

Appendix

Appendix Table 1. Manual review key (chart review inclusion/exclusion criteria) to determine asthma labels.

RULES	
<p>Must meet A1 criteria AND A2 criteria OR A3 criteria (AND ≥1 of B; criteria other than medication if A2 used) AND No criteria C (exclusion)</p>	
A. DIAGNOSTIC FEATURE	CRITERIA FOR MAKING THE DIAGNOSIS OF ASTHMA
A1. History of variable respiratory symptoms	
<p>Wheeze, shortness of breath, chest tightness, cough Note: may vary by age, across cultures (e.g. heavy breathing)</p>	<p>More than 1 episode over time AND at least 1 of the following:</p> <ul style="list-style-type: none"> - Symptoms vary over time - Symptoms vary in intensity - Symptoms worse at night or on waking - Symptoms often have clear trigger: exercise, illness, allergens, cold air, seasonal, emotion, smoke/fumes/smells, menstrual cycle, etc. - Symptoms often worse with viral infections
A2. Confirmed variable expiratory airflow limitation	
<p>Documented variability in lung function (one or more of a-f below) AND Documented airflow limitation (At least once FEV1/FVC is <0.90)</p>	<p>The greater the variation or frequency of occurrence, the more confident the diagnosis</p>
a) Positive bronchodilator (BD) response test	Increase in FEV1 of 12% or 10% predicted
b) Excessive variability in BID PEF measurements over 2 weeks	Average daily diurnal PEF variability >13%
c) Increase in lung function after 4 weeks of anti-inflammatory treatment	Increase in FEV1 by 12% and >200 mL (or PEF by >20%) from baseline, outside of respiratory infections
d) Positive exercise challenge test	Fall in FEV1 of >12% predicted, or PEF >15%
e) Positive bronchial challenge test (usually only in older teens, adults)	Fall in FEV1 from baseline of ≥20% with standard doses of methacholine or histamine, or ≥15% with standardized hyperventilation, hypertonic saline or mannitol challenge
f) Excessive variation in lung function between visits	Variation in FEV1 of >12% in FEV1 or >15% in PEF between visits (may include respiratory infections)
A3. Documented clinical response to bronchodilator (typically if unable to perform PFTs or no PFTs available)	

Documented clinical response to bronchodilators, oral/inhaled steroids	Clinical symptoms (cough/wheeze/shortness of breath, etc.) improve/resolve
B. DIAGNOSTIC FEATURE (SECONDARY)	CRITERIA SUPPORTIVE OF ASTHMA
1. Personal history	<ul style="list-style-type: none"> - Allergies (food or environmental) - Eczema NOT asthma if: chronic production of sputum, Shortness of breath with dizziness, light-headedness, or peripheral tingling (paresthesia), chest pain, exercise-induced dyspnea with noisy inspiration
2. Family history	Parent with asthma
3. Physical exam	<ul style="list-style-type: none"> - Expiratory wheeze on auscultation, prolonged expiratory phase - Nasal polyposis (allergies, but also CF) but lacking wheeze does not exclude diagnosis Eczema NOT asthma if: crackles or digital clubbing
4. Radiologic findings	Hyperinflation, flattened diaphragms, peribronchial thickening, right middle lobe syndrome in children under 5 years old
5. Elevated FeNO	<ul style="list-style-type: none"> - Decreases as ICS are started - >25 PPB
6. Labs	<ul style="list-style-type: none"> - Blood eosinophilia >300/ul or >4% - IgE >100
7. Medication	See list
C. EXCLUSION CRITERIA/ALTERNATIVE DIAGNOSES - Condition	SYMPTOMS/RESPIRATORY ISSUES
Airways malacia	Inspiratory and expiratory wheeze, not helped or worsened with beta-agonist
Airway tumor	Fixed obstruction, abnormal chest X-ray
Autoimmune disease	Interstitial lung disease
Bronchiectasis	Recurrent infections, productive cough
Cancers of the airway, chest, lung	Persistent symptoms, pulmonary side effects of chemotherapy, dyspnea
Cancers of blood, lymphatic system	Pulmonary side effects of chemotherapy, dyspnea
Central airway obstruction	Dyspnea, unresponsive to bronchodilators
Congenital airway abnormality	Persistent symptoms, dyspnea, cough
Congenital heart disease/ CHF/ pulmonary edema	Cardiac murmur, hepatomegaly, crackles
Cystic fibrosis	Excessive cough and mucus production, failure to thrive, gastrointestinal symptoms
Diaphragm disorder	Dyspnea

