

The Interagency Autism Coordinating Committee

2012 Summary of Advances

in Autism Spectrum Disorder Research



OFFICE OF
AUTISM RESEARCH
COORDINATION
NATIONAL INSTITUTES OF HEALTH

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COVER DESIGN

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ABOUT THE IACC

The Interagency Autism Coordinating Committee (IACC) is a Federal advisory committee charged with coordinating all activities concerning autism spectrum disorder (ASD) within the U.S. Department of Health and Human Services (HHS) and providing advice to the Secretary of HHS on issues related to autism. It was established by Congress under the Children's Health Act of 2000, reconstituted under the Combating Autism Act (CAA) of 2006, and renewed under the Combating Autism Reauthorization Act of 2011.

Membership of the Committee includes a wide array of Federal agencies involved in ASD research and services, as well as public stakeholders, including self-advocates, parents of children and adults with ASD, advocates, service providers, and researchers, who represent a variety of perspectives from within the autism community. This makeup of the IACC membership is designed to ensure that the Committee is equipped to address the wide range of issues and challenges faced by families and individuals affected by autism.

Under the CAA, the IACC is required to (1) develop and annually update a strategic plan for ASD research, (2) develop and annually update a summary of advances in ASD research, and (3) monitor Federal activities related to ASD.

Through these and other activities, the IACC provides guidance to HHS and partners with the broader autism community to accelerate research and enhance services with the goal of profoundly improving the lives of people with ASD and their families.

For more information about the IACC, see www.iacc.hhs.gov.

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THE 2012 IACC SUMMARY OF ADVANCES IN AUTISM SPECTRUM DISORDER RESEARCH

INTRODUCTION

Each year, the IACC releases its annual list of scientific advances that represent significant progress in the field. The 20 studies selected have given new insight into the complex causes of autism and potential risk factors, studied clues that could lead to earlier diagnosis, and evaluated promising early intervention strategies. The advances also address the prevalence of ASD both in the United States and internationally, as well as the service needs of people with ASD across the lifespan. The 2012 Summary of Advances provides short, plain language synopses of the top research breakthroughs selected by the IACC from a pool of peer-reviewed articles nominated by the members. Articles are grouped according to the questions of the IACC Strategic Plan for ASD Research. Citations for the articles selected for the Summary of Advances, as well as a complete listing of those nominated, are included at the end of the document.

ARTICLES SELECTED FOR THE 2012 SUMMARY OF ADVANCES

QUESTION 1

WHEN SHOULD I BE CONCERNED?

Six developmental trajectories characterize children with autism – Fountain C, Winter AS, Bearman PS. *Pediatrics*. 2012 May;129(5):e1112-20. [PMID: 22473372]

ASD is a neurodevelopmental disorder that varies in both symptoms and progression. While children with ASD usually retain their diagnosis throughout adolescence and adulthood, very little is known about the range of developmental trajectories across the lifespan. Based on a sample of 6,975 children born in California from 1992 through 2001 and enrolled with the California Department of Developmental Services, researchers described the six most common developmental trajectories of ASD progression throughout childhood for each of the three core ASD symptom domains—communication, social functioning, and repetitive behavior. Children with ASD were followed from diagnosis to 14 years of age using birth records and caseload records, which record symptoms, severity, and functioning across several dimensions. The six developmental trajectories identified showed considerable variation in terms of the patterns of severity and developmental progression. Those children whose symptoms were less severe when ASD was diagnosed typically improved more rapidly than those whose symptoms were more severe. Within the sample, the repetitive behavior domain remained largely stable over the study period, with only 15% of the children demonstrating either improvement or worsening of symptoms. However, many children showed significant improvement in the communication and social functioning domains, with the most rapid development occurring in children under the age of 6 with less severe symptoms. Interestingly, for both communication and social functioning domains, approximately 10% of children were identified as “bloomers”—those who had severe symptoms when diagnosed with ASD, but subsequently showed rapid and substantial improvement by adolescence. Children diagnosed with severe autism were most likely to “bloom” if they had no intellectual disability and had white, non-Hispanic mothers with a higher education level. This suggests that socioeconomic status and its impact on such factors as services access may play an important role in the developmental trajectories of children with ASD. Understanding the biological mechanisms and socioeconomic factors underlying these trajectories may yield important information for the development of future interventions and provision of services. Furthermore, the establishment of baseline trajectories will allow for more accurate measurement of the effectiveness of interventions.

Predicting the diagnosis of autism spectrum disorder using gene pathway analysis – Skafidas E, Testa R, Zantomio D, Chana G, Everall IP, & Pantelis C. *Mol Psychiatry*. 2012 Sep 11. [Epub ahead of print] [PMID: 22965006]

ASD is currently diagnosed based solely upon behavior, with no validated biomarkers to aid in the diagnosis. A genetic test for ASD with a high level of diagnostic accuracy was developed recently, drawing upon current knowledge of the genetics associated with ASD and other neurodevelopmental disorders. The test was developed using data from the Autism Genetic Resource Exchange (AGRE) database which includes genetic data from people with ASD as well as their family members. Researchers examined a central European cohort from the database to identify 237 genetic markers called single-nucleotide polymorphisms (SNPs)—which are differences in a single DNA building block, called a nucleotide—in genes that are known to be involved in biological processes that contribute to or protect an individual from developing ASD. In total, SNPs in 146 genes were identified, but eight SNPs in three genes (*KCNMB4*, *GNAO1*, and *GRM5*) were found to have the largest impact, with some conferring vulnerability for ASD and others conferring protective effects. Based on these genetic markers, researchers developed a test that takes into account both these vulnerability and protective factors when calculating an individual's overall risk for developing ASD. The test was then independently validated in central European individuals from two other databases—the Simons Foundation Autism Research Initiative (SFARI) and the Wellcome Trust 1958 normal birth cohort (WTBC) databases. The test demonstrated more than 70% accuracy in predicting risk of developing ASD in persons of central European descent in the validation sample. Thus, scientists suggest that this test shows considerable promise for detection of ASD in a genetically homogeneous group—where application of the test is limited to individuals of a similar genetic and/or ethnic background to those from which the test was derived. Importantly, the novel methodologies used for the development of this test can be replicated to develop similar tests for use in other ethnic populations. This test may assist in the early detection of ASD in babies, identifying those who would benefit from early interventions, and would be particularly relevant for families who have a history of ASD.

