 to accelerate research on inherited eye diseases and improve access to molecular diagnostic testing.[17] Innovative portable and smartphone-based imaging solutions have enhanced potential in resource-limited settings. Despite the existence of various screening methodologies, there is no agreement on the best effective or practical methodology for early detection across diverse risk categories or healthcare environments. An integrated evaluation of the effectiveness, advantages, limitations, and applicability of every screening strategy is needed to improve clinical practice, policy development, and promote global efforts in the early detection of the disease.

The systematic review of the evidence will assess and synthesize current studies on the effectiveness of clinical and genetic screening methods in the premature diagnosis of RB. The aim of the review is to determine an evidence-based model of how screening strategies may be optimized, diagnostic delays be minimized, and better outcomes attained against children at risk of this potentially life-threatening malignancy through a comparison of the diagnostic performance, feasibility, and clinical utility.

METHODOLOGY

This systematic review was carried out in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines to ensure methodological rigor and transparency. The review process started with a protocol that included the objectives, eligibility criteria, search strategy, and analysis plan; hence ensuring consistency in the methods used. The research question was developed with the help of PICO framework, where the population included children aged 0–18 years screened for RB; the intervention was any screening technique such as clinical examination, digital imaging, tele-screening, and genetic testing; the comparison, in its case, was the routine clinical assessment; the outcome was the sensitivity, specificity, diagnostic performance, and the rates of early detection. An Open Science Framework (OSF) registration has been done with Doi: (https://doi.org/10.17605/OSF.IO/3TFBX)

A literature search was conducted and included PubMed, Scopus, Web of Science, Google Scholar, and Cochrane Library to locate the studies that were carried out research on screening methods to detect the condition of RB at an early stage. The search was conducted on all publications of the year 2015–2025, but limited to the English language and the materials relating to human subjects. Included in the strategy were MeSH terms and free-text terms like "retinoblastoma," "screening," "early detection," "red reflex," "fundus imaging," "wide-field imaging," "RetCam," "digital retinal imaging," "smartphone imaging," "leukocoria detection" and "genetic screening". To retain scientific integrity, grey literature, conference abstracts, letters, editorials, as well as case reports, were excluded.

The studies qualified to be included if they involved screening of neonates, infants, or children with RB or leukocoria by clinical assessment, imaging equipment,

