#### SUPPLEMENTARY MATERIAL

# DOMAIN-SPECIFIC COGNITIVE IMPAIRMENT IN PATIENTS WITH COPD AND CONTROL SUBJECTS

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#### Neuropsychological assessment

Our primary outcome, cognitive functioning, was measured with a detailed neuropsychological assessment consisting of the following subtests:

- (a) A shortened form of the Groninger Intelligence Test (GIT) will be used to determine general intelligence. Six subtasks will be administered: (1) Vocabulary: measures verbal comprehension. In this subtest 20 words of increasing difficulty are presented of which the participant has to choose the synonym out of five alternatives. The total score ranges between 0-20, with higher scores reflecting higher level of verbal intelligence; (2) Mental rotation: measures visualization. This subtest requires participants to decide which of several smaller geometric shapes from a larger set are needed to fill a larger geometric figure. Total scores ranges between 0-20, with higher scores reflecting higher level of visuo-spatial performance; (3) Figure Discovery: measures perceptual intelligence. In this subtest the subject is shown 20 cards with silhouettes of incomplete pictures of familiar objects or animals and then has to estimate what the picture depicts. The total score ranges between 0-20, with higher scores reflecting higher level of perceptual intelligence; (4) Doing sums: measures numeracy. This subtest requires participants to complete as many adding sums as possible within a time period of 1 minute. The total score ranges between 0-32, with higher scores reflecting higher level of numeracy; (5) Analogies: measures reasoning. In this subtest the subject has to choose 1 from 5 possibilities that correctly completes a 3 x 2 matrix of logical semantic relations (e.g., black-white, highlow, hot-?). The total score ranges between 0-20, with higher scores reflecting higher level of reasoning; (6) Fluency: measures word fluency. The Animal Naming Task and the Profession Naming Task are used to assess semantic verbal fluency and require patients to generate the names of as many animals respectively professions as possible within 60 seconds. Scores are determined by summing correct responses and reflect strategydriven retrieval of information from semantic memory.(1)
- (b) Global cognitive functioning was assessed with the Mini-Mental State Examination (MMSE) as a brief screening for global cognitive functioning. This test consists of questions on orientation to time and place, registration, attention and calculation, recall, language, and visual construction to measure global cognitive functioning. The MMSE consists of 20 questions and the maximum score to achieve is 30 points, with a higher

score indicating a better cognitive performance. A score of 26-30 indicates 'normal cognitive functioning', a score of 24 or 25 'borderline normal cognitive functioning', a score below 24 'cognitive impairment' and a score below 18 'severe cognitive impairment'.(2)

- (c) The Stroop Colour-Word Test (SCW) will be used to assess cognitive flexibility and is composed of three trials using word, color, and interference cards. The first card shows names of colors, which have to be read out loud, printed in black. The second card shows patches of colors, which have to be named. The last card shows names of colors printed in incongruously colored ink and participants are instructed to name the color of the ink in the printed words. Errors, self-corrected errors, and time of completion for all trials will be recorded. The time needed for the last card will be subtracted from the mean score for the first and second cards to obtain an interference score. This interference score can be regarded as a measure of inhibition of a habitual response (reading) which is part of the domain of executive functioning.(3)
- (d) The Concept Shifting Test (CST) which is a simple pen-and-paper test which measures concept shifting and executive functioning. This test consists of three subtasks. On each test sheet, 16 small circles are grouped in a larger circle. The small circles contain numbers, letters, or both, appearing in a fixed random order. Participants are requested to cross out the items in the right order. In the final part of the test, they have to alternate between numbers (1–8) and letters (A–H). The time needed to complete each subtask and errors will be recorded. Finally, participants are presented with a condition to control for basic motor speed in which empty circles have to be marked as fast as possible in a clockwise manner. The difference between the score for the last part, corrected for basic motor speed, and the mean score for the first and second parts also corrected for basic motor speed, represent the time needed for cognitive shifting. Cognitive shifting (or mental set shifting) is considered to be part of executive functioning.(4)
- (e) The Letter Digit Substitution Test (LDST) will be used as a measure of information processing speed. A code is presented at the top of the test form, with 10 digit/letter combinations. The participants fill in digits in blank squares indexed with a letter using the code key. The key and the stimuli are the same for the oral and written versions of the LDST. The written LDST version will be administered first, immediately followed by the oral version. The number of correct substitutions made in 60 seconds is the dependent variable for both test versions.(5)
- (f) The visual verbal learning task (VVLT) visual version, will be used in order to measure memory and verbal learning. In this test, 15 words are visually presented, one after the other, at 2-s intervals. The participants are then asked to recall as many words as possible, in a random order. This procedure will be repeated five times. When the fifth trial has completed, a fixed battery of other cognitive tests will be administered for about 20 minutes. After the delay, unexpectedly for the participant, the instruction will be given to recall the words learned (delayed recall). This will be followed immediately by a recognition test, involving yes/no recognition of the fifteen words intermixed with fifteen