QUESTION 2

HOW CAN I UNDERSTAND WHAT IS HAPPENING?

Mutations in BCKD-kinase lead to a potentially treatable form of autism with epilepsy – Novarino G, El-Fishawy P, Kayserili H, Meguid NA, Scott EM, Schroth J, Silhavy JL, Kara M, Khalil RO, Ben-Omran T, Ercan-Sencicek AG, Hashish AF, Sanders SJ, Gupta AR, Hashem HS, Matern D, Gabriel S, Sweetman L, Rahimi Y, Harris RA, State MW, Gleeson JG. *Science*. 2012 Oct 19;338(6105):394-7. [PMID: 22956686]

ASD is often complicated by co-occurring conditions such as epilepsy, which occurs in about 25% of individuals with ASD, as well as intellectual disability. Analyzing the DNA of individuals with these co-occurring conditions could identify gene mutations that may contribute to the cause of ASD in this subgroup of individuals. This study used a genetic approach called whole-genome sequencing to determine the complete DNA sequences of members of three families that had children with co-occurring ASD, epilepsy, and intellectual disability. Comparing the whole genome sequences of these individuals, researchers identified a mutation present in each of the families in a gene for branched chain ketoacid dehydrogenase kinase—or *BCKDK*—that regulates a protein that breaks down certain types of naturally-occurring amino acids, called branched chain amino acids (BCAAs), that must be obtained from food. Lower levels of these BCAAs were observed in the blood of patients with the *BCKDK* mutation. In order to more fully explore the effects of the *BCKDK* mutation, researchers modified the *bckdk* gene in mice to make it non-functional and reported that the adult mice developed a number of neurological abnormalities, including epileptic seizures. Examination of the brains of these mice revealed abnormal levels of several different amino acids normally found in the brain and abnormalities in the networks of transporter proteins that are needed to help amino acids pass from the blood into the brain. The researchers hypothesized that the decreased blood levels of BCAAs caused by the mutation in the *bckdk* gene may send a signal that transport of brain amino acids into the brain is not needed, resulting in decreased availability of transporter proteins and reduced entry of amino acids into the brain. The reduced level of brain amino acids could impact neurological development and normal electrical activity in the brain. Importantly, when the mice with impaired *bckdk* gene activity were fed diets with added BCAAs, their seizures and other neurological deficits subsided. Similar dietary supplementation for the families with the *BCKDK* mutation in this study resulted in normalized blood levels of BCAAs, suggesting that it may be possible in the future to treat individuals that have the *BCKDK* mutation and co-occurring ASD, intellectual disability, and epilepsy with dietary supplementation of branched chain amino acids.

Differences in white matter fiber tract development present from 6 to 24 months in infants with autism – Wolff JJ, Gu H, Gerig G, Elison JT, Styner M, Gouttard S, Botteron KN, Dager SR, Dawson G, Estes AM, Evans AC, Hazlett HC, Kostopoulos P, McKinstry RC, Paterson SJ, Schultz RT, Zwaigenbaum L, Piven J; IBIS Network. *Am J Psychiatry*. 2012 Jun;169(6):589-600. [PMID: 22362397]

Early symptoms of ASD are generally observed to emerge within the first 2 years of life after a period of relatively typical development. This study provides evidence that, despite outward appearances, these ASD symptoms are in fact preceded by atypical brain development. Researchers studied a group of 92 infants who had older siblings with ASD and were therefore considered at “high risk” for developing ASD. Using diffusion tensor imaging (DTI)—a brain imaging technique—the brain structure in these high-risk infants was evaluated at 6, 12, and 24 months of age, before the onset of ASD symptoms. This technique allowed researchers to examine and create three-dimensional maps revealing the structure of specific white matter pathways (tracts)—bundles of nerve fibers that connect various parts of the brain—that have been associated with ASD. Behavioral assessments were conducted at 24 months, and the brain imaging scans from infants who met the behavioral criteria for ASD were compared to those from infants who did not in order to assess differences in brain structure. Images from the 6, 12, and 24-month time points were assembled to create a changing, three-dimensional picture of how the white matter pathways developed over time in these infants, allowing comparison of the developmental trajectories of infants who later were diagnosed with ASD with those who were not diagnosed with ASD. Compared to infants who did not go on to develop ASD, those who did showed differences in the development of 12 out of the 15 white matter pathways studied. At 6 months, the white matter pathways in infants that went on to develop ASD were well ordered; often more so than those who did not develop ASD. However, the white matter pathways did not continue to develop in a structured manner and by 24 months of age were visibly less ordered than those in infants who did not develop ASD. The identification of altered white matter pathway development before of the onset of ASD symptoms points to a neurobiological basis of the behavioral symptoms. Furthermore, this study provides the earliest evidence of brain differences related to the later development of ASD symptoms, pinpointing a critical period of brain development. The identification of differences in brain structure during the first year of life may lead to the development of brain imaging-based biomarkers for early identification of children who will develop ASD, allowing for earlier treatment and intervention.

Autistic-like social behaviour in Shank2-mutant mice improved by restoring NMDA receptor function

– Won H, Lee HR, Gee HY, Mah W, Kim JI, Lee J, Ha S, Chung C, Jung ES, Cho YS, Park SG, Lee JS, Lee K, Kim D, Bae YC, Kaang BK, Lee MG, Kim E. *Nature*. 2012 Jun 13;486(7402):261-5. [PMID: 22699620]

Researchers have identified a potentially treatable mechanism in the development of ASD that is caused by mutations within *SHANK2*—a gene that codes for specific structural proteins in neurons. To study the mechanisms underlying the development of ASD, scientists developed a mouse model whose genetics were manipulated to mimic mutations in *SHANK2*, found previously to be associated with ASD and intellectual disability in humans. The *SHANK2* mouse model, carrying the same mutation as found in humans with *SHANK2*-associated ASD, demonstrates what are considered ASD-like behaviors in mice, which include reduced social interaction and communication, repetitive jumping, anxiety-like behaviors, and hyperactivity. Researchers found that neurons in these mice did not function properly and exhibited impairments in the functioning of the NMDA glutamate receptor (NMDAR), which plays an important role in learning and memory. When the *SHANK2* mouse model was treated with D-cycloserine—a drug previously shown to reduce some ASD-like symptoms in mice—NMDAR function was restored, and social interactions in the mice improved. Even greater improvements were found when scientists administered CDPPB—a drug with antipsychotic and pro-cognitive effects—resulting in enhanced NMDAR function and learning in mice via activation of another glutamate receptor, mGluR5. Interestingly, while restoration of NMDAR function with D-cycloserine and CDPPB improved social interactions, other co-occurring behaviors, including jumping, anxiety-like behaviors, and hyperactivity were not altered. These findings indicate that reduced NMDAR function may contribute to the development of ASD-like behaviors in a *SHANK2* mouse model of ASD and that regulation of mGluR5 in particular may be a potential strategy to treat ASD.

