THE EPIDEMIOLOGY OF AUTISM IN CALIFORNIA

Report to the Legislature on the Principal Findings from The Epidemiology of Autism in California:

A Comprehensive Pilot Study

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Executive Summary

Autism is a neurological or brain disorder that profoundly affects a person's ability to communicate, form relationships with others, and respond appropriately to the environment. Those affected by autism fall along a spectrum of "high-functioning" individuals to individuals who lack any means of communicating with others. The prevalence of autism in the population is not well described. It was once thought that autism was relatively rare, occurring in 4-5 per 10,000 persons. More recent estimations put the prevalence of autism at 10-12 per 10,000 persons. A clear cause has not been identified, although there is evidence for genetic predisposition. Autism is more common in males and is more common in certain medical conditions. Families with one autistic child are more likely have another child with autism. However, a purely genetic basis for autism does not fully explain the increasing autism prevalence. Other theories that attempt to better explain the observed increase in autism cases include environmental exposures to substances such as mercury; viral exposures; autoimmune disorders; and childhood vaccinations.

Autism is a neurological or brain disorder that profoundly affects a person's ability to communicate, form relationships with others, and respond appropriately to the environment.

In California, persons diagnosed with full syndrome autism and other developmental disabilities qualify for services coordinated by a system of local Regional Centers. Established by the Lanterman Act in 1969, the Regional Centers are unique as a service mechanism through which the needs of developmentally disabled citizens are addressed.

In March 1999, the Department of Developmental Services issued a report titled "Changes in the Population of Persons with Autism and Pervasive Developmental Disorders in California's Developmental Services System: 1987 through 1998." The report documented an increase of 273% in reported cases of autism in California over this time period. Because of the concern over this apparent increase in autism, the State Legislature requested that the University of California's Medical Investigation of Neurodevelopmental Disorders (M.I.N.D.) Institute conduct a comprehensive pilot study to examine factors that may be associated with this increase.

The study methods are presented in detail in the full report to the Legislature. A California-wide sample of 684 children from English- or Spanish-speaking families enrolled to participate in this study. Information regarding children from two different birth year cohorts (1983-1985 and 1993-1995) was systematically collected from families of 375 children with a diagnosis of full syndrome autism and 309 children with a diagnosis of mental retardation without full syndrome autism. Data for the study came from four main sources:

1) Data from the Department of Developmental Services Client Development Evaluation Report (CDER form);
2) Regional Center records;
3) The Autism Diagnostic Interview — Revised (ADI-R); and
4) a detailed study questionnaire.

The primary findings of the study are summarized in the following list of principal aims:

- **Study Aim 1:** *To investigate whether changes over time in the criteria used to diagnosis CDER status 1 autism account for a significant proportion of the increased number of cases of autism.*

  The Regional Center designation of full syndrome autism, CDER status 1 autism, closely matched DSM-IV criteria for autism, and this did not change over time. (88% of the 1983-85 cohort met DSM-IV criteria compared to 89% of the 1993-95 cohort.) In addition, no differences over time were found in comparisons of the number of criteria met within specific components of the ADI-R. There is no evidence that a loosening in the diagnostic criteria has contributed to increased number of autism clients served by the Regional Centers.

  There is no evidence that loosening in diagnostic criteria contributed to an increase in the number of children with autism.

- **Study Aim 2:** *To investigate whether the misclassification of some cases of autism as mental retardation in the past has contributed to an apparent increase in the number of children with autism.*

  A portion of children reported by the Regional Centers as having mental retardation without full syndrome autism did meet DSM-IV criteria for autism. Of the 1983-85 cohort, 18% met criteria for autism, compared to 19% of children in the 1993-95 cohort. However, these numbers cannot be used to make reliable estimates of the number of children with autism not being counted (and not being treated), because 1) we had a relatively low response rate by families with mentally retarded children, and 2) families were more likely to agree to enroll if their mentally retarded child also had an autism spectrum disorder.

- **Study Aim 3:** *To investigate whether temporal changes in children with autism moving into California for services accounts for a significant proportion of the increased cases of autism reported to DDS.*

  The proportion of the study children with autism who are California-born is 87% of the 1983-85 group and 93% of the 1993-95 group. Thus, autistic

children in the Regional Center System are largely native to the State and are not coming disproportionately from outside California.

- **Study Aim 4:** *To describe how characteristics of children with autism have changed over time.*

Comparisons between the two age groups show many similarities and some differences. There are no significant differences in sex, race, and maternal and paternal education. Hispanic children are more likely to be included in the younger autistic group (28% in the 1983-85 group and 39% in the 1993-95 group). Parents of the older group were more likely to report that their autistic child also had mental retardation (41% vs. 21%). This is consistent with the review of Regional Center records that found a decrease in diagnosed mental retardation in the younger group (50% in the 1983-85 group vs. 22% in the 1993-95 group). Regression of developmental milestones, as determined from the ADI-R interview, did not significantly change over time (28% vs. 34%). Compared to the older group, parents of the younger group were more likely to report improvement in their child's condition over time (81% vs. 93%). Older children with autism were more likely to be reported as having tic disorders, obsessive-compulsive disorders, depression, and bipolar disorder, but this may be due to an age effect rather than a cohort effect. There were few differences over time in factors associated with the pregnancy. Gastrointestinal symptoms were more commonly reported during the first 15 months of life for the 1993-95 cohort than the older cohort. Wheat allergy was significantly more frequent (12%) for the younger group than the older group (4%). None of these differences fully explain the increase in autism cases in California.

Parent-reported regression of developmental milestones did not change over time.

- **Study Aim 5:** *To ascertain what parents of children with autism believe caused their child's autism, and to determine if this has changed over time.*

The most common parental response in both groups was no response or "Don't know" (46% and 48%). Genetics was the second most common response for both groups (31% and 27%). Immunizations were reported as a contributing factor by 18% of the older cohort and 33% of the younger cohort. Birth events were cited by about 15% of parents in both groups. Autism was attributed to environmental exposures by about 11% of the study families.

- **Study Aim 6:** *To determine if vaccination with MMR vaccine is associated with an increase in the recurrence rate of autism in subsequent siblings.*

  Avoidance or delay of at least one vaccine for the autistic child enrolled in this study was reported by 8% of older cohort parents and 22% of younger cohort parents. Similar patterns were reported with regard to avoiding/delaying vaccination of any younger siblings (10% vs. 21%). Anecdotal information prior to this study suggested that 50% of families with autistic children were avoiding immunization in their younger children, but our results show that vaccine avoidance is less common than had been suggested. As a result, the number of children necessary to answer this study aim question is far in excess of the size of this study (approximately 7,000). Until a study of that size can be done, this study aim will remain unanswered.

Major Findings

The major findings of this study are that:

- The observed increase in autism cases cannot be explained by a loosening in the criteria used to make the diagnosis.
- Some children reported by the Regional Centers with mental retardation and not autism did meet criteria for autism, but this misclassification does not appear to have changed over time.
- Children served by the State's Regional Centers are largely native born and there has been no major migration of children into California that would explain the increase in autism.
- A diagnosis of mental retardation associated with autism had declined significantly between the two age groups.
- The percentage of parent-reported regression (loss of developmental milestones) did not differ between the two age groups.
- Gastrointestinal symptoms in the first 15 months of life were more commonly reported by parents in the younger group.

Without evidence for an artificial increase in autism cases, we conclude that some, if not all, of the observed increase represents a true increase in cases of autism in California, and the number of cases presenting to the Regional Center system is not an overestimation of the number of children with autism in California.

Background

What is autism?

Treatment successes for some children diagnosed early and treated intensively have increased attention toward making the diagnosis of autism as early as possible.

Autism is a neurological or brain disorder that profoundly affects a person's ability to communicate, form relationships with others, and respond appropriately to the environment. Most autistic children look perfectly normal, but they may have behaviors, such as hand flapping, finger flickering, body rocking or spinning, which attract notice and cause concern. They may also be more sensitive to certain sights, sounds, textures, smells, and tastes. Autism has an onset before the age of 3 and ranges in its effect on development. Along the spectrum, some persons with autism are considered "high-functioning"; many can be mainstreamed into regular school classrooms, some attend college, and some find and maintain employment. At the other end of the spectrum are severely affected persons who may not have any means of communicating with others, or communicate only by repeating words or phrases. They may lack eye contact or regard for faces. They can have additional developmental problems, such as mental retardation. Aggressive and/or self-injurious behavior may be present in some cases.

The diagnostic criteria for autism are listed in the Diagnostic and Statistical Manual-IV (DSM-IV) of the American Psychiatric Association. For a detailed definition, please see Appendix 1. The diagnosis can be difficult to make, but usually results after a parent or another caretaker raises concerns about the child's development. The process of getting a diagnosis may start with a primary care doctor, then often involves developmental specialists (such as developmental pediatricians or developmental psychologists), neurologists, or specially trained social workers or registered nurses. In California, the diagnosis is often made following an evaluation of the child at the local Regional Center (described below). Treatment successes for some children diagnosed early and treated intensively have increased attention toward making the diagnosis of autism as early as possible.

History of the Regional Center System in California

In 1969, the Lanterman Mental Retardation Services Act established regional coordination of care for persons with mental retardation. This care was overseen and managed through an association of Regional Centers located throughout California. In 1973, this act was extended to serve persons with cerebral palsy, epilepsy, autism and other conditions similar in severity to mental retardation. In 1976, the Lanterman Developmental Disabilities Services Act was amended to establish the right to treatment and habilitation services for person with developmental disabilities. Children and adults are referred to their local Regional Center by health-care providers or other health or service organizations, or families may self-refer their children. An assessment is undertaken to determine if the person qualifies for services as outlined in the Lanterman Act. Typical services that are coordinated through the Regional Center include therapies such as physical therapy, occupational therapy, and speech therapy; planning for educational goals; provision of necessary medical devices, such as wheelchairs; and the provision of respite care for the family or guardians. Twenty-one Regional Centers located throughout California coordinate these services through a array of case managers, community service providers, and professional staff (i.e. psychologists, social workers, and nurses). (See Appendix 2 for locations of Regional Centers.) The Regional Center system in California is unique as a service mechanism through which the needs of developmentally disabled citizens are addressed.

Collection of Information in the Regional Center System

California's Regional Center System has compiled over 20 years of data from annual assessments of individuals who qualify for service. The Client Development Evaluation Report (CDER) is the assessment instrument that is administered to each client at intake, and yearly thereafter, to determine developmental and functional status. The types of information collected on the CDER form include reporting date, who prepared the form, developmental diagnostic information (documentation of mental retardation, cerebral palsy, autism, seizure disorder, and/or other), mental disorders, chronic major medical conditions, medications, and categorization of deficits in use of muscles, independent living, social, emotional, cognitive, and communication skills. A copy of the CDER form is included in Appendix 3.

The CDER database, a potentially rich source of statewide data regarding autism, has been primarily used for administrative purposes. Many potential problems exist in using these data for more than their primary purpose. The major drawback of these data for tracking changes in autism over time is the lack of specific and uniform criteria in establishing a diagnosis of autism across the State's Regional Centers and across time. The written guidelines for determining whether a child has autism are that "the diagnosis in this section must be provided by a person qualified to diagnose autism." The presence or absence of autism is recorded on page 3 of the CDER with one of four different codes — CDER Status 0, CDER Status 1, CDER Status 2 and CDER Status 9. CDER Status 0 is None (no evidence of autism). CDER Status 1 is labeled "Full Syndrome" autism and is believed to be roughly equivalent to meeting DSM-IV criteria for autism, but this assumption has not been validated prior to this

study. CDER Status 2 is labeled "Autism, residual state," but this designation lacks a DSM-IV equivalent. CDER Status 9 is labeled "Autism suspected, not diagnosed." An additional category for autism was coded in the data, CDER Status 4, based on diagnostic coding made on the CDER that captures other conditions along the autism spectrum, such as Pervasive Developmental Disorders (PDD), including PDD, not otherwise specified (PDD-NOS); Asperger's Disorder; Rett's Disorder; and Childhood Disintegrative Disorder. These data were used in the DDS Report discussed below. There are additional potential problems with using CDER data to track changes over time in autism. The CDER database tracks children who qualify for developmental services, but has no record of children who were assessed but did not qualify for services. By anecdotal report, the database is not always updated, even when evaluations change over time, but the extent of this problem is unknown.

A 273% increase in reported cases of autism from 1987 through 1998 is far in excess of population changes of approximately 20% for the State during the same time.

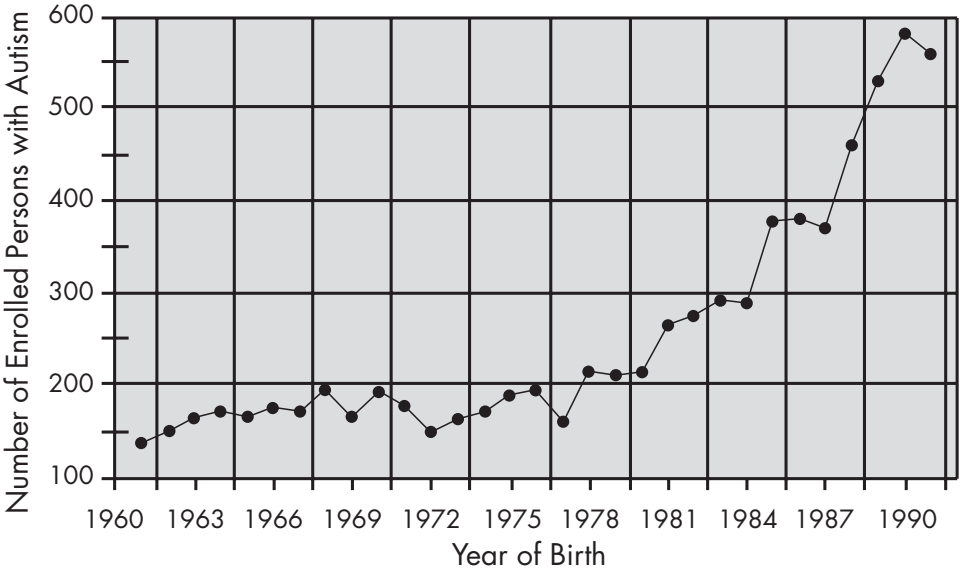
The March 1999 DDS Report to the State Legislature

In March 1999, the California Department of Developmental Services issued a report entitled "Changes in the Population of Persons with Autism and Pervasive Developmental Disorders in California's Developmental Services System: 1987 through 1998" (this report will be referenced as "the DDS Report").[1] During the 12-year period covered in the report there was a substantial (273%) increase in reported cases of autism (CDER status 1 and 2) from 2,778 to 10,360. This is far in excess of the population increase of approximately 20% for the State during this period. The report also documented a 69% increase in the total Regional Center consumer population of 80,483 to 136,383 during the same period. The number of Regional Center consumers with any designation of autism (CDER status 1, 2, 4, and 9) increased from 3,864 to 11,995, an increase of 210%. In comparison, the number of consumers with cerebral palsy increased from 19,972 to 28,529 (43%), consumers with epilepsy increased from 22,683 to 29,645 (31%), and consumers with mental retardation increased from 72,987 to 108,563 (49%). In 1988, consumers with autism in all forms accounted for 4.9% of all consumers of Regional Center services in the state. In 1997, this proportion had increased to 9.4%. These numbers pointed to increases in the total number of

children with autism and increases in the proportion of developmental disorders that are due to autism in California.

The number of cases of autism per birth year is shown in Figure 1. This figure shows relatively stable numbers of Regional Center consumers with autism until 1981, after which time the number of consumers with autism steadily increased.

Figure 1. *Distribution of birth dates of regional center eligible persons with autism*



(from "Changes in the Population of Persons with Autism and Pervasive Developmental Disorders in California's Developmental Services System: 1987 through 1998")

Legislation Authorizing This Study

The findings from the DDS Report generated much concern and controversy. In order to answer many of the questions that were raised by that report, as well as independent observations of increases in autism, the State Legislature allocated $1,000,000 for the Department of Developmental Services to "enter into an interagency agreement with the University of California's Medical Investigation of Neurodevelopmental Disorders (M.I.N.D.) Institute to prepare a comprehensive pilot study to examine all factors surrounding the increased number of persons with autism and autism spectrum disorders in California from 1977 to 1999." (SB 160) This document reports the findings from the statewide comprehensive pilot study conducted by researchers at the University of California, Davis, and their colleagues at the University of California, Los Angeles.

