

Supplementary Materials for “Type 1 Diabetes Risk Phenotypes Using Cluster Analysis”

Supplementary Tables

Supplementary Table S1. Type 1 Diabetes TrialNet Study Group

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Supplementary Table S2. List of HLA alleles included in the analysis, separately from those used for T1D GRS2 computation.

HLA Type	HLA Alleles			Count (Frequency)
	DRB1	DQA1	DQB1	
S1	04:05	03:01	02:01	40 (3.30%)
S2	04:01	03:01	03:02	458 (37.82%)
S3	03:01	05:01	02:01	535 (44.18%)
S4	04:02	03:01	03:02	65 (5.37%)
S5	04:04	03:01	03:02	171 (14.12%)

Supplementary Table S3. List of non-HLA SNPs included in the analysis, separately from those used for T1D GRS2 computation.

Non-HLA SNP ID (Chromosome, Gene)	Count (Frequency)		
	Minor Allele Homozygous	Heterozygous	Major Allele Homozygous
rs2476601 (1p13.2, PTPN22)	33 (2.73%)	310 (25.60%)	868 (71.68%)
rs2816316 (1q31.2, RGS1)	28 (2.31%)	349 (28.82%)	834 (68.87%)
rs10517086 (4p15.2, LOC105374540)	118 (9.74%)	501 (41.37%)	592 (48.89%)
rs4948088 (7p12.1, COBL)	1 (0.08%)	77 (6.36%)	1133 (93.56%)
rs1004446 (11p15.5, INS)	128 (10.57%)	537 (44.34%)	546 (45.09%)
rs2292239 (12q13.2, ERBB3)	166 (13.71%)	573 (47.32%)	472 (38.98%)
rs3184504 (12q24.12, SH2B3)	340 (28.08%)	552 (45.58%)	319 (26.34%)
rs12708716 (16p13.13, CLEC16A)	123 (10.16%)	530 (43.77%)	558 (46.08%)

Supplementary Table S4. Distribution of variables summarized as median (IQR) in the eight identified clusters.

Cluster	Age (years)	Type 1 Diabetes GRS2	Glucose AUC (mg/dl)	C-peptide AUC (pmol/ml)	Fasting Glucose (mg/dl)	Fasting C-peptide (pmol/ml)
A1	11 (7-22)	12.74 (11.28-13.75)	172 (166-186)***↑	5.04 (3.59-7.13)	93 (86-102)***↑	1.55 (0.88-2.12)
B1	12 (10-16)	13.01 (11.91-14.07)*↑	123 (115-128)***↓	5.14 (4.38-6.83)	88 (85-93)	1.47 (1.08-1.92)
B2	6 (4-8)***↓	13.11 (11.65-14.25)**↑	123 (114-132)**↓	2.62 (2.18-2.91)***↓	82 (80-88)***↓	0.72 (0.56-0.93)***↓
B3	12 (9-17)	13.05 (11.97-13.92)**↑	124 (112-133)***↓	5.36 (4.28-6.49)*↑	88 (84-94)	1.50 (1.19-2.09)*↑
B4	10 (7-14)	12.91 (11.50-13.86)	150 (146-156)***↑	4.73 (3.77-6.96)	90 (83-96)	1.38 (0.90-1.94)
C1	13 (9-33)***↑	12.04 (10.44-13.56)***↓	119 (110-131)***↓	5.49 (4.52-6.76)***↑	90 (85-94)	1.53 (1.22-1.92)***↑
C2	6 (4-8)***↓	12.64 (10.68-13.64)	120 (105-128)***↓	3.04 (2.52-3.30)***↓	86 (80-90)***↓	0.89 (0.66-1.02)***↓
C3	14 (8-35)**↑	12.13 (10.70-13.90)	153 (148-158)***↑	5.44 (3.90-7.43)**↑	94 (88-100)***↑	1.64 (1.14-2.10)**↑

* P<0.05, ** P<0.01, *** P<0.001, ↑ higher compared to the population, ↓ lower compared to the population.

Supplementary Table S4 (Continued). Distribution of variables summarized as median (IQR) in the eight identified clusters.

