

Autism Sequencing Consortium (ASC)

Memorandum of Understanding

(As modified June 23, 2014)

The following is a memorandum of understanding (MOU) for the ASC to guide collaborative interactions for autism spectrum disorder (ASD) gene discovery. This MOU is a work in progress and is expected to change as the consortium works together.

I. Guiding Principles

The collaboration is based on certain values and a shared consensus about the best way to identify ASD susceptibility loci and genes. These are outlined below:

- A. Trust.** Any memorandum of agreement is fundamentally based on a sense of mutual trust and respect among the participating groups. Without this initial trust and respect, no collaboration is possible. Members may disagree with each other but that should not erode the fundamental sense of trust and respect. Participation in the collaboration is contingent on each group affirming their commitment to this shared value.
- B. Confidentiality.** Findings and results generated by the collaborative efforts of the group will be treated as confidential and cannot be used in studies, grant applications or papers without the prior consent of the scientists involved. All scientists involved in the collaboration will declare possible conflicts of interest and agree in signing this document to confidentiality.
- C. Open Communication among senior investigators.** For this collaboration to succeed, it is extremely important that all decisions and activities be conducted in an open way. This is best accomplished through clear, frequent, and open communication among all the participating groups, either by phone, or by email. Each senior investigator is responsible for forwarding all communications to members of their own group.
- D. Timeliness of activities/research.** There is a commitment to adhere to reasonable timelines in sending the data to the common data sets, in reviewing analytic plans, carrying out analyses, and publishing papers.
- E. The use of a research group's own data in research studies outside the ASC.** There is general agreement that individual research groups are able to analyze any data they themselves have generated and have submitted to the common data set. No review of the analytic plan or molecular work is necessary.
- F. A commitment to respecting priority.** If one of the collaborating groups has positive results of some kind, using only samples and data that that group has collected themselves, there is a clear understanding that that group may publish the finding before any other member of the collaboration can follow the finding up in a publication. If however, the finding involves samples other than their own, or genetic or other data generated by the ASC, this does not apply.
- G. Junior faculty/students.** The collaboration puts a high premium on the training of students and junior faculty. Every opportunity must be given to students and junior faculty to refine their research skills and methodologies, to have an opportunity to be first

author on publications, and to take the lead in certain components of the research collaboration. In this way, the next generation of scientists in ASD research will be able to build on the results of this initial collaboration and so continue to make progress.

- H. **All parties to the collaboration benefit.** The first and foremost benefit of the ASC collaboration will be finding the genes that confer susceptibility to ASDs, leading to a better understanding of the causes of ASDs and development of potential treatments. The investigators will also benefit from authorship on ASC publications and may also benefit through increased or stable funding, further learning opportunities, the potential for career advancement, and learning more about the most appropriate strategies to uncover the genetic mechanisms of complex disease. The investigators and funding agencies may also benefit from owning intellectual property from any discoveries that are made. There is a clear recognition that for this collaboration to go ahead, any decisions that are made must attempt to provide mutual benefit for all those involved in the ASC, not just those directly responsible for a particular discovery. Admittedly it will be difficult to ensure that the benefit is equally distributed, or that it is equal in kind among all partners; nevertheless there must be an assurance of mutual benefit.
- I. **Benefits to the scientific and lay community.** As a primary goal of the ASC is to ultimately contribute to a better understanding of the causes of ASDs and, through this, to the development of potential treatments, members recognize that dissemination of information (in the form of publications) and data (in the form of raw, processed and summary data) represents an important means to provide benefit to the larger community. The ASC is committed to data sharing and creating resources for the community beyond the ASC.

II. Regular ASC Membership.

As a group, the ASC will work together to identify genes and loci for susceptibility to ASDs and genes and loci that modify phenotypes related to ASDs, and work to assemble the resources to pursue these goals. Consortium members will have pre-publication access to results generated by the ASC, and can participate in the design of experiments to achieve the goals of the consortium. To encourage participants to contribute access to samples and pre-publication data, it is important that all members of the consortium agree to freely contribute resources to the effort.

- A. **Membership eligibility.** There are a number of paths to becoming a member of the ASC, and they are detailed below.
 - a. **Data.** Investigators that contribute a minimum number of case and/or control samples with large-scale sequencing and phenotype data to the consortium (currently defined as 100 exomes or genomes or targeted sequencing from at least 500 samples).
 - b. **DNA.** In addition, groups that can contribute DNA and phenotype information for at least 150 independent affected individuals (ideally with parents or other appropriate controls), to be analyzed by the ASC (via genotyping, sequencing or other molecular approaches), are eligible for membership.
 - c. **Specialty Researchers.** Committees can identify a small number of researchers (up to three) whose expertise is crucial to the work of the ASC and is not otherwise represented in the ASC. These researchers will be eligible for ASC membership without contributing data or DNA.

- B. Data sharing.** Members agree to make raw sequencing data from ASD and/or control samples available to the group for joint analyses and for replication studies. The mechanism of sample sharing will be planned by the ASC in compliance with local human subjects Institutional Review Board (IRB) constraints.
- C. Individual data/resources versus ASC data/resources.** Membership in the ASC does not preclude members from using their own samples and their own data for their own publication and analyses. However, data generated or developed by and results produced by the consortium will be published as a group by the ASC.
- D. New members.** Membership requests will be submitted to the Membership and Authorship Committee. Potential new members should submit the following: **1)** A letter indicating agreement with the MOU; **2)** A description of samples, sequence files and phenotype data available for sharing with the consortium; **3)** A description of completed or planned sequence-based studies that will be available for joint analysis; **4)** A list of investigators at the site who are part of the team joining the consortium.