QUESTION 3

WHAT CAUSED THIS TO HAPPEN AND CAN IT BE PREVENTED?

Autism after infection, febrile episodes, and antibiotic use during pregnancy: An exploratory study –
Atladóttir HO, Henriksen TB, Schendel DE, Parner ET. *Pediatrics*. 2012 Dec;130(6):e1447-54. [PMID: 23147969]

Exposure to certain environmental factors during pregnancy has long been implicated in the potential development of ASD in offspring. Findings from animal studies suggest that the stimulation of a woman's immune system during pregnancy caused by events such as infection may be associated with abnormal brain development in the fetus. Studies in human populations, however, have yielded conflicting results concerning the relationship between maternal infection during pregnancy and ASD. Data generated from the Danish National Birth Cohort (DNBC) was used to investigate the relationship between the occurrence of common infections, episodes of fever, and the use of antibiotics during pregnancy and the risk for ASD in children. The DNBC included 96,736 children born between 1997 and 2003 whose mothers participated in telephone interviews at approximately 17 and 32 weeks into their pregnancy as well as about 6 months after birth. According to the Danish Psychiatric Central Register, 1% of the children in the DNBC had been diagnosed with ASD at the time of the study. Interviewers asked mothers participating in the study about the occurrence of infections, fever, and the use of antibiotics during their pregnancies. In general, the researchers found little evidence that various types of mild common infection or short episodes of fever during pregnancy were strong risk factors for ASD. However, evidence suggested that maternal report of influenza infection during pregnancy was associated with a doubled risk of infantile autism, a diagnosis indicating that ASD is apparent in the first 3 years of life. In addition, prolonged episodes of fever tripled the risk of infantile autism, and use of different antibiotics during pregnancy was also associated with a small increase in risk of ASD. While the authors emphasized the importance of further research to validate their findings due to the limitations of their methodology, the large scale of this population-based cohort study makes it a key finding, potentially linking ASD with maternal influenza infection, fever, and the use of antibiotics during pregnancy. Further research will be needed to confirm these potential relationships and to investigate whether immune changes in mothers may have an impact on brain development in humans.

Rate of *de novo* mutations and the importance of father's age to disease risk – Kong A, Frigge ML, Masson G, Besenbacher S, Sulem P, Magnusson G, Gudjonsson SA, Sigurdsson A, Jonasdottir A, Jonasdottir A, Wong WS, Sigurdsson G, Walters GB, Steinberg S, Helgason H, Thorleifsson G, Gudbjartsson DF, Helgason A, Magnusson OT, Thorsteinsdottir U, Stefansson K. *Nature*. 2012 Aug 23;488(7412):471-5. [PMID: 22914163]

Results of a recent study suggest that a father's age may be a larger contributor to autism risk than previously thought. Researchers from deCODE genetics in Iceland conducted a large-scale study in which they evaluated whole-genomes of 78 Icelandic families (consisting of DNA drawn from two parents and an offspring) and examined them for mutations, or changes, in the DNA. Of the 78 children included, 44 were diagnosed with ASD and 21 with schizophrenia. Results from the study demonstrated that the older the father was at the time of a child's conception, the greater the risk of having a child who developed ASD or schizophrenia. This increasing risk correlated strongly with the number of *de novo* mutations in the child's DNA, which are non-inherited changes in DNA that usually occur prior to conception in eggs or sperm and can result in the development of genetic disorders in children despite the absence of the disorder in either parent. Previous research on *de novo* mutations had been restricted to specific genes or small samples of whole-genome sequences, but the sample size in this study allowed researchers to more accurately quantify the risk of mutation across the whole genome. The study found an effective increase of more than two mutations for every year in paternal age, or a doubling in the number of mutations every 16.5 years. Such mutations can be caused by environmental influences or by errors in maintaining DNA integrity that accumulate over time. While the genetic risks to offspring of older mothers has been documented for some time, the results of this study point to the importance that a father's age plays in the occurrence of genetic mutations that can lead to disorders such as ASD and schizophrenia. Intriguingly, this study's findings also suggest that changes in demographics favoring later parenthood may be contributing to the rise in prevalence of ASD.

Patterns and rates of exonic *de novo* mutations in autism spectrum disorders – Neale BM, Kou Y, Liu L, Ma'ayan A, Samocha KE, Sabo A, Lin CF, Stevens C, Wang LS, Makarov V, Polak P, Yoon S, Maguire J, Crawford EL, Campbell NG, Geller ET, Valladares O, Schafer C, Liu H, Zhao T, Cai G, Lihm J, Dannenfelser R, Jabado O, Peralta Z, Nagaswamy U, Muzny D, Reid JG, Newsham I, Wu Y, Lewis L, Han Y, Voight BF, Lim E, Rossin E, Kirby A, Flannick J, Fromer M, Shakir K, Fennell T, Garimella K, Banks E, Poplin R, Gabriel S, DePristo M, Wimbish JR, Boone BE, Levy SE, Betancur C, Sunyaev S, Boerwinkle E, Buxbaum JD, Cook EH Jr, Devlin B, Gibbs RA, Roeder K, Schellenberg GD, Sutcliffe JS, Daly MJ. *Nature*. 2012 Apr 4;485(7397):242-5. [PMID: 22495311]

