# Chapter 2
# Literature review

## 2.1 Health economic evaluation

Drummond et al (Drummond, O'Brien, Stoddart, & Torrance, 1997) proposed distinguishing characteristics of health care evaluation by considering whether both costs (inputs) and consequences (output) of the alternatives are examined, and whether comparison of alternatives are performed. (Table 2.1) By this scheme, it is possible to classify the health economic evaluation into several categories. The cell 1, and 3 contain evaluation situations in which only costs or consequences are evaluated, these are considered to be "partial evaluation". The cell 2 represents the evaluation situation that both costs and consequences are examined, but no comparison between alternatives. This is also considered to be "partial evaluation". The cell 4 contains the evaluation situations that both costs and consequences are evaluated, and the comparison between alternatives is analyzed. This is considered to be full economic evaluation.

The cost-effectiveness analysis (CEA) is one form of full economic evaluation where both the costs and consequences of health programs or treatment are examined. The consequences or effectiveness are measured in health outcome (not in monetary term).

Table 2.1 Types of health economic evaluation

| | | Are both costs and consequences examined? | | |
|---|---|---|---|---|
| | | No | | Yes |
| | | Examines only consequences | Examines only costs | |
| Is there comparison of alternatives? | No | 1A<br>Outcome description | 1B<br>Cost description | 2<br>Cost-outcome description |
| | Yes | 3A<br>Efficacy or effectiveness evaluation | 3B<br>Cost analysis | 4<br>Cost-minimization analysis<br>Cost-effectiveness analysis<br>Cost-utility analysis<br>Cost-benefit analysis |

## 2.2 Eye Abnormalities in Children

Eye diseases and visual abnormality in children are considered significant clinical and public health problems. If not managed in a timely fashion, the conditions may lead to amblyopia (a condition in which a child encounters any conditions that disturb the visual development process and resulted in less than normal vision). The prevalence of severe visual abnormality in preschool children is estimated at 2-4%, and the prevalence increases with age due to an increase of the prevalence of refractive error.

### 2.2.1 Visual Development and Amblyopia

Vision is a developmental sensory function. The vision of a normal new born infant is relatively poor. Through proper visual stimulation in the early months and years of life, a normal visual acuity is achieved at approximately 3 years of age. If this development process is prevented by any causes, the vision will not develop properly. The disruption of the normal development of vision results in a condition called "amblyopia". If amblyopia occurs and not being treated in time, the child's vision could not be improved later in life. The period in which amblyopia could be successfully treated is call critical period, and is believed to be within the first 6-9 years of life. (Bradford, 1999)

Amblyopia is an acquired defect in monocular vision caused by abnormal visual experience early in life. (Greenwald & Parks, 2002) It is usually unilateral but may be bilateral. Amblyopia itself produces no change in the appearance of ocular structures, but it nearly always develops in association with some other condition, which is evident on physical examination and which is responsible for abnormal visual experience.

The visual system is sensitive to the effects of abnormal visual experience only during a limited time in infancy and childhood when it is immature and plastic. For humans, this period extends roughly from birth through the end of the first decade. Vulnerability is greatest during the first few months of life and decreases gradually thereafter, with apparently considerable variation from person to person in the degree of sensitivity at a particular age (especially beyond 6-9 years). The age range within which amblyopia can be induced corresponds roughly to the span of time over which visual function normally develops to full maturity, but the resulting level of vision, particularly in unilateral cases, is often far below the normal level for the age of onset.

The prevalence of eye disease and visual abnormalities in children under the age of 3 years has been estimated. Strabismus (ocular misalignment) and amblyopia account for the majority of ophthalmic abnormalities of the infant age

groups up to age 2 years; approximately 2% to 4% of preschool children have eye or visual abnormalities such as strabismus that result in or could cause amblyopia. The incidence of eye and visual abnormalities in the school age population increases with age owing predominantly to an increase in the prevalence of refractive errors. (American Academy of Ophthalmology Preferred Practice Patterns Committee, 1997)

### 2.2.2 Refractive Errors

To have a clear vision, the eyes need to have the images focus sharply on the retina. The cornea and lens make up the refractive surfaces of the eye. In a normal eye, the refractive powers of cornea and lens are proper, time image is focus at the retina. This normal refractive state of the eye is called emmetropia. If the focal point locates in front of the retina, myopia (near-sightedness) occurs. On the other hand, if the focal point locates behind the retina, hyperopia (far-sightedness) occurs. Another kind of refractive error called "astigmatism" occurs when the refracting power of the cornea and lens is different in one meridian than in another. The refractive errors can be detected by ophthalmic examination technique called refraction. (Bradford, 1999)

