

<b>QUESTION 3: WHAT CAUSED THIS TO HAPPEN AND CAN IT BE PREVENTED?</b>		
<b>IACC Strategic Plan Objectives</b>	<b>Planning Group Summary</b>	<b>Funding 2008-2013</b>
<p><b>3.S.A.</b> Coordinate and implement the inclusion of approximately 20,000 subjects for genome-wide association studies, as well as a sample of 1,200 for sequencing studies to examine more than 50 candidate genes by 2011. Studies should investigate factors contributing to phenotypic variation across individuals who share an identified genetic variant and stratify subjects according to behavioral, cognitive, and clinical features.</p> <p><i>IACC Recommended Budget: \$43,700,000 over 4 years</i></p>	<p>The recommended budget has been partially met. Progress has been made on this objective through the funding of several GWAS and sequencing projects. The current number of 6,000 GWAS subjects falls short of the goal of 20,000, but the number of whole exome sequences far exceeds 1200, and could also reach 6,000 in the next year. Whole exome sequencing has identified 7-10 candidate genes, and promises to move closer to the goal of 50 in the future. Progress is being made in CNV studies. More subtyping and genotype-phenotype work outside of syndromic forms of autism, as well as natural history studies, are needed.</p>	<b>\$38,587,633</b>
<p><b>3.S.B.</b> Within the highest-priority categories of exposures for ASD, identify and standardize at least three measures for identifying markers of environmental exposure in biospecimens by 2011.</p> <p><i>IACC Recommended Budget: \$3,500,000 over 3 years</i></p>	<p>The recommended budget has been partially met. There has been progress on the understanding of exposures, but more work needs to be done to apply this directly to autism research. Progress has been made through methodological advances embedded in epidemiological studies funded by NIEHS, but those projects are not captured by the Portfolio Analysis because they are not specific to autism. The primary obstacle to completion of this objective has been funding for exposure marker identification, rather than a lack of study of identified markers. There is a need for biomarkers of exposure; exposomics should be a priority area for future research.</p>	<b>\$813,227</b>
<p><b>3.S.C.</b> Initiate efforts to expand existing large case-control and other studies to enhance capabilities for targeted gene-environment research by 2011.</p> <p><i>IACC Recommended Budget: \$27,800,000 over 5 years</i></p>	<p>The recommended budget has been nearly met, but work still needs to continue on this objective. The funding allocated to this area so far has begun to build an infrastructure that should be expanded to include more subjects, more data, and more analytical projects. Continued benefit will be derived from past investments as these resources are expanded and pooled.</p>	<b>\$26,903,311</b>
<p><b>3.S.D.</b> Enhance existing case-control studies to enroll racially and ethnically diverse populations affected by ASD by 2011.</p> <p><i>IACC Recommended Budget: 3,300,000 over 5 years</i></p>	<p>The recommended budget has been partially met. The UCLA ACE center coded to 3.L.B. reflects some progress on this objective. Overall, however, both funding and outcomes related to this objective are far below the goal. There is a need for studies around high exposure, low socioeconomic status populations.</p>	<b>\$188,455</b>
<p><b>3.S.E.</b> Support at least two studies to determine if there are subpopulations that are more susceptible to environmental exposures (e.g., immune challenges related to infections, vaccinations, or underlying autoimmune problems) by 2012.</p> <p><i>IACC Recommended Budget: \$8,000,000 over 2 years</i></p>	<p>The recommended budget has been partially met, and the intended number of studies was exceeded. While a large amount of data has been collected relating to immunological conditions in children and mothers, broad conclusions have not been possible, and more work is needed.</p>	<b>\$3,608,312</b>
<p><b>3.S.F.</b> Initiate studies on at least 10 environmental factors identified in the recommendations from the 2007 IOM report "Autism and the Environment: Challenges and Opportunities for Research" as potential causes of ASD by 2012.</p> <p><i>IACC Recommended Budget: \$56,000,000 over 2 years (revised in 2010)</i></p>	<p>The recommended budget has not been met, and it appears that there has been a significant decrease in the number of studies related to this objective. Further work in this area is needed, and this work should focus on identifying the directionality of associations between environmental factors and ASD (causal, reactive, independent) in order to be applied to prevention and the development of therapeutics. Sophisticated methods that are being applied in other fields need to be brought into autism research.</p>	<b>\$10,794,995</b>
