

**Cognitive Behavioral Therapy and Tai Chi Reverse Cellular and Genomic Markers
of Inflammation in Late Life Insomnia: A Randomized Controlled Trial**

Supplemental Information

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Description of Subjects

Study participants, recruited by means of advertisements, were community-dwelling adults older than 55 years of age who fulfilled criteria for primary insomnia in *Diagnostic and Statistical Manual* (Fourth Edition, Text Revision [DSM-IV-TR]) (1) and for general insomnia in the *International Classification of Sleep Disorders* (Second Edition) (2). These criteria specify difficulty in initiating or maintaining sleep or non-restorative sleep for at least one month, along with significant distress and daytime impairment (3). DSM-5 revised the duration criteria from 1 to 3 months (4); we note that all participants also reported the presence of sleep difficulties ≥ 3 times per week for >3 months.

DSM-IV-TR exclusion criteria of medical and psychiatric disorders were applied along with exclusion for routine use (>2 times per week) of sedative hypnotic medications. Additional exclusion criteria were: 1) presence of another sleep disorder such as sleep apnea (apnea/hypopnea index >15), restless legs, or periodic limb movements (movement index with arousal $>15/h$) as determined by one night of polysomnography; 2) shift work, irregular sleep pattern, or delayed or advanced sleep phase as ascertained by daily diaries of sleep parameters for 2 weeks (i.e., Pittsburgh Sleep Diary); 3) regular (≥ 3 x week) use of hypnotic medications or alcohol for sleep (patients using prescribed or over-the-counter sleep medications <3 x week were enrolled after they withdrew from medications); 4) current diagnosis of major depression, unless treated and in remission; 5) cognitive impairment with score <23 on Mini-Mental Status Examination (5); 6) abnormal screening laboratory tests (i.e., complete blood count, liver function tests, thyroid function); 7) tobacco smoking; 8) body mass index >35 kg/m²; 9) debilitating condition that would impede full participation in the study; or 10) unavailability during the study period.

Description of Interventions

The cognitive behavior therapy for sleep quality (CBT) was a multicomponent (i.e., behavioral, cognitive, educational) intervention as previously described by Morin *et al.* (6), with modification to teach behavioral strategies for management of daytime activity levels and enhancement of mood. CBT was administered in groups of 7-10 subjects by two co-therapists, a licensed clinical psychologist and a Ph.D. level psychologist, each with specialty training in behavioral medicine. Using a manualized approach, each session dictated objectives, patient skills, and treatment activities, in which therapists provided direct role-playing and other skill-development exercises designed to increase patients' self-efficacy in managing their insomnia. CBT included five treatment modules: 1) *Biopsychosocial Model and Insomnia* provided sleep education and discussion of the role of biological, psychological, social, and behavioral factors that affect sleep, such as stress, cognitive arousal, poor sleep hygiene, and mood disturbance. 2) *Cognitive Restructuring and Sleep Disturbance* used cognitive restructuring principles to help patients identify maladaptive sleep cognitions, neutralize their effect, and facilitate more adaptive thinking about sleep and its importance, including training in other cognitive coping strategies such as relaxing self-talk, imagery, and distraction methods (e.g., repetition of a calming phrase, thought). 3) *Stimulus Control* targeted sleep behavior directly by instructing patients to go to bed only when sleepy; use the bed only for sleep and sexual activity and not other behaviors that compete with sleep; leave the bedroom after being unable to fall asleep within 20 minutes; repeat this process as often as necessary either before falling asleep or after awakening from sleep; and establish and adhere to a fixed time of arising each morning. The sleep restriction component was not emphasized, as shortened sleep duration may confound measures of inflammation. For example, Vgontzas *et al.* found that insomnia with short sleep duration is associated with increases in inflammation (7,8). 4) *Mood Enhancement* assisted patients in developing behavioral goals in areas where sleep has disrupted their functioning and mood (e.g., work, social, physical activity), with the use of self-rewards (e.g., leisure, resting,

relaxation), scheduling of pleasant events and mental exercises to increase awareness of positive emotional states. Whereas incorporation of this mood module expanded, theoretically and pragmatically, the scope of traditional CBT for insomnia (6), this module was very compatible with the behavioral approach to insomnia as it was designed to promote understanding of the reciprocal relationship between sleep and mood, and how to implement strategies to improve mood either as a consequence of poor sleep or as a determinant of sleep disturbance. Additionally, incorporation of this module was done in an integrated manner throughout the protocol. 5) *Skill Consolidation and Adherence* was devoted to the development of individual treatment plans for follow-up, including performance of skills, and relapse prevention training methods (9) to help patients cope with situations that have contributed to poor sleep disturbance or that have interfered with the implementation of the insomnia management protocol.

Tai Chi Chih (TCC) is also a multicomponent intervention that integrates physical, psychosocial, emotion, spiritual, and behavioral elements to target arousal mechanisms that are thought to contribute to insomnia (10-12). Because of its mind-body and “meditation through movement” attributes, TCC was well-suited to help older adults cope with fatigue, perceived physical limitations, and negative emotional states, which are commonly associated with insomnia. In contrast with CBT, TCC did not address cognitive activity underlying appraisals of disordered sleep, but instead emphasized control over physical function and arousal-related responsiveness through the performance of repetitious, nonstrenuous, slow-paced movement. TCC was administered in groups of 7-10 subjects master's level instructor who had undergone certification by the national TCC association. Using a manualized approach (13), each session provided objectives and learning activities related to sequentially learning a specific set of 20 exercises with verification of skills attainment weekly. The first 8 weeks emphasized mastery of single forms through multiple repetitions in class and at home; latter weeks focused on class consolidation of daily practice routines with natural breathing integrated into all sessions. Diary

assessments were administered to assess frequency and duration of practice between sessions and at follow-up.

Sleep Seminar (SS) was an educational intervention that provided health information related to the physical, medical, and psychosocial factors that contribute to sleep problems in aging with an emphasis on sleep education and sleep hygiene practices. SS delivered some content (i.e., sleep hygiene principles) similar to that of CBT, but in contrast to CBT, SS simply provided educational information without discussion of how these practices might be used to change sleep-wake behaviors. Educational topics included during the 16 weeks were the following: 1) Sleep in late-life including discussion of changes in sleep with aging and misperceptions about sleep duration; 2) What is insomnia, including a review of the definition of insomnia, prevalence, discussion of potential causes of insomnia, and how the sleep diary can be used to evaluate insomnia; 3) Sleep basics including the sleep cycle and stages of sleep including the role of polysomnography in the evaluation of sleep; 4) Review of how sleep changes with age, and how these changes are different than insomnia with consideration of the association between sleep and medical comorbidities; 5) Other sleep disorders and sleep problems that are not insomnia, and how to assess whether they are present including sleep apnea, restless legs syndrome, and parasomnias; 6) Impact of insomnia on health including health functioning, accidents rates, and mood problems (session included discussion of the relationship between insomnia and inflammation and cardiovascular disease risk); 7) Traditional treatment for insomnia with review of medication, non-pharmacologic therapies, and role of sleep hygiene; 8) Sleep hygiene with focus on the use of alcohol, tobacco, certain non-prescription medications, and exercise; 9) Sleep hygiene II including review of age related sleep patterns, bedtime rituals, napping, and behaviors that are not compatible with good sleep such as TV watching in bed; 10) Sleep hygiene III with focus on sleep-wake principles such as the use of regular bedtime, and the impact of the environment such as light, temperature, and noise on sleep; 11) Managing daytime stress with review of certain stress management skills such as

progressive muscle relaxation (without instruction), time management, problem solving; 12) Managing daytime stress II with presentation of the impact of the stress on certain disease risk including associations between stress and insomnia, depression and cardiovascular disease; 13) Nutrition and health aging, and relation to sleep with review of the relationships between alcohol, caffeine use, and tobacco smoking and sleep; 14) Exercise and healthy aging with focus on the relationship between aerobic fitness and sleep; and the impact of exercise on sleep patterns as related to sleep hygiene practices; 15) How to get medical help including discussion of how to talk to your physician and access wellness educational resources; 16) Review of major topics discussed with directive question and answer session.

SS was administered in groups of 7-10 subjects as didactic presentations by physicians or licensed clinical psychologists as previously described (14), followed by group discussion and self-help quizzes to assess patient learning. SS served as a control for nonspecific treatment elements such as attention, expectation for improvement, and group support that pose rival explanations for the effectiveness of CBT and TCC. As in CBT and TCC, homework was prescribed to include reading of educational materials that expanded on session information.

