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Machine Learning-Based Decision-Making in Geriatrics: Aging Phenotype Calculator and Survival Prognosis

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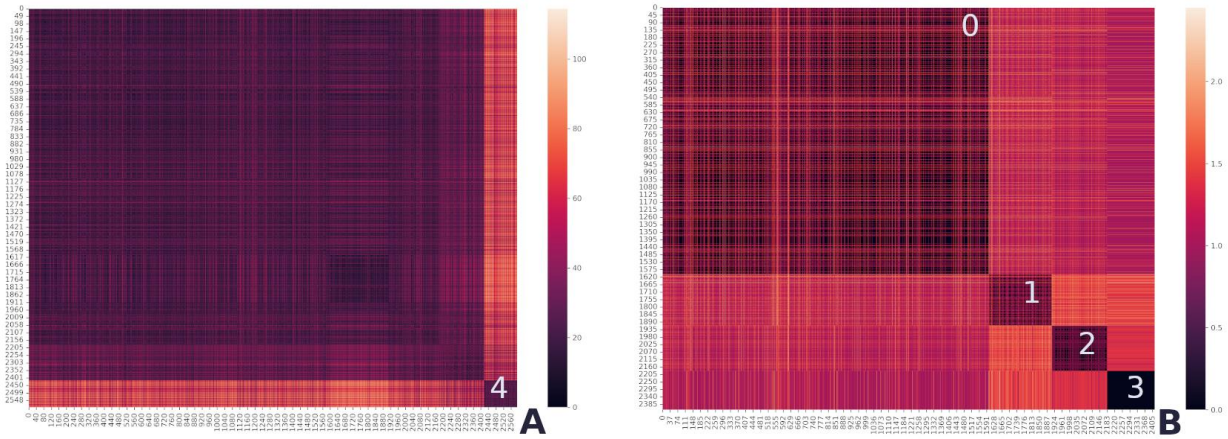

Supplementary Figure 1. Euclidean distance matrix for the first (A) and second (B) clustering steps.

Supplementary Table 1. Physical examination and laboratory testing results in different aging phenotypes (only significant).

Cluster	0	1	2	3	4	p-value (Kruskal test)
Phenotype	**Multimorbid frailty (n=1602)**	**Non-frail (n=309)**	**Metabolic frailty (N=272)**	**Cognitive frailty (N=234)**	**Functional frailty (n=175)**	
Indicator	Me [Q1-Q3]	Me [Q1-Q3]	Me [Q1-Q3]	Me [Q1-Q3]	Me [Q1-Q3]	
Current health indicators						
Right hand grip strength	13.00 [10.00 - 16.00]	13.00 [10.00 - 18.50]	13.00 [10.00 - 16.50]	10.00 [7.00 - 13.50]	7.50 [4.00 - 11.50]	$4.9*10^{-46}$
Left hand grip strength	12.00 [9.00 - 15.05]	13.50 [9.00 - 18.00]	12.00 [9.00 - 16.00]	9.00 [7.00 - 12.00]	6.25 [3.50 - 10.00]	$1.3*10^{-52}$
Systolic blood pressure	135.00 [126.00 - 146.00]	138.00 [127.00 - 150.00]	135.50 [127.00 - 148.75]	130.00 [120.00 - 150.00]	130.00 [110.00 - 140.00]	$3.1*10^{-5}$
BMI	25.50 [23.40 - 28.30]	24.80 [23.10 - 27.60]	26.60 [24.20 - 30.40]	25.15 [22.92 - 27.70]	24.20 [21.00 - 27.50]	$1.7*10^{-8}$
Waist circumference	92.00 [86.00 - 98.00]	92.00 [82.00 - 98.00]	95.00 [87.00 - 103.00]	89.50 [80.00 - 98.00]	90.00 [79.00 - 98.00]	$2.1*10^{-5}$
13B-T (total bilirubin)	8.90 [6.67 - 12.40]	10.50 [7.45 - 14.22]	8.25 [6.50 - 11.17]	8.90 [6.90 - 12.60]	8.30 [6.40 - 11.15]	$6.8*10^{-4}$
1631NTP (NT-proBNP)	621.50 [310.00 - 1489.00]	507.00 [256.00 - 1093.00]	546.50 [302.00 - 1130.75]	740.00 [390.00 - 1669.00]	787.00 [368.50 - 1774.75]	0.007
16GLU (glucose)	5.00 [4.50 - 5.60]	5.10 [4.60 - 5.70]	5.80 [5.00 - 7.57]	5.10 [4.70 - 5.70]	4.90 [4.50 - 5.70]	$2.4*10^{-20}$
172INS (insulin)	6.60 [4.60 - 10.17]	7.20 [4.90 - 11.10]	7.20 [4.93 - 11.53]	6.60 [4.40 - 11.20]	5.15 [3.60 - 8.72]	$2.9*10^{-4}$
174S-C (IGF-1)	99.40 [77.93 - 131.55]	105.75 [81.80 - 136.03]	109.80 [88.10 - 144.20]	99.70 [78.62 - 133.38]	90.85 [65.58 - 124.75]	$2.6*10^{-4}$
18HBA1 (HbA1c (glycated haemoglobin))	5.60 [5.40 - 5.90]	5.60 [5.40 - 5.90]	6.30 [5.70 - 7.15]	5.60 [5.30 - 5.80]	5.50 [5.30 - 5.80]	$2.8*10^{-44}$
22CRE (creatinine)	86.00 [72.25 - 105.75]	88.00 [75.00 - 108.00]	87.00 [72.00 - 105.75]	88.00 [73.00 - 109.00]	76.00 [61.00 - 100.25]	0.005