Cluster	HbA1c	Num. AB	GADA (DK units/mL)	IA2A (DK units/mL)	IAA (index)	ICA (JDF units)
A1	5.3 (5.1-5.6)***↑	3.0 (2.0-3.0)***↑	339 (89-621)	133 (1-269)***↑	0.0085 (0.0020-0.0262)*↑	40 (0-160)***↑
B1	5.1 (4.9-5.3)	3.0 (2.0-3.0)***↑	234 (47-538)	140 (70-187)***↑	0.0040 (0.0020-0.0125)	20 (0-160)
B2	5.1 (4.9-5.3)	3.0 (2.0-4.0)***↑	157 (24-351)*↓	268 (135-314)***↑	0.0190 (0.0050-0.0580)***↑	80 (0-160)***↑
B3	5.1 (4.9-5.3)	3.0 (3.0-3.0)***↑	468 (143-644)**↑	299 (268-334)***↑	0.0050 (0.0015-0.0205)	80 (40-320)***↑
B4	5.2 (5.0-5.4)	3.0 (2.0-4.0)***↑	333 (52-556)	277 (223-324)***↑	0.0080 (0.0020-0.0350)*↑	120 (4-320)***↑
C1	5.0 (4.9-5.2)***↓	1.0 (1.0-2.0)***↓	258 (5-559)*↓	0 (0-1)***↓	0.0030 (0.0010-0.0130)***↓	0 (0-10)***↓
C2	5.0 (4.9-5.2)**↓	2.0 (1.0-2.0)*↓	280 (32-574)	0 (0-1)***↓	0.0140 (0.0010-0.0430)**↑	0 (0-20)**↓
C3	5.2 (5.0-5.4)*↑	2.0 (1.0-2.0)**↓	271 (24-543)	0 (0-3)***↓	0.0040 (0.0010-0.0240)	0 (0-20)*↓

* P<0.05, ** P<0.01, *** P<0.001, ↑ higher compared to the population, ↓ lower compared to the population.

Supplementary Table S5. Distribution of variables summarized as median (IQR) by clusters in the validation dataset (DPT-1). The distribution of variables in a cluster is compared to the population using Wilcoxon's rank sum tests.

Cluster	Age	Glucose AUC (mg/dl)	C-peptide AUC (pmol/ml)	Fasting Glucose (mg/dl)	Fasting C-peptide (pmol/ml)
A1	12.59 (8.39-18.28)	174 (165-183)***↑	3.61 (2.57-4.99)	92 (85-98)***↑	0.90 (0.60-1.40)
B1	11.60 (8.57-13.93)	126 (119-134)	4.51 (4.04-5.19)***↑	87 (82-90)	1.30 (0.97-1.60)***↑
B2	8.08 (5.44-10.79)***↓	120 (106-132)***↓	2.51 (2.01-2.83)***↓	83 (77-89)***↓	0.60 (0.50-0.80)***↓
B3	13.37 (11.11-15.82)***↑	117 (108-127)***↓	4.30 (3.65-5.37)***↑	86 (80-90)	1.25 (0.92-1.50)***↑
B4	10.27 (8.18-12.83)	151 (148-156)***↑	3.51 (2.57-4.31)	87 (81-92)	0.80 (0.60-1.10)
C1	14.45 (10.14-21.90)***↑	121 (108-131)***↓	4.63 (4.01-5.59)***↑	86 (81-92)	1.20 (0.90-1.70)***↑
C2	8.42 (5.90-11.80)***↓	117 (104-129)***↓	2.69 (2.16-3.16)***↓	84 (78-88)***↓	0.60 (0.40-0.80)***↓
C3	12.47 (8.52-16.62)	152 (149-156)***↑	4.11 (3.09-5.22)	88 (85-94)**↑	1.00 (0.50-1.40)

