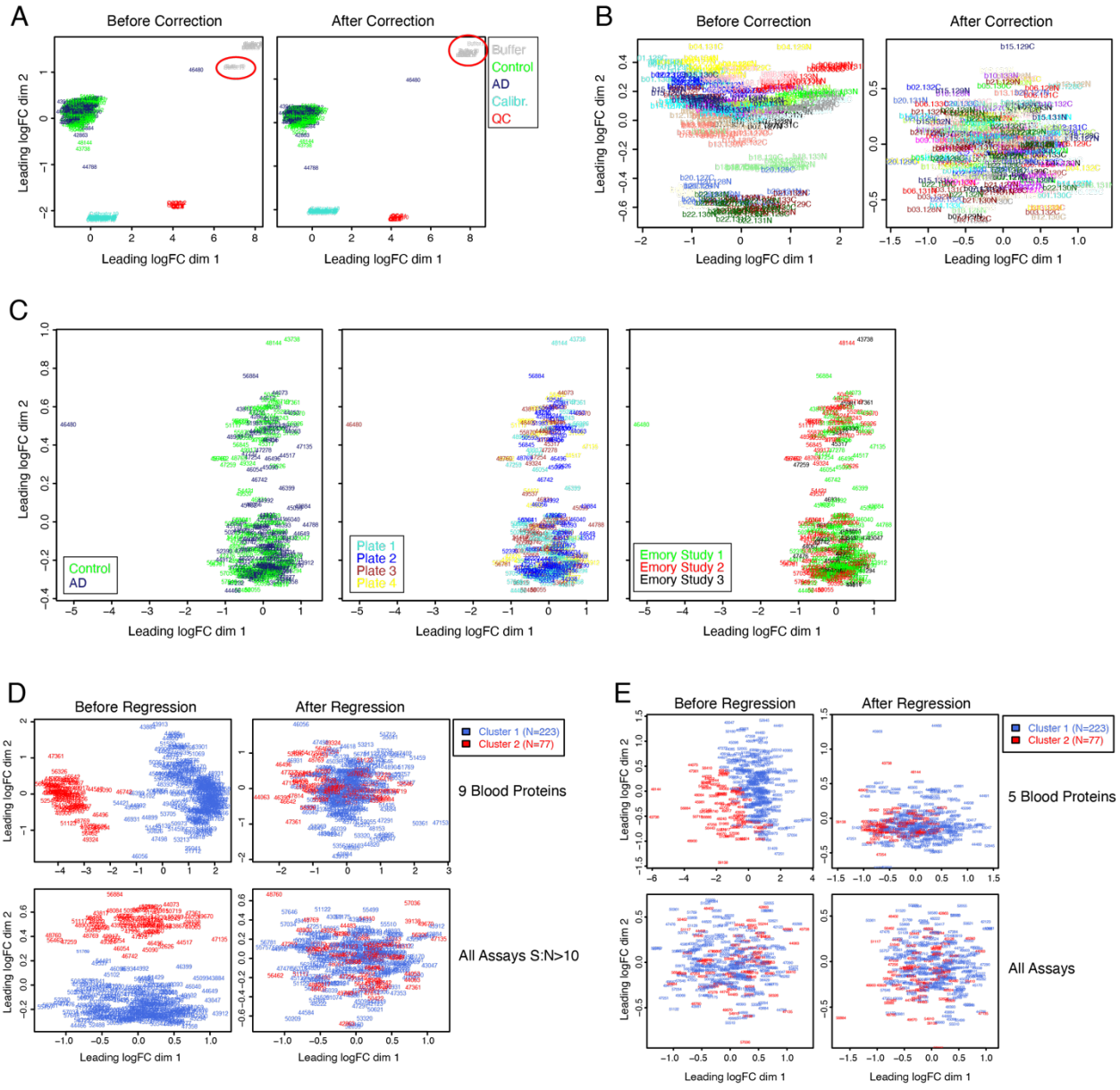
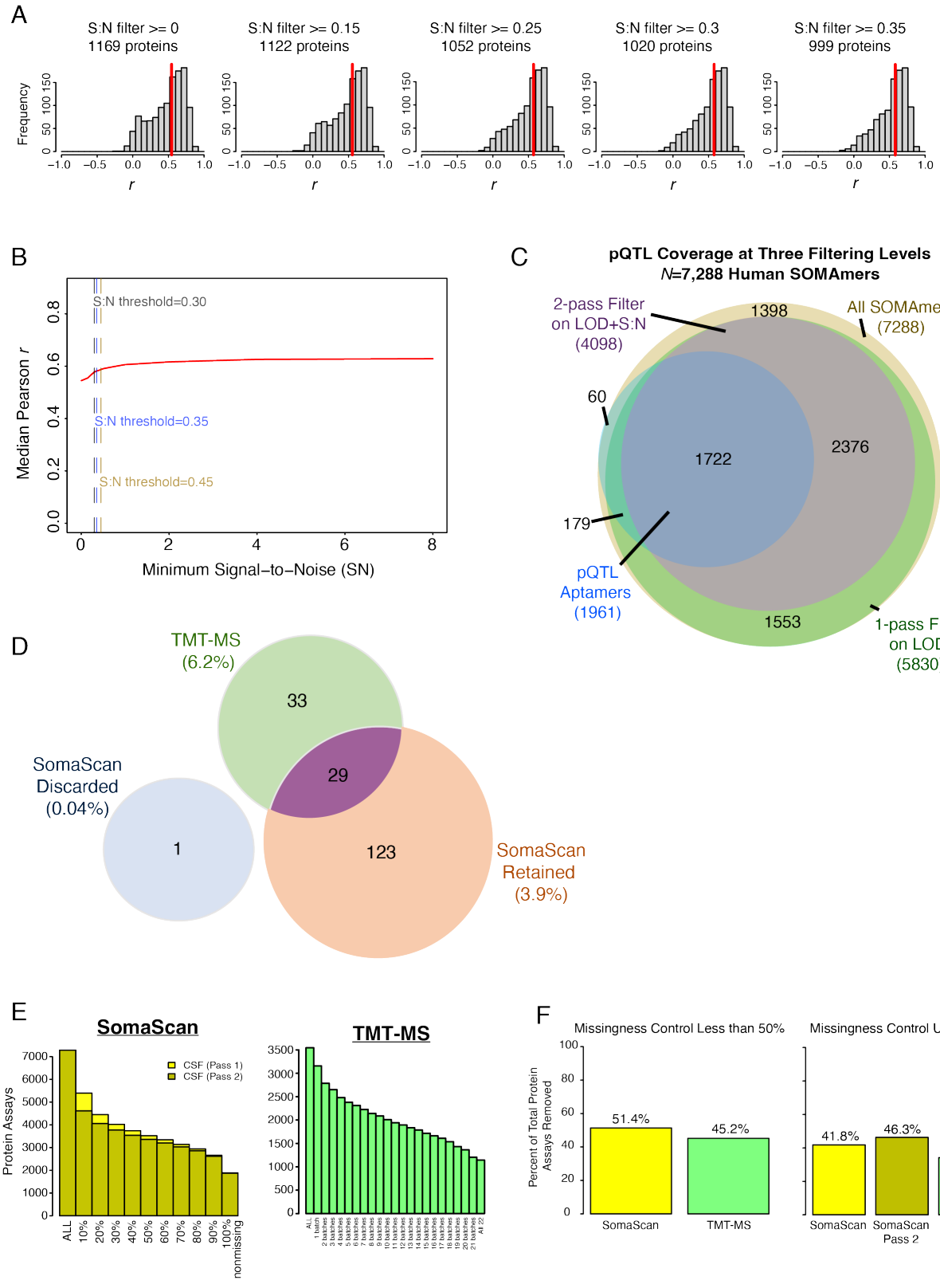
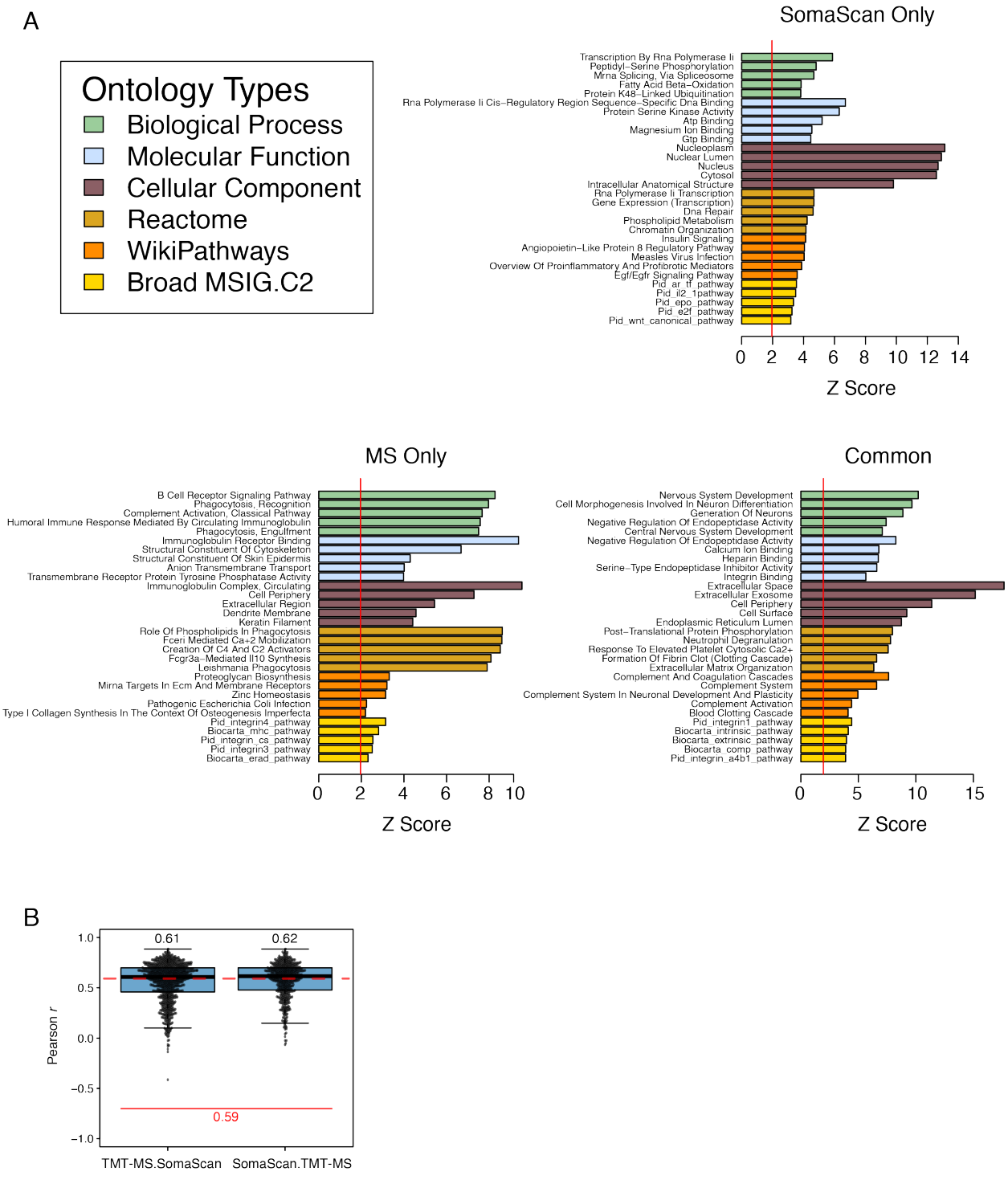


Supplementary Figure 1. Correction of Batch Effects and Nuisance Variance. (A) Multi-dimensional scaling (MDS) analysis of the SomaScan data including experimental samples, buffer samples, calibrator samples, and QC samples (*N*=344 samples, 7596 assays). Plates with significantly different background buffer signal are circled in red (left). MDS analysis of SomaScan data after median buffer background signal difference correction in the outlier plates (right). (B) MDS analysis of TMT-MS data before batch correction (left) and after batch correction using the global internal standard (right). (C) MDS analysis of SomaScan data