<p><b>3.S.G.</b> Convene a workshop that explores the usefulness of bioinformatic approaches to identify environmental risks for ASD by 2011.</p> <p><i>IACC Recommended Budget: \$35,000 over 1 year</i> *This objective was completed in 2011</p>	<p>The workshop identified in this objective was held in 2011, so this objective has been completed and a report is available. There is a need to develop an exposome. A forum for the sharing of new technologies and standardized assessments would also be useful in moving this field forward.</p>	<b>\$46,991</b>
<p><b>3.S.H.</b> Support at least three studies of special populations or use existing databases to inform our understanding of environmental risk factors for ASD in pregnancy and the early postnatal period by 2012. Such studies could include:</p> <ul style="list-style-type: none"> <li>• Comparisons of populations differing in geography, gender, ethnic background, exposure history (e.g., prematurity, maternal infection, nutritional deficiencies, toxins), and migration patterns; and</li> <li>• Comparisons of phenotype (e.g., cytokine profiles), in children with and without a</li> </ul>	<p>The recommended budget has been partially met, and the funded projects cover the objective well; there are 32 projects that are related to this objective, though more focus on use of databases than special populations. While progress is being made in this area, and it must be maintained in order to achieve this objective. A positive element of progress for this objective is the existence of large monitoring databases and projects that capitalize on those resources, such as iCARE and MINERVA. Still, there is more work to be done.</p>	<b>\$10,281,278</b>

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<p>history of autistic regression, adverse events following immunization (such as fever and seizures), and mitochondrial impairment. These studies may also include comparisons of phenotype between children with regressive ASD and their siblings.</p> <p>Emphasis on environmental factors that influence prenatal and early postnatal development is particularly of high priority. Epidemiological studies should pay special attention to include racially and ethnically diverse populations.</p> <p><i>IACC Recommended Budget: \$12,000,000 over 5 years</i></p>		
<p><b>3.S.I.</b> Support at least two studies that examine potential differences in the microbiome of individuals with ASD versus comparison groups by 2012.</p> <p><i>IACC Recommended Budget: \$1,000,000 over 2 years</i></p>	<p>The number of projects in this area has been growing, with 6 projects in 2012. The number of funded projects is large relative to the amount of funding, indicating that the projects are each small, which suggests that these projects will not be sufficient to complete this objective. The high cost of required technology could be a barrier to the completion of this objective. These smaller pilot studies are potentially underpowered. The question of sample availability is important for this objective, along with raising researcher awareness of sample repositories.</p>	<p><b>\$749,263</b></p>
<p><b>3.S.J.</b> Support at least three studies that focus on the role of epigenetics in the etiology of ASD, including studies that include assays to measure DNA methylations and histone modifications and those exploring how exposures may act on maternal or paternal genomes via epigenetic mechanisms to alter gene expression, by 2012.</p> <p><i>IACC Recommended Budget: \$20,000,000 over 5 years</i></p>	<p>The recommended budget for this objective has been partially met, and the number of projects has been exceeded, with 22 projects supported in 2012. The current momentum in this area should be maintained. An important technological need for this objective is the development of robust epigenetic measurements for small biological samples, such as blood spots. A possible barrier to research in this area is the availability and preservation quality of these samples. Large funded studies such as MARBLES might provide an opportunity to collect samples. If samples are made available, that may catalyze research in this area.</p>	<p><b>\$16,536,350</b></p>