nontarget words. Dependent variables are the total number of recalled words in the first three trials, the number of words recalled after 20 minutes and the number of words recognized in the recognition trial.(6)

- (g) Digit span from the Wechsler Adult Intelligence Scale III (WAIS-III) as a measure of short-term memory. This test consists of two parts, namely orally presented digits forward and digits backwards. Subjects are required to repeat 3 9 digits forward and 2 9 digits backwards. There are two trials at each series length, and the test continues until both trials of a series length are failed. One point is awarded for each correct trial.(7)
- (h) The key-search of the Behavioural Assessment of the Dysexecutive Syndrome will be used as a measure of executive functioning. It is claimed that this test assesses ability to plan a strategy to solve a problem (finding a key lost in a field). The score is based on a number of criteria, including whether the rater believes the strategy to be systematic, efficient and likely to be effective. A penalty is imposed for lack of speed.
- (i) The zoo-map test of the Behavioural Assessment of the Dysexecutive Syndrome as a measure of executive functions. This is a test to assess ability independently to formulate and implement a plan (high demand condition) and to follow a pre-formulated plan (low demand condition). It involves plotting or following a route through a map that does not contravene a set of rules. The score is based on the successful implementation of the plan. Penalties are imposed for rule breaks and lack of speed.(8)
- (j) A validated Dutch translation of the Cognitive Failure Questionnaire (CFQ) which is a 25item self-report inventory and comprises four main subscales: absent-mindedness, social interactions, names and words, and orientation. Participants are asked to indicate on a 5point scale how often they experience subjective cognitive failures. The scale ranges from 'never (0)', 'very rarely (1)', 'occasionally (2)', 'quite often (3)', to 'very often (4)'. Total scores range between 0-100, with a higher scores indicating more subjectively experienced cognitive failures.(9)

### Additional tables

Test name	Subscore or subtest	Parameter measures
Objective measures		
Groninger Intelligence Test (GIT)	Subtests: vocabulary, mental rotation, figure discovery, doing sums, analogies, fluency	Verbal comprehension, visualisation, perceptual intelligence, numeracy, reasoning, word fluency, and intelligence quotient (IQ)
Mini-Mental State Examination (MMSE)	Subscore: total score	Global cognitive functioning
Stroop Color-Word Test (SCWT ()	Subtests: Card I, card II, card III, interference	(Selective) attention, general information processing speed, inhibition, and interference susceptibility
Concept Shifting Test (CST)	Subtests: CST-A, CST-B, CST-C, CST interference	(Divided) attention, information processing speed, simple motor speed, visual conceptual and visuomotor tracking, and mental flexibility
Letter Digit Substitution Test (LDST)	Subtests: written, oral, motor	Attention, information processing speed, psychomotor speed
Visual Verbal Learning Test (VVLT), direct and delayed recall	Subscores: Trial 1, 2, 3, 4, and 5, total, delayed recall, recognition, retention	Verbal learning and memory
Digit Span (DS) from the WAIS-R	Subtests: Forward, backward, total	Verbal immediate memory, working memory, and general auditory attention
Behavioural Assessment of the Dysexecutive Syndrome (BADS)	Subtests: Key search, zoo map	Planning and priority setting
Subjective measures		
Cognitive Failure Questionnaire (CFQ)	Subscores: absent-mindedness, social interactions, names and words and orientation, and total score	Cognitive failures in daily life

 Table S1. Neuropsychological outcome measures

Abbreviations: BADS, Behavioural Assessment of the Dysexecutive Syndrome; CFQ, Cognitive Failure Questionnaire; CST, Concept Shifting Test; DS, Digit Span; GIT, Groninger Intelligence Test, LDST, Letter Digit Substitution Test; MMSE, Mini-Mental State Examination; SCWT, Stroop Color-Word Test; VVLT, Visual Verbal Learning Test.