III. ASC Associate Membership.

The ASC recognizes that organizations from private industry have samples and/or data that could be valuable to the activities of the Consortium. While the ASC welcomes the contribution of these resources to Consortium projects, the ASC is unable to offer regular membership to these organizations because this would pose serious and, in some cases, irreconcilable IRB and contractual issues with several of the academic affiliates of the ASC. Therefore, the ASC proposes to offer **Associate Membership** to groups from private industry who are willing to contribute sample and/or data to the ASC. Like regular members, associate members will be invited to participate in ASC conference calls and meetings, and have pre-publication access to results generated by the ASC. Associate members will also agree to the commitments of all ASC members. However, associate members will not have access to samples or raw data except their own.

IV. Provisional Membership.

The ASC offers **Provisional Membership** for investigators who are not able (at a given time) to meet the requirements for Full ASC Membership as detailed here. Provisional Members are welcome to participate in conference calls but cannot access ASC data, and would not be authors on ASC publications. Provisional Members become Full Members immediately upon fulfilling all requirements.

V. Plans for Analyses.

For maximum credibility and to advance the field, it is important for ASC to publish its main results quickly. Since there is still lack of agreement among experts as to the most appropriate analytic method, it is also important to let the individual research teams with their specific expertise address analytic problems in a new and creative manner. This document tries to steer a compromise course between tightly controlling the analyses *versus* allowing the creativity of the individual research teams to have full rein with the data accessed through the consortium.

- A. Primary Analyses.** The initial analysis of combining large-scale sequencing studies evaluating case *versus* control status will be headed by the Statistical Analysis

Committee with input from all ASC members. This analysis will lead to an initial publication and the design of additional studies undertaken by the ASC.

- B. Secondary Analyses.** One goal of the ASC is to make maximum use of the creativity and expertise of the individual research groups. These groups have all used different methods of statistical analysis to deal with issues such as mapping, variant calling, sample matching, choice of contrast groups, phenotypic heterogeneity, quantitative trait loci (QTLs), and even gene-gene and gene-environment interactions. Individual groups who contributed to the dataset will have access to the entire dataset to carry out analytic procedures. However, to make sure that there is no overlap in publications or presentations at scientific meetings arising from the collaboration, the individual groups should submit their analytic plans to both the Statistical Analysis Committee and the Coordinating Committee.
- C. Conflict Resolution.** If there is any conflict between the Statistical Analysis Committee and the individual group over the appropriateness of an analytic plan, the Coordinating Committee may call on outside expertise to help resolve the matter including an External Advisory Committee. The final decision of the Coordinating Committee will be final.
- D. Analysis on one's own data set.** Individual groups are free to carry out any analytic plan without the approval of the Coordinating Committee or the Statistical Analysis Committee if they are using data generated by them on their own samples. However, in the case of use of data collected/generated by the ASC, the analyses will be directed by the ASC. For studies not being carried out by the ASC, the individual groups should submit their analytic plans to the Statistical Analysis and Coordinating Committees, as above.

VI. Consortium Structure

- A. Executive Committee.** The Executive Committee is responsible for guiding the ASC in research, strategy, and funding decisions.
- B. Membership/Authorship Committee.** This committee is tasked with keeping track of all ASC members and conducting regular reviews to ensure that all members are compliant with membership regulations. This group conducts at least one membership review per year. They also manage authorship decisions on a case-by-case basis. At this time, authorship on an ASC manuscript is defined by having made an intellectual contribution. The ASC manuscript structure document details authorship guidelines further.
- C. Statistical Analysis Committee.** This group is responsible for the primary analysis of the data, database maintenance, and distribution of results. Proposals for analysis of ASC data will be submitted to this committee and recommendations passed to the Coordinating Committee for discussion and final decisions.
- D. Samples/Phenotypes Committee.** This committee will coordinate sample lists to minimize unwanted overlap, will assess phenotype data, and will ultimately take a lead in genotype-phenotype correlations.

- E. Coordinating Committee.** This committee is composed of the signing PI from each group. Members of this committee will be on the recurrent phone calls, participate in sub-committees, and represent their site to the ASC.

- F. Sub-committees and working groups.** Sub-committees and working groups (ad hoc or otherwise) will be added as the work progresses. Individual Committees, with the approval of the Coordinating Committee and Executive Committee, will at times designate sub-committees or working groups. This might include, for example, a writing committee. The Executive Committee and Coordinating Committee can also convene a sub-committee or working group around a certain topic, which would be charged with making recommendations back to the Executive and Coordinating Committees.

Acknowledgements: Adapted by the ASC from a document provided by Peter Szatmari that was further modified by Jerry Schellenberg.

As a member of the Autism Sequencing Consortium, I agree to the above Memorandum of Understanding.

ASC Signing PI

Name: _____
(print)

(signature)

Date: _____

Title: _____

Institution: _____

Address: _____