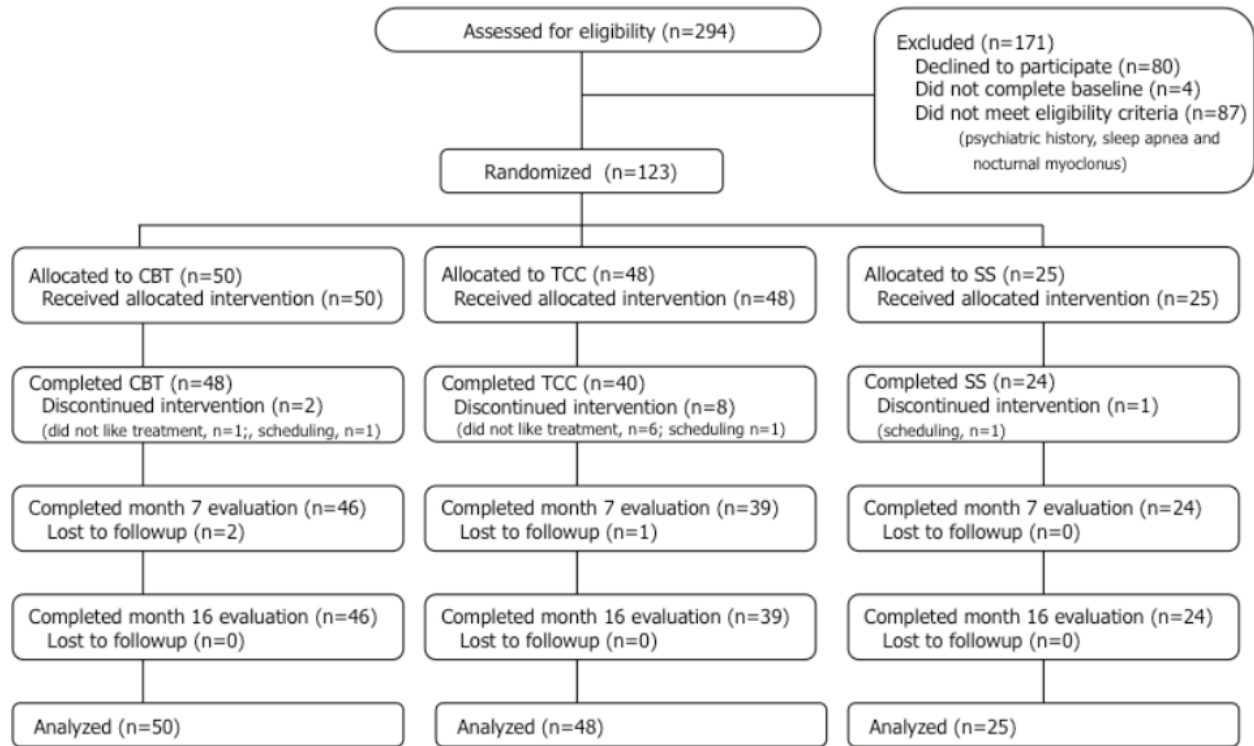


Figure S1. Screening, Randomization, and Completion of Post-Intervention, 7-Month, and 16-Month Evaluations.

Table S1. Genes differentially expressed in CBT-I vs SS Control.

Gene Symbol	Mean SS	Mean CBT-I	Difference	Fold
<i>Up-regulated</i>				
<i>PF4V1</i>	8.529	9.174	0.645	1.56
<i>DEFA3</i>	9.875	10.466	0.591	1.51
<i>DEFA1B</i>	9.670	10.260	0.589	1.51
<i>IPO8</i>	8.167	8.751	0.583	1.50
<i>LOC647450</i>	10.394	10.954	0.560	1.47
<i>DEFA1</i>	10.671	11.228	0.557	1.47
<i>FCRLA</i>	9.569	10.123	0.554	1.47
<i>LOC649923</i>	8.071	8.620	0.549	1.46
<i>LOC651751</i>	8.765	9.307	0.542	1.46
<i>LOC647506</i>	9.761	10.300	0.539	1.45
<i>MYOM2</i>	8.670	9.207	0.537	1.45
<i>TCL1A</i>	8.161	8.692	0.532	1.45
<i>VPREB3</i>	8.308	8.840	0.532	1.45
<i>CD27</i>	9.875	10.401	0.526	1.44
<i>GIMAP4</i>	11.660	12.186	0.526	1.44
<i>LOC652493</i>	10.768	11.284	0.517	1.43
<i>CNTNAP2</i>	7.680	8.191	0.511	1.43
<i>SAMD9L</i>	9.073	9.582	0.508	1.42
<i>LOC113386</i>	8.121	8.626	0.506	1.42
<i>RBPM2</i>	8.176	8.681	0.505	1.42
<i>HLA-DOB</i>	8.545	9.045	0.501	1.42
<i>LOC653600</i>	8.258	8.758	0.501	1.42
<i>LOC649210</i>	7.445	7.934	0.489	1.40
<i>LOC650263</i>	7.803	8.279	0.476	1.39
<i>GIMAP5</i>	10.208	10.682	0.474	1.39
<i>LOC652694</i>	9.465	9.930	0.465	1.38
<i>SUSD3</i>	9.232	9.691	0.459	1.37
<i>LOC642113</i>	10.903	11.357	0.454	1.37
<i>PRAGMIN</i>	8.850	9.304	0.454	1.37
<i>IGJ</i>	10.128	10.573	0.446	1.36
<i>CD24</i>	7.833	8.278	0.445	1.36

Gene Symbol	Mean SS	Mean CBT-I	Difference	Fold
<i>ISG15</i>	10.055	10.491	0.436	1.35
<i>IGLL1</i>	10.671	11.103	0.432	1.35
<i>ELANE</i>	7.955	8.381	0.426	1.34
<i>CD79B</i>	10.344	10.769	0.425	1.34
<i>TNFSF10</i>	10.034	10.457	0.423	1.34
<i>XAF1</i>	9.702	10.121	0.419	1.34
<i>FAM113B</i>	10.889	11.306	0.416	1.33
<i>PAQR8</i>	8.054	8.469	0.415	1.33
<i>DCAF7</i>	9.437	9.851	0.413	1.33
<i>CX3CR1</i>	10.346	10.758	0.412	1.33
<i>SNORD13</i>	10.701	11.107	0.407	1.33
<i>MIR1974</i>	12.316	12.721	0.404	1.32
<i>MPL</i>	8.886	9.289	0.404	1.32
<i>CAMP</i>	7.881	8.280	0.399	1.32
<i>TREML1</i>	8.723	9.120	0.397	1.32
<i>GAPT</i>	9.009	9.406	0.396	1.32
<i>HLA-DQA1</i>	11.616	12.011	0.395	1.32
<i>DKFZp761P0423</i>	8.288	8.681	0.393	1.31
<i>CTDSPL</i>	8.633	9.024	0.392	1.31
<i>LOC253039</i>	7.966	8.357	0.392	1.31
<i>LOC731682</i>	7.889	8.278	0.389	1.31
<i>SNORA12</i>	10.026	10.412	0.386	1.31
<i>OAS2</i>	9.211	9.591	0.381	1.30
<i>GIMAP8</i>	9.851	10.231	0.380	1.30
<i>MYL9</i>	7.906	8.281	0.375	1.30
<i>C9orf69</i>	8.888	9.260	0.372	1.30
<i>VPS35</i>	9.187	9.560	0.372	1.30
<i>RBM14</i>	9.960	10.330	0.370	1.29
<i>TRAF3IP3</i>	9.942	10.310	0.368	1.29
<i>GIMAP7</i>	10.799	11.165	0.366	1.29
<i>MNDA</i>	10.904	11.267	0.363	1.29
<i>LOC100133678</i>	12.133	12.494	0.360	1.28
<i>PVALB</i>	8.084	8.441	0.357	1.28
<i>SLAMF6</i>	10.092	10.449	0.357	1.28

Gene Symbol	Mean SS	Mean CBT-I	Difference	Fold
<i>LDLRAP1</i>	8.413	8.767	0.355	1.28
<i>DEFA4</i>	7.497	7.851	0.354	1.28
<i>DENND2D</i>	9.472	9.824	0.351	1.28
<i>LCN2</i>	9.497	9.848	0.351	1.28
<i>FAIM3</i>	11.568	11.917	0.349	1.27
<i>C2orf89</i>	9.440	9.789	0.349	1.27
<i>HIST1H2AC</i>	10.268	10.617	0.348	1.27
<i>SH3BGRL2</i>	9.799	10.146	0.347	1.27
<i>SEPT5</i>	11.627	11.973	0.347	1.27
<i>CLDN5</i>	8.222	8.569	0.347	1.27
<i>OAS1</i>	8.570	8.916	0.346	1.27
<i>METTL13</i>	8.007	8.352	0.345	1.27
<i>KIAA0907</i>	8.880	9.224	0.345	1.27
<i>GP9</i>	10.918	11.260	0.342	1.27
<i>TCN1</i>	8.063	8.405	0.342	1.27
<i>TMEM140</i>	9.013	9.355	0.342	1.27
<i>GIMAP6</i>	9.258	9.596	0.337	1.26
<i>LOC205251</i>	8.962	9.299	0.337	1.26
<i>LPAR5</i>	8.315	8.651	0.336	1.26
<i>STK38</i>	10.296	10.632	0.336	1.26
<i>SPSB2</i>	7.812	8.148	0.336	1.26
<i>C16orf30</i>	8.334	8.669	0.335	1.26
<i>TSPAN9</i>	8.955	9.289	0.334	1.26
<i>LRRN3</i>	8.084	8.418	0.334	1.26
<i>APOBEC3G</i>	10.023	10.355	0.332	1.26
<i>CD19</i>	9.090	9.421	0.332	1.26
<i>LOC148413</i>	9.089	9.419	0.330	1.26
<i>PLAC8</i>	11.641	11.971	0.330	1.26
<i>PI16</i>	7.762	8.091	0.329	1.26
<i>ST6GAL1</i>	9.523	9.852	0.329	1.26
<i>MYC</i>	10.363	10.690	0.328	1.26
<i>C6orf105</i>	8.235	8.561	0.326	1.25
<i>EVL</i>	12.805	13.130	0.325	1.25
<i>IFIT1</i>	8.037	8.363	0.325	1.25