Review of research on the causes of autism and other current issues

Epidemiology of Autism

Autism affects neurodevelopment in multiple and profound ways, yet much remains to be learned about what causes autism or even how common autism is. Estimates of the prevalence of autism vary, with higher rates reported in more recent studies. Prior to 1985, autism was believed to be a rare condition with an estimated prevalence of 4-5 per 10,000.[2] Since that time, prevalence estimates have been in the range of 10-12 per 10,000, but prevalence studies done in the United States have shown lower rates.[3] It is suggested that the changes in rates are due in part to changes in how autism is diagnosed. The lower prevalence estimates in the past were based on Kanner's description of the classic autism prototype, where autism usually affects children with an IQ range of 50 to 70. Most recent prevalence studies are based on DSM III-R, DSM-IV, or ICD-9 criteria, which define autism more broadly.[†] The prevalence of other autism spectrum disorders is much higher than that of autism, with estimates ranging from 1.8 per 1,000 to 5 per 1,000.[3,4] An investigation of children aged 5 to 11 years in Cambridgeshire (UK) provided an estimate of 1 in 175 for the prevalence of autism spectrum disorders, including Asperger's Disorder.[5]

Autism produces profound effects in neurodevelopment in multiple ways, yet much remains to be learned about what causes autism or even how common autism is.

Epidemiological studies demonstrate a strong genetic component. The relative sibling recurrence risk is 45-90 times that of the general population.[6] (Recurrence risk to young siblings of children with autism is 4.5% compared to the occurrence in the general population of 0.05-0.1%.) Autism occurs in males 3 to 4 times more frequently than females.[2-4] Studies of families with multiply affected members have identified many chromosomes that are highly associated with autism, but not universally found in children with autism. Twin studies have found a concordance of 36% to 91% in identical twins compared to a less than 1% concordance rate in fraternal twins.[7,8]

Many children with autism also have other medical and developmental conditions. According to previous data, the majority of children with autism (about 75%) have

† It should be noted that the change in diagnostic criteria from the Kanner definition to DSM or ICD criteria predates the increases noted in the DDS Report, which spans 1987 to 1998.

mental retardation.[9] (Whereas, the majority of children with autism spectrum disorders without "full" autism do not.[2]) Other conditions associated with autism include epilepsy, visual and auditory sensory impairments, neurofibromatosis, tuberous sclerosis, Angelman's syndrome,[10] untreated phenylketonuria, and fragile-X syndrome. However, most children with autism do not have a recognizable genetic syndrome.

The question as to when autism begins in any child remains to be answered. Some studies provide support for a prenatal or perinatal origin for autism. Data from analyses of neonatal blood spots taken from children later diagnosed with autism showed that 95% of a small sample of children with autism have elevated levels of four neuropeptides and neurotrophins.[11] However, these findings were not specific to autism and were also found in children with mental retardation, but not in children with cerebral palsy.[11] A study of morphologic changes noted at birth found that 42% of children with autism had posteriorly rotated ears, which would suggest changes that occur at least by the first month of gestation for a large number of children with autism.[12] While most children with autism display delayed development from birth, regression of development (i.e. a period of normal development then an apparent loss of developmental milestones) is reported in 30% to 35% of cases,[13-16] leading some to suspect postnatal factors contribute to the development of autism for at least some children.

The question as to when autism begins in any child remains to be answered.

Many other associations have been suggested by prior studies of autism, including viral exposures, vaccinations,[17] immunologic factors,[18] autoimmune disorders,[19,20] gastrointestinal disorders,[21] prenatal exposure to thalidomide,[22] anticonvulsants,[23] and food allergies.[24,25] The interaction between a genetic predisposition and early environmental insults has also been suggested.[26]

Viral causes have been suggested due to early findings that suggested an association between month of birth and autism,[27-29] but other studies have failed to confirm this association.[30,31] One study found that prenatal or neonatal exposure to chickenpox, measles, mumps or rubella was associated with autism, but further concluded that the attributable risk associated with these exposures is small.[32]

The possible association of autism with vaccinations has received increased scrutiny following the case series presented by Wakefield, *et al* describing regression in previously normal children, development of autism and enterocolitis, and temporal association of the MMR vaccination.[21] Vaccine strain measles in peripheral mononuclear cells was detected in three of nine children with autism in one study.[33] How-

ever, population studies have not found a causal association between MMR vaccination and autism.[13, 34] The issue is far from resolved for parents of children with autism, especially for those considering immunizations for their later-born children.

Implications of Current Understanding About Autism in the Context of the Current Study

One of the most controversial aspects of the DDS Report is whether the significant increase in numbers of Regional Center individuals with autism is due to increased rates of autism or to some other factor (or combination of factors) that artificially increases the number of children with autism presenting for services. These factors include increases in the overall population of children, loosening the criteria used to establish the diagnosis of autism, prior misclassification of autism as mental retardation, increases in the number of children with autism moving in from out-of-state, and improved case finding.

Only a small portion of the apparent increase in autism cases can be explained by the increase in the State's population.

The DDS Report did not address population growth over the time of the study. California's population increased by approximately 20% from 1985 to 1995, which is an order of magnitude less than the two- to three-fold increase in persons with autism served by the State's Regional Center system. Thus, only a small portion of the apparent increase in autism cases can be explained by the increase in the State's population.

Changes in the diagnostic criteria for a spectrum disorder can change the number of cases identified. If the criteria loosen to include more children who are less severely affected, the number of cases will be artificially increased. Following this line of reasoning, children with autistic features that do not have "full syndrome autism" (meeting DSM-IV criteria) may be given the classification of CDER status 1 autism in order to qualify them for services that would not be available to those classified as CDER Status 9 autism. This process would artificially inflate the number of cases of autism. Furthermore, the Regional Center threshold for establishing a diagnosis of CDER status 1 autism has been assumed to match the criteria from the recognized standard at the time of diagnosis. The current standard is DSM-IV, but the standard was DSM-III and DSM-IIIR during the study period for the DDS Report. Prior to this

study, the extent to which misclassification contributed to the observed increase in autism cases in California was unknown.

Recent data suggest that the increase in cases of autism matches a decrease in cases of mental retardation.[35] Changes in how both autism and mental retardation are classified could cause an artificial increase in autism cases. It is possible that children with both mental retardation and autism could be classified as having mental retardation with autistic features. This might have been recorded as something other than CDER Status 1 in the past, but now similarly affected children may be entered into the data as autistic (CDER status 1 autism) with mental retardation. Presumably, this misclassification occurred more in the past, when the imperative for early diagnosis of autism to allow for early intensive therapies was not as great.

Only a small portion of the apparent increase in autism cases can be explained by an increase in the State's population.

In-migration could contribute to a real increase in the number of cases of autism, but not be due to increased incidence rates of autism among children in California. One might postulate that children with autism from another state may move to California if their home state provides fewer services than California. The extent to which the observed increase in autism can be explained by in-migration was not known prior to this study.

Improved case finding could result in an apparent increase in the number of cases of autism in California. CDER data only describe children included in the State's Regional Center System. Children outside the Regional Center system are not counted in CDER data. Some assume that the Regional Center system captures virtually every case of autism, because the Regional Centers are pivotal in coordinating and financing services for children with autism. Still, improved recognition of autism by both parents and professionals may result in more children with autism being directed to the Regional Centers for services. Autism case finding in California could have been further increased by the implementation of early intervention programs that have increased the diagnosis and treatment of developmental disorders in infants and young children. This study does not examine the extent to which differences in case finding over time have resulted in any changes in the number of autistic children who present to the Regional Centers.

One of the reasons that the DDS Report generated so much concern is that 1) the etiology of autism is unknown and 2) the increase in reported cases of autism could be the result of a new exposure. While genetic factors are strongly associated with autism, the uncertainty about the increasing prevalence rates of autism raises doubts that

genetic factors alone are responsible. The increase in children with autism presenting for care to the Regional Center system is far in excess of what would be expected for a typical genetic condition. This uncertainty, along with parental concerns about other potential causes, has implications beyond the children with autism and their families. Some of the concern is focused on a potential association of autism with vaccinations, especially MMR. This has led to concerns among public health officials that parents will cease to follow recommended vaccination schedules, placing children at risk of contracting vaccine preventable illnesses.

Aims of the Study

The principal aims of this study are listed below:

- **Study Aim 1:** *To investigate whether changes over time in the criteria used to diagnosis CDER status 1 autism account for a significant proportion of the increased numbers of cases of autism.*
- **Study Aim 2:** *To investigate whether the misclassification of some cases of autism as mental retardation in the past has contributed to an apparent increase in the number of children with autism.*
- **Study Aim 3:** *To investigate whether temporal changes in children with autism moving into California for services account for a significant proportion of the increased cases of autism reported to DDS.*
- **Study Aim 4:** *To describe how characteristics of children with autism have changed over time.*
- **Study Aim 5:** *To ascertain what parents of children with autism believe caused their child's autism, and to determine if this has changed over time.*
- **Study Aim 6:** *To determine if vaccination with MMR vaccine is associated with an increase in the recurrence rate of autism in subsequent siblings.*

Scientific Advisory Panel

The M.I.N.D. Institute convened a Scientific Advisory Panel to review and advise the draft research proposal for the Autism Epidemiology Study.

The panel met November 11-12, 2000, in Sacramento, California. Following the recommendations that came out of that meeting, the Principal Investigator and study staff made adjustments to the focus and methodology for the study. A final proposal was sent to the Scientific Advisory Panel for review in April 2001, and some changes were made following the receipt of their comments. The names and affiliations of the Scientific Advisory Panel members are listed in Appendix 4.

Methods

Data for the study came from four main sources: 1) CDER data; 2) Regional Center charts; 3) The Autism Diagnostic Interview — Revised (ADI-R)*; and 4) a detailed study questionnaire. Additional sources of information were the Social Communication Questionnaire (SCQ)*, the Checklist for Autism in Toddlers (CHAT), the Regression Validation Interview (adapted from a questionnaire from the Autism Regression/Vaccination Study), and immunization records provided by either the participating family or a health-care provider. Details of the research methods are presented by each study aim below, followed by a description of recruitment and enrollment procedures.

Methods for Study Aim 1: *Change in diagnostic criteria associated with CDER status 1 autism.*

One possible explanation for the observed increase in number of cases of CDER status 1 autism is that the criteria for determining if a child has full syndrome autism may have changed. To study temporal changes in diagnostic criteria associated with CDER status 1 autism, DSM-IV criteria for autism were assessed in two birth cohorts of children with a diagnosis of full syndrome autism in the Regional Center system. The two birth cohorts were children born between 1983-1985 (Cohort 1) and children born between 1993-1995 (Cohort 2). A random sample of children from these two groups was systematically selected to represent each Regional Center in California. DSM-IV criteria were assessed by 1) reviewing the Regional Center record to determine documentation of diagnostic criteria applied at the time the child received the autism diagnosis; and 2) conducting an ADI-R interview with the parents or guardians of the child with autism. The ADI-R is an instrument that provides a semi-structured interview of parents or care providers of children or adults with suspected pervasive developmental disorders including autism.[36] The ADI-R can be scored to determine whether the child meets DSM-IV criteria for autism. This study instrument also probes for features of autism that may not currently apply to the child, but did occur in the past, allowing for one standard to be applied to children of different ages.

Uncertainty about the increasing prevalence rates of autism raises doubts that genetic factors alone are responsible.

Methods for Study Aim 2: *Proportion of children with DSM-IV autism classified as having mental retardation.*

Another potential explanation for the observed increase in the number of cases of autism is that some children with autism may have been misclassified as having

* Autism Diagnostic Interview-Revised (ADI-R) and Social Communication Questionnaire (SCQ), copyright 2001, Western Psychological Services, Los Angeles, CA. The U.C. Davis M.I.N.D. Institute was provided license and authorization to reprint these instruments for specific research use.

mental retardation, and that more of these misclassifications occurred in the past. The number of children with mental retardation served by the Regional Centers is significantly greater than the number of children with CDER status 1 autism, and a small change in the rate of misclassification of children reported as having mental retardation could effectively double the autism rate.

A possible explanation for an observed increase in cases of autism is that children with autism from other states move to California for care.

We investigated whether or not more children who meet autism criteria were misclassified as having mental retardation (without autism) in the past compared to the present.

Two birth cohorts of children determined to have mental retardation without CDER status 1 autism were studied to determine the proportion of these children who meet or have met DSM-IV criteria for autism. As with Study Aim 1, Cohort 1 is comprised of children born between 1983-1985 and Cohort 2 is comprised of children born between 1993-1995. For each participating child, parents or guardians completed a Social Communication Questionnaire (SCQ). The short SCQ (previously named the Autism Screening Questionnaire) can be used to screen for autistic-like behaviors. A positive score indicates that a child may have an autism spectrum disorder, but does not confirm an autism diagnosis. Positive SCQ scores were followed up with a confirmatory ADI-R. As with Study Aim 1, results of the ADI-R have been equated with DSM-IV criteria. It is recognized that DSM-IV criteria is a standard that was not established at the time that many of the children in Cohort 1 were diagnosed with mental retardation, but these criteria are the standard for comparison in this study.

Methods for Study Aim 3: *Change in in-migration of children with autism that accounts for increased number of cases of CDER status 1 autism.*

A third possible explanation for an observed increase in cases of CDER status 1 autism is that children with autism from other states move to California for care. If there has been a temporal increase in the proportion of children with autism who were born out-of-state and moved to California for developmental or educational services, then there could be an increase in the number of children with autism served by the Regional Center system that is not due to increased autism rates among the children of California. It is not expected that in-migration will account for 100% of the observed increase in cases of autism, but it could account for some portion of the observed increase.

Methods for Study Aim 4: *Change in characteristics of children with CDER status 1 autism over time.*

Some have suggested that the profile of children with autism has changed such that those autistic children who were more recently diagnosed are more likely to have higher cognitive function and to have experienced regression and gastrointestinal symptoms than children diagnosed in the more distant past. The DDS Report suggests that children more recently reported with CDER status 1 autism are less likely to have mental retardation. This finding has not been previously verified. For Study Aim 4, we evaluated the sample of children with CDER status 1 autism constructed for Study Aim 1 to assess any overall changes in demographic and other characteristics over time. Families completed a detailed study questionnaire or were interviewed to determine demographic information, presence of mental retardation, seizures, associated medical conditions, and problems or environmental exposures during the pregnancy. A history of gastrointestinal symptoms or loss of developmental milestones (regression) in the child was also ascertained. A list of questions is provided in Appendix 5.

Some have suggested that the profile of children with autism has changed.

Methods for Study Aim 5: *Determination of what families believe to be the cause of autism in their child and whether this has changed in two age cohorts.*

We asked the question, "What do you think caused your child's autism or other developmental problem?" to parents of children with autism. This question was included as part of the detailed study questionnaire or interview that was used for Study Aim 4. Responses to this question were compared between the two birth cohorts.

Methods for Study Aim 6: *Determination if vaccination with MMR increases the recurrence rate of autism in subsequent (younger) siblings.*

Based on discussions with the California Birth Defects Monitoring Program and the Centers for Disease Control in Atlanta, Georgia, anecdotal reports suggest that many — up to half — of families with one child affected with autism or PDD are opting out of vaccinating subsequent siblings with MMR. The recurrence rate of autism among families with at least one affected sibling is relatively high (approximately 5%), allowing for a "natural experiment" to investigate whether or not the rate of autism in subsequent siblings is higher among those families who elect to have siblings vaccinated with MMR, compared to families with autistic children who choose not to have subsequent siblings vaccinated with MMR.

The recurrence rate of autism among families with at least one affected sibling is relatively high allowing for a "natural experiment" to investigate whether or not the rate of autism in subsequent siblings is higher among those families who elect to have siblings vaccinated with MMR.

This study aim was investigated by including questions about siblings and vaccination choices made by parents with subsequent siblings. These questions were asked of the entire sample selected to answer Study Aims 1, 3, 4 and 5. For the sub-sample of children with autism who have younger siblings, we investigated the association of vaccination choices, specifically MMR and Hepatitis B vaccines, and the development of autism in these siblings. The incidence of autism and PDD among subsequent siblings was ascertained by asking the family to complete either the SCQ for siblings 24 months of age and older, or the CHAT for siblings 18 months of age through 23 months of age. Vaccine exposures (e.g. vaccination with MMR) were gathered by requesting a copy of the siblings' immunization records from the family or health-care provider (if the family did not have a copy). Among families with at least one child affected with autism, assuming an adequate sample, we would compare the rate of autism and/or PDD among vaccinated siblings to the rate among unvaccinated siblings (and to partially vaccinated siblings).

Recruitment and Enrollment Procedures

The CDER records formed the basis for identifying study subjects for this study. In the 1983-85 cohort, the number of children with mental retardation (without CDER status 1 autism) was 12 times greater than that of children with CDER status 1 autism. In the 1993-95 cohort, the MR numbers were only 3-fold that of the autism numbers. These changes reflect a tripling of the number of children with autism between these birth cohorts that are separated by 10 years and reduction by approximately 25% the number of children with mental retardation over this same period.

The target sample was approximately 250 children in each group (AD1, AD2, MR1 and MR2). The sampling frame was constructed to include 6 times the target number, or approximately 1500, in each group, except for the older autism group (AD1) for which there were only 991 children. Within the 4 study groups, target enrollment numbers were determined for each Regional Center based on the proportion of children with each condition (AD and MR) within each age group (Cohort 1 and Cohort 2). Further details of the selection of target sample by Regional Center and sample size calculations can be found in Appendix 6.

