

Supplementary material

Table S1. Diagnoses in children with suspected asthma after visiting the clinic* N=514

	Diagnoses	
	n (%)	
Definite diagnoses		
Asthma	259	(50)
Cough not due to asthma ¹	71	(14)
Exercise limitation not due to asthma ²	56	(11)
Allergic rhinoconjunctivitis	11	(2)
Non-CF bronchiectasis	1	(<1)
Probable diagnoses		
Asthma	97	(19)
Exercise limitation not due to asthma ²	19	(4)

*Diagnosis at the first visit at a follow up visit within 3 months if the diagnosis was unclear

¹ Recurrent colds, post infectious cough, habitual cough, etc.

² Inducible laryngeal obstruction, dysfunctional breathing, functional symptoms, etc.

Table S2. Proportion of patients who performed diagnostic tests* per centre N=514

Diagnostic tests	Centres						Total
	A N=60 n%	B N=196 n%	C N=83 n%	D N=75 n%	E N=15 n%	F N=85 n%	N=514 n%
Any allergy test ¹	60 (100)	182 (93)	74 (89)	55 (73)	15 (100)	81 (95)	467 (91)
FeNO	60 (100)	185 (94)	81 (98)	75 (100)	15 (100)	85 (100)	501 (97)
Spirometry	60 (100)	196 (100)	83 (100)	75 (100)	15 (100)	85 (100)	514 (100)
Body plethysmography	59 (98)	171 (87)	52 (63)	61 (81)	10 (67)	79 (93)	432 (84)
Bronchodilator reversibility	29 (48)	145 (74)	61 (73)	68 (91)	15 (100)	63 (74)	381 (74)
Any bronchial provocation test	13 (22)	86 (44)	23 (28)	23 (31)	7 (47)	58 (68)	210 (41)
Methacholine	7 (12)	71 (36)	2 (2)	1 (1)	-	48 (56)	129 (25)
Exercise	7 (12)	18 (9)	21 (25)	22 (29)	5 (33)	12 (14)	85 (17)
Mannitol	-	-	-	-	3 (20)	-	3 (1)

*At the first visit or at a follow up visit within 3 months

¹Allergy test either done as above or results from <6 months ago reported in referral letter.

Table S3. Diagnostic test results in patients with and without asthma N=514

Diagnostic tests	Asthma					
	Definite asthma N=259		Probable asthma N=97		Other diagnosis N=158	
	median (IQR)		median (IQR)		median (IQR)	
Any allergy test, n(%)	248	(96)	93	(95)	124	(79)
≥1 positive test n(%)	201	(74)	59	(61)	52	(36)
Number of positive tests ¹	2	(1-3)	1	(0-3)	0	(0-2)
FeNO, n(%)	227	(88)	77	(80)	134	(84)
Parts per billion	25	(12-50)	14	(8-28)	11	(7-18)
Spirometry, n(%)	253	(98)	90	(93)	152	(96)
FEV1, z-scores	-0.5	(-1.4-0.1)	-0.2	(-1.0-0.5)	0.1	(-0.6-0.8)
FEV1/FVC	82	(76-88)	90	(84-95)	88	(84-93)
FEF50, z-score	-0.8	(-1.4--0.1)	0.1	(-0.7-0.9)	0.2	(-0.4-0.9)
Bodyplethysmography, n(%)	197	(76)	73	(75)	117	(74)
sReff, kPa·s ²	1.0	(0.8-1.3)	0.8	(0.7-0.9)	0.8	(0.6-0.9)
sRtot, kPa·s ³	1.3	(1.1-1.8)	1.4	(1.3-1.5)	1.1	(1.0-1.3)
RV/TLC	30	(25-36)	30	(26-36)	29	(24-34)
Bronchodilator reversibility, n(%)	215	(83)	59	(60)	92	(59)
Increase in FEV1 in %	13	(6-25)	10	(1-26)	6	(2-18)

¹Defined as wheal size ≥3mm for mites, cat, grass, birch, mugwort and alternaria skin prick test and as ≥0.35kU/L for specific IgE test

² Reported by 4 centres

³ Reported by 2 centres

Table S4. Diagnostic accuracy of diagnostic tests to diagnose asthma N=514 (sensitivity analysis: where children with “probable asthma” are subsumed to those with “no asthma” instead of those with “no asthma”)