The prevalence of refractive errors differs among different regions and different age groups. Reported prevalence of refractive error in school children vary due to different age groups and difference in methodology. (Table 2.2)

The recent multi-country survey of refractive error in children performed in China, Chile, and Nepal demonstrates the prevalence of children with vision of 20/40 or less is about 2-10 percent and only 7-29% of these children had correcting glasses by the time of the survey. (Negrel, Maul, Pokharel, Zhao, & Ellwein, 2000) Lin, et al., surveyed 10,878 children in Taiwan and found the prevalence of myopia increased from 20% in 7-year-old children to 81% in 18-year-old children. (Lin et al., 2001)

Table 2.2 Prevalence of refractive error in school-age children

| Authors | Country | Sample size | Age | Myopia | | Hyperopia | |
|---|---|---|---|---|---|---|---|
| | | | | Definition | Prevalence | Definition | Prevalence |
| Angle & Wissmann (Angle & Wissmann, 1980) | USA | 13,536 | 12-17 | VA< 20/20* | 31.8 | NA | NA |
| Grosvenor (Grosvenor, 1988) | Vanuatu | 788 | 6-19 | ≤ -0.50 D | 2.9 | ≥ 1.25 D | 0.25 |
| Lin et al. (Lin, Hung, & Ko, 1988) | Taiwan | 2,353 | 13-16 | NA | 49.6 | > 2.00 D | 0.6 |
| Au Eong et al. (Au Eong, Tay, & Lim, 1993) | Singapore | 110,236 | 15-25 | VA ≤ 6/18* | 44.2 | NA | NA |
| Zadnik et al. (Zadnik, Satanano, & Mutti, 1994) | USA | 716 | 6-14 | ≤ -0.75 D | 7.5 | NA | NA |
| Auzemery et al. (Auzemery, Andriamanamihaja, & Boisier, 1995) | Madagascar | 1,081 | 8-14 | VA ≤ 6/9* | 0.92 | VA ≤ 6/9* | 1.11 |
| Cummings (Cummings, 1996) | UK | 1,809 | 8-10 | VA ≤ 6/9* | 24.4 | VA ≤ 6/9* | 0.6 |
| Presian & Novak (Preslan & Novak, 1996) | USA | 680 | 4-7 | < -0.5 D | 3.1 | > 4.00 D | 0.9 |

* Refers to unaided visual acuity that corrects with refraction.

D = diopters; NA = not available; VA = visual acuity

### 2.2.3 Overall prevalence of eye diseases in school children

It is generally accepted that approximately 2% to 4% of preschool children have eye or visual abnormalities. The prevalence of visual abnormalities increases with age. The most important cause of increased prevalence in school children is the refractive errors. The overall prevalence of eye diseases or visual abnormalities varies among different reports. Wedner et al, reported the prevalence of eye

diseases in primary school in Tanzania to be 3.4% (poor eyesight, significant refractive errors, amblyopia, and strabismus). (Wedner, Ross, Balira, Kaji, & Foster, 2000) Kalikivayi et al studied the visual impairment in school children in Southern India and found significantly decreased VA in 3.1% while 1.4% had eye diseases apart from refractive errors. (Kalikivayi, Naduvilath, Bansal, & Dandona, 1997) Chen et al studied the prevalence of ocular disorders among 6-7 years children in California and found eye diseases to be less than 4% while 18.5% had refractive errors. (Chen, Chang, Lee, & Wheeler, 1996)

There are few studies on visual abnormalities and refractive errors in Thailand. Ratanachu-ake S., et al, studied visual abnormalities in 3,040 school children and found abnormalities in 3.4%. (Ratanachu-ake & Untanuvatana, 1993) The prevalence increased from 2.7% in the 6-8 year-old age group to 6.1% in the over 18 year-old age group.