Test	Subscore or subtest	Parameter measures
name		
GIT-II	Animal naming (number of animal names)*	Semantic fluency
SCWT	Card III (time in seconds) <sup>+</sup>	Attentional inhibition of a dominant response
CST	CST-C (time in seconds) <sup>†</sup>	Alternating attention
LDST	60 Sec (number correct: 0-125) <sup>‡</sup>	Psychomotor speed and speed of information processing
VVLT	Total recall (number correct: 0-75) <sup>‡</sup>	Overall verbal learning
	Delayed recall (number correct: 0-15) <sup>‡</sup>	Verbal memory after an interval

Table S2. Neuropsychological tests for the evaluation of general cognitive impairment

At least 2 out of 6 subtest Z scores should be –1SD for the patients with COPD with general cognitive impairment. Abbreviations: CST, Concept Shifting Test; GIT, Groninger Intelligence Test; LDST, Letter Digit Substitution Test; SCWT, Stroop Color-Word Test; VVLT, Visual Verbal Learning Test. \*, Indicates score has no upper limit; <sup>†</sup>, Higher scores indicate worse performance; <sup>‡</sup>, Higher scores indicate better performance; Score or scale ranges are in parentheses

Test	Subscore or subtest	Parameter measures
name		
Psychom	otor speed	
SCWT	Card I (time in seconds)*	Reading speed
CST	CST-A (time in seconds) <sup>*</sup>	Simple motor speed
LDST	60 Sec written and oral (number correct: 0-125) <sup>+</sup>	Psychomotor speed and speed of information
		processing
Planning		
BADS	Key search (profile score: 0-4) <sup>+</sup>	Planning and priority setting
	Zoo map (profile score: $0-4$ ) <sup>†</sup>	
Working	memory	
VVLT	Trial 1 (number correct: 0-15) <sup>†</sup>	Immediate verbal span
DS	Backward (span: 0-7) <sup>+</sup>	Working memory
Verbal m	emory	
VVLT	Total recall (number correct: 0-75) <sup>+</sup>	Overall verbal learning and verbal memory
	Delayed recall (number correct: 0-15) <sup>†</sup>	after an interval
	Retention (percentage of words that were retained	
	from the immediate to the delayed score) <sup>+</sup>	
Cognitive	flexibility	
SCWT	Card III (time in seconds)*	Attentional inhibition of a dominant response
CST	CST-C (time in seconds)*	Alternating attention

Table S3. Neuropsychological tests for the evaluation of compound performance indices

Abbreviations: SCWT, Stroop Color-Word Test; CST, Concept Shifting Test; LDST, Letter Digit Substitution Test; BADS, Behavioural Assessment of the Dysexecutive Syndrome; VVLT, Visual Verbal Learning Test; DS, Digit Span. \*, Higher scores indicate worse performance. Score or scale ranges are in parentheses. \*, Higher scores indicate better performance.