	A+T+	A-T+	A+T-	A-T-	Sens	Spec	PPV	NPV	YI	AUC
	n	n	n	n	% (95%CI)	% (95%CI)	% (95%CI)	% (95%CI)		
Clinical tests										
Allergy test ¹										0.67
≥1 positive test*	201	111	47	108	81 (76-86)	49 (43-56)	64 (59-70)	70 (62-77)	0.30	
≥2 positive tests	154	79	94	140	62 (56-68)	64 (57-70)	66 (60-72)	60 (53-66)	0.26	
FeNO										0.70
≥20ppb	130	58	97	153	58 (51-64)	73 (66-78)	69 (62-76)	61 (55-67)	0.30	
≥21ppb	127	53	100	158	56 (49-63)	75 (68-81)	71 (63-77)	61 (55-67)	0.31	
≥23ppb*	119	44	108	167	52 (46-59)	79 (73-84)	73 (66-80)	61 (55-67)	0.32	
≥25ppb	114	41	113	170	50 (44-57)	81 (75-86)	74 (66-80)	60 (54-66)	0.31	
Spirometry										
FEV1										0.64
≤-0.2 z-score*	159	102	94	139	63 (57-69)	58 (51-64)	61 (55-67)	60 (53-66)	0.21	
≤-0.7 z-score	111	67	142	174	44 (38-50)	72 (66-78)	62 (55-69)	55 (49-61)	0.16	
≤-1.0 z-score	87	45	166	196	34 (29-41)	81 (76-86)	66 (57-74)	54 (49-59)	0.16	
FEV1/FVC										0.72
<80%	107	28	141	203	43 (37-50)	88 (83-92)	79 (71-86)	59 (54-64)	0.31	
<84%*	153	54	95	177	62 (55-68)	77 (71-82)	74 (67-80)	65 (59-71)	0.38	
<90%	202	127	46	104	81 (76-86)	45 (38-52)	61 (56-67)	69 (61-77)	0.26	
FEF50										0.73
≤-0.5 z-score*	131	46	87	155	60 (53-67)	77 (71-83)	74 (67-80)	64 (58-70)	0.37	
≤-1.0 z-score	83	27	135	174	38 (32-45)	87 (81-91)	75 (66-83)	56 (51-62)	0.25	
Bodyplethysm.										
sReff										0.68
≥0.9 kPa-s*	98	45	68	122	59 (51-67)	73 (66-80)	69 (60-76)	64 (57-71)	0.32	
≥1.0 kPa-s	81	33	85	134	49 (41-57)	80 (73-86)	71 (62-79)	61 (54-68)	0.29	
sRtot										0.64
≥1.0 kPa-s	28	18	4	6	88 (71-96)	25 (10-47)	61 (45-75)	60 (26-88)	0.13	
≥1.1 kPa-s *	25	14	7	10	78 (60-91)	42 (22-63)	64 (47-79)	59 (33-82)	0.20	
RV/TLC										0.53
≥25%*	150	134	45	52	77 (70-83)	28 (22-35)	53 (47-59)	54 (43-64)	0.05	
Bronchodilator rev.										0.60
FEV ₁										
≥7% increase*	156	75	59	76	73 (66-78)	50 (42-59)	68 (61-74)	56 (47-65)	0.23	
≥10% increase	131	66	84	85	61 (54-67)	56 (48-64)	66 (59-73)	50 (43-58)	0.17	
≥12% increase	117	62	98	89	54 (48-61)	59 (51-67)	65 (58-72)	48 (40-55)	0.13	
Bronchodilator rev. if										0.70
FEV1/FVC <80% ⁴										
≥7% increase*	83	10	18	14	82 (73-89)	58 (37-78)	89 (81-95)	44 (26-62)	0.41	
≥10% increase	68	8	33	16	67 (57-76)	67 (45-84)	89 (80-95)	33 (20-48)	0.34	
≥12% increase	60	7	41	17	59 (49-69)	71 (49-87)	90 (80-96)	29 (18-43)	0.30	