## 2.3 Screening and Screening Tests

The concept of prevention was popularized by Leavell around 1965. (Jekel, Elmore, & Katz, 1996) Based on this concept, all of the activities of health professionals have the goal of prevention. There are three levels of prevention, as shown in the table 2.3. Primary prevention is to prevent the occurrence of diseases. Secondary prevention is done when the disease occurred in its asymptomatic phase to interrupt the disease process before it creates serious outcome. Secondary prevention is aimed at early detection of disease, either through screening or case finding, followed by treatment.

Table 2.3 Levels of Prevention (modified version of Leavell's)

| Stage of Disease | Level of Prevention | Type of Response |
|---|---|---|
| Predisease | Primary prevention | Health promotion and specific protection |
| Latent disease | Secondary prevention | Presymptomatic diagnosis and treatment |
| Symptomatic disease | Tertiary prevention | Disease limitation for early symptomatic disease. Rehabilitation for late symptomatic disease |

Source: (Jekel et al., 1996)

Screening is the process of identifying a subgroup of people who are at high risk for having asymptomatic disease or who have a risk factor that puts them at high risk for developing a disease or becoming injured. A positive screening test result in an individual is not diagnostic of a disease. It merely identifies a person as being at high risk for having that disease. The persons with positive screening test should undergo further diagnostic tests to find out if they have the disease or not.

### 2.3.1 Sensitivity and Specificity

Sensitivity and specificity are two important characteristics of screening test. Sensitivity refers to the ability of a test to detect a disease when it is present. Specificity refers to the ability of a test to indicate non-disease when no disease is present. To measure the sensitivity and the specificity of any screening test, two groups of people, one group of people with disease and another group of people

without disease are needed. The screening test is performed in every person in the two group and the results of the test can be summarized in a 2 x 2 table. (Table 2.4)

Table 2.4 Standard 2 x 2 table comparing the screening test results and the true disease status of the subjects tested

| | | True Disease Status | | |
|---|---|---|---|---|
| | | Diseased | Nondiseased | Total |
| Test Result | Positive | a | b | a + b |
| | Negative | c | d | c + d |
| | Total | a + c | b + d | a + b + c + d |

Interpretation of these cells is as follows:

a = subjects with a true positive test result

b = subjects with a false positive test result

c = subjects with a false negative test result

d = subjects with a true negative test result

The characteristics of the screening test could be calculated by the following formulae.

sensitivity = a/(a+c)

specificity = d/(b+d)

The sensitivity and the specificity of the screening are the characteristic of the test. These characteristics are stable as long as the test is performed in the same

method. However, when using the screening test in different population, the positive predictive values, and the negative predictive values are varied according to the disease prevalence in the population.

The early reports of vision screening appeared since 1944. The majority of the reports focused on different screening tests. Hatch suggested that it is important to differentiate screening programs from screening tests. (Hatch, 1998) When analyzing the screening tests, most researchers paid attention on the sensitivity, specificity, false positive, false negative, etc. A screening program includes targeting a population, establishing an effective screening instrument, implementing the program, ensuring access to care for referrals, monitoring participants, and educating the population on the advantages and disadvantages of the screening program. Thus the analysis goes further until the screen positive persons reach health care facilities. Hatch also suggested the ideal disease for screening as shown in table 2.5. Considering the suggested criteria, ophthalmic diseases seem to be an ideal condition to perform screening especially ophthalmic diseases in children.

Table 2.5 Characteristics of an ideal disease for screening

| Characteristics of an ideal disease for screening |
|---|
| Easily and accurately tested |
| High prevalence |
| Chronic |
| Asymptomatic |
| Well-known natural history |
| Treatable |
| Public health burden |
| Improved prognosis with early detection |
| Treatment more cost effective when detected early |

The Thai Royal College of Ophthalmology recommends that ophthalmologic screening should be performed in children as followings (Kunavisarut, 1999):

1. Age 6 months: visual behavior screening (Recommendation power B)
2. Age 3 years: visual acuity screening; then re-screening every 1-2 years (Recommendation power A)
3. Children entering primary school and secondary school: eye examination and visual acuity screening (Recommendation power B)

[Recommendation power A: The procedure is beneficial for the people and should be performed. Recommendation power B: The procedure may be beneficial for the people and should be considered in appropriated situation.]

