ACCURACY OF SELF-REPORTED STRABISMUS

by

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ABSTRACT

Although the diagnosis of strabismus requires specialist examination, many individuals are aware that they are affected. It is thus possible that self-reporting could be sufficient for population or genetic studies of strabismus; however, the accuracy of self-reported strabismus has not previously been evaluated. In this study, participants in the *Genetics of Comitant Congenital Strabismus (CCS) Study* were asked to report whether they had strabismus prior to receiving a complete orthoptic evaluation. In 671 individuals studied, the sensitivity of self-report for detecting true CCS was 48.5%, with a specificity of 98.6%, giving a PPV of 92.6% (NPV 84.5%). Self-reporting accuracy was influenced by the direction, size and constancy of the deviation, and by sex but not education. Self-reports produced a misclassification rate of 14.5% for CCS alone and 33.1% for combined CCS or strabismus-associated conditions. Considering this high misclassification rate, self-report should not be used for clinical studies of strabismus.

LIST OF ABBREVIATIONS USED

CCS	Comitant Congenital Strabismus
CI	Confidence Interval
ICS	Incomitant Congenital Strabismus
ID	Identification
M-M	Multiple Birth Siblings
NPV	Negative Predictive Value
OR	Odds Ratio
PAWE	Power for Association with Errors
PPV	Positive Predictive Value
ROC	Receiver Operator Characteristic
SAC	Strabismus-Associated Condition
SAS	Statistical Analysis Software
S-S	Separate Birth Siblings

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CHAPTER 1 INTRODUCTION

1.1 STRABISMUS, AMBLYOPIA, AND STEREOPSIS

Strabismus is a pathological condition in which the eyes are not properly aligned. Strabismus may develop at any time, from infancy through adulthood, but is common in children. The prevalence of strabismus ranges from 1-5% in North America (Green-Simms & Mohney, 2010). The detection and treatment of childhood-onset strabismus is particularly important as strabismus can disrupt binocular vision (Hess, 1996; Hubel & Wiesel, 1965; Li et al., 2011) and untreated strabismus can lead to the development of amblyopia (Birch & Holmes, 2010; Robaei et al., 2006). Many different types of strabismus exist, though most forms may be broadly distinguished by two important characteristics: onset (congenital vs. acquired) and range of eye movements (comitant vs. incomitant).

Amblyopia refers to decreased visual acuity in an eye which otherwise has a normal potential for vision. The reduced vision results from the developing brain's adaptation to incompatible images received from the two eyes. The images may be incompatible if one is unfocused from a refractive problem, or if two disparate images are received as in strabismus (Von Noorden & Campos, 2002). If detected and treated early during childhood, amblyopia can be fully corrected, but if treatment is delayed, recovery may not be possible and vision loss will be permanent.

Stereopsis is the binocular perception of depth that results from interpretation of slight disparities in the binocular input to the visual cortex. Optimal stereopsis requires two properly aligned eyes; each receiving a clear image, binocular fusion, and simultaneous perception of images from the two eyes. As with amblyopia, if the brain is not receiving the same quality image from both eyes, or is suppressing an eye, stereopsis will be disrupted.

The consequences of strabismus continue throughout an affected person's lifetime. In a quality of life weight study of patients with adult strabismus, almost 60% of participants expressed that they would trade part of their life expectancy to be free of strabismus and its associated symptoms (Beauchamp, Felius, Stager, & Beauchamp, 2005). Successful surgery can have profound benefits, but the overall long-term results of surgery are disappointing, probably as a result of late detection and a poor understanding of the cause. Within 10 years of surgery for esotropia, half of all patients will require a reoperation (Louwagie, Diehl, Greenberg, & Mohney, 2009), and less than half of all exotropia patients have satisfactory alignment >8 years after surgery (Ekdawi, Nusz, Diehl, & Mohney, 2009). It is rare for children with congenital esotropia to ever develop high-grade stereopsis (Birch & Stager, 2006). Strabismus is associated with psychosocial disability (Jackson, Harrad, Morris, & Rumsey, 2006; James, Jenkinson, Harrad, Ezra, & Newman, 2011). The disruption of normal interpersonal eye contact causes poor self-esteem, social anxiety, and phobias. Poor eye contact and reduced stereopsis limit employment options, leading to lost productivity. The cost to society from loss of

function from strabismus and amblyopia has been estimated at well over $20 billion (Beauchamp, Felius, Beauchamp, Brown, & Brown, 2007).

1.2 Congenital and Acquired Strabismus

Strabismus presents in many forms and it is classified or distinguished based on the characteristics of the misalignment (Von Noorden & Campos, 2002). One important characteristic is age of onset. Of adults presenting to the office of a strabismus specialist, 38-49% report that their strabismus originated during childhood (Beauchamp et al., 2003; Beauchamp et al., 2005). Congenital (or infantile) strabismus develops from birth until six months of age (Von Noorden & Campos, 2002) and the definition excludes strabismus caused secondary to external injury or neurological disease. As opposed to neonatal strabismus, which presents as a mild (usually exotropic) misalignment and resolves by two to three months of age, congenital strabismus does not resolve on its own. Though not all forms of congenital strabismus are recognized at birth, it is believed that the source of the misalignment is innate and not clinically recognized until later in life (Archer, Sondhi, & Helveston, 1989; Birch, Stager, Wright, & Beck, 1998; Fu, Stager, & Birch, 2007; Pediatric Eye Disease Investigator Group, 2002). Accordingly, the term "congenital" is frequently applied to strabismus arising beyond six months of age, although this type of strabismus has also been called "early acquired strabismus" (Von Noorden & Campos, 2002).

Cases of new-onset strabismus in school-aged children and adults may result from (often unknown or poorly understood) mechanical or pathological insult to the ocular or oculomotor system. This type of strabismus is most often termed acquired or secondary strabismus. Many children with esotropia present between the ages of 2-3 years, while those with exotropia are most likely to present between 1-4 years of age (Donahue, 2007). The visual consequences of strabismus (reduction in stereopsis, development of amblyopia associated with strabismus) can vary with the age of onset, depending on whether the critical period for the development of binocular vision or visual maturation has been reached (Fawcett, 2005; Fawcett, Wang, & Birch, 2005).

1.3 Comitant and Incomitant Strabismus

A second way to broadly classify strabismus is based on its comitance; that is, whether or not the measured angle of strabismus varies with the direction of gaze (Von Noorden & Campos, 2002). Those with comitant strabismus have a full range of eye movements and the angle of misalignment is similar in different positions of gaze regardless of the fixating eye. Pattern strabismus (defined as a change in the angle of strabismus measured in up versus down gaze) and distance-near disparities (defined as a change in the angle of strabismus measured at near versus distance fixation) may occur in comitant strabismus. Comitant strabismus includes the most common forms of strabismus such as congenital esotropia, accommodative esotropia, and intermittent exotropia, and the large majority of comitant strabismus begins in childhood.

Incomitant strabismus is also known as paralytic or complex strabismus. In this condition, the angle of misalignment varies substantially in defined positions of gaze. The variation in the angle of strabismus is caused by absent, impaired, or anomalous movement of one or both eyes. Incomitant strabismus makes up 5% of all cases of strabismus (Engle, 2007). Duane syndrome and Brown syndrome are among the most common types of incomitant strabismus.

1.4 Etiology of Strabismus

Over the past decade, the causes of incomitant congenital strabismus (ICS) have become well understood. Forms of ICS can be inherited as Mendelian traits, and the genetic mutation(s) of several types have been identified. As reviewed by Engle (2007) and Oystreck (2011), anatomic, genetic, and neurodevelopmental studies all support a neurogenic etiology of ICS. These disruptions in neural development may occur at any point along efferent oculomotor pathways and result in abnormal or absent cranial nerve innervation of the extraocular muscles (Engle, 2007; Oystreck, Engle, & Bosley, 2011).

In contrast, the pathogenesis of comitant congenital strabismus (CCS) is unknown (Donahue, 2007; Tychsen et al., 2008) though two theories have been proposed. One theory, now refuted by animal studies (Tychsen et al., 2008), suggests the oculomotor system, as in ICS, is the primary source of strabismus. It asserts that there is some defect in the signal sent to the extraocular muscles, in the presence of an intact sensory system, that causes strabismus. As part of this theory, the brain is otherwise capable of binocular

vision (Chavasse (1939) cited in (Tychsen, 2010; Von Noorden & Campos, 2002)). Alternatively, Worth (1903) attributes the primary source of the problem to the sensory system. Worth's theory proposes that congenital strabismus results from a deficiency in the sensory system and the lack of binocular vision, rather than the motor system (Worth (1903) cited in (Tychsen, 2010; Von Noorden & Campos, 2002)). This theory has been supported by primate studies of infantile esotropia, whose strabismus mimics infantile esotropia found in humans (Tychsen et al., 2008). However, even this theory is not entirely supported by clinical observations, as occasional rare patients with congenital esotropia will develop high-grade stereopsis if their misalignment is corrected early in life (Wright, Edelman, McVey, Terry, & Lin, 1994).

The heritability of strabismus is well recognized and supported by population, twin and family studies (Paul & Hardage, 1994; Lorenz, 2002). Increased heritability can result from genetic or environmental factors. Although environmental risk factors such as low birth weight, prematurity, and maternal tobacco use are associated with strabismus (Chew et al., 1994; Pennefather et al., 1999; Torp-Pedersen et al., 2010a; Torp-Pedersen et al., 2010b), evidence for strong genetic liability remains when known environmental factors associated with strabismus are taken into account (Wilmer & Backus, 2009). Despite evidence of a strong genetic contribution to the development of CCS, details of its genetic architecture remain unknown.

1.5 Strabismus-Associated Conditions

As the etiology of CCS is unknown, it is important to consider strabismus-associated conditions (SAC), both those that result from strabismus and those that may contribute to the development of the condition. Study of SAC is especially important when seeking a genetic etiology for strabismus, as related genetic defects may determine the risk for developing both strabismus and SAC. Studying associated conditions may thus prove to be helpful in the determination of the underlying cause of some forms of CCS.

SAC include visual conditions that result from strabismus, such as amblyopia and decreased or absent stereopsis, including monofixation syndrome. Other conditions such as latent nystagmus, dissociated vertical deviation and inferior oblique overaction are believed to be a result of the deficits in binocular vision that occur in strabismic individuals. Lastly, refractive errors such as hyperopia and anisometropia, are also associated with strabismus.

Latent nystagmus, inferior oblique overaction and dissociated vertical deviation are most often viewed as a constellation of findings accompanying a diagnosis of infantile or congenital esotropia (Castro et al., 2011; Louwagie et al., 2009; Strominger, 2008). However, these findings may be present alone or in addition to other early onset disturbances of binocular vision (Lim, Smith, Kraft, & Buncic, 2008; Tychsen et al., 2010).

Monofixation syndrome, or microstrabismus, is a minute binocular misalignment that is too small to be detected by standard ocular motility evaluation (Campos, 2008). The hallmarks of microstrabismus or monofixation syndrome are decreased stereopsis and a central suppression scotoma noted under binocular conditions. Parents of children with congenital esotropia may have a higher prevalence of primary monofixation syndrome (Scott, Noble, Raymond, & Parks, 1994).

Studies of refractive conditions associated with strabismus have found that high and moderate hyperopia occur more often in strabismic versus non-strabismic individuals (Atkinson et al., 1996; Birch, Stager, Wang, & O'Connor, 2010; Ingram, Traynar, Walker, & Wilson, 1979; Robaei et al., 2006), and that esotropic patients are more likely to be hyperopic than exotropic patients (Abrahamsson, Fabian, & Sjostrand, 1992; Green-Simms & Mohney, 2010). Hyperopia is also more likely to increase with time in deviating esotropic eyes, which results in anisometropia (Abrahamsson et al., 1992). In the setting of a positive family history, hyperopia is a risk factor for developing esotropia or accommodative esotropia (Aurell & Norrsell, 1990; Birch, Fawcett, Morale, Weakley, & Wheaton, 2005).

1.6 Self-Report

Health care data is collected from many sources. However, all sources have limitations and errors may be present. Choosing a data source to measure “affected status” (that is, whether or not an individual has a condition) for a study is one of the critical steps in the

design of any research, as the accuracy of the data source can affect the validity of the findings. Accurate measurement of the affected status reduces the possibility of misclassifying an individual and of overestimating or underestimating the presence of the disease in the population under study (Newell, Girgis, Sanson Fisher, & Savolainen, 1999). When misclassification exists, the true association between disease and risk factors cannot be found (Flegal, Brownie, & Haas, 1986).

A research participant's affected status may be determined by several methods. Often, clinical examination is the measure of choice. Though not without limitation or measurement error, the quality of this data source is assumed to be higher than that of other sources such as medical records or self-report. Consequently, clinical examination is deemed the gold standard measurement for most studies. However, clinical examination can be logistically difficult and comes with a cost of time and resources; consequently, many large-scale studies rely on self-report to determine whether or not a condition is present.

Though frequently chosen for its relative convenience and low cost, the value of a self-reported diagnosis may be limited, (Harlow & Linet, 1989; Newell et al., 1999) as individuals may intentionally or unintentionally provide false information. Despite the wide use of self-report, it is difficult to discern which factors contribute to an accurate report for any research study. Cognitive factors such as an individual's knowledge of the targeted condition and ability to recall it, as well as motivational factors that influence an individual's willingness to report their condition, can limit the accuracy of self-report

(Brener, Billy, & Grady, 2003; J. B. Jobe, 2003). Poor knowledge can result when the individual lacks health care or when poor communication between patient and clinician leads to incomplete understanding of a diagnosis (Colditz et al., 1986; Kehoe, Wu, Leske, & Chylack, 1994). Though there is no consensus as to the effects of age, sex, education and health status (Cleary & Jette, 1984; Haapanen, Miilunpalo, Pasanen, Oja, & Vuori, 1997; Harlow & Linet, 1989; J. B. Jobe et al., 1990; Kriegsman, Penninx, Van Eijk, Boeke, & Deeg, 1996) on an individual's ability to recall a health event, recall is associated with the emotional impact of the event (Phelps & Sharot, 2008; Talarico & Rubin, 2003). Willingness to share information is sometimes restricted by confidentiality concerns particularly if an actual or perceived social stigma is associated with the targeted condition (Link & Phelan, 2006). Thus, the emotional impact and stigma of the condition being studied affects the accuracy of self-reported data, even as the influence of other contributing factors is poorly understood and must be determined individually for every condition. Any study using self-report to collect data must therefore investigate the accuracy of self-reports in order to support the validity of the study's findings.

Clinical and epidemiological studies use self-reports to ascertain the affection status of an individual as a means to measure the prevalence and associated risk factors for a wide range of diseases and conditions. Researchers often trust in the accuracy of the self-report, though the degree to which the collected data is accurate is often unknown. Several early studies have assessed the agreement between self-reported and documented medical conditions. While some research suggest self-reports are valid for certain chronic and acute conditions (Bush, Miller, Golden, & Hale, 1989; Harlow & Linet, 1989; Kehoe

et al., 1994) others indicate that self-report alone is not sufficient to accurately establish affection status of the targeted condition (Newell et al., 1999; Wu, Li, & Ke, 2000). When self-reports have been assessed for accuracy, not only does accuracy vary widely among conditions (Bush et al., 1989; Colditz et al., 1986; Kehoe et al., 1994) but the accuracy of self-report for a specific condition can vary from study to study (Kehoe et al., 1994; Wu et al., 2000). This variability among studies is related not only to inconsistencies found in disease definition but it is likely also associated with the diversity of study populations, sample sizes, reference standards, and methods of analysis used among investigations (Harlow & Linet, 1989; Newell et al., 1999).

The diversity of self-reporting accuracy also makes it difficult to detect variables associated with accurate reporting. Haapanen and colleagues (1997) found considerable agreement between self-report and medical record for conditions such as diabetes and cardiovascular diseases as a group but poorer agreement for less chronic and less symptomatically defined conditions like lower back pain and musculoskeletal disease. The authors suggested that the discrepancies found for these latter conditions were associated with the characteristics of the disease rather than the characteristics of the respondent (Haapanen et al., 1997). Although several discrepancies between physician-reported and self-reported medical conditions are outlined, Kehoe and colleagues (Kehoe et al., 1994) endorsed the findings by Colditz and colleagues (Colditz et al., 1986) that the use of self-report could be reliable for well-defined conditions, and indicated that respondent characteristics such as age, sex, education, and race may be slightly associated with reporting accuracy for some but not all diseases. With some reservation,

Kehoe et al. (1994) described the number of healthcare encounters per year as having a greater effect on accuracy; a finding supported by Haapanen et al. (1997). These observations are consistent with the observations of Harlow and Linet (1989) that frequent and recent visits to a provider for a specific condition increase the self-reporting accuracy for that condition (Harlow & Linet, 1989). Wu, Li and Ke (2000) also stress the variability of accuracy among diseases under investigation, but suggested lack of statistical power precluded the detection of statistically significant factors accounting for the observed accuracy. More recent studies maintain the variability of accuracy of self-reported disease and the lack of reliable correlates of accuracy across investigated conditions (Englert et al., 2010; Jones, Bartrop, Dickson, & Forcier, 2011; Leikauf & Federman, 2009). The inability to draw solid conclusions from the self-report literature emphasizes that self-reported data is not 100% accurate and could lead to misclassification of affected status and flawed associations.

1.6.1 Self-Reported Ophthalmic Conditions

Although self-reporting is frequently employed in ophthalmic research to assess prevalence and risk factors, few investigators assess or report the accuracy of self-reported ocular conditions. As part of the Beaver Dam Eye Study, investigators examined the accuracy of self-reported and proxy-reported diagnoses of cataract and macular degeneration (Linton, Klein, & Klein, 1991). In this population-based study, residents over 40 years of age or their proxies were interviewed by telephone. Within two years, willing participants completed an “in person” questionnaire and received an ocular

examination. A comparison of all three methods of self-report (telephone, telephone by proxy and "in person") showed good reliability. The agreement between the report of cataracts by telephone and the clinical examination was 81.2%, with a sensitivity of just 38.4% and a specificity of 97.3%. When the clinical findings were compared to the self-report at the time of the examination, the agreement was 83.6%, with a sensitivity of 46.3% and a specificity of 96.0%. The self-report of macular degeneration had an agreement of 89% between the telephone interview and examination, with a sensitivity of only 17.3% and a specificity of 96.1%. At the time of the examination, the self-report of macular degeneration agreed with the clinical findings 92% of the time, with a sensitivity of 17.9% and specificity of 98.7%. Nevertheless, the authors considered the low sensitivity of self-reporting and rated the accuracy of each measure as poor in comparison to clinical measures for both cataract and macular degeneration. They suggest that the use of any of these self-report measures in the place of a clinical diagnosis of cataract or macular degeneration could result in significant misclassification error, an underestimation of prevalence, and inadequate recognition of important associated demographic characteristics and clinical factors (Linton et al., 1991).

As part of the Physicians' Health Study, Christen and colleagues (1994) asked male physicians aged 40-84 years whether they had a diagnosis of cataract (Christen et al., 1994). Medical records confirmed 97.6% of self-reports for lens changes; however, when the clinical definition of cataract was extended to include resulting visual acuity loss of 20/30 or greater, only 50% of self-reports of cataract were confirmed. This study

emphasizes that oversimplification of self-report questions as compared to diagnostic criteria can produce a large number of false positives.

Bowie and colleagues (2003) studied the accuracy of self-reported cataract and cataract surgery provided by subjects aged 72 or older who were enrolled in the Salisbury Eye Evaluation, a population-based study of aging and visual disabilities. Self-reported cataract diagnosis showed poor accuracy as compared to clinical examination with lens grading, with a sensitivity of 55%, specificity of 77%, and positive predictive value of 76%. However, cataract surgery was more accurately self-reported: sensitivity of 94%, specificity of 100%, and positive predictive value of 95%. The authors suggest that affected status based entirely on self-reported history of cataract would result in misclassification of affection status in study participants (Bowie, Congdon, Lai, & West, 2003).

In a population of indigenous Australians (Taylor et al., 2010), cataract was over reported by 54% of the participants when compared with standardized ophthalmic examinations. Of those misreporting cataract, clinical criteria for cataract was not matched in 83%, and vision loss from a cause other than a cataract was present in the remaining 17%. Of those patients who reported a history of cataract surgery, 7% had no evidence of cataract surgery on clinical examination (Taylor et al., 2010). Goujon et al. (2010) also studied indigenous Australians and found discrepancies between self-report and clinical diagnosis for several other ophthalmic conditions. Self-reported diabetic retinopathy was not confirmed by examination in 54%, glaucoma in 85% of participants, and age related

macular degeneration in 91%. Furthermore, diabetic retinopathy was underreported for 60% of those clinically diagnosed. Taylor et al. (2010) and Goujon et al. (2010) each acknowledged that their findings challenge the accuracy of self-reported data. (Taylor et al., 2010; Goujon et al., 2010).

These studies show that awareness of ophthalmic diagnoses is variable and depending on the accuracy required, self-reports may not be sufficient.

1.6.2 Self-Reported Strabismus

Little data exists concerning the accuracy of self-reported strabismus history, whether obtained from affected patients or from parent-proxies. Many studies do not use a reference or gold standard, leaving the accuracy of the self-report untested. With a few exceptions, when a reference standard is in place, studies seldom validate the accuracy of the report of strabismus, nor do they comment on any differences observed between the reported strabismus status and the observed status derived from the reference standard (Ferreira, Oelrich, & Bateman, 2002; Rice et al., 2009; Shaaban et al., 2009). As a result, self-reported strabismus data is often used without knowledge of its accuracy.

There are only a few limited studies of the accuracy of self-reported strabismus in the literature. In the Multi-Ethnic Pediatric Eye Disease study (2008), clinical examination of Hispanic or Latino and African American participants aged 6 to 72 months confirmed only 62% of the parent-proxy self-reported strabismus diagnoses (Multi-ethnic Pediatric

Eye Disease Study Group, 2008). Chew and colleagues (1994) investigated strabismus risk factors in the Collaborative Perinatal Project cohort. Participants were examined by neurologists and pediatricians using the Hirschberg test, which is a crude measurement and only approximates manifest strabismus (Von Noorden & Campos, 2002). Gold-standard clinical examinations by an ophthalmologist or orthoptist were not performed. Of those diagnosed with strabismus, 40% of those initially diagnosed with esotropia and 100% of those initially diagnosed with exotropia, had a medical record review performed by an ophthalmologist. This chart review compared the limited ocular examination to ophthalmologist or pediatrician records of the participant. The initial diagnosis from the limited eye exam was confirmed in 83% of esotropia cases and 89% of exotropia cases (Chew et al., 1994). Since all those diagnosed with exotropia were reviewed and corrected, no misclassification of exotropia was assumed in the study, but because 60% of their esotropia cohort was not examined, they estimated a 10% misclassification rate for esotropia cases. The investigators also assume that no cases of esotropia or exotropia were missed in the participants that were not diagnosed with strabismus. In a related investigation, Podgor and colleagues used this information to recalculate the between-siblings odds ratio of strabismus, or what is their increased risk of developing strabismus because of their positive family history (Podgor, Remaley, & Chew, 1996). Associations between siblings were unchanged for exotropia as they did not believe there was any misclassification. However, adjusted associations for esotropia in separate birth sibling (S-S) and multiple birth siblings (M-M) changed from 2.6 to 3.0 for S-S and from 5.4 to 7.0 for M-M. The limited data available to date and the evidence that misclassification can substantially alter the results of genetic association studies strongly support the need

to perform robust assessment of the accuracy of self-reporting and parental proxy-reporting of strabismus.

1.7 Study Rationale

Accurate determination of affected status, the presence or absence of a condition, is vital when the end point of an analysis depends on these raw data. Misclassification of affected status in clinical and epidemiological research distorts true prevalence of a disease and obscures associated risk factors. Genetic linkage and association studies require designation of participants as affected or unaffected to maximize statistical power and the chances of finding true genotype-phenotype associations. Two common ways to obtain these data is by clinical examination and self-report. Clinical examination, considered the gold standard for diagnosis of strabismus, involves substantial time and effort on behalf of participants and clinicians. When large study populations are required, self-reported strabismus affection status could result in a substantial reduction in the time and resources required by participants and researchers. However, the accuracy of self-reported strabismus is not known, with two limited studies performed to date showing conflicting results. It is important to know if and to what extent strabismus self-reports differ from the affected status determined by clinical examination. This knowledge could be especially beneficial for large genetic studies, where time and resources devoted to ascertaining phenotype affection status by clinical examination remain high despite the reductions in time and costs to genotype samples realized from technological advances (Green & Guyer, 2011).

1.8 RESEARCH OBJECTIVES

1.8.1 Main Study Objective

To determine the accuracy of self-reported history of strabismus in family members of the patient population at Children's Hospital Boston. To answer this question, the affected status reported by participants at the time of enrollment will be compared with the findings of the orthoptic examination. The results of this work may hold significance in primary care settings where family history is used as a screening tool for surveillance or referral of suspect cases. In the research setting, it will help to determine whether future genetic research can accurately rely on a self-reported history of strabismus.

1.8.2 Secondary Objectives

a) Determine which factors may influence the accuracy of self-reported strabismus.
b) Determine the prevalence of strabismus in families of the patient population diagnosed with CCS at Children's Hospital Boston.
c) Determine the prevalence of reduced stereoacuity in family members of the patient population diagnosed with CCS at Children's Hospital Boston.

CHAPTER 2 METHODS

2.1 STUDY DESIGN

The *Strabismus Self-Reporting Accuracy Study* was designed to evaluate the accuracy of self-reported strabismus. Participants were part of a large prospective research project known as the *Genetics of Comitant Congenital Strabismus (CCS) Study*, which is being conducted at Children's Hospital Boston. The study utilized information provided by family members of patients diagnosed with CCS within the Department of Ophthalmology and enrolled in the *Genetics of CCS Study*. Participants completed a questionnaire related to their ophthalmic history and received an orthoptic examination to determine the accuracy of their self-reported status.

Ethical approval was attained from the Children's Hospital Boston Institutional Review Board (Boston, MA) as well as the Dalhousie University Health Sciences Research Ethics Board (Halifax, NS).

2.2 STUDY POPULATION

The participants were family members of patients in the Department of Ophthalmology at Children's Hospital Boston. Located in Eastern Massachusetts, the Department of Ophthalmology also serves the pediatric and adult strabismus population in Central and

Western Massachusetts in addition to the surrounding states of New Hampshire, Maine, Rhode Island, Connecticut and New York.

Any 1st or 2nd degree relative of a proband enrolled in the *Genetics of CCS Study* was eligible for inclusion in the study, excluding relatives who were already patients within the Department of Ophthalmology and would thus be aware of their affection status. No preference was given to an individual's sex, racial or ethnic origin; however, if the participants did not speak English or Spanish, they could not be enrolled in the study. There were no age restrictions for the study.

2.3 Specific Inclusion and Exclusion Criteria

All relatives of a patient with CCS within the Department of Ophthalmology at Children's Hospital Boston were eligible for inclusion in the study if the proband has enrolled in the *Genetics of CCS Study*.

