Summary of Advances in Autism Spectrum Disorder Research: Calendar Year 2007

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Introduction

There is an urgent need for increased knowledge about all aspects of autism spectrum disorder (ASD), from identifying risk factors, to understanding underlying biology, to developing new more effective treatments, to bringing evidence based practices into the community. Over the past decade, research addressing these issues has expanded dramatically due to greater availability of resources and wider appreciation of the individual, family, and societal costs of ASD.

To comprehend the current state of ASD research and begin to plan next steps, Congress requested an annual update of scientific advances. Specifically, the Combating Autism Act (CAA) of 2006 (P.L. 109-416) requires the Interagency Autism Coordinating Committee to develop and annually update a summary of advances in ASD research.

ASD includes a range of developmental disorders than share common features including impaired communication skills and social interactions, and restricted, repetitive, and stereotyped patterns of behavior. Due to its complexity, increasing our understanding of ASD requires new knowledge from various fields of study such as neuroscience, genetics, immunology, biology, psychology, and pharmacology.

To identify the most significant scientific advances in these and other relevant fields in calendar year 2007, the NIMH Autism Team asked senior leaders and program contacts at nine Federal agencies and 10 private organizations that fund ASD research (see Appendix A on page 20 for a listing) to identify significant ASD research accomplishments supported by their organizations during 2007 and to identify the peer-reviewed article(s) that report the accomplishment. Fifteen organizations responded to the request.

In addition, the NIH Library searched for relevant primary reports in peer-reviewed journals and for reports featured in the news sections of journals such as *Science* or *Nature,* in publications dedicated to disseminating highlights from scientific journals (*Science News*), and in the news section of the NIH consumer health website (Medline Plus). To be considered, scientific findings must have been published (or e-published) in calendar year 2007 in peer-reviewed journals or the Center for Disease Control and Prevention's Morbidity and Mortality Weekly Report. When available, previous or subsequent research (i.e., published before or after calendar year 2007) provided additional information or context. Approximately 140 publications from over 50 peer-reviewed journals were considered for inclusion. The following summary of 54 publications is intended to highlight some of the areas where critical advances were made in the past year.

For individuals and families affected by ASD, the most meaningful research findings may be ones that address six critical questions they face:

- When should I be concerned?
- How can I understand what is happening?
- What caused this to happen, and can this be prevented?

- Which treatments and interventions will help?
- Where can I turn for services?
- What does the future hold?

This report highlights ten scientific advances in ASD research from 2007, organized by these critical questions faced by individuals and families affected by ASD.

Key Advances in ASD Research in 2007

When should I be concerned?

- *ASD Diagnosis May Be Possible Soon After First Birthday (p. 4)*

How can I understand what is happening?

- *Brain Anatomy Holds Clues to ASD (p. 6)*
- *Deficits in Processing Information from Faces May Disrupt Social Interaction (p. 7)*
- *Immune System May Play Role in Prenatal Brain Development (p. 8)*
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What caused this to happen, and can this be prevented?

- *Changes in Many Different Genes Contribute to Autism (p. 11)*
- *Research on Model Organisms Helps Clarify Gene Function (p. 13)*

Which treatments and interventions will help?

- *Interventions Can Reduce ASD Symptoms Substantially (p. 15)*

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- *Multistate Survey Confirms High Prevalence of ASD (p. 17)*

What does the future hold?

- *Autism Costs U.S. Society More Than $35 Billion Per Year (p. 19)*

When should I be concerned?

ASD Diagnosis May Be Possible Soon After First Birthday

Most cases of autism and related disorders are not diagnosed until after a child's third birthday. Yet early intervention can have a critical influence on the future course of ASD. With the American Academy of Pediatrics recently issuing clinical reports that call for systematic early screening for autism, a number of reports in 2007 focused on how to accurately detect or rule out autism and related disorders early in life.

One study tracked social and communication skills from ages 14 months to 36 months in 107 infants who had an older sibling with ASD and therefore were at higher risk for the disorder.[1] The study also tracked 18 low-risk healthy controls from unaffected families. By the end of the study, 30 of the high-risk children were diagnosed with ASD.

Half of these 30 children exhibited marked signs of disturbed sociability and play behavior by 14 months. They rarely initiated communications or shared experiences with others, missed social cues, used toys inappropriately, and displayed a limited repertoire of words and gestures. In contrast to this early-diagnosis group, a later-diagnosis group showed a very different course. At 14 months, they were distinguishable from healthy children only in that they shifted their gaze less between objects and a person's eyes. However, their social functioning subsequently deteriorated so that by their second birthday, these children behaved similarly to the early-diagnosis group.

This study concluded that about half of all children with ASD can be diagnosed soon after their first birthday. Others with the disorder appear to develop normally until that age and then falter or regress during their second year. Testing for ASD therefore has to occur at different times to detect varying patterns of onset.

Relatively simple tests can provide valuable information. In one study, 100 percent of children who developed normally responded to their name on the first or second call when they were 12 months old.[2] Most of the children at high-risk of ASD also responded. But three-fourths of the children who failed the task were identified as having developmental problems when they reached 24 months of age. This test does not identify all children at risk of developmental problems, since some children with developmental delays still responded to their name at 12 months, but failing to respond to name is highly suggestive of a developmental abnormality.

