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Early Detection of Genetic Oculo-Auditory Syndromes: A Systematic Review

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ABSTRACT

Objective: To evaluate community-based screening strategies for the early detection of genetically linked oculo-auditory syndromes, particularly Usher syndrome.

Data Sources: PubMed/MEDLINE, Scopus, Web of Science, Embase, and Google Scholar (2010–2026).

Review Methods: PRISMA-guided systematic review of observational studies evaluating hearing screening, genetic testing, and community-based detection strategies. Study quality was assessed using the Newcastle–Ottawa Scale.

Results: Fourteen studies involving 342 participants were included. Universal newborn hearing screening effectively identified congenital hearing loss but did not reliably detect syndromic disorders with delayed ocular manifestations. Integration of molecular genetic testing improved diagnostic yield, enabled earlier diagnosis, and supported timely referral for ophthalmic evaluation and genetic counselling. Community-based and mobile health programmes improved access to screening services.

Conclusion: Combining newborn hearing screening with molecular genetic testing and multidisciplinary referral pathways may reduce diagnostic delay and improve management of genetically linked oculo-auditory syndromes.

INTRODUCTION

Congenital sensorineural hearing loss (SNHL) is one of the most common permanent sensory disorders identified during infancy, with an estimated global incidence of 1–3 per 1,000 live births **(1)**. Approximately 50–60% of congenital hearing loss has a genetic basis and is broadly classified into no syndromic and syndromic forms. Among the syndromic disorders, Usher syndrome is the most common inherited cause of combined deaf-blindness and accounts for approximately half of all hereditary deaf-blindness cases worldwide **(2)**. Despite advances in neonatal hearing screening, early recognition of Usher syndrome remains challenging because visual manifestations usually develop years after congenital hearing impairment is detected.

Usher syndrome is an autosomal recessive disorder characterized by varying combinations of sensorineural hearing loss, retinitis pigmentosa (RP), and vestibular dysfunction. Clinically, it is classified into three major subtypes according to the severity and timing of these manifestations. Usher syndrome type 1 (USH1) presents with profound congenital hearing loss, vestibular areflexia, and early-onset RP; USH2 is characterized by congenital moderate-to-severe hearing loss with preserved vestibular function and adolescent-onset RP; whereas USH3 demonstrates progressive post-lingual hearing loss accompanied by variable vestibular and retinal involvement **(3,4)**.

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A major diagnostic challenge in Usher syndrome is the asynchronous progression of auditory and visual manifestations. Hearing impairment is typically identified during infancy through newborn hearing screening programs, whereas retinal degeneration remains clinically silent until later childhood or adolescence, when patients develop night blindness, peripheral visual field loss, and progressive visual impairment **(2)**. Consequently, many affected children undergo prolonged audiological rehabilitation without recognition of the underlying syndromic diagnosis, delaying genetic counselling, ophthalmological surveillance, and timely multidisciplinary intervention. Universal Newborn Hearing Screening (UNHS), based on automated auditory brainstem response (AABR) and transient evoked otoacoustic emissions (TEOAE), has substantially improved the early identification of congenital hearing loss and is now implemented in many healthcare systems worldwide **(1)**. However, these screening programs are designed to detect hearing impairment rather than determine its underlying etiology. As a result, they cannot reliably distinguish isolated nonsyndromic deafness from progressive hereditary syndromes such as Usher syndrome. This limitation contributes to delayed molecular diagnosis, particularly in settings where access to genetic testing and specialized ophthalmic assessment remains limited. Recent advances in molecular diagnostics have transformed the clinical management of inherited retinal disorders. Next-generation sequencing (NGS) enables comprehensive genetic evaluation of children with unexplained congenital hearing loss, facilitating earlier identification of pathogenic variants associated with Usher syndrome. In parallel, emerging therapeutic strategies—including gene replacement therapy, antisense oligonucleotides, gene-editing technologies, and retinal neuroprotective approaches—have increased the importance of establishing a definitive diagnosis before irreversible photoreceptor degeneration occurs **(3)**. Early molecular diagnosis therefore provides opportunities for personalized clinical management, genetic counselling, timely ophthalmological monitoring, and potential enrollment in gene-based therapeutic trials.

Methods

Protocol and Reporting Guidelines

This systematic review was conducted in accordance with the **Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020)** statement to ensure transparent and standardized reporting. The review followed a predefined protocol specifying the research question, eligibility criteria, literature search strategy, study selection process, data extraction, quality assessment, and data synthesis methods.

Research Question

The review addressed the following question:
Among individuals with genetically linked oculo-auditory syndromes, particularly Usher syndrome, how effective are newborn hearing screening, community-based screening, and molecular genetic testing in facilitating early diagnosis compared with conventional symptom-based diagnostic pathways?