The study population was limited to those children whose CDER reports were included in the Regional Centers' administrative data. Families were asked to participate in this study based on a random sample of children who received Regional Center services. Thus, each family that was selected for the study received at least one unsolicited invitation to participate. It was our intention for this study to recruit and enroll families in the least invasive manner possible. "Low Impact" was the term we used to describe our approach to initial and follow-up contact and other study procedures. The specific procedures that we employed to contact and inform families about the study, as well as what families did if they agreed to enroll, are described below.

How we contacted families and obtained informed consent to participate.

As described previously, we had four study groups based on the child's diagnosis in CDER (full syndrome autism or mental retardation without full syndrome autism) and the year of birth (1983-85 and 1993-95). Potential study subjects were separated by cohort and by the Regional Center where they were first assessed and determined to have full syndrome autism (in the case of autism cohorts 1 and 2) or mental retardation (MR cohorts 1 and 2). These groups were then randomly sorted by Regional Center, year of birth, and diagnosis to produce a sampling frame. Recruitment proceeded by mailing a recruitment packet to families according to their position on the randomly ordered list. The packet included a letter from DDS describing the study, a one-page description of the study procedures, informed consent documents, and an anonymous response form and postage paid envelope. All items were printed in both English and Spanish. These packets served as an "introduction" of the UC Davis study staff to the potential study subjects. We conducted one follow-up mailing if we had no response within three weeks of the first mailing.

Participation in the study was voluntary. Families who declined to participate, or who didn't respond, were replaced by the next child on the random list of study subjects based on the age group, diagnosis, and the Regional Center. Families could contact us using a toll-free number or return a response form in a postage-paid envelope. Upon hearing from a family that they were interested in participating we reviewed with them the study procedures.

Chart abstraction

We requested a photocopy of the Regional Center record after receiving the written informed consent (which authorized the release of these records). Photocopies were made either by a contracted company (after the chart was pulled by Regional Center staff) or by Regional Center staff themselves.

Specific procedures for families of children with autism

Scheduling the ADI-R interview

After agreeing to participate in the study, families were scheduled for an ADI-R interview. In most instances, these interviews were conducted at the Regional Center branch office that was closest to the family. A trained, certified staff person administered the ADI-R. The instrument was translated into Spanish for use with Spanish-speaking families. Parents/guardians were paid $35 at the conclusion of the interview to compensate them for their time.

If the family reported a history of regression during the ADI-R interview, a more detailed assessment was conducted by administering the Regression Validation Interview over the telephone with a parent or guardian. The Regression Validation Interview was adapted from a questionnaire developed for the Collaborative Programs of Excellence in Autism (CPEA) Autism Regression/Vaccination Study.

Completing the study questionnaire

A copy of the study questionnaire was mailed to the family for completion upon receipt of the signed consent document. We provided a pre-addressed, postage-paid envelope in which to return the completed questionnaire. If the family requested a telephone interview to complete the study questionnaire this was set up when we received the consent document.

Evaluation of younger siblings

If there were younger half- or full siblings of the autistic subject, we requested that the parent/guardian complete one of two autism-screening tests for each younger sibling, based on the age of the sibling. For younger siblings who were younger than 18 months, we requested permission to contact the family when the child turns 24 months old to assess vaccination status and developmental outcomes.

For siblings at least 18 months of age but less than 24 months of age:

The parents/guardians were asked to complete a Checklist for Autism in Toddlers (CHAT) form for any sibling within this age group. Results were scored using standard documentation and entered into a sibling database.

For siblings at least 24 months of age:

The parents/guardians were asked to complete a SCQ for each sibling 24 months of age or older. Results were scored using standard documentation and entered into a sibling database.

Completion of enrollment

Study staff reviewed the returned questionnaires and contacted families by telephone to clarify inconsistencies or to complete responses that appeared inadvertently omitted. We sent a check in the amount of $30 to the family to thank them for completing the questionnaires.

Specific procedures for families with children with mental retardation

Completing the SCQ and study questionnaire

A copy of the study questionnaire and SCQ were mailed to the family for completion upon receipt of the signed consent document. We provided a pre-addressed, postage-paid envelope in which to return the completed questionnaire. If the family requested a telephone interview to complete these instruments this was set up when we received the consent document. Study staff reviewed returned questionnaires and contacted families by telephone to clarify inconsistencies or to complete responses that appeared inadvertently omitted.

Assessment for autism using the ADI-R

An ADI-R interview was scheduled at the local Regional Center for families of study subjects with mental retardation whose SCQ scores were positive (score ≥ 22).

Completion of enrollment

We sent a check in the amount of $35 to the family to thank them for completing the two questionnaires. If the family participated in an ADI-R interview they were also compensated $35 for their time at the interview.

Validating Study Methods and Procedures

A small study was conducted to test all aspects of the study (identification of children in two age cohorts with autism and children with mental retardation, performance of the ADI-R and SCQ, Regional Center chart abstraction, and conduct of the interview.). This study involved two Regional Centers, Alta California and Valley Mountain, due to their proximity to the M.I.N.D. Institute. The year of birth for subjects selected in the pilot differed from the statewide study, with children born in either 1986 or 1987 (Cohort A) compared to children born in 1991 or 1992 (Cohort B). Letters inviting participation in the study were sent to 100 families of children with autism (50 in each

age cohort) and 100 families of children with mental retardation (50 in each age cohort). Response rates were higher among the autism group, 38% for Cohort A and 44% for Cohort B. Fewer families whose children had mental retardation participated in the pilot, 16% of those in Cohort A and 10% of those in Cohort B. As a result of the low response rate in the MR group, incentives were increased in the statewide study. The test study suggested that there was some degree of discrepancy between the CDER record for autism and ADI-R results. Also, cases of autism were found in the MR group. The sample in the test study was too small to draw any definitive conclusions, but pilot testing demonstrated that five of six of the study aims would likely be answered by the statewide study. The test study sample size was insufficient to answer the last study aim. This study aim was included in the statewide study to provide additional data on vaccination practices in families with children with autism.

Statistical Analysis

Potential research subjects based on diagnostic group, Regional Center, and age cohort as drawn from CDER records were randomly ordered within a "cell." Recruitment proceeded in each cell until the target number was achieved or the random list was exhausted. Analysis with SUDAAN software accounted for this complex sampling strategy by nesting the analysis by Regional Center, age cohort, and condition (AD vs MR).[37] Posthoc analyses used some of the CDER data to adjust for differing response rates within cells.[38] The probability of enrollment by Regional Center, age cohort, and condition, as well as factors recorded in the CDER data that might influence the likelihood of response or enrollment were determined in these enhanced models. For both groups, these models included (1) a dichotomous variable for whether or not an individual had multiple CDER records (assuming that children with longer contact with the Regional Centers might be more inclined to participate), (2) sex, (3) a dichotomous variable for whether or not a child was living at home with their parent(s), (4) a dichotomous variable for a primary language of English, and (5) a dichotomous variable for a primary language of Spanish. For the autism groups, an additional dichotomous variable was included for whether or not a child with a CDER status 1 autism diagnosis subsequently loses that autism designation. For the MR group, an additional variable was included that specified whether or not a child had any CDER record with the designation of an autism spectrum disorder (CDER Status 2, 4, or 9). Weighting factors were determined using the calculated probability of enrollment for each subject who was sent a mailing requesting participation and factoring in the likelihood of mailing within a given cell. P-values were considered statistically significant if they were ≤ 0.05.

Recruitment and Enrollment

Table 1 summarizes the recruitment and enrollment for the study. There were differences in response rates based on the condition and the age group (response rate: AD1=18%, MR1=10%, AD2=24%, MR2 = 15%). There were also differences in response rate by Regional Center (not shown). A small number of respondents were willing to participate, but either failed to return a signed consent form or did so too late to complete the components of the study. About 5% of recruited families responded that they did not want to participate, mostly citing reasons that they were too busy, or they did not want to subject their child to any more tests. Some were already in other studies, some were dealing with acute medical problems, and some cited privacy concerns. One parent noted that her daughter had Rett's Disorder, one responded that seizures were her child's main problem, and two reported that their child did not have autism. About 15% of our mailings were returned marked "bad address." No response was obtained for 63% of those recruited despite two mailings. The proportion of the enrolled to the target enrollment was highest for the younger group with autism (93%) and lowest for the older group with MR (50%).

Table 1. *Status of recruitment and enrollment efforts as of September 30, 2002 for the Autism Epidemiology Study.*

	Birth Year 1983-85		Birth Year 1993-95	
	CDER Autism (AD1)	CDER MR (MR1)	CDER Autism (AD2)	CDER MR (MR2)
Total CDER records	991	12139	3209	9275
Sampling frame	991	1572	1554	1548
Total mailed (recruited):	892	1388	1161	1384
Enrolled	143	124	232	185
Willing, but didn't return consent	3	5	10	8
Willing but returned consent too late	4	7	10	3
Wait listed (willing but Regional Center group full)	0	0	20	7
Willing, but not English- or Spanish-speaking	1	2	3	1
Initially enrolled but later withdrew from study	13	4	9	9
Responded — not willing to enroll	44	76	48	48
Never responded	540	859	717	920
Other				
Deceased, in file, not mailed	11	71	1	46
Deceased, responded or returned	0	2	0	0
Unmatched ID Number, not mailed	4	12	1	2
Residing in another state, in file, not mailed	23	36	23	18
Residing in another state, responded or returned	3	8	8	8
Bad address in file, not mailed	38	64	15	29
Bad address, returned, undeliverable	138	292	101	193
Recruitment packets not mailed	23	1	353	69

Study Aim 1 Results

Autism Diagnostic Interviews were conducted on the majority (94% and 93%) of children in the autism groups. The results of the ADI-R were considered positive if scores in each of three domains (Qualitative Impairments in Reciprocal Social Interaction, Communication Impairments, and Repetitive Behaviors and Stereotyped Patterns) met criteria matching DSM-IV criteria for autism, and the age of onset of symptoms (age < 36 months) was consistent with a diagnosis of autism. The results of comparison between the two age cohorts of children with CDER status 1 autism are presented in Table 2.

Table 2. *Comparison of ADI-R results for children with CDER status 1 autism, by age group, Autism Epidemiology Study.*

	Birth Year 1983-85	Birth Year 1993-95	p-value
Enrolled	143	232	
ADI-R Completed	135	216	
Proportion ADI-R Completed	94.4%	93.1%	0.78
Positive ADI-R	120	193	
Proportion Positive ADI-R (Unweighted and unadjusted)	88.9%	89.4%	0.97
Proportion Positive ADI-R (Weighted, adjusted for the staged sampling design)	88.2%	88.7%	0.90
Standard Error	0.0289	0.0215	
Design Effect	1.08	0.99	

The main finding is that the vast majority of children with CDER status 1 autism met DSM-IV criteria for autism and that this close correlation differs little between the two age cohorts. Using unadjusted numbers, 88.9% of children in the 1983-85 group met DSM-IV criteria, compared to 89.4% in the 1993-95 group. The results change very little when applying a weighting factor and accounting for differences in sampling and response by Regional Center and by age cohort (88.2% and 88.7%). The design effect of nearly 1 shows that the complex sampling employed in the analysis approximates a simple random sample. This means that simple comparisons of the results closely match results from a more precise weighted and adjusted analysis. Results from both simple comparisons and the more complex, but more accurate, analyses are presented for the first three study aims to assure readers that the results presented in this report are real and not just a fabrication based on complex statistical modeling.

Thirty-eight children (15 from Cohort 1 and 23 from Cohort 2) had a negative ADI-R despite having a CDER status 1 autism designation. For Cohort 1, study questionnaires were returned for 13 of these 15 children; nine parents reported that their child had autism, two reported PDD, one reported Asperger's Disorder, and one reported Rett's Disorder. In the two remaining children whose ADI-R scores did not meet DSM-IV criteria for autism, parents had reported autism in one and PDD in the other based on answers given during the ADI-R. For Cohort 2, study questionnaires were returned for 20 of the 23 children with a negative ADI-R; 18 parents reported their child as having autism, one reported PDD, and one reported Childhood Disinte-

grative Disorder. For the remaining three children in this cohort without questionnaire responses, two parents reported their child's diagnosis as autism; the remaining parent reported attention deficit disorder, but did not specifically refute their child's diagnosis of autism. Thus, most of the children in the autism groups whose ADI-R score did not meet DSM-IV criteria for autism were somewhere on the autism spectrum.

Scores on the three main components and the age criteria were compared for the two age cohorts to test whether or not the number of criteria used to determine the diagnosis of autism differs by age cohort. Differences in mean scores would suggest that the threshold for making a designation of CDER status 1 autism had changed between the two age cohorts. The results (shown in Table 3) indicate that the threshold for making the diagnosis of autism changed little between the two age cohorts. There was a statistically significant difference in the score for age criteria with the younger cohort, but this difference of a quarter point is of little clinical significance and not likely to result in major changes in the diagnosis of autism. Likewise, the three-quarter point difference between scores for the Repetitive/Stereotypic Behaviors Section is not likely to be associated with significant changes in the diagnosis of autism. Furthermore, these two differences would exert an opposing influence on any overall change in autism diagnostic thresholds.

Table 3. *Comparisons of component scores on ADI-R for children with CDER status 1 autism who were ADI-R positive, by age group, Autism Epidemiology Study.*
(Results of weighted and adjusted analyses)

	# ADI-R Positive	Mean Score	Standard Error	Design Effect	p-value
Age criteria					
AD1 (1983-85)	120	3.26	0.11	1.27	0.03
AD2 (1993-95)	193	3.50	0.07	0.98	
Social Impairments					
AD1 (1983-85)	120	22.86	0.34	1.03	0.31
AD2 (1993-95)	193	23.33	0.31	0.87	
Repetitive/Stereotypic Behaviors					
AD1 (1983-85)	120	6.84	0.23	1.23	0.01
AD2 (1993-95)	193	6.07	0.16	0.98	
Communication Impairment — Overall					
AD1 (1983-85)	120	16.66	0.32	1.05	0.12
AD2 (1993-95)	193	16.02	0.26	0.94	
Communication Impairment — Verbal Children					
AD1 (1983-85)	93	17.88	0.32	1.03	0.20
AD2 (1993-95)	144	17.33	0.28	0.97	
Communication Impairment — Non-Verbal Children					
AD1 (1983-85)	27	13.07	0.25	0.84	0.053
AD2 (1993-95)	49	12.41	0.22	0.88	

Study Aim 2 Results

A portion of children categorized as having mental retardation by the Regional Center system met DSM-IV criteria for autism, representing an undercounting of cases of autism. Of the 1983-85 cohort, 17% met criteria for autism, compared to 21% of children in the 1993-95 cohort. When the results were weighted and the analyses adjusted for the complex sampling design, these proportions are approximately 18% for both groups. These results, shown in Table 4, demonstrate that there is not a significant difference in misclassification between the two age cohorts. For this type of misclassification to contribute to an apparent increase in autism cases, the misclassification rate would have to be greater for the older cohort. We found similar rates of misclassification in both age cohorts.

Table 4. *Autism screening and ADI-R results among children determined to have mental retardation without CDER status 1 autism, by age group, Autism Epidemiology Study.*

	Birth Year 1983-85	Birth Year 1993-95	p-value
Enrolled	124	185	
SCQ's Completed	106	153	
Completion Rate	85.5%	82.7%	0.62
SCQ Positive (score ≥ 22)	34	54	
Proportion of Positive SCQ's (unweighted and unadjusted)	32.1%	35.3%	0.71
Proportion of Positive SCQ's (Analysis weighted, adjusted)	32.9%	33.5%	0.93
Number of Follow-up ADI-R's (among the positive SCQ's)	24	37	
Number of Positive ADI-R's	16	28	
Rate of Positive ADI-R's (among the positive SCQ's)	66.7%	75.7%	0.64
Rate of Positive ADI-R's (excluding positive SCQ without a follow-up ADI-R)	16.7%	20.6%	0.56
Rate of Positive ADI-R's (excluding positive SCQ without a follow-up ADI-R) (Analysis weighted, adjusted)	18.4%	18.7%	0.96

Our estimate that 18% of children with mental retardation meet DSM-IV criteria for autism is likely to be an overestimation of the actual percentage. Parents of children in the MR groups might have been more likely to respond and enroll if they believed their child had autistic features. The low response rate in this group also increased the likelihood of a differential response ("bias") among the parental respondents. We tested whether parents of children in the MR group were more likely to respond if the CDER record indicated the child may have an autism spectrum disorder (ASD). If the CDER record was marked for Autism Status 2, 4, or 9 (defined previously) we considered this evidence for ASD. The odds ratio for enrollment given a listing of an ASD condition was 1.50, but this was not significantly different from an odds ration of 1.0 (95% confidence interval 0.82-2.75). This slight bias of enrollment

for children with ASD conditions was similar in both cohorts (odds ratios of 1.42 and 1.44).

There was a high rate of positive ADI-R's among the children whose SCQ was positive. Unfortunately, not all of these families completed an ADI-R interview. We tested for potential bias in the completion of the ADI-R's by comparing the average total SCQ score for those who completed an ADI-R with those who did not. There were 88 children with MR who scored positively on the SCQ; an ADI-R was completed on 61 and not on 27. The mean SCQ score for ADI-R completers was 25.48 ±3.01, and for those lacking ADI-R follow-up, the mean score was 25.30 ±2.80 (p=.79).