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28TP (total protein)	69.00 [64.00 - 74.00]	69.00 [65.00 - 74.00]	70.00 [64.00 - 74.00]	69.00 [66.00 - 74.00]	67.00 [61.00 - 71.00]	0.03
29A1 (alpha-1-globulin)	3.10 [2.80 - 3.50]	3.00 [2.70 - 3.30]	3.10 [2.80 - 3.50]	3.20 [2.80 - 3.60]	3.30 [3.00 - 3.70]	$3.9*10^{-5}$
30TG (triglycerides)	1.15 [0.89 - 1.48]	1.12 [0.89 - 1.54]	1.31 [0.96 - 1.81]	1.14 [0.87 - 1.49]	1.16 [0.84 - 1.49]	0.004
32HDL (HDL)	1.25 [1.05 - 1.53]	1.27 [1.01 - 1.57]	1.15 [0.94 - 1.45]	1.26 [1.07 - 1.51]	1.11 [0.96 - 1.36]	$1.3*10^{-5}$
51FERR (ferritin)	62.00 [32.00 - 112.50]	70.00 [36.50 - 121.00]	60.00 [30.00 - 115.00]	65.50 [34.25 - 118.50]	97.00 [41.00 - 175.00]	0.037
53FT3 (free T3)	3.60 [3.20 - 4.00]	3.70 [3.30 - 4.00]	3.50 [3.10 - 3.80]	3.60 [3.20 - 3.90]	3.40 [2.90 - 3.80]	$1.2*10^{-5}$
5PLT (platelets)	220.00 [183.00 - 266.75]	205.00 [171.75 - 244.50]	219.00 [177.00 - 278.00]	225.00 [184.00 - 279.00]	226.00 [181.00 - 274.00]	0.025
8ALT (alanine transaminase)	11.00 [9.00 - 15.00]	12.00 [10.00 - 16.00]	12.00 [9.00 - 16.00]	11.00 [8.00 - 15.00]	9.50 [7.00 - 14.00]	$1*10^{-4}$
928VD3 (25(OH) D, vitamin D)	9.00 [6.00 - 14.00]	11.00 [7.00 - 16.00]	9.00 [6.00 - 14.00]	8.00 [5.00 - 11.00]	7.00 [5.00 - 11.00]	$5.1*10^{-12}$
9AST (aspartate aminotransferase)	18.00 [15.00 - 21.00]	18.00 [16.00 - 21.00]	16.00 [14.00 - 20.00]	17.00 [15.00 - 22.00]	16.00 [14.00 - 19.00]	$4.6*10^{-6}$
ALB-PF (albumin)	38.40 [35.40 - 41.30]	39.50 [35.90 - 42.10]	38.80 [35.90 - 41.40]	38.40 [34.70 - 41.00]	35.00 [32.18 - 38.00]	$3.8*10^{-17}$
ALB/CRU (urine albumin-creatinine ratio)	22.00 [12.00 - 45.75]	23.00 [11.00 - 47.50]	34.00 [16.00 - 67.50]	31.00 [14.00 - 62.00]	35.00 [16.00 - 82.00]	0.007
hsCRP	2.69 [1.27 - 6.85]	2.29 [1.14 – 6.04]	2.9 [1.29 – 6.65]	2.59 [1.11 – 7.19]	4.19 [1.64 – 12.83]	0,044