Gene Symbol	Mean SS	Mean CBT-I	Difference	Fold
<i>KLRAQ1</i>	8.770	9.095	0.325	1.25
<i>ITGA2B</i>	8.865	9.186	0.321	1.25
<i>CCDC128</i>	8.603	8.921	0.319	1.25
<i>ZNF512</i>	9.459	9.777	0.319	1.25
<i>PARP4</i>	11.096	11.414	0.318	1.25
<i>PARP1</i>	10.479	10.796	0.316	1.25
<i>SELL</i>	11.783	12.100	0.316	1.25
<i>IL8RBP</i>	8.412	8.728	0.316	1.25
<i>MX1</i>	11.205	11.519	0.314	1.24
<i>GSTM3</i>	7.601	7.914	0.313	1.24
<i>GVIN1</i>	10.345	10.657	0.312	1.24
<i>LACTB2</i>	8.124	8.436	0.312	1.24
<i>M6PR</i>	10.527	10.838	0.310	1.24
<i>C14orf173</i>	9.671	9.980	0.309	1.24
<i>SLC40A1</i>	8.996	9.305	0.309	1.24
<i>LOC650761</i>	7.660	7.968	0.309	1.24
<i>EPSTI1</i>	9.645	9.954	0.309	1.24
<i>ITM2C</i>	9.504	9.810	0.306	1.24
<i>IFNAR1</i>	8.498	8.803	0.306	1.24
<i>RNASE3</i>	7.345	7.650	0.305	1.24
<i>LARP4B</i>	9.798	10.102	0.305	1.24
<i>ESAM</i>	8.717	9.022	0.304	1.24
<i>VSTM1</i>	8.161	8.465	0.304	1.23
<i>ESYT1</i>	11.152	11.455	0.303	1.23
<i>AARS</i>	9.927	10.228	0.301	1.23
<i>GNG11</i>	11.998	12.299	0.301	1.23
<i>NRGN</i>	12.158	12.456	0.299	1.23
<i>C6orf125</i>	8.807	9.105	0.299	1.23
<i>ICAM2</i>	10.970	11.269	0.299	1.23
<i>TMEM204</i>	8.481	8.778	0.298	1.23
<i>GBP4</i>	10.095	10.392	0.297	1.23
<i>SIRPG</i>	7.979	8.276	0.297	1.23
<i>LOC90925</i>	8.086	8.382	0.296	1.23
<i>IFI44L</i>	9.009	9.304	0.295	1.23

Gene Symbol	Mean SS	Mean CBT-I	Difference	Fold
<i>STMN3</i>	11.570	11.865	0.295	1.23
<i>C8orf55</i>	9.078	9.371	0.293	1.23
<i>TTC15</i>	9.282	9.574	0.293	1.23
<i>C10orf6</i>	8.495	8.788	0.292	1.23
<i>MFSD3</i>	8.264	8.556	0.292	1.22
<i>TNNC2</i>	7.697	7.989	0.292	1.22
<i>SDAD1</i>	10.290	10.581	0.291	1.22
<i>LTF</i>	7.451	7.742	0.291	1.22
<i>NQO2</i>	8.536	8.827	0.291	1.22
<i>C11orf48</i>	9.107	9.395	0.288	1.22
<i>HLA-DRB1</i>	9.240	9.528	0.288	1.22
<i>NOSIP</i>	12.082	12.369	0.287	1.22
<i>LPXN</i>	11.519	11.806	0.287	1.22
<i>UBAP2L</i>	9.461	9.743	0.282	1.22
<i>SERPINE2</i>	7.980	8.262	0.282	1.22
<i>LOC100130633</i>	8.541	8.822	0.281	1.22
<i>DDX60</i>	8.496	8.777	0.281	1.22
<i>ZFYVE26</i>	8.301	8.581	0.280	1.21
<i>C1orf149</i>	7.702	7.981	0.279	1.21
<i>GPBAR1</i>	9.674	9.953	0.279	1.21
<i>TNFRSF17</i>	7.410	7.688	0.279	1.21
<i>VWF</i>	8.105	8.384	0.279	1.21
<i>MGC15763</i>	8.981	9.260	0.278	1.21
<i>CTSG</i>	7.628	7.906	0.278	1.21
<i>RPUSD3</i>	8.902	9.180	0.278	1.21
<i>ACTN1</i>	10.086	10.364	0.278	1.21
<i>COQ9</i>	8.803	9.080	0.277	1.21
<i>CTTN</i>	8.431	8.708	0.277	1.21
<i>PVRIG</i>	9.544	9.821	0.277	1.21
<i>SLC35A5</i>	8.967	9.244	0.277	1.21
<i>TNFAIP8L2</i>	7.405	7.681	0.276	1.21
<i>C17orf62</i>	9.709	9.985	0.276	1.21
<i>LOC652102</i>	7.524	7.800	0.276	1.21
<i>PCMT1</i>	10.849	11.123	0.275	1.21

Gene Symbol	Mean SS	Mean CBT-I	Difference	Fold
<i>ALDH18A1</i>	8.146	8.420	0.274	1.21
<i>CDK2AP2</i>	8.175	8.448	0.273	1.21
<i>UFSP2</i>	8.753	9.026	0.273	1.21
<i>KIFC3</i>	8.220	8.492	0.272	1.21
<i>ALOX12</i>	8.296	8.566	0.271	1.21
<i>MGC29506</i>	8.362	8.632	0.270	1.21
<i>VCL</i>	10.892	11.162	0.270	1.21
<i>NDUFAF3</i>	10.144	10.413	0.269	1.21
<i>LOC642755</i>	9.578	9.846	0.269	1.21
<i>PDE3B</i>	8.599	8.868	0.269	1.21
<i>ZNF470</i>	7.365	7.633	0.268	1.20
<i>CD1C</i>	8.463	8.730	0.267	1.20
<i>CNDP2</i>	11.544	11.811	0.267	1.20
<i>HCP5</i>	10.682	10.948	0.266	1.20
<i>PACSIN1</i>	7.647	7.912	0.266	1.20
<i>UBASH3A</i>	8.105	8.370	0.265	1.20
<i>TMEM71</i>	10.719	10.985	0.265	1.20
<i>SNX27</i>	10.471	10.737	0.265	1.20
<i>METTL3</i>	8.615	8.880	0.265	1.20
<i>LEF1</i>	11.377	11.642	0.265	1.20
<i>C14orf167</i>	8.298	8.562	0.264	1.20
<i>NSMCE1</i>	9.921	10.184	0.264	1.20
<i>ZW10</i>	8.549	8.813	0.264	1.20
<i>LAIR2</i>	9.342	9.605	0.263	1.20
<i>Down-regulated</i>				
<i>HBEGF</i>	11.022	9.992	-1.031	0.49
<i>RGS1</i>	11.702	10.746	-0.955	0.52
<i>CXCL2</i>	9.167	8.221	-0.947	0.52
<i>NR4A2</i>	10.548	9.634	-0.914	0.53
<i>G0S2</i>	10.470	9.617	-0.853	0.55
<i>LOC645979</i>	11.672	10.836	-0.837	0.56
<i>IL1B</i>	11.241	10.421	-0.820	0.57
<i>IL8</i>	13.429	12.628	-0.802	0.57
<i>LOC641768</i>	11.744	10.952	-0.793	0.58

Gene Symbol	Mean SS	Mean CBT-I	Difference	Fold
<i>LOC441377</i>	11.899	11.119	-0.780	0.58
<i>THBS1</i>	10.172	9.392	-0.780	0.58
<i>HLA-A29.1</i>	11.813	11.048	-0.766	0.59
<i>LOC728823</i>	11.601	10.898	-0.703	0.61
<i>GABARAPL1</i>	10.780	10.097	-0.683	0.62
<i>PTGS2</i>	10.942	10.267	-0.675	0.63
<i>CCL20</i>	7.942	7.276	-0.665	0.63
<i>PFKFB3</i>	11.050	10.412	-0.638	0.64
<i>RPS26P10</i>	9.254	8.631	-0.623	0.65
<i>OSM</i>	11.222	10.623	-0.599	0.66
<i>CXCL1</i>	8.202	7.607	-0.595	0.66
<i>LOC729009</i>	12.190	11.606	-0.584	0.67
<i>PTMA</i>	10.685	10.106	-0.579	0.67
<i>EAF1</i>	9.545	8.966	-0.579	0.67
<i>HIF1A</i>	8.878	8.308	-0.570	0.67
<i>NAMPT</i>	10.307	9.738	-0.569	0.67
<i>ACSL1</i>	9.802	9.240	-0.562	0.68
<i>LOC389293</i>	8.739	8.178	-0.561	0.68
<i>LOC100131971</i>	9.555	9.000	-0.554	0.68
<i>CD83</i>	11.348	10.795	-0.553	0.68
<i>CCL3</i>	10.596	10.044	-0.553	0.68
<i>C17orf91</i>	9.853	9.307	-0.546	0.69
<i>AVPI1</i>	9.842	9.298	-0.543	0.69
<i>HECA</i>	10.084	9.545	-0.539	0.69
<i>HOXA5</i>	8.297	7.758	-0.539	0.69
<i>PLAUR</i>	10.178	9.641	-0.537	0.69
<i>SLC2A14</i>	8.442	7.907	-0.535	0.69
<i>SLC7A5</i>	9.757	9.226	-0.531	0.69
<i>SIK1</i>	9.231	8.703	-0.527	0.69
<i>ETS2</i>	9.809	9.291	-0.518	0.70
<i>MIR302C</i>	8.388	7.875	-0.514	0.70
<i>FOSB</i>	11.394	10.881	-0.512	0.70
<i>AXUD1</i>	12.164	11.672	-0.492	0.71
<i>LOC644928</i>	12.208	11.720	-0.488	0.71

