The Utility of Universal Newborn Eye Screening: A Review

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ABSTRACT: Universal newborn eye screening can identify ocular abnormalities early and help mitigate long-term visual impairment. Traditional neonatal and infant eye screening is administered by neonatologists and pediatricians using the red reflex test. If this test identifies an ocular abnormality, then the patient is examined by an ophthalmologist. Notably, the red reflex test may be unable to detect amblyogenic posterior segment pathology. Recent studies using fundus imaging and telemedicine show reduced cost of human resources and increased sensitivity compared with traditional approaches. In this review, the authors discuss universal newborn eye screening pilot programs with regard to disease prevalence, referral-warranted disease, and cost-effectiveness.

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INTRODUCTION

Vision screening is essential for early detection of preventable vision-threatening and life-threatening conditions.[1] Traditionally, vision screening is performed by non-ophthalmologists, including primary care providers and trained laypersons (eg, school or community-based screening programs).[1] It can be either provider-based or instrument-based. Provider-based screening includes the red reflex test (RRT), the most widely used test, external inspection, pupil examination, corneal light reflex test, cover test, and visual acuity, which can all be performed in the hospital or clinical setting.[2,3] These techniques are performed with varying degrees of completeness by individual providers and cannot be applied to a population unless there is investment in training large numbers of examiners. Instrument-based screening includes photo screening and handheld autorefraction and can be performed around 2 to 3 years of age and allows for faster throughput and greater scalability than provider-based testing[4]; however, it suffers from the inability to capture disease in the first 2

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or 3 years of life. Current guidelines from the American Academy of Pediatrics and the American Association for Pediatric Ophthalmology and Strabismus recommend screening all newborns and children using a combination of provider-based techniques on newborn infants before discharge from the hospital, with referral of patients with any abnormal findings to an ophthalmologist.[2,3] However, most of these traditional tests, including the RRT, have limited sensitivity and specificity, and prior studies have shown great variability in the number of children screened and quality of screening.[5-13] Therefore, relying solely on these tests can lead to missing early diagnosis of serious ocular conditions.

In high-income countries, universal hearing screening is routinely performed on newborns and recommended by the United States Preventive Services Task Force.[14] In addition to the low yield of hearing pathology detected by universal screening (1 to 2 per 1000),[15] congenital hearing loss is often a neuroprogressive condition that can worsen even if detected early, and the interventions to manage it are primarily palliative.[16] No such mandate for universal newborn eye screening exists. However, over the last 20 years, there has been a worldwide trend toward adoption of telemedicine screening for retinopathy of prematurity (ROP), another condition with a mandated screening requirement in premature infants. During the course of telemedicine screening for ROP, there were reports of coincident findings in these patients. This prompted a series of investigations into telemedicine screening of full-term healthy newborns. These universal newborn eye screening studies have revealed the proportion of newborns with ocular pathologies and that a significant portion of these pathologies can be treated and, furthermore, vision can be restored or maintained.[17-19]

Recent innovations in wide-angle digital fundus imaging and telemedicine techniques support new optimism for universal newborn eye screening, and several pilot studies evaluated the findings and effectiveness of such screening.[20-22] A recent editorial by Chee et al. recognizes the value of universal newborn eye screening to identify and intervene in individuals with ocular pathologies in an effort to improve both visual and clinical outcomes, and sheds light on important issues of overdiagnosis, cost-effectiveness, and feasibility.[12]

Individual pilot programs have reported disease incidence and rates of referral-warranted disease, and universal newborn eye screening is gaining momentum as a clinically useful screening tool. Our study aims to review and analyze the findings of previous newborn eye screening programs and provide a recommendation on its potential benefit to both the long-term health of the patient and the cost-burdened health care system.