A+T+: children with asthma diagnosis and positive test result, A-T+: children without asthma diagnosis but positive test result, A+T-: children with asthma diagnosis but negative test result, A-T-: children without asthma and negative test result, Sens: sensitivity, Spec: specificity, PPV: positive predictive value, NPV: negative predictive value, YI: Youden's-Index: Sensitivity + Specificity -1, AUC: area under the curve, FeNO: fractional exhaled nitric oxide, ppb: parts per billion, FEV₁: forced expiratory volume in 1 second, FVC: forced vital capacity, FEF50: forced expiratory flow at 50% of FVC, sReff: specific effective airway resistance, sRtot: specific total airway resistance, RV: residual volume, TLC: total lung capacity, Bronchodilator rev.: bronchodilator reversibility
Displayed cut-offs chosen based on proposed cut-offs from previous publications

*Cut-off with maximum combined sensitivity and specificity (highest Youden's-Index)

¹ Number allergens for which the skin prick test is positive: wheal size ≥ 3 or the specific IgE test was positive: ≥ 0.35 kU/l.

² Reported by 4 centres

³ Reported by 2 centres

⁴ N= 126, cut-off chosen based on proposed cut-off from previous publications and guidelines

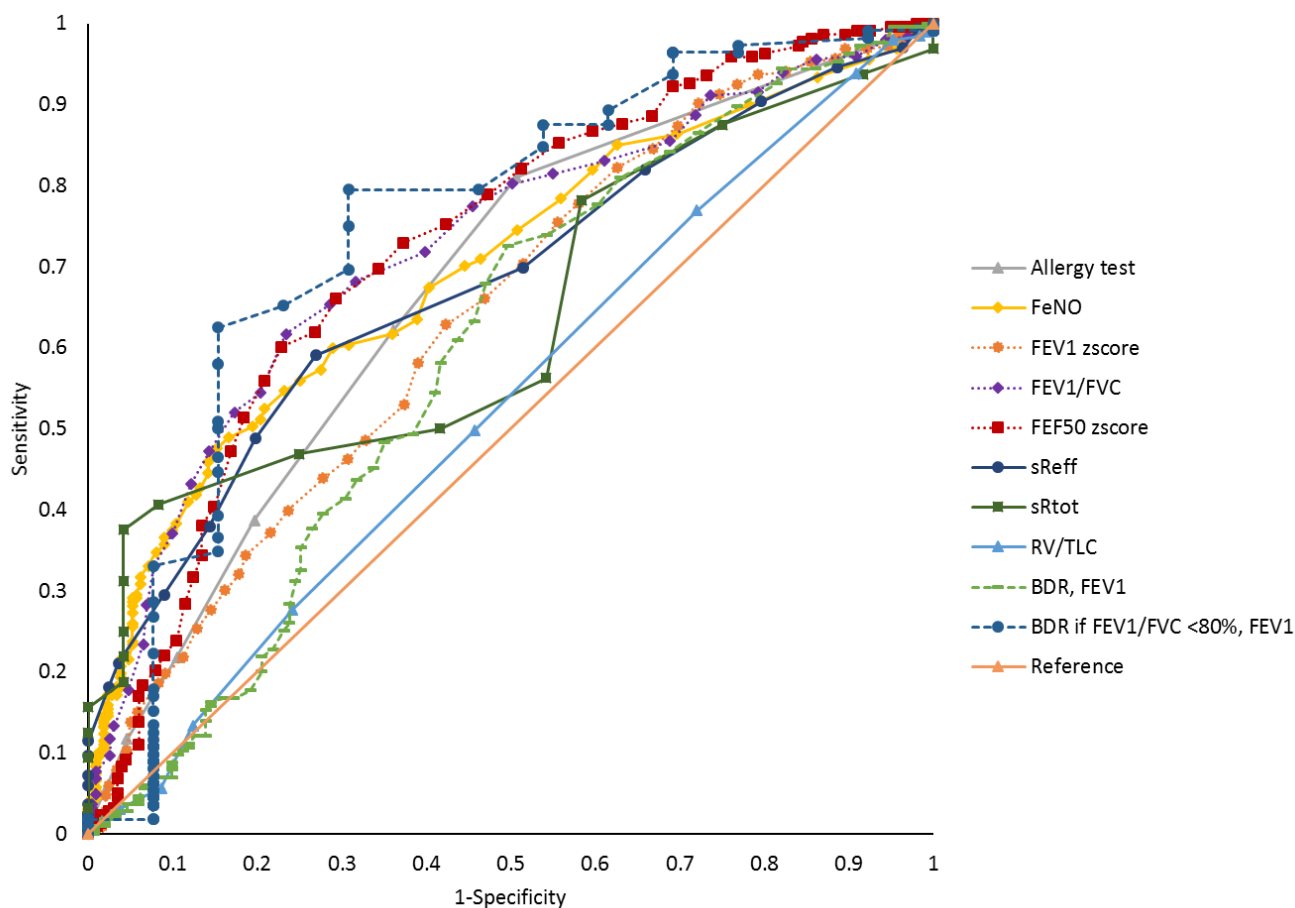


Figure S1 Receiver operating characteristics (ROC) curve of clinical tests to diagnose asthma. (Sensitivity analysis: “asthma” is defined as definite asthma and “not asthma” is defined as probable asthma or other diagnosis)

* Cut-off with maximum combined sensitivity and specificity

Test	Unit