Gene Symbol	Mean SS	Mean CBT-I	Difference	Fold
<i>MAP3K8</i>	9.947	9.460	-0.487	0.71
<i>EGR2</i>	10.079	9.595	-0.484	0.72
<i>SBDS</i>	10.304	9.825	-0.480	0.72
<i>PMAIP1</i>	8.954	8.475	-0.479	0.72
<i>LOC100129552</i>	9.002	8.525	-0.477	0.72
<i>PHLDA1</i>	8.368	7.893	-0.475	0.72
<i>LOC649143</i>	10.894	10.422	-0.473	0.72
<i>CCRN4L</i>	8.334	7.865	-0.470	0.72
<i>LGALS3</i>	9.518	9.050	-0.468	0.72
<i>CA1</i>	8.394	7.928	-0.465	0.72
<i>LOC100133823</i>	9.527	9.062	-0.465	0.73
<i>TNFAIP3</i>	12.339	11.875	-0.465	0.73
<i>SGK1</i>	12.373	11.910	-0.462	0.73
<i>TRIB1</i>	11.674	11.214	-0.460	0.73
<i>LOC650298</i>	9.615	9.166	-0.450	0.73
<i>LOC440063</i>	10.503	10.054	-0.449	0.73
<i>SERTAD1</i>	9.828	9.380	-0.448	0.73
<i>TNFRSF21</i>	8.959	8.511	-0.448	0.73
<i>ZBTB43</i>	9.409	8.962	-0.448	0.73
<i>CCL3L1</i>	9.798	9.351	-0.447	0.73
<i>RAP1GAP</i>	7.633	7.187	-0.446	0.73
<i>ATF3</i>	8.082	7.637	-0.445	0.74
<i>FTHL3</i>	11.252	10.818	-0.433	0.74
<i>LOC653778</i>	9.223	8.789	-0.433	0.74
<i>CD55</i>	9.661	9.227	-0.433	0.74
<i>GAPDHL6</i>	7.938	7.506	-0.433	0.74
<i>SGK</i>	12.835	12.404	-0.431	0.74
<i>LOC646753</i>	10.939	10.510	-0.428	0.74
<i>RIPK2</i>	11.292	10.865	-0.428	0.74
<i>HBG2</i>	10.548	10.121	-0.427	0.74
<i>IDI1</i>	9.416	8.990	-0.425	0.75
<i>C20orf108</i>	9.499	9.074	-0.425	0.75
<i>TP53INP2</i>	8.396	7.972	-0.425	0.75
<i>HBG1</i>	10.394	9.970	-0.425	0.75

Gene Symbol	Mean SS	Mean CBT-I	Difference	Fold
<i>SLC25A24</i>	8.684	8.260	-0.424	0.75
<i>FTHL8</i>	12.162	11.741	-0.421	0.75
<i>FAM46C</i>	11.589	11.172	-0.418	0.75
<i>PDE4B</i>	9.446	9.029	-0.417	0.75
<i>RAB20</i>	8.524	8.108	-0.416	0.75
<i>LOC644934</i>	12.295	11.880	-0.416	0.75
<i>REL</i>	8.390	7.975	-0.415	0.75
<i>DUSP2</i>	11.194	10.780	-0.414	0.75
<i>DDIT3</i>	9.218	8.804	-0.414	0.75
<i>CYP4B1</i>	7.754	7.342	-0.412	0.75
<i>NFIL3</i>	10.949	10.539	-0.409	0.75
<i>MAFB</i>	12.073	11.665	-0.409	0.75
<i>IER3</i>	11.169	10.765	-0.404	0.76
<i>SESN3</i>	8.136	7.736	-0.400	0.76
<i>ARL4A</i>	8.252	7.855	-0.397	0.76
<i>LOC100129650</i>	11.610	11.213	-0.397	0.76
<i>MIR130A</i>	7.900	7.504	-0.396	0.76
<i>C18orf32</i>	8.442	8.046	-0.396	0.76
<i>RASD1</i>	8.600	8.206	-0.395	0.76
<i>ETV3</i>	8.351	7.959	-0.392	0.76
<i>NRIP3</i>	8.367	7.975	-0.392	0.76
<i>FAM21D</i>	8.127	7.739	-0.388	0.76
<i>LOC643287</i>	10.536	10.148	-0.387	0.77
<i>LOC727908</i>	9.089	8.702	-0.387	0.77
<i>IRS2</i>	10.887	10.501	-0.386	0.77
<i>CHPT1</i>	10.275	9.891	-0.385	0.77
<i>FECH</i>	8.153	7.770	-0.383	0.77
<i>LOC642828</i>	11.525	11.144	-0.381	0.77
<i>NAT13</i>	8.523	8.145	-0.379	0.77
<i>RPS26L</i>	13.232	12.854	-0.378	0.77
<i>LOC391045</i>	8.487	8.110	-0.377	0.77
<i>NLRP3</i>	10.845	10.468	-0.377	0.77
<i>CYTIP</i>	8.408	8.031	-0.377	0.77
<i>CHD1</i>	10.143	9.768	-0.375	0.77

Gene Symbol	Mean SS	Mean CBT-I	Difference	Fold
<i>SAMSN1</i>	9.387	9.013	-0.373	0.77
<i>IFIT1L</i>	7.754	7.383	-0.371	0.77
<i>CLEC7A</i>	8.981	8.611	-0.370	0.77
<i>RPS26</i>	11.247	10.877	-0.370	0.77
<i>KIR3DL2</i>	8.799	8.429	-0.369	0.77
<i>TMEM176A</i>	9.106	8.737	-0.369	0.77
<i>EMP1</i>	8.936	8.569	-0.368	0.78
<i>PPP1R15A</i>	12.276	11.909	-0.367	0.78
<i>MEX3C</i>	9.832	9.466	-0.367	0.78
<i>RNF138</i>	9.801	9.435	-0.367	0.78
<i>KRT1</i>	7.567	7.202	-0.365	0.78
<i>CLK1</i>	10.422	10.060	-0.361	0.78
<i>SPRY2</i>	7.972	7.611	-0.361	0.78
<i>YOD1</i>	8.842	8.481	-0.361	0.78
<i>EBI2</i>	11.894	11.534	-0.361	0.78
<i>GPR183</i>	8.062	7.702	-0.360	0.78
<i>ISCA1</i>	9.391	9.032	-0.359	0.78
<i>EAPP</i>	10.087	9.728	-0.358	0.78
<i>RAPGEF2</i>	8.935	8.578	-0.357	0.78
<i>LOC100008589</i>	8.690	8.334	-0.357	0.78
<i>PTS</i>	9.737	9.380	-0.357	0.78
<i>FOSL2</i>	8.645	8.289	-0.356	0.78
<i>FTHL12</i>	13.391	13.036	-0.355	0.78
<i>SIRT1</i>	9.165	8.812	-0.353	0.78
<i>LOC100132863</i>	10.289	9.936	-0.353	0.78
<i>C5AR1</i>	11.206	10.855	-0.351	0.78
<i>MAFF</i>	7.980	7.629	-0.351	0.78
<i>PSCDBP</i>	10.476	10.125	-0.351	0.78
<i>PRPF18</i>	8.577	8.226	-0.351	0.78
<i>C3AR1</i>	8.821	8.472	-0.350	0.79
<i>CCDC49</i>	9.172	8.823	-0.349	0.79
<i>MTMR6</i>	9.167	8.817	-0.349	0.79
<i>OTUD1</i>	9.382	9.033	-0.349	0.79
<i>CENTG2</i>	8.565	8.217	-0.349	0.79