CLINICAL SIGNIFICANCE OF OCULAR PATHOLOGIES IN NEWBORNS – PATHOPHYSIOLOGY, PREVALENCE, AND POTENTIAL SEQUELAE

Congenital Cataracts

A congenital cataract is an opacity of the crystalline lens of the eye present at birth. Although some congenital cataracts are visually insignificant, others impede the visual axis and interfere with normal visual development, resulting in deprivation amblyopia and permanent visual impairment if not diagnosed and surgically treated as early as 6 to 10 weeks of life.[23] Hereditary congenital cataracts account for approximately 10% to 25% of congenital cataracts and the inheritance pattern is commonly autosomal dominant.[24] Other common causes are systemic diseases, ocular trauma, glucocorticoids, radiation, and low birth weight, but a significant proportion of congenital cataracts are idiopathic in etiology. Reported incidence of congenital cataracts varies, but ranges from 0.42 to 2.05 per 10,000 in low-income countries and 0.63 to 13.6 per 10,000 in high-income countries.[25] Unfortunately, without universal screening, undetected congenital cataracts continue to constitute 5% to 20% of pediatric blindness.[26]

Retinoblastoma

Retinoblastoma is the most common primary intraocular malignancy of childhood with an incidence of approximately 1 in 15,000 live births in high-income countries.[27] It most commonly originates from a biallelic inactivation of the retinoblastoma tumor suppressor gene (RB1).[28] It occurs in heritable and nonheritable forms, with the heritable form accounting for about one-third of cases.[29] Without timely diagnosis and treatment, retinoblastoma can lead to high rates of blindness and death due to rapid increase in tumor size and risk for metastasis, with a survival rate of extraocular involvement ranging from 0% to 50%.[30,31] Traditional methods of retinoblastoma screening rely on red reflex testing by primary care providers, which has demonstrable fallibility, especially for detecting lesions that are smaller and peripheral.[9,32] In addition, current screening for retinoblastoma only occurs for infants and children on the basis of a positive family history,[33-35] although only a minority of cases are heritable.

Retinopathy of Prematurity

Retinopathy of prematurity is a retinal vascular disease that occurs in preterm (≤ 30 weeks) or low birth weight (≤ 1,500 g) infants. It is the leading cause of childhood blindness worldwide and was estimated to affect 184,700 of 14.9 million preterm babies in 2010, with variation in rates in high-income compared with low- and middle-income countries.[36] The pathogenesis is thought to initially involve delayed retinal vascular growth leading to hypoxia followed by a second phase of abnormal neovascularization, which can lead to retinal detachment and severe vision loss.[37] In contrast to other ocular pathologies of newborns, current guidelines by major pediatric and ophthalmologic organizations stipulate to screen all preterm and low birth weight infants who meet the screening criteria for ROP.[2] Although only about 10% of premature infants develop ROP that require treatment, screening is rationalized by the devastating sequelae of missing a diagnosis that can lead to permanent visual impairment.[38,39]

Intraocular Hemorrhage

We know that certain types of intraocular hemorrhages increase the risk for amblyopia, namely macular hemorrhages, which impinge on the center of the macula (eg, fovea) and predispose the patient to the development of deprivation amblyopia.[40-43] Laminarity (ie, above, below, or within the retina) is less important for predisposition to deprivation. However, laminarity is useful in informing treatment consideration; both subinternal limiting hemorrhages and subhyaloid hemorrhages may benefit from surgical evacuation after 4 weeks. Intraocular hemorrhages that cause long-standing occlusion of the visual axis and diffuse damage to the fovea increase the risk for amblyopia and warrant monitoring once identified. This is because vision development is known to continue after birth and is highly plastic in the first few months of life.[19-21,44,45]

Vitreous Hemorrhage. Although vitreous hemorrhages are rare, they have been known to occur secondary to birth trauma, and an important concern when they occur is the effect on the infant's visual system leading to occlusion amblyopia.[46] Defined by the presence of blood in the space bordered by the internal limiting membrane of the retina, the nonpigmented epithelium of the ciliary body, and the lens zonular fibers and posterior lens capsule, vitreous hemorrhages can have devastating sequelae for newborns by stimulating fibrous proliferation and traction retinal detachments.[42]