filtering on only high signal-to-noise (S:N greater than 10 after background subtraction, *n*=1119) proteins and coloring samples by diagnostic status (left), the plate on which they were analyzed (middle), or the Emory study from which they were obtained (right). (D) MDS analysis of SomaScan data for a 9-blood protein signature (top) or all proteins with S:N greater than 10 (bottom) before (left) and after (right) regression of the data on the 9-blood protein eigenprotein. (E) MDS analysis of TMT-MS data for a 5-blood protein signature (top) or all proteins (bottom) before (left) and after (right) regression of the data on the 5-blood protein eigenprotein.



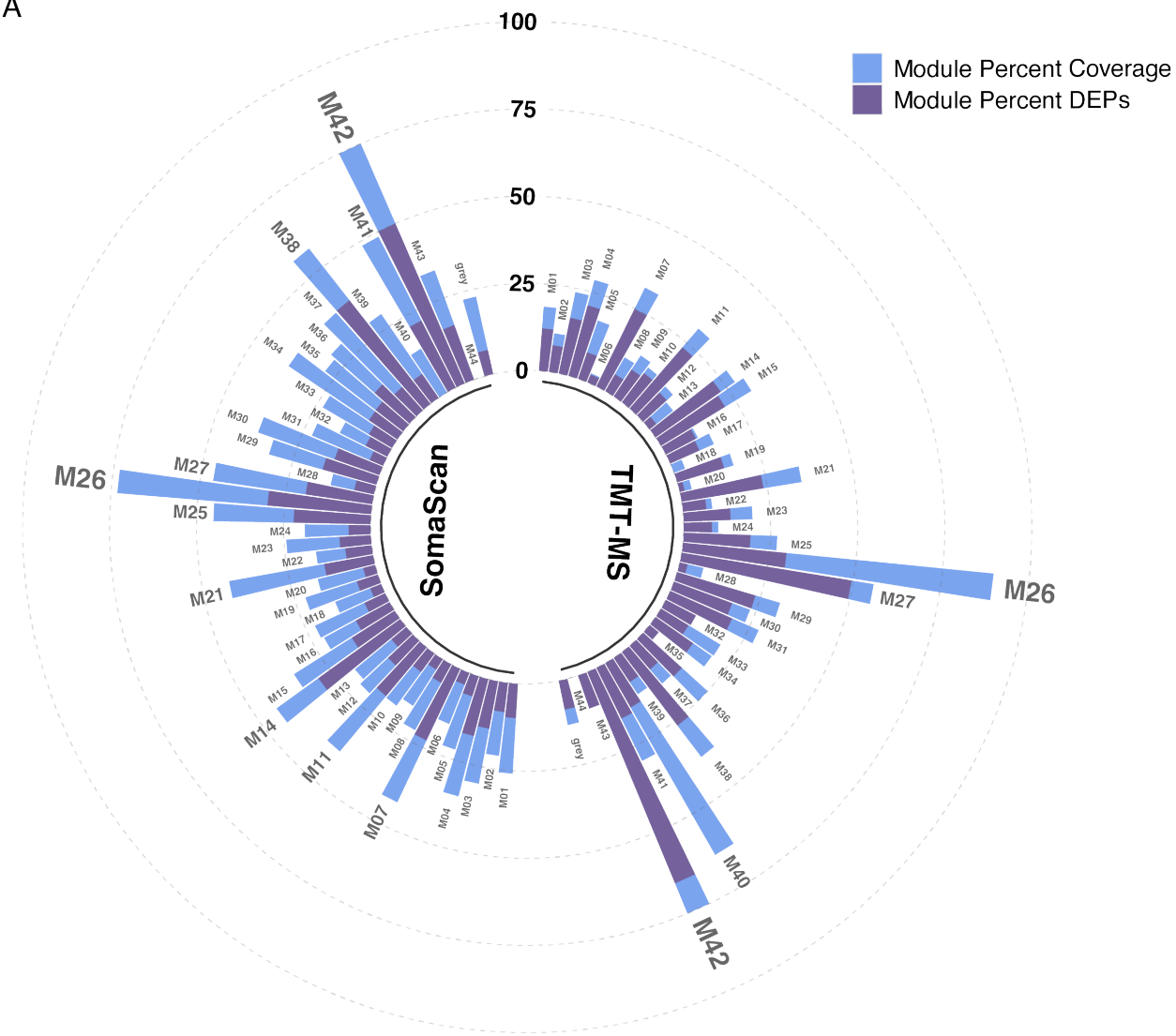
Supplementary Figure 2. Signal-to-Noise and Missingness Control. (A-C) Signal-to-noise (S:N) filtering. (A) Correlation distributions between SomaScan and TMT-MS at different S:N thresholds applied to the SomaScan data. The number of proteins used for correlation are provided in each plot, with a threshold of at least 75 observations required for correlation. The red vertical line indicates the median correlation. (B) Median correlation across different S:N thresholds applied to the SomaScan data. The vertical dashed lines indicate S:N thresholds of 0.3, 0.35, and 0.45. (C) Overlap of CSF protein quantitative trait loci (pQTLs) with SOMAmers at different levels of filtering. 1722 out of 1961 SOMAmers with pQTLs (88%) were retained after filtering the data on limit of detection (LOD) and S:N greater than 0.3, which resulted in the removal of 44% of the SomaScan assays from further analyses. If multiple SOMAmers to the same gene symbol had pQTLs, only one SOMAmer was counted in the analysis. (D) Number of CSF proteins with pQTLs by platform. For SomaScan, counts are separated by SOMAmers that were retained versus discarded after filtering on LOD and S:N thresholds. The percentage of pQTLs out of the total number of proteins tested in each group is provided. For TMT-MS, only proteins with no missing values were considered in the analysis. Further information is provided in **Supplementary Table 3**. (E, F) Missingness control. (E) The number of protein assays at different levels of missingness in SomaScan (left) and TMT-MS (right) across 300 CSF samples. The number of SomaScan assays at different levels of missingness is given for filtering only on LOD (Pass 1) and filtering on both LOD and S:N thresholds (Pass 2). (F) The percent of assays removed in SomaScan and TMT-MS data when controlling for missingness at 50% (left) and 75% (right).