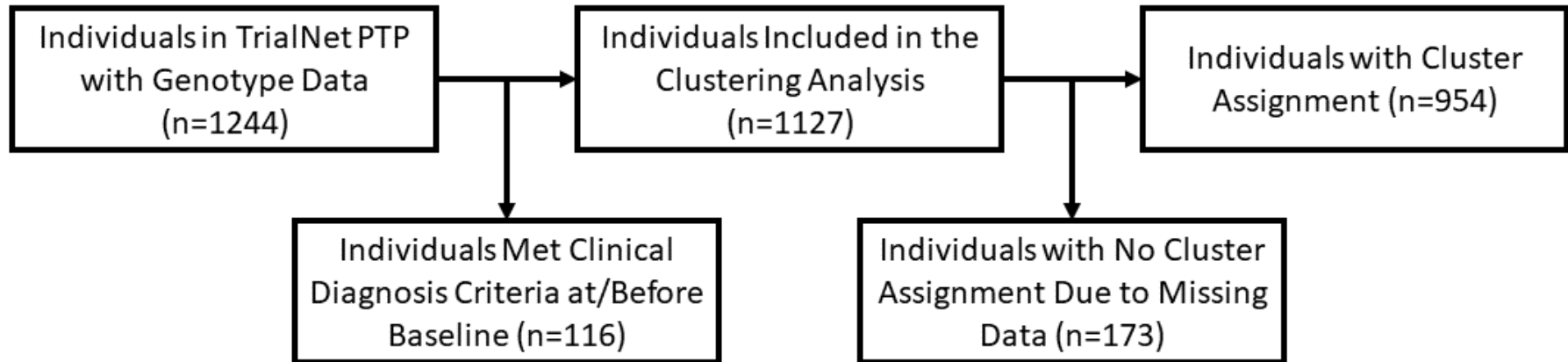
* P<0.05, ** P<0.01, *** P<0.001, ↑ higher compared to the population, ↓ lower compared to the population.

Supplementary Table S3 (Continued). Distribution of variables summarized as median (IQR) by clusters in the validation dataset (DPT-1). The distribution of variables in a cluster is compared to the population using Wilcoxon's rank sum tests.

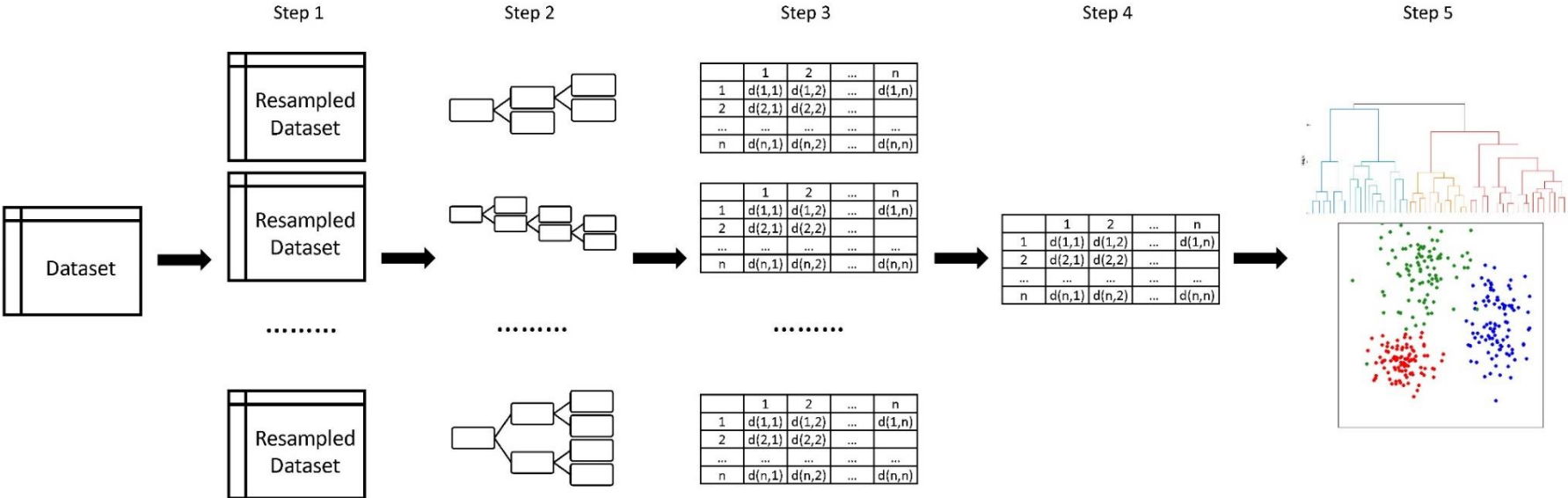
Cluster	HbA1c (%)	Num. AB	GADA (DK units/ml)	IA2A (DK units/ml)	IAA (index)	ICA (JDF units)
A1	5.5 (5.2-5.8)*↑	3 (2-3)*↑	514 (246-676)	115 (0-292)*↑	-0.0020 (-0.0191-0.0180)	160 (70-320)*↑
B1	5.3 (5.0-5.5)	3 (3-3)***↑	490 (121-635)	138 (64-196)**↑	-0.0010 (-0.0070-0.0084)	80 (40-160)
B2	5.3 (5.0-5.6)	3 (3-4)***↑	424 (126-655)	279 (150-316)***↑	0.0070 (-0.0027-0.0200)***↑	160 (80-320)***↑
B3	5.4 (5.2-5.7)	3 (3-3)***↑	485 (173-723)	317 (291-353)***↑	0.0010 (-0.0030-0.0145)	160 (80-320)***↑
B4	5.3 (5.0-5.7)	3 (3-4)***↑	531 (267-728)*↑	301 (216-345)***↑	0.0015 (-0.0045-0.0170)	320 (160-640)***↑
C1	5.3 (5.1-5.6)	2 (1-2)***↓	487 (1-764)	0 (0-1)***↓	0.0007 (-0.0083-0.0070)*↓	40 (20-160)***↓
C2	5.3 (5.0-5.5)**↓	2 (1-2)***↓	356 (1-654)**↓	0 (0-1)***↓	0.0010 (-0.0057-0.0100)	40 (20-160)***↓
C3	5.5 (5.2-5.7)	2 (2-3)	504 (90-663)	0 (0-4)***↓	-0.0010 (-0.0100-0.0134)	80 (40-160)