Retinal Hemorrhage. Retinal hemorrhage (RH) is one of the most commonly seen ocular abnormalities in newborns with a reported incidence that varies widely from 2% to 50%.[19,21,44] Vaginal delivery, particularly when the birth is assisted with forceps or vacuum, increases the risk for RH and the mechanism is related to the increase in intracranial pressure as the head passes through the birth canal, which can cause stasis in the central retinal vein and acute pressure changes in the central retinal artery.[40,47] Although most RHs, especially mild and moderate, in newborns resolve spontaneously within 1 to 2 weeks, some RHs are severe and slow-resolving, as previously discussed, and can adversely impact visual development.[19-21,44,45]

Submacular Hemorrhage. In addition to vitreous and retina hemorrhages, submacular hemorrhages can also obstruct the visual axis and cause deprivational amblyopia due to the compromise of central vision. Therefore, the traditional assumption that hemorrhages are benign and self-resolving conditions lacks strong evidence.[20,45] Instead, it is thought that slow-resolving hemorrhages that obstruct the visual axis for a sufficient period can lead to deprivational amblyopia with ophthalmoscopic findings later in the child's life deemed strabismic or idiopathic.[20] Therefore, although there is no treatment for most RHs, early detection of RH and intervention for the resulting strabismic or deprivational amblyopia with patching, cycloplegics, and correcting refractive errors improve the visual outcomes.[48]

Other Ocular Abnormalities

The list of ocular abnormalities that can be identified and intervened upon with universal newborn eye screening includes persistent fetal vasculature, corneal leukoma, uveitis, salt and pepper retinopathy, familial exudative vitreoretinopathy, incontinentia pigmenti, hamartomas, Cherry red spots, Coats' disease, congenital glaucoma, congenital hypertrophy of the retinal pigment epithelium, optic nerve coloboma, and many infectious etiologies.[18,21,45,49] Early detection of some of these conditions allows for early intervention and improved outcomes. In addition, it may prompt early work-up of serious systemic conditions that have high morbidity and mortality. Prior studies demonstrated that a significant cohort of children continue to have vision disorders that go undetected or are missed by traditional screening methods, such as the red reflex test.[9,11,13,50-53] Therefore, universal eye screening could allow for early detection of these conditions and provide children with the opportunity to receive early intervention and improved outcomes.

CURRENT PRACTICES IN NEWBORN EYE SCREENING

Characteristics of Current Newborn Eye Screening Using Red Reflex Testing

Current guidelines from the American Academy of Pediatrics and the American Association for Pediatric Ophthalmology and Strabismus for the detection of newborn ocular pathology primarily focuses on performing the RRT by a trained pediatrician or primary care physician before discharge from the neonatal nursery and during all routine health visits.[2] This test is performed in a darkened room by projecting the light onto both eyes of the child simultaneously from approximately 18 inches away.[2] It uses transmission of light from the ophthalmoscope through all the ocular media and its reflectivity off the retina back through the aperture of the ophthalmoscope to the eye of the examiner.[2] The test is considered normal when the reflections of the two eyes are equivalent in color, intensity, and clarity and there are no opacities within the area of either or both red reflexes.[54]

The RRT is effective at detecting dense opacity within the optical axis (cornea, lens, vitreous), particularly those that are large (eg, > 1 mm), centrally located, and anterior (eg, congenital cataract and leukoma). However, at a standard red reflex testing distance, the total area of retina visible to the examiner (ie, field of view) using a direct ophthalmoscope at neutral setting is only 0.15% of the optic disc with a resolution of about 1 mm. Although the field of view can be slightly improved by the examiner having eccentric views and a dynamic examination, this is practically not possible because of the small pupils and the need to perform the RRT directly in front of the patient to allow simultaneous visibility of the red reflexes of both eyes. Therefore, RRT is much less effective at detecting posterior segment pathologies, such as retinal and vitreous hemorrhages, retinoblastoma and other tumors, retinopathies, and retinal detachment, which are the most common ocular pathologies identified in newborns (**Table 1**), as we will discuss later in this article. Indeed, multiple studies have found poor to moderate sensitivity of the RRT in detecting posterior segment pathology, with some studies reporting sensitivity as low as 0%.[32,55,56] As an alternative, wide-field digital imaging (WFDI) has been suggested as an alternative.