CCS and its associated conditions are defined as:

a) Strabismus – manifest or intermittent strabismus of any angle, or phoria greater than 10 prism diopters.
b) Anisometropia – spherical equivalent or astigmatic difference between eyes of ≥1.5 diopters.
c) High hypermetropia – hyperopic refractive error of ≥ 5.00 diopters.

d) Amblyopia – vision loss in one eye causing two or more lines difference in logMAR visual acuity secondary to strabismus, anisometropia, or refractive deprivation.

Exclusion criteria are:

a) Not genetically related to an individual with CCS (*The Genetics of CCS Study* requires at least one family member to be diagnosed with strabismus).
b) Already a patient in the Ophthalmology Department at Children's Hospital Boston (Patients seen within the Department of Ophthalmology are aware of their affected status as it has already been determined by orthoptic or ophthalmic examination).
c) Presence of an eye condition that prevents sensorimotor examination or prevents definite diagnosis of congenital strabismus (i.e., a condition such as macular degeneration that has caused poor visual acuity, or a condition such as thyroid eye disease that may cause a secondary strabismus).
d) Unwilling to participate.
e) Incapable of giving consent and not having a legal guardian willing or able to do so.
f) Unable to speak English or Spanish.

Patients with a non-heritable cause for strabismus were not included in the genetic study; hence their family members are not included in the *Strabismus Self-Reporting Accuracy Study*. The *Genetics of CCS Study* excludes patients with any of the following:

a) Strabismus with a non-heritable etiology causing acquired vision loss.
b) Structural brain abnormalities.

c) Conditions causing occlusion of the eye and leading to deprivation amblyopia.
d) A molecularly defined genetic syndrome or other diagnoses associated with strabismus such as trisomy 21 or any form of craniosynostosis.
e) Other conditions likely to cause vision loss with secondary strabismus including trauma or structural ocular abnormalities.

2.4 Recruitment Process

As the *Strabismus Self-Reporting Accuracy Study* is a subset of the *Genetics of CCS Study*, the recruitment process for the *Genetics of CCS Study* is described.

The Business Intelligence Team at Children's Hospital Boston used the hospital's scheduling system, the EPIC Oracle data warehouse, to generate an Excel file containing the following fields: medical record number, first name, middle initial, last name, sex, date of birth, address, home phone number, upcoming ophthalmology appointment date and time, upcoming ophthalmology appointment location, appointment notes, and clinical provider. The files were emailed on a monthly basis to the research coordinator.

Once emailed to the research coordinator, the appointment data files were reviewed alongside the medical records to determine whether patients met criteria for the study. Potential study participants were then sent an introductory letter and brochure providing information on the study (Appendix A). A stamped, return-addressed postcard was also enclosed which contained a unique identifying code. If the individual did not wish to be

contacted further, they were asked to return the postcard; if the post card was not returned, they were contacted by phone approximately two weeks after the mailing of the introductory letter. Once contact was made and the family agreed to participate, a time to meet and enroll in the study was arranged.

2.5 Enrollment Process

Participants were enrolled as part of the *Genetics of CCS Study*. The three components of the enrollment process: informed consent, participant questionnaire, and orthoptic screening are described. The enrollment process took 20 minutes per individual and up to 60 minutes if several family members were enrolled. Participants were enrolled at Children's Hospital Boston in the Department of Ophthalmology.

At the time of enrollment, participants were given a unique, numerical identification code. Only those present for enrollment, or involved with data collection, were aware of the family name, otherwise, participants are known only by their study identification number.

2.5.1 Informed Consent

At enrollment, the research coordinator or assistant attained the informed consent in person. The participant read and signed the consent form. All questions of the prospective participants were answered by the research assistant or coordinator prior to signing, and

the participants were provided with a copy of the signed consent form. Those under the age of 18 years were required to have a parent or legal guardian sign the consent form, but when capable, children were also asked to sign to indicate their assent. The consent form is attached (Appendix B).

The consent form was not specific to the *Strabismus Self-Reporting Accuracy Study* or the *Genetics of CCS Study*. Instead, it is the general consent form used for all studies performed in the Engle Laboratory at Children's Hospital Boston. It covers the secondary use of the data for the *Strabismus Self-Reporting Accuracy Study.* Coverage includes both the written questionnaire (which records the reporting of strabismus), and the orthoptic examination.

2.5.2 Participant Questionnaire

Once the consent form was signed, participants were asked to complete a self-administered questionnaire that included questions on the individual's ocular and general medical history as well as basic demographic information. Every participant was required to complete a questionnaire. Parents completed one for themselves and also a proxy questionnaire for any children who were enrolled and unable to complete independently.

Questions specifically related to the *Strabismus Self-Reporting Accuracy Study* asked whether or not the participant has strabismus or amblyopia, or was ever treated for strabismus or amblyopia. To assist with understanding and recognition, questions

included both common lay terminology for strabismus (e.g., “crossed” or “wandering” eye) and medical language. A handout defining some of the questionnaire’s terminology was also provided (Appendix C). Participants recorded their answers by checking one of the three possible responses provided for each question (“Yes’, “No”, or “I’m not sure”.) The full participant questionnaire is presented in Appendix D. The research coordinator or assistant was available to assist with any further questions.

2.5.3 Orthoptic Examination

The orthoptic examination is a sensorimotor evaluation designed to detect all forms of strabismus as well as any associated conditions. The examination was performed at the time of enrollment by a clinically experienced orthoptist in the Department of Ophthalmology. The examination was completed on a research basis; therefore it did not become part of a participant’s medical record, nor was there a charge for the examination. The orthoptic examination consisted of:

a) Brief ocular history – participants were asked if they had strabismus or amblyopia or were ever treated for strabismus or amblyopia
b) Measurement of optical correction and refractive status as well as visual acuity
c) Binocularity, fusion, and stereoacuity: efforts were made to ensure the highest level was achieved. This included additional plus lenses for presbyopic participants and proper illumination for all testing.
d) Ocular alignment in primary position as well as diagnostic gaze positions
e) Extraocular motility

f) Other findings:

   a. Pupil examination

   b. Lid position

   c. Nystagmus

Guidelines for the examination of participants and for entering and categorizing their data can be found in the *Comitant Congenital Strabismus Study: Data Collection and Entry Reference Manual* (Appendix E). If the participant was found to have a condition that they were not aware of, or if the examining orthoptist had any concerns about a known condition, the participant was urged to see their primary care doctor or an ophthalmologist.

2.6 Data Entry

The results of the orthoptic screening were recorded on standard clinical examination forms in use at the Children's Hospital Boston Department of Ophthalmology (Appendix F). The examination forms were entered into the 'eye examination' section of the Engle Laboratory's customized genetic pedigree software () in accordance with the reference manual. This ensured consistent and reproducible assessment of the phenotype of all participants. An example of the Progeny Genetics database eye examination data is provided in Appendix G.

Once the examination data was entered, the participant was coded as "Affected with CCS", "Affected with a condition associated with CCS" or "Unaffected". If affected, they were further labeled as to their specific condition as diagnosed by the orthoptist. If a diagnosis of CCS was recorded, one of the following conditions was also used to label participants:

a) Esotropia: manifest esotropia in primary position
b) Infantile Esotropia: manifest esotropia that develops within the first six months of life
c) Accommodative Esotropia: manifest esotropia reduces with hyperopic correction to a range that fusion may be achieved (less than 10 prism diopters) or reliably demonstrate fusion. If bifocals are required to reduce the deviation to 10 prism diopters or less it's acceptable.
d) Intermittent Esotropia: patient has an intermittent esotropia at any point during the examination in primary position.
e) Esophoria: esophoria of 10 prism diopters or more in primary position
f) Exotropia: manifest exotropia in primary position
g) Infantile Exotropia: manifest exotropia that develops within the first six months of life.
h) Intermittent Exotropia: intermittent exotropia at any point during the examination in primary position
i) Exophoria: exophoria of 10 diopters or more in primary position
j) Microstrabismus or monofixation syndrome: small angle manifest deviation in primary position, deviation may be difficult to detect, but must demonstrate

reduced stereopsis and central suppression scotoma for monofixation syndrome diagnosis.

k) Strabismus surgery – unknown diagnosis: diagnosis of exclusion for participants whose original deviation is unknown but report and show evidence of prior strabismus surgery. All those reporting a history of strabismus surgery were coded as affected, and the original deviation was recorded when known.

If a strabismus-associated condition (SAC) was diagnosed, one or more of the following conditions was also used to further label participants:

a) Refractive conditions:
    a. Anisometropia: 1.5 Diopters or more difference in refractive error (spherical equivalent or astigmatic value)
    b. High hyperopia: 5.00 Diopters or more of hyperopia.
    c. Anisometropia + High hyperopia: meets criteria for both anisometropia and high hyperopia
b) Decreased stereo: Low grade stereoacuity: With proper optical correction, and ideal lighting and instruction, participant is unable to achieve better than 60 seconds of arc (range will be 60-3000 seconds of arc). Clinical judgment needs to be implemented when testing young children.

The participant questionnaire data was entered into the database by the research coordinators while the orthoptic screening data was entered by orthoptists. All who collected or entered data were trained to use the Progeny Genetics database in three

sessions by the Research Director or the Lead Orthoptist. The first session oriented the user to the database and walked them through the data entry process. During the second session, the user entered data under direct supervision. In the final session, the user entered data independently, but all data was reviewed. Once all three training sessions were completed, users were able to enter data, however, the Research Director of the Engle Lab and the Lead Orthoptist continued to audit data entry regularly. At the time of data extraction, the Lead Orthoptist had entered directly, or audited, more than 86% of the phenotypic data for *Strabismus Self-Reporting Accuracy Study.*

2.7 Data Extraction

The Progeny Genetics database was queried using the following search criteria:

a) All those with a participant identification (ID) except those also coded as the index case (proband).
b) All those with a participant ID except if they also had a Children's Hospital Boston medical record number.
c) All those with a participant ID that also completed an orthoptic examination.

This query was designed to identify all family members who participated in the study and completed an orthoptic examination, and who were not already patients of the Department of Ophthalmology at Children's Hospital Boston. As the *Genetics of CCS Study* is ongoing, only participants from the study inception date, March 1, 2005, until August 31, 2010 were included.

Once the individuals were identified, the following information was displayed:

a) Participant ID
b) Date of birth
c) Date of enrollment or orthoptic examination
d) Educational level
e) Race
f) Sex
g) Affected status – determined by orthoptic screening
h) Diagnosis – determined by orthoptic screening
i) Deviation in prism diopters at near and distance with and without correction
j) Answers to self report questions:
    a. Do you have the same eye condition as the original study subject?
    b. Do you have strabismus or amblyopia?
    c. Have you had amblyopia treatment?
    d. Have you had eye muscle surgery?

Using this information, a few additional pieces of data were added to the extracted database:

a) All participants were recoded with a second non-identifiable ID that was unrelated to the original CCS study ID.

b) The answers from the self-report questions were combined to form a simple, "Yes," "No," or "Unsure" response to globally answer the question, "Do you have strabismus or a condition associated with strabismus?" If participants were found to have high hyperopia or anisometropia, the questionnaire was reviewed and the eye examination was checked to determine whether glasses were worn.

c) If responses to the participant questionnaire section on strabismus were incomplete, then the history obtained verbally at the time of enrollment and recorded on the orthoptic examination form were used in its place. The self-reported history at the time of the orthoptic examination was often combined with the response provided to the research assistant, to answer the question "Do you have strabismus or a condition associated with strabismus?"

d) The source of the data used to answer the self-reported question regarding strabismus was indicated as the "participant questionnaire," "orthoptic examination and verbal report at enrollment," or the "orthoptic examination" alone.

e) The age at the time of enrollment or orthoptic examination was calculated.

f) After reviewing the age at the time of enrollment, educational level and family tree, it was retrospectively determined whether the patient or a parent had completed the questionnaire. It was assumed that all of those 18 years and older completed their own report. If a parent completed the report on behalf of the child, their education level was entered. If both parents were present, they most often worked together to complete each child's questionnaire, and so the highest education level of either parent was indicated.

g) For those diagnosed with CCS on the orthoptic examination, the deviation measured in prism diopters was recorded. The largest deviation was chosen from primary position at near or distance with or without optical correction if worn by the participant.

The following data were submitted for statistical review.

a) ID: Specifically the new ID assigned to the *Strabismus Self-Reporting Accuracy Study* participants.
b) Affection status: Affected status as determined by the orthoptic screening.
c) Diagnosis: Ophthalmic diagnosis of the participant as determined by the orthoptic screening.
d) Maximal size of the deviation in prism diopters.
e) Self-reported status: Affected status as reported by the participant.
f) Self or parental: Whether it was truly self-reported or reported by a parent.
g) Type of report: The source of the self–report.
h) Sex: Of the participant.
i) Education: The educational level of the participant if self reported. If reported by a parent, their educational level was recorded.

2.8 Statistical Analysis

To determine the accuracy of self-reported strabismus, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) with 95% confidence intervals (CI) were calculated. Sensitivity, specificity, PPV and NPV were calculated using the following parameters: True positive (TP), defined as those that have strabismus as determined by the orthoptic examination, and who correctly identified themselves as having strabismus by their self-report; False positive (FP), defined those that self-reported strabismus but were not found to have strabismus on the orthoptic examination; True negative (TN), defined as those that do not have strabismus as determined by the orthoptic examination, and who correctly identified themselves as not having strabismus by their self-report; False negative (FN), defined as those that self-reported not having strabismus, but were found to have strabismus on the orthoptic examination. Sensitivity was calculated as: Sensitivity = TP / (TP + FN). Specificity was calculated as: Specificity = TN / (TN + FP). PPV was calculated as: PPV = TP / (FP + TP). NPV was calculated as: NPV = TN / (FN + TN). The overall accuracy was calculated as: Accuracy = TP + TN / (TP + TN + FP + FN). Misclassification was calculated by subtracting the overall accuracy from 100.

Prevalence of strabismus and prevalence of reduced stereoacuity were estimated by percentage with 95% CI using the proc FREQ procedure within Statistical Analysis Software (SAS) to provide descriptive statistics, and to create frequency and cross-tabulation tables.

Factors considered to potentially influence the accuracy of the self-report, such as educational background, sex, direction of the deviation, size of the deviation, and the control of the deviation, were tested by Fisher's exact test. All tests were two-sided, with the type I error set at 0.05. Multivariate logistic regression was used to evaluate the simultaneous effects of these multiple factors to the probability of positive self-reports in affected patients. All analysis was conducted using SAS (Statiscal Analysis Software 9.2, North Carolina).

CHAPTER 3 RESULTS

3.1 Overview of Participants

Detailed results of the participant data obtained for the *Strabismus Self-Reporting Accuracy Study* from July 1, 2005 through August 31, 2010 are presented in **Table 1**. Of the 1990 family members enrolled in the *Genetics of CCS Study* during this time, 876 had orthoptic examination data. Of these, 185 were either patients within the Ophthalmology Department at Children's Hospital Boston, or had brought outside eye examination records that were entered into the Progeny Genetics database in lieu of completing an orthoptic examination. Another 7 participants were excluded because they had a structural eye problem (i.e., orbital tumor, macular degeneration, anomalous optic nerve, etc.) and 13 participants were excluded as the orthoptic examination could not conclusively determine whether they were affected or unaffected (i.e., patient cooperation, monovision and trial lenses were unavailable, or equipment failure). This left 671 participants who met inclusion criteria. The age of enrolled family members ranged from under one year up to 84 years, with a mean of 33.9 years (standard deviation 16.8 years). Of these 671 participants, 83 (12.4%) reported having strabismus, or an associated condition, and 572 (85.3%) reported not having strabismus. The remaining 16 individuals (2.4%) reported they were uncertain whether or not they had strabismus.

The orthoptic examination diagnosed 135 participants (20.1 %) with a form of CCS and 162 (24.1%) with a SAC. By orthoptic examination, the remaining 374 patients (55.7%) were unaffected with strabismus or a SAC.

In 143 cases (21.3%), a proxy made the self-report. The proxy reports agreed with the orthoptic examination in 77.5% of cases. The remaining 528 self-reports (78.7%) had no proxy. The self-report was obtained entirely from the participant questionnaire for 454 participants (67.7%), from a combination of the orthoptic examination and verbal report at enrollment in 188 (28.0%), and entirely from the orthoptic history in 29 (4.3%). Of note, when self-reports were available from multiple sources, there were 19 discrepancies between the reports. Therefore, when comparisons could be made between different reports they were in agreement 95.8% of the time.

The majority of participants, 429, were female (63.9%). Almost 60% of participants had a college education, and of those participants approximately half, or 29.5% of the total population had a graduate or professional education. For the remaining participants, 10.4% had a high school education, 2.8% had some college education and 0.3% had a grade school education. The educational background question was not answered by 27.7% of participants.

Most of the 671 participants were Caucasian (80.8%). Other races selected on the questionnaire were ‘Black, Non-Hispanic’ (5.1%), ‘Hispanic’ (4.2%), ‘Asian or Pacific Islander’ (2.5%), and ‘Native American or Alaskan’ (0.3%). The remaining participants

described themselves as ‘Unknown’ (4.5%) or ‘Other’ (1.1%) while 1.6% did not record a response.

Table 1: *Strabismus Self-Reporting Accuracy Study* participant data (N = 671). CCS, comitant congenital strabismus; SAC, strabismus-association condition.

		Number (n)	Percent (%)
Self-report status	Affected with Strabismus	83	12.4
	Unaffected with Strabismus	572	85.2
	Uncertain	16	2.4
Orthoptic examination status	Affected CCS	135	20.1
	Affected SAC	162	24.1
	Unaffected	374	55.7
Type of report	Participant Questionnaire	454	67.7
	Enrollment and Examination	188	28.0
	Examination	29	4.3
Actual self-report	Yes	528	78.7
	Proxy (parental)	143	21.3
Sex	Female	429	63.9
	Male	242	36.1
Education	Grade school	2	0.3
	High school	70	10.4
	Some College	19	2.8
	College or University	198	29.5
	Graduate or Professional	196	29.2
	Not recorded	186	27.7
Race	White, Non Hispanic	542	80.8
	Black, Non Hispanic	34	5.1
	Hispanic	28	4.2
	Asian or Pacific Islander	17	2.5
	Native American or Alaskan	2	0.3
	Other	7	1.0
	Unknown	30	4.5
	Not recorded	11	1.6

3.2 Self-Report Data

The orthoptic diagnoses of the 83 participants with self-reported strabismus (as determined by the orthoptic examination) are presented in **Table 2**. Only 6% of those who reported strabismus had no detectable CCS or SAC and had not reported surgical correction of strabismus or had any signs of prior strabismus surgery.

Table 2: The orthoptic examination diagnosis of those that reported 'yes' when asked whether they were affected with strabismus.

Status	Number (n)	Percent (%)
Affected with CCS	63	75.9
Affected with SAC	15	18.1
Unaffected	5	6.0
Total	83	100.0

The orthoptic status of the 572 participants who reported that they did not have strabismus is presented in **Table 3**. Of these, 37.1% had either CCS or SAC.

Table 3: The orthoptic examination diagnosis of those that reported 'no' when asked whether they were affected with strabismus.

Status	Number (n)	Percent (%)
Affected with CCS	67	11.7
Affected with SAC	145	25.4
Unaffected	360	62.9
Total	572	100.0

Table 4 shows the 16 participants that were uncertain of whether or not they had strabismus or an associated condition. Of these participants 6 individuals or 31.2% had CCS, while another 12.5% had a SAC. The remaining 56.2% were unaffected.

Table 4: The orthoptic examination diagnosis of those that reported they were 'uncertain' when asked whether they were affected with strabismus.

Status	**Number (n)**	**Percent (%)**
Affected with CCS	5	31.25
Affected with SAC	2	12.5
Unaffected	9	56.25
Total	16	100.0

The specific strabismus phenotypes of those diagnosed with CCS are detailed in **Table 5**. This includes the 63 participants affected from **Table 2**, the 67 from **Table 3** and the 5 from **Table 4**.

Table 5: Comitant congenital strabismus phenotypes in the study population. The first five diagnoses, esotropia or esophoria, describe deviations where one eye turns inward. Exophoria, intermittent exotropia and exotropia describe deviations where one eye turns outward. Microstrabismus or monofixation syndromes are small angle deviations, and strabismus surgery (unknown diagnosis) describes participants that reported a history of strabismus surgery, but are unaware of which direction their eye originally turned.

Comitant Congenital Strabismus	**Number (n)**	**Percent (%)**
Accommodative Esotropia	1	0.7
Esophoria	13	9.6
Esotropia	23	17.0
Infantile Esotropia	4	3.0
Intermittent Esotropia	19	14.1
Exophoria	31	23.0
Intermittent Exotropia	21	15.6
Exotropia	5	3.7
Microstrabismus or Monofixation syndrome	9	6.7
Strabismus surgery (unknown diagnosis)	9	6.7
Total CCS Affected	135	100

Table 6 includes the breakdown of those diagnosed with a SAC and their specific phenotype as determined by the orthoptic examination. The most common condition associated with strabismus in our study population was decreased stereopsis (87%). This was distantly followed by anisometropia (8%) and high hyperopia (2.5%).

Table 6: Specific strabismus-associated conditions in the study population. Anisometropia and high hyperopia are refractive conditions and decreased stereopsis implies subnormal binocular vision.

Strabismus-Associated Conditions	Number (n)	Percent (%)
Anisometropia	13	8.0
Anisometropia & Decreased stereo	2	1.2
High hyperopia	4	2.5
High hyperopia & Decreased stereo	1	0.6
Decreased stereo	141	87.0
Cranial nerve IV palsy*	1	0.6
Total SAC Affected	162	100

*Participant diagnosed with congenital cranial nerve IV palsy. Excluded from CCS definition, therefore placed in SAC category for the purpose of this study. For the *Genetics of CCS Study*, has been diagnosed with incomitant congenital strabismus (ICS).

3.3 Accuracy of Self-Reports

When self-reports for participants diagnosed with CCS were analyzed and compared to the gold standard orthoptic examination, the sensitivity was 48.5% and the specificity was 98.6%. The positive predictive value was 92.6% and the negative predictive value was 84.5%. When the analysis was expanded to include those diagnosed with either CCS or a SAC, the sensitivity decreased to 26.9% and specificity remained at 98.6%. The positive and negative predictive values were 94.0% and 62.9% respectively. A summary of these data points can be viewed in **Table 7**.

Table 7: The accuracy of self-reports of the presence of strabismus. CCS, comitant congenital strabismus; SAC, strabismus-associated condition; DS, decreased stereopsis.

	CCS	CCS + SAC	CCS + (SAC - DS)
Sensitivity (%)	48.5	26.9	49.0
Specificity (%)	98.6	98.6	98.6
PPV (%)	92.6	94.0	93.5
NPV (%)	84.5	62.9	82.8

When the 'uncertain' self-reports are excluded, almost half of those affected with CCS (48.5%) are aware they have strabismus, but only 9.4% of those with a SAC are aware of their status. However, though it is possible that participants might be aware that they have strabismus or one of the associated condition such as high hyperopia or anisometropia, its less likely that they would know they have decreased stereopsis. For this reason, and considering the large percentage of patients who were considered to have a SAC as a result of decreased stereopsis, the analysis was repeated after excluding those with decreased stereopsis from the SAC group. The adjusted analysis including sensitivity, specificity, positive and negative predictive values can be viewed in the last column of **Table 7**. Again disregarding the 'uncertain' self-reports, the adjusted analysis revealed that only 4.2% of those with decreased stereopsis reported having strabismus or a condition associated with strabismus. This was significantly different from the rest of those in the SAC group where 52.9% were aware that they had strabismus or an associated condition, and 48.5% in the affected group that knew they had strabismus ($p<0.001$, Fisher's exact test). There was no significant difference between the SAC group (excluding those with decreased stereopsis) and those with CCS ($p=0.80$, Fisher's exact test) as about half of each group was aware of their status.

A graph illustrating the awareness level of participants in the various categories can be seen in **Figure 1**.

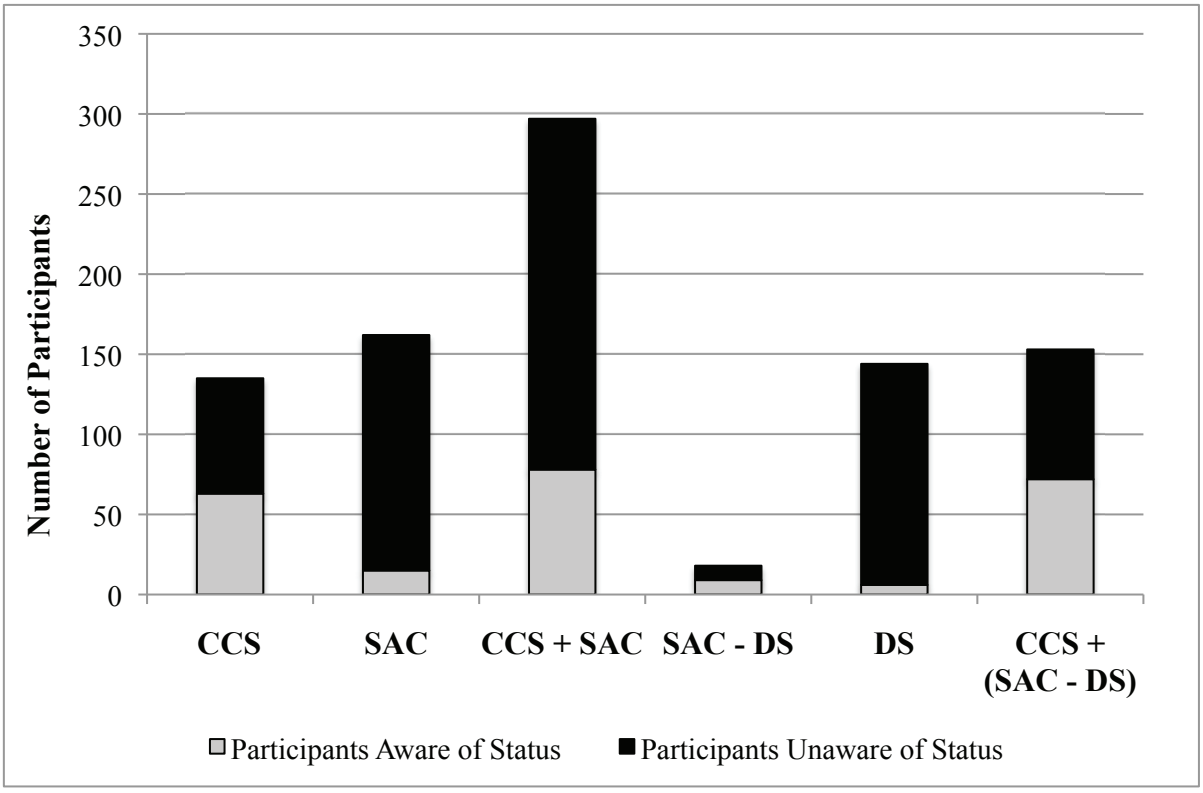

Figure 1: Awareness of self-reported strabismus in patients with or without CCS and SAC. CCS, comitant congenital strabismus; SAC, strabismus-associated condition; DS, decreased stereopsis. The black and grey bars combined represent the total number of participants.