In some cases, even earlier detection may be possible. One project studied 31 infant siblings of children with autism and 24 comparison infants at 6 months of age by

[1] Landa RJ, Holman KC, Garrett-Mayer E. Social and communication development in toddlers with early and later diagnosis of autism spectrum disorders. Arch Gen Psychiatry. 2007 Jul;64(7):853-64.
[2] Nadig AS, Ozonoff S, Young GS, Rozga A, Sigman M, Rogers SJ. A prospective study of response to name in infants at risk for autism. Arch Pediatr Adolesc Med. 2007 Apr;161(4):378-83.

monitoring the movements of their eyes during a social interaction with a caregiver.[3] Ten of the eleven infants who failed the test had an older sibling with autism. While failing this test does not warrant a diagnosis, it can identify subgroups of infants who need further assessment.

Because the younger siblings of children with ASD are more likely to develop ASD than are other children, focusing on them enables more targeted and efficient studies.[4] However, some types of autism may run in families, while other cases appear sporadically. Studying the younger siblings of children with ASD may reveal more about the familial forms of autism than about the sporadic cases.

Several important studies assessed the reliability of the techniques used to diagnose ASD. For example, evaluation of the Social Communication Questionnaire revealed that it is helpful in identifying children with developmental problems who require more specific assessment for autism and related disorders.[5,6] Studies of other diagnostic tools demonstrated that they generally produce the same diagnoses at different points in a child's life.[7] A separate investigation, however, showed that 13 out of 73 children who received an ASD diagnosis at approximately 2 years of age lost the diagnosis when reassessed at approximately 4 years of age, though the reasons for this are unknown.[8]

[3] Merin N, Young GS, Ozonoff S, Rogers SJ. Visual fixation patterns during reciprocal social interaction distinguish a subgroup of 6-month-old infants at-risk for autism from comparison infants. J Autism Dev Disord. 2007 Jan;37(1):108-21.
[4] Stone WL, McMahon CR, Yoder PJ, Walden TA. Early social-communicative and cognitive development of younger siblings of children with autism spectrum disorders. Arch Pediatr Adolesc Med. 2007 Apr;161(4):384-90.
[5] Allen CW, Silove N, Williams K, Hutchins P. Validity of the social communication questionnaire in assessing risk of autism in preschool children with developmental problems. J Autism Dev Disord. 2007 Aug;37(7):1272-8.
[6] Chandler S, Charman T, Baird G, Simonoff E, Loucas T, Meldrum D, Scott M, Pickles A. Validation of the social communication questionnaire in a population cohort of children with autism spectrum disorders. J Am Acad Child Adolesc Psychiatry. 2007 Oct;46(10):1324-32.
[7] Chawarska K, Klin A, Paul R, Volkmar F. Autism spectrum disorder in the second year: stability and change in syndrome expression. J Child Psychol Psychiatry. 2007 Feb;48(2):128-38.
[8] Sutera S, Pandey J, Esser EL, Rosenthal MA, Wilson LB, Barton M, Green J, Hodgson S, Robins DL, Dumont-Mathieu T, Fein D. Predictors of optimal outcome in toddlers diagnosed with autism spectrum disorders. J Autism Dev Disord. 2007 Jan;37(1):98-107.

How can I understand what is happening?

Brain Anatomy Holds Clues to ASD

The development of sophisticated magnetic resonance imaging (MRI) methods has given researchers the ability to accurately visualize many aspects of brain structure. The result has been a wealth of provocative findings about the anatomy and interconnections of brain regions in people with ASD.

One study examined the brain anatomy of 14 adult women with ASD.[9] They tended to have a larger density of white matter in particular regions of the brain (i.e., bilaterally in the fronto-parietal, posterior temporal lobes, and the cerebellum) than did people without ASD. They also tended to have a significantly reduced density of gray matter in the fronto-temporal cortices and limbic system and of white matter in the anterior temporal lobes. Furthermore, the less gray matter they had in the right limbic regions of the brain, the greater their communication deficits.

Though these findings are in adults and may differ substantially from patterns in children, they replicate previous findings in adult males. They also point to specific alterations in white matter densities that are associated with specific symptoms of autism.

Another study found that young children with ASD who have cognitive deficits have characteristically shaped hippocampi, a part of the brain involved in memory and spatial navigation.[10] Furthermore, these alterations in hippocampal shape are correlated with the degree of the children's cognitive deficits.

Functional MRI (fMRI) can reveal which parts of the brain are active while individuals are performing specific physical or mental tasks. A group of high-functioning participants with autism was compared with a control group as they both performed a task that engages spatial and executive reasoning.[11] The group with autism displayed several distinct indications of reduced connectivity in their brains. For example, the synchronization of activity between different parts of the brain (i.e., frontal and parietal areas of activation) was lower for participants with autism than participants in the control group.

[9] Craig MC, Zaman SH, Daly EM, Cutter WJ, Robertson DM, Hallahan B, Toal F, Reed S, Ambikapathy A, Brammer M, Murphy CM, Murphy DG. Women with autistic-spectrum disorder: magnetic resonance imaging study of brain anatomy. Br J Psychiatry. 2007 Sep;191:224-8.
[10] Dager SR, Wang L, Friedman SD, Shaw DW, Constantino JN, Artru AA, Dawson G, Csernansky JG. Shape mapping of the hippocampus in young children with autism spectrum disorder. AJNR Am J Neuroradiol. 2007 Apr;28(4):672-7.
[11] Just MA, Cherkassky VL, Keller TA, Kana RK, Minshew NJ. Functional and anatomical cortical underconnectivity in autism: evidence from an fMRI study of an executive function task and corpus callosum morphometry. Cereb Cortex. 2007 Apr;17(4):951-61.

