

Supplemental Online Content

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eFigure. Participant Flow Chart

eTable 1. St. Jude Lifetime Cohort Aging-Related Deficits Accumulation Index

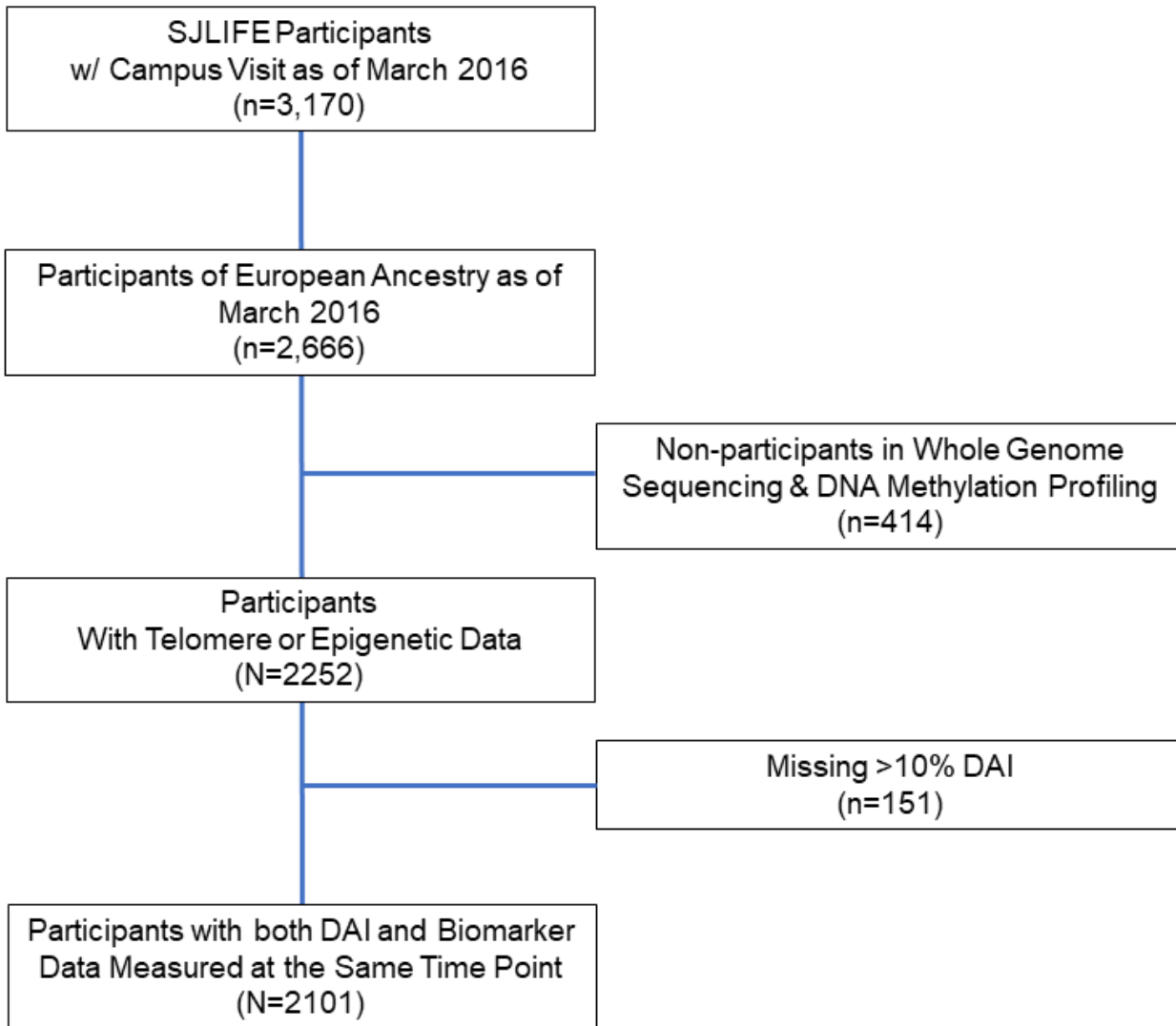
eTable 2. Characteristics of Those With and Without Complete Data

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This supplemental material has been provided by the authors to give readers additional information about their work.