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<i>CCNH</i>	8.785	8.437	-0.348	0.79
<i>CCL3L3</i>	11.219	10.872	-0.347	0.79
<i>FAM116A</i>	10.196	9.849	-0.347	0.79
<i>SLC4A1</i>	7.936	7.590	-0.347	0.79
<i>CXCL16</i>	10.383	10.038	-0.346	0.79
<i>PDE4D</i>	8.472	8.127	-0.345	0.79
<i>MAPK6</i>	9.745	9.401	-0.344	0.79
<i>SNIP1</i>	9.874	9.530	-0.344	0.79
<i>TWISTNB</i>	8.167	7.824	-0.342	0.79
<i>CLEC11A</i>	8.302	7.960	-0.342	0.79
<i>SNORD3D</i>	9.898	9.556	-0.342	0.79
<i>MICALCL</i>	7.915	7.573	-0.342	0.79
<i>SKP1</i>	10.383	10.042	-0.341	0.79
<i>PNO1</i>	8.565	8.225	-0.340	0.79
<i>ANKDD1A</i>	8.350	8.010	-0.340	0.79
<i>LOC440280</i>	9.832	9.492	-0.340	0.79
<i>PTGES3</i>	10.233	9.893	-0.339	0.79
<i>JMJD1A</i>	9.424	9.085	-0.339	0.79
<i>HLA-C</i>	10.041	9.704	-0.338	0.79
<i>HMGB1</i>	9.005	8.668	-0.338	0.79
<i>ISCA1L</i>	8.742	8.405	-0.337	0.79
<i>LOC100129657</i>	10.552	10.216	-0.337	0.79
<i>dJ341D10.1</i>	9.242	8.907	-0.335	0.79
<i>HEBP2</i>	11.292	10.958	-0.334	0.79
<i>LOC650646</i>	13.913	13.580	-0.334	0.79
<i>FTHL11</i>	12.323	11.989	-0.333	0.79
<i>GRASP</i>	8.516	8.183	-0.333	0.79
<i>LOC654103</i>	9.904	9.571	-0.333	0.79
<i>SLC2A3</i>	13.384	13.053	-0.331	0.80
<i>DNAJB9</i>	10.155	9.824	-0.331	0.80
<i>FTHL2</i>	11.917	11.587	-0.330	0.80
<i>NEU4</i>	7.285	6.956	-0.329	0.80
<i>MXD1</i>	10.432	10.103	-0.328	0.80
<i>EGR1</i>	11.860	11.532	-0.328	0.80

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<i>EIF1B</i>	11.323	10.995	-0.328	0.80
<i>PYROXD1</i>	7.997	7.669	-0.328	0.80
<i>TLR1</i>	8.381	8.054	-0.327	0.80
<i>THBD</i>	7.891	7.565	-0.326	0.80
<i>ZFP36L1</i>	10.857	10.530	-0.326	0.80
<i>MGC61598</i>	8.655	8.330	-0.325	0.80
<i>KBTD8</i>	8.730	8.406	-0.325	0.80
<i>SLC16A6</i>	8.759	8.438	-0.322	0.80
<i>FTH1</i>	11.495	11.174	-0.321	0.80
<i>LOC728732</i>	10.309	9.988	-0.321	0.80
<i>TXNL1</i>	8.316	7.995	-0.321	0.80
<i>TMOD1</i>	7.800	7.480	-0.320	0.80
<i>SRXN1</i>	9.541	9.222	-0.319	0.80
<i>LOC100131164</i>	7.646	7.328	-0.319	0.80
<i>LOC100133591</i>	7.596	7.277	-0.319	0.80
<i>GPR65</i>	9.792	9.475	-0.317	0.80
<i>LOC284988</i>	9.022	8.705	-0.317	0.80
<i>IFP38</i>	10.239	9.923	-0.316	0.80
<i>LOC100132673</i>	12.890	12.574	-0.316	0.80
<i>NFIX</i>	8.104	7.788	-0.316	0.80
<i>LOC731878</i>	10.520	10.204	-0.315	0.80
<i>SAR1A</i>	9.657	9.342	-0.315	0.80
<i>YES1</i>	8.076	7.761	-0.314	0.80
<i>JUN</i>	11.446	11.131	-0.314	0.80
<i>LOC100132394</i>	9.575	9.261	-0.314	0.80
<i>UPLP</i>	10.156	9.842	-0.314	0.81
<i>LOC644423</i>	8.137	7.823	-0.314	0.81
<i>SLC22A4</i>	8.151	7.838	-0.313	0.81
<i>SAP30</i>	8.592	8.280	-0.312	0.81
<i>LOC341315</i>	11.265	10.952	-0.312	0.81
<i>BCL3</i>	10.782	10.471	-0.311	0.81
<i>IFNG</i>	7.852	7.542	-0.310	0.81
<i>KIR2DL1</i>	8.826	8.517	-0.309	0.81
<i>LOC645691</i>	9.764	9.456	-0.308	0.81

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<i>SELK</i>	9.728	9.420	-0.308	0.81
<i>MIR1275</i>	7.701	7.394	-0.308	0.81
<i>ITPRIP</i>	10.721	10.414	-0.308	0.81
<i>TNF</i>	8.938	8.631	-0.307	0.81
<i>DDIT4</i>	12.087	11.781	-0.307	0.81
<i>ERRFI1</i>	7.624	7.318	-0.307	0.81
<i>GNAI3</i>	9.122	8.816	-0.306	0.81
<i>TUBB2A</i>	8.044	7.739	-0.305	0.81
<i>LOC645381</i>	8.874	8.570	-0.304	0.81
<i>PTGER4</i>	11.597	11.293	-0.304	0.81
<i>FEM1C</i>	10.339	10.035	-0.304	0.81
<i>LOC653171</i>	10.204	9.900	-0.304	0.81
<i>TMEM188</i>	9.720	9.417	-0.303	0.81
<i>LOC644191</i>	11.364	11.062	-0.302	0.81
<i>GADD45A</i>	9.252	8.949	-0.302	0.81
<i>LOC727821</i>	10.265	9.963	-0.302	0.81
<i>HMGB1L1</i>	9.300	8.998	-0.302	0.81
<i>EIF1AX</i>	8.349	8.047	-0.302	0.81
<i>SEPT7</i>	8.722	8.420	-0.301	0.81
<i>BTG3</i>	9.083	8.782	-0.301	0.81
<i>PDZD8</i>	8.443	8.142	-0.301	0.81
<i>LOC728142</i>	8.224	7.924	-0.301	0.81
<i>HLX</i>	8.932	8.632	-0.300	0.81
<i>C14orf11</i>	7.304	7.003	-0.300	0.81
<i>TFRC</i>	10.874	10.574	-0.300	0.81
<i>B3GNT5</i>	7.223	6.925	-0.299	0.81
<i>ZNF683</i>	9.405	9.107	-0.298	0.81
<i>RAP1BL</i>	9.742	9.444	-0.298	0.81
<i>USMG5</i>	8.096	7.798	-0.297	0.81
<i>LOC151579</i>	10.594	10.297	-0.297	0.81
<i>FAM162A</i>	7.906	7.610	-0.297	0.81
<i>DUSP5</i>	10.727	10.430	-0.297	0.81
<i>KIR2DS5</i>	8.792	8.496	-0.296	0.81
<i>LOC729255</i>	9.206	8.910	-0.296	0.81

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<i>TOP1P2</i>	7.725	7.428	-0.296	0.81
<i>JUNB</i>	11.995	11.699	-0.296	0.82
<i>LOC100132658</i>	9.460	9.164	-0.296	0.82
<i>CEBPD</i>	12.898	12.602	-0.296	0.82
<i>BCL2A1</i>	7.750	7.455	-0.295	0.82
<i>FAM49B</i>	9.535	9.240	-0.295	0.82
<i>C15orf48</i>	7.737	7.442	-0.295	0.82
<i>SFRS11</i>	8.104	7.810	-0.294	0.82
<i>LOC728098</i>	9.451	9.157	-0.294	0.82
<i>GYPB</i>	7.307	7.014	-0.293	0.82
<i>S100A12</i>	11.216	10.924	-0.292	0.82
<i>SMNDC1</i>	9.358	9.068	-0.291	0.82
<i>LOC100129742</i>	12.945	12.654	-0.291	0.82
<i>VTI1B</i>	9.462	9.172	-0.290	0.82
<i>ZNF281</i>	9.794	9.504	-0.290	0.82
<i>POLR2J2</i>	9.077	8.789	-0.289	0.82
<i>AHSP</i>	9.094	8.806	-0.289	0.82
<i>OLR1</i>	7.717	7.429	-0.288	0.82
<i>CKS2</i>	8.664	8.376	-0.288	0.82
<i>C13orf15</i>	11.977	11.689	-0.288	0.82
<i>CISD2</i>	8.703	8.415	-0.288	0.82
<i>LCOR</i>	9.303	9.015	-0.288	0.82
<i>FRG1</i>	10.358	10.071	-0.287	0.82
<i>APOBEC3A</i>	7.820	7.535	-0.285	0.82
<i>NBPF8</i>	9.644	9.358	-0.285	0.82
<i>WDR26</i>	9.746	9.461	-0.285	0.82
<i>WSB2</i>	8.676	8.391	-0.285	0.82
<i>ATP1B1</i>	8.439	8.154	-0.285	0.82
<i>GAB2</i>	8.911	8.627	-0.284	0.82
<i>NT5C3L</i>	8.384	8.101	-0.284	0.82
<i>LOC650128</i>	8.382	8.101	-0.282	0.82
<i>RIOK3</i>	10.768	10.487	-0.281	0.82
<i>RPS26P11</i>	12.795	12.514	-0.281	0.82
<i>IRAK3</i>	9.962	9.682	-0.281	0.82