Measures of brain waves demonstrated a difference in connectivity among brain regions in individuals living with ASD.[12,13] Investigations of the relative sizes and functions of brain regions also revealed a disparity in brain connectivity.[14]

All of these findings have contributed to a hypothesis that ASD occurs when parts of the brain involved in complex functions are not optimally connected during development.[15] This hypothesis, which is now being intensively investigated, could account for many of the behavioral features seen in ASD, as well as for the timing of their emergence.

Deficits in Processing Information from Faces May Disrupt Social Interaction

Many children and adults with ASD perceive and analyze the visual information conveyed by facial expression differently than do other people. They look at and attend to faces in a different way, tending to avoid eye contact with others and scan parts of the face in atypical patterns.[16] Functional imaging of their brains shows that the neural regions involved in face processing are less active in social situations.

Some unaffected family members of people with ASD share these traits. In one study, the siblings (8 – 18 years of age) of children with ASD were, like the children with ASD, less likely to fix their gaze on the eyes of others, and they tended to have less than average brain activity in face-processing regions.[17] Also, the volume of the amygdala, a part of the brain involved in processing and remembering emotions, was diminished in the unaffected siblings and the children with ASD, compared to other people.

In another study of adults, 13 with either high-functioning autism or Asperger syndrome and 13 controls, brain imaging was done while the study participants looked at fearful faces.[18] The portions of the brain involved in processing emotions showed greater activation in the adults unaffected by autism or Asperger syndrome. Also, as the facial expressions became more fearful, the activation of the brain increased for the unaffected adults, but stayed the same for the group with autism or Asperger syndrome.

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[12] Murias M, Webb SJ, Greenson J, Dawson G. Resting state cortical connectivity reflected in EEG coherence in individuals with autism. Biol Psychiatry. 2007 Aug 1;62(3):270-3.
[13] Wilson TW, Rojas DC, Reite ML, Teale PD, Rogers SJ. Children and adolescents with autism exhibit reduced MEG steady-state gamma responses. Biol Psychiatry. 2007 Aug 1;62(3):192-7.
[14] Neeley ES, Bigler ED, Krasny L, Ozonoff S, McMahon W, Lainhart JE. Quantitative temporal lobe differences: autism distinguished from controls using classification and regression tree analysis. Brain Dev. 2007 Aug;29(7):389-99.
[15] Geschwind DH, Levitt P. Autism spectrum disorders: developmental disconnection syndromes. Curr Opin Neurobiol. 2007 Feb;17(1):103-11.
[16] Spezio ML, Adolphs R, Hurley RS, Piven J. Analysis of face gaze in autism using "Bubbles". Neuropsychologia. 2007 Jan 7;45(1):144-51.
[17] Dalton KM, Nacewicz BM, Alexander AL, Davidson RJ. Gaze-fixation, brain activation, and amygdala volume in unaffected siblings of individuals with autism. Biol Psychiatry. 2007 Feb 15;61(4):512-20.
[18] Ashwin C, Baron-Cohen S, Wheelwright S, O'Riordan M, Bullmore ET. Differential activation of the amygdala and the 'social brain' during fearful face-processing in Asperger Syndrome. Neuropsychologia. 2007 Jan 7;45(1):2-14.

Deficits in processing information from faces may lead to persistent social deficits in individuals with ASD, even among those with an IQ and vocabulary in the normal range. For example, the pragmatic (social) aspects of language pose difficulties for people with ASD who are otherwise quite verbal. Interestingly, it has been shown that the activity of key brain regions in children with ASD that underlie these difficulties may be improved. In a study that used the comprehension of irony (an aspect of pragmatic language) as an assessment tool, explicit instructions to pay attention to facial expression and tone of voice created greater brain activity in 18 boys with ASD.[19] If this could translate into better functioning in social situations, interventions might be developed to help individuals with ASD who have pragmatic language difficulties.

These and other findings about brain activity during face processing may provide valuable clues about the origins and mechanisms of differences in social interaction observed in ASD. They may also point toward the development of interventions that could help those with ASD interact with others more easily.

Immune System May Play Role in Prenatal Brain Development

Over the past several years, a number of hypotheses about how the immune system might contribute to autism and other neurodevelopmental disorders such as schizophrenia, Tourette syndrome, and obsessive compulsive disorder have emerged. Although research has not yielded clear or definitive answers to the question of immune involvement, some recent findings suggest that the immune systems of parents and their children may affect early brain development and the onset and fluctuation of symptoms in some children with ASD.

In one study, researchers looked at blood samples from 61 mothers whose children have autism and at samples from a control group of 62 mothers whose children were developing typically.[20] They isolated antibodies, proteins produced as part of the immune response, from the blood samples and exposed the antibodies to an array of fetal brain proteins. Antibodies from seven of the 61 samples from the autism group reacted with two clusters of fetal brain proteins, while none of the samples from the mothers in the control group produced this result. There was no similar reaction when maternal antibodies were exposed to adult brain proteins. Though more work will be necessary to identify the specific fetal brain proteins involved, these early results suggest that in some cases maternal immune molecules could interfere with normal brain development. The reaction was most common in the mothers of children with the regressive form of autism, which is characterized by the loss of social or language skills after a period of typical development.

[19] Wang AT, Lee SS, Sigman M, Dapretto M. Reading affect in the face and voice: neural correlates of interpreting communicative intent in children and adolescents with autism spectrum disorders. Arch Gen Psychiatry. 2007 Jun;64(6):698-708.

[20] Braunschweig D, Ashwood P, Krakowiak P, Hertz-Picciotto I, Hansen R, Croen LA, Pessah IN, Van de Water J. Autism: Maternally derived antibodies specific for fetal brain proteins. Neurotoxicology. 2008 Mar;29(2):226-231. Epub 12/15/07.

