Online Supplementary file

PICADAR- a screening tool for primary ciliary dyskinesia

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e-Appendix 1.

The development and validation of PICADAR+S

For patients with at least 1 sibling (irrespective of PCD diagnosis in the sibling), an alternative scoring tool, PICADAR+S was developed.

By means of the same methods used to develop PICADAR, 28 potential predictors (including siblings with PCD, yes/no) were entered into the model individually using stepwise logistic regression. This model retained 8 significant predictors which were in order of importance; siblings with PCD, situs inversus, full term gestation, SCBU, cardiac defect, rhinitis, neonatal chest symptoms, and ears & hearing symptoms (Table E4).The accuracy of the best model was 92% and sensitivity and specificity was 75% and 96% respectively. Good agreement was also shown through the Hosmer-Lemeshow test (p=0.33). From the final prediction model, a simplified practical prediction tool, PICADAR+S, was developed to assess the probability that a patient with a sibling had PCD. ROC analysis showed good discriminant ability for the model (AUC= 0.94; CI 0.90-0.97) and the predicative tool (AUC=0.94; CI 0.90-0.97) (Figure E2).

The maximum score is 20 with individual predicators having integer scores of 1 to 5 (Figure E3). A score of 20 corresponded to a 100% probability of having PCD (Table E5). Sensitivity and specificity was 0.93 and 0.75 for a score of 6 points and 0.15 and 1.00 for a score of 14 (Table E6).This provided cut-off values for likelihood of PCD where a score of $\leq$6, $\geq$7$\leq$13, $\geq$14. In the derivative PCD+ group, 10.7% had a score $\leq$6, 41.1% had a score $\geq$7$\leq$13, and 48.2%

had a score ≥14. The percentage in each group for the PCD- group was 72.3% with a score ≤6, 27.7% with a score ≥7≤13, and 0.0% had a score ≥14 (Table E7).

The application of the PICADAR+S rule in the validation group ranged from 0 to 19 (9.4 ± 4.9) was tested on 56 positive and 47 negative referrals. Again there was a significant difference between the mean PICADAR+S scores in the diagnostic outcome groups (PCD+12.7 ± 3.9; PCD- 5.6 ± 2.6; $P < 0.001$). Good discriminant ability was maintained when used in the validation group with an AUC of 0.93 (95% CI, 0.88- 0.97) (Figure E4). For this population, 16.0% of PCD+ had a score ≤6, 16.0% had a score ≥7≤13 and 67.1% had a score ≥14. The percentage of PCD- in each group was 76.6% with a score ≤6, 21.3% with a score ≥7≤13, and 2.1% with a score ≥14 (Table E7).

Supplementary figures

Figure E1: Histograms showing distributions of scores for A. PICADAR for PCD+ and B. PICADAR for PCD-in the derivation group, C. PICADAR for PCD+ in the validation group and D. PICADAR for PCD- in the validation group.