* P<0.05, ** P<0.01, *** P<0.001, ↑ higher compared to the population, ↓ lower compared to the population.

Supplementary Figure S1. CONSORT diagram of analyzed samples.



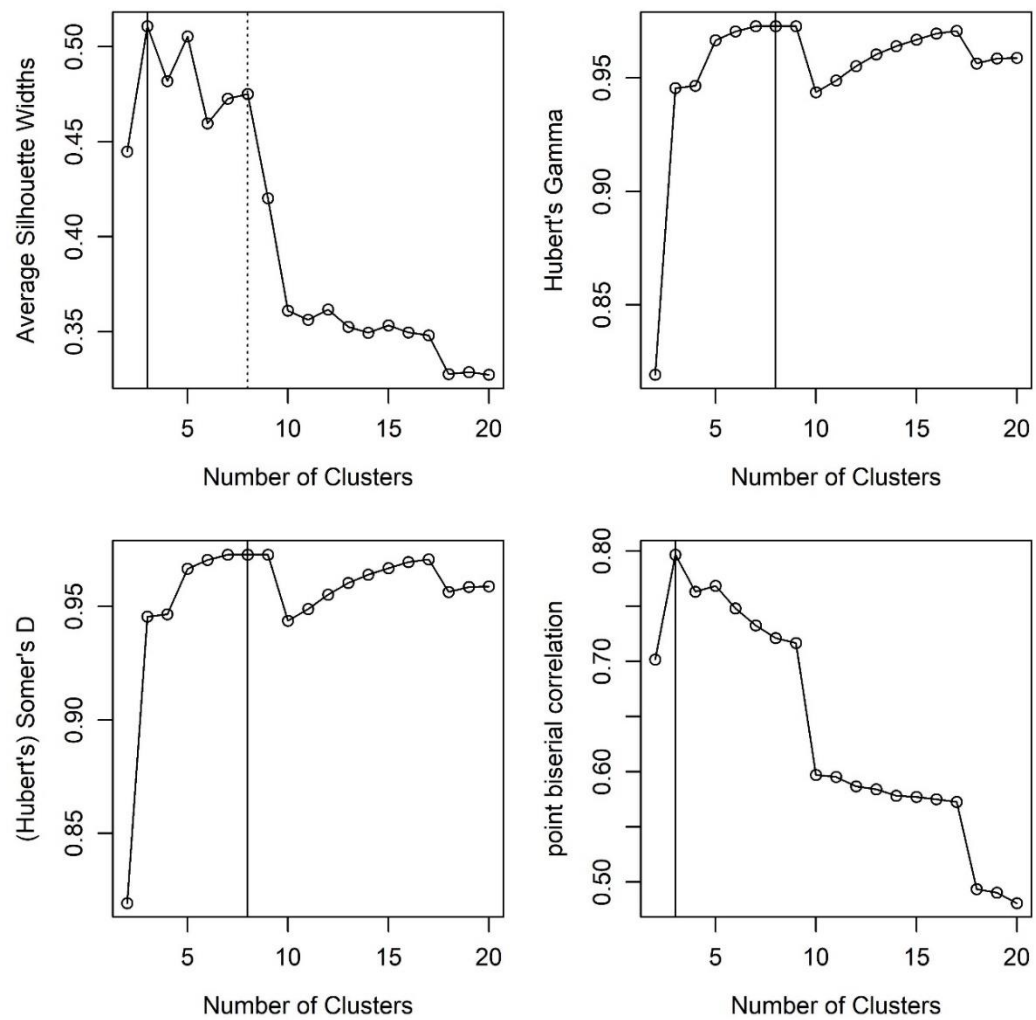
Supplementary Figure S2. A visual illustration of the outcome-guided clustering algorithm.