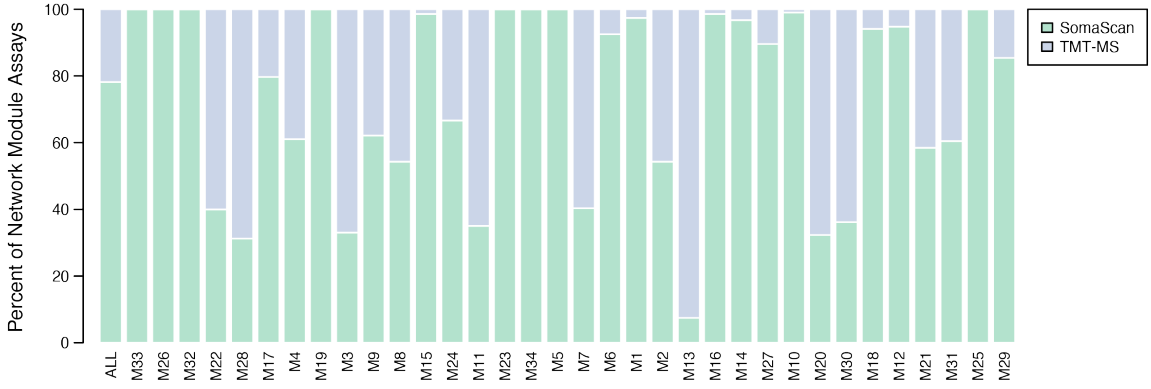
Supplementary Figure 3. Ontology Analysis and Cross-Platform Correlation. (A) Ontology analysis corresponding to the Venn diagram in **Figure 2A**. The vertical red line indicates significant enrichment at a *z* score of 1.96. Broad MSIG.C2, Broad Institute Molecular Signatures C2 database. (B) Cross-platform correlation after filtering for significantly

differentially abundant proteins in either TMT-MS or SomaScan platforms. The horizontal dashed red line indicated the median correlation without filtering on differentially abundant proteins in either platform. The median correlation did not significantly increase when filtering on differentially abundant proteins in TMT-MS prior to correlation (TMT-MS.SomaScan) or in SomaScan prior to correlation (SomaScan.TMT-MS).

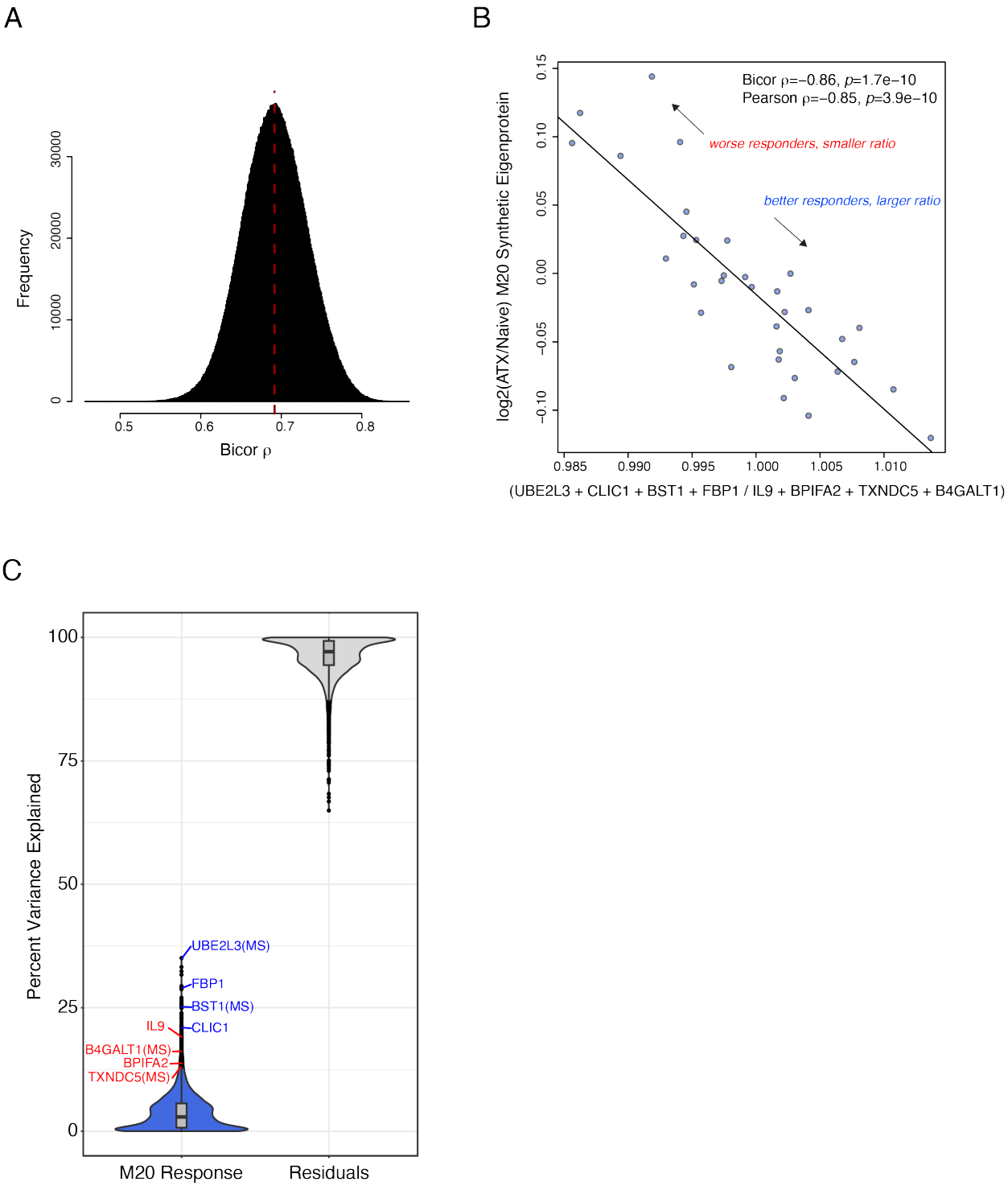
A



B

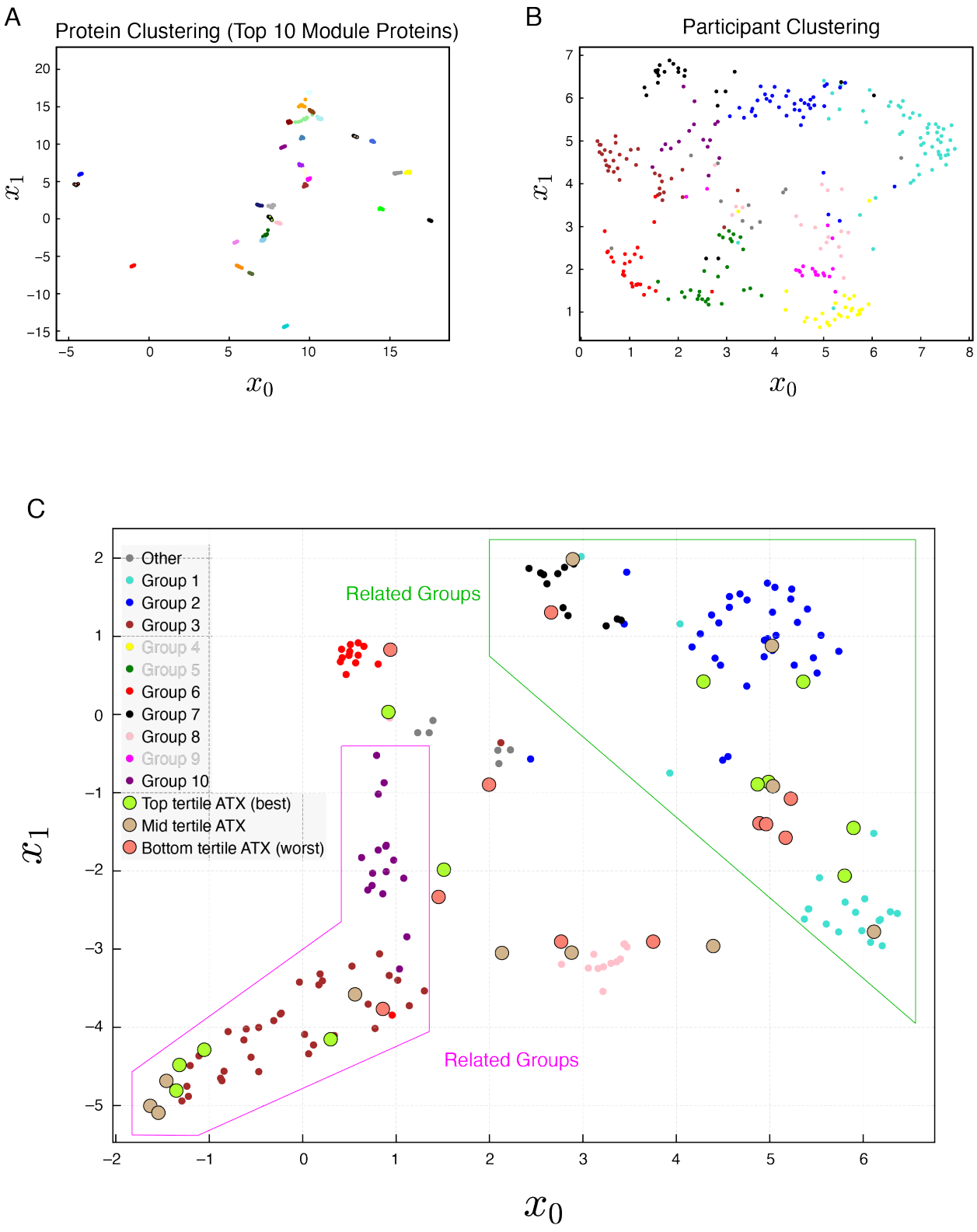


Supplementary Figure 4. AD Brain Network Module Coverage and Network Module Platform Composition. (A) Module percent coverage of a previously described AD brain protein network(*2*) by SomaScan and TMT-MS platforms, including coverage of proteins that show significant changes in abundance in AD within each module. (B) Percent of assays in each CSF network module from SomaScan or TMT-MS measurements.