Hyperventilation, dysfunctional breathing	Dizziness, paresthesia, sighing
Immunodeficiency (acquired or congenital)	Recurrent infections, bronchiectasis
Inhaled foreign body	Sudden onset of symptoms, unilateral wheeze, symptoms do not respond to asthma medication
Interstitial/parenchymal lung disease	Dyspnea, non-productive cough, finger clubbing
Neuromuscular disease	Hypotonia, ineffective airway clearance
Post-radiation lung disease	Dyspnea, interstitial lung disease
Post-transplant	Immunocompromised, recurrent infections
Primary ciliary dyskinesia	Recurrent infections, productive cough, sinusitis
Pulmonary aspiration	Dysphagia, coughing when eating, hypotonia
Pulmonary embolism	Dyspnea, chest pain
Pulmonary fibrosis	Hypoxemia at rest, crackles on exam, poor growth
Pulmonary hypertension	Dyspnea
Vascular ring/sling	Fixed obstruction, no response to beta-agonist
Vocal cord dysfunction	Dyspnea, inspiratory wheeze (stridor)

FEV1= forced expiratory volume in 1 second, FVC=forced vital capacity, PEF=peak expiratory flow, PFT=pulmonary function test, FeNO=fractional exhaled nitric oxide, ICS=inhaled corticosteroid, IgE=immunoglobulin E

Appendix Table 2. Asthma Medications

Asthma Medications	
Short-acting Beta-agonist	<p>Route: Inhaled, nebulized, oral (PO) Albuterol (Albuterol, Albuterol Sulfate, Ventolin, Proventil, ProAir, Accuneb, VoSpire ER) Levalbuterol (Xopenex HFA) Metaproterenol (Alupent) Pirbuterol (Maxair) Terbutaline (Brethine)</p>
Long acting Beta-agonist	<p>Route: Inhaled, nebulized Aformoterol (Brovana) Formoterol (Foradil) Indacaterol (Arcapta) Salmeterol (Serevent)</p>
Combination Bronchodilators	<p>Route: Inhaled, nebulized Albuterol+ipratropium (Combivent MDI , Respimat, Duoneb) Umeclidinium + vilanterol (Anoro Ellipta)</p>
Methylxanthines	<p>Route: oral (PO), intravenous (IV) Aminophylline Theophylline (Slo-Bid, Theo, Theodur, Theolair, Uniphyll)</p>
Anticholinergic Agents	<p>Route: Inhaled Aclidinium bromide (Turdoza Pressair) Ipratropium bromide (Atrovent) Tiotropium bromide (Spiriva HandiHaler, Respimat) Umeclidinium bromide (Incruse Ellipta)</p>
Combination bronchodilators	<p>Route: Inhaled, nebulized Albuterol+ipratropium (Combivent, Respimat, DuoNeb) Umeclidinium+vilanterol (Anoro Ellipta)</p>
Mast Cell Stabilizers	<p>Route: Inhaled, nebulized Cromolyn sodium, cromoglycate (Intal) Nedocromil (Tilade)</p>
Inhaled Corticosteroids	<p>Route: inhaled Beclomethasone propionate (QVAR) Budesonide (Pulmicort Turbuhaler, Pulmicort Flexhaler, Pulmicort Respules) Ciclesonide (Alvesco) Flunisolide (Aerobid, Aerobid-M, Aerospan 80) Fluticasone propionate (Flovent HFA, Flovent Diskus) Mometasone (Asmanex HFA, Asmanex Twisthaler) Triamcinolone acetonide (Azmacort)</p>

<p>Inhaled Corticosteroid + Long-Acting Beta Agonist</p>	<p>Route: Inhaled Budesonide-Formoterol (Symbicort HFA) Fluticasone furoate + Vilanterol (Breo Ellipta) Fluticasone-salmeterol (Advair HFA, Advair Diskus, AirDuo Respiclick) Mometasone-formoterol (Dulera HFA)</p>
<p>Leukotriene Antagonists (LTA)</p>	<p>Route: Oral (PO) Montelukast (Singulair) Zafirlukast (Accolate) Zileuton (Zyflo, Zyflo CR)</p>
<p>Biologics</p>	<p>Benralizumab (Fasenra) Dupilumab (Dupixent) Mepolizumab (Nucala) Omalizumab (Xolair) Reslizumab (Cinqair)</p>