Outcome measure	<b>COPD</b> patients	Controls	Adjusted P-
	(n=90)	(n=90)	value*
Global cognitive functioning			
MMSE, mean (SD) <sup>+</sup>	27.4 (2.3)	28.1 (1.6)	0.068
Global cognitive impairment (MMSE ≤24), n (%)	7 (7.8)	2 (2.2)	0.356
Domain-specific cognition			
Psychomotor speed (compound z-score), mean (SD)	-0.5 (1.1)	0.3 (0.7)	< 0.001
SCWT card I, mean (SD) <sup>†</sup>	19.1 (5.6)	17.0 (2.6)	0.035
CST-A, mean (SD)	28.1 (15.8)	21.2 (5.6)	0.003
LDST 60 sec written, mean (SD)	25.2 (7.2)	31.7 (5.7)	<0.001
LDST 60 sec oral, mean (SD)	31.1 (7.5)	37.1 (6.5)	<0.001
Planning (compound z-score), mean (SD)	-0.3 (0.8)	0.3 (0.6)	< 0.001
BADS key search, mean (SD)	2.2 (1.5)	3.1 (1.2)	0.004
BADS zoo map, mean (SD) <sup>+</sup>	2.2 (0.8)	2.7 (0.7)	< 0.001
Working memory (compound z-score), mean (SD)	-0.6 (0.8)	-0.2 (0.8)	0.087
VVLT trial 1, mean (SD)	4.4 (1.9)	5.5 (2.1)	0.003
DS backward, mean (SD)	3.0 (1.1)	3.1 (1.2)	0.485
Verbal memory (compound z-score), mean (SD)	-0.5 (1.1)	0.0 (1.0)	0.004
VVLT total recall 1–5, mean (SD)	40.2 (10.8)	47.3 (10.2)	< 0.001
VVLT delayed recall, mean (SD)	7.3 (3.5)	9.1 (3.2)	0.011
VVLT retention max, mean (SD) <sup>+</sup>	0.6 (0.3)	0.7 (0.2)	0.060
Cognitive flexibility (compound z-score), mean (SD)	-1.2 (1.6)	-0.0 (0.8)	< 0.001
SCWT card III, mean (SD) <sup>+</sup>	60.9 (26.7)	43.0 (13.0)	< 0.001
CST-C, mean (SD)	51.1 (26.3)	35.3 (11.6)	< 0.001
General cognitive impairment (2 out of 6 subtest Z	51 (56.7)	12 (13.3)	0.128
scores -1SD), n (%)			
Cognitive complaints			
CFQ absent-mindedness, mean (SD)	8.2 (5.4)	7.1 (3.6)	0.615
CFQ social interactions, mean (SD)	5.7 (3.3)	4.9 (2.2)	0.685
CFQ names and words, mean (SD)	5.7 (2.6)	4.9 (2.0)	0.028
CFQ orientation, mean (SD)	2.7 (2.6)	2.3 (1.7)	0.638
CFQ total score, mean (SD)	31.8 (17.3)	27.3 (11.0)	0.843

Table S4. Raw unadjusted means on neuropsychological measures, compound z-scores, and *P*-values adjusted for matching variables and comorbidities in patients with COPD and controls

Abbreviations: BADS, Behavioural Assessment of the Dysexecutive Syndrome; CFQ, Cognitive Failure Questionnaire; CST, Concept Shifting Test; DS, Digit Span; LDST, Letter Digit Substitution Test; MMSE, Mini-Mental State Examination; SCWT, Stroop Color-Word Test; SD, standard deviation; VVLT, Visual Verbal Learning Test. \*, Adjusted for matching variables age, educational level, and smoking status, and comorbidities (myocardial infarction, peripheral vascular disease, hemiplegia, clinically relevant symptoms of depression, and clinically relevant symptoms of anxiety). <sup>+</sup>, Nonparametric statistical tests have been used because of skewed data.

Table S5. Raw unadjusted means on neuropsychological measures and compound z-scores in patients with
COPD with and without oxygen therapy