Mutations in particular genes are believed, in many instances, to contribute to the risk of developing ASD. However, to date only a small fraction of ASD cases have been linked to known genetic risk factors. This is thought to be largely due to the lack of comprehensive scientific knowledge available on risk-determining genes that may play a role in ASD. Researchers have confronted this issue by examining the rate of *de novo* mutations—those arising spontaneously in reproductive cells but absent from the non-reproductive cells of either parent—in the DNA of individuals with ASD. With this approach, scientists examined the gene-rich regions of DNA known as exomes from people with ASD and their parents and identified *de novo* point mutations—or mutations in a single letter in the DNA code—that correlated with increased risk for ASD. They discovered that the number of *de novo* mutations in an individual with ASD is highly correlated with the age of both the mother and the father at the time of the child's conception, pointing to elevated risk as a parent ages and accumulates more mutations in their reproductive cells' DNA. Furthermore, the researchers found that *de novo* mutations in individuals with ASD are distributed across many genes and each mutation appears to contribute only modestly to the occurrence of ASD, indicating that any one mutation is unlikely to be the sole cause of ASD in an individual. Although in general it does not appear that families with a member affected by ASD have a particularly elevated rate of *de novo* mutation that would suggest special vulnerability to mutations, researchers found that the genes carrying *de novo* point mutations are highly related and share common biological pathways, and they are often linked to genes closely associated with ASD and other intellectual disabilities. Based on this discovery, researchers examined variations in two genes (*CHD8* and *KATNAL2*) in 935 individuals with ASD and 870 controls and found significant evidence that mutations within these genes indicated susceptibility for ASD. Investigators concluded that while the role of a single *de novo* mutation is limited in its ability to implicate a specific gene as a risk factor for ASD, predictive models that can assess *de novo* mutations in multiple genes at once in large data samples are important in the identification of genuine autism risk factors.

Sporadic autism exomes reveal a highly interconnected protein network of *de novo* mutations

– O’Roak BJ, Vives L, Girirajan S, Karakoc E, Krumm N, Coe BP, Levy R, Ko A, Lee C, Smith JD, Turner EH, Stanaway IB, Vernet B, Malig M, Baker C, Reilly B, Akey JM, Borenstein E, Rieder MJ, Nickerson DA, Bernier R, Shendure J, Eichler EE. *Nature*. 2012 Apr 4;485(7397):246-50. [PMID: 22495309]

Despite scientific evidence linking genetics to the development of ASD, more than 70% of ASD cases still have no known genetic cause. It is suggested that *de novo* mutations—those arising spontaneously in the DNA of reproductive cells and absent in the DNA of non-reproductive cells of either parent—may be involved in the incidence of ASD in families with no history of the disorder, also known as “sporadic” families. While previous studies have found that *de novo* copy number variations (CNVs), or large duplications or deletions in DNA, contribute to autism risk, this study focused on understanding the contribution of point mutations (or single nucleotide variants – SNVs) and other small mutations to the incidence of ASD in sporadic families. Researchers analyzed gene-rich regions of DNA (exomes) from 209 sporadic families consisting of children with ASD and their parents (who do not have ASD) and found that *de novo* mutations are four times more likely to be contributed by the father than by the mother. Furthermore, it was observed that the number of *de novo* mutations increases with the age of the father at the time of the child’s conception. Researchers were able to determine that 39% of the most disruptive *de novo* mutations (those most negatively affecting normal gene expression) were in genes that belonged to a highly interconnected network of genes associated with aspects of brain development or previously linked to ASD. The two specific genes containing the most recurring mutations among the 209 sporadic families were *CHD8*, a gene involved in remodeling chromatin (the DNA and protein complex that makes up chromosomes) to regulate gene expression, and Netrin-G1 (*NTNG1*), a gene that helps guide growing neurons and has been associated with atypical cases of Rett syndrome. Further genetic screening of 2,500 individuals identified additional disruptive *de novo* mutations in genes also implicated in ASD and other neurodevelopmental disorders (*GRIN2B*, *LAMC3*, and *SCN1A*). Based on these and other similar findings delineating the genetic distribution of *de novo* mutations in relation to ASD, researchers conclude that there is overwhelming diversity in the range and location of such mutations on the genome. Thus, scientists emphasize the need to continue using multiple techniques and large sample cohorts to identify additional genetic risk factors with the potential to lead to development of diagnostic biomarkers and new therapeutic approaches for ASD.

***De novo* mutations revealed by whole-exome sequencing are strongly associated with autism –**

Sanders SJ, Murtha MT, Gupta AR, Murdoch JD, Raubeson MJ, Willsey AJ, Ercan-Sencicek AG, DiLullo NM, Parikshak NN, Stein JL, Walker MF, Ober GT, Teran NA, Song Y, El-Fishawy P, Murtha RC, Choi M, Overton JD, Bjornson RD, Carriero NJ, Meyer KA, Bilguvar K, Mane SM, Sestan N, Lifton RP, Günel M, Roeder K, Geschwind DH, Devlin B, State MW. *Nature*. 2012 Apr 4;485(7397):237-41. [PMID: 22495306]

De novo gene mutations that arise spontaneously in reproductive cells or embryos are a key target of interest in the exploration of non-inherited causes of ASD in which neither parent has the disorder. Previous research has indicated that spontaneous or *de novo* copy number variations (CNVs), in which large sections of DNA are altered, contribute to risk for ASD. Less is known about whether spontaneous alterations in single base pairs within the DNA code, called *de novo* point mutations or single nucleotide variants (SNVs), may also play a role in elevating ASD risk. In this study, through sequencing of gene-rich regions of DNA (exomes) in a cohort of 928 individuals with ASD and their unaffected parents/siblings, scientists have uncovered compelling evidence on the contribution of *de novo* SNVs to risk for ASD. The researchers examined highly disruptive *de novo* SNVs (those most negatively affecting normal gene expression) and determined that such mutations in genes specific to the brain were significantly associated with ASD. To specify which genes contribute relatively greater risk, scientists estimated that the probability of two or more disruptive *de novo* mutations occurring in the same genes in unrelated individuals was highly unlikely. According to this measurement threshold, scientists identified *SCN2A*—a gene associated with epilepsy and ASD—as the only gene within the cohort that contains a disruptive *de novo* SNV in two individuals with ASD. In a combined analysis with genetic data from another cohort of 414 individuals with ASD, an additional two genes (*KATNAL2* and *CHD8*) were further identified as significantly associated with ASD. Researchers noted that although there is overwhelming genetic diversity in the frequency and location of *de novo* events throughout the genome, the technique of assessing disruptive *de novo* events clustered within the genes of unrelated individuals can reliably identify risk-contributing gene variants. This research will prove crucial in the continued exploration of genetic risk factors in ASD.