Supplementary Figure 5. Prediction of ATX Response Using a Protein Ratio. (A) Possible combinations of a four-protein ratio in ATX naïve individuals in which the numerator contained four proteins positively correlated with M20 response and the denominator contained four

proteins negatively correlated with M20 response were tested for correlation with the log2(ATX/naïve) M20 synthetic eigenprotein. Distribution of correlations with M20 response is shown. Red vertical line indicates the median correlation. (B) Correlation for the ratio able to best predict M20 response (*n*=34). One outlier is excluded from visualization. UBE2L3, ubiquitin-conjugating enzyme E2 L3; CLIC1, chloride intracellular channel protein 1; BST1, ADP-ribosyl cyclase/cyclic ADP-ribose hydrolase 2; FBP1, fructose-1,6-bisphosphatase 1; IL9, interleukin-9; BPIFA2, BPI fold-containing family A member 2; TXNDC5, thioredoxin domain-containing protein 5; B4GALT1, beta-1,4-galactosyltransferase 1. (C) Variance partition on the M20 response illustrating that all the proteins in the ratio had strong covariance with the log2(ATX/naïve) M20 synthetic eigenprotein (M20 response; blue, positive correlation; red, negative correlation; MS, mass spectrometry measurement).



Supplementary Figure 6. Multi-dimensional Data Reduction of Proteins and People. (A)

The top ten hub proteins from each network module were visualized in two-dimensional space

across participants by uniform manifold approximation and projection (UMAP). Points are colored by network module as defined by the weighted co-expression network algorithm (WGCNA) used to construct the co-expression network. (B) Participants were visualized in two-dimensional space across the top ten hub proteins from each network module by UMAP. Participants are colored based on their group as defined by WGCNA. (C) UMAP visualization of the ten participant groups as defined by WGCNA. Groups 4, 5, and 9 are excluded for clarity. The baseline CSF proteomes of individuals treated with ATX were divided into tertiles based on degree of ATX response and projected onto the groups. Green and magenta polygons highlight groups related in the hierarchical clustering network.