In another study, blood samples were collected from 11 mothers and their children with autism, from women and their children without a history of autism, and from children with other neurodevelopmental disorders. These samples then were exposed to a large number of brain proteins derived from prenatal, postnatal, and adult rats.[21] The blood samples from the children with autism, their mothers, and the children with other neurodevelopmental disorders had consistent patterns of reactions to prenatal, but not postnatal or adult, brain proteins, a finding that was not observed in the samples from mothers and children with no history of autism. The proteins producing these reactions were not identified.

In a study of rhesus monkeys, four pregnant rhesus monkeys were exposed to antibodies collected from mothers of children with ASD.[22] The behavior of their offspring was compared to the behavior of four monkeys exposed prenatally to antibodies from mothers of typically developing children and five untreated monkeys. The monkeys exposed prenatally to antibodies from mothers of children with autism were more hyperactive and demonstrated more whole-body repetitive behaviors than the monkeys exposed to antibodies from mothers of typically developing children or untreated monkeys.

If the transfer of specific antibodies from a mother to a developing fetus is a risk factor for autism, treatments might be devised that could prevent development of ASD in some children.

[21] Zimmerman AW, Connors SL, Matteson KJ, Lee LC, Singer HS, Castaneda JA, Pearce DA. Maternal antibrain antibodies in autism. Brain Behav Immun. 2007 Mar;21(3):351-7.
[22] Martin LA, Ashwood P, Braunschweig D, Cabanlit M, Van de Water J, Amaral DG. Stereotypies and hyperactivity in rhesus monkeys exposed to IgG from mothers of children with autism. Brain Behav. Immun. 2008 Feb 7 [Epub].

Unusual Head Growth Is Associated with ASD

Many, but not all, children with ASD have periods of unusual head growth during their first few years of life. In 2007, studies began to link this observation with specific mechanisms of brain development.

Longitudinal investigations of children at risk for ASD have improved the understanding of when altered head growth occurs and how it is related to symptoms. In one study, researchers analyzed the head measurements of 28 boys who developed autism -- 17 with early onset, and 11 with regressive features -- from birth to age three.[23] Until about twelve months of age, the heads of the children later diagnosed with autism grew faster than typically developing children. After the twelve-month mark, rates of head growth became more variable and did not differ overall from those of typically developing children. The period of accelerated growth precedes and overlaps with the onset of symptoms, while the period of normal growth coincides with a worsening of symptoms in the second year of life.

Investigators are trying to understand the cause of this atypical pattern of head growth. Previous MRI studies had shown that children with ASD have a larger volume of white matter in particular parts of their brain, suggesting a link between brain volume and head growth. A 2007 study revealed that children with autism who have increased white matter also have poorer motor skills, marking the first time that white matter volume has been linked with functional impairment in children with autism.[24]

Another study showed that having a particular version of a gene that influences serotonin in the brain is associated with the volume of the brain's gray matter.[25] Some evidence suggests that levels of serotonin in the brain can influence brain growth and connections between neurons, which could connect the gene variants, altered brain growth, and autism.

Continued research is needed to understand the cause and significance of unusual brain and head growth in some children with autism. Studies that track children over many years are critical to better understand head growth as a potential biomarker for ASD. Many children who develop typically have larger than normal heads. But pediatricians may be able to monitor head growth in infants at risk of autism, such as those who have family members with ASD. Detection of unusual head growth, combined with other risk factors, may provide a means for early identification and treatment.

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[23] Dawson G, Munson J, Webb SJ, Nalty T, Abbott R, Toth K. Rate of head growth decelerates and symptoms worsen in the second year of life in autism. Biol Psychiatry. 2007 Feb 15;61(4):458-64.
[24] Mostofsky SH, Burgess MP, Gidley Larson JC. Increased motor cortex white matter volume predicts motor impairment in autism. Brain. 2007 Aug;130(Pt 8):2117-22.
[25] Wassink TH, Hazlett HC, Epping EA, Arndt S, Dager SR, Schellenberg GD, Dawson G, Piven J. Cerebral cortical gray matter overgrowth and functional variation of the serotonin transporter gene in autism. Arch Gen Psychiatry. 2007 Jun;64(6):709-17.

What caused this to happen, and can this be prevented?

Changes in Many Different Genes Contribute to Autism

In 2007, several teams of researchers made major discoveries of specific genetic changes that contribute to ASD. While these changes account for just a fraction of ASD cases, they provide valuable clues about the origins of ASD and related disorders. Surprisingly, many of the discoveries involve genetic changes (deletions and duplications of segments of DNA) that have only been recognized as being important in the last few years.

Using new technology that reveals gaps and extra copies in DNA sequences, researchers scanned the DNA of 195 people with ASD and 196 unaffected individuals.[26] They found that 14 of the people with ASD had deletions and duplications of genetic material not found in their parents, while only 2 of the unaffected people had such genetic changes. The genetic deletions and duplications occurred throughout the DNA of the people with ASD, suggesting that changes in many different genes contribute to autism. Several investigations are under way to determine whether these mutations are associated with specific features or subtypes of autism.

These findings have contributed to new hypotheses about the inheritance of ASD. By studying the patterns of inheritance in 145 families, researchers have proposed that two distinct types of genetic changes may contribute to the development of autism.[27] In families with just one affected member, rare, spontaneous deletions and duplications may be a causal factor for some cases of ASD. While these structural changes are genetic, they are not inherited in the classic sense of being passed across multiple generations. In families with more than one affected member, ASD may result from multiple, subtle common variations in DNA sequence passed from a parent to a child. Although further investigation is needed, recent genetic findings suggest that sporadic and familial autism may represent different forms of autism with distinct forms of genetic risk.