Wide-Field Digital Imaging for Newborn Eye Screening

Wide-field digital imaging is a fast, diagnostic tool that uses less light than indirect ophthalmoscopy to acquire sharp and detailed images after pupil dilation and does not require a dark environment for use.[49,57] These images can be stored with the patient's information for remote review and longitudinal follow-up. WFDI obtains six images per eye using the 130° lens, one anterior to evaluate pupil dilation and neovascularization as well as media opacity, and five posterior images: optic nerve centered, optic nerve superior, optic nerve inferior, optic nerve nasal, and optic nerve temporal.[20,32] Each of the posterior images has 130° field of view and they overlap to provide an effective field of vision of 181°, which covers 98% of the infant retina.[20,32] The resolution of these images is 10 µm to 50 µm (0.01 mm to 0.05 mm) in contrast to the 1 mm resolution of RRT. Multiple universal newborn eye screening programs have implemented WFDI to screen newborns during different time periods after birth.[20,22,58,59]

REFERRAL-WARRANTED DISEASE IDENTIFIED WITH UNIVERSAL NEWBORN EYE SCREENING PILOT PROGRAMS

In accordance with general clinical practice, we define a diagnostic concept of "referral warranted" (RW) to mean the detection of abnormality that should trigger further evaluation via referral. This encompasses a diagnosis that meets any of the following criteria:

- progressive;
- visual threatening;
- inflammatory;
- infectious;
- neoplastic;
- related to genetic abnormality;
- related to systemic disease;
- impacted visual function; and/or
- could benefit from monitoring, treatment, intervention, surgery, patching, spectacles, injections, gene therapy, chemotherapy or other treatment.

Clinical Characteristics of Referral-Warranted Disease Identified by Newborn Eye Screening Pilot Programs

Multiple studies have evaluated the ocular findings in universal newborn eye screening pilot programs and all of them detected referral-warranted disease that would likely have been missed without universal newborn eye screening. Most of these programs used fundus images to screen healthy full-term newborns within a few days to few weeks of birth (**Table 1**), whereas some programs were extensions of an already established program for ROP screening.[59] Among the 17 studies included in this review, the proportion of total pathology identified among all eligible patients was 11.4% and ranged from 2.2% to 41.2%.[36,54] These were heterogeneously designed studies with different metrics for outcomes. However, each study presented a tabular output of disease and pathology findings.

TABLE 1

Study Characteristics and Disease Incidence Among Universal Newborn Eye Screening Pilot Programs

					Disease Incidence							
Year	Author	Country	Time Period	Timing of Initial Screening	Congenital Cataract	Familial Exudative Vitreoretinopathy	Retinoblastoma	Corneal Leukoma	Persistent Fetal Vasculature	Retinal Hemorrhage	Vitreous Hemorrhage	Macular Hemorrhage
2013	Li[21]	China	May 2010-June 2011	within 42 days	0.06%	0.42%	0.06%	0.03%	0.06%	6.02%	-	1.88%
2015	Jayadev[59]	India	January 2011-December 2011	between 14-98 days	0.97%	-	0.14%			2.28%	-	
2015	Perilli[64]	Italy	June 2011-February 2014	within 3 days	0.14%	-	-		0.02%	1.58%	-	-
2015	Vinekar[22]	India	September 2012-March 2013	within 3 days	0.10%	-	0.10%		2.10%	2.45%	-	0.59%
2015	Zhao[19]	China	May 2012-November 2012	within 7 days	-	-	-		-	24.52%	-	2.72%
2016	Callaway[20]	United States	July 2013-July 2014	within 2 days for vaginal delivery and 3 days for cesarean section	-	-	-		-	19.31%	-	3.00%
2016	Sun[55]	China	September 2014-March 2015	between 2-4 days	0.09%	-	0.01%		0.05%	21.99%	0.50%	-
2017	Yanli[63]	China	January 2013-December 2014	within 7 days	-	-	-		-	39.36%	-	6.02%
2017	Li[45]	China	March 2010-February 2014	within 28 days	0.13%	-	0.06%	0.01%	0.03%	18.97%	-	3.00%
2017	Pu[43]	China	September 2012-June 2015	within 3 days	-	-	-		-	17.61%	0.19%	-
2018	Chen[17]	China	January 2013-February 2015	within 3 days	-	-	-		-	22.06%	-	-