If all of the positive SCQ results were followed up with an ADI-R interview, it is likely that more children in the MR group would have been found to meet DSM-IV criteria for autism. However, there are many potential problems with these data which limit our ability to produce an accurate estimate of the misclassification of autism among children reported with mental retardation. Misclassification would have to occur more frequently in the past and less frequently currently to produce an apparent rise in autism. We found no evidence that such a difference exists.

Among the 44 children in the MR group who met DSM-IV criteria for autism based on the ADI-R, some parents reported an autism diagnosis while most did not.

Among the 44 children in the MR group who met DSM-IV criteria for autism based on the ADI-R, some parents reported an autism diagnosis while most did not. In Cohort 1, study questionnaires were completed on 14 of the 16 children with a positive ADI-R. Autism was reported by three parents and was not reported by 11. Of these 11, one child was reported to have Childhood Disintegrative Disorder, two were reported to have PDD, one was reported to have Prader-Willi syndrome, six had no autism spectrum disorder, and one had an unknown condition. Families for two children in Cohort 1 did not complete the questionnaire, but did report fragile X syndrome with autistic tendencies (1) and a duplication on the X chromosome (1) during the ADI-R interview. In Cohort 2, questionnaire data were available for 27 of 28 study subjects. Autism was noted on the study questionnaire by eight parents and PDD by seven parents. The other 12 parents did not report an autism spectrum disorder diagnosis. The one remaining study subject was reported to have cerebral palsy and microcephaly.

Study Aim 3 Results

Place of birth was compared for each age cohort among children with CDER status 1 autism to determine whether the apparent increase in autism numbers can be attributed in part to large numbers of children with autism moving into California. Table 5 shows the results of these place-of-birth analyses. The vast majority of children with autism were born in California. The trend for a greater proportion of California births among the younger children with autism is the opposite that would be necessary for increased numbers of autism cases to be due to children with autism moving into California. The finding that a greater proportion of older children are born out-of-state would be expected with the older group having more time to be comprised of children born elsewhere and then move into the State.

Table 5. *Place of birth comparisons for children with CDER status 1 autism, by age group and ADI-R status, Autism Epidemiology Study.*

CDER Status 1 Autism	**Birth Year 1983-85**	**Birth Year 1993-95**	**p-value**
Enrolled	143	232	
Study Surveys completed	117	189	
California birth	105	178	
Proportion of CA Births (unweighted and unadjusted)	89.7%	94.2%	0.23
Proportion of CA Births (Analysis weighted, adjusted)	88.5%	93.0%	0.25
CDER Status 1 Autism and +ADI-R	**Birth Year 1983-85**	**Birth Year 1993-95**	**p-value**
Positive ADI-R	100	161	
California birth among +ADI-R	89	152	
Proportion of CA Births (unweighted and unadjusted)	89.0%	94.4%	0.17
Proportion of CA Births (Analysis weighted, adjusted)	87.3%	92.9%	0.22

In summary, mobility of children with autism does not account for any of the observed increase in autism in the Regional Center System.

Study Aim 4 Results

We analyzed demographic characteristics of children with CDER status 1 autism. We limited the study sample to those children who met DSM-IV criteria for autism based on the results of the ADI-R interview. Characteristics were compared between the two age groups as in previous analyses. We postulated that significant differences in certain demographic characteristics may help explain the observed increase in autism in California. Basic demographic characteristics for children with autism are shown in Table 6. There were no significant differences between the age groups for sex, race, and maternal or paternal education. Patterns of dominant handedness (i.e. right-handed, left-handed, both) were not significantly different between the two age groups (data not shown). About 75% of parents reported their children were right-handed. Just over 7% of the older cohort and nearly 13% of the younger cohort were reported to be ambidextrous.

Table 6. *Demographic characteristics of children with full syndrome autism, by older and younger birth cohorts, Autism Epidemiology Study.*

	Birth Year 1983-85 (N=100)	Birth Year 1993-95 (N=161)	
Characteristic	**Percentage**	**Percentage**	**p-value**
Male sex	90.4%	83.7%	0.08
Race/Ethnicity*:			
White	68.3%	78.3%	0.12
African-American	8.9%	7.4%	0.68
Asian/Pacific Islander	19.5%	14.5%	0.40
Native American	3.5%	3.0%	0.82
Hispanic	27.6%	39.0%	0.06
Parent educational level:			
Father with high school diploma or higher	87.0%	77.6%	0.06
Father with college associate's degree or higher	40.3%	38.7%	0.81
Mother with high school diploma or higher	86.5%	89.1%	0.54
Mother with college associate's degree or higher	35.5%	33.3%	0.70

Study sample was limited to those children who met DSM-IV criteria for autism based on the ADI-R interview. All percentages are weighted and adjusted for the study's sampling design.
**Parents could select multiple responses for the race/ethnicity question.*

Parents of autistic children did not universally report the diagnosis of "full syndrome" autism. Table 7 shows the diagnoses that the parents reported. A greater proportion of older children were reported to have a diagnosis of Asperger's Disorder. This finding may be due to a shift over time in how high functioning children have been labeled. While most parents reported that their child's autism improved over

time, parents of children in the younger cohort were more likely to do so (results shown in Table 8).

Table 7. *Percentage of children with a diagnosis of autism or other autistic disorders as reported by parents, by older and younger birth cohorts, children with full syndrome autism, Autism Epidemiology Study.*

	Birth Year 1983-85 (N=100)	Birth Year 1993-95 (N=161)	
Autism Spectrum Diagnosis (multiple responses allowed)	**Percentage**	**Percentage**	**p-value**
Autism or autistic disorder	84.2%	88.6%	0.34
Asperger's disorder	15.4%	1.7%	<0.001
Childhood disintegrative disorder	0.0%	1.1%	0.13
PDD-NOS*	20.9%	14.5%	0.21
Rett's syndrome	0.0%	0.0%	-
Unknown	2.0%	2.9%	0.72

Study sample was limited to those children who met DSM-IV criteria for autism based on the ADI-R interview. All percentages are weighted and adjusted for the study's sampling design.
**Pervasive developmental disorder, not otherwise specified*

Table 8. *Improvement in child's autism as reported by parents, by older and younger birth cohorts, children with full syndrome autism, Autism Epidemiology Study.*

	Birth Year 1983-85 (N=100)	Birth Year 1993-95 (N=161)	
Parent report of improvement in child's autism	**Percentage**	**Percentage**	**p-value**
Child's autism has improved	80.8%	93.3%	0.01
Those who answered "yes, autism improved" noted improvements in these areas:			
Social interactions	83.3%	82.6%	0.90
Language/communication	87.7%	90.9%	0.43
Behavior/interests/activities	75.0%	81.0%	0.30

Study sample was limited to those children who met DSM-IV criteria for autism based on the ADI-R interview. All percentages are weighted and adjusted for the study's sampling design.

We found that a diagnosis of mental retardation associated with autism had declined significantly between the two birth cohorts. This decline was consistent in the CDER data, in Regional Center documentation, and with what parents reported to us on the study questionnaire. The definition of mental retardation as used in CDER and Regional Center record documentation is the presence of mild mental retardation or below (IQ ≤ 70). For the study questionnaire, parents were asked "Has your child been diagnosed with mental retardation?," and a Yes or No response was required. Table 9 shows these results.

Table 9. *Presence of mental retardation as documented by CDER, Regional Center record, and parental report, by older and younger birth cohorts, children with full syndrome autism, Autism Epidemiology Study.*

	Birth Year 1983-85		Birth Year 1993-95		
Associated mental retardation	**Sample size**	**%**	**Sample size**	**%**	**p-value**
MR documented in CDER record	120	60.5%	193	26.7%	<0.001
MR documented in Regional Center record	119	49.7%	185	22.3%	<0.001
MR reported by parents	100	41.3%	161	20.8%	<0.001

Study sample was limited to those children who met DSM-IV criteria for autism based on the ADI-R interview. All percentages are weighted and adjusted for the study's sampling design.

Parents of the younger group of autistic children were less likely to report that their child was diagnosed with a tic disorder, depression, or obsessive-compulsive disorder. These differences may be age-related, and over time these disorders may develop in the younger group.

Table 10. *Parent-reported conditions associated with autism diagnoses, by older and younger birth cohorts, children with full syndrome autism, Autism Epidemiology Study.*

	Birth Year 1983-85 (N=100)	Birth Year 1993-95 (N=161)	
Associated Conditions (multiple responses allowed)	**Percentage**	**Percentage**	**p-value**
Epilepsy	14.8%	9.8%	0.27
Cerebral palsy	2.6%	1.4%	0.41
Tic disorder	7.4%	0.6%	0.02
Obsessive-compulsive disorder	20.5%	5.1%	<0.001
Depressive disorder	15.7%	1.1%	<0.001
Bipolar disorder	0.7%	0.6%	0.95

Study sample was limited to those children who met DSM-IV criteria for autism based on the ADI-R interview. All percentages are weighted and adjusted for the study's sampling design.

Most children with autism did not have a family history of autism. Table 11 presents family histories as reported by parents, and compares these histories by birth cohort. The younger group of children with autism was less likely to have a family history of mental retardation.

Table 11. *Family history of autism or other conditions/disorders as reported by parents, by older and younger birth cohorts, children with full syndrome autism, Autism Epidemiology Study.*

	Birth Year 1983-85 (N=100)	Birth Year 1993-95 (N=161)	
Reported Family History	**Percentage**	**Percentage**	**p-value**
Autism	12.9%	16.3%	0.47
Asperger's disorder	5.7%	4.7%	0.73
PDD-NOS	2.9%	7.3%	0.07
Mental retardation	30.5%	16.2%	0.01
Tic disorder	3.8%	3.3%	0.82
Obsessive-compulsive disorder	9.2%	8.7%	0.89
Depressive disorder	31.3%	27.4%	0.49
Bipolar disorder	10.5%	8.2%	0.53

Study sample was limited to those children who met DSM-IV criteria for autism based on the ADI-R interview. All percentages are weighted and adjusted for the study's sampling design.

We asked the family to complete questions about the pregnancy if the biological mother was available to answer the questions. The use of medications or other therapies to become pregnant was reported more frequently by the parents of the younger autism cohort. Overall this involved less than 10% of this group. Additional details of these comparisons are shown in Table 12. Serious viral illnesses were reported in 10% to 13% of pregnancies; most were attributed to flu, and they differed little by age group (Table 13). About 15% of mothers reported receiving a vaccination or shot during pregnancy. Again, there were few age group differences. A health-care provider prescribing bed rest during the pregnancy, due to complications such as vaginal bleeding, elevated blood pressure, or pre-term labor, was reported by about 15% of mothers of autistic children in both cohorts (data not shown).

Table 12. *Percentage of mothers reporting use of medical treatments to become pregnant, by older and younger birth cohorts, children with full syndrome autism, Autism Epidemiology Study.*

	Birth Year 1983-85 (N=100)	Birth Year 1993-95 (N=161)	
	Percentage	**Percentage**	**p-value**
Mother used any medical treatment to help become pregnant	3.6%	9.7%	0.08
Medical treatments that were used:			
Took medicine to stimulate ovulation	3.6%	7.9%	0.19
Received hormone shots	1.8%	2.7%	0.57
Treatment/surgery for blocked fallopian tubes	0.9%	0.7%	0.87
Artificial insemination	0.0%	2.9%	0.07
In-vitro fertilization	0.0%	4.4%	0.08

Study sample was limited to those children who met DSM-IV criteria for autism based on the ADI-R interview. All percentages are weighted and adjusted for the study's sampling design.

Table 13. *Percentage of mothers reporting events during pregnancy, by older and younger birth cohorts, children with full syndrome autism, Autism Epidemiology Study.*

	Birth Year 1983-85 (N=100)	Birth Year 1993-95 (N=161)	
Pregnancy event	**Percentage**	**Percentage**	**p-value**
Flu (respiratory illness with fever, body aches)	8.8%	8.3%	0.89
Any shot or vaccination during the pregnancy	15.6%	13.4%	0.11
Any pre-term labor	14.8%	8.6%	0.17
Took medicine to stop the pre-term labor	8.4%	2.5%	0.06
Received medicine to induce or augment uterine contractions	32.7%	34.9%	0.73

Study sample was limited to those children who met DSM-IV criteria for autism based on the ADI-R interview. All percentages are weighted and adjusted for the study's sampling design.

Questions about maternal substance use before and during pregnancy were asked and the results are summarized in Table 14. Most respondents answered the questions about alcohol and cigarette use. Due to the sensitive nature of drug use questions, they were omitted from early questionnaires until an NIH Certificate of Confidentiality was obtained. Maternal alcohol use prior to pregnancy was about 30% for both birth cohorts. A decline in alcohol use after the mother became aware of her pregnancy was reported for both birth cohorts. There were no significant differences in maternal cigarette smoking or drug use between birth cohorts. For drug use, we queried about the use of marijuana, cocaine, methamphetamines, heroin, methanol, PCP/"angel dust," barbiturates, or LSD immediately preceding or during the pregnancy. There were not enough positive responses on any individual item to support additional analyses.

Table 14. *Prenatal exposure to alcohol, cigarettes, and street drugs by older and younger birth cohorts, children with full syndrome autism, Autism Epidemiology Study.*

	Birth Year 1983-85 (N=100)	**Birth Year 1993-95 (N=161)**	
	Percentage	**Percentage**	**p-value**
Had any alcoholic beverages ≤ 12 months before child was born	34.7%	29.2%	0.39
	Ave # drinks/mo.	**Ave # drinks/mo.**	
Average number of drinks per month before learned of pregnancy	2.74	2.45	0.79
	Percentage	**Percentage**	
Had any alcoholic beverages after learned of pregnancy and before child was born	3.0%	5.4%	0.28%
	Ave # drinks/mo.	**Ave # drinks/mo.**	
Average number of drinks per month after learned of pregnancy and before child was born	0.18	0.37	0.39
	Percentage	**Percentage**	
Had any cigarettes ≤ 12 months before child was born	14.5%	9.7%	0.26
Had any cigarettes after learning of pregnancy and before child born	10.3%	6.4%	0.28
Used any street drugs ≤ 12 months before child was born	10.2%	6.3%	0.37
Used any street drugs after learning of pregnancy and before child born	7.4%	6.5%	0.83

Study sample was limited to those children who met DSM-IV criteria for autism based on the ADI-R interview. All percentages are weighted and adjusted for the study's sampling design.

Virtually all children with autism received at least one vaccination and this did not differ across birth cohorts (98.4% vs. 99.4%, p=.49). There was, however, a substantial difference in families' decisions to avoid or delay at least one vaccination among the older cohort as compared with the younger cohort (7.9% vs. 21.5%, p<.001). As expected, the older group was more likely to have any younger siblings (56.7% vs. 44.8%, p=.07). For families with younger siblings, parents of children in the younger

cohort were more likely to avoid or delay at least one vaccination for a younger sibling (9.5% vs. 20.7%, p=.06).

We asked questions about the presence of specific gastrointestinal (GI) symptoms at various ages. Results of birth cohort comparisons are shown in Table 15. Reported GI symptoms were more common among the younger cohort, especially constipation in the first year, when solid foods were introduced, and when the child was making the transition to table foods. Vomiting was also more commonly reported in the younger cohort during this time period. No differences between age cohorts were noted beyond 15 months of age.

Table 15. *Percentage of children with a history of gastrointestinal symptoms as reported by parents, by older and younger birth cohorts, children with full syndrome autism, Autism Epidemiology Study.*

	Birth Year 1983-85 (N=100)	**Birth Year 1993-95 (N=161)**	
	Percentage	**Percentage**	**p-value**
No gastrointestinal problems in the newborn period	59.7%	52.1%	0.24
Percentage of specific gastrointestinal problems during the newborn period:			
Constipation	13.5%	21.8%	0.08
Diarrhea	14.0%	12.5%	0.73
Vomiting or reflux	10.9%	20.1%	0.03
Other*	7.1%	5.5%	0.67
No gastrointestinal problems when introduced solid foods	71.2%	59.5%	0.047
Percentage of specific gastrointestinal problems when introduced solid foods:			
Constipation	8.1%	17.9%	0.01
Diarrhea	7.0%	11.8%	0.12
Vomiting or reflux	4.0%	9.5%	0.06
Other*	3.3%	2.3%	0.72
No gastrointestinal problems when transitioned to table foods	73.7%	59.3%	0.01
Percentage of specific gastrointestinal problems when transitioned to table foods:			
Constipation	6.4%	19.1%	<0.001
Diarrhea	10.4%	15.5%	0.21
Vomiting or reflux	1.6%	5.6%	0.05
Other*	3.4%	5.2%	0.47
No gastrointestinal problems from age 15 months to the present	59.6%	58.0%	0.81
Percentage of specific gastrointestinal problems at or after age 15 months:			
Constipation	19.3%	24.0%	0.36
Diarrhea	10.7%	14.0%	0.42
Vomiting or reflux	5.5%	6.7%	0.70
Abdominal pain or cramping	6.8%	7.9%	0.72

Study sample was limited to those children who met DSM-IV criteria for autism based on the ADI-R interview. All percentages are weighted and adjusted for the study's sampling design.
**Includes gas, bloody diarrhea, problems swallowing, colic.*

We asked the parents if their child had any food allergies, and if yes, to what food is the child allergic. Results are shown in Table 16. Overall, about a quarter of the parents in both cohorts reported food allergies. Allergies to milk or dairy products were most common, although not significantly different between the two age groups. Reported wheat allergies had increased significantly in the younger age group (3.8% vs. 11.5%).