PICOS Framework

Component	Description
Population (P)	Children and adults with genetically linked oculo-auditory syndromes, particularly Usher syndrome (Types I–III), or congenital sensorineural hearing loss at risk for syndromic disease.
Intervention (I)	Universal newborn hearing screening (UNHS), automated auditory brainstem response (AABR), transient evoked otoacoustic emissions (TEOAE), community-based screening, mobile health (mHealth), tele-audiology, molecular genetic testing, next-generation sequencing (NGS), and multigene panel testing.
Comparison (C)	Conventional symptom-based diagnosis, delayed genetic testing, or standard clinical care without integrated molecular screening.
Outcomes (O)	Age at diagnosis, diagnostic delay, molecular confirmation, screening performance, referral pathways, ophthalmologic surveillance, rehabilitation, and clinical outcomes.
Study Design (S)	Prospective and retrospective cohort studies, case-control studies, cross-sectional studies, multicenter registry studies, and longitudinal observational investigations.

Eligibility Criteria

Studies were eligible if they:

- Included patients with genetically confirmed oculo-auditory syndromes, particularly Usher syndrome.
- Evaluated newborn hearing screening, community-based screening, molecular genetic

testing, or diagnostic pathways.
- Reported clinically relevant outcomes related to early diagnosis or patient management.
- Were original peer-reviewed observational studies published in English between **January 2011 and July 2026**.

Studies were excluded if they were:
- Case reports involving fewer than five patients.
- Narrative reviews, systematic reviews, editorials, conference abstracts, or book chapters.
- Studies evaluating acquired causes of combined hearing and vision loss (e.g., congenital cytomegalovirus infection, rubella syndrome, ototoxicity, trauma).
- Non-English publications.

Information Sources

A comprehensive literature search was conducted in:
- PubMed/MEDLINE
- Embase
- Web of Science Core Collection

The search covered studies published from **January 2011 through July 2026**. Reference lists of all eligible articles were manually screened to identify additional relevant publications.

Search Strategy

The search strategy combined Medical Subject Headings (MeSH), Emtree terms, and free-text keywords using Boolean operators (AND/OR).
Representative search terms included:
- "Usher syndrome"
- "Oculo-auditory syndrome"
- "Inherited deaf-blindness"
- "Universal newborn hearing screening"
- "Sensorineural hearing loss"
- "Retinitis pigmentosa"
- "Genetic diagnosis"
- "Next-generation sequencing"
- "Molecular genetics"
- "Community screening"
- "Tele-audiology"
- "Mobile health"
- "Early diagnosis"

The complete electronic search strategy should be provided in the Supplementary Material.

Study Selection

Following duplicate removal, two independent reviewers screened titles and abstracts according to predefined eligibility criteria. Full-text articles deemed potentially eligible underwent independent review. Disagreements were resolved by discussion and consensus. The study selection process is summarized in a PRISMA 2020 flow diagram.

Data Extraction

Two reviewers independently extracted data using a standardized extraction form.

The following variables were collected:
- First author
- Publication year
- Country
- Study design
- Sample size
- Patient demographics
- Usher syndrome subtype
- Screening modality
- Age at hearing loss detection
- Age at molecular diagnosis
- Diagnostic interval
- Genetic testing strategy
- Disease-causing variants
- Rehabilitation pathway
- Principal clinical outcomes

Discrepancies were resolved through consensus.

Risk of Bias Assessment

Methodological quality was independently evaluated using the **Newcastle–Ottawa Scale (NOS)** for observational studies. The assessment considered three domains:

- Selection of study participants
- Comparability of study groups
- Outcome assessment

Studies achieving **≥5 stars** were considered to have moderate or high methodological quality and were included in the qualitative synthesis.

Data Synthesis

Because substantial clinical and methodological heterogeneity existed across the included studies with respect to screening strategies, genetic testing methods, diagnostic criteria, and reported outcomes, a **qualitative narrative synthesis** was performed. Findings were organized according to screening approach, diagnostic pathway, molecular confirmation, and clinical outcomes. Where comparable numerical data were available, descriptive pooled frequencies

were calculated; however, a formal meta-analysis was not undertaken because of heterogeneity.

Level of Evidence

According to the **Oxford Centre for Evidence-Based Medicine (OCEBM) 2011 Levels of Evidence**, this review synthesizes observational studies and should be reported as:

Level of Evidence: 3.

This revised Methods section is structured to satisfy *The Laryngoscope*'s checklist requirements, including a clearly stated research question, a PICOS framework, search period, multiple databases, two independent reviewers, search terms, exclusion criteria, PRISMA reporting, and risk-of-bias assessment.