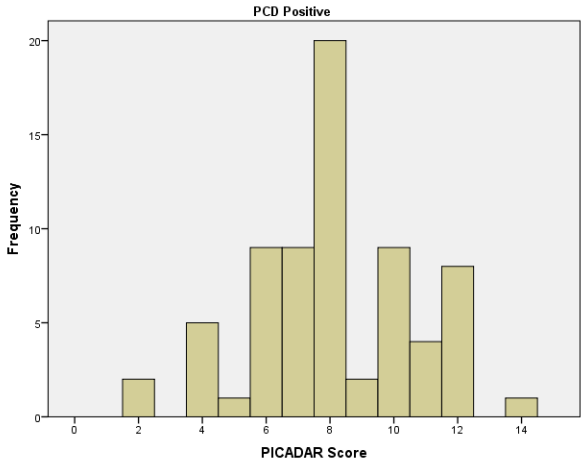
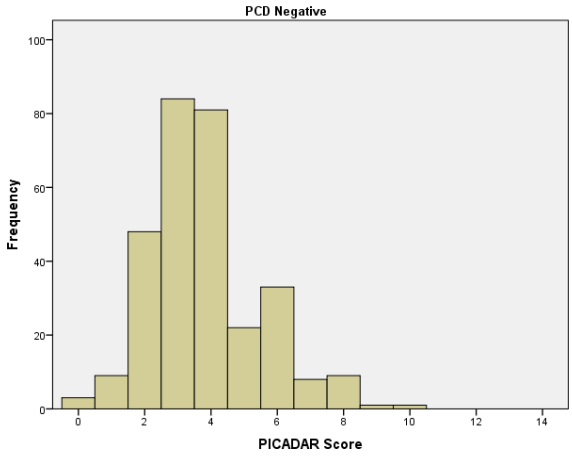
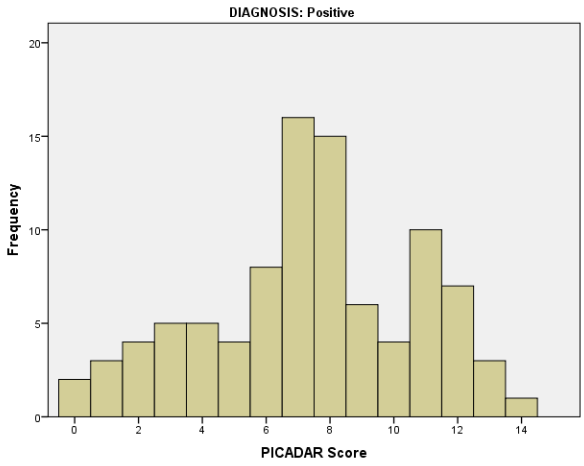
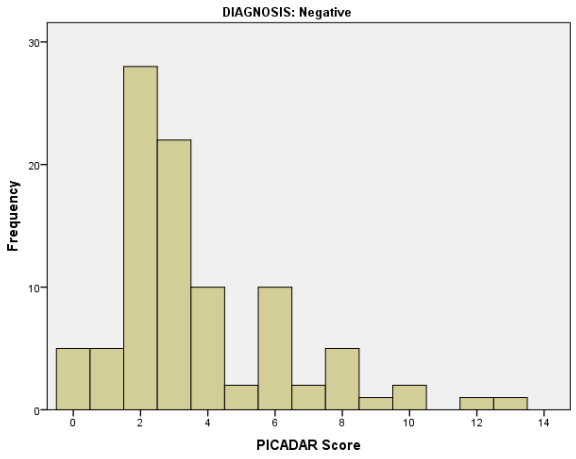
<table>
<tr><td>A: PCD+</td><td>B: PCD-</td></tr>
<tr><td> 
</td><td> 
</td></tr>
<tr><td>C: PCD+</td><td>D: PCD-</td></tr>
<tr><td> 
</td><td> 
</td></tr>
</table>

Figure E2: PICADAR+S: receiver operating characteristics for the best prediction model (AUC= 0.94; CI 0.90-0.97) and the predication tool (AUC=0.94; CI 0.90-0.97) in the derivation group. PICADAR+S can be used by individuals with one or more siblings.