Supplementary Table 2. Pairwise phenotype comparison

Cluster	**0VS1**	**0VS2**	**0VS3**	**0VS4**	**1VS2**	**1VS3**	**1VS4**	**2VS3**	**2VS4**	**3VS4**
Indicator	p-value of pairwise comparisons (Mann–Whitney U test) adjusted for multiple testing									
MMSE	**$1.3*10^{-8}$**	0.026	**$2.3*10^{-121}$**	**$1.5*10^{-36}$**	**$1.8*10^{-10}$**	**$5.2*10^{-77}$**	**$2.9*10^{-34}$**	**$1.1*10^{-48}$**	**$3.7*10^{-15}$**	1
FAB	1	1	**$8.6*10^{-52}$**	**$2.7*10^{-42}$**	0.36	**$5.7*10^{-38}$**	**$4.5*10^{-32}$**	**$6.7*10^{-24}$**	**$1.5*10^{-22}$**	1
MNA	0.77	1	**$1.1*10^{-15}$**	**$5.4*10^{-41}$**	1	**$2.3*10^{-16}$**	**$2.0*10^{-33}$**	**$8.9*10^{-9}$**	**$1.7*10^{-27}$**	**$6*10^{-9}$**
Right hand hand grip strength	1	1	**$1.6*10^{-14}$**	**$1.2*10^{-34}$**	1	**$2.8*10^{-10}$**	**$5.4*10^{-25}$**	**$4.2*10^{-7}$**	**$5.5*10^{-21}$**	**$2.4*10^{-6}$**
Left hand hand grip strength	1	1	**$8.5*10^{-16}$**	**$5.7*10^{-38}$**	1	**$4.1*10^{-14}$**	**$1.5*10^{-30}$**	**$2.3*10^{-7}$**	**$6.1*10^{-23}$**	**$1*10^{-7}$**
SPPB	**$5.6*10^{-164}$**	0.149	**$2.9*10^{-23}$**	**$2.2*10^{-74}$**	**$9.4*10^{-95}$**	**$1.6*10^{-87}$**	**$3.1*10^{-74}$**	**$6*10^{-7}$**	**$1.8*10^{-45}$**	**$2.1*10^{-25}$**
Barthel	**$4.4*10^{-43}$**	1	**$3.9*10^{-22}$**	**$2.2*10^{-103}$**	**$6.4*10^{-35}$**	**$1.7*10^{-50}$**	**$2.5*10^{-73}$**	**$1.4*10^{-8}$**	**$6.5*10^{-69}$**	**$9*10^{-64}$**
IADL	**$1.5*10^{-27}$**	1	**$1.6*10^{-21}$**	**$1.9*10^{-79}$**	**$3.4*10^{-20}$**	**$5*10^{-35}$**	**$4.3*10^{-64}$**	**$8*10^{-9}$**	**$2.6*10^{-47}$**	**$1.6*10^{-15}$**