3.4 Other Factors Related to Accuracy of Self-Report

In the study population 20.1% of participants were diagnosed with CCS; however, CCS was diagnosed in significantly more males (26.4%) than females (16.5%), (p=0.002, Fisher's exact test) as shown in **Table 8**. When sex was compared for accuracy of self-

report (reports made by proxies were excluded), sensitivity, specificity and positive predictive value did not differ significantly between males and females. The negative predictive value of self-reported strabismus was significantly higher in females (87.3%) than in males (70.3%), ($p<0.001$, Fisher's exact test), indicating that males were less likely than females to be aware of strabismus when it was present, even though they were more likely to be affected.

In the study population, 24.1% of participants were diagnosed with a SAC. While slightly more female participants (26.1%) than male participants (20.7%) were diagnosed with a SAC, this difference was not significant ($p=0.14$, Fisher's exact test, and there was no significant difference in sensitivity, specificity, positive or negative predictive value). The combined CCS + SAC prevalence was 47.1% for males and 42.7% for females, again not significantly different ($p=0.26$, Fisher's exact test, and no difference for sensitivity, specificity, positive or negative predictive value).

Table 8: Sex and the prevalence of strabismus and associated conditions. CCS, comitant congenital strabismus; SAC, strabismus-associated condition

	Female (%)	**Male (%)**	**P-value**
CCS	16.5	26.4	0.002
SAC	26.1	20.7	0.14
CCS+SAC	47.1	42.7	0.26

Self-reporting accuracy of participants with a high school education was compared with the accuracy of those with college or university education and above (**Table 9**.) No significant difference was found in these two groups; education was therefore not felt to be a factor in the accuracy of self-reported strabismus in our study population.

Table 9: The accuracy of self-reports with education as a factor.

	High School	College and Above	P-value
Sensitivity (%)	50.0	57.1	0.55
Specificity (%)	98.0	98.6	0.56
PPV (%)	91.7	93.6	1.00
NPV (%)	81.7	86.9	0.30

The self-reporting accuracy of participants with inward deviations (esotropia, intermittent esotropia, esophoria and accommodative esotropia) was compared with the accuracy of those with outward deviations (exotropia, intermittent exotropia, exophoria). Participants with prior strabismus surgery were excluded from this analysis, as the current direction of deviation may not match the original deviation. Of those affected, 32 had prior surgery, leaving 103 available for review. The participants with an inward deviation were significantly more likely to know that they had strabismus than those with an outward deviation (**Figure 2**.) Of those with an inward deviation, 47.4% were aware that they had strabismus while only 17.6% of those with an outward deviation were aware (p=0.0026, Fisher's exact test).

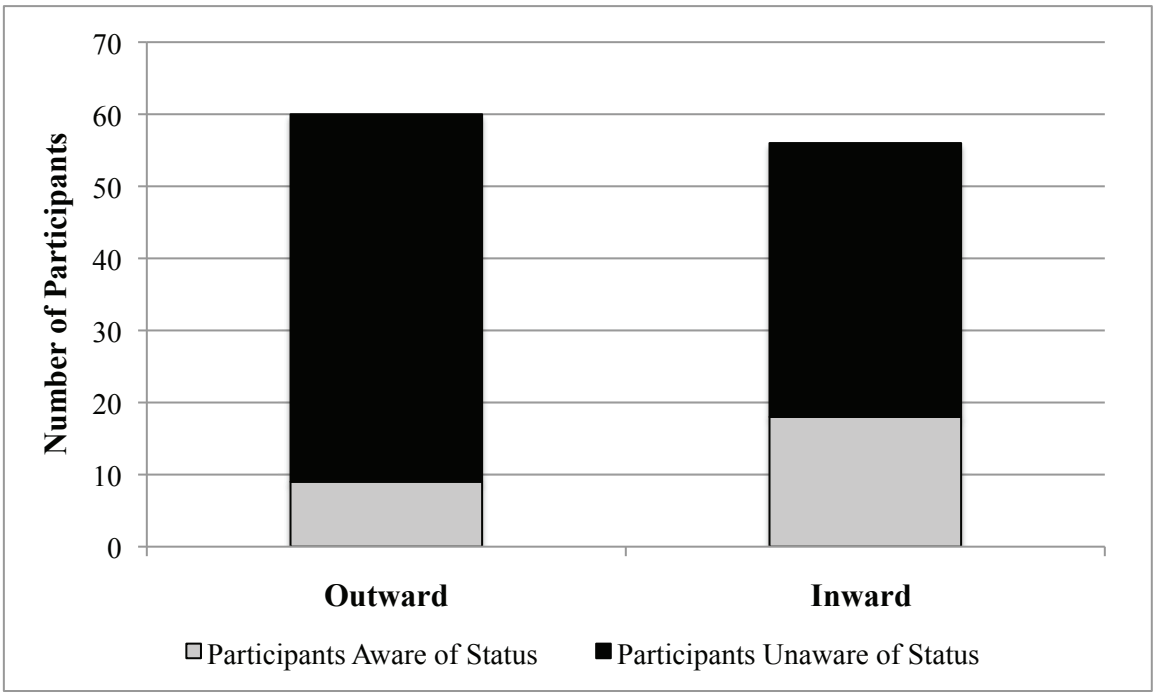

Figure 2: Comparison of participant awareness of strabismus with inward and outward deviations (p=0.0026, Fisher's exact test). The black and grey bars combined represent the total number of participants.

The size of the deviation was also examined as a potential factor influencing the accuracy of self-reported strabismus. Of those affected with strabismus, the magnitude of the ocular misalignment ranged from 0 prism diopters for those with a microstrabismus or monofixation syndrome up to 70 prism diopters. Again, those with previous strabismus surgery were excluded from this analysis as well as one patient whose deviation could not be accurately measured due to limited cooperation, leaving 102 participants to review. The groups were sub-divided at 15 prism diopters based on evidence from studies that strabismus is cosmetically apparent at approximately 12.5 – 15 prism diopters (Larson, Keech, & Verdick, 2003; Reinecke, Sterling, & Wizow, 1991; Weissberg, Suckow, & Thorn, 2004). Of those with a deviation less than 15 prism diopters, 25.4% (16 of 63

participants) were aware that they had strabismus (**Figure 3**). Significantly more participants with a deviation of 15 prism diopters or more 48.6% (17 of 35 participants) were aware of their strabismus (p=0.002, Fisher's exact test).

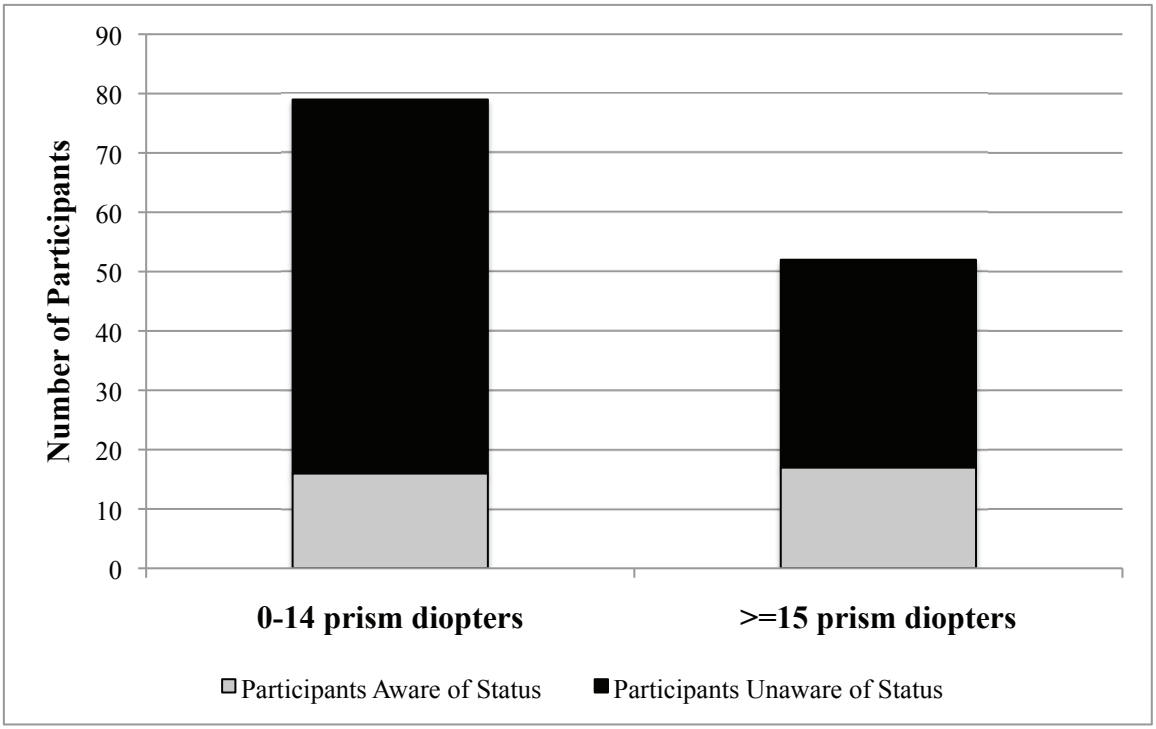

Figure 3: Self-reporting accuracy based upon the angle of strabismus (p=0.002, Fisher's exact test). The black and grey bars combined represent the total number of participants.

The clinical literature is supported in this study using a receiver operating characteristic (ROC) curve. The ROC curve utilizes sensitivity and specificity of the self-report along with the related indices, true positives and false positives. All possible measurements of the angle of strabismus, i.e., 0 through 65 prism diopters were employed in this analysis to determine which measured angle of strabismus yields the highest proportion of true positives with the lowest proportion of false positives. The ROC curve suggests 15 prism diopters as the cut point where the patients with larger angle had highest positive self-

report rate and the patients with smaller angle had the highest negative self-report rate.

Figure 4 shows the cut off at 15.

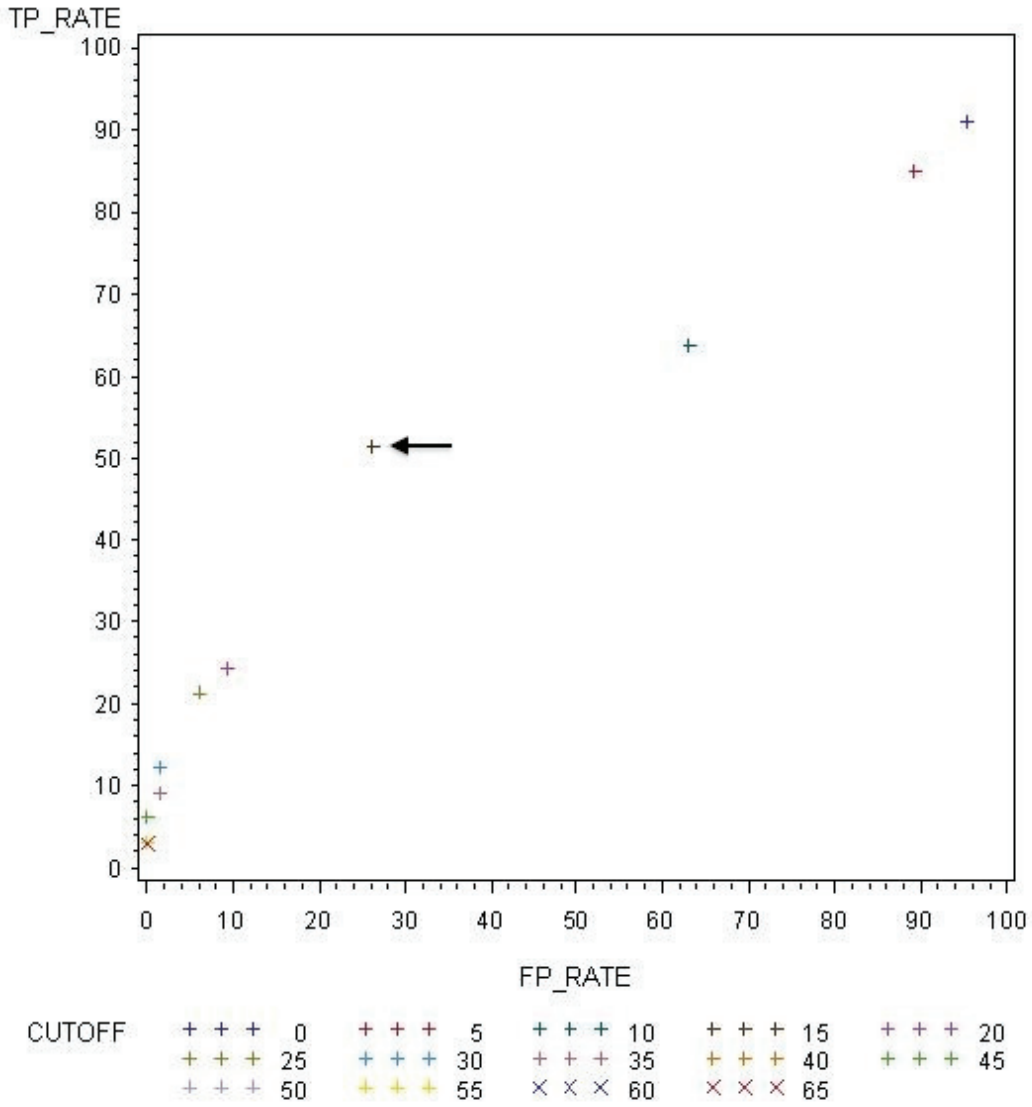

Figure 4: The ROC analysis of self-report accuracy and the angle of strabismus. TP_RATE is the percent of positive self-reports from patients with larger angle than the cut point, and FP_RATE is the percent of negative self-reports from patients with larger angle than the cut point. The cut point of 15 prism diopters is indicated with an arrow.

As anticipated, participants with a manifest deviation (esotropia and exotropia) were much more aware of their strabismus (52.1%) than those with a latent deviation (esophoria and exophoria) (4.9%, $p<0.001$, Fisher's exact test, **Figure 5**). Only the 103 participants who had not had prior strabismus surgery were included.

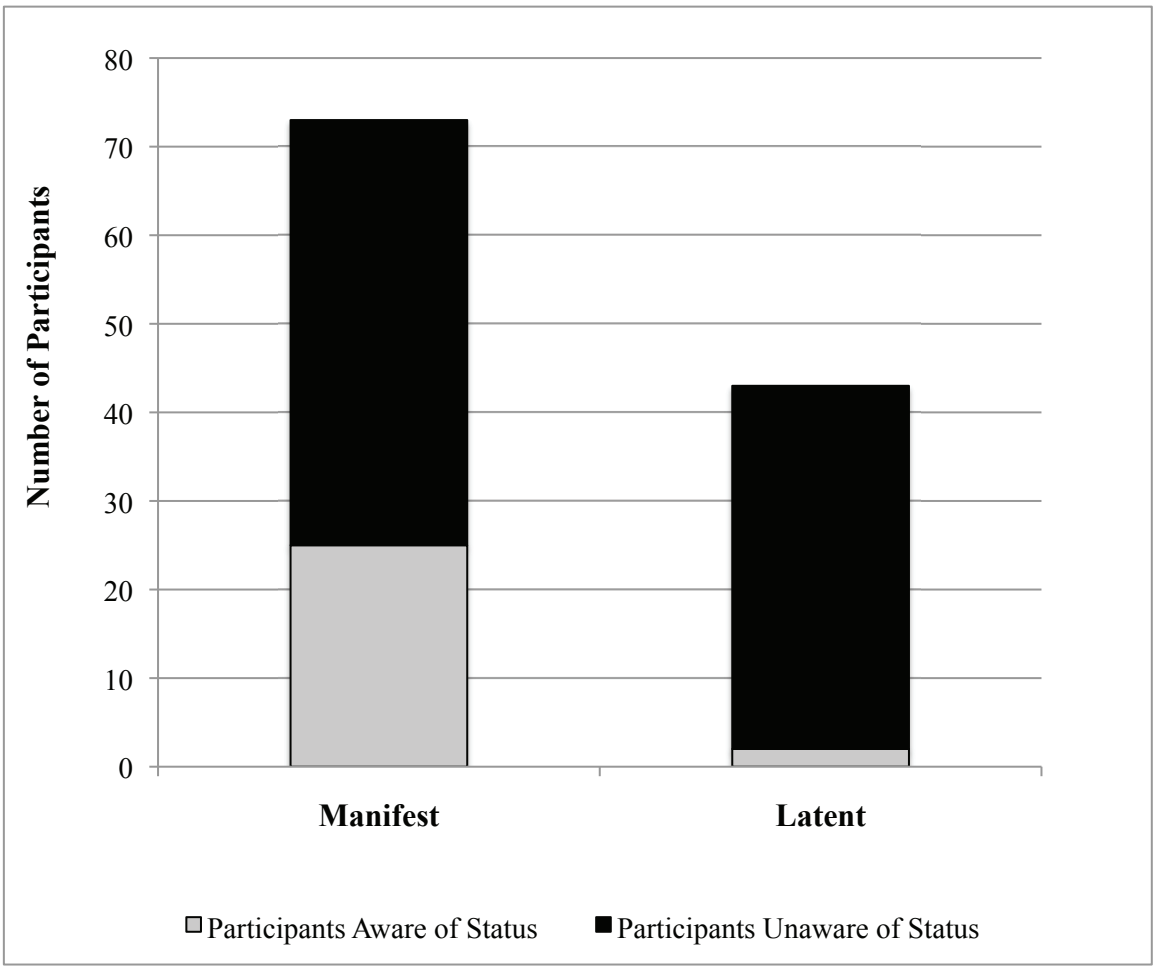

Figure 5: Self-reporting accuracy of latent vs. manifest deviations ($p<0.001$, Fisher's exact test). Manifest indicates a constant misalignment of the eyes, while latent implies that the deviation is controlled.

Multivariate logistic regression was used to control for overlapping contributions of related factors to the self-perception of strabismus. This allowed for a more accurate

interpretation of the true contribution of specific factors. After multivariate analysis, direction of the deviation (OR = 3.66, p = 0.021, multivariate logistic regression) and control of the deviation (OR = 19.61, p = 0.0002, multivariate logistic regression) remained significant factors.

CHAPTER 4 DISCUSSION

4.1 SELF-REPORTED ACCURACY

4.1.1 Comitant Congenital Strabismus

The main objective of this study was to determine the accuracy of self-reported strabismus in the population of subjects enrolled in the comitant congenital strabismus (CCS) study. It was determined that the overall accuracy of self-reported strabismus, as ascertained by gold standard orthoptic examination, was 85.5%. The accuracy can be further analyzed by looking at the data from two perspectives: based of the orthoptic examination results, or based on the self-report.

The results of the orthoptic examination reveal that *specificity* of self-reporting was high indicating that when an orthoptic examination determined that a participant did not have strabismus, 98.6% of the participants correctly reported that they were unaffected. However, the *sensitivity* was much lower, indicating that when orthoptic examination determined that the participant has strabismus, only 48.5% of the individuals correctly self-reported their affected status. This is further revealed when analyzed from the perspective of the participant's self-report. If an individual in this study reported that they had strabismus, there was a 92.6% chance that they were correct. If an individual reported that they did not have strabismus, there was an 84.5% chance that they were

correct. The negative predictive value of 84.5% was higher than the sensitivity because of the low prevalence of strabismus. That is, even though many of the participants incorrectly reported their condition, the prevalence of strabismus in the population is low that a random guess of "no strabismus" would usually be correct. The practical result of this study is that if affected status were gathered solely by self-report, 14.5% of participants would be classified incorrectly.

4.1.2 Strabismus-Associated Conditions

The genetic factors that contribute to the development of strabismus are likely to contribute to the presence of strabismus-associated conditions (SAC). For a genetic study that relies on self-reporting, it is therefore essential to know whether those with a SAC are aware of their affected status. Again, from the perspective of the orthoptic examination, the *specificity* of self-reported SAC remained high at 98.6%, indicating few false reports were given when the orthoptic examination determined that participants did not have a SAC. However the *sensitivity* of self-reported SAC was only 26.9%. When this is combined with the somewhat higher prevalence of SAC in the population, the negative predictive value was only 62.9%. That is, of those with CCS, 48.5% knew that they were affected, while only 9.4% of those with a SAC were aware. The misclassification rate of self-reporting for the combined CCS and SAC participants would be 33.1%.

Aside from those previously diagnosed and treated for strabismus, it is reasonable to assume that some participants would know or suspect that they have strabismus, based not only on physical appearance, but also due to functional symptoms or consequences that they might experience. For instance, individuals may be aware of a fixation preference (one eye with better visual acuity than the other) or an inability to appreciate 3D technology. Similarly, those with glasses are aware of their condition, and may admit to having one eye that is stronger or better than the other due to unequal refractive error. Though it may be reasonable to expect these individuals know or suspect they have strabismus or a refractive condition, it is much less valid to assume participants would have knowledge of their level of stereoacuity. To determine just how important a factor stereoacuity was to the SAC data, the accuracy of the self-reports was re-examined after excluding those with decreased stereopsis from the affected participants. The remaining SAC participants had refractive conditions associated with strabismus; anisometropia, high hyperopia, and (in one case) congenital cranial nerve IV palsy. In this group, 52.9% reported that they were affected, confirming that poor self-knowledge of stereoacuity contributed to the low accuracy of self-reporting of SAC overall. Despite this, stereoacuity remains an important SAC to consider in patients with strabismus, and therefore for the remainder of the analysis, participants with reduced stereopsis were included.

4.2 Implications for Genetic Studies

The implications of these findings are essential to the *Genetics of CCS Study* and other studies of strabismus that consider self-report as a means to determine affected status in the place of clinical examinations. In the *Genetics of CCS Study*, if only DNA from the proband is used, no misclassification will exist as all probands received eye examinations. However if self-report is relied upon for family members, and trios or linkage analysis is completed, misclassification is induced. The Power for Association With Errors (PAWE) software (Buyske, Yang, Matise, & Gordon, 2009; Gordon, Finch, Nothnagel, & Ott, 2002; Gordon, Levenstien, Finch, & Ott, 2003) was used to quantify the consequences of these misclassifications. Considering the misclassification rate of approximately 15%, and using a prevalence of 4%, a study relying exclusively on self-reported affected status would have a 16% loss of statistical power. To compensate for this loss, an increased sample size is required, with consequences on a logarithmic scale. These results justify the extra time and expense required to perform orthoptic evaluations to confirm the affected status of every participant in a genetic study.

4.3 Factors Influencing Accuracy

Possible predictors of accurate self-report were examined. The educational background of the participant or proxy and the sex of those making the self-report were evaluated. Additionally, characteristics of strabismus such as the direction, size, and constancy (or control) were examined as potential influencing factors.

Previous studies of self-report accuracy have examined the impact of educational background. Christen and colleagues (1994) reported that adult male physicians with cataract did not demonstrate 100% agreement between self-report and their personal medical records. In fact, when the definition of a cataract was extended to include lens changes that impaired visual acuity to 20/30 or worse, there was only 50% correlation between report and medical records (Christen et al., 1994). In contrast, Bowie and colleagues (2003) determined that the educational background of the respondent influenced the accuracy of proxy-reported cataract. Those with a high school education or higher were better able to accurately report whether a sibling was diagnosed with a cataract (Bowie et al., 2003); however, they did not consider whether education was a factor in an individual's self-report. In the present study, educational background was not a predictor of accuracy of strabismus self-report. This may be due to the nature of strabismus. Participants know their status based on symptoms or observation. This knowledge is not dependent on level of education. It must be noted that this finding may be limited, as nearly 30% of our participants did not report their educational level. It is not possible to determine whether participants intentionally omitted this information, but if those with lower educational levels intentionally chose not to report, the results might have been influenced.

The sex of the participant had little impact on the accuracy of self-report. Negative predictive value was the only significant finding as more female participants were able to successfully identify themselves as not having strabismus than male participants, despite

a significantly higher prevalence of CCS in males than females in this study. When only the cosmetic impact of strabismus is considered, the psychosocial literature may help explain why females accurately report that they do not have strabismus. Durnian and colleagues (2010) reported that female patients scored lower on a strabismus quality of life questionnaire than males (Durnian, Owen, Baddon, Noonan, & Marsh, 2010). They attributed this to social and media pressure placed on women and the idealized picture of facial 'beauty'. Facial beauty is often attributed to the symmetry of one's appearance, and this symmetry is affected when a noticeable strabismus compromises the ocular alignment of the non-fixing eye (Durnian, Noonan, & Marsh, 2011). Because of this social pressure, females may spend more time analyzing their appearance and checking for any asymmetry. If more acutely aware of their appearance, they may more definitively state that they do not have strabismus than males, who may less intensely scrutinize their appearance. Though the Durnian study takes the patients' own perception and experience into account, there is also evidence that others judge females with strabismus more harshly than males with strabismus in terms of finding employment as well as promotions (Coats, Paysse, Towler, & Dipboye, 2000; Goff, Suhr, Ward, Croley, & O'Hara, 2006; Mojon-Azzi SM & Mojon DS, 2009).

The direction of the strabismus also significantly influenced the accuracy of self-reporting. In this study, nearly half or 47.4% of those with an inward deviations, or esotropia, were aware that they had strabismus, while less than 20% or 17.6% of those with outward deviations, or exotropia were aware that they were affected with strabismus. The role of the direction of strabismus in its detection is controversial in the

literature. Larson and colleagues (2003) found that esotropia and exotropia were equally detectable by both lay and experienced examiners (Larson et al., 2003), and both esotropic and exotropic patients appear to be equally bothered by their strabismus or encounter equal amounts of social bias (Durnian et al., 2010; Nelson, Gunton, Lasker, Nelson, & Drohan, 2008). Additional studies have shown that exotropia is easier for both lay and experienced examiners to detect (Reinecke et al., 1991; Weissberg et al., 2004) and people with exotropia encounter more social bias (Mojon-Azzi SM & Mojon DS, 2009; Mojon-Azzi, Potnik, & Mojon, 2008). The findings are in contrast to those of Goff (2006) and Olitsky (1999) who reported that those with esotropia are discriminated against more often (Goff et al., 2006; Olitsky et al., 1999), and that despite nearly equal quality of life scores, people with esotropia felt that others underestimated their intelligence more often than people with exotropia.

Besides direction, the magnitude and constancy of the strabismus are also associated with awareness of affected status. The size of the deviation significantly affected the accuracy of self-reported strabismus. Those with a small angle deviation (less than 15 prism diopters) were aware that they were affected 25% of the time while closer to 50% were aware when the angle of deviation was 15 prism diopters or greater. The 15 prism diopter mark, which was the cutoff point determined by an ROC analysis of the CCS cohort in this study, is supported in the literature as the angle when both esotropia and exotropia are cosmetically recognized (Larson et al., 2003; Reinecke et al., 1991; Weissberg et al., 2004). Intuitively, it makes sense that those diagnosed with larger deviations would be more likely to be aware of their strabismus, as larger deviations would be more apparent

to the individual as well as others around him or her. A limitation of this study is that the largest deviation measurement in prism diopters was used for the analysis whether at near or distance, with or without optical correction. The reasoning behind this approach was that individuals look at themselves from all angles, and with and without glasses or contact lenses. However, perhaps a standard distance should have been used such as the near measurement used by Jackson and colleagues (2006), or the distance measurement as used by Nelson and colleagues (2008) (Jackson et al., 2006; Nelson et al., 2008).