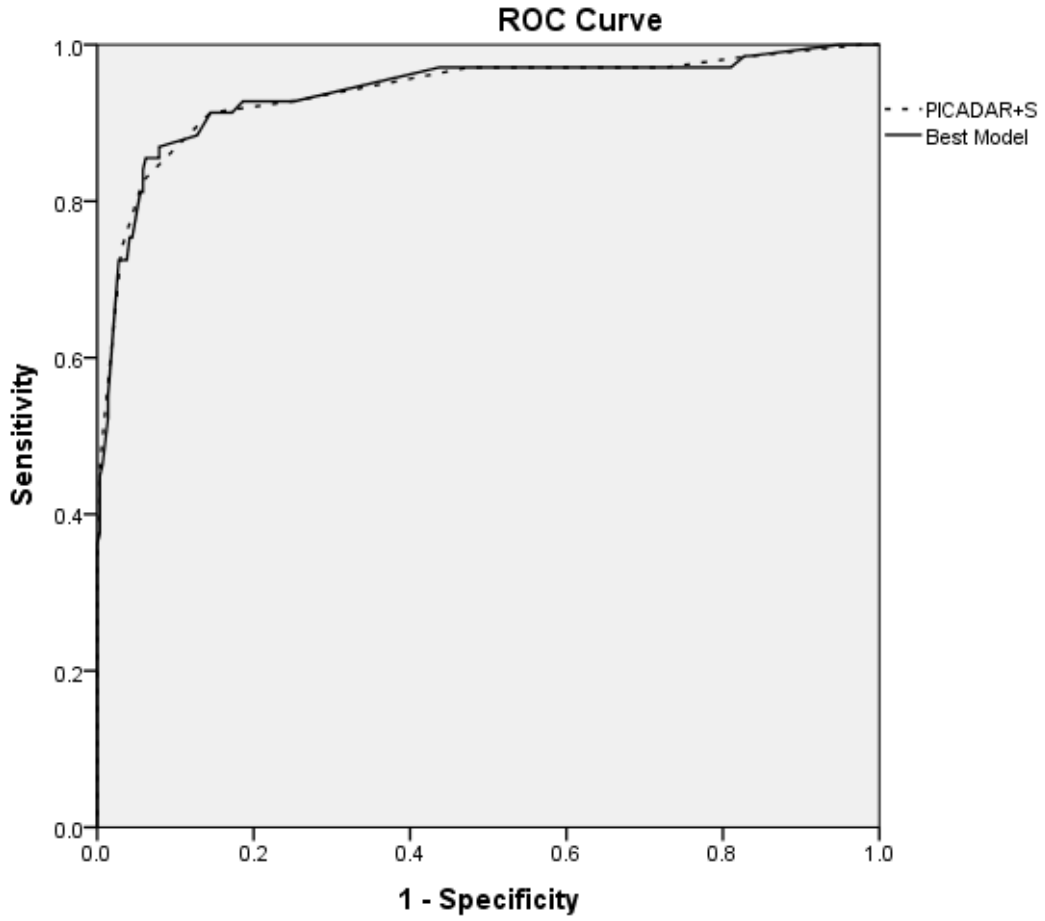


Figure E3: PICADAR score: a list of 8 simple questions which can be used in any patient with 1 or more siblings and with chronic respiratory symptoms starting in early childhood. The total score is calculated (Figure 3(a)) and the individual probability of having PCD diagnosis can be estimated from Figure 3(b).

Figure 3(a)

PICADAR+S		
Does the patient have a daily wet cough that started in early childhood?	No- STOP. PICADAR-S is not designed for patients without a wet cough	
Does the patient have a brother or sister?	No-STOP and complete PICADAR. PICADAR-S is only for patients with siblings	
1. Does the patient have a sibling diagnosed already with PCD	Yes	5
2. Was the patient born preterm or full term?	Term	2
3. Did the patient experience chest symptoms in the neonatal period (eg. tachypnoea, wet cough, pneumonia)?	Yes	2
4. Was the patient admitted to a neonatal unit?	Yes	2
5. Does the patient a situs abnormality (situs inversus or heterotaxy)?	Yes	4
6. Does the patient have a congenital heart defect?	Yes	2
7. Does the patient experience persistent perennial rhinitis (>3 months)	Yes	2
8. Does the patient experience chronic ear and hearing symptoms (glue ear, serous otis media, hearing loss, ear perforation, past history of ear surgery i.e. grommets)	Yes	1
	Total Score =	

Figure 3(b)