Allergy test npos	increase of 1 positive skin prick or specific IgE test
FeNO	increase of 1 parts per billion (ppb)
FEV1	increase of 0.1 z-score
FEV1/FVC	increase of 1%
FEF50	increase of 0.1 z-score
sReff	decrease of 0.01 kPa·s
sRtot	decrease of 0.01 kPa·s
RV/TLC	increase of 5%
Bronchodilator reversibility (BDR), FEV ₁	increase of 1% in FEV ₁

Table S5. Diagnostic test results in steroid naive patients with and without asthma N=271

Diagnostic tests	Asthma					
	Definite asthma N=108		Probable asthma N=48		Other diagnosis N=115	
	median (IQR)		median (IQR)		median (IQR)	
Any allergy test, n(%)	101	(94)	46	(96)	86	(75)
≥1 positive test n(%)	87	(81)	31	(65)	39	(34)
Number of positive tests ¹	2	(1-4)	1	(0-3)	0	(0-2)
FeNO, n(%)	90	(83)	42	(88)	98	(85)
Parts per billion	33	(13-54)	17	(8-31)	13	(7-20)
Spirometry, n(%)	102	(94)	46	(96)	112	(97)
FEV1, z-scores	-0.5	(-1.3-0.1)	-0.1	(-1.0-0.5)	0.1	(-0.6-0.9)
FEV1/FVC	82	(77-88)	89	(83-92)	89	(86-95)
FEF50, z-score	-0.7	(-1.4-0.1)	0.1	(-0.7-0.9)	0.2	(-0.2-0.9)
Bodyplethysmography, n(%)	80	(74)	36	(75)	88	(77)
sReff, kPa·s ²	1.0	(0.7-1.3)	0.8	(0.7-0.9)	0.8	(0.6-0.9)
sRtot, kPa·s ³	1.3	(1.1-2.3)	1.4	(1.3-1.5)	1.0	(1.0-1.2)
RV/TLC	28	(24-33)	29	(25-37)	30	(24-34)
Bronchodilator reversibility, n(%)	85	(79)	30	(63)	66	(57)
Increase in FEV1 in %	13	(6-25)	5	(2-19)	7	(2-28)

¹Defined as wheal size ≥3mm for mites, cat, grass, birch, mugwort and alternaria skin prick test and as ≥0.35kU/L for specific IgE test

² Reported by 4 centres

³ Reported by 2 centres

Table S6. Diagnostic accuracy of diagnostic tests to diagnose asthma N=271 (sensitivity analysis: in steroid naïve children)