Similarly, constancy of deviation has a large impact on the accuracy of self-reported strabismus. As anticipated, participants with a manifest or constant deviations were more aware of their affected status (50% of cases) than those with a phoric or latent deviation (5% of cases). By definition, latent deviations would be less symptomatic as they are rarely or never present, compared to those with manifest deviations that are constantly present. The psychosocial literature helps explain why those with manifest and large angle strabismus may more accurately self-report their strabismus. Studies have shown that these individuals are more likely to have cosmetically noticeable strabismus and are more likely to encounter bias in society. The emotional impact associated with this bias would likely result in greater recall, even in those who may no longer manifest strabismus. Even those were treated for amblyopia as a child may self-report more accurately, as amblyopia treatment alone has been found to affect self-esteem and create distress (Hrisos, Clarke, & Wright, 2004; Koklanis, Abel, & Aroni, 2006).

Sixteen participants (2.4 %) reported that they were uncertain whether or not they had strabismus. Of these, 31.2% had CCS, while another 12.5% had a SAC. The remaining 56.2% were unaffected. It is possible that the unaffected participants who self-reported strabismus (or were uncertain) may have "outgrown" their strabismus and thus were no longer suffering from strabismus symptoms including the psychosocial bias. However, those who were affected with CCS or a SAC on orthoptic examination may have only suspected that they had a condition but never had this confirmed by a health care professional. For this reason perhaps they were reluctant to report 'yes' when asked if they had strabismus or a SAC.

4.4 Prevalence of Strabismus and Reduced Stereoacuity

The prevalence of strabismus in family members in the present study was 20.1%. This is comparable to what has been found in other studies of familial strabismus, which have ranged from 9% in first-degree relatives (Hu, 1987) to 30-40% if one or both parents are affected (Richter (1967) cited in (Young & Khazaeni, 2005)). Additionally, the prevalence of decreased stereopsis in the present study was 21.5%. The prevalence of stereopsis has been measured in few studies. Cantolino and von Noorden (1969) reported a rate of 'sensory and motor anomalies' of 54% and microstrabismus of 7.6% in the family members of patients with microstrabismus (Cantolino & Von Noorden, 1969). Scott and colleagues found a prevalence of microstrabismus of 9% in families of patients with congenital esotropia (Scott et al., 1994).

CCS was diagnosed in significantly more males (26.4%) than females (16.5%), despite males being less aware that they have strabismus. Studies investigating the prevalence or genetics of strabismus do not report prevalence based on sex, though some studies report on sex differences in specific strabismus subtypes. Donnelly and colleagues (2005) observed that male participants had a higher prevalence of fully and partially accommodative esotropia as well as astigmatic anisometropia than their female counterparts. However, the female participants were more likely to be diagnosed with exotropia or intermittent exotropia (Donnelly, Stewart, & Hollinger, 2005). The finding that intermittent exotropia was more prevalent in females was also reported by Nusz and colleagues (2005). Though an X-linked dominant inheritance pattern would explain why nearly twice as many females were affected as males, the authors recognized that such a simple inheritance pattern is highly unlikely, and could only be considered if other factors such as lyonization, incomplete penetrance, or environmental influence on the genes involved. Nusz et al. considered the unlikely possibility that the increased female prevalence was observed because parents sought out treatment more frequently for their daughters than for their sons (Nusz, Mohney, & Diehl, 2005).

In a study of patients with congenital esotropia and their parents, Scott and colleagues found that fathers had primary monofixation syndrome more often than mothers (12% versus 1.5%, respectively), while mothers had esotropia more often than fathers (12% versus 6%, respectively). They postulated that perhaps a higher number of abnormal genes were needed in the male than in the female to produce esotropia, while fewer genes were required to cause monofixation syndrome (Scott et al., 1994). The association

between strabismus and decreased stereopsis or monofixation syndrome in family members has not been noted in any other studies investigating the genetic cause of strabismus. Population and clinic based studies have had mixed data on sex differences in strabismus. It may be of interest for further study to examine whether any sex bias occurs in familial strabismus, particularly whether any difference occurs regarding specific types of strabismus.

4.5 Study Limitations

4.5.1 Population

The study population for the present study was not representative of the general population. To discover disease-associated genes, populations enriched with characteristics of the disease are frequently recruited (Antoniou & Easton, 2003). The present study is a subset of the *Genetics of CCS Study*, in which at the minimum, one family member by definition had CCS or a SAC, and thus introduced bias into the study population. In order to be enrolled, participants were required to have a family member diagnosed and currently being treated for strabismus or an associated condition, by a pediatric ophthalmologist. This biased the study population in two ways. First, it is expected that these family members would have more knowledge of strabismus than the general population and therefore might be more aware of their own status. Second, there is an increased prevalence of strabismus in our population as participants all had a positive family history. This means that our participants were more likely to have

strabismus than the general population, and also more likely to be aware that they had strabismus. Beyond the *Genetics of CCS Study* these results will be informative for any similar populations assembled for genetic or clinical research in strabismus. However, it should be cautioned that these results cannot be applied to the general population.

4.5.2 Questionnaire

The questionnaire used reflected questions typically used during a clinical encounter and as such was not validated. This questionnaire primarily identified those with strabismus. Questions were asked about related conditions such as amblyopia and refractive errors, however, specific questions such as "do you have difficulty with depth perception" or "do you have reduced depth perception" were not asked. Though questions regarding binocularity and stereoacuity may be difficult to answer, these questions should be added to future questionnaires in order to fairly evaluate participant knowledge of these functions or characteristics. Perhaps careful wording to determine whether there is an actual problem with the binocular perception of depth versus fine or gross motor delays and incorporating questions about 3D technology may be helpful.

In many cases it was clear either that both parents completed the questionnaire together or that only one parent was available. However it was not always clear which parent completed the questionnaire, or if both parents contributed to the answers. Future questionnaires should also include the relationship of all individuals who contributed to completing the questionnaire.

This study has led to modifications and additions to the *Genetics of CCS* questionnaire.

4.5.3 Ophthalmic examination

A complete ophthalmic examination was not administered as part of the *Genetics of CCS Study*. In its place a brief orthoptic examination was used to screen for and diagnose strabismus. It is possible that by only completing sensorimotor exams, an ocular disease unknown to the participants could be secondarily causing strabismus or a SAC. This risk of this is low, and was considered acceptable to the study design. Though the orthoptic examination administered by experienced clinical orthoptists was considered the gold standard, there is a chance that strabismus could have been misclassified in some cases.

4.5.4 Refractive status

The most common problem encountered at the ophthalmic examinations was that participants who wore glasses did not have their glasses with them, and those wearing contact lenses were unaware of the strength of their lenses. Additionally, several participants had undergone refractive or cataract surgery, in which case we were unable to determine their original refractive status. This may have lead to under-coding of refractive conditions such as high hyperopia or anisometropia.

Autorefractions were completed for ease and speed as well as to attract as many participants as possible. Cycloplegic refractions (or cycloplegic autorefractions) would have been ideal, as recent research has shown that there is a significant difference between cycloplegic and manifest autorefractions up to the age of 20 years (Kearns et al., 2010). However, there are several reasons why this was not feasible in this study. First, the instillation of drops is administered under the order of a pediatric ophthalmologist, and would have to be scheduled accordingly. Second, an additional time commitment would be required to allow for pupil dilation and recovery. This additional time, plus the added inconvenience of cycloplegia, would have dissuaded many participants from taking part in the research or of the eye exams. Lastly, although manifest autorefraction may miss some cases of hyperopia, patients who developed strabismus, amblyopia, or reduced stereopsis as a result of microstrabismus would have been detected by other testing.

4.5.5 Stereoacuity

The best attempt was made to achieve the highest level of stereoacuity in each participant. Proper illumination and optical correction was in place, and additional plus lenses were provided in an effort to improve reduced stereoacuity in participants with presbyopia. A strict age cut-off was not used to determine what was age appropriate decreased stereopsis. Instead, clinical judgment was used to determine whether children truly had decreased stereopsis, or whether they simply were not capable of performing

the test. The preference was to code as accurately as possible in children, but under-coding was preferred rather than over-coding decreased stereopsis.

4.6 Future Studies

The present study identified a number of factors that influence the accuracy of self-reported strabismus. An increased sample size would allow for analysis of additional subpopulations and provide the power to detect smaller – but perhaps significant – differences between groups. Future studies that include questions referencing stereoacuity would improve the evaluation of participant understanding of SACs. Additional questions that examine participant knowledge of strabismus and the emotional impact of diagnosis may also be considered for future studies. Lastly, this study attempted to only identify the question of whether participants are aware that they have strabismus or an associated condition, but the accuracy a specific type of strabismus or condition was not examined. Future studies could build on this study and answer whether participants are aware of their form of strabismus.

4.7 Conclusions

The *Strabismus Self-Reporting Accuracy Study* investigates a condition that has an early onset and whose subtle forms are not always detected (Campbell & Charney, 1991; Larson et al., 2003; Weissberg et al., 2004). Though many studies of strabismus rely on self-report, the results of this study suggest that self-reports should not be utilized for

research that requires precise quantification of strabismus or strabismus associated conditions. If self-reported status must be used, increases in sample size of orders of magnitude will be required to attain similar statistical power. Therefore, any study investigating the genetic contributors to strabismus should include clinical examinations of all participants in order to achieve the most accurate data set.

REFERENCES

Abrahamsson, M., Fabian, G., & Sjostrand, J. (1992). Refraction changes in children developing convergent or divergent strabismus. *The British Journal of Ophthalmology, 76*(12), 723-727. doi:10.1136/bjo.76.12.723

Antoniou, A. C., & Easton, D. F. (2003). Polygenic inheritance of breast cancer: Implications for design of association studies. *Genetic Epidemiology, 25*(3), 190-202. doi:10.1002/gepi.10261

Archer, S. M., Sondhi, N., & Helveston, E. M. (1989). Strabismus in infancy. *Ophthalmology, 96*(1), 133-137.

Atkinson, J., Braddick, O., Robier, B., Anker, S., Ehrlich, D., King, J., . . . Moore, A. (1996). Two infant vision screening programmes: Prediction and prevention of strabismus and amblyopia from photo- and videorefractive screening. *Eye, 10*(2), 189-198. doi:10.1038/eye.1996.46

Aurell, E., & Norrsell, K. (1990). A longitudinal study of children with a family history of strabismus: Factors determining the incidence of strabismus. *The British Journal of Ophthalmology, 74*(10), 589-594. doi:10.1136/bjo.74.10.589

Beauchamp, C., Felius, J., Beauchamp, G. R., Brown, M., & Brown, C. (2007). The economic value added for care of amblyopia, strabismus, and asthma. *Journal of American Association for Pediatric Ophthalmology and Strabismus, 11*(1), 76. doi:10.1016/j.jaapos.2006.11.017

Beauchamp, G. R., Black, B. C., Coats, D. K., Enzenauer, R. W., Hutchinson, A. K., Saunders, R. A., . . . Felius, J. (2003). The management of strabismus in adults–I. clinical characteristics and treatment. *Journal of American Association for Pediatric Ophthalmology and Strabismus, 7*(4), 233-240. doi:10.1016/S1091-8531(03)00112-5

Beauchamp, G. R., Felius, J., Stager, D. R., & Beauchamp, C. L. (2005). The utility of strabismus in adults. *Transactions of the American Ophthalmological Society, 103*, 164-71; discussion 171. Retrieved from http://www.aosonline.org/xactions/2005/1545-6110_v103_p164.pdf

Birch, E., Stager, D., Wright, K., & Beck, R. (1998). The natural history of infantile esotropia during the first six months of life. *Journal of American Association for Pediatric Ophthalmology and Strabismus,* 2(6), 325-8. doi:10.1016/S1091-8531(98)90026-X

Birch, E. E., Fawcett, S. L., Morale, S. E., Weakley, D. R., Jr., & Wheaton, D. H. (2005). Risk factors for accommodative esotropia among hypermetropic children. *Investigative Ophthalmology & Visual Science, 4*6(2), 526-529. doi:10.1167/iovs.04-0618

Birch, E. E., & Holmes, J. M. (2010). The clinical profile of amblyopia in children younger than 3 years of age. *Journal of American Association for Pediatric Ophthalmology and Strabismus, 1*4(6), 494-497. doi:10.1016/j.jaapos.2010.10.004

Birch, E. E., & Stager, D. R., Sr. (2006). Long-term motor and sensory outcomes after early surgery for infantile esotropia. *Journal of American Association for Pediatric Ophthalmology and Strabismus, 1*0(5), 409-413. doi:10.1016/j.jaapos.2006.06.010

Birch, E. E., Stager, D. R., Sr., Wang, J., & O'Connor, A. (2010). Longitudinal changes in refractive error of children with infantile esotropia. *Eye, 2*4(12), 1814-1821. doi:10.1038/eye.2010.129

Bowie, H., Congdon, N. G., Lai, H., & West, S. K. (2003). Validity of a personal and family history of cataract and cataract surgery in genetic studies. *Investigative Ophthalmology & Visual Science, 4*4(7), 2905-2908. doi:10.1167/iovs.02-1055

Brener, N. D., Billy, J. O., & Grady, W. R. (2003). Assessment of factors affecting the validity of self-reported health-risk behavior among adolescents: Evidence from the scientific literature. *The Journal of Adolescent Health, 3*3(6), 436-457. doi:10.1016/S1054-139X(03)00052-1

Bush, T. L., Miller, S. R., Golden, A. L., & Hale, W. E. (1989). Self-report and medical record report agreement of selected medical conditions in the elderly. *American Journal of Public Health, 7*9(11), 1554-1556. doi:10.2105/AJPH.79.11.1554

Buyske, S., Yang, G., Matise, T. C., & Gordon, D. (2009). When a case is not a case: Effects of phenotype misclassification on power and sample size requirements for the transmission disequilibrium test with affected child trios. *Human Heredity, 6*7(4), 287-292. doi:10.1159/000194981

Campbell, L. R., & Charney, E. (1991). Factors associated with delay in diagnosis of childhood amblyopia. *Pediatrics, 8*7(2), 178-185. Retrieved from http://pediatrics.aappublications.org/content/87/2/178.full.pdf+html

Campos, E. C. (2008). Why do the eyes cross? A review and discussion of the nature and origin of essential infantile esotropia, microstrabismus, accommodative esotropia, and acute comitant esotropia. *Journal of American Association for Pediatric Ophthalmology and Strabismus, 12*(4), 326-331. doi:10.1016/j.jaapos.2008.03.013

Cantolino, S. J., & Von Noorden, G. K. (1969). Heredity in microtropia. *Archives of Ophthalmology, 8*1(6), 753-757. Retrieved from http://archopht.ama-assn.org/cgi/reprint/81/6/753

Castro, P. D., Pedroso, A., Hernandez, L., Naranjo, R. M., Mendez, T. J., & Arias, A. (2011). Results of surgery for congenital esotropia. *MEDICC Review, 1*3(1), 18-22. Retrieved from http://www.medicc.org/mediccreview/articles/mr_179.pdf

Chew, E., Remaley, N. A., Tamboli, A., Zhao, J., Podgor, M. J., & Klebanoff, M. (1994). Risk factors for esotropia and exotropia. *Archives of Ophthalmology, 11*2(10), 1349-1355. Retrieved from http://archopht.ama-assn.org.ezproxy.library.dal.ca/cgi/reprint/112/10/1349

Christen, W. G., Glynn, R. J., Seddon, J. M., Manson, J. E., Buring, J. E., & Hennekens, C. H. (1994). Confirmation of self-reported cataract in the physicians' health study. *Ophthalmic Epidemiology,* 1(2), 85-91. doi:10.3109/09286589409052364

Cleary, P. D., & Jette, A. M. (1984). The validity of self-reported physician utilization measures. *Medical Care, 2*2(9), 796-803. Retrieved from http://www.jstor.org/stable/3764604

Coats, D. K., Paysse, E. A., Towler, A. J., & Dipboye, R. L. (2000). Impact of large angle horizontal strabismus on ability to obtain employment. *Ophthalmology, 10*7(2), 402-405. doi:10.1016/S0161-6420(99)00035-4

Colditz, G. A., Martin, P., Stampfer, M. J., Willett, W. C., Sampson, L., Rosner, B., . . . Speizer, F. E. (1986). Validation of questionnaire information on risk factors and disease outcomes in a prospective cohort study of women. *American Journal of Epidemiology, 123*(5), 894-900. Retrieved from http://aje.oxfordjournals.org/content/123/5/894.full.pdf+html

Donahue, S. P. (2007). Clinical practice. Pediatric strabismus. *The New England Journal of Medicine, 356*(10), 1040-1047. doi:10.1056/NEJMcp051888

Donnelly, U., Stewart, N., & Hollinger, M. (2005). Prevalence and outcomes of childhood visual disorders. *Ophthalmic Epidemiology, 12*(4), 243-250. doi:10.1080/09286580590967772

Durnian, J. M., Noonan, C. P., & Marsh, I. B. (2011). The psychosocial effects of adult strabismus: A review. *The British Journal of Ophthalmology, 95*(4), 450-453. doi:10.1136/bjo.2010.188425

Durnian, J. M., Owen, M. E., Baddon, A. C., Noonan, C. P., & Marsh, I. B. (2010). The psychosocial effects of strabismus: Effect of patient demographics on the AS-20 score. *Journal of American Association for Pediatric Ophthalmology and Strabismus, 14*(6), 469-471. doi:10.1016/j.jaapos.2010.08.013

Ekdawi, N. S., Nusz, K. J., Diehl, N. N., & Mohney, B. G. (2009). Postoperative outcomes in children with intermittent exotropia from a population-based cohort. *Journal of American Association for Pediatric Ophthalmology and Strabismus, 13*(1), 4-7. doi:10.1016/j.jaapos.2008.06.001

Engle, E. C. (2007). Genetic basis of congenital strabismus. *Archives of Ophthalmology, 125*(2), 189-195. doi:10.1001/archopht.125.2.189

Englert, H., Muller-Nordhorn, J., Seewald, S., Sonntag, F., Voller, H., Meyer-Sabellek, W., . . . Willich, S. N. (2010). Is patient self-report an adequate tool for monitoring cardiovascular conditions in patients with hypercholesterolemia? *Journal of Public Health (Oxford, England), 3*2(3), 387-394. doi:10.1093/pubmed/fdq013

Fawcett, S. L. (2005). Disruption and reacquisition of binocular vision in childhood and in adulthood. *Current Opinion in Ophthalmology, 1*6(5), 298-302. Retrieved from http://journals.lww.com/co-ophthalmology/Abstract/2005/10000/Disruption_and_reacquisition_of_binocular_vision.5.aspx

Fawcett, S. L., Wang, Y. Z., & Birch, E. E. (2005). The critical period for susceptibility of human stereopsis. *Investigative Ophthalmology & Visual Science, 4*6(2), 521-525. doi:10.1167/iovs.04-0175

Ferreira, R., Oelrich, F., & Bateman, B. (2002). Genetic aspects of strabismus. *Arquivos Brasileiros De Oftalmologia, 65*(2), 171-175. doi:10.1590/S0004-27492002000200004

Flegal, K. M., Brownie, C., & Haas, J. D. (1986). The effects of exposure misclassification on estimates of relative risk. *American Journal of Epidemiology, 12*3(4), 736-751. Retrieved from http://aje.oxfordjournals.org/content/123/4/736.full.pdf+html

Fu, V. L. N., Stager, D., & Birch, E. (2007). Progression of intermittent, small-angle, and variable esotropia in infancy. *Investigative Ophthalmology Visual Science, 4*8(2), 661-664. doi:10.1167/iovs.06-0717

Goff, M. J., Suhr, A. W., Ward, J. A., Croley, J. K., & O'Hara, M. A. (2006). Effect of adult strabismus on ratings of official U.S. army photographs. *Journal of American Association for Pediatric Ophthalmology and Strabismus, 1*0(5), 400-403. doi:10.1016/j.jaapos.2006.04.011

Gordon, D., Finch, S. J., Nothnagel, M., & Ott, J. (2002). Power and sample size calculations for case-control genetic association tests when errors are present: Application to single nucleotide polymorphisms. *Human Heredity, 5*4(1), 22-33. doi:10.1159/000066696

Gordon, D., Levenstien, M. A., Finch, S. J., & Ott, J. (2003). Errors and linkage disequilibrium interact multiplicatively when computing sample sizes for genetic case-control association studies. *Pacific Symposium on Biocomputing,* 8, 490-501. Retrieved from http://helix-web.stanford.edu/psb03/gordon.pdf

Goujon, N., Brown, C. M., Xie, J., Arnold, A. L., Dunn, R. A., Keeffe, J. E., & Taylor, H. R. (2010). Self-reported vision and health of indigenous Australians. *Clinical & Experimental Ophthalmology, 38*(8), 796-804. doi:10.1111/j.1442-9071.2010.02306.x

Green, E. D., & Guyer, M. S. (2011). Charting a course for genomic medicine from base pairs to bedside. *Nature, 470*(7333), 204-213. doi:10.1038/nature09764

Green-Simms, A., & Mohney, B. G. (2010). Epidemiology of pediatric strabismus. In B. Lorenz, & M. C. Brodsky (Eds.), *Pediatric ophthalmology, neuro-ophthalmology, genetics: New concepts in pathophysiology, diagnosis, and treatment* (pp. 1-9). Berlin Heidelberg: Springer. Retrieved from http://dx.doi.org/10.1007/978-3-540-85851-5

Haapanen, N., Miilunpalo, S., Pasanen, M., Oja, P., & Vuori, I. (1997). Agreement between questionnaire data and medical records of chronic diseases in middle-aged and elderly Finnish men and women. *American Journal of Epidemiology, 145*(8), 762-769. doi:10.1093/aje/145.8.762

Harlow, S. D., & Linet, M. S. (1989). Agreement between questionnaire data and medical records: The evidence for accuracy of recall. *American Journal of Epidemiology, 129*(2), 233-248. Retrieved from http://aje.oxfordjournals.org/content/129/2/233.full.pdf+html

Hess, R. F. (1996). Is amblyopia an impediment to binocular function? *Eye, 10*(2), 245-249. doi:10.1038/eye.1996.53

Hrisos, S., Clarke, M. P., & Wright, C. M. (2004). The emotional impact of amblyopia treatment in preschool children: Randomized controlled trial. *Ophthalmology, 111*(8), 1550-1556. doi:10.1016/j.ophtha.2003.12.059

Hu, D. N. (1987). Prevalence and mode of inheritance of major genetic eye diseases in china. *Journal of Medical Genetics, 24*(10), 584-588. doi:10.1136/jmg.24.10.584

Hubel, D. H., & Wiesel, T. N. (1965). Binocular interaction in striate cortex of kittens reared with artificial squint. *Journal of Neurophysiology, 28*(6), 1041-1059. Retrieved from http://jn.physiology.org/content/28/6/1041.full.pdf+html

Ingram, R. M., Traynar, M. J., Walker, C., & Wilson, J. M. (1979). Screening for refractive errors at age 1 year: A pilot study. *British Journal of Ophthalmology, 63*, 243-250. doi:10.1136/bjo.63.4.236

Jackson, S., Harrad, R. A., Morris, M., & Rumsey, N. (2006). The psychosocial benefits of corrective surgery for adults with strabismus. *The British Journal of Ophthalmology, 9*0(7), 883-888. doi:10.1136/bjo.2005.089516

James, H., Jenkinson, E., Harrad, R., Ezra, D. G., & Newman, S. (2011). Appearance concerns in ophthalmic patients. *Eye, 2*5(8), 1039-1044. doi:10.1038/eye.2011.116

Jobe, J. B. (2003). Cognitive psychology and self-reports: Models and methods. *Quality of Life Research, 1*2(3), 219-227. doi:10.1023/A:1023279029852

Jobe, J. B., White, A. A., Kelley, C. L., Mingay, D. J., Sanchez, M. J., & Loftus, E. F. (1990). Recall strategies and memory for health-care visits. *The Milbank Quarterly, 6*8(2), 171-189. Retrieved from http://www.jstor.org/stable/3350095

Jones, M. P., Bartrop, R., Dickson, H. G., & Forcier, L. (2011). Concordance between sources of morbidity reports: Self-reports and medical records. *Frontiers in Pharmacology,* 2, 16. doi:10.3389/fphar.2011.00016

Kearns, L. S., Hewitt, A. W., Ruddle, J. B., Bigault, O., Staffieri, S. E., Sanfillipo, P., . . . Mackey, D. A. (2010). Up to what age is a cyclopleged refraction required? Results from the twins eye study Tasmania (TEST). *ARVO Meeting Abstracts, 5*1(5), 1716. Retrieved from http://abstracts.iovs.org//cgi/content/abstract/51/5/1716

Kehoe, R., Wu, S. Y., Leske, M. C., & Chylack, L. T., Jr. (1994). Comparing self-reported and physician-reported medical history. *American Journal of Epidemiology, 13*9(8), 813-818. Retrieved from http://aje.oxfordjournals.org/content/139/8/813.full.pdf+html

Koklanis, K., Abel, L. A., & Aroni, R. (2006). Psychosocial impact of amblyopia and its treatment: A multidisciplinary study. *Clinical & Experimental Ophthalmology, 3*4(8), 743-750. doi:10.1111/j.1442-9071.2006.01317.x

Kriegsman, D. M. W., Penninx, B. W. J. H., Van Eijk, J. T. M., Boeke, A. J. P., & Deeg, D. J. H. (1996). Self-reports and general practitioner information on the presence of chronic diseases in community dwelling elderly : A study on the accuracy of patients' self-reports and on determinants of inaccuracy. *Journal of Clinical Epidemiology, 4*9(12), 1407-1417. doi:10.1016/S0895-4356(96)00274-0

Larson, S. A., Keech, R. V., & Verdick, R. E. (2003). The threshold for the detection of strabismus. *Journal of American Association for Pediatric Ophthalmology and Strabismus,* 7(6), 418-422. doi:10.1016/j.jaapos.2003.09.011

Leikauf, J., & Federman, A. D. (2009). Comparisons of self-reported and chart-identified chronic diseases in inner-city seniors. *Journal of the American Geriatrics Society, 5*7(7), 1219-1225. doi:10.1111/j.1532-5415.2009.02313.x

Li, J., Thompson, B., Lam, C. S., Deng, D., Chan, L. Y., Maehara, G., . . . Hess, R. F. (2011). The role of suppression in amblyopia. *Investigative Ophthalmology & Visual Science, 5*2(7), 4169-4176. doi:10.1167/iovs.11-7233

Lim, H. T., Smith, D. R., Kraft, S. P., & Buncic, J. R. (2008). Dissociated vertical deviation in patients with intermittent exotropia. *Journal of American Association for Pediatric Ophthalmology and Strabismus, 1*2(4), 390-395. doi:10.1016/j.jaapos.2007.11.019

Link, B. G., & Phelan, J. C. (2006). Stigma and its public health implications. *Lancet, 367*(9509), 528-529. doi:10.1016/S0140-6736(06)68183-X

Linton, K. L., Klein, B. E., & Klein, R. (1991). The validity of self-reported and surrogate-reported cataract and age-related macular degeneration in the beaver dam eye study. *American Journal of Epidemiology, 134*(12), 1438-1446. Retrieved from http://aje.oxfordjournals.org/content/134/12/1438.full.pdf+html

Lorenz, B. (2002). Genetics of isolated and syndromic strabismus: Facts and perspectives. *Strabismus, 10*(2), 147-156. doi:10.1076/stra.10.2.147.8133

Louwagie, C. R., Diehl, N. N., Greenberg, A. E., & Mohney, B. G. (2009). Long-term follow-up of congenital esotropia in a population-based cohort. *Journal of American Association for Pediatric Ophthalmology and Strabismus, 13*(1), 8-12. doi:10.1016/j.jaapos.2008.06.013

Mojon-Azzi SM, & Mojon DS. (2009). Strabismus and employment: The opinion of headhunters. *Acta Ophthalmologica, 87*(7), 784. doi:10.1111/j.1755-3768.2008.01352.x

Mojon-Azzi, S. M., Potnik, W., & Mojon, D. S. (2008). Opinions of dating agents about strabismic subjects' ability to find a partner. *The British Journal of Ophthalmology, 92*(6), 765-769. doi:10.1136/bjo.2007.128884

Multi-ethnic Pediatric Eye Disease Study Group. (2008). Prevalence of amblyopia and strabismus in African American and Hispanic children ages 6 to 72 months: The multi-ethnic pediatric eye disease study. *Ophthalmology, 115*(7), 1229-1236.e1. doi:10.1016/j.ophtha.2007.08.001

Nelson, B. A., Gunton, K. B., Lasker, J. N., Nelson, L. B., & Drohan, L. A. (2008). The psychosocial aspects of strabismus in teenagers and adults and the impact of surgical correction. *Journal of American Association for Pediatric Ophthalmology and Strabismus, 12*(1), 72-76.e1. doi:10.1016/j.jaapos.2007.08.006

Newell, S. A., Girgis, A., Sanson Fisher, R. W., & Savolainen, N. J. (1999). The accuracy of self-reported health behaviors and risk factors relating to cancer and cardiovascular disease in the general population: A critical review. *American Journal of Preventive Medicine, 17*(3), 211-229. doi:10.1016/S0749-3797(99)00069-0

Nusz, K. J., Mohney, B. G., & Diehl, N. N. (2005). Female predominance in intermittent exotropia. *American Journal of Ophthalmology, 140*(3), 546-547. doi:10.1016/j.ajo.2005.03.026

Olitsky, S. E., Sudesh, S., Graziano, A., Hamblen, J., Brooks, S. E., & Shaha, S. H. (1999). The negative psychosocial impact of strabismus in adults. *Journal of American Association for Pediatric Ophthalmology and Strabismus,* 3(4), 209-211. doi:10.1016/S1091-8531(99)70004-2

Oystreck, D., Engle, E., & Bosley, T. (2011). Recent progress in understanding congenital cranial dysinnervation disorders. *Journal of Neuro-Ophthalmology, 3*1(1), 69-77. doi:10.1097/WNO.0b013e31820d0756

Paul, T. O., & Hardage, L. K. (1994). The heritability of strabismus. *Ophthalmic Genetics, 15*(1), 1-18. doi:10.3109/13816819409056905

Pediatric Eye Disease Investigator Group. (2002). The clinical spectrum of early-onset esotropia: Experience of the congenital esotropia observational study. *American Journal of Ophthalmology, 133*(1), 102-108. doi:10.1016/S0002-9394(01)01317-4

Pennefather, P. M., Clarke, M. P., Strong, N. P., Cottrell, D. G., Dutton, J., & Tin, W. (1999). Risk factors for strabismus in children born before 32 weeks' gestation. *The British Journal of Ophthalmology, 8*3(5), 514-518. doi:10.1136/bjo.83.5.514

Phelps, E. A., & Sharot, T. (2008). How (and why) emotion enhances the subjective sense of recollection. *Current Directions in Psychological Science: A Journal of the American Psychological Society, 1*7(2), 147-152. doi:10.1111/j.1467-8721.2008.00565.x

Podgor, M. J., Remaley, N. A., & Chew, E. (1996). Associations between siblings for esotropia and exotropia. *Archives of Ophthalmology, 11*4(6), 739-744. Retrieved from http://archopht.ama-assn.org/cgi/reprint/114/6/739

Reinecke, R., Sterling, R., & Wizow, S. (1991). Accuracy of judgments of the presence or absence (non-primary) gaze and the presence or absence of strabismus. *Binocular Vision Strabismus Quarterly,* 6, 189–96.