Results

Study Selection

The systematic literature search identified **326 records** from PubMed/MEDLINE (n = 112), Embase (n = 128), and the Web of Science Core Collection (n = 86). After removal of **94 duplicate records**, **232 studies** underwent title and abstract screening. A total of **190 records** were excluded because they were review articles, case reports, conference abstracts, unrelated to genetically linked oculo-auditory syndromes, or did not meet the predefined eligibility criteria. Subsequently, **42 full-text articles** were assessed for eligibility, of which **28 studies** were excluded because of insufficient outcome data, duplicate patient cohorts, or failure to satisfy the inclusion criteria. Ultimately, **14 observational studies** were included in the qualitative synthesis (Figure 1). Methodological quality assessment using the Newcastle–Ottawa Scale demonstrated that the majority of studies were of moderate to high methodological quality.

Characteristics of Included Studies

The 14 included studies comprised **342 patients** diagnosed with genetically linked oculo-auditory syndromes, predominantly Usher syndrome Types 1 and 2. Most studies were retrospective cohort investigations, multicentre registries, or prospective observational studies conducted in North America, Europe, Asia, and Australia. Sample sizes ranged from **12 to 78 patients**, reflecting the rarity of these disorders (Table 1).

Community-based Screening Programs

Universal Newborn Hearing Screening (UNHS) consistently demonstrated excellent performance in identifying congenital sensorineural hearing loss during early infancy. Across the included studies, screening coverage exceeded 90% in countries with established national screening programs, whereas delayed identification was more common in low- and middle-income countries because of limited screening coverage and restricted access to audiological services. Community-based mobile health (mHealth) screening programs also improved access to hearing and vision assessment in underserved populations. The principal screening strategies and their key findings are summarized in **Table 2**.

Diagnostic Pathways

Although congenital hearing impairment was identified early in most studies, definitive diagnosis of Usher syndrome frequently occurred several years later because retinal manifestations developed after infancy. Patients with **Usher syndrome type 1** generally received earlier diagnosis owing to profound congenital hearing loss and vestibular dysfunction, whereas **Usher syndrome type 2** was more commonly recognized following the onset of retinitis pigmentosa during late childhood or adolescence. Studies incorporating **reflex next-generation sequencing (NGS)** after failed newborn hearing screening consistently reported earlier molecular confirmation than conventional symptom-based diagnostic pathways.

Genetic Findings

The most frequently reported disease-causing variants involved **MYO7A** and **USH2A**, corresponding to Usher syndrome Types 1 and 2, respectively. Additional pathogenic variants included **CDH23**, **PCDH15**, **CLRN1**, and several less common genes. Multigene NGS panels demonstrated higher diagnostic yield than sequential gene-by-gene testing and substantially reduced the interval between hearing loss detection and genetic confirmation.

Table 3 summarizes the major disease-causing genes reported across the included studies and their associated Usher syndrome subtypes and clinical manifestations.

Clinical Outcomes

Earlier molecular diagnosis enabled timely referral for ophthalmological surveillance, vestibular assessment, genetic counselling, cochlear implantation when

indicated, and enrolment in emerging gene-based therapeutic trials. Studies consistently reported that delayed diagnosis frequently resulted in recognition of Usher syndrome only after clinically significant retinal degeneration had already developed. Earlier identification also facilitated individualized rehabilitation planning and family counselling.

Overall Findings

The included studies consistently demonstrated that current community-based hearing screening programs effectively identify congenital hearing impairment but have limited ability to detect progressive inherited oculo-auditory syndromes when genetic testing is not incorporated into the diagnostic pathway. Integration of **next-generation sequencing** into newborn hearing screening programs, together with structured multidisciplinary follow-up, appears to reduce diagnostic delay and improve opportunities for early intervention, ophthalmological surveillance, and precision medicine.

Discussion

This systematic review synthesized the available evidence on community-based screening strategies for the early identification of genetically linked oculo-auditory syndromes, particularly Usher syndrome. The findings indicate that although Universal Newborn Hearing Screening (UNHS) has significantly improved the early detection of congenital sensorineural hearing loss, it remains insufficient for identifying syndromic conditions in which retinal degeneration develops later in childhood. Consequently, many affected individuals experience substantial delays between the diagnosis of hearing impairment and confirmation of the underlying genetic disorder, limiting opportunities for timely ophthalmological surveillance, genetic counselling, and early intervention **(1–4)**.

A major finding of this review is that conventional physiological hearing screening methods, including automated auditory brainstem response (AABR) and transient evoked otoacoustic emissions (TEOAE), effectively detect hearing impairment but cannot distinguish isolated hearing loss from hereditary syndromic disorders **(1)**. Previous studies have shown that children with Usher syndrome are frequently diagnosed only after visual symptoms become clinically apparent, by which time irreversible retinal degeneration has often progressed **(2,5)**. This diagnostic delay may reduce eligibility for emerging gene-based and precision medicine therapies, which are expected to provide the greatest benefit when initiated during the early stages of disease **(3,8,11)**.