Appendix Table 3. Chicago and PheKB Exclusion Criteria Diagnoses

Exclusion Criteria - Chicago Algorithm		
Cancers of the airways and thorax	ICD-9	160.xx to 165.xx
	ICD-10	C30.** to C39.*
Secondary malignancy of the respiratory system	ICD-9	197.0 to 197.3
	ICD-10	C78.**
Malignancy of lymphatic and hematopoietic systems	ICD-9	200.xx to 208.xx
	ICD-10	C81.88 to C96.**
Benign neoplasm of the bronchus and lung	ICD-9	212.3
	ICD-10	D14.30
Human immunodeficiency virus HIV disease	ICD-9	042
	ICD-10	B20.**
Retrovirus infections	ICD-9	079.5x
	ICD-10	B97.3
Asymptomatic and serologic HIV infection	ICD-9	V08, 795.71
	ICD-10	Z21 and R75
Alpha 1-antitrypsin deficiency	ICD-9	273.4
	ICD-10	E88.01
Cystic fibrosis and other metabolic disorders	ICD-9	277.xx, V77.6, V83.81
	ICD-10	E84.*, Z13.228
Acute pulmonary heart disease (cor pulmonale, embolism)	ICD-9	415.x
	ICD-10	I00.* to I02.**, I05.** to I09.**, I10.** to I16.**, I20.** to I25.**, I26.** to I28.**, I30.** to I52.**, I60.** to I69.**, I70.** to I79.**, I80.** to I89.**, I95.** to I99.**
Chronic pulmonary heart disease	ICD-9	416.x
	ICD-10	I00.* to I02.**, I05.** to I09.**, I10.** to I16.**, I20.** to I25.**, I26.** to I28.**, I30.** to I52.**, I60.** to I69.**, I70.** to I79.**, I80.** to I89.**, I95.** to I99.**
Paralysis of vocal cord or larynx	ICD-9	478.3x
	ICD-10	J38.00, J38.01, J38.02
Other diseases of vocal cords (vocal cord dysfunction)	ICD-9	478.5
	ICD-10	J38.3
Chronic obstructive pulmonary disease (COPD)	ICD-9	491.xx, 496

	ICD-10	J41.0, J41.1, J44.9, J44.1, J44.0, J41.8, J42
Emphysema	ICD-9	492.x
	ICD-10	J43.9
Bronchiectasis	ICD-9	494.xx
	ICD-10	J47.9
Extrinsic allergic alveolitis	ICD-9	495.x
	ICD-10	J47.1
Pneumoconioses and post-radiation lung disease	ICD-9	500.x - 508.x
	ICD-10	J61, J62.8, J63.*, J66.*, J64, J68.*, J69.*, J70.*
Malignant pleural effusion	ICD-9	511.81
	ICD-10	J91.0
Pulmonary fibrosis	ICD-9	515
	ICD-10	J84.10, J84.89
Other alveolar and parietoalveolar pneumonopathy	ICD-9	516.x
	ICD-10	J84.*
Lung involvement in conditions declassified elsewhere	ICD-9	517.x
	ICD-10	J17, M34.81, J99
Allergic bronchopulmonary aspergillosis	ICD-9	518.6
	ICD-10	B44.81
Disorders of diaphragm	ICD-9	519.4
	ICD-10	J98.6
Congenital abnormalities of lower airways and lungs	ICD-9	748.2 to 748.9
	ICD-10	Q31.0, Q31.1, Q31.3, Q31.8, Q32.1, Q32.4, Q33.0, Q33.2, Q33.3, Q33.6, Q33.9, Q33.4, Q33.1, Q33.5, Q33.8, Q34.0, Q34.1, Q34.8, Q34.9
Respiratory distress syndrome	ICD-9	769.xx
	ICD-10	P22.0
Chronic bronchitis and emphysema	ICD-9	V81.3
	ICD-10	Z13.83
Bronchopulmonary dysplasia	ICD-9	770.7
	ICD-10	P27.0, P27.1, P27.8
Prematurity (born <35 weeks), 765.28 and 765.29 are allowed	ICD-9	765.21 to 765.27
	ICD-10	P07.21, P07.22, P07.23, P07.24, P07.26, P07.31, P07.32, P07.33, P07.34, P07.35, P07.36, P07.37
Aspiration syndrome/foreign body	ICD-9	934.8