Rice, A., Nsengimana, J., Simmons, I. G., Toomes, C., Hoole, J., Willoughby, C. E., . . . Inglehearn, C. F. (2009). Replication of the recessive STBMS1 locus but with dominant inheritance. *Investigative Ophthalmology & Visual Science, 5*0(7), 3210-3217. doi:10.1167/iovs.07-1631

Robaei, D., Rose, K. A., Kifley, A., Cosstick, M., Ip, J. M., & Mitchell, P. (2006). Factors associated with childhood strabismus: Findings from a population-based study. *Ophthalmology, 11*3(7), 1146-1153. doi:10.1016/j.ophtha.2006.02.019

Scott, M. H., Noble, A. G., Raymond, W. R.,4th, & Parks, M. M. (1994). Prevalence of primary monofixation syndrome in parents of children with congenital esotropia. *Journal of Pediatric Ophthalmology and Strabismus, 3*1(5), 298-301; discussion 302.

Shaaban, S., Matsuo, T., Fujiwara, H., Itoshima, E., Furuse, T., Hasebe, S., . . . Ohtsuki, H. (2009). Chromosomes 4q28.3 and 7q31.2 as new susceptibility loci for comitant strabismus. *Investigative Ophthalmology & Visual Science, 50*(2), 654-661. doi:10.1167/iovs.08-2437

Strominger, M. B. (2008). *Pediatric ophthalmology and strabismus*. Philadelphia , PA: Mosby Elsevier. Retrieved from http://www.sciencedirect.com/science/book/9780323051682

Talarico, J. M., & Rubin, D. C. (2003). Confidence, not consistency, characterizes flashbulb memories. *Psychological Science, 1*4(5), 455-461. doi:10.1111/1467-9280.02453

Taylor, H. R., Xie, J., Arnold, A. L., Goujon, N., Dunn, R. A., Fox, S., & Keeffe, J. (2010). Cataract in indigenous Australians: The national indigenous eye health survey. *Clinical & Experimental Ophthalmology, 3*8(8), 790-795. doi:10.1111/j.1442-9071.2010.02337.x

Torp-Pedersen, T., Boyd, H. A., Poulsen, G., Haargaard, B., Wohlfahrt, J., Holmes, J. M., & Melbye, M. (2010a). In-utero exposure to smoking, alcohol, coffee, and tea and risk of strabismus. *American Journal of Epidemiology, 17*1(8), 868-875. doi:10.1093/aje/kwq010

Torp-Pedersen, T., Boyd, H. A., Poulsen, G., Haargaard, B., Wohlfahrt, J., Holmes, J. M., & Melbye, M. (2010b). Perinatal risk factors for strabismus. *International Journal of Epidemiology, 3*9(5), 1229-1239. doi:10.1093/ije/dyq092

Tychsen, L. (2010). Visual cortex mechanisms of strabismus: Development and maldevelopment. In B. Lorenz, & M. C. Brodsky (Eds.), *Pediatric ophthalmology, neuro-ophthalmology, genetics: New concepts in pathophysiology, diagnosis, and treatmen*t (pp. 41-57). Berlin Heidelberg: Springer. Retrieved from http://dx.doi.org/10.1007/978-3-540-85851-5;

Tychsen, L., Richards, M., Wong, A., Foeller, P., Bradley, D., & Burkhalter, A. (2010). The neural mechanism for latent (fusion maldevelopment) nystagmus. *Journal of Neuro-Ophthalmology, 3*0(3), 276-283. doi:10.1097/WNO.0b013e3181dfa9ca

Tychsen, L., Richards, M., Wong, A., Foeller, P., Burhkalter, A., Narasimhan, A., & Demer, J. (2008). Spectrum of infantile esotropia in primates: Behavior, brains, and orbits. *Journal of American Association for Pediatric Ophthalmology and Strabismus, 1*2(4), 375-380. doi:10.1016/j.jaapos.2007.11.010

Von Noorden, G. K., & Campos, E. C. (2002). *Binocular vision and ocular motility: Theory and management of strabismu*s (6th ed.). St. Louis, Missouri: Mosby Inc.

Weissberg, E., Suckow, M., & Thorn, F. (2004). Minimal angle horizontal strabismus detectable by lay observers. *Optometry and Vision Science: Official Publication of the American Academy of Optometry, 8*1(7), 505-509. Retrieved from http://journals.lww.com/optvissci/pages/default.aspx

Wilmer, J. B., & Backus, B. T. (2009). Genetic and environmental contributions to strabismus and phoria: Evidence from twins. *Vision Research, 4*9(20), 2485-2493. doi:10.1016/j.visres.2009.08.006

Wright, K. W., Edelman, P. M., McVey, J. H., Terry, A. P., & Lin, M. (1994). High-grade stereo acuity after early surgery for congenital esotropia. *Archives of Ophthalmology, 11*2(7), 913-919. Retrieved from http://archopht.ama-assn.org/cgi/reprint/112/7/913

Wu, S. C., Li, C. Y., & Ke, D. S. (2000). The agreement between self-reporting and clinical diagnosis for selected medical conditions among the elderly in Taiwan. *Public Health (Nature), 11*4(2), 137.

Young, T. L., & Khazaeni, L. M. (2005). Genetics of eye disease. In R. D. Harley, L. B. Nelson & S. E. Olitsky (Eds.), *Harley's pediatric ophthalmolog*y (5th ed., pp. 1-51). Philadelphia, PA: Lippincott Williams & Wilkins. Retrieved from http://www.springerlink.com

APPENDIX A: INTRODUCTORY LETTER AND STUDY BROCHURE

Children's Hospital Boston
Center for Strabismus Research

HARVARD MEDICAL SCHOOL

DAVID G. HUNTER, M.D. Ph.D.
Ophthalmologist-In-Chief
Associate Professor of Ophthalmology

ELIZABETH C. ENGLE, M.D.
Program in Genomics
Associate Professor of Neurology

PHYSICIAN NAME
Physician Title

Parents of _____
Street Address
City, State Zip Code of Parent

Date

Dear Parents of _____

We are writing to inform you about an opportunity to participate in a research project at Children's Hospital Boston. As you know, you or your child recently visited the Department of Ophthalmology for an eye examination, where strabismus (or a condition such as farsightedness or amblyopia that is sometimes seen in combination with strabismus) was diagnosed. We are working with colleagues at Children's Hospital Boston to identify gene(s) involved in the various forms of strabismus, and we are therefore contacting you to ask if you are willing to learn more about our study

The Department of Ophthalmology and the Program in Genomics & Neuroscience at Children's Hospital Boston have teamed up together to examine the causes of strabismus, amblyopia, and ptosis. We know that in some individuals genes inherited from our parents contribute to these conditions, while in other cases environmental factors play an important role. We hope that the knowledge we gain from this research will improve our understanding of strabismus, amblyopia, and ptosis and some day lead to early diagnosis and better treatment.

We hope that you will be willing to talk or e-mail with one of our study coordinators: Caroline Andrews, Sarah Wichland or Carrie Pierce about the study. Allowing us to contact you does not mean that you have agreed to participate in the study, but only that you are willing to discuss it with us further. If you would **not** like to be called, however, please indicate this by mailing back to us the enclosed stamped, addressed postcard. This postcard has been coded so that only the study coordinators will know that it came from you. If we do not receive the postcard in the next two weeks: Caroline, Sarah or Carrie will telephone or e-mail you to discuss the study. You may also contact a research coordinator, Dr. Engle, Dr. Hunter, or your ophthalmologist at any time should you have any questions or concerns regarding this study.

A brochure with a more detailed description of the research study and our contact information is enclosed. You can also read about our research study on the Engle lab website: www.childrenshospital.org/research/engle/

We hope to have the opportunity to speak with you.

Yours sincerely,

David G. Hunter, M.D. Ph.D Elizabeth C. Engle, M.D. Physician Name**Sample Postcard:**
Postcard will be coded for each potential participants and will read:

CLS 14076, 300 Longwood Avenue Boston, MA 02115
Tel: (617) 919 2168 / (617) 919 2164

Please do not contact me regarding your research study.

ID: _____

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Who are we?

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Children's Hospital Boston Harvard Medical School

Genetic Study of Strabismus & Amblyopia

Children's Hospital Boston Center for Strabismus Research

Program in Genomics, Neuroscience and Department of Ophthalmology
Boston, Massachusetts

Strabismus and genetics

Strabismus ("crossed" or "wandering" eyes) is a misalignment of the eyes that affects 2-4% of the population. Strabismus causes loss of binocular vision and amblyopia (vision loss in a structurally normal eye), which if not treated early in life, may eventually lead to blindness.

Researchers at Children's Hospital Boston are investigating the causes of strabismus by identifying genetic variations that are associated with its occurrence. We hope that this study will lead to a better understanding of strabismus and to new forms of diagnosis and treatment.

Who is eligible to participate?

Families seen in the Department of Ophthalmology at Children's Hospital Boston who have at least one family member diagnosed with strabismus or a condition known to be associated with strabismus (such as amblyopia or farsightedness) are eligible to participate.

When possible, we would like to enroll the entire family. We would like to enroll the siblings and parents of eligible patients. If more than one family member has any of these conditions, we would like to enroll other relatives as well.

Participation

Participation in the study entails a one-time visit, which can be combined with a regular clinic visit to the Department of Ophthalmology at Children's Hospital Boston or can be arranged at an independent time. Medical information and DNA samples obtained will be accessible only by researchers working on this project.

Cost/time commitment

Enrollment will take approximately 1 hour. There is no fee to participate in this study, and as a token of our appreciation each family will receive either $10 of Children's Hospital Boston Café food vouchers or a Children's Hospital Boston parking voucher.

What will we do?

We will obtain your family's informed consent and medical/family history.

We will perform eye examinations and video recordings of previously unexamined family members.

We will obtain a blood sample (about 2 tablespoons) or saliva from which we will later isolate genetic material (DNA).

Results

In this ongoing study, we are comparing the genetic makeup and medical information from different families to determine which genetic factors play a role in strabismus. We hope this work will enhance the identification of individuals at risk, improve our ability to detect and prevent amblyopia and loss of binocular vision, and provide insight into the causes of strabismus.

Since this is a research study, individual results will not be reported to families. However, families are encouraged to call or e-mail at any time to ask about the overall progress of this research. If desired, we would also notify participants if relevant genetic testing becomes available.

Confidentiality

Results obtained from this study are confidential and are not placed in the medical records of participating children or their families. Medical information and DNA samples obtained will be accessible only by researchers working on this project. Only at the participant's request would we make this information available to others.

APPENDIX B: PARTICIPANT CONSENT FORM

Children's Hospital Boston

RESEARCH CONSENT FORM

Protocol Title: Genetic studies of Strabismus, Congenital Cranial **Dysinnervation Disorders (CCDD's)** and their associated anomalies.

(Consent C: For patients at Children's Hospital Boston)

MRN#:

DOB:

Pt Name:

Gender:

Doctor Directing Research: Elizabeth C. Engle, MD
Phone: 617-919-4030; email: elizabeth.engle@childrens.harvard.edu

About this consent form

Please read this form carefully as it tells you important information about a research study. A member of our research team will also talk to you about taking part in this research study. In order to decide whether or not you want to be a part of this research study, you should understand enough about its risks and benefits to make an informed judgment. If you decide to take part in this research study, you will be asked to sign the form to show that you wish to take part.

Why is this research study being done?

We are a group of scientists and doctors at Children's Hospital Boston who are studying the genetic causes of strabismus, congenital cranial dysinnervation disorders (CCDD's) and their associated anomalies.
You have been asked to be a part of this study because you or a member of your family has been diagnosed with one of these disorders. This consent form gives you detailed information about the procedures, risks and benefits of the study so that you can decide whether or not you want to be a part of this research.

Genes are found in the cells of our body and are the instructions that tell our body how to grow and develop. They are passed on to us (inherited) from our parents. The DNA sequence that makes up our genes is remarkably similar from one person to the next, but tiny variations do occur, rendering each of us a unique individual. Most of these changes in our genes are harmless and cause such variation as eye color and height. There can also be changes in genes that cause them not to work properly and lead to health problems or disease. We wish to determine and understand which genes are important for brain development by studying the changes in genes of individuals who have disorders affecting their eye movement, cranial nerve abnormalities and their associated anomalies. We hope that the knowledge we gain from this research will lead to improved diagnosis, management and treatment of these conditions.

Our research is federally funded by the National Institute of Health (NIH). We expect to enroll 1800 patients in this research study per year, and anticipate about 1300 of these will be from Children's Hospital. This research is ongoing and will be undertaken in the Engle Laboratory, located in the Center for Life Science Building of Children's Hospital Boston.

Procedure:

Medical and family history:

You are being asked to participate in this study because you or a member of your family has strabismus, a CCDD or associated anomaly. We are asking you to participate whether you were born into this family or married a

member of this family. If you choose to participate, you will be asked questions about yourself, your children, siblings, grandparents, and possibly other family members. These questions may include age, ethnic background, health status and the biological relationship between individuals. In addition, with your permission, we may review your medical records or contact your health care provider to gain further information about your strabismus, CCDD and associated medical conditions.

Sample collection:
You will be asked to give a sample of saliva or blood, from which we can study your genetic material (DNA). Providing a blood sample will involve our taking approximately 1 to 6 teaspoons of blood from a vein in your arm. If there are costs for your blood draw or transportation to the appointment to have your blood drawn for participation in this research, we will refund these costs to you if you give us the receipt(s) showing the exact cost and date of service.

The sample donation will need to be performed only once unless the laboratory procedures fail, in which case a second sample may be requested. Alternatively, we may take a small swab of cells from your inner cheek, a sample of mouthwash that you have swished in your mouth, or some cut fingernails from which we can isolate a smaller amount of DNA. Finally, if you or your child is scheduled to undergo surgery for the eye movement disorder, we may ask your surgeon if any muscle tissue normally removed during the surgery is available for examination and study.

Research use of samples:
DNA obtained from your sample may be used to search, identify and study genes involved in strabismus, cranial nerve abnormalities and their associated anomalies. We may use techniques that study all of your genes, only some of your genes and/or parts of your genetic material that do not have a currently known purpose or function. We may undertake linkage analysis on your DNA and others to determine the genetic location where a gene associated with your disorder may lie. Once a region has been localized to a chromosomal location, it is possible to identifiy the causative gene by screening sequences within that region. If a change is identified, then sequencing a subset of the population for this gene will determine whether the change in the normal gene sequence is a polymorphism (non disease causing) or pathogenic (disease causing).

Other techniques may include whole genome analysis in which all or most of your genetic code is studied and used to find the causes of your disorder, or the disorder in your family. In some cases we may use blood that has already been drawn to grow your blood cells in a dish. Blood cells grown in this manner can survive indefinitely, providing a greater source of genetic material. We may also use your blood to examine your chromosomes for abnormalities that may cause the eye movement disorder.

Confidentiality and storage of research information, samples and data:
Information collected about you during this study will be given a unique code number and will not be put in your medical record. Your sample(s) and research data will be associated with your unique code only and stored without your name, medical record number or other identifying information. The information, samples and data will be accessible to the research study staff only and will be stored within the research laboratory in a secure and locked location and/or on a password-protected database at Children's Hospital Boston. Only the research study staff will be

able to identify which sample(s), information and data belong to you and this link to your identity will not be shared with anyone outside of the study.

As part of this research we would like to store any remaining sample for future use. The remaining samples may be stored indefinitely and may be used for future studies on strabismus, congenital cranial dysinnervation disorders (CCDD's) and their associated anomalies. The samples will remain in the possession of Dr. Engle or her successors here at Children's Hospital Boston. If Dr. Engle chooses to share your samples with other investigators, your samples will be made anonymous and distributed without your name, medical record number, or other information linking the sample to you. Your identity will not be shared with outside researchers without explicit consent. If at any time you would like to have your sample removed from storage, please let us know and it will be transferred or destroyed according to your wishes. Results obtained prior to your sample removal will remain part of the study.

In order to allow researchers to share results, the National Institutes of Health (NIH) and other organizations have developed special data/information banks that collect and analyze DNA samples and results of whole genome studies. If provided to them, these central banks would store your genetic information and sample(s) and give them to other researchers to do more studies. Your sample(s) and data would be sent with your unique code number only; no identifiable information about you would ever be given to central banks. We do not think there will be further risks to your privacy and confidentiality by sharing your samples and whole genome information with these banks. There are many safeguards in place to protect your information and sample(s) while they are stored in these banks and used for research.

A copy of this consent form will NOT be placed in you/your child's medical record.

In addition, to provide you with additional protection we have a Certificate of Confidentiality (CC) from the US government. It adds special protection for research information that identifies you. It says we do not have to identify you, even under a court order or subpoena. The government may see your information if it audits us. This Certificate does not mean the government approves or disapproves of our project.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

The Certificate of Confidentiality does not prevent the researchers from disclosing voluntarily, without your consent, information that would identify you as a participant in the research project under the following circumstances: if the researchers are concerned that you may be suicidal (thinking about killing yourself) or otherwise at immediate risk for seriously harming yourself or others they will need to notify your primary care provider or counselor and/or involve your parents or guardian according to standard clinic practice or if, during your participation in this study, we learn about serious harm to you or someone else, such as child abuse, we will take steps to protect you or other people, including notifying the Department of Social Services or other authorities.

Cost/time commitment:
Your participation in the study should take no more than an hour. There is no fee for you to participate, as the costs associated with this study are covered by research funds. You will not be paid or otherwise compensated for your participation.

Photographing and videotaping eye movements:

If you agree, we will also photograph and/or video-record your eye movements. These recordings will be used to review your eye movements in the future. Also, with your permission, we may use these recordings in medical teaching and medical publications. These recordings will not be used except as described above, and will not be released to anyone else. Please indicate below whether you agree to this or not.

□ Yes, I do □ No, I do not agree to have my eye movements photographed and/or videotaped.

□ Yes, I do □ No, I do not give permission for these photographs and/or videotapes to be used in medical teachings, and/or publications.

Recontact for additional data or participation in future studies:

Over time we may wish to obtain updated information from participants. In addition, other studies may arise as a direct result of this study. Please indicate below whether we are permitted to contact you in the future:
□ Yes, I do □ No, I do not wish to be contacted in the future in order to provide additional clinical information.
□ Yes, I do □ No, I do not wish to be contacted if future studies arise.

Risks and Discomforts:
Risks associated with a blood draw are minor discomfort and bruising. When possible we will draw blood at the time of a clinically indicated procedure so that you will not need to have blood drawn only for research purposes. There is no risk associated with providing a saliva sample.

There is a chance that participation in this study could cause psychological distress. Some people involved in genetic studies have felt anxious about the possibility of carrying an altered gene that places them at risk or that may be passed on to children. If these feelings arise at any time during the study, you may contact us and we will arrange for you to speak with a genetic counselor.

You should also be aware that there might be social and economic disadvantages, which can be associated with the gathering of genetic information. You should know that our testing might find an inherited defective gene, which puts you at risk for a genetic disorder in the future. Genetic information divulged to the wrong source, could affect you and your family (if an insurance company or employer acquired this genetic information) or socially. We will do our best to keep all information confidential and only with your permission would we make this information available to others. The results of the genetic tests performed for research purposes will not be placed in your medical record. In this manner it will be unlikely that an insurance company or employer would ever learn of such

results. You should be aware that we may detect instances of non-paternity (the discovery through the analysis of genetic testing that the father is someone other than who he was thought to be), and such information may interfere with our analysis. This non-paternity information will be kept in the strictest confidence and will not be divulged to anyone.

Potential Benefits:

You and your family may not directly benefit by participating in this research, however we hope that in the future information obtained from this study will help us understand the genetic causes of strabismus, CCDD's and associated anomalies. This may eventually lead to new forms of treatment and diagnosis. An annual newsletter will be mailed to you and will include general information about grouped results although no individual information will be reported in the newsletter.

Research result possibilities and reporting:

This research study is meant to find genes that are important for strabismus and cranial nerve development, although we cannot study all possible diseases and genes. During the course of this research, we might find the gene(s) or a common variant that causes, or is associated with the strabismus, CCDD or associated anomaly in you/your child. Although we do not intend to, we might also find a gene that causes a different disorder or uncovers a risk of developing a disorder or disease in the future that is unrelated to the reason for your/your child's participation in this study.

You have the option of knowing if our study finds a genetic change in the sample collected from you/your child that, based on current scientific data and knowledge, could be (1) the cause of the disorder in you/your child or (2) the cause of another disorder or disease that could significantly affect your/your child's health or medical care. The latter (#2) would only include results that are proven to have a known significant effect on human health. You also have the option of not learning any results from this research.

Results from research genetic testing may take months or years to complete. It is possible that there will be no results from the research on your/your child's sample. If you wish to inquire into the progress of this research, you are welcome to do so at any time.

Since our research laboratory is not certified for reporting results to patients, we cannot give you results from our research genetic testing. However, if we find a result as described above, we may be able to have these results confirmed by a CLIA-certified clinical laboratory. A CLIA lab is a lab that is authorized to release results from patient tests for clinical and diagnostic purposes. Result confirmation by a CLIA lab would involve the participation of your/your child's health care provider(s) and obtaining a new blood or saliva sample from you/your child. The result would be given to your health care provider and then to you with appropriate medical and genetic counseling. Your result could then be used for clinical and diagnostic purposes and could become part of your/your child's medical record. Testing in a CLIA lab could involve costs not covered by medical insurance.

Please read the statements below and check next to the one that states your current wishes about results from this research study.

1. ☐ I do not want to learn about results found out about me/my child. Please do not contact me.

OR

2. ☐ I want to learn only about results found about me/my child that could explain the condition that was **the reason for my/my child's research participation (strabismus, CCDD or associated anomaly).**

OR

3. ☐ I want to learn about results found about me/my child, including results that could (1) explain my/my **child's condition** (strabismus, CCDD or associate anomaly) and/or (2) be the cause of another disorder or disease **that could significantly affect my/my child's health or medical c**are but is unrelated to the reason for my/my **child's research participation.**

You can change your mind about whether or not to receive results from this research at any time by contacting the Study Contacts listed below. The Study Contacts are also available to discuss your options further at your request.

Alternatives:

Participation in this research is completely voluntary. You should not feel any pressure to participate. If you do not want to participate it will not interfere with any future care you or your family receives at this institution.

What information do I need to know about the Health Insurance Portability and Accountability Act (HIPAA)?

During this research, information about your or your child's health will be collected. In general, under federal law, information about patients is private, but there are exceptions and you should know who will have access to this information and might see it. Researchers may be collecting information about you or your child from medical records. They may also learn things from procedures that are part of the research itself such as tests, office visits, questionnaires and interviews.

The following people will be able to see this information:

- Medical and research staff at Children's Hospital, including people listed on your informed consent.
- Medical staff who are directly involved in your care that is related to the research or arise from it.
- People who oversee, advise or conduct research at Children's Hospital, and people who oversee or evaluate research and care, including the Committee on Clinical Investigation, staff working on quality improvement, and other clinicians and administrative staff of Children's Hospital.
- People from agencies and organizations that provide independent accreditation and oversight of research
- Sponsors or others involved in funding the research
- Federal agencies that oversee or review research information.
- Government agencies and sponsors.
- If some law or court requires us to share the information, we would have to follow that law or final ruling

You/your child should be aware that the federal privacy rule does not cover all of these possible uses. This means that once some of the above mentioned users receive your/your child's health information they do not have to follow the same rules. Other laws may or may not protect sharing of private health information. If you have a question about this you may contact the Children's Hospital Privacy Officer at 617-355-5502.