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2018	Goyal[58]	India	March 2014-October 2015	within 28 days	-	-	-		-	13.28%	-	0.35%
2018	Gursoy[60]	Turkey	January 2012-December 2015	within 6 months	-	0.12%	0.06%		1.21%	0.76%	-	-
2018	Ma[49]	China	April 2015-April 2016	within 42 days	0.21%	0.42%	-	0.40%	-	6.65%	0.21%	0.21%
2018	Tang[18]	China	January 2009-July 2017	within 42 days	0.22%	0.11%	0.03%		0.16%	6.41%	-	0.64%
2019	Simkin[62]	New Zealand	June 2015-December 2016	2 days	0.29%	-	-		-	14.45%	-	2.20%
2020	Fei[61]	China	July 2016-June 2017	within 7 days	0.25%	0.45%	0.01%		-	-	-	0.55%

Overall, total RW cases constituted 5.7% (n = 17,578) of all eligible patients (n = 309,458) and ranged from 0.2% to 26.5% (**Table 2**).[12,39] In the few studies that reported the specific management of these patients, 0.1% to 3.7% and 0.1% to 1.0% of the referred cases required medical and surgical intervention, respectively.

The most common ocular abnormalities were retinal hemorrhages across all studies (mean: 13.6%, range: 1.6% to 39.4%). Importantly, mean incidence of macular hemorrhage was 1.9% (range: 0.2% to 6.0%). The mean incidence of vitreous hemorrhage, reported in three studies, was 0.3% (range: 0.2% to 0.5%).[43,49,55] These studies did not investigate the long-term visual outcomes of these patients, especially those who had severe and slow-resolving hemorrhages. The other commonly detected abnormalities in universal newborn eye screening programs were persistent fetal vasculature (mean: 0.5%, range: 0.1% to 2.1%), familial exudative vitreoretinopathy (mean: 0.3%, range: 0.1% to 0.5%), congenital cataracts (mean: 0.3%, range: 0.1% to 1.0%), and corneal leukoma (mean: 0.2%, range: 0.1% to 0.4%). Importantly, multiple studies detected early retinoblastoma (mean: 0.06%, range: 0.01% to 0.1%).[18,21,22,45,55,59-61]

Safety and Implementation of Universal Newborn Eye Screening Pilot Programs

The majority of programs conducted their newborn screening with a version of the RetCam Wide-Field Digital Imaging System (Clarity Medical Systems, Pleasanton, CA).[17-22,43,45,49,55,58-63] Only Perilli et al. conducted their screening using direct ophthalmoscopy, which only has a 5-degree field of view.[64] The median number of views per eye was five with an interquartile range of 4 to 5.3 views. Physicians were most commonly the photographer or examiner with the exception of five studies that used a technician, a nurse, or an optometrist.[20,22,58,59,62] Nearly half of the studies reported no adverse effects or complications during or after newborn eye screening. The two studies that reported adverse effects included Chen et al., which cited 6% of cases with oxygen desaturation during the exam re-

TABLE 2

Referral-Warranted Disease Rates Among Universal Newborn Eye Screening Pilot Programs