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<i>RGS2</i>	13.302	13.022	-0.281	0.82
<i>JMY</i>	8.178	7.898	-0.280	0.82
<i>STK17B</i>	10.779	10.500	-0.279	0.82
<i>LOC400061</i>	8.359	8.080	-0.279	0.82
<i>LOC729208</i>	11.818	11.540	-0.278	0.83
<i>ADM</i>	10.486	10.208	-0.278	0.83
<i>LOC100132715</i>	10.794	10.516	-0.278	0.83
<i>MGAT4A</i>	9.850	9.571	-0.278	0.83
<i>LOC392285</i>	10.178	9.901	-0.278	0.83
<i>ANXA2P1</i>	10.009	9.732	-0.278	0.83
<i>TMEM176B</i>	8.228	7.950	-0.278	0.83
<i>PHACTR1</i>	7.945	7.668	-0.277	0.83
<i>LOC651202</i>	12.440	12.163	-0.277	0.83
<i>ALAS2</i>	8.912	8.636	-0.276	0.83
<i>RIPK5</i>	8.598	8.323	-0.276	0.83
<i>CES1</i>	8.688	8.413	-0.275	0.83
<i>KLHL24</i>	9.410	9.135	-0.274	0.83
<i>NXT1</i>	10.783	10.509	-0.274	0.83
<i>ZEB2</i>	9.832	9.558	-0.274	0.83
<i>TREM1</i>	9.032	8.759	-0.273	0.83
<i>LOC727984</i>	10.480	10.207	-0.273	0.83
<i>IMPA1</i>	8.743	8.471	-0.272	0.83
<i>CTSL1</i>	9.798	9.526	-0.272	0.83
<i>LOC389599</i>	8.980	8.709	-0.272	0.83
<i>AGFG1</i>	8.370	8.098	-0.272	0.83
<i>LOC650898</i>	7.749	7.478	-0.271	0.83
<i>IL6</i>	7.772	7.501	-0.271	0.83
<i>LOC338758</i>	12.398	12.128	-0.270	0.83
<i>LOC389787</i>	13.215	12.945	-0.270	0.83
<i>S1PR3</i>	7.953	7.683	-0.270	0.83
<i>METRNL</i>	9.533	9.264	-0.270	0.83
<i>NACAP1</i>	9.799	9.530	-0.270	0.83
<i>BCL6</i>	10.327	10.057	-0.270	0.83
<i>CDKN1A</i>	11.438	11.168	-0.269	0.83

Gene Symbol	Mean SS	Mean CBT-I	Difference	Fold
<i>NMD3</i>	9.454	9.185	-0.269	0.83
<i>RBM39</i>	9.427	9.158	-0.269	0.83
<i>EPB42</i>	7.559	7.291	-0.268	0.83
<i>LOC728643</i>	11.523	11.255	-0.268	0.83
<i>PPIF</i>	7.873	7.605	-0.268	0.83
<i>C6orf160</i>	12.153	11.885	-0.268	0.83
<i>SIAH2</i>	9.324	9.056	-0.268	0.83
<i>TLE3</i>	7.809	7.542	-0.268	0.83
<i>SELENBP1</i>	7.791	7.523	-0.267	0.83
<i>C9orf21</i>	9.346	9.079	-0.267	0.83
<i>IKZF5</i>	8.359	8.092	-0.267	0.83
<i>ABCA1</i>	8.704	8.437	-0.267	0.83
<i>IER3IP1</i>	8.648	8.382	-0.267	0.83
<i>LOC286512</i>	11.009	10.743	-0.266	0.83
<i>PIM3</i>	8.924	8.658	-0.266	0.83
<i>ETNK1</i>	8.232	7.966	-0.266	0.83
<i>SUMO1P3</i>	9.105	8.839	-0.266	0.83
<i>ZBTB2</i>	8.004	7.739	-0.266	0.83
<i>PNPLA8</i>	8.275	8.010	-0.265	0.83
<i>LOC128192</i>	10.068	9.804	-0.265	0.83
<i>RNF10</i>	9.702	9.437	-0.265	0.83
<i>BIRC2</i>	9.645	9.380	-0.264	0.83
<i>C1orf55</i>	9.976	9.712	-0.264	0.83
<i>ENC1</i>	8.989	8.725	-0.264	0.83
<i>LOC197135</i>	8.652	8.388	-0.264	0.83
<i>FLJ20273</i>	8.077	7.814	-0.264	0.83
<i>LOC641848</i>	10.774	10.511	-0.263	0.83
<i>FAM26F</i>	8.951	8.688	-0.263	0.83
<i>LOC100129028</i>	13.117	12.854	-0.263	0.83
<i>KLF4</i>	10.219	9.957	-0.263	0.83
<i>KLHL2</i>	8.227	7.964	-0.263	0.83
<i>RSRC2</i>	9.892	9.630	-0.262	0.83

Table S2. Genes differentially expressed in TCC vs SS Control

Gene Symbol	Mean SS	Mean TCC	Difference	Fold
<i>Up-regulated</i>				
<i>LOC653600</i>	8.258	9.023	0.766	1.70
<i>DEFA1B</i>	9.670	10.410	0.739	1.67
<i>KRT72</i>	8.066	8.749	0.684	1.61
<i>RPS4Y1</i>	8.486	9.160	0.674	1.60
<i>DEFA3</i>	9.875	10.542	0.666	1.59
<i>HLA-DRB1</i>	9.240	9.879	0.640	1.56
<i>HLA-DRB5</i>	8.098	8.718	0.620	1.54
<i>SNHG8</i>	8.537	9.157	0.620	1.54
<i>LOC100133662</i>	7.930	8.527	0.597	1.51
<i>DEFA1</i>	10.671	11.240	0.569	1.48
<i>CD24</i>	7.833	8.365	0.532	1.45
<i>CAMP</i>	7.881	8.358	0.478	1.39
<i>DEFA4</i>	7.497	7.965	0.468	1.38
<i>CCL2</i>	7.850	8.309	0.459	1.38
<i>KRT73</i>	7.704	8.157	0.453	1.37
<i>CNTNAP2</i>	7.680	8.128	0.448	1.36
<i>DKFZp761P0423</i>	8.288	8.727	0.439	1.36
<i>MYOM2</i>	8.670	9.083	0.413	1.33
<i>LTF</i>	7.451	7.863	0.411	1.33
<i>ELANE</i>	7.955	8.342	0.388	1.31
<i>LOC652694</i>	9.465	9.847	0.383	1.30
<i>EIF1AY</i>	7.635	8.013	0.379	1.30
<i>CD79B</i>	10.344	10.721	0.377	1.30
<i>CEACAM8</i>	7.117	7.492	0.376	1.30
<i>RPS4Y2</i>	7.652	8.015	0.362	1.29
<i>LOC253039</i>	7.966	8.323	0.357	1.28
<i>FCRLA</i>	9.569	9.925	0.356	1.28
<i>PRAGMIN</i>	8.850	9.203	0.353	1.28
<i>HLA-DOB</i>	8.545	8.877	0.332	1.26
<i>LRRN3</i>	8.084	8.412	0.328	1.26
<i>FAM113B</i>	10.889	11.215	0.326	1.25
<i>GTSCR1</i>	8.145	8.463	0.318	1.25

Gene Symbol	Mean SS	Mean TCC	Difference	Fold
<i>SCGB3A1</i>	7.307	7.619	0.312	1.24
<i>VSTM1</i>	8.161	8.471	0.310	1.24
<i>CYorf15A</i>	7.673	7.983	0.310	1.24
<i>VPREB3</i>	8.308	8.616	0.309	1.24
<i>LOC341346</i>	7.059	7.365	0.306	1.24
<i>TACSTD2</i>	6.939	7.237	0.297	1.23
<i>CEACAM6</i>	7.279	7.576	0.296	1.23
<i>PI16</i>	7.762	8.058	0.296	1.23
<i>CTSG</i>	7.628	7.916	0.288	1.22
<i>RNASE3</i>	7.345	7.627	0.282	1.22
<i>GIMAP4</i>	11.660	11.942	0.281	1.22
<i>BCAS4</i>	8.242	8.518	0.276	1.21
<i>E2F5</i>	8.029	8.302	0.273	1.21
<i>TCL1A</i>	8.161	8.433	0.273	1.21
<i>JARID1D</i>	7.519	7.791	0.271	1.21
<i>CD27</i>	9.875	10.146	0.271	1.21
<i>FCRL5</i>	7.438	7.708	0.269	1.21
<i>CYP3A7</i>	6.862	7.129	0.267	1.20
<i>CACNA1I</i>	8.076	8.341	0.266	1.20
<i>MEF2C</i>	8.017	8.280	0.263	1.20
<i>Down-regulated</i>				
<i>HBEGF</i>	11.022	10.187	-0.835	0.56
<i>CCL3</i>	10.596	9.816	-0.780	0.58
<i>G0S2</i>	10.470	9.699	-0.771	0.59
<i>CA2</i>	10.428	9.660	-0.768	0.59
<i>LOC100008588</i>	10.230	9.478	-0.752	0.59
<i>PTGS2</i>	10.942	10.265	-0.677	0.63
<i>CXCL2</i>	9.167	8.509	-0.659	0.63
<i>IL1B</i>	11.241	10.602	-0.639	0.64
<i>CCL3L1</i>	9.798	9.167	-0.631	0.65
<i>RGS1</i>	11.702	11.076	-0.626	0.65
<i>CCL3L3</i>	11.219	10.596	-0.623	0.65
<i>HIST1H3H</i>	9.268	8.652	-0.616	0.65
<i>ZNF683</i>	9.405	8.795	-0.610	0.66