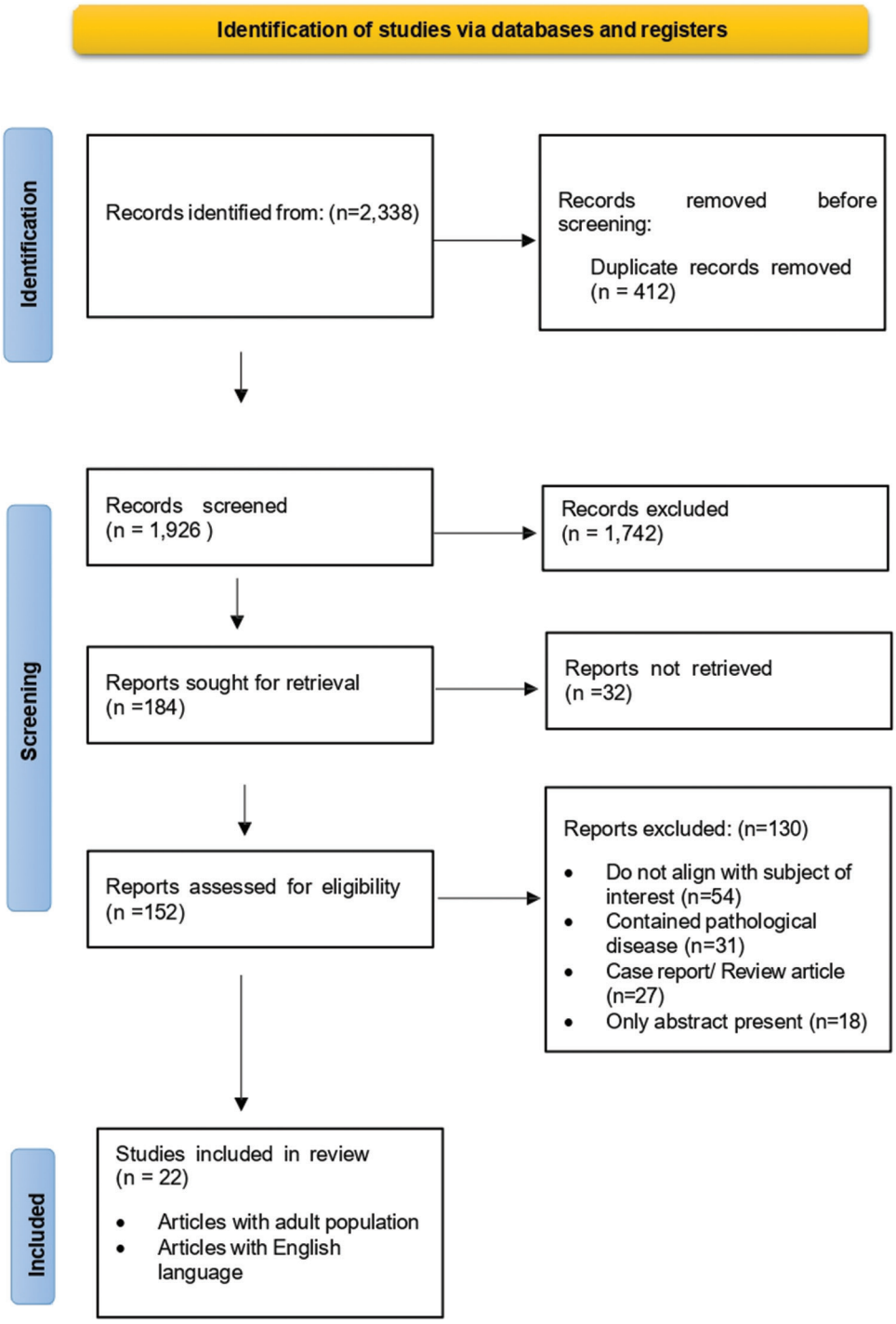

Figure 1: Preferred reporting items for systematic reviews and meta-analyses flow-diagram

smartphone-based applications, or genetic assays. Other studies that were included involved screening of high-risk children with RB1 mutations. Eligible studies included prospective and retrospective cohort design, cross-sectional designs, diagnostic accuracy designs, and program evaluations. The exclusion criteria were studies that were centered on prenatal diagnosis, surveillance in at-risk family members not under the population screening, treatment outcome, less than ten participants, and non-human research.

In Figure 1, PRISMA Diagram, database searches revealed 2,338 records. Following the elimination of 412 duplicates, 1,926 titles and abstracts were evaluated. They eliminated 1,742 due to their irrelevance to RB screening or early detection. Full-text retrieval was attempted for 184 articles; however, 32 were unsuccessful. Out of the 152 full-text articles, 130 were excluded for various reasons: misalignment with the review focus (n = 52), emphasis on pathological or clinical disease progression instead of screening (n = 34), case reports or review articles (n = 26), availability limited

to abstracts (n = 12), or methodological deficiencies (n = 6). The conclusive systematic review comprised 22 articles that fulfilled all inclusion criteria following this rigorous screening process.

The diagnostic performance results (sensitivity and specificity) were summarized and compared descriptively across different screening modalities, for example, red reflex testing, wide-field digital retinal imaging (WFDRI) systems (e.g. RetCam, PEEK, iCam, and smartphone-based attachments), automated leukocoria detection applications, and even RB1 genetic screening. A special focus was made on evaluating the practicality and usefulness of every modality in different clinical and resource contexts. Quality of methodology and the risk of bias of diagnostic accuracy studies incorporated were assessed with Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool. The ethics approval of the institution was not considered to be necessary, as the review incorporated published information.