Year	Author	Country	Number of Eligible Patients	Total Pathology N (%)	Referral-Warranted Disease N (%)
2013	Li[21]	China	3,573	871 (24.4)	107 (3.0)
2015	Jayadev[59]	India	1,450	111 (7.7)	39 (2.7)
2015	Perilli[64]	Italy	5,000	899 (18.0)	12 (0.2)
2015	Vinekar[22]	India	1,021	48 (4.7)	18 (1.8)
2015	Zhao[19]	China	1,199	294 (24.5)	50 (4.2)
2016	Callaway[20]	United States	202	41 (20.3)	6 (3.0)
2016	Sun[55]	China	7,641	2,178 (28.5)	123 (1.6)
2017	Yanli[63]	China	3,054	1,202 (39.4)	184 (6.0)
2017	Li[45]	China	15,284	3,171 (20.7)	438 (2.9)
2017	Pu[43]	China	3,123	550 (17.6)	210 (6.7)
2018	Chen[17]	China	68	15 (22.1)	18 (26.5)
2018	Goyal[58]	India	1,152	172 (14.9)	19 (1.6)
2018	Gursoy[60]	Turkey	3,214	75 (2.2)	33 (1.0)
2018	Ma[49]	China	481	198 (41.2)	30 (6.2)
2018	Tang[18]	China	19,9851	18,198 (9.1)	13,349 (6.7)
2019	Simkin[62]	New Zealand	346	55 (15.9)	13 (3.8)
2020	Fei[61]	China	62,799	7,262 (11.6)	2,929 (4.7)
		Total N (%)	309,458	35,340 (11.4)	17,578 (5.7)

covered by the end,[17] and Li et al., who reported 0.03% had a subconjunctival hemorrhage, 0.007% had a palpebral conjunctival hemorrhage, 0.05% of patients had transient apnea, 0.007% had cyanosis, and 0.06% had emesis out of the 15,284 patients screened (**Table A**, which can be found in the online version of this article).[45]

Insights From the Overall Rate of Referral-Warranted Disease

Most congenital ocular diseases can be identified at birth, and many of them are amenable to sight-saving treatment or management. The majority of the 5.7% of RW disease, which is on average nearly half of total ocular pathology, that was captured by these universal newborn eye screening pilot programs represent conditions that could have carried significant morbidity and mortality among patients who would not necessarily be examined under current screening guidelines.

This early identification of treatable ocular disorders, such as congenital cataract, congenital glaucoma, and posterior uveitis, results in better visual outcomes and, subsequently, quality of life, in these patients. In addition, early treatment of some ocular conditions, such as retinoblastoma, can be lifesaving. On the other hand, early identification of some untreatable ocular disorders, such as congenital anomalies of the retina and optic disc, prompts other systemic (eg, neuroimaging and endocrine tests), metabolic, and genetic work-up that help in early diagnosis and management of serious systemic diseases to decrease the impact of poor developmental outcomes. Finally, early detection of many ocular disorders allows for early and intensive treatment of amblyopia, which could decrease

its long-term negative consequences on social interactions, school performance, motor tasks, and confidence.[65-68]

Several newborn screening tests are performed to look for developmental, genetic, and metabolic disorders at the newborn period.[69] Compared with the incidence of many other disorders screened in newborns, such as phenylketonuria (1 in 10,000 to 15,000),[70] hypothyroidism (1 in 3,000 to 4,000),[71] cystic fibrosis (1 in 2,500 to 3,500 in white newborns),[72] or hearing loss (1 in 500 to 1,000),[15] universal newborn eye screening programs identified a higher incidence of ocular disorders that warranted referral and possible treatment to prevent childhood blindness and its devastating consequences. Ludwig et al. reported that the number of newborns needed to screen to detect any posterior segment abnormality with WFDI as compared with a pediatrician's RRT was four, and to detect potentially visually threatening pathologies was seven,[32] both much lower the 878 newborns needed to screen to detect hearing loss in the United States.[14] Importantly, studies have not reported any significant adverse effects of perinatal imaging or examination of the eye.[17,20,22,49,55,58,60-62,64] Indeed, the risk-benefit principle justified implementing guidelines to screen all premature babies who meet specific criteria for ROP. This strongly suggests that universal newborn eye screening using WFDI will play an important role in promoting pediatric eye and general health in healthy newborns. A significant percentage of newborns may be lost to follow-up for a WFDI eye screening once they leave the hospital, which greatly increases the proportion of ocular pathology missed and sight lost. Therefore, it is important to implement universal eye screening using WFDI for all newborns before discharge from the neonatal nursery.