Outcome measure	COPD patients with	COPD patients without	P-value
	oxygen therapy (n=18)	oxygen therapy (n=72)	
Global cognitive functioning			
MMSE, mean (SD) <sup>*</sup>	27.3 (2.9)	27.4 (2.1)	0.620
Global cognitive impairment (MMSE	2 (11.1)	5 (6.9)	0.426
≤24), n (%)			
Domain-specific cognition			
Psychomotor speed (compound z-	-0.6 (1.4)	-0.4 (0.9)	0.912
score), mean (SD) <sup>*</sup>			
SCWT card I, mean (SD) <sup>*</sup>	19.4 (8.6)	19.1 (4.6)	0.443
CST-A, mean (SD) <sup>*</sup>	31.9 (29.1)	27.2 (10.2)	0.972
LDST 60 sec written, mean (SD)	24.1 (8.1)	25.5 (6.9)	0.479
LDST 60 sec oral, mean (SD)	31.3 (8.9)	31.1 (7.2)	0.911
Planning (compound z-score), mean	-0.0 (0.8)	-0.3 (0.7)	0.200
(SD)			
BADS key search, mean (SD)*	2.8 (1.5)	2.1 (1.5)	0.071
BADS zoo map, mean (SD)	2.2 (0.8)	2.2 (0.8)	0.753
Working memory (compound z-score),	-0.4 (0.9)	-0.6 (0.7)	0.350
mean (SD)			
VVLT trial 1, mean (SD)*	4.9 (2.1)	4.2 (1.8)	0.158
DS backward, mean (SD)*	2.9 (1.1)	3.0 (1.1)	0.941
Verbal memory (compound z-score),	-0.3 (1.1)	-0.5 (1.1)	0.418
mean (SD)			
VVLT total recall 1–5, mean (SD)	41.7 (12.5)	39.9 (10.4)	0.535
VVLT delayed recall, mean (SD)	7.8 (3.9)	7.2 (3.4)	0.529
VVLT retention max, mean (SD)*	0.7 (0.3)	0.6 (0.3)	0.904
Cognitive flexibility (compound z-	-1.3 (1.8)	-1.1 (1.5)	0.793
score), mean (SD) <sup>*</sup>			
SCWT card III, mean (SD)*	61.1 (33.4)	60.8 (25.0)	0.493
CST-C, mean (SD)*	59.1 (39.6)	49.0 (21.8)	0.259
General cognitive impairment (2 out of	9 (50.0)	42 (58.3)	0.353
6 subtest Z scores -1SD), n (%)			
Cognitive complaints			
CFQ absent-mindedness, mean (SD)*	9.2 (5.9)	8.0 (5.3)	0.268
CFQ social interactions, mean (SD)	5.9 (3.7)	5.7 (3.2)	0.823
CFQ names and words, mean (SD)	5.8 (3.1)	5.6 (2.5)	0.840
CFQ orientation, mean (SD)*	2.7 (3.4)	2.6 (2.4)	0.656
CFQ total score, mean (SD)*	34.0 (21.0)	31.2 (16.4)	0.668

Abbreviations: BADS, Behavioural Assessment of the Dysexecutive Syndrome; CFQ, Cognitive Failure Questionnaire; CST, Concept Shifting Test; DS, Digit Span; LDST, Letter Digit Substitution Test; MMSE, Mini-Mental State Examination; SCWT, Stroop Color-Word Test; SD, standard deviation; VVLT, Visual Verbal Learning Test..\*, Nonparametric statistical tests have been used because of skewed data.

Outcome measure	COPD patients with	COPD patients	P-
	symptoms of	without symptoms of	value
	depression (n=19)	depression (n=71)	
Global cognitive functioning			
MMSE, mean (SD) <sup>*</sup>	27.9 (1.7)	27.2 (2.4)	0.321
Global cognitive impairment (MMSE ≤24), n	1 (5.3)	6 (8.5)	0.542
(%)			
Domain-specific cognition			
Psychomotor speed (compound z-score),	-0.4 (0.9)	-0.5 (1.1)	0.925
mean (SD) <sup>*</sup>			
SCWT card I, mean (SD)*	18.9 (4.6)	19.2 (5.8)	0.953
CST-A, mean (SD)*	25.9 (6.7)	28.7 (17.4)	0.707
LDST 60 sec written, mean (SD)	25.2 (7.8)	25.2 (7.0)	0.983
LDST 60 sec oral, mean (SD)	30.8 (6.4)	31.2 (7.8)	0.867
Planning (compound z-score), mean (SD)	-0.3 (0.7)	-0.2 (0.8)	0.559
BADS key search, mean (SD)*	2.0 (1.6)	2.3 (1.5)	0.507
BADS zoo map, mean (SD)	2.2 (0.6)	2.2 (0.9)	0.945
Working memory (compound z-score), mean (SD)	-0.6 (0.5)	-0.6 (0.8)	0.919
VVLT trial 1, mean (SD) <sup>*</sup>	4.8 (2.3)	4.3 (1.8)	0.440
DS backward, mean (SD)*	2.7 (1.0)	3.1 (1.1)	0.277
Verbal memory (compound z-score), mean (SD)	-0.3 (0.9)	-0.5 (1.1)	0.465
VVLT total recall 1–5, mean (SD)	43.0 (8.7)	39.5 (11.2)	0.213
VVLT delayed recall, mean (SD)	8.0 (2.4)	7.1 (3.7)	0.335
VVLT retention max, mean (SD)*	0.7 (0.2)	0.6 (0.3)	0.498
Cognitive flexibility (compound z-score), mean (SD)*	-1.3 (1.3)	-1.2 (1.6)	0.409
SCWT card III, mean (SD)*	62.3 (17.7)	60.5 (28.7)	0.134
CST-C, mean (SD) <sup>*</sup>	50.0 (20.1)	51.3 (27.9)	0.839
General cognitive impairment (2 out of 6	13 (68.4)	38 (53.5)	0.184
subtest Z scores -1SD), n (%)			
Cognitive complaints			
CFQ absent-mindedness, mean (SD)*	11.1 (6.7)	7.4 (4.8)	0.013
CFQ social interactions, mean (SD)	6.8 (3.8)	5.4 (3.1)	0.097
CFQ names and words, mean (SD)	5.6 (2.9)	5.7 (2.5)	0.947
CFQ orientation, mean (SD)*	3.5 (3.4)	2.4 (2.4)	0.109
CFQ total score, mean (SD) <sup>*</sup>	39.4. (22.3)	29.7 (15.3)	0.054