Table 16. *Percentage of children with a history of food allergies as reported by parents, by older and younger birth cohorts, children with full syndrome autism, Autism Epidemiology Study.*

	Birth Year 1983-85 (N=100)	Birth Year 1993-95 (N=161)	
Reported Food Allergies	**Percentage**	**Percentage**	**p-value**
Any food allergies	23.8%	25.1%	0.81
Milk or dairy	15.6%	19.3%	0.45
Wheat	3.8%	11.5%	0.01
Eggs	0.9%	3.5%	0.09
Nuts (peanuts, walnuts, etc.)	4.0%	3.3%	0.76
Fruit or berries	1.9%	2.8%	0.60
Vegetables (including tomatoes)	0.0%	1.8%	0.07
Shellfish (shrimp, crab, etc.)	2.2%	1.1%	0.44

Study sample was limited to those children who met DSM-IV criteria for autism based on the ADI-R interview. All percentages are weighted and adjusted for the study's sampling design.

Regression on developmental milestones was assessed by several methods: the inclusion of a series of questions on the study questionnaire, evaluating regression questions from the ADI-R, and administering a follow-up questionnaire for children whose ADI-R indicated regression. More than half of the parents from each birth cohort reported on the study questionnaire that their child had undergone regression. We clarified some of these statements through follow-up phone calls or the additional questionnaire. Many parents were confusing delay in the acquisition of a milestone with regression of a milestone that had been achieved. The distinction between these two developmental issues was made clear during the ADI-R interview, thus the reports of regression from the ADI-R were consistently less frequent (approximately 30%). Nonetheless, both results from the study questionnaire and ADI-R interview show that there were no differences based on birth cohort on the proportion of parents reporting a history of regression in their autistic child.

We followed up reports of regression from the ADI-R by administering a more detailed interview with the parent. These interviews were conducted over the telephone and lasted about thirty minutes. The results of these interviews are summarized in Table 16. Most parents reported that the onset of regression occurred before 36 months of age (75% vs. 80%, p=.86) For those children with regression prior to 36 months, most parents (>75%) reported that their child stopped using words for at least one month. We asked the parents to report the number of words the child was using before this loss of words. The average number of words used prior to regression was

higher for the younger cohort (7.8 vs. 10.9). In summary, the rate of regression of developmental milestones observed in this study is similar to previous published reports (approximately 30% using the ADI-R) and this rate differed little between the two birth cohorts.

Table 17. *Regression of developmental milestones as reported by parents, by older and younger birth cohorts, children with full syndrome autism, Autism Epidemiology Study.*

	Birth Year 1983-85 (N=103)	Birth Year 1993-95 (N=174)	
Evaluation of Regression	**Percentage**	**Percentage**	**p-value**
Regression reported on study questionnaire	60.2%	53.7%	0.31
Regression reported on ADI-R	27.8%	33.6%	0.28
Total number with regression on ADI-R	33	63	
Total number with follow-up questionnaire results	20	45	
Percentage with reported regression by 36 months of age	71.0%	81.9%	0.35
Stopped using words for at least one month	69.1%	70.2%	0.93
Mean total number of words prior to regression (mean +/– SE)	7.8±0.75	10.9±0.93	0.01

Study sample was limited to those children who met DSM-IV criteria for autism based on the ADI-R interview. All percentages are weighted and adjusted for the study's sampling design.

Study Aim 5 Results

We asked the parents, "What do you think caused your child's autism and/or other developmental problem?" We provided a large blank area for parents to write in their response. These were then reviewed and categorized. The responses from parents of children with CDER status 1 autism who met DSM-IV criteria are shown in Table 17. We included those that represented at least 1% of parental responses within either birth cohort and we compared responses between birth cohorts. The most frequent response was "don't know" or leaving that part of the questionnaire blank. The frequency of this response did not differ between birth cohorts. The next most frequent response category was immunizations, with 18.3% of older cohort parents and 33.0% of the younger cohort parents attributing their child's autism to immunizations. Analysis of data from the ADI-R interview showed that parents who reported regression of developmental milestones were much more likely to attribute their child's autism to immunizations (30.5% vs. 49.8% in cohorts 1 and 2 respectively). Genetics was next most frequently cited by parents of children with autism (30.6% vs. 26.6%). Pregnancy related events, birth trauma, and environmental exposures were also mentioned as causes for autism.

Table 18. *Parent responses to question, "What do you think caused your child's autism and/or other developmental problem?" by older and younger birth cohorts, children with full syndrome autism, Autism Epidemiology Study.*

	Birth Year 1983-85 (N=100)	Birth Year 1993-95 (N=161)	
Parent Responses	**Percentage**	**Percentage**	**p-value**
"Don't know" or no response	45.7%	47.9%	0.74
Genetics	30.6%	26.6%	0.49
Pregnancy Related	24.1%	16.3%	0.16
Immunizations (all responses):	18.3%	33.0%	0.005
Immunizations in general	14.9%	26.5%	0.02
DTaP or DTP	4.7%	1.1%	0.10
MMR	1.1%	6.5%	0.005
Birth Events (Adverse)	13.5%	14.6%	0.80
Environmental Exposure	10.0%	12.1%	0.59
Drug Use – Illegal	5.9%	2.7%	0.31
Emotional Trauma	3.5%	3.0%	0.81
Mercury Poisoning	3.3%	3.9%	0.86
Brain Abnormalities	2.7%	1.2%	0.48
Head Trauma	2.7%	1.3%	0.60
Allergies	2.3%	5.4%	0.14
Syndromes (e.g. Fragile X)	2.3%	1.1%	0.41
Virus	2.0%	1.1%	0.57
Ear Infections	1.8%	2.9%	0.49
Drug Use – Over the counter or prescription	1.4%	2.4%	0.51
Antibiotics	1.3%	3.5%	0.18
Gastrointestinal Disorders	0.6%	2.4%	0.16
Nutrition	0.0%	2.9%	0.02
Traumatic Surgery	0.0%	1.8%	0.06
High Fever	0.0%	1.1%	0.13

Study sample was limited to those children who met DSM-IV criteria for autism based on the ADI-R interview. All percentages are weighted and adjusted for the study's sampling design.

Study Aim 6 Results

To assess the association between immunizations and the development of autism, we designed part of this study to make use of potential "natural experiment." It has been anecdotally reported that a significant number of families with autistic children is avoiding or delaying some or all vaccinations in younger siblings. Recurrence of autism within families is more common than in the general population, but still is relatively low (2%-10%). Assuming a recurrence rate of 5%, about 1 in 20 younger siblings would be diagnosed with autism. We postulated that if vaccinations contribute to the development of autism, there should be an observable difference in the proportion of siblings with autism when comparing vaccinated siblings with unvaccinated siblings.

Avoidance of at least one vaccine in younger siblings was reported by 10% of the older cohort and 21% of the younger cohort.

In this study, about half of the children with autism had any younger siblings at the time they were enrolled to participate. Avoidance of at least one vaccine in younger siblings was reported by 10% of the older cohort and 21% of the younger cohort. However, the total number of vaccine-avoidant younger siblings in both birth cohorts was only 19, which is insufficient to answer the question posed in this study aim. Based on our findings of 1) the proportion of families with an autistic child that have subsequent children, and 2) the proportion of families who are avoiding or delaying vaccination in younger siblings, we calculated that we would need a sample size of 7,000 families to properly answer this question.

Conclusion

The rise in the number of autism cases in California has been a cause for much concern. How to respond to these increasing numbers has been a point of major debate. Increases of the magnitude that have been reported challenge our limited understanding of the cause or causes of autism. It is natural to discount that which we do not understand or force it to fit a paradigm with which we are comfortable. This study has been an attempt to determine whether or not the increased numbers are due to a real epidemic, or if the rise in autism cases can be explained by factors that have artificially created that increase.

Has there been a loosening in the criteria used to diagnose autism, qualifying more children for Regional Center services and increasing the number of autism cases? We did not find this to be the case.

These results show that approximately 90% of children reported by the Regional Center System as having CDER status 1 autism met DSM-IV criteria for autism. More importantly, this close correspondence did not differ between the two birth cohorts. Our results, based on ADI-R interviews with families, are similar to the findings of a recently published study that evaluated Regional Center records[35]. This study by Croen and colleagues, using the birth cohorts 1983-85 and 1993-95, found that 85% of children with CDER status 1 autism in the older cohort and 84% of the younger cohort met DSM-IV criteria for autism. Using the same birth cohorts, our study found that 88% and 89% met DSM-IV criteria for autism. Although Croen and colleagues did not conduct independent confirmation of the autism diagnosis (as was performed in this study with the ADI-R), nonetheless both studies concluded that the diagnosis of autism was reliable for most children in the Regional Center system.

The Autism Epidemiology Study required that families consent to participate, and our response rate was low (18% and 24% in the two age cohorts). One must consider the effects of unmeasurable biases that may have influenced a family's willingness to respond to our letter and participate in the study. This influence on participation would have to affect one birth cohort differently than the other to alter the overall results. Our findings on the percentage of autism cases meeting DSM-IV criteria were comparable in both birth cohorts. The Croen study, which was not subject to participation biases, had results similar to our own. This replication of findings gives added weight to our results.

Has the increase in cases of autism been created artificially by having "missed" the diagnosis in the past, and instead reporting autistic children as "mentally retarded?" This explanation was not supported by our data.

In our sample of children with mental retardation (MR) we did find that 18%-19% met DSM-IV criteria for autism. However, this percentage was consistent in the two birth cohorts. So, while misclassification occurs, children were not disproportionately misclassified in the past compared with the present. We might have attributed some percentage of the rise in autism cases to misclassification if we had found a difference between the two age groups, but we did not find a difference. In the aforementioned Regional Center record review study, the researchers found misclassification in 10% of the older MR cohort but in only 3.9% of the younger MR cohort. They interpreted

these results to mean that the reliability of the CDER diagnosis of MR for children qualifying for Regional Center services had changed during the study period. However, the Regional Center record would have documentation of autism only when an autism diagnosis is considered. In our study, there were some cases of children in the MR group who met DSM-IV criteria for autism even though their CDER records did not record a CDER status 1 autism diagnosis. There were other children in this study group who met DSM-IV criteria for autism whose Regional Center record would not have supported this diagnosis. Thus, a record review alone may result in an undercount of misclassification compared with active screening. Our findings, based on screening for autistic spectrum disorders with the SCQ and verifying an autism diagnosis with the ADI-R, are in contrast to their results.

In the Autism Epidemiology Study, the response rate was especially low for families whose children had a primary diagnosis of MR and not autism (10% for the older cohort and 15% for the younger cohort). As with Study Aim 1, we must assess this low participation rate and how it may have affected our results and conclusions. Examining our enrolled subjects with the CDER data, we found that parents of children with MR were more likely to enroll if their child had been reported with an autism spectrum disorder (CDER status 2, 4, or 9). However the odds of enrollment for an MR subject with an autism spectrum disorder were consistent in the two birth cohorts (odds ratio 1.42 in the older cohort and 1.44 in the younger cohort), so this enrollment bias did not differentially affect the MR group. The overall effect of this bias, where families whose child may have an autism spectrum disorder were somewhat more willing to participate, is to assume that the rate of misclassification for the whole group of children with MR in the Regional Center system is lower than the 18% estimate that we calculated.

It is worth considering what these misclassification numbers mean. Because the number of children in the MR group has historically been much larger than the autism group, even a modest rate of misclassification significantly increases the number of children who meet criteria for autism. For example, if the rate were 10% in the older cohort as reported by Croen et al, that translates to an additional 1,214 children with autism in the 1983-85 birth cohort (0.10 * 12,139). That would raise the total for that birth cohort from 991 to 2,205, more than doubling the number of children identified with full syndrome autism. There were fewer children reported with MR and not autism in the younger cohort, so the increase in autism cases would be less dramatic. The low enrollment rate in the MR groups and the bias in enrollment do limit our ability to state what the exact amount of misclassification appears to be. We can assume it is no higher than 18% and similar in the two birth cohorts. Universal autism screening of children with mental retardation by the California Regional Center System would definitively answer this important question. Such systematic screening could be done as part of the annual reassessment of children receiving Regional Center services and would likely further increase the number of autism cases reported.

Can the observed increase be accounted for an increase in the overall State population during the time period or by children with autism moving into California? No, increases in the State population account for less than 10% of the rise in case reports, and most children with autism served by the Regional Center System were born in

California. Based on parental report, 93% of children in the younger cohort and 87% of children in the older cohort were born in the State. To attribute some of the increase in autism cases to children with autism moving into California, we would have expected to see a greater proportion of out-of-California births among the younger children with autism. The finding that a greater proportion of older children are born out-of-state is not unexpected, given that the older group has had more time to move into California.

One additional issue regarding mobility should be mentioned. We found 57 instances where a child reported with autism in California and counted in the CDER database was no longer residing in the State. The cumulative total of cases in California probably represents an overestimation of known Regional Center clients, although not significantly so, based on our observations. Out-migration would be more likely to decrease prevalent cases in the older age cohort, as the greater period of time would increase the likelihood of a change in residence. Adjusting for out-migration then would decrease the number of cases in the older cohort and create a steeper increase in cases than has been reported.

In this study we asked many questions of parents. We compared the responses between the two birth cohorts, searching for differences in the hope of explaining what changing factors might have caused this increase in autism. No single factor investigated could explain the tripling in cases. Differences that were noted between the two groups include reports of more gastrointestinal symptoms during infancy in the younger group; and less mental retardation in the younger group. Regression of developmental milestones, as reported during the ADI-R, had not significantly increased in the younger group. On a more hopeful note, most parents reported improvements in their child's autism. Improvements were noted especially by parents of the younger children with autism.

What do parents think caused their child's autism? The data showed that participants in the study have a range of beliefs as to what causes autism. Most parents said that they "don't know" or they did not respond. Genetics and pregnancy- or birth-related events were frequently reported by parents. Immunization concerns ranked among the top responses. There is a high level of concern about immunizations and their association with autism. Unfortunately, this report was unable to evaluate the association of immunizations with autism recurrence in families due to our low number of unvaccinated younger siblings (Study Aim 6).

The Autism Epidemiology Study did not find evidence that the rise in autism cases can be attributed to artificial factors, such as loosening of the diagnostic criteria for autism; more misclassification of autism cases as mentally retarded in the past; or an increase in in-migration of children with autism to California. Without evidence for an artificial increase in autism cases, we conclude that some, if not all, of the observed increase represents a true increase in cases of autism in California, and the number of cases presenting to the Regional Center system is not an overestimation of the number of children with autism in California.

Appendix 1

DSM-IV Diagnostic Criteria for 299.0 Autistic Disorder

(I) A total of six (or more) items from (A), (B), and (C), with at least two from (A), and one each from (B) and (C)

(A) Qualitative impairment in social interaction, as manifested by at least two of the following:

1. Marked impairments in the use of multiple nonverbal behaviors such as eye-to-eye gaze, facial expression, body posture, and gestures to regulate social interaction.
2. Failure to develop peer relationships appropriate to developmental level.
3. A lack of spontaneous seeking to share enjoyment, interests, or achievements with other people, (e.g., by a lack of showing, bringing, or pointing out objects of interest to other people).
4. Lack of social or emotional reciprocity (Examples: Not actively participating in simple social play or games, preferring solitary activities, or involving others in activities only as tools or "mechanical" aids).

(B) Qualitative impairments in communication as manifested by at least one of the following:

1. Delay in, or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mime).
2. In individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others.
3. Stereotyped and repetitive use of language or idiosyncratic language.
4. Lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level.

(C) Restricted repetitive and stereotyped patterns of behavior, interests and activities, as manifested by at least one of the following:

1. Encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus.
2. Apparently inflexible adherence to specific, nonfunctional routines or rituals.
3. Stereotyped and repetitive motor mannerisms (e.g. hand or finger flapping or twisting, or complex whole-body movements).
4. Persistent preoccupation with parts of objects.