	A+T+	A-T+	A+T-	A-T-	Sens	Spec	PPV	NPV	YI	AUC
	n	n	n	n	%	%	%	%		
					(95%CI)	(95%CI)	(95%CI)	(95%CI)		
Clinical tests										
Allergy test ¹										0.71
≥1 positive test*	118	39	29	47	80 (73-86)	55 (44-65)	75 (68-82)	62 (50-73)	0.35	
≥2 positive tests	90	26	57	60	61 (53-69)	70 (59-79)	78 (69-85)	51 (42-61)	0.31	
FeNO										0.71
≥20ppb	75	25	57	73	57 (48-65)	74 (65-83)	75 (65-83)	56 (47-65)	0.31	
≥21ppb	72	23	60	75	55 (46-63)	77 (67-85)	76 (66-84)	56 (47-64)	0.31	
≥23ppb	69	17	63	81	52 (43-51)	83 (74-90)	80 (70-88)	56 (48-64)	0.35	
≥25ppb	66	15	66	83	50 (41-59)	85 (76-91)	81 (71-89)	56 (47-64)	0.35	
≥28ppb*	62	11	70	87	47 (38-56)	89 (81-94)	85 (75-92)	55 (47-63)	0.36	
Spirometry										
FEV1										0.65
≤-0.2 z-score	83	44	65	68	56 (48-64)	61 (51-70)	65 (56-74)	51 (42-60)	0.17	
≤-0.7 z-score*	60	23	88	89	41 (33-49)	79 (71-87)	72 (61-82)	50 (43-58)	0.20	
≤-1.0 z-score	42	17	106	95	28 (21-36)	85 (77-91)	71 (58-82)	47 (40-54)	0.13	
FEV1/FVC										0.69
<80%	47	6	100	99	32 (25-40)	94 (88-98)	87 (77-96)	50 (43-57)	0.26	
<86%*	88	26	59	79	60 (51-68)	75 (66-83)	77 (68-85)	57 (49-66)	0.35	
<90%	109	58	38	47	74 (66-81)	45 (35-56)	65 (58-72)	55 (44-66)	0.19	
FEF50										0.70
≤-0.3 z-score*	70	18	61	77	53 (45-62)	81 (72-88)	80 (70-87)	56 (47-64)	0.34	
≤-1.0 z-score	40	5	91	90	31 (23-39)	95 (88-98)	89 (76-96)	50 (42-57)	0.25	
Bodyplethysm.										
sReff										0.62
≥0.9 kPa·s*	47	20	54	55	47 (37-57)	73 (62-83)	70 (58-81)	50 (41-60)	0.20	
≥1.0 kPa·s	37	15	64	60	37 (27-47)	80 (69-88)	71 (57-83)	48 (39-58)	0.17	
sRtot										0.77
≥1.0 kPa·s	13	7	2	6	87 (60-98)	46 (19-75)	65 (41-85)	75 (35-97)	0.33	
≥1.5 kPa·s *	13	4	2	9	87 (60-98)	69 (39-91)	76 (50-93)	82 (48-98)	0.56	
RV/TLC										0.51
≥35%*	25	17	88	69	22 (15-31)	80 (70-88)	60 (43-74)	44 (36-52)	0.02	
Bronchodilator rev.										
FEV ₁										0.56
≥7% increase*	75	32	40	34	65 (56-74)	52 (39-64)	70 (60-79)	46 (34-58)	0.17	
≥10% increase	66	27	49	39	57 (48-67)	59 (46-71)	71 (61-80)	44 (34-55)	0.16	
≥12% increase	59	25	56	41	51 (42-61)	62 (49-74)	70 (59-80)	42 (32-53)	0.13	
Bronchodilator rev. if FEV1/FVC <80% ⁴										0.87
≥7% increase	37	1	8	4	82 (68-92)	80 (28-99)	97 (86-99)	33 (10-65)	0.62	
≥10% increase*	30	0	15	5	67 (51-80)	99 (48-99)	99 (88-99)	25 (9-49)	0.67	
≥12% increase	26	0	19	5	58 (42-72)	99 (48-99)	99 (87-99)	21 (7-42)	0.58	

A+T+: children with asthma diagnosis and positive test result, A-T+: children without asthma diagnosis but positive test result, A+T-: children with asthma diagnosis but negative test result, A-T-: children without asthma and negative test result, Sens: sensitivity, Spec: specificity, PPV: positive predictive value, NPV: negative predictive value, YI: Youden's-Index: Sensitivity + Specificity -1, AUC: area under the curve, FeNO: fractional exhaled nitric oxide, ppb: parts per billion, FEV₁: forced expiratory volume in 1 second, FVC: forced vital capacity, FEF50: forced expiratory flow at 50% of FVC, sReff: specific effective airway resistance, sRtot: specific total airway resistance, RV: residual volume, TLC: total lung capacity,