There is no set time for destroying this information and no time limit for its use. Researchers continue to analyze date for many years and it is not possible to know when they will be done.

You or your child do not have to sign this form. If the form is not signed, however, you will not be able to participate in the study. Not signing will not affect your care or your child's care at Children's Hospital in any way now or in the future. Also, there will be no penalty or loss of benefits if you choose not to sign and participate.

You or your child also have the right to withdraw from this study at any time. You have the right to end your permission for Children's Hospital to use or share the protected information about you or your child that was collected as part of the research.

Researchers may also continue to use information already collected to protect the integrity of the study. This means that your withdrawal won't make the whole study useless. Once you remove your permission and you or your child is no longer in the study, no more private health information will be collected. If you wish to withdraw you will need to do so in writing. Your investigator will have a form for you to use. If you or your child decide to share private information with anyone not involved in the study, the federal law designed to protect privacy may no longer apply to this information.

Although there are some legal limitations, you or your child have the right to get protected information resulting from this research that relates to your treatment or to payments. This information is available after the study analysis is done. To request the information, please contact the Hospital's Privacy Officer at 617-355-5502. If you have questions, please be sure to ask for answers.

Research at Children's Hospital: Children's Hospital has recently developed a web-based, interactive educational program for parents called "A Parent's Guide to Medical Research." To find out more about research at Children's Hospital, please visit the program at www.researchchildren.org

Children's Hospital is interested in hearing your comments, answering your questions and responding to any concerns regarding clinical research at Children's Hospital. If you would like further information about the type of clinical research performed at the hospital or have suggestions, questions or concerns regarding clinical research you may send an email to cci@childrens.harvard.edu or call 617 355-7052 between the hours of 8:30 and 5:00.

INVESTIGATOR'S AND/OR ASSOCIATE'S STATEMENT:

I have fully explained to all involved parties (participant/parent/guardian as applicable) the nature and purpose of the above-described procedures and the risks involved in its performance. I have provided the subject/family with the Privacy Rule if requested. I have answered and will answer all questions to the best of my ability. I will inform the participant of any changes in the procedures or the risks and benefits if any should occur during or after the course of the study. I have given a copy of the consent/ authorization form to the subject/family.

☒ _____

Date (MM/DD/YEAR) Signature of Investigator or Associate

Children's Hospital Boston

RESEARCH CONSENT FORM

CONSENT/AUTHORIZATION:

*If the child to be involved in this research study is a foster child or a ward of the state please notify the researcher or their staff who is obtaining your consent.

I understand that I may use the following contact information to reach the appropriate person/office to address any questions or concerns I may have about this study. I know:

I can call …	At …	If I have questions or concerns about …
Investigator: Dr. Engle	Phone: 617-919-4030 Pager: 617-355-7243 # 1992	▪ General questions about the study. ▪ Research-related injuries or emergencies. ▪ Any research-related concerns or complaints.
Study Contact: Caroline Andrews	Phone: 617-919-2168 ▪	▪ General questions about the study. Research-related injuries or emergencies. ▪ Any research-related concerns or complaints.
Office of Clinical Investigations	Phone: 617-355-7052	▪ Rights of a research subject. ▪ Use of protected health information. ▪ Compensation in event of research-related injury ▪ Any research-related concerns or complaints. ▪ If investigator/study contact cannot be reached. ▪ If I want to speak with someone other than the Investigator, Study Contact or research staff.

I have been satisfactorily informed of the above-described procedure with its possible risks and benefits. I have been provided with the applicable Privacy Rule provisions under the Health Insurance Portability and Accountability Act. I give permission for my/my child's participation in this study and for use of the associated protected health information as described above.

I understand that participation in this study is voluntary. If I refuse to participate or choose to drop out of the study at any time, I understand there will be no penalty or loss of benefits to which I am otherwise entitled, and this decision will not affect present or future care by the doctors or the hospital. I am signing this consent form before participating in any research activities. I have been given a copy of this form.

☒ _____ _____ _____
Date (MM/DD/YEAR) *If subject less than 18yrs:* Signature of Parent or Guardian Relationship to child
or, *If subject 18yrs or older:* Signature of Adult Participant

☒ _____ _____
Date (MM/DD/YEAR) Signature of Child/Adolescent Participant

☒ If child/adolescent's assent not obtained above, please specify why (*e.g. too young, subject sedated*):
_____

WITNESS SIGNATURE REQUIRED BELOW ONLY IF: (check which one applies)

☐ the consent document needs to be read to subject or legal representative or
☐ communication impairments limit the subject's ability to clearly express consent or
☐ required by sponsor/CCI.
☐ other reason: please specify _____

I confirm that the information in this consent form was accurately explained to, and understood by the subject or legally authorized representative, and that informed consent was given freely.

☒ _____ _____
Date (MM/DD/YEAR) Signature of Witness

This section to be modified by the Clinical Investigation Office only.

Protocol #: 05-03-036R Activation date: October 17, 2010 Expiration date: October 16, 2011

APPENDIX C: PATIENT'S GLOSSARY OF TERMS

Eye Conditions and Descriptions: Below are the names and description of eye disorders studied.

Common Strabismus and Refractive Conditions
Amblyopia: Amblyopia is poor or reduced vision in an eye that that is otherwise normal (no structural cause for vision loss). Amblyopia can occur for a variety of reasons, but it is generally because the eye did not develop normal sight during early childhood. It is sometimes called "lazy eye." The eye with the poorer vision is amblyopic.
Anisometropia: Anisometropia occurs when there is a difference in prescription between the two eyes. For example, one eye may be normal and the other may be nearsighted or farsighted. Anisometropia can cause amblyopia in some cases.
Dissociated Vertical Deviation (DVD): DVD is a condition where the non-fixating eye tends to drift upward and outward.
Esotropia (ET): Esotropia is an inward turning of one or both eyes. An infantile ET begins at birth or in the first year of life. Accomodative ET is caused by focusing efforts as the eyes try to see near objects clearly.
Exotropia (XT): Exotropia refers to an outward turn of the eye. It may occur from time to time or it may be constant.
Hyperopia (Far-sighted): Farsightedness is a focusing problem of the eye. Typically, more effort is required to foucs at near, however, depending on the degree you may have no problems focusing, or need glasses for near and/or distance. The farsighted eye has no problem viewing distant objects. Farsighted prescriptions begin with a "+", i.e. +3.00
Hypertropia: Hypertropia involves the upward drift of one eye while the other drifts downward.

Complex Strabismus
Brown Syndrome: Brown Syndrome (BS) is a mechanical problem with the superior oblique muscle. When a patient with Brown's syndrome looks to the side of the un-affected eye, one eye appears higher than the other. When the patient looks straight ahead their eye may look normal or the affected eye may look lower.
Congenital Fibrosis of the Extra Ocular Muscles (CFEOM): Individuals affected with CFEOM are born with ophthalmoplegia (an inability to move the eyes in certain directions) and ptosis (droopy eyelids). The eyes are also usually fixed in an abnormal position and typically affected individuals have difficulty looking upwards.
Congenital Ptosis: Ptosis is the most common anomaly of the eyelid. It presents as an abnormal drooping of the upper eyelid.
Congenital 3rd Nerve Palsy: Congenital 3rd nerve palsy involves the eye muscles under the control of the third nerve. The affected eye is usually below midline and turned out with limited upward, downward, and inward movement. A congenital 3rd nerve palsy may be partial or complete.
Congenital 6th Nerve Palsy: A 6th nerve palsy causes the eye to turn in when looking straight, and the affected eye may not be able to move out to the side fully. A compensatory head posture toward the affected eye may be adopted. The palsy may involve one or both eyes.
Double Elevator Palsy: Double elevator palsy involves weakened elevator muscles (muscles that make the eye look up) with the eye positioned below midline when looking straight ahead and reduced ability to elevate it.
Duane's Syndrome: Duane Syndrome is present at birth and involves limited eye movement inward towards the nose, outward towards the ear, or in both directions. When the affected eye looks towards the nose, the eyeball pulls in and the eye opening narrows.
Horizontal Gaze Palsy (HGP): Horizontal Gaze Palsy is rarely reported in isolation. HGP with facial weakness is Moebius Syndrome. HGP with scoliosis is the only consistent inherited form of HGP.
Marcus Gunn Jaw Winking Syndrome: Marcus Gunn consists of elevation or depression of the eyelid on chewing/suckling and may occur either in one or both eyes, with or without congenital ptosis (drooping eyelid).
Moebius Syndrome: Moebius is characterized by horizontal gaze palsy and facial paralysis. Individuals with Moebius may have absent facial expression, lack lateral eye movements, and be unable to blink.
Wildervanck Syndrome: Wildervank Syndrome is a combination of Duane's Syndrome, hearing loss and Kleippel-Feil anomaly (fusion of two or more cervical vertiebrae). Torticollis and scoliosis may also be present.

APPENDIX D: PARTICIPANT QUESTIONNAIRE

Children's Hospital Boston Center for Strabismus Research
Genetic studies of Strabismus, Congenital Cranial Dysinnervation Disorders (CCDDs) and their associated anomalies

PARTICIPANT CONTACT DETAILS & MEDICAL QUESTIONNAIRE

To be completed by the Research Study Coordinator:
Study Participant ID number: Coordinator initials:
Date Form Completed: MM/DD/YYYY __/ __/ ____

This form should be completed by or on behalf of each participating family member:

Study Participant Demographics

Name: _____ Date of Birth:__ / __ / ____

Gender: ❑ Male ❑ Female

Street Address: _____ Apt/Unit # _____

City: _____ State: _____ Zip Code: _____ Country:_____

Home Tel: ( ) _____ Cell Phone: ( ) _____

Email: _____

Ethnic Background
The National Institute of Health (who are sponsoring our research) require us to collect information on your ethnic background. Would you describe yourself as:

White, non Hispanic | Hispanic | Native American or Alaskan | Black, non Hispanic
Asian or Pacific Islander | Other

Please describe your ethnic background in detail eg. Mixed European Ancestry: _____

Are you the original study subject, i.e. the person in your family initially identified with the eye disorder? Yes No

If NO, what is your relation to the original study subject?

Father *Mother* *Sister* *Brother*
Grandmother *Grandfather* *Uncle* *Aunt* *Cousin*

Other (please describe):

History of Eye Symptoms/Problems
(*In the following section, please provide details relating to your ocular health history*) :

What is the name of the eye disorder(s) of the original study subject? _____
(Please see attached key for further details and descriptions of eye conditions we are studying)

Do you have this eye disorder?

❑ Yes →

Were you born with the eye disorder? ❑ Yes ❑ No ❑ I'm not sure
If NO, how old were you when you were diagnosed? _____

Has the eye condition changed over time? ❑ Yes ❑ No ❑ I'm not sure

If YES, please describe how your eye condition has changed:_____

_____

❑ No →

Do you have a different eye disorder? ❑ Yes _____

❑ No ❑ I'm not sure

❑ I'm not sure

Have you ever seen an ophthalmologist? (eye doctor)	❑ Yes ❑ No ❑ I'm not sure
Have you ever had a drooping eyelid (congenital ptosis)?	❑ Yes ❑ No ❑ I'm not sure
Have you ever had a crossed or wandering eye (amblyopia)?	❑ Yes ❑ No ❑ I'm not sure
Have you ever had double vision?	❑ Yes ❑ No ❑ I'm not sure
Do you ever tilt your head when looking straight?	❑ Yes ❑ No ❑ I'm not sure
Have you ever undergone eye muscle surgery?	❑ Yes ❑ No ❑ I'm not sure
Have you ever worn a patch or used eye drops (atropine penalization) for eye correction?	❑ Yes ❑ No ❑ I'm not sure
Have you ever worn glasses or contacts?	❑ Yes ❑ No ❑ I'm not sure

If you answered YES to any of the above questions, please provide further details (i.e. age of onset of eye condition, dates of surgery, name of procedure if known, reason for glasses, etc.)

_____

_____

Ophthalmologist Information: *If you currently see an ophthalmologist or have seen one in the past, please provide his or her contact information. If your ophthalmologist is at Children's Hospital Boston, you need only provide his/her name.*
Name: _____ Street Address: _____ City: _____ State: _____ Zip: _____ Country: _____ Office Tel: ( ) _____ Fax No: ( ) _____ Email: _____

Other Eye Conditions:	
Do you have a coloboma? (Absence or defect of ocular tissue ranging from a small pit in the optic disk to extensive defects in the iris, ciliary body, choroid, retina, or optic disk),	❑ Yes ❑ No ❑ I'm not sure
Do you have microphthalmia? (Abnormally small eye)	❑ Yes ❑ No ❑ I'm not sure
Do you have epibulbar dermoids? (Eye tumors that are not recurrent or progressive)	❑ Yes ❑ No ❑ I'm not sure
Do you have any abnormal ocular features? (eg. epicanthal folds-tissue overlapping the nasal corner of the eye, telecanthus- increased distance between the inner corners of the eyes, slanting of the palpebral fissure(s)-openingfor the eyes between the eyelids?)	❑ Yes ❑ No ❑ I'm not sure
Do you have any retinal defects? (retinal tears, detachments, etc.)	❑ Yes ❑ No ❑ I'm not sure
Do you have any visual impairment other than previously noted?	❑ Yes ❑ No ❑ I'm not sure
If you answered YES to any question above, please describe: _____ _____	

Family Ocular History Chart:
If you are the original study subject, please complete this page by circling as appropriate. See accompanying eye disorder sheet to provide further details. If you are not the main study subject, please continue to Page 5.

Glasses before age 6	Mother (M)	Father (F)	Brother	Sister	½ sibling through M/F	Grand-Father / Mother	Aunt / Uncle	Other:
Patching	Mother	Father	Brother	Sister	½ sibling through M/F	Grand-Father / Mother	Aunt / Uncle	Other:
Amblyopia ("Lazy Eye")	Mother	Father	Brother	Sister	½ sibling through M/F	Grand-Father / Mother	Aunt / Uncle	Other:
Common Strabismus	Mother	Father	Brother	Sister	½ sibling through M/F	Grand-Father / Mother	Aunt / Uncle	Other:
Eye Muscle Surgery	Mother	Father	Brother	Sister	½ sibling through M/F	Grand-Father / Mother	Aunt / Uncle	Other:
Congenital ptosis (Drooping eye since birth)	Mother	Father	Brother	Sister	½ sibling through M/F	Grand-Father / Mother	Aunt / Uncle	Other:
Complex Strabismus	Mother	Father	Brother	Sister	½ sibling through M/F	Grand-Father / Mother	Aunt / Uncle	Other:
Childhood glaucoma	Mother	Father	Brother	Sister	½ sibling through M/F	Grand-Father / Mother	Aunt / Uncle	Other:
Glaucoma	Mother	Father	Brother	Sister	½ sibling through M/F	Grand-Father / Mother	Aunt / Uncle	Other:
Childhood cataracts	Mother	Father	Brother	Sister	½ sibling through M/F	Grand-Father / Mother	Aunt / Uncle	Other:
Childhood blindness	Mother	Father	Brother	Sister	½ sibling through M/F	Grand-Father / Mother	Aunt / Uncle	Other:
Blindness	Mother	Father	Brother	Sister	½ sibling through M/F	Grand-Father / Mother	Aunt / Uncle	Other:
Macular Degeneration	Mother	Father	Brother	Sister	½ sibling through M/F	Grand-Father / Mother	Aunt / Uncle	Other:
Diabetic Eye Disease	Mother	Father	Brother	Sister	½ sibling through M/F	Grand-Father / Mother	Aunt / Uncle	Other:
Other Eye Disease (retinal detachment, etc.)	Mother	Father	Brother	Sister	½ sibling through M/F	Grand-Father / Mother	Aunt / Uncle	Other:
Skeletal abnormality	Mother	Father	Brother	Sister	½ sibling through M/F	Grand-Father / Mother	Aunt / Uncle	Other:

Family Ocular History Chart continued:
If you are the original study subject, please complete this page by circling as appropriate. See accompanying eye disorder sheet to provide further details. If you are not the main study subject, please continue to Page 5.

Organ abnormality	Mother	Father	Brother	Sister	½ sibling through M/F	Grand-Father / Mother	Aunt / Uncle	Other:
Neurological Disorder	Mother	Father	Brother	Sister	½ sibling through M/F	Grand-Father / Mother	Aunt / Uncle	Other:
Genetic Disorder	Mother	Father	Brother	Sister	½ sibling through M/F	Grand-Father / Mother	Aunt / Uncle	Other:
Other Disorder	Mother	Father	Brother	Sister	½ sibling through M/F	Grand-Father / Mother	Aunt / Uncle	Other:

If you selected 'Other' please provide further details: _____

_____

Medical History:
Please provide information regarding your medical history in the following sections. These sections should be completed by, or on behalf of, all participants

Birth History	
Were you born full term?	❑ Yes ❑ No ❑ I'm not sure
If NO, after how many weeks gestations were you born?	_____ weeks
How many pregnancies did your mother have?	_____ pregnancies
Of these pregnancies, how many were live births?	_____ live births
What was your birth weight?	_____lbs _____ oz ❑ I'm not sure
How old was your mother when you were born?	_____ years old ❑ I'm not sure
How old was your father when you were born?	_____ years old ❑ I'm not sure
Were any medications used during pregnancy?	❑ Yes ❑ No ❑ I'm not sure
If YES please describe when during pregnancy:	
If YES please list all medications taken:	

Birth History continued	
Did your mother smoke cigarettes during her pregnancy with you?	❑ Yes ❑ No ❑ I'm not sure
If YES, please specify:	❑ Until _____weeks gestation **OR** ❑ Throughout pregnancy _____ cigarettes per day
Did your mother drink alcohol during her pregnancy with you?	❑ Yes ❑ No ❑ I'm not sure
If YES, how much?	❑ Until _____weeks gestation **OR** ❑ Throughout pregnancy _____ drinks per week
Did your mother have any complications during her pregnancy with you? (eg. placenta previa, gestational diabetes, etc.)	❑ Yes ❑ No ❑ I'm not sure
If YES please describe:	
Were there any complications during delivery? (i.e. abnormal presentation, c-section, etc.)	❑ Yes ❑ No ❑ I'm not sure
If YES please describe:	
Did you have a prolonged hospital stay after birth?	❑ Yes ❑ No ❑ I'm not sure
If YES please describe:	
Did you fail to thrive in height, weight or head circumference after birth?	❑ Yes ❑ No ❑ I'm not sure
If YES please describe:	

General Review	
Which is your dominant hand?	❑ Right ❑ Left ❑ Ambidextrous ❑ I'm not sure
What is your current height?	_____ Feet _____ Inches ❑ I'm not sure
Please describe your current educational experience.	❑ Grade School ❑ Middle School ❑ High School ❑ College / University ❑ Graduate/Professional
If YES please describe:	
Have you ever undergone chromosomal (genetic) analysis?	❑ Yes ❑ No ❑ I'm not sure
If YES please describe:	
Have you ever undergone imaging study (eg. CT, MRI)	❑ Yes ❑ No ❑ I'm not sure
If YES please describe:	
Have you ever undergone any testing other than already indicated?	❑ Yes ❑ No ❑ I'm not sure
If YES please describe:	
Have you ever undergone surgery or been hospitalized?	❑ Yes ❑ No ❑ I'm not sure
Please list any medications that you are currently taking.	

Ear / Hearing Function	
Have you had a history of chronic ear infections?	❑ Yes ❑ No ❑ I'm not sure
Do you have any hearing loss?	❑ Yes ❑ No ❑ I'm not sure
22a. If YES, please check all that apply:	❑ Conductive ❑ Sensorineural ❑ Unilateral ❑ Bilateral ❑ High frequency ❑ Low frequency ❑ Congenital ❑ Acquired ❑ Stable ❑ Fluctuating
Do you have any ear abnormalities including low set ears, abnormal lobe shape, or pre-auricular appendages?	❑ Yes ❑ No ❑ I'm not sure
If YES please describe:	

Developmental History	
Do you have/have you ever had any developmental delays?	❑ Yes ❑ No ❑ I'm not sure
If YES, please check all that apply:	❑ Gross Motor ❑ Speech and Language ❑ Fine Motor ❑ Social
Do you have/have you ever had any learning disabilities?	❑ Yes ❑ No ❑ I'm not sure
If YES please describe:	
Do you have Attention Deficit (Hyperactivity) Disorder?	❑ Yes ❑ No ❑ I'm not sure
If YES please describe:	
Do you have Autism Spectrum Disorder?	❑ Yes ❑ No ❑ I'm not sure
If YES please describe:	

Neurological Function	
Have you ever been diagnosed with depression, a mood disorder or other psychiatric disease?	❑ Yes ❑ No ❑ I'm not sure
If YES please describe:	
Do you have a history of seizures?	❑ Yes ❑ No ❑ I'm not sure
Do you have/have you ever had altered facial sensation?	❑ Yes ❑ No ❑ I'm not sure
Do you have/have you ever had facial weakness?	❑ Yes ❑ No ❑ I'm not sure
Do you have/have you ever had problems swallowing?	❑ Yes ❑ No ❑ I'm not sure
Do you have/have you ever had problems tasting?	❑ Yes ❑ No ❑ I'm not sure
Do you have/have you ever had a Peripheral Neuropathy (a condition of the nervous system that usually causes tingling, burning and/or weakness in the face, hands, arms, legs and./or torso)?	❑ Yes ❑ No ❑ I'm not sure
If YES, is it:	❑ Axonal ❑ Myelinating ❑ I'm not sure
Do you have/have you ever had any muscle weakness?	❑ Yes ❑ No ❑ I'm not sure

Neurological Function continued	
If YES, is it:	❑ Progressive ❑ Static ❑ Improving ❑ I'm not sure
Do you have/have you ever had abnormal muscle tone?	❑ Yes ❑ No ❑ I'm not sure
If YES, is it:	❑ Low ❑ High ❑ I'm not sure
Do you have/have you ever had episodes of ataxia (clumsy and unsteady movement of the limbs)?	❑ Yes ❑ No ❑ I'm not sure
Do you have/have you ever had any other neurological issues?	❑ Yes ❑ No ❑ I'm not sure
If you answered YES above, please describe in more detail:	

Heart, Lung and Gastrointestinal Function	
Do you have/have you ever had any congenital (since birth) heart defects?	❑ Yes ❑ No ❑ I'm not sure
Do you have/have you ever had any other cardiac problems?	❑ Yes ❑ No ❑ I'm not sure
Do you have/have you ever had any allergies/asthma?	❑ Yes ❑ No ❑ I'm not sure
Do you have/have you ever had any other respiratory problems	❑ Yes ❑ No ❑ I'm not sure
Do you have/have you ever had any gastrointestinal problems? (eg. Gastroesophageal Reflux Disease (GERD), irritable bowel syndrome, Celiac Disease, constipation, etc.)	❑ Yes ❑ No ❑ I'm not sure
If you answered YES to heart, lung and gastrointestinal function, please describe in more detail:	

Urinary/Genital Function	
Do you have/have you ever had any problems or birth anomalies related to your kidneys (eg. ectopic kidney—a kidney not located in its normal place, multicystic dysplastic kidney-development of cysts in the kidney, hydronephrosis-abnormal kidney enlargement)?	❑ Yes ❑ No ❑ I'm not sure
Do you have/have you ever had any genitalia or reproductive organ problems or birth anomalies?	❑ Yes ❑ No ❑ I'm not sure

If you answered YES above, please describe in more detail:

Musculoskeletal & Ectodermal (Skin) Function	
Do you have fused vertebrae?	❑ Yes ❑ No ❑ I'm not sure
Do you have Scoliosis?	❑ Yes ❑ No ❑ I'm not sure
Do you have Arthrogryposis (stiff joints and abnormal muscle development)?	❑ Yes ❑ No ❑ I'm not sure
Do you have/have you ever had any upper limb defects (eg. arm, hand, finger)?	❑ Yes ❑ No ❑ I'm not sure
Do you have/have you ever had any lower limb defects (eg. leg, foot, toes)?	❑ Yes ❑ No ❑ I'm not sure
Do you have/have you ever had any problems or birth anomalies related to your skin, hair, teeth, or nails? (i.e. eczema, soft teeth, missing nails, etc.)	❑ Yes ❑ No ❑ I'm not sure
If you answered YES above, please describe in more detail:	

Is there any other information related to your medical history or family history you feel would be helpful for this study?

_____

_____

_____

Thank you for completing our questionnaire!

APPENDIX E: COMITANT CONGENITAL STRABISMUS STUDY: DATA COLLECTION AND ENTRY REFERENCE MANUAL

Comitant Congenital Strabismus Study

Data Collection and Entry Reference Manual

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Last modified: October 2010

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Introduction

Comitant congenital strabismus (CCS) is one of the most common ophthalmological disorders affecting 1-4% of the population. It includes diagnoses such as infantile esotropia, intermittent exotropia, and accommodative esotropia. Despite the term 'comitant', this group also includes simple forms of A or V pattern strabismus, or vertical strabismus in side gazes. It does not include any paralytic or restrictive forms of strabismus, or incomitant congenital strabismus (ICS).

Individuals affected with CCS often have associated findings that may either contribute to or result from the strabismus. These include hyperopia of varying degrees, anisometropia (asymmetric refraction), reduced stereopsis, and certain forms of vertical strabismus including dissociated vertical deviation and inferior oblique overaction. For this reason, we not only collect information related directly to strabismus, but we also record information on these conditions associated with strabismus.

There is considerable debate in current literature on how best to define different types of strabismus and its associated conditions. These definitions vary depending on treatment versus diagnostic criteria. Von Noorden's *Binocular Vision and Ocular Motility*[1] lists 14 different types of comitant esodeviations, but also recognizes that in clinical situations, overlap exists between many of the diagnoses. Similarly, the definitions of high hyperopia and anisometropia vary in the literature depending in part on whether they are *treatment* criteria or *diagnostic* criteria. Criteria are also related to the age of the patient. According to the American Academy of Ophthalmology (AAO) Preferred Practice Pattern published for the treatment of hyperopia,[2] a refractive error of +4.50 to +6.00 diopters requires treatment in the absence of strabismus, and +2.00 diopters or more requires treatment in the presence of esotropia.[3] Furthermore, bilateral amblyopia has been reported in patients with hyperopia of +4.50 diopters. For these reasons, we have chosen our ranges of +3.50 to +5.00 as moderate hyperopia and +5.00 or more as high hyperopia. While the AAO describes anisometropia as requiring treatment with 2.00 diopters of spherical difference in myopic patients, 1.00 diopter difference in hyperopic patients and 2.00 diopters of astigmatic difference, for consistency we have chosen a single diagnostic value of 1.50 diopters difference in spherical equivalent or cylinder value alone as cited in the screening study by Nassif et al 2006.[4] We have simplified our phenotyping guidelines in order to capture pertinent findings, and to keep the demands of this study reasonable for busy pediatric ophthalmology and adult strabismus clinics.