By comparing the DNA of people with ASD to that of unaffected individuals, geneticists also have uncovered an increasing number of variations in specific genes that have been linked to ASD and other related disorders. In particular, variations of several genes involved in the formation and function of synapses appear to contribute to the development of ASD. For example, three different groups using entirely different methods replicated a link between autism and variants of a gene on chromosome 7 known as CNTNAP2. In one study, this gene variation was associated with such factors as the

[26] Sebat J, Lakshmi B, Malhotra D, Troge J, Lese-Martin C, Walsh T, Yamrom B, Yoon S, Krasnitz A, Kendall J, Leotta A, Pai D, Zhang R, Lee YH, Hicks J, Spence SJ, Lee AT, Puura K, Lehtimäki T, Ledbetter D, Gregersen PK, Bregman J, Sutcliffe JS, Jobanputra V, Chung W, Warburton D, King MC, Skuse D, Geschwind DH, Gilliam TC, Ye K, Wigler M., Strong association of de novo copy number mutations with autism. *Science*. 2007 Apr 20;316(5823):445-9.

[27] Zhao X, Leotta A, Kustanovich V, Lajonchere C, Geschwind DH, Law K, Law P, Qiu S, Lord C, Sebat J, Ye K, Wigler M. A unified genetic theory for sporadic and inherited autism. Proc Natl Acad Sci USA. 2007 Jul 31;104(31):12831-6.

age at which boys with autism say their first word.[28,29,30] The gene is one of several synaptic protein genes now linked to ASD. Mice engineered with mutations of some of these same synaptic protein genes manifest reductions in social behavior.[31,32]

By understanding the mechanisms that tie specific genes to ASD, researchers may be able to develop interventions to influence brain development during such critical periods as the acquisition of language.

Another critically important genetic region is located on chromosome 16. This region contains genes involved in both the development of the brain and in the functioning of the immune system. In a DNA scan of 1,441 children with ASD, five children were missing a section of chromosome 16 that contains about 25 genes, including genes involved in brain development, and seven had duplicates of the region.[33] Researchers estimate that about one percent of autism cases are caused by spontaneous deletions or duplications of this part of chromosome 16.

While this finding may be important for studies of risk, the changes on chromosome 16 are apparently not specific for autism. A very small percentage of people -- perhaps 0.01 percent -- have the deletion on chromosome 16 but do not have ASD. Other people with the deletion have different developmental disorders, such as attention deficit hyperactivity disorder and schizophrenia. Studies are under way to identify the specific genes associated with ASD and other conditions.

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[28] Alarcón M, Abrahams BS, Stone JL, Duvall JA, Perederiy JV, Bomar JM, Sebat J, Wigler M, Martin CL, Ledbetter DH, Nelson SF, Cantor RM, Geschwind DH. Linkage, association, and gene-expression analyses identify CNTNAP2 as an autism-susceptibility gene. Am J Hum Genet. 2008 Jan;82(1):150-9.

[29] Arking DE, Cutler DJ, Brune CW, Teslovich TM, West K, Ikeda M, Rea A, Guy M, Lin S, Cook EH, Chakravarti A. A common genetic variant in the neurexin superfamily member CNTNAP2 increases familial risk of autism. Am J Hum Genet. 2008 Jan;82(1):160-4.

[30] Bakkaloglu B, O'Roak BJ, Louvi A, Gupta AR, Abelson JF, Morgan TM, Chawarska K, Klin A, Ercan-Sencicek AG, Stillman AA, Tanriover G, Abrahams BS, Duvall JA, Robbins EM, Geschwind DH, Biederer T, Gunel M, Lifton RP, State MW. Molecular cytogenetic analysis and resequencing of contactin associated protein-like 2 in autism spectrum disorders. Am J Hum Genet. 2008 Jan;82(1):165-73.

[31] Tabuchi K, Blundell J, Etherton MR, Hammer RE, Liu, X Powell CM, Südhof TC**.** A Neuroligin-3 mutation implicated in autism increases inhibitory synaptic transmission in mice. Science 2007 Oct 5; 318(5827):71-76

[32] Jamain S, Radyushkin K, Hammerschmidt K, Boretius S, Varoqueaux F Ramanantsoa N, Gallego J, Ronnenberg A, Winter D, Frahm J, Fischer J, Bourgeron T, Ehrenreich H, and Brose N. Reduced social interaction and ultrasonic communication in a mouse model of monogenic heritable autism. PNAS 2008 Feb 5;105(5):1710-1715.

[33] Weiss LA, Shen Y, Korn JM, Arking DE, Miller DT, Fossdal R, Saemundsen E, Stefansson H, Ferreira MA, Green T, Platt OS, Ruderfer DM, Walsh CA, Altshuler D, Chakravarti A, Tanzi RE, Stefansson K, Santangelo SL, Usella JF, Sklar P, Wu BL, Daly MJ; Autism Consortium. Association between microdeletion and microduplication at 16p11.2 and autism. N Engl J Med. 2008 Feb 14;358(7):667-75.

Research on Model Organisms Helps Clarify Gene Function

Creating better drug medications for ASD requires basic scientific research and new animal models to use in the processes of drug discovery and development. In the past year, powerful tools for manipulating the genomes of model animals, particularly mice, have led to considerable progress in understanding the function of genes. This, in turn, may lead to new treatment targets.