(II) Delays or abnormal functioning in at least one of the following areas, with onset prior to age 3 years:

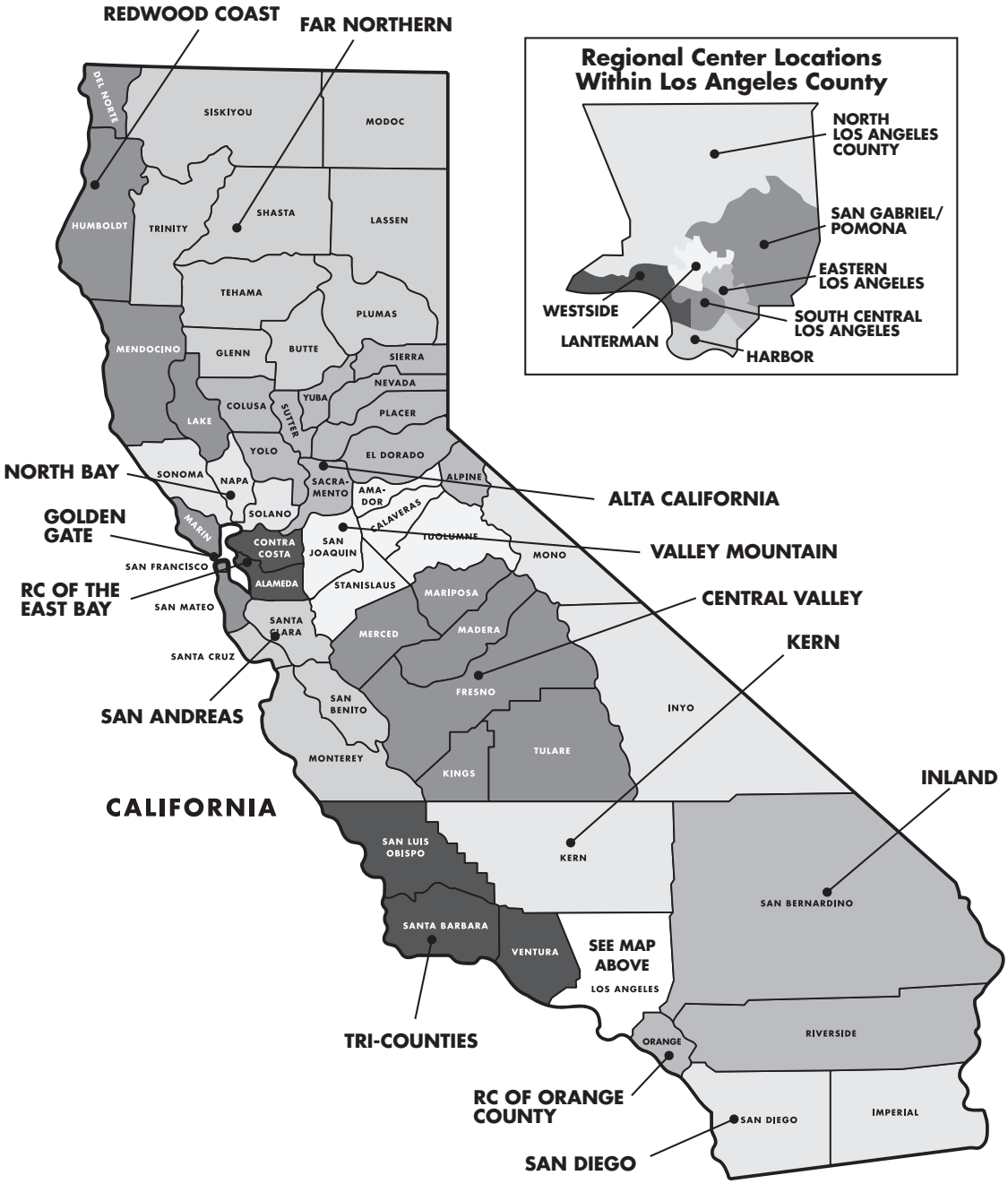
(A) Social interaction
(B) Language as used in social communication
(C) Symbolic or imaginative play

(III) The disturbance is not better accounted for by Rett's Disorder or Childhood Disintegrative Disorder.

Source: The American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Washington D.C., American Psychiatric Association, 1994.

Appendix 2

Regional Center Locations



Appendix 3

State of California—Health and Welfare Agency
CLIENT DEVELOPMENT EVALUATION REPORT
1 3753 (3/86)

Department of Developmental Services

DIAGNOSTIC ELEMENT

REPORT AND CLIENT INFORMATION

Report and Client Identifier

(See Manual pg. VI. 1. 1)

1. Reporting Date (M M D D Y Y)
2. Client Identifier
3. Client Birthdate (M M D D Y Y)
4. Sex — M—Male, F—Female
5. Height — inches
6. Weight — pounds
7. Date Weighed (M M Y Y)

Client Locator
(See Manual pg. VI.3. 1)

8. Program
9. Section
10. Unit

FORM PREPARATION INFORMATION

Physician: _____ Name _____ Signature _____ Title

Psychologist: _____ Name _____ Signature _____ Title

CPC/Team Leader or other person completing form: _____ Name _____ Signature _____ Title

CLIENT DEVELOPMENT EVALUATION REPORT
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DEVELOPMENTAL DIAGNOSTIC INFORMATION

DEVELOPMENTAL DISABILITIES

Record in this section specified diagnosis(es) of the client's disability(ies). Pertinent diagnoses include levels and types, and etiologic factors (causes) of the disabilities. Code the diagnoses using ICD-9-CM and Risk Factor codes, as applicable, according to manual instructions for each specific item.

MENTAL RETARDATION

Level of Retardation (See Manual pg. VI 5.2)

(ICD-9-CM Code)

11. ___ . ___

000.0	No Retardation	318.1	Severe
317	Mild	318.2	Profound
318.0	Moderate	319	MR unspecified (level)

Etiology
(ICD-9-CM Code)

12a. ___ . ___

12b. ___ . ___

13. ___ **Date of Last Evaluation**
M M Y Y

DEVELOPMENTAL CENTER CLIENTS ONLY

Intelligence Quotient

14. ___

Intelligence Test

15. ___

Adaptive Behavior Rating

16. ___

0	Normal	3	Severe
1	Mild	4	Profound
2	Moderate	5	Unknown

CEREBRAL PALSY (See Manual pg. VI 6.1)

If the client has Cerebral Palsy or other type of motor dysfunction (code "1" in Item 17), enter the ICD-9-CM etiology code(s) i Items 18a / 18b for either condition (CP or "other motor dysfunction ")

17. ___ **Presence of Cerebral Palsy**
- 0 No CP or other significant motor dysfunction
- 1 Has CP or other significant motor dysfunction

19. ___ **Level of Motor Dysfunction**
- 1 Mild, doesn't limit activity
- 2 Moderate, in between mild and severe
- 3 Severe, significantly impairs or precludes activity
- 9 CP suspected, level undetermined

21. ___ **Location of Motor Dysfunction**

1	Monoplegia	5	Paraplegia
2	Hemiplegia	6	Quadriplegia
3	Diplegia	7	Other
4	Triplegia		

Etiology
(ICD-9-CM Code)

18a. ___ . ___

18b. ___ . ___

20. ___ **Type of Motor Dysfunction**
- 1 Spasticity (includes Hypertonia and Rigidity
- 2 Ataxia
- 3 Dyskinesis (includes Athetosis and Dystonia
- 4 Hypotonia
- 5 Other (includes mixed)

22. ___ **Condition Impact**

CLIENT DEVELOPMENT EVALUATION REPORT

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AUTISM (See Manual pg. VI.7.1)

23. ___ **Autism**

- 0 None
- 1 Autism, full syndrome
- 2 Autism, residual state
- 9 Autism suspected, not diagnosed

Contributing Factors
(ICD-9-CM Code)

24a. ___ . ___

24b. ___ . ___

25. ___ **Date of Determination** (M M Y Y)

26. ___ **Condition Impact**

EPILEPSY/SEIZURE DISORDER (See Manual pg. VI.8.1)

If the client has only one type of seizure, record it in 27a and also complete 27b and 27c for that type. If the client has more than one type of seizure, record the other types in 28a and 29a and complete the b and c items for these other types.

Type of Seizure

27a. ___ 28a. ___ 29a. ___

- 0 Does not have seizure disorder
- 1 Partial, with elementary symptomatology
- 2 Partial, with complex symptomatology
- 3 Partial, secondarily generalized
- 4 Generalized, Absences (Petit Mal)
- 5 Generalized, Bilateral massive epileptic myoclonic
- 6 Generalized, Infantile spasms
- 7 Generalized, Tonic-Clonic (Grand Mal)
- 8 Generalized, Atonic/Akinetic
- 9 Other/Undetermined

Seizure Frequency

27b. ___ 28b. ___ 29b. ___

- 1 History of seizures, none in two years
- 2 History of seizures, none in one year
- 3 One to six per year
- 4 Seven to 11 per year
- 5 One per month (approximate)
- 6 One per week (approximate)
- 7 One per day (approximate)
- 8 More than one per day
- 9 Frequency undetermined

27c. ___ **Condition Impact** 28c. ___ **Condition Impact** 29c. ___ **Condition Impact**

Etiology
(ICD-9-CM Code)

30a. ___ . ___

30b. ___ . ___

31. ___ **Client takes anticonvulsant medication**
1 = Yes 2 = No

32. ___ **Status Epilepticus**
Has the client had Status Epilepticus in the past year?
1 = Yes 2 = No 3 = Not known

CLIENT DEVELOPMENT EVALUATION REPORT

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OTHER TYPE OF DEVELOPMENTAL DISABILITY (See Manual pg. VI.9.1)

Use this section to identify any developmental disability(ies) other than those listed above (mental retardation, cerebral palsy, etc.) "Other" developmental disabilities are conditions which are similar or closely related to mental retardation or which rec treatment similar to that required for mentally retarded individuals.

		Type of Other Disability (ICD-9-CM Code)		Etiology (ICD-9-CM Code)
33a.	_____ (Specify)	___ . ___	34a.	___ . ___
33b.	_____ (Specify)	___ . ___	34b.	___ . ___

RISK FACTOR (for use in etiology items 12a-b, 18a-b, 24a-b, 30a-b, and 34a-b.) (See Manual pg. VI.10.1)

1 = Yes 2 = No 9 = Unknown

Indicate whether each of the following factors was associated with the client's developmental disability(ies), as specified above. Code "1" for Yes if there are reasonable data to suggest the disability was associated with or significantly impacted by the factor. Code "2" for No if the factor does not pertain to the disability and Code "9" for an unknown association.

35. ___ Low birth weight or preterm labor with complications
36. ___ Teenage pregnancy (17 years and younger)
37. ___ Maternal age 35 years or older at time of delivery
38. ___ Accidents of near drowning
39. ___ Accidents involving an automobile
40. ___ Accidents involving other types of vehicles
41. ___ Accidents of other types
42. ___ Environmental toxins (pesticides, lead, etc.)
43. ___ Drug or alcohol abuse
44. ___ Psychosocial (environmental) deprivation
45. ___ Family history of mental retardation
46. ___ Child abuse or neglect
47. ___ Other causes
48. ___
49. ___

MENTAL DISORDERS (See Manual pg. VI.11.1)

If applicable, enter below the diagnosis(es) that describes the client's mental disorder. If the client does not have a mental disorder, enter 000o00 in item 50a and leave 51a–53c blank. Use DSM-III codes for the mental disorders as Axes I and II. Do not enter developmental disability diagnosis(es), including Autism.

Type of Mental Disorder (DSM-III Code)

	Axis I		Date of Last Evaluation		Condition Impact
50a.	___ . ___	50b.	M M Y Y	50c.	___
51a.	___ . ___	51b.	M M Y Y	51c.	___

	Axis II		Date of Last Evaluation		Condition Impact
52a.	___ . ___	52b.	M M Y Y	52c.	___
53a.	___ . ___	53b.	M M Y Y	53c.	___

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CHRONIC MAJOR MEDICAL CONDITION(S) (See Manual pg. VI.12.1)

List below major chronic, recurrent medical problems, other than developmental disability, that have significant impact on the client's service provision (i.e., diabetes, heart condition, chronic U.R.I., hepatitis, etc.). If there is no medical condition, enter 000o00 in Item 54a and leave Items 55a–59b blank.

	Condition Type(s) (Specify)	Condition (ICD-9-CM-Code)		Condition Impact
54a.				54b.
55a.				55b.
56a.				56b.
57a.				57b.
58a.				58b.
59a.				59b.

OTHER DIAGNOSTIC INFORMATION

HEARING (See Manual pg. VI.13.1)

60. **Level of Hearing Loss Uncorrected**

- 0 Hearing within normal limits
- 1 Mild to moderate hearing loss (hard of hearing)
- 2 Severe hearing loss
- 3 Profound hearing loss
- 4 Hearing loss, one ear
- 9 Hearing loss suspected, severity undetermined

61. **Level of Hearing Loss Corrected**

- 0 Hearing within normal limits
- 1 Mild to moderate hearing loss
- 2 Severe hearing loss
- 3 Profound hearing loss
- 8 Correction not possible
- 9 Hearing not corrected

VISION (See Manual pg. VI.14.1)

62. **Level of Vision Loss Uncorrected**

- 0 Vision within normal limits
- 1 Mild impairment
- 2 Moderate impairment
- 3 Severe impairment (legally blind)
- 4 Total blindness (no light perception)
- 5 Vision loss, one eye
- 9 Vision loss suspected, severity undetermined

63. **Level of Vision Loss Corrected**

- 0 Vision within normal limits
- 1 Mild impairment
- 2 Moderate impairment
- 3 Severe impairment
- 8 Correction not possible
- 9 Vision not corrected

CLIENT DEVELOPMENT EVALUATION REPORT
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BEHAVIOR MODIFYING DRUGS (See Manual pg. VI.15.1)

Types of Prescribed Medication for Maladaptive Behavior

1 = Yes 2 = No

64. ___ Antipsychotic
65. ___ Antidepressant
66. ___ Antianxiety
67. ___ Sedative/Hypnotic
68. ___ Stimulant
69. ___ Other Psychotropic Drug

70. ___ **History of Prescribed Medication for Maladaptive Behavior**

(Do not include medications given only for seizures, sedatives given for examinations or clinics, etc., or medications given on an infrequent PRN basis.)

1 Currently receiving one or more prescribed medication(s)
2 Medication(s) discontinued within six months
3 Medication(s) discontinued more than six months but less than one year
4 Medication(s) discontinued more than one year but less than four years
5 Has not received medication(s) during past four years
6 No known documented history of receiving medication(s)

ABNORMAL INVOLUNTARY MOVEMENTS (See Manual pg. VI.16.1)

(COMPLETE FOR DEVELOPMENTAL CENTER CLIENTS ONLY)

Types of Involuntary Movements

1 = Yes 2 = No

71. ___ Parkinsonism 72. ___ Dystonia 73. ___ Dyskinesia 74. ___ Akathisia 75. ___ Paroxysmal

SPECIAL HEALTH CARE REQUIREMENTS (See Manual pg. VI.17.1)

If the client has special health care requirements, enter the codes for these requirements in Items 76–85. Up to 10 special health care requirements can be entered. If the client has no special health care requirements, enter "00" in Item 76 and leave Items 77–85 blank.

76. ___ 77. ___ 78. ___ 79. ___ 80. ___

81. ___ 82. ___ 83. ___ 84. ___ 85. ___

CLIENT DEVELOPMENT EVALUATION REPORT

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SPECIAL CONDITIONS OR BEHAVIORS (See Manual pg. VI. 18.1)

OPTIONAL: For use in rate justification for out-of-home or day program placement, complete for clients as necessary. Code 1 = Yes ONLY if external documentation of the given condition/behavior exists. If the answer to a particular item is unknown, use code 3.

1 = Yes 2 = No 3 = Unknown

86. ___ Does the client display maladaptive sexual behavior?

87. ___ Has the client engaged in any assaultive behaviors that have or could have resulted in serious bodily injury or death?

88. ___ Has the client attempted suicide in the past five years?

89. ___ Does the client habitually engage in theft?

90. ___ Has the client participated in acts of vandalism or other acts of property destruction?

91. ___ Has the client been convicted of any substance-abuse or alcohol-abuse related offenses?

92. ___ Does the client have a recent history of abusing drugs or alcohol?

93. ___ Does the client have a history of habitual lying?

94. ___ Does the client display behaviors which could result or have resulted in fire setting?

SPECIAL LEGAL CONDITIONS (See Manual pg. VI. 18.4)

Please complete for each client.

1 = Yes 2 = No

95. ___ Is the client currently on probation, county or state parole, or commitment under Penal Code or Welfare and Institutions Code sections relating to a criminal offense?

96. ___ Is the client currently on Diversion pursuant to Penal Code sections 1001.20 et seq.?

97. ___ Is the client currently a person within the provisions of Welfare and Institutions Code section 6500 et seq. (dangerous mentally retarded individual committed by the court)?

98. ___ Is the client currently under a Lanterman-Petris-Short (mental health) conservatorship?

99. ___ Is the client currently a conservatee under the Probate Code (conserved because client is unable to make informed application and consent to treatment)?

100. ___ Is the client currently a dependent child of the Court (Welfare and Institutions Code section 300 et seq.)?