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GDS-5	0.617	1	**$6.5*10^{-18}$**	**$2.2*10^{-37}$**	**0.002**	**$6*10^{-21}$**	**$1.9*10^{-35}$**	**$2.4*10^{-5}$**	**$2.9*10^{-19}$**	**$5.5*10^{-5}$**
Assistance in social and everyday living scale	**$1.5*10^{-18}$**	1	**$7.1*10^{-21}$**	**$7.4*10^{-95}$**	**$1.9*10^{-12}$**	**$1.3*10^{-34}$**	**$2.3*10^{-72}$**	**$5.3*10^{-10}$**	**$1.1*10^{-59}$**	**$7.2*10^{-42}$**
Systolic blood pressure	1	1	1	**$1*10^{-5}$**	1	1	**$3.6*10^{-5}$**	1	**0.001**	0.075
Diastolic blood pressure	1	1	1	0.193	1	1	0.339	1	0.186	**0.018**
BMI	1	**0.002**	1	**0.002**	**$5.6*10^{-4}$**	1	0.962	**0.007**	**$2.8*10^{-7}$**	1
Waist circumference	1	0.09	0.068	1	**0.047**	1	1	**$1*10^{-4}$**	0.125	1
Total bilirubin	**0.016**	1	1	1	**0.001**	1	**0.006**	1	1	1
Homocysteine	1	1	**0.01**	1	1	**0.006**	1	**$7.8*10^{-4}$**	1	1
NT-proBNP	1	1	1	1	1	**0.037**	0.157	0.546	1	1
Glucose	1	**$1.7*10^{-21}$**	1	1	**$4.2*10^{-9}$**	1	1	**$9.3*10^{-7}$**	**$3.2*10^{-8}$**	1
Insulin	1	1	1	**0.018**	1	1	**0.001**	1	**$2.5*10^{-4}$**	0.422
IGF-1	1	**0.027**	1	1	1	1	0.054	1	**0.001**	1
HbA1c (glycated haemoglobin, Hb)	1	**$5.5*10^{-41}$**	1	0.068	**$7.5*10^{-23}$**	1	0.104	**$5.3*10^{-24}$**	**$5*10^{-22}$**	1
Creatinine	1	1	1	**0.005**	1	1	**0.002**	1	0.185	**0.017**
Total protein	1	1	1	**0.024**	1	1	**0.011**	1	0.249	0.074
alpha-1-globulin	1	1	1	**0.028**	1	**0.012**	**$1.2*10^{-4}$**	1	0.145	1
Triglycerides	1	**$4.7*10^{-4}$**	1	1	0.312	1	1	**0.024**	0.607	1
HDL	1	**0.004**	1	**0.003**	0.149	1	0.067	1	1	0.466
Ferritin	1	1	1	**0.012**	1	1	1	1	0.114	1
Free T3	1	1	1	**0.001**	**0.03**	1	**$1.6*10^{-5}$**	1	1	0.069
Platelets	**0.038**	1	1	1	1	**0.020**	0.605	1	1	1
Testosterone	**$6.7*10^{-4}$**	1	1	1	**$1.5*10^{-5}$**	**0.043**	**$8.2*10^{-5}$**	1	1	1
Alanine transaminase	1	1	1	**0.004**	1	1	**$6.6*10^{-5}$**	1	**0.03**	1
Vitamin D (25(OH) D)	**0.004**	1	**0.01**	**$4*10^{-4}$**	1	**$1.1*10^{-7}$**	**$2.4*10^{-8}$**	0.091	**0.005**	1
Albumin in the urine (concentration)	1	1	1	0.14	1	1	0.843	1	1	1ju
Aspartate aminotransferase	1	**0.022**	1	**0.002**	**0.009**	1	**$3*10^{-4}$**	1	1	0.674
Albumin	0.665	1	1	**$2*10^{-14}$**	1	0.229	**$1.7*10^{-16}$**	1	**$2.8*10^{-12}$**	**$2.6*10^{-6}$**
ALB/CRU (urine albumin-creatinine ratio)	1	**0.047**	1	1	1	1	1	1	1	1
hsCRP	1	1	1	**0.025**	1	1	**0.0098**	1	0.93	0.49
Monocytes, %	1	0.095	1	**0.001**	**0.001**	0.127	**$8.9*10^{-6}$**	1	1	1

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Supplementary Table 3. Frequency of occurrence of the APOE genotypes

Genotype	Cluster 0 (1,602)	Cluster 1 (309)	Cluster 2 (272)	Cluster 3 (234)	Cluster 4 (175)	Entire sample	p-value (chi square)
ε2ε2	19 (1.2%)	6 (1.9%)	1 (0.4%)	3 (1.3%)	2 (1.1%)	31 (1.2%)	0.005
ε2ε3	228 (14.2%)	56 (18.1%)	40 (14.7%)	41 (17.5%)	33 (18.9%)	398 (15.3%)	
ε2ε4	18 (1.1%)	4 (1.3%)	3 (1.1%)	3 (1.3%)	5 (2.9%)	33 (1.3%)	
ε3ε3	1166 (72.5%)	218 (70.6%)	204 (75%)	144 (61.5%)	109 (62.3%)	1841 (70.8%)	
ε3ε4	165 (10.3%)	25 (8.1%)	23 (8.5%)	40 (1.3%)	26 (14.9%)	279 (10.7%)	
ε4ε4	6 (0.4%)	0 (-)	1 (0.4%)	3 (1.3%)	0 (-)	10 (0.4%)	

