APPENDIX 1: METHODS

In spring 2014, representatives from seven NIH Institutes (National Institute of Neurological Disorders and Stroke, National Cancer Institute, National Center for Advancing Translational Sciences, National Heart, Lung, and Blood Institute, National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Mental Health, and Eunice Kennedy Shriver National Institute of Child Health and Human Development) along with the Department of Defense Tuberous Sclerosis Complex Research Program (DOD TSCRP) and the Tuberous Sclerosis Alliance formed a workshop organizing committee (Appendix 2) and recruited four co-Chairs to cover the following broad areas of TSC manifestations: (1) Molecular Pathways and Therapeutic Opportunities (chaired by Brendan Manning); (2) Growth and Tumor Biology (Elizabeth Henske); (3) Neurocognition (Mustafa Sahin); and (4) Epilepsy in TSC (Kevin Ess). In preparation for the workshop, the Chairs established and led four working groups in these areas, including 12-15 members in each group. Working Group (WG) members (Appendix 2) were recruited to ensure broad and diverse expertise in the topic area and included basic, translational and clinical scientists from both academia and industry along with representatives from the NIH, DOD TSCRP and TS Alliance. Prior to the workshop, each WG convened by multiple conference calls and email to discuss topic areas including progress, gaps/needs and opportunities in each area, and to develop a preliminary set of research recommendations and priorities for discussion at the workshop. Because the WGs deliberated independently of each other, Chairs met before the workshop to share their groups' recommendations, and to identify convergent themes and common research priorities across the WGs.

Importantly, the workshop organizers also felt that it was critical to learn directly from those affected by TSC and their caregivers what aspects of TSC had the greatest impact on their lives and, thus, should be a priority for research. The TS Alliance distributed an online survey in December 2014 to collect such input from the TSC community. The most common and the most problematic manifestations for most individuals with TSC were neurological and neurocognitive: epilepsy, learning and memory difficulties, behavioral or social issues, anxiety, and sleep problems. However, individuals and caregivers were also burdened by the presence of – or the high likelihood of developing – neoplastic lesions and tumors including renal angiomyolipomas (AML), lymphangioleiomyomatosis (LAM), angiofibromas and subependymal giant cell astrocytomas (SEGAs).

The March 2015 workshop consisted of summaries from the Chairs of the WG discussions including progress to date in the field, short talks from invited speakers and a series of breakout sessions to address and further refine the recommendations and shared priorities identified from the pre-meeting deliberations (Appendix 3: workshop agenda and list of meeting participants). From the integrated priorities of the WGs and from the patient and family survey, five major topic areas were identified which formed the central themes of the workshop deliberations; these priority areas included: 1) Understanding phenotypic heterogeneity in TSC; 2) Gaining a deeper knowledge of TSC signaling pathways and the cellular consequences of TSC deficiency; 3) Improving TSC disease models; 4) Developing clinical biomarkers for TSC; 5) Facilitating therapeutics and clinical trials research. The breakout sessions were tasked with developing a preliminary set of research recommendations for each of these areas, which were then deliberated by all workshop participants. The final 2015 Research Recommendations for TSC are presented in this manuscript.