### 2.3.2 Visual Acuity (VA) Tests

Vision is one of the most important senses. It has been said that approximately 80% of the information from the outside world is incorporated through the visual pathways. Loss of vision has a profound effect on the quality of life. Yet, for all vision's importance to each of us, the most common clinical measurement of it is relatively crude and narrow. The process of vision includes many functions, such as central resolution (visual acuity), minimal light sensitivity, contrast sensitivity, detection of motion, color perception, color contrast, and peripheral vision (divided into spatial, temporal, motion detection) plus the interpretive processes that occur in the inner retina and the cerebral cortex. In the normal clinical setting, we measure only one of these functions - central resolution at high contrast (visual acuity). That this one simple test does a pretty good job of detecting most visual dysfunction is truly amazing. Despite the fact that visual acuity is to all of visual perception as the elephant's trunk is to the whole elephant, it works as an acceptable screening test in the real world. (Kniestedt & Stamper, 2003)

### 2.3.3 Definition and terminology of visual acuity

There are several tests for measuring the visual acuity. All tests quantify the capability of the persons to see detail. The most basic form of visual perception is detecting light. The simplest visibility target is a point of light, such as a star. To be able to see the light depends on intensity rather than size of the light. Most of the VA tests are more than just detecting light. Some tests are the measurement of the ability to discriminate two stimuli separated in space at high contrast compared with the background. The minimal angle of resolution that allows a human optic system to identify two points as different stimuli is defined as the threshold of resolution; visual acuity is the reciprocal of the threshold of resolution. Most of the VA tests used clinically depend on discriminating letters or numbers on a chart. This task requires the ability to resolve the image as well as recognition of the form and shape of the letters or numbers on the chart, which are processes that also involve higher centers of visual perception. Thus the VA tests can be classified according to the testing criteria to be: minimum visible, minimum resolvable or minimum discriminable. (Table 2.6)

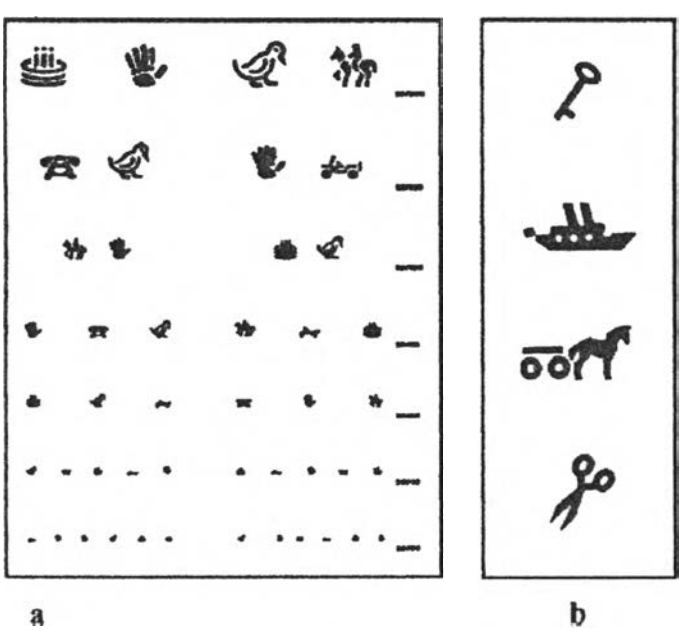


Figure 2.1 The pictorial VA chart (a. Allen chart, b. Osterberg chart)

The VA tests vary in the chart types, such as: wall charts, illuminated wall charts, projector charts, computer monitor screens, or near charts. They also vary in the test targets (optotypes), such as: pictograms, E-game, Landolt Cs, alphabet characters or numeric characters. Some test targets (E-game, Landolt Cs) measures more on the minimal resolvable criterion, while others such as alphabet or numeric characters need some more of the cortical interpretation. These targets vary in difficulty of interpretation according to the design of the characters. For example, the letters (C, D, O, G, and E) are inherently harder to recognize than others (A, J, L).