Supplementary Table 4. Results of logistic regression using APOE genotypes

Cluster	ε2		ε4	
	coef	p-value	coef	p-value
0	-0.2257	0.3	-0.1519	1
1	0.3008	0.47	-0.4823	0.2
2	-0.1286	1	-0.2805	1
3	0.1423	1	0.6885	0.001
4	0.2959	1	0.5721	0.07

Supplementary Table 5. Comparison of the socioeconomic backgrounds (only significant)

Cluster		0	1	2	3	4	p-value (chi square)
Phenotype		Multimorbid frailty (n=1,602)	Non-frail (n=309)	Metabolic frailty (n=272)	Cognitive frailty (n=234)	Functional frailty (n=175)	
Параметр		n (%)	n (%)	n (%)	n (%)	n (%)	
Lifelong residence	Rural	87 (5.7%)	19 (6.7%)	6 (2.3%)	14 (6.8%)	22 (15.8%)	3*10-4
	Urban	1418 (94.3%)	264 (93.3%)	253 (97.7%)	191 (93.2%)	117 (84.2%)	
Education	Primary school or unfinished primary school	94 (5.8%)	27 (8.7%)	18 (6.6%)	35 (15.2%)	23 (13.2%)	3.46*10-7
	Middle school or unfinished middle school	197 (12.3%)	23 (7.4%)	36 (13.2%)	36 (15.6%)	28 (16.1%)	
	Complete high school	271 (17%)	46 (14.9%)	48 (17.7%)	56 (24.2%)	32 (18.4%)	
	Vocational school	135 (8.4%)	25 (8.1%)	15 (5.5%)	13 (5.6%)	4 (2.3%)	
	Training school	278 (17.4%)	38 (12.3%)	44 (16.2%)	30 (13%)	27 (15.5%)	
	Undergraduate	23 (1.4%)	3 (1%)	6 (2.2%)	1 (0.4%)	4 (2.3%)	
	Graduate	557 (35%)	140 (45.3%)	93 (34.2%)	55 (23.8%)	53 (30.5%)	
	Postgraduate	43 (2.7%)	7 (2.3%)	12 (4.4%)	5 (2.2%)	3 (1.7%)	
Occupation	Primarily physical	370 (23.3%)	78 (25.6%)	62 (22.9%)	83 (35.8%)	54 (312%)	0.018
	Primarily intellectual	582 (36.7%)	120 (39.3%)	111 (41%)	71 (30.6%)	67 (39.6%)	
	Intellectual + physical	636 (40%)	107 (35.1%)	98 (36.1%)	78 (33.6%)	48 (28.4%)	
Peak income	Low	109 (7.2%)	26 (9.2%)	16 (6.2%)	32 (15.6%)	28 (20.3%)	1.6*10-9