QUESTION 4

WHICH TREATMENTS AND INTERVENTIONS WILL HELP?

Effects of STX209 (arbaclofen) on neurobehavioral function in children and adults with fragile X syndrome: A randomized, controlled, phase 2 trial – Berry-Kravis EM, Hessler D, Rathmell B, Zarevics P, Cherubini M, Walton-Bowen K, Mu Y, Nguyen DV, Gonzalez-Heydrich J, Wang PP, Carpenter RL, Bear MF, Hagerman RJ. *Sci Transl Med.* 2012 Sep 19;4(152):152ra127. [PMID: 22993294]

While the genes implicated in the development of ASD number in the hundreds, much attention has focused on fragile X syndrome (FXS). FXS, caused by a mutation on a single gene (known as *FMR1*), is the most common single-gene cause of ASD and of inherited intellectual disability in boys. In FXS, the mutation of *FMR1* causes an overabundance of the excitatory neurotransmitter, glutamate, at the synapses between neurons in the brain, interfering with transmission of signals from one brain cell to the next. There has been recent interest in identifying drugs that may alter this signaling pathway, restoring the function of synapses in people with FXS, with the goal of targeting symptoms of FXS for which no direct treatments currently exist, including intellectual disability, irritability, aggression, seizures, and autistic behavior. In this study, researchers conducted a clinical trial evaluating the behavioral effects of a compound known as STX209 (arbaclofen), which stimulates release of an inhibitory neurotransmitter called GABA (gamma aminobutyric acid) in the brain, resulting in reduction of glutamate and improved functioning of synapses. The drug was tested for its efficacy in the treatment of irritable behavior in a group of individuals with FXS (55 male, 8 female) 6 to 39 years old. Based on scientific findings in animals demonstrating that arbaclofen can successfully treat behavioral symptoms in mouse models of FXS, clinical researchers in this study assessed whether arbaclofen can similarly improve symptoms in human FXS patients. Results of this research indicated that while treatment with arbaclofen did not affect behavioral scoring for irritability symptoms or aggression, treated individuals with FXS did exhibit significant improvement in the performance of social functions. Such results suggest that arbaclofen and related compounds may have potential for improving social functioning in individuals with FXS and other related neurodevelopmental disorders associated with social disabilities, like ASD, which may, in turn, improve quality of life.

Early behavioral intervention is associated with normalized brain activity in young children with autism – Dawson G, Jones EJ, Merkle K, Venema K, Lowy R, Faja S, Kamara D, Murias M, Greenson J, Winter J, Smith M, Rogers SJ, Webb SJ. *J Am Acad Child Adolesc Psychiatry*. 2012 Nov;51(11):1150-9. [PMID: 23101741]

Early Start Denver Model (ESDM) is a developmental, relationship-based early behavioral intervention for children aged 12 to 48 months that incorporates techniques from applied behavior analysis (ABA). ESDM emphasizes social engagement through features such as parent-training, joint activities, imitation skills, and communication development. Previously published randomized clinical trial data indicated that children with ASD who received ESDM for 2 years had improved autism symptoms, IQ, language, and adaptive behaviors.¹ In this study, researchers present additional findings from the same trial in which the relationship between ESDM and functional activity in the brains of children with ASD was evaluated. At the end of the trial, researchers evaluated electrical brain activity recorded in response to social (faces) versus nonsocial (toys) stimuli from 4-year-old children with ASD who participated in either ESDM or community interventions (referral to local providers in the area). Four-year-old typical children served as a comparison group. Results indicated that when viewing images of faces versus objects, children who received ESDM showed patterns of brain activity that were similar to the typical group, characterized by greater brain activation while viewing the social than the nonsocial stimuli. Furthermore, the improved pattern of brain activity in the ESDM group was also found to be associated specifically with improved social behaviors. In contrast, children in the community intervention group demonstrated the reverse pattern of brain activation, with delayed neural response to social stimuli and increased brain activation during the viewing of object images. The results of this study represent the first demonstration that early behavioral intervention can measurably affect brain activity and related social behaviors, suggesting that the intervention may influence brain development and have the potential to increase positive behavioral outcomes for children with ASD.

¹ Randomized, controlled trial of an intervention for toddlers with autism: The Early Start Denver Model. Dawson G, Rogers S, Munson J, Smith M, Winter J, Greenson J, Donaldson A, Varley J. *Pediatrics*. 2010 Jan;125(1):e17-23.

Effects of a brief Early Start Denver Model (ESDM)-based parent intervention on toddlers at risk for autism spectrum disorders: A randomized controlled trial – Rogers SJ, Estes A, Lord C, Vismara L, Winter J, Fitzpatrick A, Guo M, Dawson G. *J Am Acad Child Adolesc Psychiatry*. 2012 Oct;51(10):1052-65. [PMID: 23021480]

Research has shown that early behavioral interventions can improve symptoms in some children with ASD, leading to an emphasis on early diagnosis and treatment. One such intervention is the Early Start Denver Model (ESDM), an intensive early behavioral intervention for children under 3 years old with ASD that combines principles of applied behavior analysis (ABA) therapy with relationship-focused developmental approaches. Previous research indicated that the ESDM intervention provided by trained therapists improved IQ, language, and adaptive behaviors in children with ASD after 15 to 20 hours of therapy per week for 2 years.² However, including parents in early interventions has been shown to be important for successful outcomes. Thus, this study was conducted to evaluate the effectiveness of a brief, low-intensity, parent-based ESDM intervention (P-ESDM). This randomized controlled trial of 98 families with children 12 to 24 months of age that were at risk for ASD (based on screenings and clinical assessment) compared one group of children who received the P-ESDM intervention to a group of children who received typical community interventions. To deliver the P-ESDM intervention, parents were trained during a 1-hour session each week with their children where they received instruction and coaching on one of the ten core skills of the ESDM program. The two groups of parents and children were assessed at the beginning of the study and after completion of the 12-week P-ESDM training. At the end of the study, both the P-ESDM and community intervention groups of parents showed improved interaction skills with their children, and both groups of children showed developmental gains and a reduction in core ASD symptoms. However, there was no clear benefit of one intervention over the other, and the authors noted that the study design may have inhibited parents in the P-ESDM group from receiving as much information as the parents in the community intervention group. Children in the community intervention group also received significantly more hours of intervention than children in the P-ESDM group. Notably, however, younger children in both groups made more developmental gains than older children, and a greater number of hours of intervention were associated with improvement in children's behavior. Thus, while parent-implemented interventions have not yet shown the same level of improvement observed in intensive treatment studies, these results provide important evidence about the age and intensity at which interventions could be most effective.