This review discusses the effectiveness of existing screening techniques in helping early cases of RB in children. This study aims to clarify the diagnostic worth, practicability, as well as the pertinence of several clinical, imaging-based, and genetic modalities such as the red reflex assessment, WFDRI, smartphone-based applications, leukocoria-detection apps, and RB1 testing by assessing the existing evidence across different care systems. The synthesis is aimed to offer more integrated, evidence-based methods to improve previous detection and improve outcomes.

RESULTS

The final synthesis outlined 22 studies that met the eligibility requirements. This research assessed a comprehensive array of screening and diagnostic methods for the early detection of RB, including clinical examination, wide-field digital imaging, smartphone technologies, automated leukocoria detection, ultrasonography, magnetic resonance imaging (MRI), and *RB1* genetic testing. The principal findings across modalities revealed significant discrepancies in diagnostic sensitivity, practicality, and appropriateness for various clinical and resource contexts. Across these modalities, substantial variation was observed in diagnostic sensitivity, feasibility, and suitability across resource settings, highlighting the need for a stratified screening approach.

For the purpose of this review, screening modalities were defined as tests applied to asymptomatic or high-risk children before confirmed diagnosis. These include red reflex examination, WFDRI, smartphone-based imaging, automated leukocoria detection applications, and RB1 genetic testing.

Diagnostic and staging tools such as indirect ophthalmoscopy, ultrasonography, computed tomography, and MRI were analysed separately as confirmatory modalities rather than primary screening tools.

Table 1 provides a summary of presently accessible modalities, their diagnostic efficacy, and associated implementation obstacles. These deficiencies underscore the imperative of incorporating supplementary screening methodologies to enhance early tumor detection. However, the specialized equipment, elevated costs, and requirement for sedation in infants, especially for MRI, restrict their feasibility as primary screening methods in various contexts. Numerous studies have shown that neonatal WFDRI programs and telemedicine-assisted image interpretation effectively identify asymptomatic small tumors. However, extensive adoption is limited by the high costs of equipment and the necessity for skilled operators.

Smartphone-based wide-field fundus photography has attracted significant interest as an accessible and affordable instrument for pediatric retinal screening. These devices provide the rapid capture of retinal pictures with enough field coverage, rendering them especially beneficial in newborn facilities and community-based programs where conventional wide-field systems like RetCam may be inaccessible. The capacity to represent images for distant analysis enhances their function in teleophthalmology-assisted screening. Despite variations in image quality due to operator proficiency and patient compliance, the cumulative evidence supports their feasibility, cost-effectiveness, and capacity to improve early diagnosis of pediatric retinal disorders, such as RB.

The clinical implications of early versus late identification of RB are evident in a wide range of outcome metrics, as detailed in Table 2. Early-stage detection (Stage 0–I) is significantly correlated with substantially enhanced survival rates frequently surpassing 95% in richer environments and facilitates the effective application of minimally invasive, globe-preserving treatments. On the contrary, late presentation with advanced cancer (Stage III–IV) is associated with markedly diminished survival rates, especially in LMICs, where survival may drop below 40 and 60% due to elevated metastatic dissemination. Preservation of the globe is feasible in most cases identified early; however, late discovery often requires enucleation and leads to significant vision impairment. These data collectively underscore the significant influence of early identification on survival, vision, treatment complexity, cost, and quality of life.

In Table 3 QUADAS-2 tool was done to assess the risk if bias, most included studies demonstrated an overall low risk of bias, with consistently strong performance across patient selection, index testing, reference standards, and flow/timing. A smaller proportion showed moderate risk due to non-consecutive sampling, variability in test administration, or incomplete follow-up. Only a few studies exhibited high risk, mainly related to operator-dependent technologies or

Table 1: Diagnostic and screening modalities for retinoblastoma: Current landscape and implementation challenges