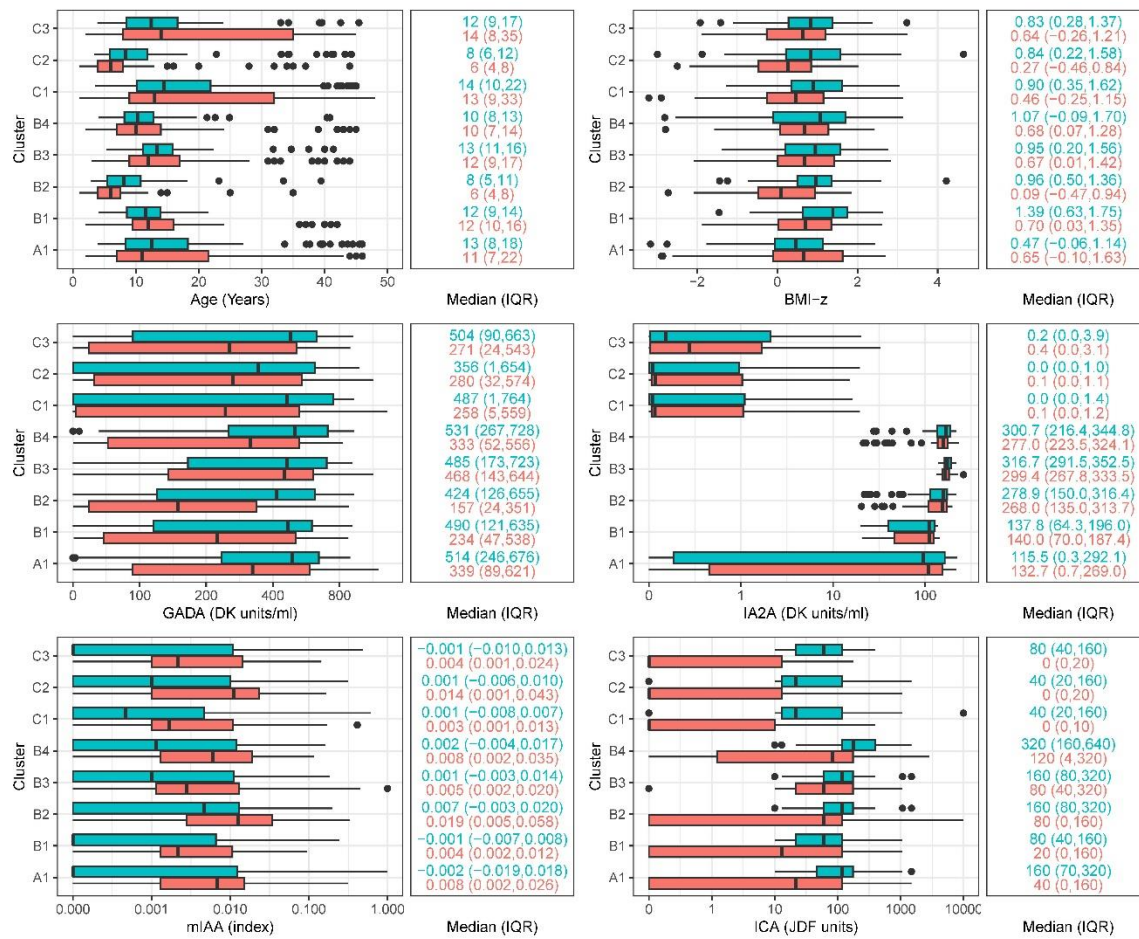
Supplementary Figure S3. Distribution of DPTRS and Index60 by cluster. Red bars in each cell represent the percentage of individuals in the DPTRS/Index60 intervals for each cluster.