² Randomized, controlled trial of an intervention for toddlers with autism: The Early Start Denver Model. Dawson G, Rogers S, Munson J, Smith M, Winter J, Greenson J, Donaldson A, Varley J. *Pediatrics*. 2010 Jan;125(1):e17-23.

QUESTION 5

WHERE CAN I TURN FOR SERVICES?

Occurrence and family impact of elopement in children with autism spectrum disorders – Anderson C, Law JK, Daniels A, Rice C, Mandell DS, Hagopian L, Law PA. *Pediatrics*. 2012 Nov;130(5):870-7. [PMID: 23045563]

Anecdotal accounts have suggested that elopement, or wandering, behavior is common in children with ASD, but little research had been done to characterize this behavior or to determine its frequency. This study used the Interactive Autism Network (IAN), an online research database and autism registry supported by Autism Speaks, the Simons Foundation, and the National Institute of Mental Health, to conduct a survey of families to determine the extent to which children with ASD wander away from a supervised, safe place or from the care of a responsible person. Families enrolled in IAN that had a child with ASD who was between 4 and 17 years old were invited to participate in the survey of wandering behavior, which was developed by ASD researchers, clinicians, and parent advocates. Of the 1,218 children with ASD and their 1,076 siblings without ASD included in the study, nearly half (49%) of the children with ASD had attempted to wander at least once since the age of 4, compared to only 13% of their siblings without ASD. Wandering behavior was more common among children with greater autism severity. Most frequently, the children wandered from home or school settings, or while on shopping trips with their families. Twenty-six percent of the families with children with ASD reported at least one instance when their child was missing long enough to cause concern. Children were missing for an average of 41.5 minutes and many faced close calls with traffic injury (65%) or drowning (24%) during this time. Parents and caregivers reported multiple potential motivations for their child's wandering, including the desire to explore, trying to find a place that they enjoy, escaping an anxious situation, and escaping uncomfortable sensory stimuli. Wandering behavior also had a large impact on the families of children with ASD, including disrupted sleep, avoidance or lack of enjoyment in activities outside of the home, and increased levels of stress. Fifty percent of families reported that they had not received any guidance on how to prevent or address wandering behaviors, and future research is needed to identify the best ways to support these families. This initial characterization and documentation of wandering behavior in children with ASD provides a foundation for additional research on wandering to further define this behavior and develop effective prevention and intervention strategies.

Excess mortality and causes of death in autism spectrum disorders: A follow up of the 1980s Utah/UCLA Autism Epidemiologic Study – Bilder D, Botts EL, Smith KR, Pimentel R, Farley M, Viskochil J, McMahon WM, Block H, Ritvo E, Ritvo RA, Coon H. *J Autism Dev Disord.* 2013 May; 43(5):1196-204. [PMID: 23008058]

Although previous studies have reported increased mortality rates for people with ASD, there has been limited knowledge regarding the causes of death and whether certain subpopulations may be at higher risk. Using data from a study in Utah from the 1980s that assessed the statewide prevalence of autism, a group of researchers examined the records of the original study population three decades later to evaluate the long-term rates and causes of mortality among individuals diagnosed with ASD. This follow-up study included 305 individuals who were either diagnosed with ASD during the initial study (using the Diagnostic and Statistical Manual of Mental Disorders (DSM)-III) or through re-evaluation and reclassification based on more recent diagnostic criteria (DSM IV-TR). By the end of 2011, 29 of the 305 individuals (9.5%) had died. Thus, the hazard rate ratio for individuals with ASD compared to those without ASD was 9.9, meaning that an individual with ASD was 9.9 times more likely to have died over a certain time period than someone in the general population. These hazard rate ratios decreased slightly when family members (cousins or siblings) without ASD were used as controls, indicating that familial factors, either environmental or genetic, may also contribute to mortality. Overall, the hazard rate ratio of 9.9 in this study is higher than any previous studies, in which hazard rate ratios for individuals with ASD ranged from 0 to 5.6. The main causes of death for individuals in this study, obtained from death certificates, were respiratory, cardiac, and epileptic events, and the mortality rate increased with the severity of intellectual disability. Relatively few deaths were due to unnatural causes such as accidents or suicide. The general association of increased mortality risk with the presence of co-occurring conditions and intellectual disability, rather than with ASD itself, highlights the importance of coordinated medical care for those individuals with ASD who have multiple co-occurring medical issues in addition to the classic symptoms associated with ASD.

QUESTION 6

WHAT DOES THE FUTURE HOLD, PARTICULARLY FOR ADULTS?

Do sheltered workshops enhance employment outcomes for adults with autism spectrum disorder? –
Cimera RE, Wehman P, West M, Burgess S. *Autism*. 2012 Jan;16(1):87-94. [PMID: 21610189]

The transition to employment is one point of the lifespan when extra support programs could help individuals with ASD prepare for the challenges of the workplace environment. Sheltered workshops are programs that assist people with disabilities in preparing for competitive employment by providing skill training, job counseling, and other related services, in addition to work experiences alongside other individuals with disabilities. This study assessed whether sheltered workshops resulted in improved employment outcomes for individuals with ASD versus entering community-based employment without having prior sheltered workshop experience. Using the U.S. Department of Education's Rehabilitation Services Administration (RSA) 911 database, which contains records of everyone who applies for vocational rehabilitation services, researchers compared two groups of supported employees with ASD. Supported employees receive vocational assistance such as job coaches, job development and training, transportation, assistive technology, and individually tailored supervision to help them maintain employment. One of the groups was composed of individuals with ASD who had participated in sheltered workshops prior to entering supported employment in the community, and the other group of individuals had not participated in sheltered workshops and directly entered supported, community-based employment. The two groups were compared in four areas, including rates of employment, hours worked, wages earned, and cost of services received. Results showed no difference between the two groups in terms of rate of employment or number of hours worked. However, the earnings of individuals who had participated in sheltered workshops were significantly less than those who had not had a sheltered workshop experience prior to seeking supported, community-based employment, and the cost to provide services for the individuals in sheltered workshops was significantly more than the comparison group. Thus, these data indicated that individuals with ASD do not achieve better employment outcomes if they participate in sheltered workshops prior to enrolling in supported, community-based employment programs. The researchers suggested that these unexpected results could be influenced by a number of factors. For example, individuals in sheltered workshops may have been more severely impaired compared to individuals who did not participate in the workshops, or participants and families in the sheltered workshops may have been concerned about losing disability benefits if they became employed at higher pay levels, so they may have

intentionally accepted underemployment in order to maintain benefits. Conversely, another possibility is that individuals who did not participate in sheltered workshops may have been more challenged and motivated to get and keep higher paying jobs, or they may have learned better work behaviors that helped them gain and maintain higher levels of employment. Additional research into the factors that contribute to successful competitive employment for individuals with ASD will be needed to continue optimizing vocational services for this population.