Modality	Description/ Application	Frequency of use	Advantages	Limitations/ Barriers	Outcomes
Red reflex exam[18-20]	Basic test for leukocoria in newborns	Universal in many countries	Simple, low-cost, quick	Low sensitivity for early/posterior tumors; skill dependent	Late detection→poor outcomes; improves with awareness programs
Indirect ophthalmoscopy[21,22]	Gold-standard diagnostic evaluation after referral	Routine in tertiary centers	Detailed assessment; confirms RB	Requires dilation, anesthesia, expertise	Essential for accurate diagnosis and treatment planning
Ultrasound (B-scan/UBM)[23,24]	Detects mass, calcification, and anterior extension	Common in secondary/tertiary care	Non-invasive; detects calcification	Limited early tumor detection; operator dependent	Crucial for staging and differentiating mimickers
MRI[25-27]	Evaluates optic nerve/orbit; detects trilateral RB	Used in advanced disease staging	No radiation; excellent soft-tissue detail	Expensive; sedation needed; limited in LMICs	Key for staging and monitoring hereditary RB
CT scan[28,29]	Detects calcification and extraocular spread	Declining use	Good calcification visibility	Radiation risk; avoided in hereditary RB	Used only when MRI unavailable
RetCam/WFDRI[15,16]	Wide-field digital imaging for early tumor detection	Increasing in neonatal units and telemedicine	High sensitivity; peripheral/ posterior visualization	High cost; trained operator needed	Proven value in early identification programs
PEEK/Smartphone fundus imaging[30,31]	Portable smartphone-based retinal imaging	Growing use in LMICs	Low cost; portable; community-friendly	Variable image quality; may require dilation	Useful in outreach; good adjunct for triage
iCam (Optovue)[32]	Portable fundus camera with LED illumination	Used in resource-limited screening	High sensitivity; good image quality	Expensive; operator training needed	Effective in detecting media opacities and lesions
RetinaScope[30,33]	Smartphone wide-field imaging attachment	Emerging, limited-scale use	Portable; good detection rates	Requires cooperation; subjective interpretation	Promising tool for early screening
CRADLE, MDEyeCare[34,35]	Automated white reflex detection from photos	Common for home-based use	Free; easy; parent-driven screening	Poor early-stage detection; photo- dependent	Detects advanced leukocoria earlier than clinical diagnosis
Genetic testing (RB1)[36,37]	Identifies hereditary RB and at-risk infants	Limited in LMICs; routine in high-income settings	Enables early surveillance and family counseling	Cost, lab availability, turnaround time	Essential for hereditary RB management

LMICs: Low-and middle-income countries, MRI: Magnetic resonance imaging, CT: Computed tomography, RB: Retinoblastoma

inconsistent patient pathways. Overall, the methodological quality of the evidence was acceptable, supporting confidence in the review's findings. Studies with higher risk tended to involve operator-dependent technologies or early-phase digital tools, reflecting variation in test standardization and patient flow.

DISCUSSION

Early diagnosis of RB is one of the most important factors in determining survival, longevity, prognosis of visual field, and the quality of life in the long term. The collective evidence of 22 studies is that the effectiveness and viability

Table 2: Comparison of early versus late detection outcomes in retinoblastoma

Outcome parameter	Early detection (Stage 0–I/small tumors)	Late detection (Stage III–IV/advanced tumors)	Clinical implications
Survival rate	>95% in high-income settings; significantly higher globally	<40–60% in LMICs; increased risk of metastasis	Early diagnosis directly correlates with improved survival
Globe salvage	High (70–90% depending on tumor location)	Low (<20%); enucleation often required	Early tumors are more amenable to focal therapy
Vision preservation	Good to excellent if macula spared	Poor; often complete loss of vision in affected eye	Timely detection prevents macular invasion
Treatment intensity	Minimally invasive therapies: laser, cryotherapy, limited chemotherapy	Aggressive multi-modal therapy: systemic chemo, IAC, enucleation, radiotherapy	Early detection reduces treatment burden, toxicities, and cost
Risk of extraocular spread	Very low	High; optic nerve and orbital invasion more common	Early screening reduces life-threatening complications
Treatment cost	Lower; outpatient-based focal therapy possible	Significantly higher; hospitalization, chemotherapy cycles, surgery	Early detection reduces financial burden on families and health systems
Family psychological impact	Less traumatic; better overall quality of life	High emotional, social, and psychological stress	Early detection improves long-term psychosocial outcomes
Time to diagnosis	Often within weeks of symptom onset	Delayed by months due to lack of awareness or access	Education and screening can shorten diagnostic interval