eFigure: Participant Flow Chart



eTable 1: St. Jude Lifetime Cohort Aging-Related Deficits Accumulation Index

DAI Construct	SJLIFE ITEM	Value/Criteria	DAI Item Weight
1. Can take bath/shower	Does your health now limit you in Bathing or dressing yourself? If so, how much?	Yes limited a lot	1
		Yes, limited a little	0.5
		No Not limited at all	0
		Missing	-
2. Can walk	Does your health now limit you in Walking 100 yards? If so, how much?	Yes limited a lot	1
		Yes, limited a little	0.5
		No Not limited at all	0
		Missing	-
3. Health limited moderate activities	Does your health now limit you in Moderate activities? If so, how much?	Yes limited a lot	1
		Yes, limited a little	0.5
		No Not limited at all	0
		Missing	-
4. Can eat and dress	Because of any impairment of health problems, do you need the help of other persons with personal care needs, such as eating, bathing dressing or getting around your home?	Yes	1
		No	0
		Missing	-
5. Take care of one's self	Because of any impairment or health problems do you need the help of other persons in handling routine needs, such as everyday household chores, doing necessary business, shopping, or getting around for other purposes?	Yes	1
		No	0
		Missing	-
6. Trouble getting to bathroom on time	Have you ever been told by a doctor or other health care professional that you have or have had urinary incontinence?	Yes, and the condition is still present	1
		No or Yes but the condition is no longer present	0
		Missing	-
7. Health limited climbing stairs	Does your health now limit you in climbing several flights of stairs? If so, how much?	Yes limited a lot	1
		Yes, limited a little	0.5
		No Not limited at all	0
		Missing	-
8. Can go shopping for groceries or clothes	Does your health now limit you in lifting or carrying groceries? If so, how much?	Yes limited a lot	1
		Yes, limited a little	0.5
		No Not limited at all	0
		Missing	-
9. Can do your housework	During the past 4 weeks, how much did pain interfere with your normal work,	Extremely	1
		Quite a bit	0.75

DAI Construct	SJLIFE ITEM	Value/Criteria	DAI Item Weight
	including both work outside the home and housework?	Moderately	0.5
		A little bit	0.25
		Not at all	0
		Missing	-
10. Pain	How much bodily pain have you had during the past 4 weeks?	Very Severe	1
		Severe	0.8
		Moderate	0.6
		Mild	0.4
		Very Mild	0.2
		None	0
		Missing	-
11. General Health	In general, how would you say your health is?	Poor	1
		Fair	0.75
		Good	0.5
		Very Good	0.25
		Excellent	0
		Missing	-
12. Physical health limited work or activities	During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health? A: Cut down on the amount of time you spent on work or other activities	All of the time	1
		Most of the time	0.75
		Some of the time	0.5
		A little of the time	0.25
		None of the time	0
		Missing	-
13. Emotional problems limited work or activities	During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems? A: Cut down on the amount of time you spent on work or other activities.	All of the time	1
		Most of the time	0.75
		Some of the time	0.5
		A little of the time	0.25
		None of the time	0
		Missing	-
14. Physical or emotional health interfered with social activities	During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?	Extremely	1
		Quite a bit	0.75
		Moderately	0.5
		Slightly	0.25
		Not at all	0
		Missing	-
	During the past 4 weeks, how much of the time have you had any of the	All of the time	1
		Most of the time	0.75

DAI Construct	SJLIFE ITEM	Value/Criteria	DAI Item Weight
15. Physical health resulted in accomplishing less	following problems with your work or other regular daily activities as a result of your physical health? B: Accomplished less than you would like	Some of the time	0.5
		A little of the time	0.25
		None of the time	0
		Missing	-
16. Emotional problems resulted in accomplishing less	During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems? B: Accomplished less than you would like.	All of the time	1
		Most of the time	0.75
		Some of the time	0.5
		A little of the time	0.25
		None of the time	0
17. Had a lot of energy	How much of the time during the past four weeks did you have a lot of energy?	Missing	-
		All of the time	0
		Most of the time	0.25
		Some of the time	0.5
		A little of the time	0.75
		None of the time	1
18. Felt downhearted or blue	How much of the time during the past four weeks have you felt downhearted and depressed?	Missing	-
		All of the time	1
		Most of the time	0.75
		Some of the time	0.5
		A little of the time	0.25
19. Felt calm or peaceful	How much of the time during the past four weeks have you felt calm and peaceful?	Missing	-
		All of the time	0
		Most of the time	0.25
		Some of the time	0.5
		A little of the time	0.75
20. Heart Disease Comorbidity:	Clinically Assessed and CTCAE Graded Cardiovascular Conditions <ul style="list-style-type: none"> - Atrioventricular Heart Block - Conduction Abnormalities - Prolonged QT Interval - Cardiac Dysrhythmia 	≥ 1 Grade 3 or 4 Condition	1