Table 2.6 Classification of visual acuity according to criteria

| Criterion | Minimum visible | Minimum resolvable | Minimum discriminable |
|---|---|---|---|
| Task | Determine presence or absence of a target | Determine presence of, or distinguish between more than one, identifying feature in a visible target | Determine relative location of two or more visible features with respect to each other |
| Typical forced choice psychophysical question: | Is there a line in this field?<br>If there was a line in the field, was it horizontal or vertical? | Are there one or two lines? | Is the gap in the C up, down, right, or left?<br>Is the upper line to the right or the left of the lower line? |
| Physiologic basis: | Local brightness difference threshold | Detection of brightness differences between several adjoining small areas | Assignment of relative local signs to two or more suprathreshold visual features |
| Method of measurement: | Vary object size | Vary object size or spacing between object components | Vary relative location of features |
| Magnitude of best threshold: | Approximately 1 sec of arc | Approximately 30 sec. of arc | Approximately 1 – 3 sec of arc |
| Effect of image degradation | Moderate | Serious | Slight (except in stereoacuity) |

Note: Minimum resolvable = minimum separable = ordinary visual acuity.

Minimum discriminable = Vernier acuity = hyperacuity.

Source: (Westheimer, 1987)

The test targets (optotypes) in the charts vary in sizes. The important characteristics of the test targets are the width of the optotypes' line as well as the overall height of the optotyes. The typical VA charts present various sizes of optotypes from large to small. The threshold of the smallest optotypes that the patient could read is the visual acuity of the patient. There are several measurement scales used in the VA tests, such as Snellen fraction in US system, Snellen fraction in metric system, decimal system, or minimal angle of resolution (MAR), etc. (Table 2.7)

Table 2.7 Visual acuity measurement scales

| Jaeger | Point | Letter size (M) | Snellen fraction (US) | Snellen fraction (metric) | Decimal | LogMAR |
|---|---|---|---|---|---|---|
| 19 | 60 | 6.3 M | 20/320 | 6/96 | 0.063 | 1.2 |
| 18 | 40 | 5.0 M | 20/250 | 6/76 | 0.08 | 1.1 |
| 16 | 26 | 4.0 M | 20/200 | 6/60 | 0.1 | 1.0 |
| 14 | 24 | 3.2 M | 20/160 | 6/48 | 0.125 | 0.9 |
| 12 | 18 | 2.5 M | 20/125 | 6/38 | 0.16 | 0.8 |
| 10 | 14 | 2.0 M | 20/100 | 6/30 | 0.2 | 0.7 |
| 8 | 12 | 1.6 M | 20/80 | 6/24 | 0.25 | 0.6 |
| 6 | 9 | 1.25 M | 20/63 | 6/20 | 0.32 | 0.5 |
| 5 | 8 | 1.0 M | 20/50 | 6/15 | 0.40 | 0.4 |
| 3-4 | 6 | 0.8 M | 20/40 | 6/12 | 0.50 | 0.3 |
| 2-3 | 5 | 0.63 M | 20/32 | 6/10 | 0.63 | 0.2 |
| 1-2 | 4 | 0.5 M | 20/25 | 6/7.5 | 0.80 | 0.1 |
| 1+ | 3 | 0.4 M | 20/20 | 6/6 | 1.0 | 0 |

Source: (Kniestedt & Stamper, 2003)

In 1862, Snellen introduced a system for measuring visual acuity. (Davidson, 1991) The Snellen chart was commonly used in clinical practice until now. The standard Snellen eye chart contains lines of letters that are not related to one another by a linear size progression in a geometric or logarithmic sense. The main disadvantages of former charts are inconsistent increase in letter size from one line to another. The numbers of letter in each line, as well as the difficulty are not equal. With the need for a better VA tests for clinical trials, the new standard of VA tests are developed based on the design created by Bailey and Lovie. (Bailey & Lovie, 1976) These VA tests are usually called Bailey & Lovie or the ETDRS style charts. (The ETDRS is the abbreviation for the Early Treatment Diabetic Retinopathy Study.) The VA charts used in the Sight for Kids program are also the ETDRS style charts.