This manual is designed to aid in data collection and entry of the ophthalmic exam findings in order to standardize the phenotyping of participants within our institution as well as our

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[1] Von Noorden GK, Campos EC (2004). *Binocular Vision and Ocular Motility.* St. Louis, MO: Mosby, Inc.
2 American Academy of Ophthalmology Pediatric Ophthalmology/Strabismus Panel. Preferred Practice Pattern® Guidelines. Pediatric Eye Evaluations. San Francisco, CA: American Academy of Ophthalmology; 2007. Accessed 6/28/2010 at: http://www.aao.org/ppp.
[3] American Academy of Ophthalmology Refractive Management/Intervention Panel. (September 2007). Preferred practice pattern (R): Refractive errors & refractive surgery. Accessed 6/17/ 2010 from http://www.aao.org/ppp
[4] Nassif DS, Piskun NV, Hunter DG. (2006). The pediatric vision screener III: Detection of strabismus in children. *Arch Ophthalmol* 124:509-513.

collaborative sites. While we have made every effort to simplify and clarify our phenotyping guidelines, there will be instances where patients do not appear to fit precisely into one category, and clinical judgment needs to be used. For example, both hyperopia and stereoacuity may be age dependant. According to the AAO Preferred Practice Guidelines,[2] hyperopia of +6.00 D should be considered high in an infant 12 months of age or less, while +5.00 can be considered high at the age of 1-2 years. For stereoacuity, if the patient is unable to fully comprehend, or attend to the testing, they cannot be scored as "low grade stereopsis". In these cases, please record the score achieved and list in the comment section that "stereopsis limited as patient was 2 years old," "unable to comprehend testing", etc. Proper and consistent categorization of patients is essential to the success of the study. Whenever there is a question about how patient data should be entered, please contact us. Thank you for participating in this effort!

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Summary of goals of the CCS study

- Enroll patients and their families with comitant congenital strabismus and associated features.
- Perform detailed sensorimotor examinations on patients.
- Carefully screen family members for strabismus and conditions associated with amblyopia and strabismus.
- Perform genetic studies on the families and individuals with these congenital eye disorders.
- Following identification of genetic variants that cause or are associated with strabismus, correlate participants' strabismus phenotypes with their underlying genotypes (phenotype-genotype correlations).

Inclusion Criteria:

- Manifest or intermittent comitant strabismus of any angle
- Latent or phoric comitant strabismus of 10 prism diopters or more

Exclusion Criteria:

- Strabismus with a non-heritable etiology or structural ocular abnormality causing acquired vision loss
- Structural brain abnormalities as determined by neuroimaging
- Conditions causing occlusion of the eye and leading to deprivation amblyopia
- Molecularly defined genetic syndromes or other diagnoses associated with strabismus such as trisomy 21 or craniosynostosis.

Definitions of Affection Status

1. Affected with strabismus

Participants with one or more of the following criteria are to be scored as 'affected with strabismus':

- Manifest or intermittent strabismus of any size.
- Phoric deviations of 10 prism diopters or more.
- Status post surgery for congenital comitant strabismus.

2. Affected with a strabismus-associated condition

Participants with one or more of the following criteria are to be scored as 'affected with a strabismus-associated condition':

- Anisometropia: Spherical equivalent or astigmatic difference 1.5 diopters or greater.
- Moderate hyperopia: Hyperopia of +3.50 to +4.75
- High hyperopia: Hyperopia of +5.00 diopters or more
- Low-grade stereopsis: Stereopsis or fusion without high-grade stereopsis. Stereoacuity within the range of 60 – 3000 seconds of arc.
- Vertical strabismus: Typically small angle vertical deviations such as dissociated vertical deviation or inferior oblique overaction. Do not include participants in this group that have ICS suspected of having a restrictive or paralytic component.

3. Questionably affected with strabismus

Participants with one or more of the following criteria are to be scored as 'questionably affected with strabismus':

- A history of patching (without findings on current orthoptic exam or without access to suitable medical records)
- A history of eye exercises (without findings on current orthoptic exam or without access to suitable medical records)
- Convergence insufficiency (without a significant X(T) – as diagnosed by detailed orthoptic exam)

Introduction to the Progeny Database

We use the SQL **Progeny genetic data management software** for this study (www.progenygenetics.com). Progeny provides software tools to assist researchers with the management of clinical, genotypic, and sample data integrated into one database, and thus is suitable for use by our international consortium. The database is also encrypted and conforms to HIPAA, 21 CFR Part 11, and GLP guidelines. This database has been custom-designed for this study and can be utilized to track patients, record data, and draw family trees with corresponding genetic haplotype and/or SNP data. This provides a high level of data security and the ability to fully audit records. The software has been developed to house specific phenotypic data, and an electronic representation of the ophthalmologic clinical exam sheet used at CHB has been created to facilitate accurate recording. The software is available both in Windows and in a custom-designed, browser-based environment. The Windows version is available for use at Children's Hospital Boston (CHB), and the web browser version is available to our collaborators and for use at CHB. Our collaborators have the option of purchasing their own Progeny license, but CCS information must be uploaded to the web-based application. The website may be found at the following address: rc-progeny.tch.harvard.edu/engle

All persons using the database are required to first complete a tutorial with the Engle Lab's Clinical Research Program Director, Caroline Andrews, and the Lead Orthoptist, Sarah MacKinnon. Once the tutorial is completed, a username and password will be provided to the database user by Ms. Andrews. Each collaborator's access will be restricted to allow viewing and entering data from his or her location folder only. Data entries of each collaborator will be audited by the CHB group to ensure information is complete and accurate.

Once users are signed in to the database, they will be able to select their CCS folder and begin entering pedigrees. When the appropriate folder has been chosen, the "add new pedigree" icon can be selected, a pedigree name assigned and the family tree drawn by following the prompts provided when right clicking the mouse.

Next, a unique ID is assigned to each individual who has participated in the study and for whom accompanying information and sample data requires database entry. This is done by double clicking on the individual and selecting the "Individual data sheet" prompt, and then entering the individual's unique identification code. For CHB participants, this data is entered into the field: "Participant ID"; for collaborating sites, this field is entered into the "Collaborating investigator ID" field (the "Participant ID" field will then be entered by Ms Andrews, or her designate, upon pedigree sample receipt in the lab and review of data).

Once a unique individual ID is assigned, and while the user is still in the pedigree viewer pane, the spreadsheet mode is selected and the CHB questionnaire format selected and loaded. This format has been created to mimic the participant questionnaire page layout precisely, enabling simultaneous data entry for each individual within the pedigree. Alternatively, the user may opt to enter each participant's medical history while in the "Individual data sheet", which will require opening each individual separately, a more time consuming method of data entry.

Once the pedigree is created and demographic information has been properly entered, and while in the pedigree viewer pane, sample data can be entered by first right clicking on the appropriate individual, and then selecting "Add sample". This field and additional data pertaining to the sample origin, volume contained etc. is entered by Ms Andrews or her designate only, and is the same identifier as previously provided in the "Participant ID" field. CHB study staff will enter this data for the collaborating sites upon sample receipt and when reviewing pedigree data entry for accuracy and completion.

Upon completion of the above, the ophthalmic data may be entered using the shortcuts described in detail in the sections that follow. The first tab viewed will be the participant's medical history, followed by the ophthalmic data sheets.

Shortcut tabs

A shortcut has been created to input the phenotypic data into the custom Progeny database we have designed. There are several tabs for the ophthalmic data:

- Summary page
- Binocular vision
- Visual acuity
- Primary gaze measurements
- Ocular motility
- Strabismus measurements
- Other findings

= Indicates field ID

1st Tab: Summary page

Aim: Highlights and summarizes the phenotypic data.

Strabismus study identifier:
- Will be provided by Engle lab for CHB patients
- Offsite locations will determine their own IDs

CHB MRN:
- Medical record number for CHB patients

Affection status:
For a detailed description of terms below, please refer to *Definitions of Affection Status* on page 6.
- Affected = affected with strabismus
- Associated affected = affected with a strabismus-associated condition
- Questionably affected= questionably affected with strabismus
- Unaffected
- Unknown

Date of exam

For probands:
- When multiple exams are available in a patient chart, our preference is to use the information from a single exam whenever possible.
- Exam should include: complete data; good co-op for reliable observations; optimal correction in place; prior to strabismus surgery or other intraorbital or intraocular procedures.
- If the exam with the most accurate sensorimotor data does not have a refraction, or is missing other critical pieces of information, data may be used from another visit, but please record that date in the comment section.
- When data differs from one visit to another; "worst" data (largest deviation or refraction with anisometropia) should be recorded.
- In some cases, "worst" data may be from different exams. Make sure to record different dates if needed.

For family members
- At time of examination
- If outside records are available, data can be entered at examiner's discretion. Date should reflect the date of that exam.

Cooperation for exam:

- Good = good cooperation (default answer)
- Poor = poor cooperation
- Unknown = cooperation was not recorded

Examined by:

- Text field. Enter initials of orthoptist, MD or other clinician that performed the exam (enter multiple names if applicable). For use at CHB or collaborating site.

Data input by:

- Enter name of CHB orthoptist entering data into progeny.

Collaborator data input:

- Text field. Enter initials of orthoptist/ophthalmic tech entering data into progeny from a collaborating site.

Exam completed

Rationale: To highlight under what circumstances the data was collected in this subject

- Normal = Unaffected patient (default answer)
- Before treatment = Affected patient, no prior treatment
- After treatment, before surgery = Affected patient, has had prior treatment i.e. optical correction, amblyopia treatment, but not surgery (including Botox). Please use this option even if surgery is not indicated for the patient.
- After all treatments = After treatment including surgery (including Botox)

Optical correction:

Rationale: To identify patients who were wearing glasses (or given a prescription for glasses.

- Yes: wearing glasses (or glasses were prescribed) at the time of exam
- No: not wearing glasses (or glasses were not prescribed) at the time of exam (default answer)

Amblyopia treatment

Rationale: to identify which patients enrolled had amblyopia treatment at any time. To accept reliable patient histories (examiner discretion) about past use of patching, optical or pharmacological penalization to treat weak vision.

- Yes = present or past amblyopia therapy performed.
- No = no past or present amblyopia therapy (default answer)

Surgical intervention

Rationale: To identify which patients have had strabismus surgery.

- No: patient has not had prior strabismus surgery
- Yes: patient has undergone strabismus surgery (default answer)

Directional classification

Rationale: To identify the direction of misalignment. All applicable categories should be selected. If patient is unaffected, but a small angle phoria exists, direction should be indicated. Deviation that is recorded should be before surgical intervention, even if that means relying on the patient's history of their original deviation and its direction.

- Normal: No misalignment detected
- Eso: Esophoria, Intermittent Esotropia, or Esotropia is noted
- Exo: Exophoria, Intermittent Exotropia or Exotropia is noted
- Vertical: Hyper or hypo deviation is noted. May be phoric, intermittent or manifest
- DVD: DVD is noted on exam

Control of Strabismus:

Rationale: To understand the control of the patient's strabismus with optimal optical correction in place. All applicable categories should be selected.

- Ortho: no deviation noted in primary position
- Phoria: phoria noted in primary position
- Tropia: manifest deviation in primary position
- Intermittent: patient was able to control deviation during portion of the exam in primary position
- Accommodative: Eso deviation reduces with hyperopic correction or +3.00 lenses by 10 prism diopters or more.

Sensory status:

Rationale: To understand patient's level of binocularity. All applicable categories should be selected. If a proband develops high-grade stereopsis over time, this should be recorded prior to any surgical intervention.

- High-grade stereopsis: Stereoacuity of 50 seconds of arc or better.[5] If patient is younger, clinician's judgment should be used. Bifoveal fusion
- Low-grade stereopsis: Stereoacuity within the range of 60 – 3000 seconds of arc.
- Fusion: Patient demonstrates some level of sensory or motor fusion; however no stereopsis could be demonstrated.
- Suppression: Patient suppresses an eye during testing (on any test of binocularity, or if manifest deviation is present and patient does not note diplopia when questioned).
- Amblyopia: Patient has or had amblyopia. Amblyopia will be defined as two or more difference in best-corrected acuity, or strong fixation preference in those unable to perform recognition acuity.
- Monofixation syndrome: Patient demonstrates gross binocularity or peripheral fusion in the presence of a central suppression scotoma or small angle strabismus
- Diplopia: Patient reports diplopia on exam, which is consistent with exam findings.

[5] Scott MH, Raymond WR, Parks MM (1994). Prevalence of primary monofixation syndrome in parents of children with congenital esotropia. *J Ped Ophthalmol Strabismus*. 31, 298-301; discussion 302.

Comitancy:
Rationale: To document whether strabismus was comitant or incomitant.

- Comitant: Strabismus was measured to be similar in all positions of gaze.
- A pattern: Minimum of 10 prism diopters difference in horizontal strabismus measurements between upgaze and downgaze. Eso deviation 10 pd larger in upgaze, Exo deviation 10 pd smaller in upgaze.
- V pattern: Minimum of 15 prism diopters difference in horizontal strabismus measurements between upgaze and downgaze. Eso deviation increased by 15 pd in down gaze. Exo deviation decreases by 15 pd in downgaze.
- Lateral incomitance: Minimum of 10 prism diopters difference in strabismus measurements between right and left gaze.
- D/N disparity: Minimum of 10 diopters of difference in horizontal misalignment measured between distance and near.
- Complex: participant has complex strabismus that is incomitant and does not fit into one of the patterns above.

Refractive status:
Rationale: To summarize the refractive status and group the patients into specific categories

- Emmetropia: Less than 3.5 D of hyperopia and less than 0.5 D of myopia with astigmatism less than 1.5 D.
- Anisometropia: 1.5 D or more difference in refractive error (spherical equivalent or astigmatic value). Difference must be present on refraction, not just on glasses.
- Astigmatism: 1.5 D or more of astigmatism.
- Moderate hyperopia: 3.5 D or more of hyperopia
- High hyperopia: > or = +5.00 D of hyperopia
- Myopia: 0.5 D or more of myopia.

Diagnosis Fields

- Horizontal alignment:
  - **Esotropia:** Manifest esotropia in primary position
  - **Infantile Esotropia:** Manifest esotropia that develops within the first six months of life
  - **Accommodative Esotropia:** Manifest esotropia reduces with hyperopic correction to a range that fusion may be achieved (less than 10 prism diopters) or reliably demonstrate fusion. If bifocals are required to reduce the deviation to 10 prism diopters or less it's acceptable.[6]
  - **Intermittent Esotropia**: Patient has an intermittent esotropia at any point during the examination in primary position.
  - **Esophoria**: Esophoria of 10 prism diopters or more in primary position
  - **Acquired Esotropia**: Acute acquired non-accommodative esotropia. Ophthalmologist has ruled out other causes of esotropia.
  - **Exotropia:** manifest exotropia in primary position
  - **Infantile Exotropia:** manifest exotropia that develops within the first six months on life.

[6] Raab EL (2001). Monitoring of controlled accommodative esotropia. *Trans Am Ophthalmol Soc* 99:225-8; discussion 228-31.

- **Intermittent Exotropia:** intermittent exotropia at any point during the examination in primary position
- **Exophoria:** Exophoria of 10 diopters or more in primary position
- **Microstrabismus**: small angle manifest deviation in primary position.
- **Decreased stereo:** Low grade stereoacuity: With proper correction, and ideal lighting and instruction, participant is unable to achieve better than 60 seconds of arc (range will be 60-3000 seconds of arc). Please use clinical judgment when testing young children. If stereoacuity seems reasonable for their age, please do not use this diagnosis. Please note; these patients will only be 'affected with a condition associated with strabismus".
- **Patching:** Diagnosis of exclusion for family members only. History of patching as a child for amblyopia treatment, but unable to verify source of amblyopia during the exam or family member was not available for examination. Please note: these patients will only be considered 'questionably affected'.
- **Strabismus surgery** – unknown diagnosis: Diagnosis of exclusion for family members or probands whose original deviation is unknown.
- **Exercises:** diagnosis of exclusion for family members only. History of exercises as a child, no other diagnosis could be made from eye exam (or family member was not available for examination). Please note, these patients will only be 'questionably affected'.

- Vertical alignment:
  - **Yes:** patient has vertical misalignment of their eyes. Vertical phoria, tropia, intermittent deviation or DVD.
  - **No:** no vertical misalignment is present.
  - **Questionable:** affected: patient is suspected of having a vertical misalignment, but it could not be verified by exam.

- Refraction:
  - Anisometropia: 1.5 Diopters or more difference in refractive error (spherical equivalent or astigmatic value)
  - Moderate hyperopia: 3.5 to 5.00 Diopters of hyperopia.
  - High hyperopia: Greater than or equal to +5.00 Diopters of hyperopia.
  - Anisometropia + moderate hyperopia: meets criteria for both anisometropia and moderate hyperopia
  - Anisometropia + High hyperopia: meets criteria for both anisometropia and high hyperopia
  - Questionably affected: suspect one of the refractive diagnoses above but unable to verify by exam.

- Ptosis >= 2mm:
  - Yes: patient has a ptosis of 2mm or more.
  - No: patient has no, or less than 2 mm of ptosis.
  - Questionably affected: patient is suspected of having a ptosis, but it could not be verified by exam.

Data reviewed by:
Rationale: To list which CHB orthoptist reviewed participant's data

- SM
- JB

Aware that they are affected?
Rationale: To track the number of patients that are unaware that they are "affected" with strabismus or a condition associated with strabismus. *Please only fill out for family member's eye exams.*

- Yes
- No
- N/A (will default to this for probands)

Incomplete data:
Rationale: To track which participants (not probands) need to be re-called for another eye screening
Text field: Please describe what needs to be checked/repeated and why (if relevant).

Comments:
Rationale: List any comments relevant to patient exam, diagnosis or eventual outcome if known.
Text field: Please enter any comments.

Ophthalmological exam details:
Research assistants will use this at time of enrollment.
Orthoptists are not able to enter in this field and should use comment box.

2nd Tab: Binocular Vision

Aim: The objective is to determine the binocular status of the patient. Ideal to prove the highest level achievable i.e. high-grade stereoacuity however documenting the presence of any level of binocular co-operation is valuable. Please ensure that optical correction is used in order to demonstrate presence of high grade stereopsis.

AHP = anomalous head posture to achieve either fusion or to improve vision in cases of nystagmus; tick if present (regardless of mechanism causing the AHP).

Stereopsis

First preference is to demonstrate stereopsis:

- Presence of stereo on a single test is sufficient.
- *However*, if a negative result is found on your preferred test, try at least one other additional stereo test to prove a clear negative response.

Fly = Titmus fly booklet

- 0 = negative for perception of depth (wings sticking off page)
- 3000 = positive for perception of depth; need to ensure a true perception and not an artifact. Non-verbal responses accepted e.g. by touch.
- Attempted = inconclusive for the presence of stereopsis

Animals = Titmus or Randot booklet

- 1= first animal is correctly identified (400 seconds of arc).
- 2= first and second animals are correctly identified (200 seconds of arc)
- 3= all animals are correctly identified (100 seconds of arc)

Randot = Randot circles

- 1= first circle is correctly identified (400 seconds of arc)
- 2= first two circles are correctly identified (200 seconds of arc)
- 3= first three circles are correctly identified (140 seconds of arc)
- 4= first four circles are correctly identified (100 seconds of arc)
- 5= first five circles are correctly identified (70 seconds of arc)
- 6= first six circles are correctly identified (50 seconds of arc)
- 7= first seven circles are correctly identified (40 seconds of arc)
- 8= first eight circles are correctly identified (30 seconds of arc)
- 9= first nine circles are correctly identified (25 seconds of arc)
- 10= all 10 circles are correctly identified (20 seconds of arc)

Titmus = Titmus circles

- 1= first circle is correctly identified (800 seconds of arc)
- 2= first two circles are correctly identified (400 seconds of arc)
- 3= first three circles are correctly identified (200 seconds of arc)
- 4= first four circles are correctly identified (140 seconds of arc)
- 5= first five circles are correctly identified (100 seconds of arc)
- 6= first six circles are correctly identified (80 seconds of arc)
- 7= first seven circles are correctly identified (60 seconds of arc)
- 8= first eight circles are correctly identified (50 seconds of arc)
- 9= first nine circles are correctly identified (40 seconds of arc)

Frisby = Seconds of arc determined by plate size and distance using Frisby stereotest. Patient must reliably identify the location of the circle, typically a minimum of 3 times.

- 20"
- 30"
- 40"
- 55"
- 75"
- 85"
- 110"
- 150"
- 170"
- 215"
- 340"
- 600"
- Negative: no stereopsis demonstrated
- Attempted: test attempted, inconclusive

Lang = Lang I stereotest (please note Lang II available for Mackey pedigrees with 200, 400, 600 seconds of arc options)

- Yes = positive response. Ideal response would be for the patient to name the pictures. If unable to name, a positive response can be recorded if the examiner if they are confident that the patient perceived the picture.
- No = negative response. Patient unable to perceive pictures.

TNO = Scores for the test figures are recorded. Patient must reliably demonstrate which sector is missing from the disc.

- 480"
- 240"
- 120"
- 60"
- 30"
- 15"

Fusion

Failing to demonstrate stereopsis secondary tests of binocular vision should be attempted i.e. W4D.

W4D near: Worth 4 dot tested at near. All attempts should be made to get the most accurate answers from those examined.

- 4 lights = 4 lights are simultaneously perceived
- R supp = lights from the right eye are not perceived
- L supp = lights from the left eye are not perceived
- Alt supp = either eye is suppressed during the test
- Diplopia = 5 lights are simultaneously perceived during the test
- Unreliable = attempted, but a reliable response could not be recorded.

W4D distance: Worth 4 dot tested in the distance using a flashlight. All attempts should be made to get the most accurate answers from those examined.

- 4 lights = 4 lights are simultaneously perceived
- R supp = lights from the right eye are not perceived
- L supp = lights from the left eye are not perceived
- Alt supp = either eye is suppressed during the test
- Diplopia = 5 lights are simultaneously perceived during the test
- Unreliable = attempted, but a reliable response could not be recorded.

4 pd BO/BI: 4 prism diopter test for central suppression scotoma.
To be tested at distance fixation to the smallest target seen by each eye (ideally a 20/40 optotype). Should be repeated until a clear response is reliably observed.

- Positive RE: no movement is seen when the prism is placed in front of the right eye while the patient fixates in the distance on a small target; conclusively demonstrates central suppression of the right eye. To confirm: movement is seen when the prism is placed in front of the left eye.
- Positive LE: no movement is seen when the prism is placed in front of the left eye while the patient fixates in the distance on a small target; conclusively demonstrates central suppression of the left eye. To confirm: movement is seen when the prism is placed in front of the right eye.
- Negative: central suppression is not identified in either eye.
- Attempted: test was attempted, but patient's response was inconclusive.

20 pd BO:
To be tested with loose prism while patient fixating on a near target.

- Fusion: patient overcame the induced deviation, typically a version, then vergence will be seen when positive response.
- No fusion: no movement of the eyes is observed, or the prism induces an exo deviation.
- Attempted: attempted but inconclusive (generally due to poor patient cooperation)

NPC: Near point of convergence; recorded in centimeters, from bridge of nose to target. Objective determination by examiner, distance where eyes are unable to maintain convergence. Should be repeated a minimum of three times.
When range is given, i.e. 4-6 cm, larger number should be recorded.
Acceptable techniques:

- RAF
- Ruler

- Field values are from 0 (to nose) to 15 cm, in 1 cm increments. The final field value is " very remote" for beyond 15 cm.
- If old records are being used, and the numerical value is not listed, the following numbers can be used:
  - Unlimited: if converges to end of nose well maintained = 0 cm
  - Good: 6 cm
  - Moderate: 10 cm
  - Remote: 15 cm

Bagolini: Tested at near using Bagolini striated lenses. All attempts should be made to get the most accurate answers from those examined.

- Fusion = "X" is perceived by patient
- R supp = line from the right eye is not perceived
- L supp = line from the left eye is not perceived
- Central suppression = central portion of the "X" is suppressed
- Alt supp = either eye is suppressed during the test
- Diplopia = Two lines are perceived simultaneously but an "X" is not seen.
- Unreliable = attempted, but a reliable response could not be recorded.

Sensory impression:
Rationale: To summarize the sensory status.

- High grade stereoacuity: 50 seconds of arc or better
- Low grade stereoacuity: 60-3000 seconds of arc
- Fusion (no-stereo): Fusion demonstrated, but no stereo detected.
- No fusion: No fusion or stereo demonstrated
- Unable: unable to test or inconclusive responses

N.B.: If coarse or fusion is selected, please be sure to rule out the presence of a monofixation syndrome. Clinical tests should be performed in cases where there is suspicion of monofixation or microstrabismus. Need to demonstrate the presence of peripheral fusion and the presences of a central scotoma – W4D of differing sizes, Bagolini central scotoma, and/or 4PD base out test. Please remember that if stereo is not high grade the participant will be coded as questionably affected despite absence of strabismus or amblyopia (unless the patient is unable to cooperate or too young to demonstrate high grade stereopsis – clinical judgment should be used).

Comments:
Please include results from any other tests here or any other observations noted during the sensorimotor exam. Comments that pertain to patient cooperation that may limit results should also be written. For example if patient is only able to achieve 100 seconds of arc, but they are two years old, please write, "Low grade stereo, but ok for age", and in that case you would not code as questionably affected.

3rd Tab: Visual acuity

Aim: To determine the best corrected visual acuity and rule out amblyopia. This section also determines the refractive status of the patient, and is used to decide whether significant anisometropia is present.

At the minimum, best-corrected, monocular distance visual acuity and a refraction are required data points for this section. A cycloplegic refraction is needed for probands, but an autorefraction is acceptable for family members. Pinhole is also a required field if acuity is not 20/20 in each eye.

Please see conversion table below to convert your findings into our format. If exact data point is not found, please select the closest number. Round your acuity down (worst acuity) if needed. +/- letters will be ignored for acuity scoring.

20 ft	6 m	Decimal	Log MAR	Jaeger
20 / 400	6 / 120	0.05	+1.3	J19
20 / 320	6 / 95	0.06	+1.2	J18
20 / 250	6 / 75	0.08	+1.1	J17
20 / 200	6 / 60	0.1	+1.0	J16
20 / 160	6 / 48	0.125	+0.9	J15
20 / 125	6 / 38	0.16	+0.8	J14
20 / 100	6 / 30	0.2	+0.7	J13
20 / 80	6 / 24	0.25	+0.6	J11
20 / 63	6 / 19	0.32	+0.5	J9
20 / 50	6 / 15	0.4	+0.4	J7
20 / 40	6 / 12	0.5	+0.3	J5
20 / 32	6 / 9.5	0.63	+0.2	J3
20 / 25	6 / 7.5	0.8	+0.1	J2
20 / 20	6 / 6	1.0	0	J1
20 / 16	6 / 4.8	1.25	-0.1	J1+
20 / 12.5	6 / 3.8	1.6	-0.2	
20 / 10	6 / 3	2.0	-0.3	

Visual acuity

Vision test:
Please record the acuity test used. Letters are preferred if possible; tests are listed in order of preference:

- ETDRS
- Snellen
- HOTV
- Lea symbols
- Allen cards
- Teller acuity
- Cardiff Cards
- Kay pictures
- Keeler LogMAR

Test format:
Please record the format of the test. Lines preferred when possible, with next preference given to crowding bars.