DAI Construct	SJLIFE ITEM	Value/Criteria	DAI Item Weight
	<ul style="list-style-type: none"> - Sinus Bradycardia - Sinus Tachycardia - Cardiomyopathy - Right Ventricular Systolic Dysfunction - Cor Pulmonale - Pulmonary Hypertension - Heart Valve Disorder - Pericarditis - Aortic Root Aneurysm - Atrial Myxoma - Thrombus - Vascular Disease - Hypertriglyceridemia - Hypercholesterolemia - Myocardial Infarction - Raynaud's Phenomenon 	<p>≥ 1 Grade 2 Condition (but no grade 3 or 4)</p> <p>None or Only Grade 1 Conditions</p> <p>Missing</p>	<p>0.5</p> <p>0</p> <p>-</p>
21. Diabetes Comorbidity	Clinically Assessed and CTCAE Graded Abnormal Glucose Metabolism	<p>≥ 1 Grade 3 or 4 Condition</p> <p>≥ 1 Grade 2 Condition (but no grade 3 or 4)</p> <p>None or Only Grade 1 Conditions</p> <p>Missing</p>	<p>1</p> <p>0.5</p> <p>0</p> <p>-</p>
22. Respiratory Comorbidity:	<p>Clinically Assessed and CTCAE Graded Respiratory Conditions</p> <ul style="list-style-type: none"> - Asthma - Chronic Obstructive Pulmonary Disease - Obstructive, Restrictive, Diffusion Deficits - Pleural Space Disorders - Pulmonary Embolism - Obstructive Sleep Apnea 	<p>≥ 1 Grade 3 or 4 Condition</p> <p>≥ 1 Grade 2 Condition (but no grade 3 or 4)</p> <p>None or Only Grade 1 Conditions</p> <p>Missing</p>	<p>1</p> <p>0.5</p> <p>0</p> <p>-</p>
23. Chronic Liver, Kidney, or Gastrointestinal Comorbidity:	<p>Clinically Assessed and CTCAE Graded Gastrointestinal/Renal Conditions</p> <ul style="list-style-type: none"> - Constipation - Cholecystitis - Chronic Kidney Disease - Chronic Hematuria - Dysphagia 	<p>≥ 1 Grade 3 or 4 Condition</p>	<p>1</p>

DAI Construct	SJLIFE ITEM	Value/Criteria	DAI Item Weight
	<ul style="list-style-type: none"> - Esophageal Stricture - Esophageal Varices - Esophagitis - Enterocolitis - Fecal Incontinence - Gastritis/Duodenitis - Gastroesophageal Reflux Disease - Hepatopathy - Hepatic Failure - Pancreatitis - Pancreatic Insufficiency - Fibrosis/Cirrhosis - Portal Hypertension - Proctitis - Steatohepatitis - Veno-occlusive Disease of Liver - Urinary Bladder Dysfunction - Urinary Tract Calculi 	≥ 1 Grade 2 Condition (but no grade 3 or 4)	0.5
		None or Only Grade 1 Conditions	0
		Missing	-
24. Other Cancer/Leukemia Comorbidity:	Secondary and Recurrent Malignancies excluding "Non Melanoma Skin Cancer"	≥ 1 Grade 3 or 4 Condition	1
		≥ 1 Grade 2 Condition (but no grade 3 or 4)	0.5
		None or Only Grade 1 Conditions	0
		Missing	-
25. Glaucoma, Cataracts, or decreased vision Comorbidity:	<p>Have you ever been told by a doctor or other health care professional you have or have had legal blindness, problems with double vision, or other eye problems?</p> <p>Clinically Assessed and CTCAE Graded Ocular Conditions</p> <ul style="list-style-type: none"> - Cataract - Glaucoma 	≥ 1 Grade 3 or 4 Condition	1
		≥ 1 Grade 2 Condition (but no grade 3 or 4)	0.5
		None or Only Grade 1 Conditions	0
		Missing	-
26. Blood Pressure Comorbidity:	Clinically Assessed and CTCAE Graded Hypertension	≥ 1 Grade 3 or 4 Condition	1
		≥ 1 Grade 2 Condition (but no grade 3 or 4)	0.5
		None or Only Grade 1 Conditions	0