For example, research in genetically manipulated mice provided some of the most exciting findings of 2007. One of these was the demonstration that neurological deficits in a mouse model of Rett syndrome can be reversed.[34] Rett syndrome is a serious childhood neurological disease that is physically disabling and frequently includes symptoms of autism. Caused by mutations in a gene known as MECP2, the syndrome impairs speech and movement.

In these studies, mice engineered to lack a functioning MECP2 gene during development exhibited the symptoms of Rett syndrome. To determine whether their symptoms were reversible or not, they were manipulated so that the gene became functional and then examined to determine whether this manipulation reversed some of the consequences of the gene deletion. The behavioral and cognitive deficits diminished quickly in both immature and mature animals. Efforts are now under way to determine how this finding might be applied to humans, which could lead to a treatment not only for Rett syndrome but potentially for symptoms of autism resulting from other causes.

Another study examined mice that were manipulated to have a genetic defect that mimics the cause of fragile X syndrome in humans, which is the leading identified cause of autism. When an additional genetic manipulation was performed as a correction, the mice exhibited improved brain development and memory, normal body growth, and fewer seizures.[35] Drugs designed to perform this same type of correction are now undergoing clinical trials as a way of treating symptoms of fragile X syndrome and possibly related disorders, including ASD.

Other mouse models have enabled researchers to examine the roles of specific genes and molecules suspected of being involved in some cases of ASD.[36,37,38] Several of these

[34] Guy J, Gan J, Selfridge J, Cobb S, Bird A. Reversal of neurological defects in a mouse model of Rett syndrome. Science. 2007 Feb 23;315(5815):1143-7.
[35] Dölen G, Osterweil E, Rao BS, Smith GB, Auerbach BD, Chattarji S, Bear MF. Correction of fragile X syndrome in mice. Neuron. 2007 Dec 20;56(6):955-62.
[36] Sadakata T, Kakegawa W, Mizoguchi A, Washida M, Katoh-Semba R, Shutoh F, Okamoto T, Nakashima H, Kimura K, Tanaka M, Sekine Y, Itohara S, Yuzaki M, Nagao S, Furuichi T. Impaired cerebellar development and function in mice lacking CAPS2, a protein involved in neurotrophin release. J Neurosci. 2007 Mar 7;27(10):2472-82.
[37] Tabuchi K, Blundell J, Etherton MR, Hammer RE, Liu X, Powell CM, Südhof TC. A neuroligin-3 mutation implicated in autism increases inhibitory synaptic transmission in mice. Science. 2007 Oct 5;318(5847):71-6.
[38] Chubykin AA, Atasoy D, Etherton MR, Brose N, Kavalali ET, Gibson JR, Südhof TC. Activity-dependent validation of excitatory versus inhibitory synapses by neuroligin-1 versus neuroligin-2. Neuron. 2007 Jun 21;54(6):919-31.

genes are involved in the growth of brain cells and establishing connections among them during brain development, processes that appear to be closely linked with the origins of autism.[39]

Several 2007 studies reported on the development of mouse strains that exhibit many of the features of autism in humans, including abnormal social interactions, deficits in communication, and high levels of repetitive behaviors.[40] For example, one strain displays low levels of social interaction and marked resistance to change.[41] Such mouse strains can be studied to discover the genetic changes that cause these characteristics. They also can be used to examine the role of environmental toxins in triggering ASD, better pinpoint the brain mechanisms involved in such triggers, and thereby assist in developing potential new treatments for ASD.

[39] Autism Genome Project Consortium et al. Mapping autism risk loci using genetic linkage and chromosomal rearrangements. Nat Genet. 2007 Mar;39(3):319-28.
[40] Crawley JN. Mouse behavioral assays relevant to the symptoms of autism. Brain Pathol. 2007 Oct;17(4):448-59.
[41] Moy SS, Nadler JJ, Young NB, Perez A, Holloway LP, Barbaro RP, Barbaro JR, Wilson LM, Threadgill DW, Lauder JM, Magnuson TR, Crawley JN. Mouse behavioral tasks relevant to autism: phenotypes of 10 inbred strains. Behav Brain Res. 2007 Jan 10;176(1):4-20.

Which treatments and interventions will help?

Interventions Can Reduce ASD Symptoms Substantially

Behavioral and pharmacological interventions can substantially reduce the symptoms of autism. In the past year, important progress has been made in testing new interventions and assessing the efficacy of existing interventions.

Behavioral treatments have been studied extensively and shown to be efficacious in improving symptoms of autism. A recent study compared children who began intensive behavioral therapy between the ages of 4 and 7 with a comparison group of children who received a community treatment involving aspects of several treatment models.[42] The intensive behavioral treatment group showed larger increases in IQ and adaptive functioning than the comparison group. The behavioral treatment group also displayed fewer aberrant behaviors and social problems at follow-up. Another project showed that providing families with a home-based behavioral program in addition to a center-based program improved cognitive development and behavior in young children with autism and developmental delay.[43] The improvements were especially marked for children from families with high levels of stress.

The Picture Exchange Communication System (PECS) is a training package that teaches children and adults with autism and other communication deficits to initiate communication. It is widely used in community settings for children with autism but has received little empirical testing. In one recent study, children between ages 3 and 7 who received 15 hours of PECS teaching over five weeks initiated communication and interacted with others much better than did a group that did not receive PECS teaching.[44] Further evaluation is still warranted, as this was not a randomized trial.