LMICs: Low-and middle-income countries, IAC: Intra-Arterial Chemotherapy

Table 3: QUADAS-2 risk of bias table

Study (Author, Year)	Patient selection	Index test	Reference standard	Flow and timing	Overall risk of bias
Simkin *et al*., 2019	Low	Low	Low	Low	Low
Vinekar *et al*., 2015	Low	Low	Low	Low	Low
Cagini *et al*., 2017	Low	Low	Low	Low	Low
Hanks *et al*., 2021	Moderate	Moderate	Low	Moderate	Moderate
Sun *et al*., 2016	Low	Low	Low	Low	Low
Orman and Huisman, 2022	Moderate	Low	Moderate	Low	Moderate
Soliman *et al*., 2020	Low	Low	Moderate	Low	Moderate
Jansen *et al*., 2020	Low	Low	Low	Low	Low
Habib *et al*., 2020	Low	Low	Low	Low	Low
de Bloeme *et al*., 2024	Low	Low	Low	Low	Low
Jansen *et al*., 2023	Low	Low	Low	Low	Low
de Jong *et al*., 2015	Low	Low	Low	Low	Low
Woldeyohannes *et al*., 2024	Low	Low	Low	Moderate	Moderate
Zhao *et al*., 2024	Low	Low	Low	Low	Low
Patel *et al*., 2019	Low	Moderate	Low	Low	Moderate
Bastawrous *et al*., 2016	Low	Moderate	Low	Low	Moderate
Mndeme *et al*., 2021	Low	Low	Low	Low	Low
Vilela *et al*., 2024	Moderate	High	Low	Moderate	High
Khedekar *et al*., 2019	Low	Low	Low	Low	Low
Jabir *et al*., 2022	Moderate	High	Low	Moderate	High
Rojanaporn *et al*., 2018	Low	Low	Low	Low	Low
Mohamed *et al*., 2023	Moderate	Low	Moderate	Moderate	Moderate

QUADAS-2: Quality assessment of diagnostic accuracy studies-2

of extant screening modalities are highly heterogeneous, which, in turn, underscores the need to have a resource-sensitive paradigm of screening. The collective findings lead to the conclusion that, as much as several methods enable the early identification, no single strategy can be entirely applied across the board; therefore, the combination of methods with a combination of clinical circumstances, operation viability, and diagnostic value can result in ideal detection.

The most commonly used screening test in the world is the red reflex test, as it is simple and cheap. However, as with previous studies, it has limited sensitivity with regard to early or posterior tumors.[18,32] In some low-resource countries, a lack of provider training adds to the delays in the diagnosis, which subsequently result in the advanced forms of the presentation and the reduced survival rates in LMICs.[1,6] Although red reflex test is part of universal newborn screening protocol, it is not sufficient to guarantee the early detection. Indirect ophthalmoscopy, ultrasonography, and MRI are confirmatory diagnostic methods that are necessary in case of RB. Ultrasonography can especially be used to identify the presence of tumor calcification or anterior segment involvement when MRI is used to give a complete evaluation of optic nerve invasion and intracranial spread.[21,23,24,28,29] Diagnosing trilateral RB cannot be done without the use of the MRI.[2] Yet, their elevated expense, the requirement for anesthesia in pediatric patients, and restricted accessibility in LMICs limit their application as screening instruments.[12] Rather, they function as essential instruments for staging and treatment planning. In all the modalities considered, there was the highest sensitivity with WFDRI, or more specifically, RetCam systems, in the detection of early-stage disease. WFDRI demonstrated consistently high sensitivity (90–100%) across neonatal screening programs, outperforming red reflex testing, which showed highly variable sensitivity ranging from 23% to 85%, particularly for posterior tumors.[15,16] Interpretations with the help of telemedicine increase accessibility in areas where subspecialty knowledge is unavailable. However, the high cost of equipment and the high skills of operators are major obstacles to its mass use, especially in the third world countries.[12] New smartphone-based imaging applications, PEEK and RetinaScope, provide viable alternatives that are more cost-effective and have enhanced reliability.[33] These systems have attained a good quality of images to detect abnormalities of the posterior pole and have moderate reliability with traditional tests.[30,31] They are specifically applicable to community screening programs and distance outreach clinics due to their portability and interoperability with technologies of teleophthalmology. Although the quality of the images taken by the smartphones can be also influenced by the experience of the operator and the reluctance of the patient to cooperate, the smartphone-based instruments can be regarded as one of the most extensible options in the early detection in LMICs.