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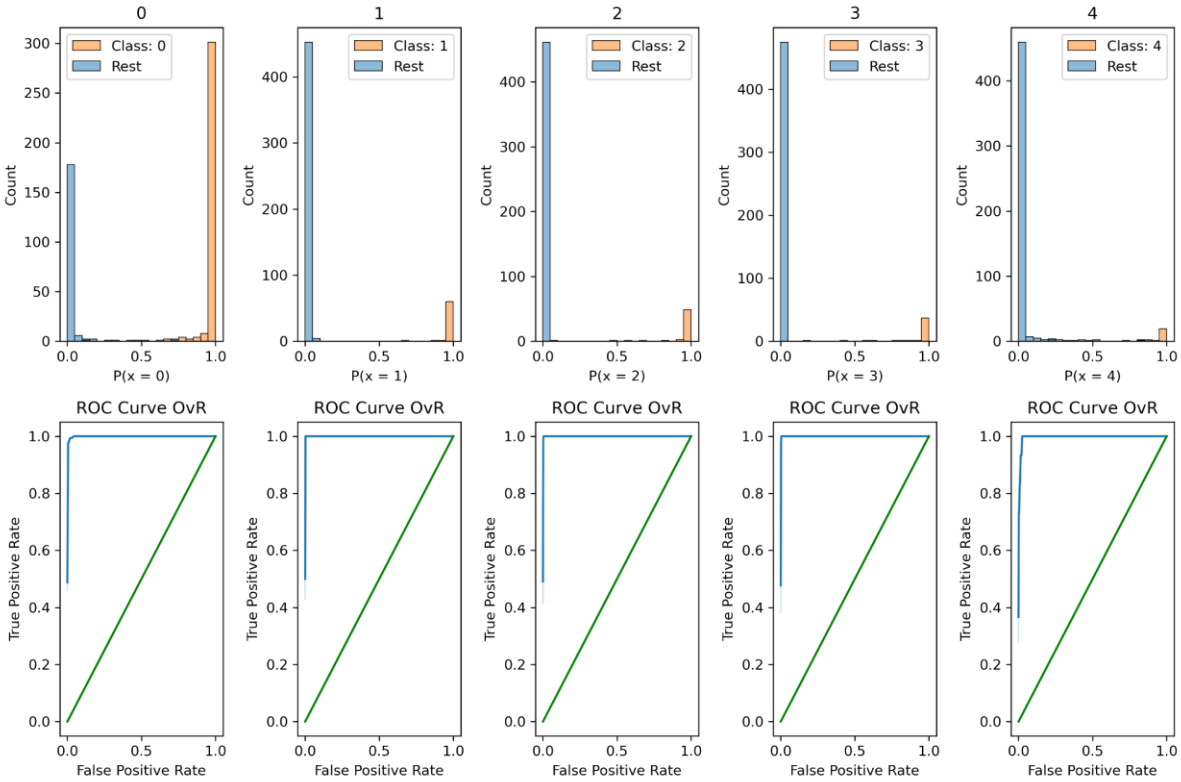
	Medium	1235 (82%)	201 (71%)	211 (81.5%)	153 (74.6%)	87 (63%)	
	High	162 (10.8%)	56 (19.8%)	32 (12.3%)	20 (9.8%)	23 (16.7%)	
Lifelong hobby	No	832 (56.1%)	182 (65%)	129 (49.6%)	140 (69.3%)	79 (58.1%)	0.002
	Yes	652 (43.9%)	98 (35%)	131 (50.4%)	62 (30.7%)	57 (41.9%)	

Supplementary Table 6. Effects of the background and socioeconomic background on the aging phenotype (based on logistic regression adjusted for age and sex).

Indicator	Non-frailty		Multimorbid frailty		Metabolic frailty		Cognitive frailty		Functional frailty	
	OR	p-val	OR	p-val	OR	p-val	OR	p-val	OR	p-val
Residence	1.21	1	0.84	1	2.94	0.319	0.92	1	**0.34**	**$6.2*10^{-4}$**
Graduate/undegraduate	1.00	1	1.41	0.196	1.18	1	**0.58**	**0.013**	0.83	1
Intelelctual work	0.95	1	1.19	1	1.19	1	0.7	0.504	1.08	1
High peak income	0.69	0.095	**1.72**	**0.041**	1.11	1	0.83	1	1.54	1
Low peak income	**0.59**	**0.01**	1.27	1	0.62	1	1.9	0.064	**2.65**	**$7*10^{-4}$**
Lifelong hobby	1.19	1	0.75	0.983	1.44	0.172	**0.53**	**0.006**	0.91	1



Supplementary Figure 2. Calculator quality assessment on the test set.