Table S6. Raw unadjusted means on neuropsychological measures and compound z-scores in patients with COPD with and without clinically relevant symptoms of depression

Abbreviations: see table S4.<sup>\*</sup>, Nonparametric statistical tests have been used because of skewed data.

Outcome measure	COPD patients with	COPD patients	P-
	(n=28)	anxiety (n=62)	value
Global cognitive functioning			
MMSE, mean (SD) <sup>*</sup>	27.3 (2.5)	27.4 (2.2)	0.891
Global cognitive impairment (MMSE ≤24), n (%)	3 (10.7)	4 (6.5)	0.376
Domain-specific cognition			
Psychomotor speed (compound z-score), mean (SD)*	-0.4 (1.0)	-0.5 (1.1)	0.889
SCWT card I, mean (SD)*	19.0 (5.1)	19.2 (5.8)	0.747
CST-A, mean (SD) <sup>*</sup>	25.8 (7.7)	29.2 (18.3)	0.403
LDST 60 sec written, mean (SD)	25.6 (8.2)	25.0 (6.7)	0.689
LDST 60 sec oral, mean (SD)	30.9 (7.5)	31.2 (7.6)	0.885
Planning (compound z-score), mean (SD)	-0.3 (0.7)	-0.2 (0.8)	0.631
BADS key search, mean (SD)*	2.0 (1.5)	2.3 (1.5)	0.416
BADS zoo map, mean (SD)	2.3 (0.7)	2.2 (0.9)	0.629
Working memory (compound z-score), mean (SD)	-0.6 (0.7)	-0.5 (0.8)	0.618
VVLT trial 1, mean (SD) <sup>*</sup>	4.8 (2.1)	4.2 (1.7)	0.232
DS backward, mean (SD)*	2.6 (1.0)	3.1 (1.1)	0.036
Verbal memory (compound z-score), mean (SD)	-0.4 (1.0)	-0.5 (1.1)	0.448
VVLT total recall 1–5, mean (SD)	43.2 (10.6)	38.9 (10.7)	0.083
VVLT delayed recall, mean (SD)	8.0 (3.2)	7.0 (3.6)	0.325
VVLT retention max, mean (SD)*	0.7 (0.2)	0.6 (0.3)	0.427
Cognitive flexibility (compound z-score), mean (SD) <sup>*</sup>	-1.2 91.5)	-1.2 (1.6)	0.428
SCWT card III, mean (SD) *	61.8 (24.8)	60.5 (27.7)	0.491
CST-C, mean (SD)*	49.5 (17.7)	51.7 (29.5)	0.679
General cognitive impairment (2 out of 6	18 (64.3)	33 (53.2)	0.227
subtest Z scores -1SD), n (%)			
Cognitive complaints			
CFQ absent-mindedness, mean (SD)*	9.6 (6.1)	7.6 (5.0)	0.113
CFQ social interactions, mean (SD)	6.4 (3.4)	5.4 (3.2)	0.202
CFQ names and words, mean (SD)	5.4 (2.9)	5.8 (2.5)	0.503
CFQ orientation, mean (SD)*	3.2 (3.0)	2.4 (2.4)	0.223
CFQ total score, mean (SD)*	35.4 (19.9)	30.1 (15.9)	0.255

Table S7. Raw unadjusted means on neuropsychological measures and compound z-scores in patients with COPD with and without clinically relevant symptoms of anxiety

Abbreviations: see table S4.<sup>\*</sup>, Nonparametric statistical tests have been used because of skewed data.

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