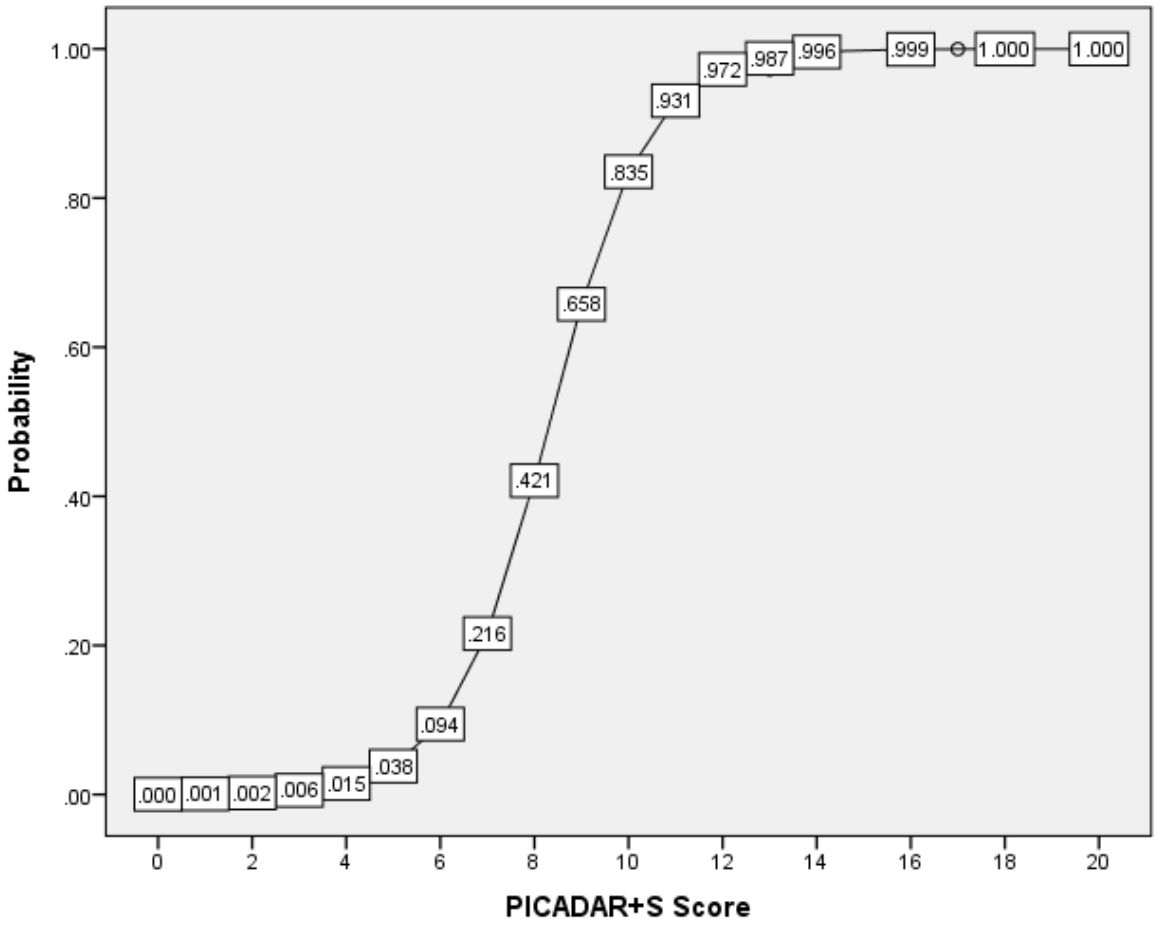
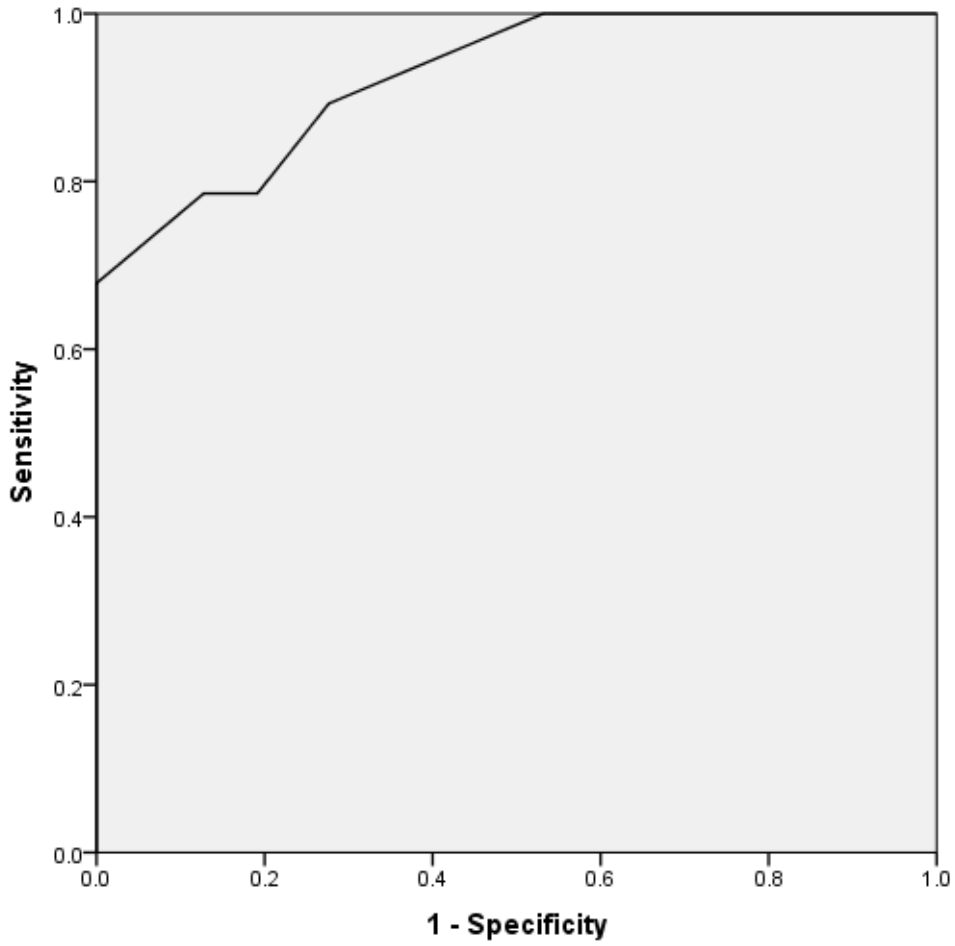

Probability
1.00
.80
.60
.40
.20
.00
.000
.001
.002
.006
.015
.038
.094
.216
.421
.658
.835
.931
.972
.987
.996
.999
1.000
1.000
0
2
4
6
8
10
12
14
16
18
20
PICADAR+S Score

Figure E4: Receiver operating characteristics predictive tool PICADAR+S (AUC 0.93; CI, 0.88-0.97) in the validation group.