COSTS AND FEASIBILITY OF UNIVERSAL NEWBORN SCREENING ROLL-OUT

Potential Financial, Life, and Quality of Life Loss Incurred by Vision Loss and Blindness

Recent estimates for the global financial cost of blindness from childhood range from USD $2.7 to $6 billion.[73] However, data on mortality (years of life lost through premature blindness associated death) and morbidity (years of disability experienced) attributed to childhood blindness is limited, and our understanding of the cost-effectiveness of vision loss in children requires further investigation to quantify the impact of amblyopia on utility and quality of life.[74-77]

A separate body of literature has demonstrated the impact of pediatric vision impairment on quality of life that spans several aspects including challenges with educational attainment, job choices, psychosocial development, self-perception, and family well-being among others.[78-82] This literature, when considered with prior cost-effectiveness analyses conducted for amblyopia and ROP screening, likely indicates that the benefits of these interventions are underestimated.[83-85]

Furthermore, a recent study by Goyal et al. demonstrated the cost benefit of a universal newborn eye screening program when accounting for the burdensome financial costs incurred to both the health care system and family when a child goes blind.[58] This is echoed in studies that found treatment of amblyopia resulted in a quality-adjusted life year gain of $2,281 (range: $2,053 to $2,509) and that ROP screening results in an approximate annual cost savings of nearly $3 million.[76,86,87] Together, these studies portray a consistent message that newborn eye screening is cost-effective and that the cost-effectiveness is likely underestimated given the limited body of knowledge on the effect of childhood vision loss on quality of life and utility. Despite the limitations of data on cost-effectiveness of newborn eye screening, this should not be a reason for deferring the adoption of screening programs, and decision-makers should consider other alternative and references cases, such as amblyopia or ROP screening, when evaluating its implementation.[83-85,88]

Technological Advances in Telemedicine and Artificial Intelligence

With new innovations in health technology, the system and labor costs of universal newborn eye screening roll-out have the potential to be driven down. Similar to ROP screening, telemedicine can address the labor shortage required to ensure universal screening by reducing the number of bedside examinations.[20,22,58] In addition, efficient fundus imaging, task-shifted from ophthalmologists to technicians and other health professionals, and reliable, centralized image evaluation systems can mitigate the cost and labor concerns around universal newborn eye screening.[12]

Another important new technology that will lower the cost of universal newborn eye screening is artificial intelligence (AI).[89-91] Recent advances in AI within ophthalmology, such as U.S. Food and Drug Administration approval of IDx-DR (a program that uses deep learning techniques to detect referable diabetic retinopathy retinal images; Digital Diagnostics, Coralville, IA), have led to algorithms with improved

diagnostic accuracy across age, race, and ethnicity; the removal of required expert human review of normal images; and real-time clinical decision-making at the point of care.[92,93] Not only can this technology reduce the burden of image review on ophthalmologists, but it can also remove the influence of subjective factors by solely relying on data to make predictions. While the validation of these methods for ROP screening and pediatric cataracts is currently underway, the accuracy of AI for this use would be aided by the increase in images available for training.[94-97] A recent review by Reid et al. outlined the current limitations of AI in pediatric ophthalmology and the need for pediatric-specific models, reproducibility, and comparability.[10] Because large datasets of images are required to train and improve the accuracy of AI algorithms, a potential benefit of universal newborn eye screening would be the creation of a global machine learning repository to catalyze the development of these technologies.

Challenges of Universal Newborn Eye Screening

Other important considerations of universal newborn eye screening include the increased demand of experienced image graders, as prior studies have shown this expertise impacts diagnostic accuracy.[98,99] However, some studies described in this review are alleviating these demands through well-designed telemedicine programs.[20,22,58] Furthermore, Goyal et al. noted the possibility that many abnormalities captured in their study were diseases for which late detection would not have changed the outcome.[58] However, these authors, as well as those from many other studies, recognize the significance of detecting vision-threatening diagnoses, such as retinoblastoma, posterior uveitis, or significant retinal hemorrhage, which can be missed with traditional screening methods.[9,11-13,50-52] Even so, the origin of several amblyopia cases remains unknown and may be better classified with universal newborn eye screening.[100-103] Furthermore, the studies included in this review demonstrate that a significant proportion of ocular abnormalities required a referral to a specialist for follow-up or intervention, which further justifies the implementation of universal newborn eye screening. Future work to critically evaluate the long-term visual benefit to patients and cost-effectiveness of universal newborn eye screening is needed.