Bronchodilator rev.: bronchodilator reversibility

Displayed cut-offs chosen based on proposed cut-offs from previous publications

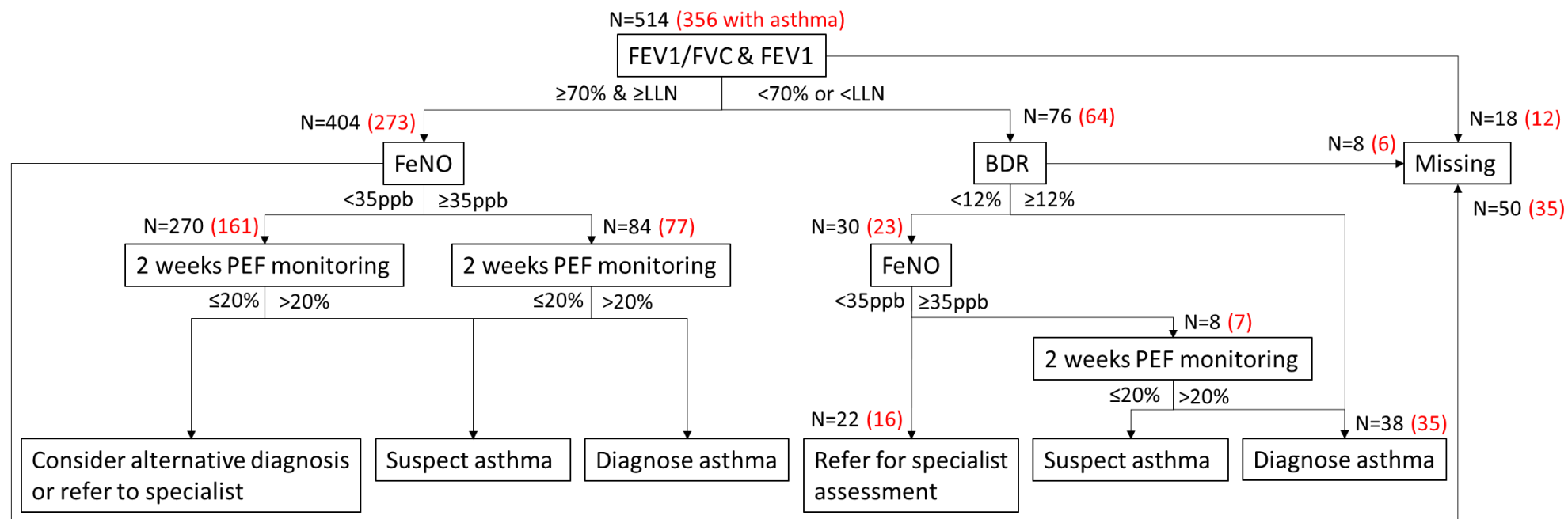
*Cut-off with maximum combined sensitivity and specificity (highest Youden's-Index)

¹ Number allergens for which the skin prick test is positive: wheal size ≥ 3 or the specific IgE test was positive: ≥ 0.35 kU/l.

² Reported by 4 centres

³ Reported by 2 centres

⁴ N= 51, cut-off chosen based on proposed cut-off from previous publications and guidelines



	Asthma +	Asthma -	Total
Algorithm +	35	3	38
Algorithm -	16	6	22
Total	51	9	60

Sens = $35/51 = 0.69$
 Spec = $6/9 = 0.67$
 PPV = $35/38 = 0.92$
 NPV = $6/22 = 0.27$

Figure S2 Diagnostic accuracy of the diagnostic algorithm proposed by the NICE guideline

Numbers in black: number of patients at this step. Numbers in red: number of patients with doctor diagnosed asthma at this step. Algorithm +: diagnose asthma or suspect asthma. Algorithm - : refer for specialist assessment or consider alternative diagnosis. FEV1: forced expiratory volume in 1 second. FVC: forced vital capacity. BDR: bronchodilator reversibility. FeNO: fractional exhaled nitric oxide. PEF: peak expiratory flow.

*362 patients would need 2 weeks PEF monitoring.