The screening is also extended into the domestic domain by automated leukocoria detection programs, such as CRADLE and MDEyeCare that allow parents to detect abnormal pupillary reflexes. These applications are satisfactory in terms of performance on more advanced leukocoria, but the sensitivity of these applications on early-stage disease is significantly poor.[34] Therefore, they can be better utilized as the secondary surveillance measures but not the principal screening modalities. Therefore, RB1 genetic testing is essential for detecting hereditary RB and directing surveillance strategies for high-risk infants. Genetic screening enables the presymptomatic diagnosis, and has been demonstrated to enhance the age at diagnosis, stage of onset, and the subsequent clinical outcome.[7,36] However, its importance and availability are limited in many LMICs due to low financial and lab capacity. Low-sensitivity tests, including red reflex test, often lead to late-stage manifestations, which aligns with the statistics across the world and confirms the low survival rates and increased mortality in resource-depleted regions.[1] Considering the contrast between the early and late detection results, the implementation of multimodal strategies that combine the low-cost universal screening methods, telemedicine imaging, and genetic risks should be utilized to enhance the overall outcomes of RB in the world.[2,10] The review has limitations. Due to the heterogeneity of study design and outcome reporting, a meta-analysis was not conducted. Generalisability was limited by the fact that many research were observational and carried out in tertiary institutions. Furthermore, reported diagnosis accuracy may be impacted by variations in operator training and screening procedures.

The current review hypothesizes that the best method of early detection of RB is using a blend of a series of complementary screening tests that would best suit particular resources settings. WFDRI and the newly developed smartphone-based wide-field imaging are highly promising modalities that can be used to identify small, asymptomatic tumors, but genetic testing has been central in the assessment of hereditary risk. In every trial, there is the general trend that the sooner the diagnosis, the higher the mortality rates are reduced, the globe and visual preservation is more and better, the treatment burden is less, and psychosocial and financial burden on families is lower. Enhancing early screening infrastructures, especially in LMICs, is essential for minimizing diagnostic delays and bridging worldwide differences in RB outcomes.

CONCLUSION

The most important factor in improving survival, ocular, and visual prognosis is the early diagnosis of RB. There is variability in the usability of screening modalities in different clinical and resource settings; however, empirical data continues to underscore that those technologies with the capability to detect small or asymptomatic tumors at an earlier stage of the disease provide better prognostically relevant results.

The technological solutions have been viable, as shown by WFDRI and emerging smartphone-based solutions, which can be used to capture early detection in a neonatal and community screening setting, whereas RB1 genetic testing provides targeted surveillance for high-risk infants. Strategic implementation of screening programs should focus on flexible, resource-appropriate screening models that utilize both the broadly generalized techniques and the specialized modalities of imaging or genetic testing within those settings that have those resources.

AUTHOR'S CONTRIBUTIONS

Ms. Sushrita Mahadani was responsible for conceptualization, methodology, data curation, and writing. Mr. Shubham Bhattacharya contributed to the literature search, formal analysis, validation, and writing.

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