Gene Symbol	Mean SS	Mean TCC	Difference	Fold
<i>USMG5</i>	8.096	7.508	-0.588	0.67
<i>RGS18</i>	12.002	11.414	-0.588	0.67
<i>HBG1</i>	10.394	9.830	-0.565	0.68
<i>NR4A2</i>	10.548	9.987	-0.561	0.68
<i>IL8</i>	13.429	12.889	-0.540	0.69
<i>MGC13057</i>	9.677	9.146	-0.531	0.69
<i>LOC645128</i>	9.104	8.594	-0.510	0.70
<i>C21orf7</i>	12.233	11.725	-0.508	0.70
<i>GNG11</i>	11.998	11.498	-0.500	0.71
<i>CCL20</i>	7.942	7.447	-0.495	0.71
<i>CA1</i>	8.394	7.908	-0.486	0.71
<i>JUNB</i>	11.995	11.515	-0.480	0.72
<i>ACRBP</i>	9.998	9.521	-0.477	0.72
<i>PLAUR</i>	10.178	9.707	-0.471	0.72
<i>HBG2</i>	10.548	10.081	-0.467	0.72
<i>TNFAIP3</i>	12.339	11.873	-0.466	0.72
<i>THBS1</i>	10.172	9.708	-0.464	0.73
<i>FLJ45337</i>	8.855	8.393	-0.462	0.73
<i>IFIT1L</i>	7.754	7.293	-0.461	0.73
<i>CLEC1B</i>	9.369	8.911	-0.458	0.73
<i>MIR302C</i>	8.388	7.935	-0.453	0.73
<i>LOC728835</i>	10.508	10.056	-0.452	0.73
<i>HIST1H3F</i>	9.117	8.680	-0.437	0.74
<i>DUSP2</i>	11.194	10.758	-0.437	0.74
<i>IFNG</i>	7.852	7.418	-0.434	0.74
<i>ETS2</i>	9.809	9.381	-0.428	0.74
<i>TRIB1</i>	11.674	11.246	-0.428	0.74
<i>FOS</i>	13.555	13.128	-0.427	0.74
<i>HBD</i>	9.830	9.404	-0.426	0.74
<i>NAT8B</i>	8.548	8.123	-0.425	0.75
<i>HOXA5</i>	8.297	7.875	-0.423	0.75
<i>NFIL3</i>	10.949	10.536	-0.413	0.75
<i>CLC</i>	11.244	10.840	-0.404	0.76
<i>SNCA</i>	10.195	9.792	-0.403	0.76

Gene Symbol	Mean SS	Mean TCC	Difference	Fold
<i>RNF144B</i>	9.316	8.913	-0.403	0.76
<i>SLC25A24</i>	8.684	8.283	-0.400	0.76
<i>CD8A</i>	11.595	11.203	-0.392	0.76
<i>FECH</i>	8.153	7.762	-0.392	0.76
<i>LOC441763</i>	8.586	8.195	-0.390	0.76
<i>MMD</i>	11.547	11.157	-0.390	0.76
<i>GABARAPL1</i>	10.780	10.393	-0.387	0.77
<i>YOD1</i>	8.842	8.456	-0.386	0.77
<i>GAPDHL6</i>	7.938	7.554	-0.384	0.77
<i>MXD1</i>	10.432	10.048	-0.384	0.77
<i>CCL4L2</i>	9.536	9.153	-0.384	0.77
<i>PFKFB3</i>	11.050	10.667	-0.383	0.77
<i>EPB49</i>	8.624	8.242	-0.382	0.77
<i>HIST1H4H</i>	8.166	7.784	-0.382	0.77
<i>RHOU</i>	10.351	9.969	-0.381	0.77
<i>PPP1R15A</i>	12.276	11.899	-0.378	0.77
<i>HBE1</i>	7.277	6.900	-0.377	0.77
<i>NAMPT</i>	10.307	9.933	-0.374	0.77
<i>SNORD3D</i>	9.898	9.527	-0.371	0.77
<i>SLC4A1</i>	7.936	7.566	-0.370	0.77
<i>CRISPLD2</i>	10.020	9.652	-0.368	0.78
<i>OSM</i>	11.222	10.855	-0.367	0.78
<i>HIST1H2AC</i>	10.268	9.902	-0.367	0.78
<i>MIR1974</i>	12.316	11.951	-0.365	0.78
<i>CXCL1</i>	8.202	7.839	-0.363	0.78
<i>RAP1GAP</i>	7.633	7.271	-0.363	0.78
<i>LOC100131164</i>	7.646	7.284	-0.362	0.78
<i>EBI2</i>	11.894	11.534	-0.360	0.78
<i>RIPK2</i>	11.292	10.934	-0.359	0.78
<i>CEBPD</i>	12.898	12.539	-0.359	0.78
<i>PDZK1IP1</i>	8.380	8.022	-0.358	0.78
<i>RIOK3</i>	10.768	10.411	-0.357	0.78
<i>TMEM111</i>	11.593	11.239	-0.355	0.78
<i>SIAH2</i>	9.324	8.970	-0.354	0.78

Gene Symbol	Mean SS	Mean TCC	Difference	Fold
<i>SLC2A14</i>	8.442	8.090	-0.352	0.78
<i>ADIPOR1</i>	10.676	10.324	-0.351	0.78
<i>LOC100132394</i>	9.575	9.224	-0.351	0.78
<i>SLC7A5</i>	9.757	9.407	-0.351	0.78
<i>FOSB</i>	11.394	11.048	-0.346	0.79
<i>RNU4ATAC</i>	8.918	8.575	-0.344	0.79
<i>LOC728069</i>	11.123	10.783	-0.340	0.79
<i>GMPR</i>	8.464	8.125	-0.339	0.79
<i>OLFM1</i>	7.703	7.365	-0.338	0.79
<i>WDR40A</i>	9.914	9.580	-0.334	0.79
<i>AVPI1</i>	9.842	9.512	-0.330	0.80
<i>NRGN</i>	12.158	11.829	-0.329	0.80
<i>HIST2H2BE</i>	10.363	10.035	-0.328	0.80
<i>LOC100134364</i>	9.283	8.955	-0.327	0.80
<i>SNIP1</i>	9.874	9.547	-0.327	0.80
<i>GYPB</i>	7.307	6.981	-0.326	0.80
<i>RAB20</i>	8.524	8.199	-0.325	0.80
<i>RILPL2</i>	10.925	10.603	-0.322	0.80
<i>ISCA1L</i>	8.742	8.421	-0.321	0.80
<i>XK</i>	7.720	7.399	-0.321	0.80
<i>BCL3</i>	10.782	10.462	-0.319	0.80
<i>EIF1B</i>	11.323	11.003	-0.319	0.80
<i>SIK1</i>	9.231	8.912	-0.318	0.80
<i>LOC653635</i>	8.473	8.155	-0.318	0.80
<i>MPP1</i>	10.749	10.432	-0.318	0.80
<i>CCL4L1</i>	8.939	8.623	-0.316	0.80
<i>CHMP1B</i>	11.457	11.141	-0.316	0.80
<i>SLC25A37</i>	9.318	9.003	-0.314	0.80
<i>HLX</i>	8.932	8.619	-0.313	0.81
<i>MEIS1</i>	8.307	7.994	-0.313	0.81
<i>RHOB</i>	10.245	9.933	-0.312	0.81
<i>ZBTB43</i>	9.409	9.097	-0.312	0.81
<i>CYP4B1</i>	7.754	7.442	-0.311	0.81
<i>HEMGN</i>	7.573	7.263	-0.311	0.81

Gene Symbol	Mean SS	Mean TCC	Difference	Fold
<i>CD69</i>	11.890	11.580	-0.310	0.81
<i>DUSP5</i>	10.727	10.418	-0.309	0.81
<i>FBXO7</i>	9.566	9.260	-0.306	0.81
<i>C20orf108</i>	9.499	9.194	-0.306	0.81
<i>DNAJB9</i>	10.155	9.851	-0.305	0.81
<i>GYPC</i>	10.795	10.490	-0.304	0.81
<i>NT5C3</i>	11.046	10.744	-0.303	0.81
<i>PDK4</i>	8.926	8.624	-0.303	0.81
<i>PDZD8</i>	8.443	8.140	-0.302	0.81
<i>LOC100128731</i>	13.276	12.974	-0.301	0.81
<i>HLA-DQB1</i>	9.807	9.506	-0.301	0.81
<i>LOC100133565</i>	7.782	7.482	-0.300	0.81
<i>CCRN4L</i>	8.334	8.035	-0.300	0.81
<i>SELK</i>	9.728	9.431	-0.297	0.81
<i>SDPR</i>	11.461	11.165	-0.296	0.82
<i>PER1</i>	8.014	7.719	-0.295	0.82
<i>MKRN1</i>	12.420	12.125	-0.295	0.82
<i>BTG3</i>	9.083	8.789	-0.295	0.82
<i>LOC649143</i>	10.894	10.601	-0.294	0.82
<i>IL10RA</i>	11.284	10.990	-0.293	0.82
<i>CISD2</i>	8.703	8.410	-0.293	0.82
<i>SMPDL3A</i>	8.547	8.254	-0.293	0.82
<i>LOC100133477</i>	11.413	11.120	-0.293	0.82
<i>ENC1</i>	8.989	8.697	-0.292	0.82
<i>MIR1978</i>	14.190	13.898	-0.292	0.82
<i>CXCL16</i>	10.383	10.092	-0.291	0.82
<i>LOC652864</i>	9.491	9.201	-0.291	0.82
<i>GNA15</i>	10.342	10.052	-0.290	0.82
<i>SESN3</i>	8.136	7.846	-0.290	0.82
<i>UBXN6</i>	9.674	9.386	-0.288	0.82
<i>F13A1</i>	10.642	10.354	-0.288	0.82
<i>ZDHHC7</i>	11.653	11.365	-0.288	0.82
<i>SNHG5</i>	13.192	12.905	-0.287	0.82
<i>TMOD1</i>	7.800	7.514	-0.287	0.82