THE CDER EVALUATION ELEMENT

MOTOR DOMAIN

1 ☐ **Rolling and Sitting**
- 1= Does not lift head when lying on stomach
- 2= Lifts head when lying on stomach
- 3= Lifts head and chest using arm support when lying on stomach
- 4= Rolls from side to side
- 5= Rolls from front to back only
- 6= Rolls from front to back and back to front
- 7= Maintains sitting position with minimal support for at least five (5) minutes
- 8= Sits without support for at least five (5) minutes
- 9= Assumes and maintains sitting position independently

2 ☐ **Hand Use**
- 1= No functional use of hand
- 2= Uses raking motion or grasps with hand
- 3= Uses thumb and fingers of hand in opposition
- 4= Uses fingers independently of each other

3 ☐ **Arm Use**
- 1= No functional use of arm
- 2= Moves arm from shoulder but does not extend or flex arm (i.e., does not have control of elbow joint)
- 3= Partially extends arm
- 4= Fully extends arm

4 ☐ **Crawling and Standing**
- 1= Does not crawl, creep or scoot
- 2= Crawls, creeps, or scoots
- 3= Pulls to a standing position
- 4= Stands with support for at least one (1) minute
- 5= Stands unsteadily alone for at least one (1) minute
- 6= Stands well alone, balances well for at least five (5) minutes

5 ☐ **Ambulation**
- 1= Does not walk
- 2= Walks with support
- 3= Walks unsteadily alone at least ten (10) feet
- 4= Walks well alone at least twenty (20) feet, balances well

6 ☐ **Climbing Stairs**
(rate use of ramps for persons using wheelchairs)
- N= No opportunity to use stairs (or ramps)
- 1= Does not move up or down stairs (or ramps)
- 2= Moves up and down stairs (or ramps) with help
- 3= Moves up and down stairs (or ramps) with hand rail independently
- 4= Moves up and down stairs (or ramps) without need for handrail

7 ☐ **Wheelchair Mobility**
- N= Does not use wheelchair
- 1= Sits in wheelchair, does not move wheelchair by self
- 2= Assists in moving wheelchair
- 3= Moves self with some bumping and/or difficulty in steering
- 4= Moves or guides chair independently and smoothly

INDEPENDENT LIVING DOMAIN

8 ☐ **Food Preparation**
- N= Client is in a service setting in which he/she is prevented from preparing food
- 1= Does not prepare food
- 2= Prepares simple foods without cooking (sandwich, cold cereal, etc.)
- 3= Cooks simple foods (eggs, soup, frozen dinners, etc.)
- 4= Prepares complete meal

9 ☐ **Bedmaking**
- N= Client is in a service setting in which he/she is prevented from bedmaking
- 1= Does not make bed
- 2= Attempts bedmaking but does not complete
- 3= Makes bed completely but not neatly. (sheets and blankets appear wrinkled, bedspread is on crooked, etc.)
- 4= Completes bedmaking neatly and independently

10 ☐ **Washing Dishes**
- N= Client is in a service setting which he/she is prevented from dishwashing
- 1= Does not wash dishes
- 2= Attempts dishwashing but does not complete
- 3= Completes dishwashing but with unacceptable results (water left on counter, or floor, dishes chipped, etc.)
- 4= Completes dishwashing neatly and independently

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11 ☐ **Household Chores**
(other than food preparation, bedmaking, washing dishes)
N= Client is in a service setting in which he/she is prevented from doing household chores
1= Does not do household chores
2= Attempts household chores but does not complete
3= Does household chores, but not neatly (leaves dirt on floor, spills garbage, etc.)
4= Completes household chores neatly and independently

12 ☐ **Basic Medical Self-Help**
(first aid, nonprescription medication)
N= Client is in a service setting in which he/she is prevented from performing basic medical self-help skills
1= Does not display any medical self-help skills
2= Seeks aid in treatment of minor injuries
3= Performs simple first aid tasks (applies bandaids, ice to a burn)
4= Has basic medical self-help skills and uses nonprescription medications (aspirin, cough drops, etc.) appropriately

13 ☐ **Self-Medication**
N= Does not require any routine prescription medication or is in a service setting in which he/she is prevented from self-medication
1= Does not take any medication by self
2= Takes own medication with supervision and/or assistance
3= Takes own medication if reminded of time and/or dosage
4= Independently takes own medication as prescribed

14 ☐ **Eating**
1= Does not feed self, must be fed completely
2= Attempts to finger feed but needs assistance
3= Finger feeds self without assistance
4= Feeds self using spoon, with spillage
5= Feeds self using fork and spoon, with spillage
6= Uses eating utensils with no spillage

15 ☐ **Toileting**
1= Not toilet trained or habit trained
2= Is habit trained
3= Indicates need to toilet self and/or must be placed on toilet or bedpan
4= Goes to toilet by self, needs assistance to complete toileting
5= Goes to toilet by self, completes by self

16 ☐ **Level of Bladder Control**
1= No control
2= Some bladder control, accidents during waking hours (once a week or more)
3= Control during day, wets at night
4= Complete control

17 ☐ **Level of Bowel Control**
1= No control
2= Some bowel control, accidents during waking hours (once a week or more)
3= Control during day, soils at night
4= Complete control

18 ☐ **Personal Hygiene**
(brushing teeth, washing, and behaviors specifically related to gender and age, e.g., shaving, hair care, menses, use of deodorant)
1= Does not tend to own personal hygiene
2= Tends to some personal hygiene needs but does not complete
3= Tends to and completes some but not all personal hygiene tasks
4= Tends to own personal hygiene independently

19 ☐ **Bathing**
1= Does not bathe or shower self
2= Performs some bathing or showering tasks, but not all
3= Bathes or showers self independently

20 ☐ **Dressing**
1= Does not put on any clothing by self
2= Cooperates in putting on clothes (raises arms, etc.)
3= Puts on some clothes by self
4= Puts on all clothes but does not tie shoes, close all fasteners or attend to other details
5= Dresses self completely including all fasteners and other details (buttons, zippers, shoes)

21 ☐ **Movement in Familiar Setting**
1= Does not move about in a familiar setting
2= Moves about is a familiar setting but does not successfully move around obstructions or from room to room
3= Moves about in a familiar setting and successfully moves around objects but has difficulty going from room to room
4= Knows way around and moves about successfully in a familiar setting

22 ☐ **Movement in Unfamiliar Setting**
1= Does not move about in unfamiliar settings
2= Moves about in unfamiliar setting but does not successfully move around obstructions or from place to place
3= Moves about in unfamiliar setting and successfully moves around objects but has difficulty going from place to place
4= Finds way around and moves about successfully in an unfamiliar setting

23 ☐ **Transportation About Community**
N= No public transportation available
1= Does not use public transportation
2= Uses public transportation with physical assistance and/or accompaniment
3= Uses public transportation independently for a simple direct trip
4= Uses public transportation independently for a complex route

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24 ☐ **Money Handling**
1= Does not use money
2= Uses money, but is unable to provide appropriate amount (gives 10c to purchase any item in store, etc.)
3= Uses money, but does not usually make and/or count change correctly
4= Adds coins of various denominations, makes and/or counts change to $1
5= Makes and/or counts change, any amount

25 ☐ **Making Purchases**
1= Does not make purchases
2= Identifies items desired to purchase, but does not make purchase
3= Manages purchases with some difficulty
4= Manages purchases independently

26 ☐ **Ordering Food in Public**
1= Does not order food at public eating places
2= Orders snacks (ice cream, hot dogs, tacos, etc.)
3= Orders simple meals (hamburgers and fries, tacos and beans, etc.), may require assistance
4= Orders complete meals independently

SOCIAL DOMAIN

27 ☐ **One-to-One Interaction with Peers**
(friends, classmates, co-workers, etc.)
1= Does not enter into interaction
2= Enters into interaction only when others initiate
3= Initiates interaction in familiar or previously successful situations or settings
4= Initiates interaction in both familiar and unfamiliar situations or settings

28 ☐ **One-to-One Interaction with Persons Other than Peers**
(store clerks, foster parents, teachers, bus drivers, etc.)
1= Does not enter into interaction
2= Enters into interaction only when others initiate
3= Initiates interaction in familiar or previously successful situations or settings
4= Initiates interaction in both familiar and unfamiliar situations or settings

29 ☐ **Friendship Formation**
(close social relationships)
1= Does not form friendships
2= Potential friends must initiate friendships
3= Initiates and establishes friendships

30 ☐ **Friendship Maintenance**
(for at least three months)
1= Does not maintain friendships
2= Maintains friendships only in stable or familiar settings (classroom, residence, etc.)
3= Maintains friendships in many different sett

31 ☐ **Participation in Social Activities**
1= Does not participate in social activities
2= Participates in social activities only with considerable encouragement
3= Participates in social activities with some encouragement
4= Does not need encouragement to participate in social activities

32 ☐ **Participation in Group Projects**
1= Does not participate in group projects
2= Participates in group projects but efforts do not contribute to group effort
3= Participates in group projects but efforts only partially contribute to group effort
4= Participates in group projects and efforts contribute to the completion of the project

33 ☐ **Unacceptable Social Behavior**
(stealing, excessive screaming, teasing, lying, etc.)
1= Unacceptable social behaviors prevent social participation
2= Unacceptable social behaviors often disrupt social participation
3= Unacceptable social behaviors seldom interfere with social participation
4= Unacceptable social behaviors do not occur or do not interfere with social participation

EMOTIONAL DOMAIN

34 ☐ **Aggression**
1=Has had one or more violent episodes, causing serious physical injury within past year
2=Has had one or more violent episodes, causing minor physical injury within past year
3=Resorting to verbal abuse and threats are typical of client's behavior but client has r caused physical injury within past year
4=Episodes of displaying anger are undetected or rare and appropriate to the situation

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35 ☐ **Frequency of Self-Injurious Behavior**
(biting, scratching, putting inappropriate objects into ear, mouth, etc.)

1= Displays self-injurious behavior at least once a day and/or may require restraint as a preventive measure
2= Displays self-injurious behavior at least once a week
3= Displays self-injurious behavior at least once a month
4= Displays self-injurious behavior not more than three (3) times a year
5= Rarely or never displays self-injurious behavior

36 ☐ **Severity of Self-Injurious Behavior**
(biting, scratching, putting inappropriate objects into ear, mouth, etc.)

1= Self-injurious behavior causes severe injury at least once per week which requires a physician's attention
2= Self-injurious behavior causes severe injury at least once a month which requires physician's attention and/or minor injury at least once per week which requires first aid
3= Self-injurious behavior causes severe injury at least once a year which requires physician's attention and/or minor injury at least once per month which requires first aid
4= Behavior exists but no apparent injury occurs
5= Rarely or never displays self-injurious behavior

37 ☐ **Smear Feces**

1= Smears feces at every opportunity unless prevented
2= Smears feces once per week or more
3= Smears feces not so often as once a week
4= Smears feces only when agitated or nervous
5= Never smears feces

38 ☐ **Destruction of Property**

1= Has caused serious property damage within the past year
2= Has caused minor property damage on six (6) or more occasions within the past year
3= Has caused minor property damage on two (2) to five (5) occasions within the past year
4= Has caused minor property damage once during the past year
5= Does not damage property

39 ☐ **Running or Wandering Away**

1= Running or wandering away occurs daily unless prevented
2= Running or wandering away occurs weekly but not daily unless prevented
3= Running or wandering away occurs at least once a month
4= Running or wandering away occurs at least once every three months
5= Running or wandering away occurs at least once a year
6= Running or wandering away is threatened but not attempted
7= Does not run or wander away

40 ☐ **Depressive-like Behavior**
(listlessness, excessive crying and weeping, suicidal threats, etc.)

Y= Client is too young to display this type of behavior
D= Client is too disabled to display this type of behavior
1= Depressive-like behavior inhibits all functions (prevents interaction with others, daily activities, etc.)
2= Depressive-like behavior substantially affects all functions (limits communication and typical performance in daily activities, etc.)
3= Depressive-like behavior has minimal effect on functioning (attends to daily activities with slight decrease in performance, etc.)
4= No evidence of depressive-like behavior (maintains typical daily activities, etc.)

41 ☐ **Reaction to Frustration**

Y= Client is too young to display this type of behavior
D= Client is too disabled to display this type of behavior
1= Becomes aggressive or hostile in most daily situations when thwarted, hindered or obstructed
2= Becomes aggressive or hostile at least once a week when thwarted, hindered or obstructed
3= Becomes aggressive or hostile less often than once a week when thwarted, hindered or obstructed
4= Deals effectively with frustrating situations; rarely becomes aggressive or hostile when thwarted, hindered or obstructed

42 ☐ **Repetitive Body Movements**
(hand flapping, rocking and other stereotypic behaviors)

Y= Client is too young to display this type of behavior
D= Client is too disabled to display this type of behavior
1= Repetitive body movements occur continuously (without cessation) during waking hours
2= Repetitive body movements occur continuously but client can be distracted from behavior (when attending to task, etc.)
3= Some repetitive body movements occur daily regardless of situation
4= Repetitive body movements occur only under conditions of excitement and/or stress
5= No apparent repetitive body movements

43 ☐ **Inappropriate Undressing**

Y= Client is too young to display this type of behavior
D= Client is too disabled to display this type of behavior
1= Undresses self inappropriately in shopping centers, playgrounds, schoolrooms, etc.
2= Undresses self in residence inappropriately more than once per week
3= Undresses self in residence inappropriately not more than once per week
4= Does not undress self inappropriately

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44 ☐ **Hyperactivity**
(as manifested by over-excitability, restlessness, constant movement; exclude CNS spastic movements)

D= Client is too disabled to display this type of behavior
1= Is hyperactive in all environments even with individual attention (one-to-one supervision)
2= Is hyperactive except when given individual attention (one-to-one supervision)
3= Is hyperactive only in stressful situations (when in groups of unfamiliar people, when being reprimanded, etc.); hyperactivity is otherwise controlled by behavior modification techniques and/or medication
4= Hyperactivity is controlled by behavior modification techniques and/or medication
5= No apparent hyperactivity

45 ☐ **Temper Tantrums**
(emotional outbursts)

D= Client is too disabled to display this type of behavior
1= Typically displays temper tantrums daily and/or may require restraint as a preventive measure
2= Typically displays temper tantrums at least once a week but not daily
3= Typically displays temper tantrums at least once a month but not weekly
4= Displays temper tantrums not more than three (3) times a year
5= Does not display temper tantrums

46 ☐ **Resistiveness**
(inappropriately stubborn and uncooperative)

Y= Client is too young to display this type of behavior
D= Client is too disabled to display this type of behavior
1= Is resistive in all situations
2= Is resistive in one or more situations
3= Is resistive only in stressful situations (when in groups of unfamiliar people, when being reprimanded, etc.)
4= Is not resistive

47 ☐ **Adjustment to Changes in Social Relationships**
(change of caretaker, disruption of friendship group)

D= Client is too disabled to display this type of behavior
1= Changes in social relationships cause disruption of typical functioning which extends over at least a 3-month period
2= Changes in social relationships cause disruption of typical functioning but there is improvement within one month
3= Changes in social relationships do not appear to disrupt typical functioning
4= Changes in social relationships appear to lead to improvement and personal growth

48 ☐ **Adjustment to Changes in Physical Environment**

D= Client is too disabled to display this type of behavior
1= Changes in physical environment cause disruption of typical functioning which extends over at least a 3-month period
2= Changes in physical environment c J disruption of typical functioning but there is improvement within one month
3= Changes in physical environment do not appear to disrupt typical functioning
4= Changes in physical environment appear to lead to improvement and personal growth

COGNITIVE DOMAIN

49 ☐ **Auditory Perception**
(hearing aid may be worn)

1= Does not react to sounds
2= Demonstrates startle response to loud sounds
3= Turns head or eyes towards sound source
4= Responds differently to voices compared to other sounds (by smiling or paying attention to the voices)
5= Responds to voices of familiar people differently from strangers' voices
6= Recognizes words that sound different ("cat" and "door")
7= Recognizes words that sound the same ("hit" and "sit")

50 ☐ **Visual Perception**
(glasses may be worn)

1= Does not explore visually (includes continuous staring)
2= Some visual exploration, but does not follow moving objects
3= Eyes follow moving objects
4= Rotates head and inspects surroundings (if no motor limitations)
5= Searches for object which disappears from sight
6= Responds differently to grossly different objects (a ball and a pencil)
7= Responds differently to similar objects (a cat and a dog)
8= Responds differently to objects (based on differences of color, size or shape)

51 ☐ **Associating Time with Events and Actions**

1= Does not associate events and actions with time
2= Associates regular events with morning, noon, or night
3= Associates regular events with a specific hour (dinner is at six)
4= Associates events with specific time in past, present and future (the ball game is six tomorrow)

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52 ☐ **Number Awareness**

1= Does not count
2= Counts, but inaccurately or by rote
3= Counts to 10 and associates single-digit numbers with quantities
4= Counts to 10 and understands relative values (5 is larger than 3)
5= Counts, including use of multi-digit numbers, and associates multi-digit numbers with quantities

53 ☐ **Writing Skills**
(including Braille and typing)