DPTRS	A1	B1	B2	B3	B4	C1	C2	C3
< 4.5	0.9%	6.0%	0.0%	1.3%	0.0%	13.0%	3.8%	6.7%
[4.5,5.0)	0.9%	8.0%	0.0%	7.7%	1.4%	9.7%	1.3%	7.8%
[5.0,5.5)	2.7%	12.0%	0.0%	14.1%	4.3%	14.2%	0.0%	4.4%
[5.5,6.0)	4.5%	10.0%	3.8%	20.5%	2.9%	20.2%	7.7%	7.8%
[6.0,6.5)	2.7%	26.0%	5.7%	19.2%	17.4%	24.5%	20.5%	8.9%
[6.5,7.0)	8.2%	24.0%	30.2%	33.3%	14.5%	13.3%	30.8%	14.4%
[7.0,7.5)	8.2%	14.0%	41.5%	2.6%	21.7%	4.8%	25.6%	15.6%
[7.5,8.0)	20.0%	0.0%	13.2%	1.3%	26.1%	0.3%	9.0%	21.1%
[8.0,8.5)	20.9%	0.0%	5.7%	0.0%	11.6%	0.0%	1.3%	11.1%
8.5+	30.9%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	2.2%
Index60	A1	B1	B2	B3	B4	C1	C2	C3
< -2.0	1.7%	5.1%	0.0%	1.1%	0.0%	3.8%	0.0%	5.0%
[-2.0,-1.5)	2.6%	1.7%	0.0%	4.6%	1.4%	3.0%	0.0%	4.0%
[-1.5,-1.0)	3.5%	10.2%	0.0%	6.9%	7.2%	7.5%	0.0%	5.9%
[-1.0,-0.5)	2.6%	13.6%	0.0%	10.3%	4.3%	21.2%	0.0%	6.9%
[-0.5,0.0)	5.2%	16.9%	1.7%	24.1%	8.7%	29.3%	2.2%	8.9%
[0.0,0.5)	8.7%	28.8%	11.9%	29.9%	11.6%	22.6%	22.0%	8.9%
[0.5,1.0)	6.1%	22.0%	30.5%	17.2%	17.4%	10.8%	40.7%	18.8%
[1.0,1.5)	14.8%	1.7%	42.4%	5.7%	31.9%	1.9%	26.4%	22.8%
[1.5,2.0)	23.5%	0.0%	13.6%	0.0%	15.9%	0.0%	8.8%	18.8%
2.0+	31.3%	0.0%	0.0%	0.0%	1.4%	0.0%	0.0%	0.0%

Supplementary Figure S4. Measures for determining the number of clusters.



Supplementary Figure S5. Distribution of variables by clusters and the corresponding median (IQR) in the validation dataset (DPT-1) (blue bars) and the analysis dataset (TrialNet PTP) (orange bars).



Supplementary Figure S5 (Continued). Distribution of variables by clusters and the corresponding median (IQR) in the validation dataset (DPT-1) (blue bars) and the analysis dataset (TrialNet PTP) (orange bars).