Gene Symbol	Mean SS	Mean TCC	Difference	Fold
<i>BMP6</i>	8.454	8.170	-0.284	0.82
<i>GP9</i>	10.918	10.634	-0.284	0.82
<i>HBM</i>	7.977	7.694	-0.283	0.82
<i>C9orf21</i>	9.346	9.064	-0.282	0.82
<i>HIST1H2AE</i>	7.894	7.612	-0.281	0.82
<i>TMEM176A</i>	9.106	8.825	-0.281	0.82
<i>ISCA1</i>	9.391	9.110	-0.281	0.82
<i>HRASLS2</i>	7.583	7.303	-0.280	0.82
<i>ITPRIP</i>	10.721	10.442	-0.280	0.82
<i>MGC13005</i>	8.281	8.002	-0.279	0.82
<i>CFD</i>	12.611	12.333	-0.279	0.82
<i>CD55</i>	9.661	9.382	-0.279	0.82
<i>NFIX</i>	8.104	7.826	-0.278	0.83
<i>MIR1275</i>	7.701	7.424	-0.278	0.83
<i>CHSY1</i>	11.017	10.739	-0.278	0.83
<i>FOXO3</i>	9.983	9.706	-0.277	0.83
<i>AXUD1</i>	12.164	11.886	-0.277	0.83
<i>SLC2A3</i>	13.384	13.107	-0.277	0.83
<i>EGR2</i>	10.079	9.802	-0.277	0.83
<i>GLRX5</i>	12.163	11.886	-0.276	0.83
<i>MAP3K8</i>	9.947	9.671	-0.276	0.83
<i>LOC391045</i>	8.487	8.211	-0.276	0.83
<i>CREG1</i>	10.992	10.716	-0.276	0.83
<i>PHLDA1</i>	8.368	8.092	-0.276	0.83
<i>FAM46C</i>	11.589	11.314	-0.276	0.83
<i>ARL4A</i>	8.252	7.977	-0.275	0.83
<i>YPEL5</i>	11.991	11.716	-0.274	0.83
<i>ATF3</i>	8.082	7.809	-0.274	0.83
<i>FBXL11</i>	10.803	10.530	-0.273	0.83
<i>LOC100129650</i>	11.610	11.337	-0.273	0.83
<i>TMEM140</i>	9.013	8.741	-0.272	0.83
<i>SNORD3C</i>	8.577	8.305	-0.272	0.83
<i>BCL2L1</i>	9.934	9.663	-0.271	0.83
<i>RPPH1</i>	8.357	8.087	-0.270	0.83

Gene Symbol	Mean SS	Mean TCC	Difference	Fold
<i>IFNGR1</i>	11.778	11.508	-0.270	0.83
<i>LOC389293</i>	8.739	8.469	-0.270	0.83
<i>ASGR1</i>	10.950	10.680	-0.270	0.83
<i>SNHG9</i>	10.914	10.645	-0.269	0.83
<i>TMEM158</i>	9.861	9.593	-0.268	0.83
<i>DNAJB6</i>	10.274	10.007	-0.267	0.83
<i>C21orf81</i>	7.757	7.490	-0.267	0.83
<i>CEBPZ</i>	11.082	10.815	-0.266	0.83
<i>FPR2</i>	8.347	8.081	-0.266	0.83
<i>UBAP1</i>	10.111	9.845	-0.266	0.83
<i>NME4</i>	9.745	9.479	-0.266	0.83
<i>PMAIP1</i>	8.954	8.688	-0.266	0.83
<i>SELENBP1</i>	7.791	7.525	-0.265	0.83
<i>IL6</i>	7.772	7.507	-0.265	0.83
<i>LOC646513</i>	7.815	7.551	-0.264	0.83
<i>TSG101</i>	10.237	9.973	-0.264	0.83
<i>HRASLS3</i>	9.652	9.389	-0.264	0.83
<i>ZMIZ1</i>	10.868	10.605	-0.263	0.83
<i>NOP10</i>	12.290	12.028	-0.263	0.83

Supporting Information: Exploratory Gene Set Enrichment Analysis

Results of pathway discovery analyses using Gene Set Enrichment Analysis with annotation libraries representing Gene Ontology terms, KEGG pathways, and Biocarta pathways.

NAME	SIZE	ES	NES	NOM p-val	FDR q-val	FWER p-val
<i>Up-regulated in CBT *</i>						
BIOCARTA_PGC1A_PATHWAY	22	0.52082425	1.552498	0.012422361	0.5870969	0.608
BIOCARTA_STATHMIN_PATHWAY	18	0.6895524	1.6168551	0.031128405	0.6090747	0.436
<i>Down-regulated in CBT (Up-regulated in CBT vs. SS) *</i>						
BIOCARTA_LONGEVITY_PATHWAY	15	-0.81566095	-2.0018673	0	0.00554113	0.005
BIOCARTA_IGF1_PATHWAY	21	-0.5847969	-1.595097	0.014227643	0.37429705	0.498
BIOCARTA_NTHI_PATHWAY	24	-0.69617516	-1.5326787	0.01622718	0.26414937	0.668
BIOCARTA_IL1R_PATHWAY	32	-0.70354766	-1.5563744	0.018036073	0.33817348	0.612
BIOCARTA_VEGF_PATHWAY	29	-0.49327794	-1.4889152	0.018181818	0.28670296	0.774
BIOCARTA_ERYTH_PATHWAY	15	-0.71767753	-1.5979928	0.021956088	0.54675853	0.487
BIOCARTA_LAIR_PATHWAY	17	-0.729171	-1.5447263	0.027944112	0.2689689	0.644
BIOCARTA_NGF_PATHWAY	18	-0.6003564	-1.5810516	0.031311154	0.32484016	0.538
BIOCARTA_ETS_PATHWAY	18	-0.6165029	-1.5227926	0.0327553	0.25532025	0.687
BIOCARTA_INSULIN_PATHWAY	22	-0.545544	-1.5143887	0.034343433	0.2470022	0.708
BIOCARTA_EIF_PATHWAY	16	-0.48663598	-1.5529187	0.036585364	0.2936218	0.623
BIOCARTA_CYTOKINE_PATHWAY	21	-0.6481439	-1.4579014	0.040816326	0.29016426	0.838

* All findings nominally significant at $p < .05$ in GSEA analyses using Biocarta gene set annotations.

NAME	SIZE	ES	NES	NOM p-val	FDR q-val	FWER p-val
<i>Up-regulated in TCC *</i>						
none						
<i>Down-regulated in TCC (Up-regulated in TCC vs. SS) *</i>						
BIOCARTA_IL6_PATHWAY	22	-0.7462543	-1.4785315	0.003034901	0.7241734	0.566
BIOCARTA_STEM_PATHWAY	15	-0.67289776	-1.6998838	0.012345679	0.1567801	0.08
BIOCARTA_P53HYPOXIA_PATHWAY	22	-0.5548962	-1.4673682	0.023255814	0.40840283	0.591
BIOCARTA_ERYTH_PATHWAY	15	-0.6958326	-1.6558483	0.027253669	0.13455929	0.14
BIOCARTA_NGF_PATHWAY	18	-0.6173523	-1.433575	0.027732464	0.42898822	0.665
BIOCARTA_ETS_PATHWAY	18	-0.6381832	-1.355856	0.03255814	0.45191863	0.791
BIOCARTA_INSULIN_PATHWAY	22	-0.6081079	-1.3938653	0.036565978	0.48670775	0.733
BIOCARTA_HER2_PATHWAY	22	-0.60167724	-1.4745817	0.04217926	0.5669438	0.574
BIOCARTA_BCELLSURVIVAL_PATHWAY	15	-0.59838057	-1.4729756	0.04761905	0.46045184	0.576

* Results represent all findings nominally significant at $p < .05$ in GSEA analyses using Biocarta gene set annotations.

CONSORT CHECKLIST

Table. CONSORT 2010 Checklist of Information to Include When Reporting a Randomized Trial^a

Section and Topic	Item No.	Checklist Item	Reported on Page No.
Title and abstract	1a	Identification as a randomized trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction Background and objectives	2a	Scientific background and explanation of rationale	3-4
	2b	Specific objectives or hypotheses	4
Methods Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	5
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5
Outcomes	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	6
	6b	Any changes to trial outcomes after the trial commenced, with reasons	5
Sample size	7a	How sample size was determined	7
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomization Sequence generation	8a	Method used to generate the random allocation sequence	5
	8b	Type of randomization; details of any restriction (such as blocking and block size)	5
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	5
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	5
	11b	If relevant, description of the similarity of interventions	5
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	8
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	8
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	9
	13b	For each group, losses and exclusions after randomization, together with reasons	9
Recruitment	14a	Dates defining the periods of recruitment and follow-up	5
	14b	Why the trial ended or was stopped	5
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	25
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	8
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	10-12
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory	12
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	9
Comment			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	15
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	15
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	13-14
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	2
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	17

^aWe strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomized trials, noninferiority and equivalence trials, nonpharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up-to-date references relevant to this checklist, see <http://www.consort-statement.org>.

Supplemental References

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