CONCLUSION

In this review, we found that 5.7% of nearly 310,000 infants had referral-warranted disease based on published worldwide literature from the last decade. Although the proportion of ocular abnormalities and RW disease identified varied among studies, this information, combined with recent advances in telemedicine and fundus imaging, suggest the important benefits that universal newborn eye screening can offer. These potential benefits must be considered in the context of cost, labor demands, and over-diagnosis, but telemedicine approaches to ROP screening are important examples of successful application of this emerging technology. Future work is needed to determine the cost-effectiveness and morbidity or mortality avoided with universal newborn eye screening programs.

Literature Search

A thorough narrative literature search was performed by a domain expert on Medline from 2010 to 2020. We included peer-reviewed articles of pilot universal newborn eye screening programs, and those judged to be of clinical importance were included.

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TABLE A

Methods, Techniques, and Adverse Effects of Universal Newborn Eye Screening Pilot Programs

Year	Author	Intended Population	Technique	FOV	Views/Eye	Photographer	Safety/Adverse Effects
2013	Li[21]	Term	RetCam	130°	4	Physician	Not reported
2015	Jayadev[59]	ROP	RetCam Shuttle	130°	4	Technician	Not reported
2015	Perilli[64]	Term	Direct Ophthalmoscopy	5°	1	Physician	No adverse effects to tropicamide
2015	Vinekar[22]	Term	RetCam Shuttle	130°	Video and Stills	Technician	No ocular or systemic complications during or after any examination
2015	Zhao[19]	Term	RetCam III	130°	Not reported	Physician	Not reported
2016	Callaway[20]	Term	RetCam III	130°	6	Nurse	No episodes of clinically significant bradycardia, allergic reactions to drops, or corneal abrasions during the screening or after discharge
							Apart from temporary eyelid swelling and contact dermatitis from eye drops after the examinations, there were no other severe complications such as bradycardia and
2016	Sun[55]	Term	RetCam III	130°	6	Physician	respiratory depression during and after examinations
2017	Yanli [63]	Term	RetCam III	130°	Not reported	Physician	Not reported
							Subconjunctival hemorrhage (0.03%), Palpebral conjunctival hemorrhage (0.007%), Corneal abrasion/opacity (0%), Tachycardia/bradycardia requiring intervention (0%),
2017	Li[45]	Term	RetCam III	130°	4	Physician	Transient apnea (0.05%), Transient cyanosis (0.007%), Intubation (0%), Death (0%), Emesis (0.06%)
2017	Pu[43]	Newborn	RetCam	130°	4	Physician	Not reported
2018	Chen [17]	Term	RetCam III	130°	5	Physician	Oculocardiac Reflex (210% decrease in HR from baseline) (0%), oxygen desaturation (220% decrease from baseline) (6%); all recovered by end of exam
2018	Goyal[58]	Term	RetCam III	130°	5	Optometrist	No significant adverse events after examination
2018	Gursoy[60]	Term/Preterm	RetCam	130°	Not reported	Physician	All examinations were performed without any systemic complications
2018	Ma[49]	Term	RetCam III	130°	5	Physician	No ocular or systemic complications during or after any examination
2018	Tang[18]	Term/Preterm	RetCam	130°	Not reported	Physician	Not reported
2019	Simkin[62]	Newborn	RetCam III/Shuttle	130°	5	Nurse or Photographer	No adverse events, allergic reactions, significant bradycardia, or corneal abrasions at or after screening
2020	Fei [61]	Newborn	RetCam III	130°	6	MD	None of the screened neonates had any significant adverse events during or after the examination