1= Does not copy or trace
2= Copies from model or traces
3= Prints (no model) single letters or name only
4= Prints single words only
5= Prints words and sentences legibly
6= Uses longhand for words and sentences

54 ☐ **Reading Skills**
(including Braille)

1= Does not read
2= Recognizes single letters
3= Reads simple words but does not comprehend
4= Reads and comprehends simple words
5= Reads and comprehends simple sentences
6= Reads and comprehends complex sentences and stories

55 ☐ **Attention Span**

1= Does not keep attention focused on a single activity
2= Keeps attention focused on a single activity for less than one minute
3= Keeps attention focused on a single activity between one and five minutes
4= Keeps attention focused on a single activity between five and fifteen minutes
5= Keeps attention focused on a single activity between fifteen and thirty minutes
6= Keeps attention focused on a single activity for more than thirty minutes

56 ☐ **Safety Awareness**
(following safety rules and avoiding hazardous situations)

1= Frequently endangers self, must be supervised at all times
2= Occasionally endangers self, requires supervision on a daily basis
3= Endangers self only in unfamiliar situations or settings
4= Typically does not endanger self

57 ☐ **Remembering Instructions and Demonstrations**

1= Does not display memory of instructions or demonstrations
2= Displays memory of instructions or demonstrations if they are repeated three or more times and the client is prompted in recall
3= Displays memory of instructions or demonstrations if they are given once and the client is prompted in recall
4= Displays memory of instructions or demonstrations without prompting if they are given once

COMMUNICATION DOMAIN

58 ☐ **Word Usage**

1= No use of words
2= Uses simple (one-syllable) words and associates words with appropriate objects
3= Uses complex words and associates words with appropriate objects, but has a limited vocabulary
4= Has a broad vocabulary, understands meaning of words and uses them in appropriate contexts

59 ☐ **Expressive Nonverbal Communication**
(not including sign language or communication aids)

1= No expressive nonverbal communication
2= Expresses needs or reactions by squirming, returning smiles, etc.
3= Communicates by pointing, shaking head, leading by the hand, etc.
4= Gestures with hands, uses facial expressions for communication

60 ☐ **Receptive Nonverbal Communication**
(not including sign language)

1= Does not demonstrate understanding of gestures (tactile or visual) or facial expressions
2= Demonstrates understanding of simple gestures ("yes", "no", pointing to an object)
3= Demonstrates understanding of complex gestures
4= Demonstrates understanding of a series of gestures (tactile or visual)

61 ☐ **Receptive Language**

1= Does not understand speech
2= Understands simple words
3= Understands simple phrases or instructions
4= Understands meaning of simple conversation and combination of verbal instructions
5= Understands meaning of story plot and complex conversation

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62 ☐ **Expressive Language**

1= Makes no sound
2= Babbles but says no words
3= Says simple words
4= Says two-word sentences ("I go," "Give me," etc.)
5= Says sentences of three or more words
6= Carries on basic conversation
7= Carries on more complex conversation

63 ☐ **Receptive Sign Language**

N= Skills not needed
1= Does not respond to signs or fingerspelling
2= Responds to one to nine signed basic survival words (stop, restroom, come, etc.) as well as other common signs (simple commands, food, clothing, etc.)
3= Responds to signed complex commands made up of two or more parts ("Go to the bathroom and bring me a towel")
4= Responds to signed complex commands, directions and explanations with a combination of signs and simple fingerspelling
5= Responds to signed questions (3 or more words) with a combination of signs and fingerspelling

64 ☐ **Expressive Sign Language**

N= Skills not needed
1= Does not sign or imitate signs
2= Imitates sign language but makes no meaningful signs
3= Makes one to nine signs independently to indicate a need
4= Makes ten or more signs independently to indicate needs
5= Makes twenty or more signs independently to indicate needs and/or simple conversation
6= Makes fifty or more signs, fingerspells simple words and makes simple sentences
7= Signs and fingerspells independently in carrying on conversations as well as expressing needs

65 ☐ **Expressive Communication With Aids**

(includes all types of specialized devices which allow or facilitate communication)

N= Aids not needed
1= Does not communicate with aids
2= Communicates single words or ideas
3= Forms short sentences; combines subject and verb
4= Communicates combinations of sentences and groups of ideas together

66 ☐ **Clarity of Speech**

1= Makes no sounds
2= No intelligible speech
3= Speech understood only by those who know the client well
4= Speech understood by strangers with some difficulty
5= Speech is readily understandable to a strange

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Appendix 4

Scientific Advisory Panel

We gratefully acknowledge the members of the Scientific Advisory Panel, and thank them for their valuable contributions to the research design of the Autism Epidemiology Study.

Name/Title	Affiliation
Coleen Boyle, Ph.D. Associate Director for Science and Policy	National Center for Birth Defects and Developmental Disabilities Centers for Disease Control and Prevention Atlanta, Georgia
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Marc B. Schenker, M.D., M.P.H. Professor and Chair	Department of Epidemiology and Preventive Medicine University of California, Davis Davis, California
James Schlesselman, Ph.D. Professor of Biostatistics and Epidemiology	University of Miami School of Medicine Department of Epidemiology and Public Health Miami, Florida
Samuel Shapiro, M.B., B.Ch., F.R.C.P.(E) Professor of Epidemiology	Columbia University School of Public Health New York, New York
Walter O. Spitzer, M.D., M.P.H. Professor of Epidemiology (Emeritus)	McGill University Montreal, Quebec Canada

Appendix 5

List of questions asked on the Autism Epidemiology Study Questionnaire

Families of all children participating in the study were asked to complete a questionnaire (either by self-completing a written questionnaire or by phone interview). The content of the questionnaire included:

- Demographic information
  - Race/ethnicity
  - Place of birth
  - Handedness (right/left/both)
  - Parental education
  - Birth order
- Mobility, including place of birth, movement into or within California up to the age of five
- Diagnostic information
  - Determination of diagnosis of autism
  - Presence or absence of mental retardation, including a question about IQ scores
  - Presence or absence of seizure history
  - Presence or absence of cerebral palsy
  - Presence or absence of other potential co-morbid conditions
- Family history (grouped under first degree, second degree, or greater than second degree relatives):
  - Autism or related disorders
  - Tic disorder, obsessive-compulsive disorder, depressive disorder, bipolar disorder
  - Mental retardation
- Perinatal complications
  - Infertility treatments
  - Viral infections while pregnant
  - Vaccinations while pregnant
  - Augmentation or induction of labor
  - Exposure to alcohol, cigarettes, or street drugs during the pregnancy
- Immunization/vaccination history of the child and younger siblings
- History of significant gastrointestinal symptoms
- History of regression of developmental milestones
- What does the family think caused their child's autism or other developmental problem?
- Interest in participating in future follow-up studies.

Appendix 6

Sample Size Calculations for each Study Aim

Study Aim 1

CDER Data – Identification of Study Subjects

CDER data from all 21 Regional Centers in California were used to identify two groups of children with CDER status 1 autism based on age criteria. The California Department of Developmental Services provided CDER data grouped by Regional Centers for the years 1986 to 1999.

We constructed a sampling frame using all records for children with CDER status 1 autism born in 1983-1985 and 1993-1995. We created an unduplicated list of individual children with autism. The CDER record that first reported the diagnosis of CDER status 1 autism determined the Regional Center and county for that case.

The target study sample was 250 children in each age cohort (year of birth 1983-1985 vs. 1993-1995). With this sample size, we could determine whether or not 20% (or more) of the observed increase in cases of autism was due to changes in diagnostic criteria.

Table A1: *Cases of CDER status 1 autism by Regional Center and the Corresponding Sample for Study Aim 1, Autism Epidemiology Study.*

CDER status 1 autism by Regional Center	CDER Cases, by year of birth			Sample size, by year of birth	
	1983-85	1993-95	Ratio	1983-85	1993-95
Alta California Regional Center	51	90	1.8	13	7
Central Valley Regional Center	16	61	3.8	4	5
Eastern Los Angeles Regional Center	46	263	5.7	12	21
Far Northern Regional Center	15	37	2.5	4	3
Golden Gate Regional Center	41	86	2.1	11	7
Harbor Regional Center	51	298	5.8	13	24
Inland Regional Center	40	199	5.0	11	16
Kern Regional Center	16	37	2.3	4	3
Lanterman Regional Center	45	206	4.6	12	17
North Bay Regional Center	26	70	2.7	7	6
North Los Angeles County Regional Center	99	283	2.9	25	23
Redwood Coast Regional Center	12	18	1.5	3	2
Regional Center of Orange County	75	267	3.6	19	21
Regional Center of the East Bay	64	191	3.0	17	15
San Andreas Regional Center	26	101	3.9	7	8
San Diego Regional Center	81	256	3.2	21	20
San Gabriel/Pomona Regional Center	74	169	2.3	19	14
South Central Los Angeles Regional Center	96	142	1.5	25	12
Tri-Counties Regional Center	28	163	5.8	8	13
Valley Mountain Regional Center	13	63	4.8	4	5
Westside Regional Center	75	208	2.8	19	17
TOTALS	991	3,209		258	259

Two-stage sampling was done to obtain a study sample that was representative of the entire State. Table A1 shows these stratifications by Regional Center. The target number of children sampled from each Regional Center was proportional to the number of children with CDER status 1 autism in each Regional Center for each age cohort. A randomly ordered list was created for each Regional Center. Recruitment packets were mailed based on these randomly order lists. Bad addresses and refusals were replaced by the next child on the randomized list from the same center as the non-participating family. Similarly, non-responders were replaced if they failed to respond to the second mailing.

Sample size considerations:

- Number of cases of CDER status 1 autism in the 1983-85 cohort = 991
- Number of cases of CDER status 1 autism in the 1993-95 cohort = 3209
- Observed increase in number of cases between the cohorts = 2218

Assumptions

We made several assumptions to estimate the sample size needed for this study. We did not have data a priori on changes in the threshold for meeting a diagnosis of CDER status 1 autism. We chose to use DSM-IV criteria as the standard for full syndrome autism across both age cohorts, and to assess how closely the diagnosis of CDER status 1 autism matched this criteria. We assumed that 85% of cases of CDER Status 1 would meet DSM-IV criteria for autism for Cohort 1. With this assumption, the 991 CDER status 1 cases would represent 842 "true cases" and 149 cases of something other than full syndrome autism. If there is no difference between the two cohorts then 85% of Cohort 2 would meet DSM-IV criteria, representing 2728 "true cases" and 481 cases that are not full syndrome autism (out of 3,209 CDER status 1 cases).

Estimation of cohort size necessary to detect a change in the diagnostic criteria used for CDER status 1 autism

A change in the diagnostic threshold for the cases of CDER status 1 autism could account for some of the observed increase between the two cohorts. There are 2,218 more cases of CDER status 1 autism in Cohort 2 than Cohort 1. For a change in diagnostic threshold to account for all of the observed increase in autism cases, only 842 of the 3,209 CDER status 1 autism cases would meet DSM-IV criteria for autism. At this extreme, only 18 study subjects (9 from each cohort) would be necessary to show a change in the diagnostic threshold of this magnitude (assuming power = 80% and $p \leq 0.05$).

While hypothetically possible, it was highly unlikely that only 1 out of 4 CDER status 1 autism cases would meet DSM-IV criteria. If loosening of the diagnostic criteria were to contribute to an artificial increase in the reported cases of autism, it was more likely that it would only be responsible for a portion of the increase. A total sample of 500 (250 from each cohort) would be large enough to detect the difference in correspondence rates of 85% and 75%. If diagnostic criteria changed by this amount, then it would account for 20% of the observed increase in cases.

Study Aim 2

CDER Data – Identification of Study Subjects

CDER data from all 21 Regional Centers in California were used to identify two groups of children with mental retardation without CDER status 1 autism. The California Department of Developmental Services provided CDER data grouped by Regional Centers for the years 1986 to 1999. To be comparable with other aspects of this study, we limited the study population to two birth cohorts of children, year of birth 1983-85 and 1993-95. Sampling was based on an unduplicated list of children with mental retardation without CDER status 1 autism.

The target study sample was 250 in each age group. This would permit determination of whether or not 50% (or more) of the observed increase in cases of autism is due to a change in the rate of misclassification of autism among children listed as having mental retardation.

Table A2. *Cases of Mental Retardation without status 1 autism by regional center and the corresponding sample for Study Aim 2.*

Mental Retardation (without status 1 autism) by Regional Center	CDER Cases, by year of birth			Sample size, by year of birth	
	1983-85	1993-95	Ratio	1983-85	1993-95
Alta California Regional Center	736	265	0.36	16	8
Central Valley Regional Center	795	512	0.64	17	14
Eastern Los Angeles Regional Center	461	335	0.73	10	9
Far Northern Regional Center	315	229	0.73	7	7
Golden Gate Regional Center	407	235	0.58	9	7
Harbor Regional Center	612	478	0.78	13	13
Inland Regional Center	1,146	961	0.84	24	26
Kern Regional Center	358	232	0.65	8	7
Lanterman Regional Center	526	306	0.58	11	9
North Bay Regional Center	318	286	0.90	7	8
North Los Angeles County Regional Center	653	517	0.79	14	14
Redwood Coast Regional Center	201	97	0.48	5	3
Regional Center of Orange County	780	705	0.90	17	19
Regional Center of the East Bay	668	387	0.58	14	11
San Andreas Regional Center	542	478	0.88	12	13
San Diego Regional Center	1,078	1,036	0.96	23	28
San Gabriel/Pomona Regional Center	572	489	0.85	12	14
South Central Los Angeles Regional Center	616	510	0.83	13	14
Tri-Counties Regional Center	452	340	0.75	10	10
Valley Mountain Regional Center	558	554	0.99	12	15
Westside Regional Center	345	323	0.94	8	9
Total	12,139	9,275	0.76	262	258

Assumptions

The rate of misclassification (cases of MR without CDER status 1 autism that meet DSM-IV criteria) was unknown at the outset of this study. For the purposes of sample size calculation, the rate of misclassification was assumed to decrease from 1983 to

1995. Assuming a 5% misclassification rate among 1993-1995 cohort, then all of the observed increase in autism cases could be explained if the misclassification rate among children with MR in 1983-1985 is 22% (22% * 12139 – 5% * 9275 = 3209-991). The sample size necessary to detect a difference between 5% and 22% is 124 (62 in each group). Such an extreme change in misclassification was unlikely. Misclassification, if it were a factor, would more likely contribute to a portion of the observed increase in autism cases.

A sample size of 500 (250 in each age group) would provide 80% power to detect a difference between 5% and 12% with a p-value of 0.05. Misclassification among children determined to have mental retardation without CDER status 1 autism has the potential to account for a large number of "missing" cases of autism. A 5% misclassification rate among the 12,139 children in the 1983-1985 cohort could account for 607 missing cases of autism compared to the 991 children identified with CDER status 1 autism in this same age cohort. If as many as 12% of children classified as having mental retardation were found to meet DSM-IV criteria for autism, then 1,457 such children would have been missed in the older cohort, representing 147% more than the 991 children identified.

Study Aim 3

The sample size considerations for this study aim were similar to that for Study Aim 1. The target study sample was 250 for each birth cohort.

Sample size considerations

To estimate sample size the following assumptions and considerations were made: The sample size would be sufficient to detect whether or not an increase in in-migration accounts for 20% of the increased number of children with autism. The assumptions for this study aim were based on verbal reports by Dr. Croen in advance of her recently published study[35] that showed 85% of CDER status 1 autism cases match to a California birth certificate. Sample size estimates were based on a power of 80% and a p-value of 0.05.

If 20% of the increased number of cases were due to increases in in-migration among children with autism, then 25% of the younger age cohort with CDER status 1 autism would need to have been born out-of-state, as compared to 15% of the older cohort. A comparison of two proportions, 15% and 25%, requires 249 children with CDER status 1 autism in each age group, or approximately 500 study participants.

Study Aim 4

Study Aims 1 and 2 determined the sample size for this study aim. A target sample of 500 children with CDER status 1 autism and 500 children with mental retardation was attempted. If the full sample were enrolled then comparisons between age cohorts would allow for detection of a 12% difference between groups.

Study Aim 5

Study Aim 1 determines the sample size for this study aim. Families of 500 children with CDER status 1 autism will be queried. Comparisons will be made between age cohorts, allowing detection of differences of 12% or more.

Study Aim 6

The sample size requirements for this study aim are as follows: with the assumption of an approximate 5% autism or PDD recurrence risk within families with at least one affected child, using an alpha of 0.05, with 474 families in each study arm (exposed/unexposed) we would have 90% power to find a two-fold increased risk for autism/PDD secondary to vaccination. With 159 families in each study arm, we would have 90% power to find a three-fold increased risk secondary to vaccination. It was unknown how many children with autism selected for the study would have younger siblings who are at least 18 months of age. We aimed to have 159 families in each study arm but realized that we might need to expand the number of families to include additional eligible families. Based on the proportion of study children with younger siblings and the proportion of families choosing to refuse or avoid vaccinations for younger siblings, sample size calculations would be done to determine the number of additional families that would need to be recruited to accomplish this study aim. If feasible, it would be attempted.

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