DAI Construct	SJLIFE ITEM	Value/Criteria	DAI Item Weight
		Missing	-
27. Cerebrovascular disease	Clinically Assessed and CTCAE Graded Neurologic Conditions - Cerebrovascular Disease - Intracranial Hemorrhage - Cerebrovascular Accident	≥ 1 Grade 3 or 4 Condition	1
		≥ 1 Grade 2 Condition (but no grade 3 or 4)	0.5
		None or Only Grade 1 Conditions	0
		Missing	-
28. Osteoporosis Comorbidity	Clinically Assessed and CTCAE Graded Bone Mineral Density: BMD below expected range for age and sex (adjusted for amputation)	≥ 1 Grade 3 or 4 Condition	1
		≥ 1 Grade 2 Condition (but no grade 3 or 4)	0.5
		None or Only Grade 1 Conditions	0
		Missing	-
29. Thyroid Comorbidity	Clinically Assessed and CTCAE Graded Endocrine Conditions: - Hypothyroidism - Hyperthyroidism - Thyroid cyst/nodule - Hypoparathyroidism - Hyperparathyroidism	≥ 1 Grade 3 or 4 Condition	1
		≥ 1 Grade 2 Condition (but no grade 3 or 4)	0.5
		None or Only Grade 1 Conditions	0
		Missing	-
30. Shingles or other chronic infections	Have you ever had Zoster (shingles)? And do you take chronic medications because of shingles? Clinically Assessed and CTCAE Graded - Immunodeficiency - Chronic Hepatitis - HIV Infection	Any grade 3 or higher condition or Any "yes, and the condition is still present" (for questionnaire)	1
		Any grade 2 or higher condition or Any "yes, and the condition is still present" (for questionnaire)	0.5
		No grade 2 or higher condition and No or Yes, but the condition is no longer present (for questionnaire)	0
		Missing	-
32. Weight/BMI	Self-reported current weight and height	Obese BMI ≥ 30	1
		Underweight BMI < 18.5	1
		Normal/Overweight BMI ≥ 18.5 and < 30	0
		Missing	-
33. Poly-pharmacy	Self-reported medications taken regularly during the last two years	≥ 5 Prescription Meds	1
		< 5 Prescription Meds	0
		Missing	-
34. Timed Up and Go	Timed Up and Go[1, 2]	> 6 seconds	1
		≤ 6 seconds	0

DAI Construct	SJLIFE ITEM	Value/Criteria	DAI Item Weight
		Missing	-
35. Depression	Brief Symptom Inventory Depression Subscale[3]	T-Score <=65	0
		65> T-score <=70	0.5
		T-score >70	1
		Missing	-
36. Anxiety	Brief Symptom Inventory Anxiety Subscale[3]	T-Score <=65	0
		65> T-score <=70	0.5
		T-score >70	1
		Missing	-
37. Fatigue	Vitality subscale of Short-Form Health Survey-36[4]	T-Score <10 th percentile	1
		T-Score >=10 th percentile	0
		Missing	-
38. Balance Problems	Have you ever been told by a doctor or other health care professional you have or have had problems with balance, equilibrium or ability to reach for or manipulate objects?	Any "yes, and the condition is still present"	1
		No or Yes, but the condition is no longer present, not sure	0
		Missing	-
39. Hearing Problems	Have you ever been told by a doctor or other health care professional you have or have had hearing loss requiring hearing aid, deafness, tinnitus ?	Any "yes, and the condition is still present"	1
		No or Yes, but the condition is no longer present	0
		Missing	-
40. Smell and taste problems	Have you ever been told by a doctor or other health care professional you have or have had abnormal sense of taste or loss of taste or smell lasting for 3 months or more?	Any "yes, and the condition is still present"	1
		No or Yes, but the condition is no longer present	0
		Missing	-
41. Weakness	Have you ever been told by a doctor or other health care professional you have or have had weakness or inability to move arms or legs?	Yes and the condition is still present	1
		No or Yes but the condition is longer present	0
		Missing	-
42. Loss of sense of touch	Have you ever been told by a doctor or other health care professional you have or have had decreased sense of touch or feeling in hands, fingers, arms or legs	Yes and the condition is still present	1
		No or Yes but the condition is longer present	0
		Missing	-
43. Problems chewing and swallowing	Have you ever been told by a doctor or other health care professional you have or have had problems chewing or swallowing solids or liquids?	Yes and the condition is still present	1
		No or Yes but the condition is longer present	0
		Missing	-