<p><b>3.S.K.</b> Support two studies and a workshop that facilitate the development of vertebrate and invertebrate model systems for the exploration of environmental risks and their interaction with gender and genetic susceptibilities for ASD by 2012.</p> <p><i>IACC Recommended Budget: \$1,535,000 over 3 years</i></p>	<p>While the recommended budget has been partially met and some projects have been funded in this area, it appears that there is a downward trend. Projects by Tychele Turner at Johns Hopkins and Donna Werling at UCLA are using animal models to investigate sex differences in autism, and these projects are coded to 2SB. The following workshop touched on this topic, but it was not the main focus of the workshop: <a href="http://www.niehs.nih.gov/health/assets/docs/a_e/autism_and_the_environment_meeting_report.pdf">http://www.niehs.nih.gov/health/assets/docs/a_e/autism_and_the_environment_meeting_report.pdf</a>. The development of animal models for more broad ASD research is coded to question 4, and the use of such models to answer environmental exposure questions is a next step for this objective.</p>	<p><b>\$1,287,763</b></p>
<p><b>3.L.A.</b> Conduct a multi-site study of the subsequent pregnancies of 1,000 women with a child with ASD to assess the impact of environmental factors in a period most relevant to the progression of ASD by 2014.</p> <p><i>IACC Recommended Budget: \$11,100,000 over 5 years</i></p>	<p>The recommended budget for this objective was met, but emphasis on this objective should continue in the future. The Group is concerned about the lack of continued funding for EARLI. More positively, MARBLES is continuing and analytical projects of the previously collected EARLI data are also in process. A barrier to this sort of work is the extremely high cost of building the infrastructure necessary; therefore, it is important to maintain these cohorts where possible, to collect a wide range of samples, and to use them for multiple studies to capitalize on investments made.</p>	<p><b>\$15,194,483</b></p>
<p><b>3.L.B.</b> Identify genetic risk factors in at least 50% of people with ASD by 2014.</p> <p><i>IACC Recommended Budget: \$33,900,000 over 6 years</i></p>	<p>While the recommended budget for this objective has been met, further work is needed to identify genetic risk factors in at least 50% of people. Whole exome analysis puts the current progress at 20% of people, and inclusion of CNV data might push it toward 30%. The initial budget recommendation for this objective was made based on the assumption that GWAS studies would provide risk factor identification, but sequencing has proven more fruitful. Since this technique is more expensive, a higher budget will be required to meet the goal of 50%.</p>	<p><b>\$169,806,458</b></p>
<p><b>3.L.C.</b> Determine the effect of at least five environmental factors on the risk for subtypes of ASD in the prenatal and early postnatal period of development by 2015.</p> <p><i>IACC Recommended Budget: \$25,100,000 over 7 years</i></p>	<p>The recommended budget was partially met, and several projects were funded, but it appears there is a downward trend. Epidemiological studies coded to other objectives (e.g. EARLI) may also represent progress in this area. A barrier to the completion of this objective is the undefined nature of ASD subtypes, both phenotypically and etiologically. This field is still developing and needs support.</p>	<p><b>\$5,349,089</b></p>
<p><b>3.L.D.</b> Support ancillary studies within one or more large-scale, population-based surveillance and epidemiological studies, including U.S. populations, to collect data on environmental factors during preconception, and during prenatal and early</p>	<p>The recommended budget for this objective has been met, with most of the studies coded to this area relating to CADDRE. The funds allocated to this objective to date have been used for data collection and the development of infrastructure, so continued funding will be needed to support analysis</p>	<p><b>\$63,013,714</b></p>

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<p>postnatal development, as well as genetic data, that could be pooled (as needed) to analyze targets for potential gene/environment interactions by 2015.</p> <p><i>IACC Recommended Budget: \$44,400,000 over 5 years</i></p> <p>Not specific to any objective (Core Activities)</p>	<p>studies. Both molecular and environmental data are needed.</p>
	<p><b>\$17,656,815</b></p>
<p><b>Total funding for Question 3</b></p>	<p><b>\$380,818,136</b></p>