- Line
- Isolated
- Crowding bars
- Unknown
- N/A

Near test:
If tested, please indicate which type of test was completed.

- Letters
- Symbols

Vision:
There are several potential fields to record vision data. All are not required, but please complete all testing necessary to achieve best-corrected acuity and to diagnose or rule out amblyopia.

sc: without optical correction
cc: with optical correction
Right eye, **Left eye** and/or with **Both eyes** open

Field options:

- 20/10
- 20/15
- 20/20
- 20/25
- 20/30
- 20/40
- 20/50
- 20/60
- 20/70
- 20/80
- 20/100
- 20/125
- 20/160
- 20/200
- 20/250
- 20/300
- 20/400
- <20/400
- CF: count fingers
- HM: hand motion
- LP: light perception
- NLP: no light perception
- F+F: fix and follow
- CSM: central steady maintained
- BTL: blink to light

Preferential looking:
Teller acuity cards

sc: without optical correction
cc: with optical correction
Right eye, **Left eye** and/or with **Both eyes** open
Exact numbers may not be listed, but please select the closest Snellen equivalent or cycles per degree. Round to the lower (poorer) acuity if needed.

Field options:

- 20/16 - 38
- 20/23- 27
- 20/32 - 19
- 20/45 - 13
- 20/63 – 9.6
- 20/66 -9.1
- 20/89 – 6.8
- 20/94 – 6.4
- 20/130 – 4.5
- 20/180 – 3.3
- 20/190 – 3.1
- 20/260 – 2.4
- 20/270 - 2.2
- 20/360 – 1.7
- 20/380 – 1.6
- 20/470 – 1.3
- 20/540 - 1.1
- 20/670 – 0.9
- 20/710 – 0.84
- 20/960 – 0.63
- 20/1000 – 0.6
- 20/1400 – 0.44
- 20/1900 – 0.31
- 20/2000 – 0.30
- 20/2700 – 0.22

Near vision

If near vision is tested (optional; please test if needed for diagnosis or relevant to patient). Near test used should already have been selected (see above).

- Near vision:
  - Please indicate vision level under all applicable fields.
    - Right eye
    - Left eye
    - Both eyes
  - Field options (vision levels are listed above under acuity).

Pinhole:
Required field if acceptable vision level is not achieved and amblyopia cannot be ruled out. Please test in all those that are cooperative if acuity is not 20/20. Field options are listed above under visual acuity, but include, NI which means 'no improvement'.

Refraction and Correction:

Both of the above subcategories above have the same field options. If the refraction or correction are outside of the range, use the highest value and give the actual value in the comment field.

Sphere:
Values range from -22.00 to +25.00 in 0.25 diopter increments.

Cylinder:
Values range from -10.00 to +10.00 in 0.25 diopter increments.

Axis:
Values range from 0 to 180 in 5 degree increments.

Manifest: non-cycloplegic (no drops/undilated) refraction. Please record the sphere, cylinder and axis as appropriate. There is also a place to record the vision with the manifest refraction in place.

Cycloplegic: refraction after the patient has been fully dilated using cycloplegic drops such as cyclogyl. Please record the sphere, cylinder and axis as appropriate. There is also a place to record the vision with the refraction in place.

Manifest Autorefraction: manifest refraction as determined by an autorefractor. Please record the sphere, cylinder and axis as appropriate.

Cycloplegic Autorefraction: cycloplegic refraction as determined by an autorefractor. Please record the sphere, cylinder and axis as appropriate.

Glasses: The measurement of the pair of glasses used for the exam should be read using a lensmeter. If the patient wears contact lenses, the Rx can also be written here, but this should be noted in the comments section. It should also be noted how the CL Rx was known, for example, "per patient" or "read from box". If a prior Rx was for anisometropia or hyperopia that has resolved, please record and put date of Rx in the comment field.

Readers: The measurement of the reading glasses should be placed here.

Comment: Text box for any relevant comments, dates of other refractions and their results, or if autorefraction was attempted but not successful. Also any notes about vision, CL, or exact refraction if out of range available above, should be placed here.

4th Tab: Primary Gaze Measurements

Aim: To accurately determine the ocular alignment in primary position

Distance and Near:
All measurements will be taken while the patient is in primary position (the patient should be looking directly ahead with no head posture; the head should be in a "straight" position). Near measurements should be taken at 1/3m and distance measurements should be taken at approximately 4-6m (depending on lane length).

There are several potential fields available to record measurements. All are not required, but those relevant should be completed when possible. Both the horizontal and vertical measurements should be completed when detected.

APCT: Alternate prism cover test. This is the preferred measurement as it measures the full deviation; latent and manifest.

APCT +3.00: Alternate prism cover test with +3.00 lenses. This measurement is only used at near to try and reduce accommodative convergence in attempt to decrease an esotropia or to increase an exotropia.

SPCT: Simultaneous prism cover test. Measures the manifest component only, which may be useful if the deviation "builds".

Krimsky: Position of the light reflex centered with a prism. Prism may be placed over the fixing or non-fixing eye when there is no motility restriction noted.

sc: without optical correction

cc: with optical correction

Horizontal deviation:

- No horizontal: no horizontal deviation is detected
- E: an esophoria, or latent inward deviation, is detected
- E(T): an intermittent esotropia is detected
- ET: a constant esotropia is detected
- X: an exophoria, or latent outward deviation, is detected
- X(T): an intermittent exotropia is detected
- XT: a constant exotropia is detected
- Not measured: this measurement was not completed

Horizontal prism diopters:

- Measured using prism diopters
- From 0 - 100+ prism diopters.
- Please select the value that is closest to that measured. If needed, please round your value up. For example if measurement is written of ET 35-40, please record as a 40.
- If entering data from a medical record that did not specifically indicate the prism diopters, the following guideline should be used:
    - "Flick": 2 prism diopters
    - "Small": 10 prism diopters
    - "Medium" or "moderate": 25 prism diopters
    - "Large": 40 prism diopters
    - "Marked": 50 prism diopters

Vertical deviation:

- No vertical: No vertical deviation was detected
- RH: latent upward deviation of the right eye or a right hyperphoria is detected. Conversely, a left hypophoria may have also been measured, but should be recorded as a RH.
- RH(T): intermittent right hypertropia, or an intermittent left hypotropia is detected
- RHT: a constant right hypertropia or left hypotropia is detected.
- RHT + DVD: a right hypertropia with dissociated vertical deviation is noted.
- LH: a latent upward deviation of the left eye or a left hyperphoria is detected. Conversely, a right hypophoria may have also been measured, but should be recorded as an LH.
- LH(T): intermittent left hypertropia, or an intermittent right hypotropia is detected.
- LHT: constant left hypertropia or right hypotropia is noted.
- LHT + DVD: a left hypertropia with dissociated vertical deviation is noted.
- DVD: dissociated vertical deviation is detected with no other vertical deviation.
- Not measured: this measurement was not completed

Vertical prism diopters:

- Measured using prism diopters
- From 0 - 60 prism diopters.
- Please select the value that is closest to that measured. If needed, please round your value up. For example if measurement is written of RH(T) 15-20, please record as a 20.
- If entering data from a medical record that did not specifically indicate the prism diopters, the following guideline should be used:
    - "Flick": 2 prism diopters
    - "Small": 10 prism diopters
    - "Medium" or "moderate": 25 prism diopters
    - "Large": 40 prism diopters

5th Tab: Ocular Motility

Careful measurements of the ocular motility should be recorded in this section. If found to be abnormal and the participant has consented, photographic documentation should also be completed. Photos can be added into a later tab.

All fields are required to be completed on this page.

A description exists in the database for the primary field of action of each muscle, but it can also be seen below:

- RSR: Right superior rectus; elevation of the right eye in abduction.
- RLR: Right lateral rectus; abduction of right eye.
- RIR: Right inferior rectus; depression of the right eye in abduction.
- RIO: Right inferior oblique; elevation of the right eye in adduction.
- RMR: Right medial rectus; adduction of right eye.
- RSO: Right superior oblique; depression of the right eye in adduction.
- LIO: Left inferior oblique; elevation of the left eye in adduction.
- LMR: Left medial rectus; adduction of the left eye.
- LSO: Left superior oblique; depression of the left eye in adduction
- LSR: Left superior rectus; elevation of the left eye in abduction.
- LLR: Left lateral rectus; abduction of the left eye
- LIR: Left inferior rectus; depression of the left eye in abduction

Field options:

- While motility is most often scored on +4 (gross overaction) to -4 (gross underaction, not past midline) we included the range for +5 to -5 at 0.5 increments.

6th Tab: Strabismus Measurements

Strabismus measurements are required in the following positions of gaze (unless they are not possible due to patient age or cooperation):

- Up gaze
- Down gaze
- Right gaze
- Left gaze
- Right and left head tilt are required if a vertical deviation is present.

The following measurements are optional:

- Right up gaze
- Right down gaze
- Left up gaze
- Left down gaze

The field options are the same as in "Primary Gaze Measurements". APCT (Alternate Prism Cover Test) should be used to measure in the positions of gaze if possible. If another type of measurement is used, please note in the comments section. Measurements should be completed at distance fixation.

7th Tab: Other Findings:

This tab is a catch all for the remaining ophthalmic findings that may be relevant to the phenotyping of the study participants.

Nystagmus:

- If nystagmus is noted, it must be described to the best of the examiner's ability.
- If there is no nystagmus, please tick the "None" box beside Nystagmus.
- The following fields are required if nystagmus is present:
    - Type:
        - Pendular
        - Jerk
        - Pendular/jerk
    - Direction:
        - Horizontal
        - Vertical
        - Rotary
        - Combination
    - Amplitude:
        - Large
        - Medium
        - Small
        - Tiny
    - Frequency:
        - High
        - Moderate
        - Low
    - Constancy:
        - Manifest
        - Latent
        - Manifest/latent
        - Endgaze
        - Intermittent
    - Null point:
        - Primary position
        - Right gaze
        - Left gaze
        - Up gaze
        - Down gaze
        - Right up gaze
        - Right down gaze
        - Left up gaze
        - Left down gaze
        - Combination
        - Convergence

Ptosis:

- First step is to tick whether there is:
  - No ptosis
  - Right ptosis
  - Left ptosis
  - If bilateral ptosis is noted, please tick both right and left.
- If ptosis exists in one or both eyes, please complete the drop down menus:
  - IPF: inter-palpebral fissure height:
    - Measured in millimeters
    - From 0-15 mm in 1 mm increments
  - MRD: distance between the lid margin and light pupillary light reflex
    - Measured in millimeters
    - From 1-10 mm in 1 mm increments
  - Levator: amount of levator function
    - Measured in millimeters
    - From 0-20 mm in 1 mm increments

Head Position:

- To documents any ocular head posture that is consistently noted during the exam.
- If head posture is variable, please enter the most common value and then note in the comments section.
- Specifically describe the AHP in terms of:
  - Head tilt:
    - Right
    - Left
    - No tilt
  - If head tilt exists, please measure/estimate the degrees of the tilt. Field values are 0 -45 degrees, in 1 degree increments
  - Head turn "face turn":
    - Right
    - Left
    - None
  - If head turn exists, please measure/estimate the degrees of the turn. Field values are 0-90 degrees, in 1 degree increments
  - Chin:
    - Up
    - Down
    - None
  - If chin up/down HP exists, please measure/estimate the degrees of the AHP. Field values are 0-35 degrees, in 1 degree increments

Pupils:

- Please note whether pupil size, shape and reaction is:
  - Normal
  - Abnormal
  - Not tested
- If pupils are abnormal, please provide additional details in the comment section.

Optic Nerves:

- Please record the optic nerve evaluation are summarize the results:
  - Normal
  - Abnormal
  - Not tested
- If optic nerves are abnormal, please provide additional details in the comment section.

Double Maddox:

- If subjective torsion is suspected, please evaluate.
- Record values for each eye individually:
  - Incyclotorsion
  - Excylotorsion
  - No torsion
  - Not measured
- If torsion exists, please enter the degrees. Range is 0-30 degrees in 1 degree increments

Fundus Torsion:

- If tested, please enter the fundus (anatomic) torsion results.
- Strategy for measuring torsion is based on Dr. Guyton's strategy published in AOJ 1983. [7]
- First select whether there is intorsion or extorsion and its grade of 1, 2, 3 or 4.

Comments:

Text box for any comments related to the above fields. Please mention any anomalous findings in this section. Also, since this is the last tab, any other findings relevant to the participant should be noted here such as known results from treatment (surgical, amblyopia, etc.)

Maps of Binocular Function:

- Please upload if available:
  - Lancaster Red Green
  - Lees Screen
  - Hess Screen
  - Synoptophore results

Fundus Pictures:

Upload fundus photos if available.

Strabismus photos can be uploaded on another tab (photos only).

[7] Guyton D (1983). Clinical Assessment of Ocular Torsion. *Am Orthopt J*, 33:7-15.

APPENDIX F: CHILDREN'S HOSPITAL BOSTON DEPARTMENT OF OPHTHALMOLOGY CLINICAL EXAMINATION FORM

Children's Hospital Boston
Department of Ophthalmology

☐ Linda R. Dagi, MD ☐ Anne B. Fulton, MD ☐ David G. Hunter, MD, PhD ☐ Kathryn B. Miller, OD
☐ Robert A. Petersen, MD ☐ Richard M. Robb, MD ☐ Sonia Sethee, OD ☐ Lois E. H. Smith, MD, PhD
☐ Deborah K. VanderVeen, MD ☐ Carolyn Wu, MD ☐ Other:

Affix label or fill in Name, History #, and Date of exam:

REASON FOR VISIT Accompanied by: ☐ Father ☐ Mother ☐ Other:

☐ INITIAL VISIT **REFERRED BY:**
OR **CHIEF COMPLAINT:**

☐ **RETURN VISIT:** _____ days / wks / mos / yrs later / post-op
for follow-up of:

Assistant: _____ (last name)

AGE: _____ years, _____ months

HISTORY OF PRESENT ILLNESS: ☐ No changes since last visit

PAST OCULAR HISTORY:

Current Therapy: ☐ None

Patching: RE LE ____ hours per day, _____ days/week

Penalization: 1% atropine RE LE qD qOD _____ days/week

BIRTH HISTORY: (pediatric patients):
☐ No problems with pregnancy, delivery, or perinatal period

PAST MEDICAL HISTORY:
☐ No significant illnesses or operations

REVIEW OF SYSTEMS:
☐ Other systems including constitutional, ears, nose, mouth, and throat, cardiovascular, respiratory, gastrointestinal, genitourinary, musculoskeletal, integumentary, neurologic, psychiatric, endocrine, hematologic, and allergic are reported normal or unchanged from the previous exam unless otherwise noted or as indicated on the questionnaire.

MEDICATIONS: ☐ None

FAMILY HISTORY:
☐ Unremarkable for strabismus, amblyopia, or other eye disease

ALLERGIES: ☐ None known

SOCIAL HISTORY:

MAJOR FINDINGS **MENTAL STATUS:** ☐ Alert and cooperative **DYNAMIC RETINOSCOPY:** ☐ Rapid, complete, and steady OU

VISUAL ACUITY: Sn HOTV ATS LEA AC PLT Letters Symbols

V OD: OD: N OD: W
OS: OS: OS:
SC: CC: PH:
OU: OU: OU:

WEARING: Sphere Cyl Axis Prism, READING ADD
OD: ____ ____ x ____
OS: ____ ____ x ____

MANIFEST REFRACTION

	Sphere	Cyl	Axis	
OD:	____	____ x	____	→ 20/
OS:	____	____ x	____	→ 20/

CYCLOPLEGIC REFRACTION:

	Sphere	Cyl	Axis	
OD:	____	____ x	____	→ 20/
OS:	____	____ x	____	→ 20/

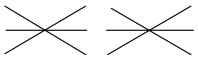
SENSORIMOTOR EVALUATION: ☐ Detailed exam ordered because of the complexity of the case.

FIXATION:
Dist: Fuses RE LE Alt
Near: Fuses RE LE Alt

DEVIATIONS: ☐ No shift at distance or near ☐ Reflexes centered
RE fixing: (Comitant) LE fixing:

NYSTAGMUS:
☐ None

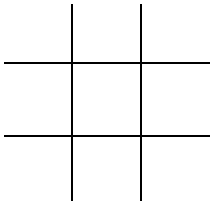
DUCTIONS: ☐ Full OU
VERSIONS: ☐ Comitant OU



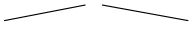
Dsc: _____
Dcc: _____
Nsc: _____
Ncc: _____
Ncc with +3.00 sph:

Performed by: _____ (last name)

PATTERN:
☐ No significant A or V pattern



☐ **LANCASTER RED-GREEN TEST:** (separate sheet)
HEAD TILT TEST:



Double Maddox rods: _____

SENSORY TESTING
☐ Attempted, but unable to evaluate
Frisby: Lang: + –
+ – Fly (3000 sec arc)
Animals: Titmus: Randot circles:
__/3 ____/9 ____/10
400 800 80 400 50
200 400 60 200 40
100 200 50 140 30
140 40 100 25
100 70 20
Random Dot E at ___m

W4D: Dist. Stereo:
D: __/4 circles
N: 240
180
120
60
Vect. alt.letters
fuses, suppress OD OS

NPC:
Vergences:
☐ Normal 20 pd BO test

SENSORIMOTOR IMPRESSION:

150681 Pkg/500 6/03

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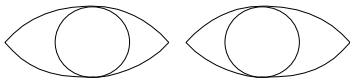
Affix label or fill in Name, History #, and Date of exam:

EXTERNAL EXAM
- ☐ No tilt or turn
- ☐ Orbits and lacrimal systems normal
- ☐ No ptosis



PUPILS: ☐ Normal size, shape, and reactivity OU
☐ No afferent pupillary defect OU

SLIT LAMP EXAM: ☐ Normal cornea, anterior chamber, and lens by hand light OU

CONJUNCTIVA:	☐ White and quiet OU
CORNEA:	☐ Normal tear film, epithelium, stroma, OU
ANTERIOR CHAMBER:	☐ Normal depth, no cells or flare OU
IRIS:	☐ Normal, color_____
LENS:	☐ Clear, with normal capsule, cortex, and nucleus OU
ANT. VITREOUS:	☐ Clear

INTRAOCULAR PRESSURE (tactile) : normal OU ☐ Attempted, but unable to evaluate
(applanation / Tonopen) :

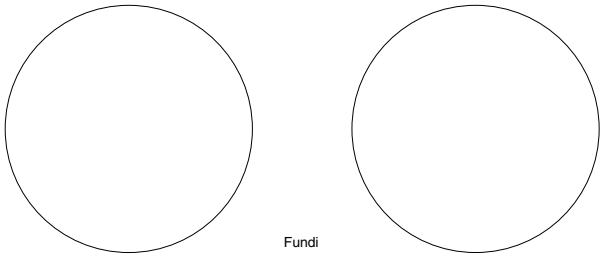
RE: _____ LE: _____

VISUAL FIELDS:
- ☐ Attempted, but unable to evaluate
- ☐ Full to confrontation, each eye
- ☐ Perimetry performed (separate sheet)

Dilation: Time:_____

Cyclomydril Cyclogyl 1% PE 2.5% Tropicamide 1% Spray

POSTERIOR SEGMENT (undilated / dilated) :
☐ Disc, nerve fiber layer, macula, vessels, and posterior pole normal OU



Fundi

Fundus torsion: ☐ No abnormal torsion OU
OD: _____ extorsion _____ intorsion
OS: _____ extorsion _____ intorsion

Photos taken ☐

Dye disappearance test:
Ptosis evaluation

	OD	OS
IPF:		
MRD:		
K cover:		
LF s F c F		
LI:		
Shape:		

Color vision
OD:____
OS:____

Amsler Grid
☐Wnl OU

ASSESSMENTS / DIAGNOSES:

PROCEDURES / PLANS:

Follow-up:

Resident Physician (Sign and Print Name): _____

I have personally confirmed the pertinent elements of the above history and examination and discussed the findings and plans with the patient.

☐ Exceptions:

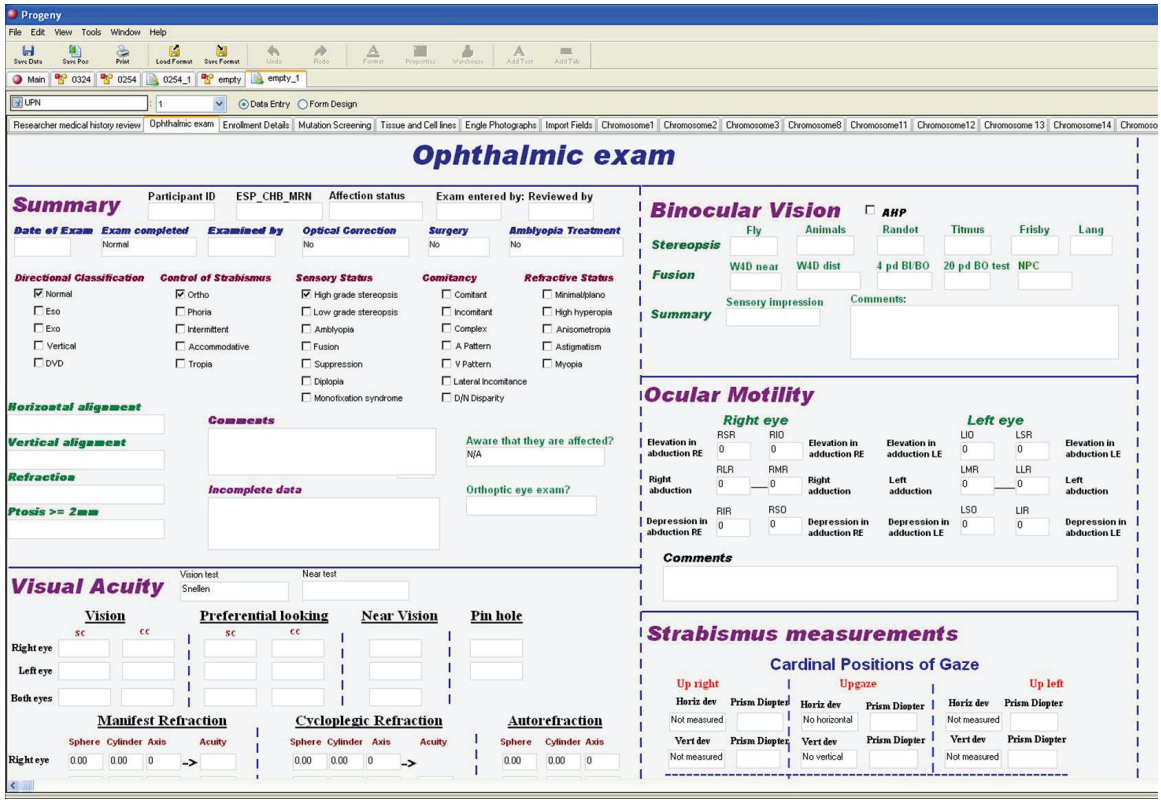
Signature (attending physician): _____

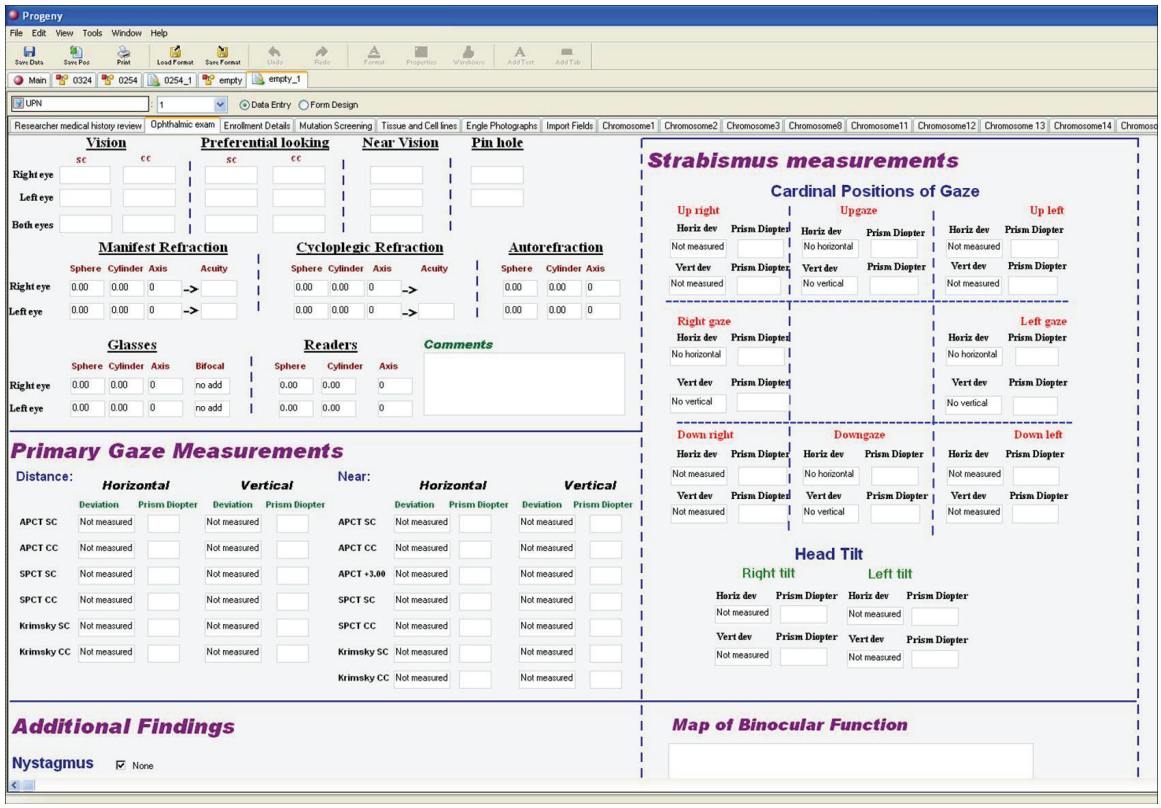
☐ Dictated
☐ No Dictation

☐ Dilation
☐ No Dilation

APPENDIX G: EXAMPLE OF PROGENY GENETICS DATABASE

ORTHOPTIC EXAMINATION DATA




Progeny
File Edit View Tools Window Help
Main 0324 0254 0254_1 empty empty_1
UPN
Data Entry
Form Design
Researcher medical history review
Ophthalmic exam
Enrollment Details
Mutation Screening
Tissue and Cell lines
Engle Photographs
Import Fields
Chromosome1
Chromosome2
Chromosome3
Chromosome8
Chromosome11
Chromosome12
Chromosome 13
Chromosome14
Vision
Preferential looking
Near Vision
Pin hole
Manifest Refraction
Cycloplegic Refraction
Autorefraction
Glasses
Readers
Comments
Primary Gaze Measurements
Distance:
Near:
Horizontal
Vertical
Deviation
Prism Diopter
APCT SC
APCT CC
APCT +3.00
SPCT SC
SPCT CC
Krimsky SC
Krimsky CC
Not measured
Strabismus measurements
Cardinal Positions of Gaze
Up right
Upgaze
Up left
Right gaze
Left gaze
Down right
Downgaze
Down left
Horiz dev
Vert dev
Prism Diopter
Not measured
No horizontal
No vertical
Head Tilt
Right tilt
Left tilt
Additional Findings
Nystagmus
None
Map of Binocular Function