Supplementary tables

Table E1: Clinical characteristics of the validation group (n=187) comparing PCD positive (n=93) and negative (n=94) groups.

	Total	**PCD positive**	**PCD negative**	**Odds ratio**	**p-value**
	n= 187 (%)	**n=93 (%)**	**n =94 (%)**		
Neonatal symptoms					
Neonatal respiratory support	55 (31.8%)	41 (48.8%)	14 (15.7%)	5.1 (2.5-10.4)	P<0.001
Neonatal chest symptoms	79 (44.9%)	63 (72.4%)	16 (18%)	11.9 (5.8-24.5)	P<0.001
Neonatal Rhinitis	57 (32.8%)	49 (57.6%)	8 (9%)	13.8 (5.9-32.1)	P<0.001
Chronic symptoms					
Chronic wet cough	161 (87.5%)	91 (98.9%)	70 (76.1%)	28.6 (3.8-21.7.3)	P<0.001
Chronic rhinitis	116 (63.4%)	79 (85.9%)	37 (40.7%)	8.8 (4.3-18.2)	P<0.001
Chronic sinusitis	16 (8.9%)	14 (15.7)	2 (2.2%)	0.1 (0.0-0.6)	P=0.006
Hearing loss	48 (26.8%)	40 (44.4%)	8 (9%)	8.1 (3.5-18.7)	P<0.001
Chronic acute otis media	35 (20.2%)	27 (32.1%)	8 (9%)	0.2 (0.1-0.5)	P<0.001
Chronic glue ear	58 (31.1%)	47 (54.7%)	11 (12.4%)	0.1 (0.1-0.3)	P<0.001
Ear surgery	30 (16.1%)	23 (26.1%)	7 (7.9%)	0.2 (0.1-0.6)	P=0.002
Other clinical characteristics					
SCBU	75 (42.4%)	55 (63.2%)	20 (22.2%)	6.7 (3.1-11.7)	P<0.001
Congenital cardiac defect	27 (14.8%)	10 (10.9%)	17 (18.7%)	0.5 (0.2-1.2)	P=0.140
Situs inversus	54 (30%)	41 (45.6%)	13 (14.4%)	4.9 (2.4-10.2)	P<0.001
Family history of disease					
PCD in sibling(s)	35 (20.8%)	31 (36.5%)	4 (4.8%)	0.5 (0.4-0.7)	P<0.001
PCD in extended family	9 (5.9%)	8 (10.8%)	1 (1.3%)	0.1 (0.0-0.9)	P<0.001
Family history of asthma	34 (22.8%)	16 (22.2%)	18 (23.4%)	1.1 (0.5-2.3)	P=0.867
Consanguinity	40 (27.8%)	37 (50.7%)	3 (4.2%)	0.0 (0.0-0.1)	P<0.001

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Table E2: Important factors for prediction of PCD selected by using logistic regression; sensitivity analysis from the pooled results from 5 multiple imputations.

	RC: Main model	OR (95% CI)	p-value	*Simplified RC tool
Situs abnormality	3.72	41.48 (15.65 – 109.93)	<0.001	4
Gestational age (full term)	1.90	6.73 (2.20 - 20.61)	0.012	2
SCBU	1.99	7.35 (2.97 - 18.17)	<0.001	2
Cardiac defect	1.84	6.31 (1.10 - 36.08)	0.038	2
Rhinitis	1.29	3.64 (1.42- 9.32)	0.017	2
Neonatal chest symptoms	1.74	5.70 (2.38 – 13.66)	0.027	2
Ears and hearing symptoms	1.11	3.03 (1.36 – 6.75)	0.010	1