Figure 2.2 The Teller preferential test chart using grating target


Figure 2.3 The ETDRS VA chart

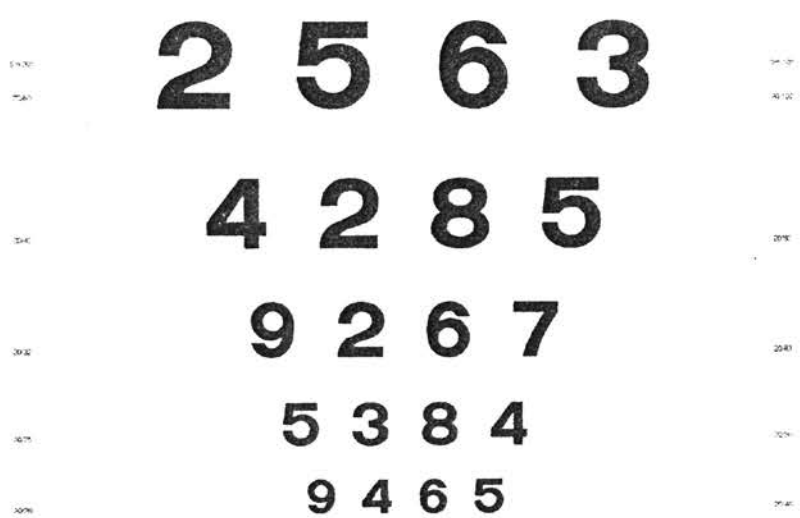


Figure 2.4 The VA chart used in the Sight for Kids program

### 2.3.4 Stereopsis Tests

Stereopsis is defined as the appreciation of relative depth due to retinal disparity. (Cooper, 1991) All stereopsis testing requires a situation in which each eye sees at least two targets from a different vantage point. One of the targets must be located on the horopter, whereas the other must be located off the horopter. The stereopsis test may be used as screening test for the following reasons:

Normal stereopsis is required for certain vocations, such as airline pilots, stereophotogrammers, or microsurgeons.

Stereopsis measurement is important in the diagnosis of various binocular abnormalities.

Stereopsis test have been used in detection of certain neurologic conditions, particularly right posterior cerebral lesions. (Ross, 1983)

Stereopsis test can detect uniocular abnormality which can be missed by the VA test.

In 1947, Wirt introduced a hand-held card for the measurement of near stereopsis. (Cooper, 1991) The test was the first clinical stereopsis test to utilize polarized vectographic sheets which produced separate images to each eye. The Wirt test was later incorporated in the Titmus stereotest. (Titmus Optical Co.) The other stereopsis test using polarized vectographic sheets methods are Randot test. The Randot test uses the random dots stereograms technique proposed by Julesz in 1960, to prevent the monocular clues for the patients. (Julesz, 1960) The TNO stereopsis test uses the red-green anaglyphs to create retinal disparity. The main disadvantage of the vectographic stereopsis tests is the high cost of the tests. Each set of commercial available tests costs more than 20,000 Baht.

Another group of stereopsis tests are called "real" stereo tests. These tests present real objects to the patients. The patients could perceive the difference in

depth. The examples of the real stereo tests are the Howard-Dolman stereo test, and the Frisby test. (Cooper, 1991)

The Howard-Dolman stereo test consists of one stationary rod and one movable rod. The subject views the rods, which are located at distance, and moves the movable rod just in front or just behind the stationary rod.

The Frisby stereo test is a near stereo test made of Plexiglas sheets, printed with random dot stereogram (RDS) format. The patients are asked to identify the area of printed pattern that is printed on the other side of the Plexiglas sheet. The degree of stereopsis depends on the thickness of the Plexiglas and the test distance. (Table 2.8)

Table 2.8 Stereoacuity (second of arc) on the Frisby test as a function of test distance

| Distance from patient (cm) | 6 mm thickness | 3 mm thickness | 1 mm thickness |
|---|---|---|---|
| 30 | 600 | 300 | 100 |
| 40 | 340 | 170 | 55 |
| 50 | 215 | 110 | 35 |
| 60 | 150 | 75 | 25 |
| 70 | 110 | 55 | 20 |
| 80 | 85 | 40 | 15 |
| 90 | 67 | 33 | 11 |
| 100 | 54 | 27 | 9 |

There are several screening tests being used such as visual acuity test, retinoscopy, cover test, external examination, and ophthalmoscopy. (Hatch, 1998) Stereopsis tests have been used for screening with sensitivity about 90%. (Rutstein & Corliss, 2000) There are several stereopsis tests such as the Frisby test, fly test, random dot stereogram, TNO test, and AO vectograph. Each screening test or combination of tests has its sensitivity and specificity.

Tong et al, (Tong et al., 2002a) studied the use of the visual acuity test in school children and found the sensitivity and the specificity to be 72% and 97% respectively. Robinson et al, (Robinson, Bobier, Martin, & Bryant, 1999a) studied the use of combination screening tests (VA, stereoacuity, and alignment test) and found the sensitivity to be 60-71% and the specificity to be 70-80%.