Postsecondary education and employment among youth with an autism spectrum disorder – Shattuck PT, Narendorf SC, Cooper B, Sterzing PR, Wagner M, Taylor JL. *Pediatrics*. 2012 Jun;129(6):1042-9. [PMID: 22585766]

In the U.S. alone this year, approximately 50,000 adolescents with ASD will turn 18 years old and age out of the education system that provided them with much-needed supports, raising national concern over how society will be able to ensure quality of life across the lifespan for these individuals. Relatively little research has focused on this topic, and generalizability has been limited in previous studies by small samples. However, the findings prior to this study suggested low rates of employment and postsecondary education for youth with ASD. In this study, researchers used data from the 500 parents/guardians and youth who took part in the U.S. Department of Education's National Longitudinal Transition Study 2 (NLTS2)—a 10-year prospective study of youth receiving special education services through their transition to adulthood—from which they examined participation in postsecondary employment, college or university education, or vocational training in a large national sample. The findings indicated that post-high school, 34.7% of youth with ASD had attended university or college, 55.1% had held paid employment since high school, and 9.3% had attended a vocational or technical education program. However, more than half of those who left high school in the past 2 years had not participated in employment or education. Compared with youth in the three other disability categories studied—speech impairment, learning disability, and mental retardation—those with ASD had significantly lower rates of employment. In addition, individuals within this group from lower-income families, with greater functional impairments, or of Hispanic or African-American ethnicity were at heightened risk of poor education and employment outcomes. Overall, the findings indicate that youth with ASD have poor postsecondary employment and education outcomes, especially in the first 2 years after high school. As the size of the young adult ASD population continues to grow, further research is needed to understand how transition planning before the end of high school can facilitate improved continuation on to postsecondary activities.

Developmental trajectories in adolescents and adults with autism: The case of daily living skills –

Smith LE, Maenner MJ, Seltzer MM. *J Am Acad Child Adolesc Psychiatry*. 2012 Jun;51(6):622-31. [PMID: 22632621]

Developing independence in daily living skills is an important factor for successful outcomes for adolescents and adults with autism spectrum disorders (ASD). Daily living skills are the behaviors that are necessary for age-appropriate, independent functioning in social, communication, daily living, or motor areas. However, few studies have explored how daily living skills are developed in adolescents and adults with ASD. This study investigated the change in daily living skills over a 10-year period in 406 adolescents and adults with ASD between 10 and 52 years old. As a context for comparison, a group of individuals with Down syndrome (DS) were also studied because these individuals tend to have higher levels of daily living skills than those with other intellectual disabilities. Researchers evaluated the individuals with ASD and DS using the Waisman Activities of Daily Living Scale (W-ADL) at four time points during the 10-year study. The W-ADL enables parents to rate their son or daughter's level of independence on 17 items, including personal care, housekeeping, and meal-related activities. Based on results from the W-ADL, investigators developed a growth curve to show the path of change in daily living skills. The daily living skills of individuals with ASD improved through their adolescence and early 20s, but then leveled off in their late 20s. Additionally, having an intellectual disability was associated with lower initial levels of daily living skills as well as slower skill growth over time for individuals with ASD. In contrast, the individuals with Down syndrome continued to gain daily living skills over time. These results indicate that while adolescence is a period of growth and improvement in a variety of areas for individuals with ASD, research is needed to explore what factors may facilitate continued growth in daily living skills for adults with ASD. Developing the best methods to encourage this growth could enable adults with ASD to live more independent lives.

A systematic review of vocational interventions for young adults with autism spectrum disorders – Taylor JL, McPheeters ML, Sathe NA, Dove D, Veenstra-Vanderweele J, Warren Z. *Pediatrics*. 2012 Sep;130(3):531-8. [PMID: 22926170]

The transition to adulthood is a challenging time for many individuals with ASD. Moving from the supports provided by the education system to employment can be particularly difficult, and interventions targeted at this transition may improve outcomes and quality of life for adults with ASD. This study systematically reviewed existing research on the effectiveness of vocational/employment interventions for individuals with ASD between 13 and 30 years of age. Researchers found only five studies related to vocational intervention that met the requirements to be included in this review (for example, studies had to have at least 20 participants). All five studies focused on “on-the-job” supports as the particular vocational/employment intervention. The studies were each determined to be of poor quality because they were relatively small and lacked the random assignment, appropriate control groups, and follow-up study that would be necessary to draw strong conclusions about the effectiveness of the programs. However, each of the studies did find evidence of positive benefits for vocational interventions on employment measures or ASD symptoms. Thus, while the strength of evidence for positive outcomes of vocational interventions is insufficient at this time, possibly due to the emerging nature of this field of research, this review indicates that future research using more rigorous study methods should be done to more conclusively determine whether vocational/employment interventions are helpful as well as which types of interventions may be most effective. In particular, long-term data need to be collected to assess the length of time that improvements continue after an intervention stops, and the outcome measures should be broadened to include factors such as quality of life, social and residential outcomes, and educational achievement. Research into understanding how individual differences in ASD (such as symptom severity or co-occurring conditions) may affect which interventions are most beneficial could enable targeting interventions to those who will receive the most benefit. The financial impact of vocational/employment interventions on individuals, families, and the overall economy should also be investigated. Collectively, these additional studies could help create the evidence base needed to better serve the growing number of individuals with ASD approaching adulthood.

QUESTION 7

WHAT OTHER INFRASTRUCTURE AND SURVEILLANCE NEEDS MUST BE MET?