RC, Regression coefficient; *OR,* Odds ratio

*Regression coefficient are rounded to the nearest integer

Table E3: The probability a PCD+ diagnosis for each total PICADAR score result

PICADAR Total Score ≥:	**Probability of PCD+**
0	0.12%
1	0.31%
2	0.78%
3	1.95%
4	4.74%
5	11.10%
6	23.88%
7	44.07%
8	66.44%
9	83.26%
10	92.59%
11	96.91%
12	98.75%
13	-
14	99.80%

Table E4: Factors for prediction of PCD selected by stepwise logistic regression for patients with 1 or more siblings

	RC: Main model	OR (95% CI)	p-value	*Simplified RC tool
Family history PCD (siblings)	5.38	218.19 (19.2 - 2470.8)	<0.001	5
Situs inversus	3.92	50.56 (14.9 – 170.6)	<0.001	4
Gestational age (full term)	2.27	9.72 (2.7 - 34.9)	0.001	2
SCBU	2.10	8.21 (8.9 - 22.6)	<0.001	2
Cardiac defect	1.92	6.84 (1.20 - 39.0)	0.03	2
Rhinitis	1.69	5.44 (1.7- 17.5)	0.004	2
Neonatal chest symptoms	1.62	5.05 (1.8 – 13.7)	0.001	2
Ears and hearing symptoms	1.21	3.37 (1.3 – 8.4)	0.010	1

RC, Regression coefficient; *OR,* Odds ratio

*Regression coefficient of the main model multiplied are rounded to the nearest integer and assessed so clinical accuracy of these individual scores

Table E5. The probability a PCD+ diagnosis for each total PICADAR+S score result

PICADAR +S Total Score ≥:	**Probability of PCD+**
0	0.00%
1	0.10%
2	0.21%
3	0.60%
4	1.47%
5	3.79%
6	9.44%
7	21.58%
8	42.08%
9	65.75%
10	83.52%
11	93.05%
12	97.25%
13	98.94%
14	99.59%
15	-

16	99.94%
17	99.97%
18	99.99%
19	-
20	100.00%

Table E6: Performance measure including sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the PICADAR+S prediction tool for different cut-off values calculated from the derivation group and validation group

	Derivative group				Validation group			
Cut-off ≥:	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
0	>0.99	<0.01	0.12	NA	>0.99	<0.01	1.0	NA
1	>0.99	0.01	0.12	1.00	-	-	-	-
2	>0.99	0.02	0.12	1.00	>0.99	0.09	0.52	1.0
3	0.99	0.17	0.13	0.99	-	-	-	-
4	0.97	0.27	0.15	0.99	0.97	0.40	0.62	0.93
5	0.97	0.52	0.21	0.99	0.90	0.70	0.75	0.88
6	0.93	0.75	0.34	0.99	0.88	0.82	0.83	0.87
7	0.91	0.86	0.47	0.99	0.79	0.85	0.84	0.80
8	0.83	0.94	0.65	0.98	0.76	0.96	0.95	0.80
9	0.74	0.97	0.77	0.96	0.60	0.96	0.94	0.71
10	0.46	>0.99	1.00	0.93	0.58	0.99	0.98	0.70
11	0.42	>0.99	1.00	0.93	0.45	0.99	0.98	0.64
12	0.33	>0.99	1.00	0.92	0.40	0.99	0.98	0.62
13	0.26	>0.99	1.00	0.91	0.32	0.99	0.98	0.59
14	0.15	>0.99	1.00	0.90	0.24	>0.99	1.00	0.57
15	-	-	-	-	0.16	>0.99	1.00	0.54
16	0.10	>0.99	1.00	0.89	0.09	>0.99	1.00	0.52
17	0.04	>0.99	1.00	0.88	0.08	>0.99	1.00	0.52
18	0.03	>0.99	1.00	0.88	-	-	-	-
19	0.01	>0.99	1.00	0.88	-	-	-	-
20	<0.01	>0.99	NA	0.88	-	-	-	-

Table E7: The distribution (n (%)) of PCD+ and PCD- scores using PICADAR+S in the derivation group and in the validation group (only children <18 included).

	Derivation group n=281				Validation group n=103		
	≤6 n (%)	**≥7≤13 n (%)**	**≥14 n (%)**		**≤6 n (%)**	**≥7≤13 n (%)**	**≥14 n (%)**
PCD+ (n=50)	2 (4.0%)	22 (44.0%)	26 (52.0%)	**PCD+ (n=56)**	6 (10.7%)	23 (41.1%)	27 (48.2%)
PCD- (n=231)	191 (82.7%)	39 (16.8%)	1 (0.4%)	**PCD- (n=47)**	34 (72.3%)	13 (27.7%)	0 (0.0%)