DAI Construct	SJLIFE ITEM	Value/Criteria	DAI Item Weight
44. Vigorous Activity	Does your health now limit you in vigorous activities, such as running, lifting heavy objects, participating in strenuous sports?	Yes limited a lot	1
		Yes, limited a little	0.5
		No Not limited at all	0
		Missing	-
44. Arthritis	Clinically Assessed and CTCAE graded: -arthritis -arthralgia	≥ 1 Grade 3 or 4 Condition	1
		≥ 1 Grade 2 Condition (but no grade 3 or 4)	0.5
		None or Only Grade 1 Conditions	0
		Missing	-

eTable 2: Characteristics of those with and without complete data.

	Without Biomarker Data n=565	With Biomarker Data n=2101
Age at Baseline Evaluation (mean(SD))	30.5 (8.0)	32.5 (8.6)
	N(%)	N(%)
Sex		
Female	264 (46.7)	979 (46.6)
Male	301 (53.3)	1122 (53.4)
Diagnosis		
Retinoblastoma	17 (3.0)	53 (2.5)
Wilms tumor	24 (4.2)	135 (6.4)
Others	44 (7.8)	114 (5.4)
Acute lymphoblastic leukemia	202 (35.8)	717 (34.1)
Acute Myeloid Leukemia	43 (7.6)	54 (2.6)
CNS tumor	51 (9.0)	227 (10.8)
Neuroblastoma	15 (2.7)	105 (5.0)
Hodgkin lymphoma	64 (11.3)	260 (12.4)
Non-Hodgkin lymphoma	34 (6.0)	166 (7.9)
Osteosarcoma	24 (4.2)	72 (3.4)
Ewing sarcoma	17 (3.0)	75 (3.6)
Soft tissue sarcoma	30 (5.3)	123 (5.9)
Cranial Radiation ¹		
No	342 (62.2)	1431 (68.8)
Yes	208 (37.8)	649 (31.2)
Chest Radiation ²		
No	391 (71.1)	1611 (77.3)
Yes	159 (28.9)	474 (22.7)
Abdomen/Pelvic radiation ³		
No	354 (64.5)	1456 (69.9)
Yes	195 (35.5)	628 (30.1)
Vincristine		
No	187 (33.1)	610 (29.0)
Yes	378 (66.9)	1491 (71.0)
Anthracyclines		
No	203 (35.9)	872 (41.5)
Yes	362 (64.1)	1229 (58.5)
Alkylating Agents		
No	198 (35.0)	861 (41.0)
Yes	367 (65.0)	1240 (59.0)
Platinum Agents		

	Without Biomarker Data n=565	With Biomarker Data n=2101
Age at Baseline Evaluation (mean(SD))	30.5 (8.0)	32.5 (8.6)
	N(%)	N(%)
No	476 (84.2)	1867 (88.9)
Yes	89 (15.8)	234 (11.1)
Corticosteroids		
No	277 (49.0)	1074 (51.1)
Yes	288 (51.0)	1027 (48.9)
Neurosurgery		
No	512 (90.6)	1853 (88.2)
Yes	53 (9.4)	248 (11.8)

eTable 3: Specific results from linear regression models examining the associations of mean LTL and EAA among survivors of childhood cancer.