Prevalence of Autism Spectrum Disorders - Autism and Developmental Disabilities Monitoring Network, 14 Sites, United States, 2008 – Centers for Disease Control and Prevention (CDC); Autism and Developmental Disabilities Monitoring Network - Surveillance Year 2008 Principal Investigators. *MMWR Surveill Summ.* 2012 Mar; 61(3):1-19. [PMID: 22456193]

The Centers for Disease Control and Prevention's (CDC) Autism and Developmental Disabilities Monitoring (ADDM) Network is an active surveillance system established in 2000 to monitor the prevalence of ASD in children in the U.S., and new prevalence statistics are released every 2 years. CDC issued its latest prevalence estimate from the 2008 surveillance year, which was based on a study population of 337,093 8-year-old children at 14 sites across the country. Among these children, those whose health or education records showed possible signs of ASD were selected for a detailed records review by trained clinicians to determine whether or not the child had ASD. With these data, the estimated prevalence of ASD in 2008 across all ADDM sites was 1 in 88 children. However, the prevalence range among the sites differed considerably, from 4.8 per 1,000 children (1 in 208) in Alabama to 21.2 per 1,000 children (1 in 47) in Utah. Overall, the average prevalence amounts to a 23% increase from 2006 to 2008 and a 78% increase from 2002 to 2008. As in previous years, the prevalence of ASD in boys (1 in 54) was significantly higher than the prevalence among girls (1 in 252). The prevalence of ASD also varied by race and ethnicity, with the highest prevalence in non-Hispanic white children (12 per 1,000), compared to non-Hispanic black children (10.2 per 1,000) and Hispanic children (7.9 per 1,000). Over time, the largest increases in ASD prevalence were found among Hispanic children and non-Hispanic black children as well as among children without co-occurring intellectual disabilities. Together, the results of this report suggested that ASD prevalence has been rising in most ADDM Network sites, but the extent to which these increases reflected better identification of children with ASD as a result of increased awareness and access to services versus true increases in prevalence of ASD was not known. Further investigation is needed to determine how disparities related to race, ethnicity, and societal factors (such as income, education, and occupation) could affect the prevalence estimates. For example, disparities in access to services or trained professionals who can provide a proper diagnosis could result in an underestimation of the number of children with ASD in a given population. Continued surveillance efforts will be needed to monitor changes in prevalence over time to ensure that appropriate services are made available to help children with ASD achieve their greatest potential.

ARTICLES SELECTED FOR THE 2012 SUMMARY OF ADVANCES

QUESTION 1: WHEN SHOULD I BE CONCERNED?

Fountain C, Winter AS, Bearman PS. Six developmental trajectories characterize children with autism. *Pediatrics*. 2012 May;129(5):e1112-20. [PMID: 22473372]

Skafidas E, Testa R, Zantomio D, Chana G, Everall IP, & Pantelis C. Predicting the diagnosis of autism spectrum disorder using gene pathway analysis. *Mol Psychiatry*. 2012 Sep 11. [Epub ahead of print] [PMID: 22965006]

QUESTION 2: HOW CAN I UNDERSTAND WHAT IS HAPPENING?

Novarino G, El-Fishawy P, Kayserili H, Meguid NA, Scott EM, Schroth J, Silhavy JL, Kara M, Khalil RO, Ben-Omran T, Ercan-Sencicek AG, Hashish AF, Sanders SJ, Gupta AR, Hashem HS, Matern D, Gabriel S, Sweetman L, Rahimi Y, Harris RA, State MW, Gleeson JG. Mutations in BCKD-kinase lead to a potentially treatable form of autism with epilepsy. *Science*. 2012 Oct 19;338(6105):394-7. [PMID: 22956686]

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QUESTION 4: WHICH TREATMENTS AND INTERVENTIONS WILL HELP?

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Rogers SJ, Estes A, Lord C, Vismara L, Winter J, Fitzpatrick A, Guo M, Dawson G. Effects of a brief Early Start Denver Model (ESDM)-based parent intervention on toddlers at risk for autism spectrum disorders: A randomized controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2012 Oct;51(10):1052-65. [PMID: 23021480]

QUESTION 5: WHERE CAN I TURN FOR SERVICES?

Anderson C, Law JK, Daniels A, Rice C, Mandell DS, Hagopian L, Law PA. Occurrence and family impact of elopement in children with autism spectrum disorders. *Pediatrics*. 2012 Nov;130(5):870-7. [PMID: 23045563]

Bilder D, Botts EL, Smith KR, Pimentel R, Farley M, Viskochil J, McMahon WM, Block H, Ritvo E, Ritvo RA, Coon H. Excess mortality and causes of death in autism spectrum disorders: A follow up of the 1980s Utah/UCLA Autism Epidemiologic Study. *J Autism Dev Disord*. 2012 Sep 25. 2013 May; 43(5):1196-204. [PMID: 23008058]

QUESTION 6: WHAT DOES THE FUTURE HOLD, PARTICULARLY FOR ADULTS?

Cimera RE, Wehman P, West M, Burgess S. Do sheltered workshops enhance employment outcomes for adults with autism spectrum disorder? *Autism*. 2012 Jan;16(1):87-94. [PMID: 21610189]

Shattuck PT, Narendorf SC, Cooper B, Sterzing PR, Wagner M, Taylor JL. Postsecondary education and employment among youth with an autism spectrum disorder. *Pediatrics*. 2012 Jun;129(6):1042-9. [PMID: 22585766]

Smith LE, Maenner MJ, Seltzer MM. Developmental trajectories in adolescents and adults with autism: The case of daily living skills. *J Am Acad Child Adolesc Psychiatry*. 2012 Jun;51(6):622-31. [PMID: 22632621]

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QUESTION 7: WHAT OTHER INFRASTRUCTURE AND SURVEILLANCE NEEDS MUST BE MET?

Centers for Disease Control and Prevention (CDC); Autism and Developmental Disabilities Monitoring Network - Surveillance Year 2008 Principal Investigators. Prevalence of Autism Spectrum Disorders - Autism and Developmental Disabilities Monitoring Network, 14 Sites, United States, 2008. *MMWR Surveill Summ*. 2012 Mar; 61(3):1-19. [PMID: 22456193]

FULL LISTING OF NOMINATED ARTICLES

(SELECTED ARTICLES APPEAR IN BLUE)

QUESTION 1: WHEN SHOULD I BE CONCERNED?

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