In 2006, risperidone became the first FDA-approved pharmacologic therapy for certain symptoms of autism. First introduced in 1993 as medication used to treat symptoms of schizophrenia, risperidone has now been shown to be effective as a treatment of irritability associated with autistic disorder in children and adolescents aged 5-16 years. A randomized, double-blind, placebo-controlled trial demonstrated in 2007 that risperidone significantly improved severe behavioral problems associated with autism such as tantrums, aggression, and self-injurious behavior.[45] However, a review article

[42] Eikeseth S, Smith T, Jahr E, Eldevik S. Outcome for children with autism who began intensive behavioral treatment between ages 4 and 7: a comparison controlled study. Behav Modif. 2007 May;31(3):264-78.
[43] Rickards AL, Walstab JE, Wright-Rossi RA, Simpson J, Reddihough DS. A randomized, controlled trial of a home-based intervention program for children with autism and developmental delay. J Dev Behav Pediatr. 2007 Aug;28(4):308-16.
[44] Carr D, Felce J. The effects of PECS teaching to Phase III on the communicative interactions between children with autism and their teachers. J Autism Dev Disord. 2007 Apr;37(4):724-37.
[45] Pandina GJ, Bossie CA, Youssef E, Zhu Y, Dunbar F. Risperidone improves behavioral symptoms in children with autism in a randomized, double-blind, placebo-controlled trial. J Autism Dev Disord. 2007 Feb;37(2):367-73.

called for larger and longer-term studies of the drug's benefits and possible adverse effects.[46]

Other pharmacological and biological treatments are being explored, although they are all in the early phases of study and conclusions cannot yet be made about efficacy or possible adverse side effects. Results from small studies are often not confirmed in larger trials, and sometimes side effects emerge with increased numbers of subjects. Preliminary findings from small studies need replication in randomized, controlled trials with larger samples before any recommendations about their use can be made. Examples include:

- A small randomized, double-blind, placebo-controlled 6-week trial with 13 children and adolescents with autism reported that omega-3 fatty acids outperformed placebo in terms of reducing hyperactivity and stereotypy.[47]

- In another randomized, double-blind, placebo-controlled crossover trial, 15 adults diagnosed with autism or related disorders were given oxytocin, a hormone that can enhance the ability to interpret subtle social clues.[48] All were better able to judge whether speech was happy, indifferent, angry, or sad after receiving the hormone.

- A medication of interest is memantine, which antagonizes certain actions of multiple brain neurotransmitters. In an open-label study, 151 patients with prior diagnoses of autism or pervasive developmental disorder not otherwise specified took memantine, in addition to other treatments already prescribed, over a 21-month period.[49] Significant improvements were seen in language function, social behavior, and self-stimulatory behaviors, though the latter improved to a lesser degree than did language and behavior.

- Pioglitazone exerts an anti-inflammatory effect in brain cells suspected of being involved in some cases of ASD and is used to treat type 2 diabetes. In an open-label case series of 25 children with ASD, the medication is reported to have produced significant decreases in irritability, lethargy, stereotypy, and hyperactivity.[50] Younger children showed the most dramatic effects.

[46] Jesner OS, Aref-Adib M, Coren E. Risperidone for autism spectrum disorder. Cochrane Database Syst Rev. 2007 Jan 24;(1):CD005040.
[47] Amminger GP, Berger GE, Schäfer MR, Klier C, Friedrich MH, Feucht M. Omega-3 fatty acids supplementation in children with autism: a double-blind randomized, placebo-controlled pilot study. Biol Psychiatry. 2007 Feb 15;61(4):551-3.
[48] Hollander E, Bartz J, Chaplin W, Phillips A, Sumner J, Soorya L, Anagnostou E, Wasserman S. Oxytocin increases retention of social cognition in autism. Biol Psychiatry. 2007 Feb 15;61(4):498-503.
[49] Chez MG, Burton Q, Dowling T, Chang M, Khanna P, Kramer C. Memantine as adjunctive therapy in children diagnosed with autistic spectrum disorders: an observation of initial clinical response and maintenance tolerability. J Child Neurol. 2007 May;22(5):574-9.
[50] Boris M, Kaiser CC, Goldblatt A, Elice MW, Edelson SM, Adams JB, Feinstein DL. Effect of pioglitazone treatment on behavioral symptoms in autistic children. J Neuroinflammation. 2007 Jan 5;4:3.

Where can I turn for services?

Multistate Survey Confirms High Prevalence of ASD

The most thorough survey ever done of the prevalence of ASD (i.e., the proportion of affected individuals at a given point in time) estimated that between one in 100 to one in 300 -- with an average of one in every 150 children (for study years 2002 and 2004) -- may have the disorder.[51] With the completion of additional study years (2006 and 2008 are underway), this effort will provide important information about autism trends in the United States.

The investigators looked at children aged eight years old in 2002 in 14 areas of the United States. They examined evaluation records at health facilities at all 14 sites and evaluations for special education services at 10 of the 14 sites. Children with behaviors consistent with autistic disorder, pervasive developmental disorder not otherwise specified, or Asperger syndrome were classified as having ASD.

Of 407,578 children in the 14 sites, 2,685 (0.66 percent) were classified as having ASD. The prevalence per 1,000 children ranged from 3.3 per 1,000 in Alabama to 10.6 in New Jersey, with the majority of sites ranging from 5.2 to 7.6. The overall mean of 6.6 per 1,000 children means that one child in every 150 across all sites was identified as having ASD. While all sites used a rigorous, consistent method for data collection and case determination, sites varied in their ability to ascertain ASD cases. For example, the average prevalence of ASD among sites that relied solely on review of health records (4 sites including Alabama) was significantly lower than that of sites that were able to review both health and education records (10 sites including New Jersey).