	Mean LTL Residual			Epigenetic Age Acceleration		
	Adjusted Mean (95%CI)	Adjusted Mean Difference (95%CI)	p-value	Adjusted Mean (95%CI)	Adjusted Mean Difference (95%CI)	p-value
Overall						
Low DAI (<0.2)	0.03(-0.03, 0.09)	0.0 (ref.)	-	-0.84(-1.23, -0.45)	0.0 (ref.)	-
Medium DAI (0.2 to <0.35)	-0.05(-0.16, 0.06)	-0.07 (-0.22, 0.07)	0.426	0.93 (0.23, 1.64)	1.77(0.85, 2.69)	<.001
High DAI (>=0.35)	-0.04(-0.18, 0.11)	-0.06 (-0.25, 0.12)	0.679	2.82 (1.87, 3.78)	3.66 (2.47, 4.85)	<.001
Overall Model 2¹						
Low DAI (<0.2)	0.019(-0.07, 0.08)	0.0 (ref.)	-	0.07(-0.38, 0.51)	0.0 (ref.)	-
Medium DAI (0.2 to <0.35)	-0.051(-0.16, 0.06)	-0.06(-0.20, 0.08)	0.575	1.27(0.57, 1.96)	1.20(0.32, 2.09)	0.005
High DAI (>=0.35)	-0.03(-0.18, 0.12)	-0.04(-0.22, 0.15)	0.864	2.63(1.70, 3.55)	2.56(1.41, 3.71)	<.001
Acute Lymphoblastic Leukemia						
Low DAI (<0.2)	-0.06(-0.16, 0.04)	0.0 (ref.)	-	-0.77(-1.39, -0.16)	0.0 (ref.)	-
Medium DAI (0.2 to <0.35)	-0.08(-0.27, 0.12)	-0.02(-0.27, 0.23)	0.982	1.50(0.36, 2.63)	2.27(0.78, 3.76)	0.001
High DAI (>=0.35)	0.01(-0.28, 0.29)	0.06(-0.29, 0.41)	0.902	1.08(-0.61, 2.77)	1.85(-0.22, 3.93)	0.088
Hodgkin Lymphoma						
Low DAI (<0.2)	-0.09(-0.26, 0.08)	0.0 (ref.)	-	3.80(2.71, 4.87)	0.0 (ref.)	-
Medium DAI (0.2 to <0.35)	-0.21(-0.49, 0.07)	-0.11(-0.50, 0.27)	0.741	4.17(2.42, 5.92)	0.37(-2.02, 2.76)	0.922
High DAI (>=0.35)	-0.08(-0.37, 0.21)	0.01(-0.38, 0.41)	0.996	6.00(4.16, 7.84)	2.20(-0.27, 4.68)	0.089
CNS Tumors						
Low DAI (<0.2)	0.11(-0.10, 0.32)	0.0 (ref.)	-	-1.85(-3.08, -0.62)	0.0 (ref.)	-
Medium DAI (0.2 to <0.35)	-0.10(-0.41, 0.21)	-0.21(-0.64, 0.22)	0.458	-2.27(-4.12, -0.42)	-0.41(-2.96, 2.13)	0.916
High DAI (>=0.35)	0.22(-0.24, 0.67)	0.11(-0.47, 0.69)	0.893	2.49(-0.29, 5.26)	4.34(0.82, 7.86)	0.012
Age <30						
Low DAI (<0.2)	-0.02(-0.11, 0.08)	0.0 (ref.)	-	-0.66 (-1.24, -0.08)	0.0 (ref.)	-
Medium DAI (0.2 to <0.35)	-0.01(-0.23, 0.20)	0.01(-0.27, 0.28)	0.999	1.42(0.12, 2.72)	2.08(0.45, 3.71)	0.009
High DAI (>=0.35)	-0.26(-0.64, 0.12)	-0.24(-0.69, 0.21)	0.407	4.28(1.90, 6.67)	4.94(2.14, 7.75)	<.001
Age 30 to <40						
Low DAI (<0.2)	0.13(0.03, 0.22)	0.0 (ref.)	-	-0.49(-1.13, 0.15)	0.0 (ref.)	-
Medium DAI (0.2 to <0.35)	-0.09(-0.27, 0.09)	-0.22(-0.45, 0.01)	0.066	0.01(-0.23, 0.24)	-0.12(-0.42, 0.17)	0.573
High DAI (>=0.35)	0.76(-0.37, 1.90)	1.26(-0.24, 2.75)	0.115	1.75(0.19, 3.31)	2.24(0.31, 4.17)	0.019
Age 40+						
Low DAI (<0.2)	-0.07(-0.20, 0.05)	0.0 (ref.)	-	-1.63(-2.54, -0.71)	0.0 (ref.)	-
Medium DAI (0.2 to <0.35)	-0.04(-0.21, 0.13)	0.04(-0.20, 0.28)	0.926	0.55 (-0.70, 1.77)	2.17 (0.43, 3.92)	0.011
High DAI (>=0.35)	-0.001 (-0.20, 0.19)	0.08 (-0.19, 0.34)	0.766	2.78(1.37, 4.19)	4.41(2.50, 6.31)	<.001

Note: All models were adjusted for sex and time since diagnosis. ¹ Model 2 is further adjusted for treatment exposures that are associated with either mLTL or EAA.

eTable 4: Distribution of DAI groups by age categories.

	Age Group		
	<30	30 to <40	40+
DAI			
Low	617 (79.5)	553 (69.4)	266 (50.4)
Medium	120 (15.5)	158 (19.8)	150 (28.4)
High	39 (5.0)	86 (10.8)	112 (21.2)