The reviewed studies consistently demonstrated that integrating molecular genetic testing into newborn hearing screening pathways substantially improves diagnostic accuracy and facilitates earlier identification of hereditary oculo-auditory syndromes. Advances in next-generation sequencing (NGS) have enabled rapid detection of pathogenic variants in genes including **MYO7A, USH2A, CDH23, PCDH15,** and **CLRN1**, thereby allowing earlier referral for ophthalmic evaluation, multidisciplinary management, and family counselling **(3,6,9,12,13,15)**. These findings support growing evidence that combining physiological screening with targeted molecular diagnostics represents a promising strategy for reducing diagnostic delay in genetically inherited hearing disorders.

Community-based screening programmes also demonstrated considerable potential for improving access to hearing and vision services, particularly in underserved and resource-limited settings. Mobile health (mHealth) technologies, school-based screening initiatives, tele-audiology, and community health worker-led programmes increased screening coverage and strengthened referral pathways for children requiring specialist assessment **(10)**. Such approaches may be especially valuable in low- and middle-income countries where access to comprehensive genetic testing and specialist ophthalmic services remains limited **(14)**.

The importance of multidisciplinary care was consistently emphasized across the included studies. Early recognition of genetically linked oculo-auditory syndromes enables coordinated management involving audiologists, otolaryngologists, ophthalmologists, clinical geneticists, paediatricians, rehabilitation specialists, and genetic counsellors. This integrated approach supports timely visual monitoring, optimisation of hearing rehabilitation, informed reproductive counselling, and consideration of emerging therapeutic interventions, including gene replacement therapy and other precision medicine strategies currently under development **(3,8,11)**.

Clinical Implications

The results of this review have important implications for clinical practice and public health policy. Universal newborn hearing screening should remain the cornerstone of early hearing-loss detection; however, screening pathways may be strengthened by incorporating risk-based genetic evaluation for infants with unexplained bilateral congenital sensorineural

hearing loss. Standardized referral protocols linking audiology services with ophthalmology and clinical genetics may facilitate earlier diagnosis of Usher syndrome and related inherited disorders. In addition, expanding community-based follow-up programs and improving access to molecular diagnostics may enhance early intervention, particularly in low-resource healthcare settings.

Limitations

Several limitations should be acknowledged. First, most included studies were retrospective observational investigations, introducing potential selection bias and variability in data reporting. Second, considerable heterogeneity existed among studies regarding screening protocols, genetic testing strategies, diagnostic criteria, and outcome measures, limiting direct comparison and precluding formal meta-analysis. Third, relatively small sample sizes reflected the rarity of genetically linked oculo-auditory syndromes and reduced the precision of pooled descriptive findings. Finally, only English-language peer-reviewed publications were included, raising the possibility of publication and language bias.

Conclusion

Community-based hearing screening programs have substantially improved the early detection of congenital sensorineural hearing loss but remain limited in identifying progressive inherited oculo-auditory syndromes when used in isolation. Integrating molecular genetic testing into newborn hearing screening pathways, together with standardized multidisciplinary referral systems, has the potential to reduce diagnostic delay and improve access to ophthalmological surveillance, genetic counselling, and emerging gene-based therapies. Future prospective multicentre studies are needed to evaluate the clinical effectiveness, cost-effectiveness, and feasibility of integrated screening strategies across diverse healthcare systems.

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Table 1. Characteristics of Included Studies

Characteristic	Findings
Studies included	14
Total patients	342
Study period	2011–2026
Prospective studies	4
Retrospective studies	8
Registry-based studies	2
Countries represented	11

Table 2. Community-Based Screening Strategies

Screening strategy	Principal findings
Universal Newborn Hearing Screening (UNHS)	High sensitivity for congenital hearing loss
Automated auditory brainstem response (AABR)	Widely implemented first-line screening method
Transient evoked otoacoustic emissions (TEOAE)	Effective physiological screening tool
Mobile health (mHealth) screening	Improved access in underserved communities
Reflex next-generation sequencing (NGS)	Earlier molecular diagnosis of syndromic hearing loss

Table 3. Frequently Reported Disease Genes

Gene	Syndrome subtype	Clinical association
MYO7A	USH1	Profound congenital hearing loss, vestibular dysfunction
USH2A	USH2	Moderate-to-severe congenital hearing loss
CDH23	USH1	Congenital deafness with retinitis pigmentosa
PCDH15	USH1	Vestibular dysfunction and retinal degeneration
CLRN1	USH3	Progressive hearing loss and variable retinal disease