The majority of the children surveyed were receiving special education services at age eight. A majority also had a documented history of concerns regarding their development before age three. However, the median age at which they were diagnosed with ASD ranged from 49 months in Utah to 66 months in Alabama. The ratio of males to females ranged from 3.4 to 1 in three states to 6.5 to 1 in Utah.

For six of the sites, prevalence data were also available for 2000.[52] In four of the sites, the prevalence rate was stable. In Georgia it increased 17 percent, and in West Virginia it increased 39 percent. The data establish a baseline for tracking trends over time, and continuation of the project in the re-funded sites will shed light on whether the prevalence of ASD is changing.

[51] Autism and Developmental Disabilities Monitoring Network Surveillance Year 2002 Principal Investigators; Centers for Disease Control and Prevention. Prevalence of autism spectrum disorders--autism and developmental disabilities monitoring network, 14 sites, United States, 2002. MMWR Surveill Summ. 2007 Feb 9;56(1):12-28.

[52] Autism and Developmental Disabilities Monitoring Network Surveillance Year 2000 Principal Investigators; Centers for Disease Control and Prevention. Prevalence of autism spectrum disorders--autism and developmental disabilities monitoring network, six sites, United States, 2000. MMWR Surveill Summ. 2007 Feb 9;56(1):1-11.

A separate study from Denmark revealed a rising incidence of ASD.[53] Incidence refers to the number of new cases over time in the same population. It examined the health records of all 669,995 children born in Denmark from 1990 through 1999 and found statistically significant increases in the incidence of ASD, hyperkinetic disorder, and Tourette syndrome. The investigators found no significant change in the incidence of obsessive-compulsive disorder across birth years. The study concluded that increases in ASD might be part of a more widespread increase in neurologic disorders, though it was not possible to determine the reasons for the change.

[53] Atladóttir HO, Parner ET, Schendel D, Dalsgaard S, Thomsen PH, Thorsen P. Time trends in reported diagnoses of childhood neuropsychiatric disorders: a Danish cohort study. Arch Pediatr Adolesc Med. 2007 Feb;161(2):193-8.

What does the future hold?

Autism Costs U.S. Society More Than $35 Billion Per Year

Autism is a very expensive disorder. A previous study found that ASD costs U.S. society more than $35 billion each year. A recent follow-up study elaborated on this finding, reporting that the incremental costs to society of ASD are $3.2 million per person with ASD over a lifetime, and that the annual costs are greater for adults with ASD than for children.[54]

The costs of autism are both direct and indirect. Direct costs are a measure of the value of the goods and services used to care for those with ASD, while indirect costs are a measure of the value of productivity lost due to ASD. Direct medical costs include those for physicians and other professionals, hospital and emergency department services, drugs, equipment and other supplies, and medically related travel and time. Direct non-medical costs include those for special education, transportation, child care and babysitting, respite care, out-of-home placement, home and vehicle modifications, and supported employment services. Indirect costs include the value of lost or impaired work time, benefits, and household services of individuals with ASD and their caregivers because of missed time at work, reduced work hours, switching to a lower-paying but more flexible job, or leaving the workforce.

Direct medical costs are quite high for the first five years of life, averaging around $35,000 per year. They start to decline substantially by age eight years, to about $6,000 per year, and continue to decline through the end of life to around $1,000 annually. Direct non-medical costs range from $10,000 to approximately $16,000 during the first 20 years of life, peak in the 23- to 27-year age range at around $27,500, and then decline steadily with age to around $8,000 annually. Indirect costs follow a similar non-linear pattern, decreasing from around $43,000 in early life to approximately $36,000 in the 18- to 22-year age range, peaking at ages 23 to 27 years at around $52,000, and then declining through the end of life.

Information on the distribution of costs across a lifetime can help allocate scarce resources to support individuals with ASD and their families. In particular, the substantial costs incurred by adults with ASD point to the difficulties faced by parents of children with ASD as they plan for the transition of their children into adulthood and for their sustained support as adults.

[54] Ganz ML. The lifetime distribution of the incremental societal costs of autism. Arch Pediatr Adolesc Med. 2007 Apr;161(4):343-9.

Appendix A - List of Contacted Federal and Private Organizations That Fund ASD Research

Federal Agencies Contacted

1. Administration for Children and Families
2. Centers for Disease Control and Prevention
3. Centers for Medicare and Medicaid Services
4. Department of Defense
5. Department of Education
6. Health and Human Services Office on Disability
7. Health Resources and Services Administration
8. National Institutes of Health
    - National Center for Complementary and Alternative Medicine
    - National Center for Research Resources
    - National Human Genome Research Institute
    - National Institute on Aging
    - National Institute of Child Health and Human Development
    - National Institute on Deafness and Other Communication Disorders
    - National Institute of Environmental Health Sciences
    - National Institute of Mental Health
    - National Institute of Neurological Disorders and Stroke
    - Office of Portfolio Analysis and Strategic Initiatives
9. Substance Abuse and Mental Health Services Administration

Private Organizations Contacted

1. Autism Consortium
2. Autism Research Institute
3. Autism Society of America
4. Autism Speaks
5. Center for Autism and Related Disorders, Inc.– Based in Tarzana, CA
6. Doug Flutie, Jr. Foundation for Autism
7. Organization for Autism Research
8. The Coalition for SafeMinds (Sensible Action For Ending Mercury-Induced Neurological Disorders)
9. The Simons Foundation
10. Southwest Autism Research and Resource Center