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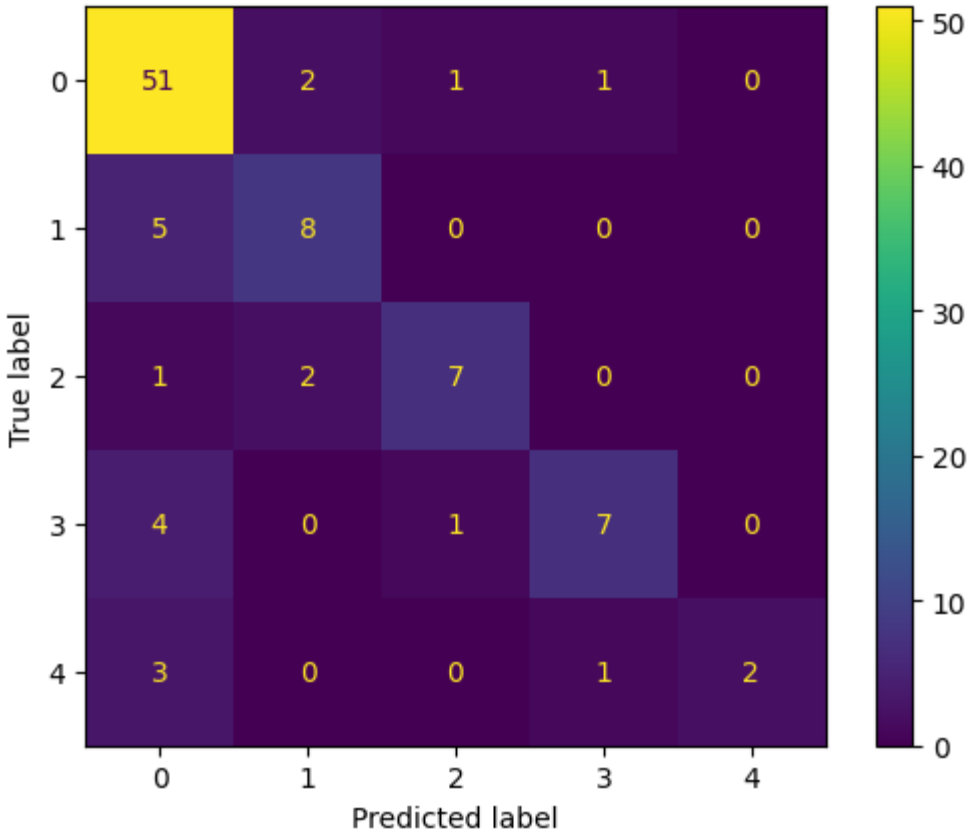

Supplementary Figure 3. Validation error matrix for geriatrician 1.

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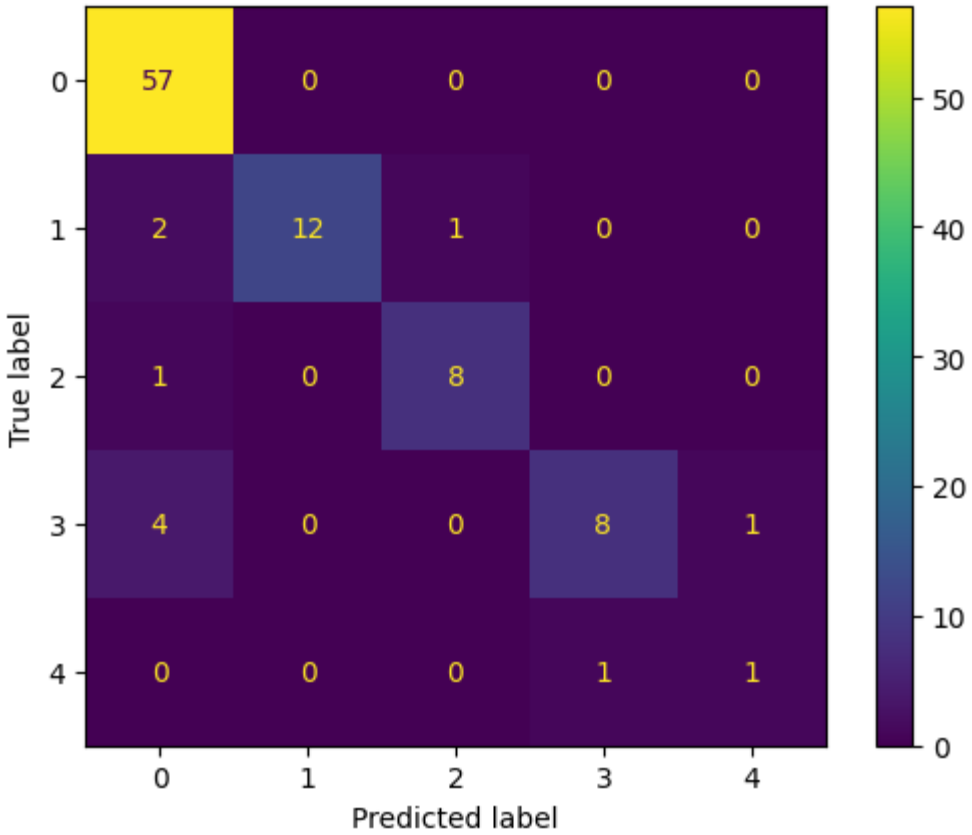

Supplementary Figure 4. Validation error matrix for geriatrician 2.