	ICD-10	T17.800A, T17.808A, T17.810A, T17.818A, T17.820A, T17.828A, T17.890A, T17.898A
Post-transplant lymphoproliferative disorder (PTLD)	ICD-9	238.77
	ICD-10	D47.Z1
Systemic lupus erythematosus, scleroderma, dermatomyositis	ICD-9	710.x
	ICD-10	M32.10, M34.0, M34.1, M34.9, M35.00, M35.01, M33.90, M33.20, M35.8, M35.5, M35.9
Rheumatoid arthritis and other inflammatory polyarthropathies	ICD-9	714.x
	ICD-10	M06.9, M05.00, M05.30, M05.60, M06.1, M08.00, M08.3, M08.40, M12.00, M05.10, M06.4
Complications of transplanted organ	ICD-9	996.8x
	ICD-10	T86.*
Surgical operation with transplant of whole organ	ICD-9	E878.0
	ICD-10	Y83.0
Organ or tissue replaced by transplant	ICD-9	V42.x
	ICD-10	Z94.*, Z95.*
Awaiting organ transplant status	ICD-9	V49.83
	ICD-10	Z76.82
Aftercare following organ transplant	ICD-9	V58.44
	ICD-10	Z48.298
Cerebral palsy	ICD-9	343.x
	ICD-10	G80.*
Spinal muscular atrophy and other motor neuron diseases	ICD-9	335.x
	ICD-10	G12.*
Muscular dystrophies and other myopathies	ICD-9	359.x
	ICD-10	G72.*, G73.*
Heart failure	ICD-9	428.x
	ICD-10	I50.*
Exclusion Criteria from PheKB		
Vocal cord dysfunction	ICD-9	478.3**
	ICD-10	J38.00, J38.01, J38.02
Post-transplant lymphoproliferative disorder (PTLD)	ICD-9	238.77
	ICD-10	D47.Z1
Cystic fibrosis and other metabolic disorders	ICD-9	277.**
	ICD-10	E84.*, Z13.228, Z14.1
Bronchitis, emphysema	ICD-9	490-492.**, V81.3

	ICD-10	Z13.83
Diseases of the respiratory system	ICD-9	494-496.**
	ICD-10	J47.9, J67.* , J44.9
Respiratory distress syndrome	ICD-9	769.**
	ICD-10	P22.0
Organ or tissue replaced by transplant	ICD-9	996.8, E878.0, V42, V49.83, V58.44
	ICD-10	T86.*

ICD=International Classification of Diseases

Appendix Table 4. Details of errors and proposed solutions.

Rules		Algorithm	Potential Error Reason	Potential Error Type	Proposed Solution
1	Visit 1: ICD asthma-related dx	CAPriCORN	<ul style="list-style-type: none"> • Diagnosis may be filed without a confirmatory note • Erroneous diagnosis filed 	FP	<ul style="list-style-type: none"> • Include "in-person" visits relevant to clinic, hospital, ER, urgent care • Include encounters after the EHR activated • Include encounters with associated notes
			<ul style="list-style-type: none"> • Asthma not yet diagnosed 	FN	<ul style="list-style-type: none"> • Include broader asthma definition DRG • Stricter criteria of dx+med, with the addition of NLP/predictive analytics
	Visit 1: ICD asthma-related dx + med	PheKB	<ul style="list-style-type: none"> • Diagnosis may exist without supporting documentation • Can be an erroneous diagnosis • Medication may not be current 	FP	<ul style="list-style-type: none"> • Include "in-person" visits relevant to clinic, hospital, ER, urgent care • Include encounters after the EHR activated • Include encounters with associated notes
			<ul style="list-style-type: none"> • Asthma not yet diagnosed • Medication filed on different date or location 	FN	<ul style="list-style-type: none"> • Include broader asthma definition DRG • NLP, Exploratory data/predictive analytics
2	Visit 2: ICD asthma-related dx OR med	CAPriCORN	<ul style="list-style-type: none"> • Diagnosis may be filed without a confirmatory note • Erroneous diagnosis filed • Medication may not be current • Second note may be part of the first illness 	FP	<ul style="list-style-type: none"> • "In-person" visits relevant to clinic, hospital, ER, urgent care • Include encounters after the EHR activated • Include encounters with associated notes • Episodes >1 month apart
			<ul style="list-style-type: none"> • Only 1 note with confirmatory asthma history documented • Asthma not yet diagnosed 	FN	<ul style="list-style-type: none"> • Include broader asthma definition DRG • NLP, Exploratory data/predictive analytics
	Visit 2: ICD asthma-related dx + med	PheKB	<ul style="list-style-type: none"> • Diagnosis may be filed without a confirmatory note • Erroneous diagnosis filed • Medication may not be current 	FP	<ul style="list-style-type: none"> • "In-person" visits relevant to clinic, hospital, ER, urgent care • Include encounters after the EHR activated

			<ul style="list-style-type: none"> • Second note may be part of the first illness 		<ul style="list-style-type: none"> • Include encounters with associated notes • Episodes >1 month apart
			<ul style="list-style-type: none"> • Asthma not yet diagnosed • Medication filed on different date or location 	FN	<ul style="list-style-type: none"> • Include broader asthma definition DRG • NLP, Exploratory data/predictive analytics
3	Text: >=3 visits in 1 year with "wheezing" or "asthma"	PheKB	<ul style="list-style-type: none"> • Picks up those words in erroneous contexts (templates, FH, etc) 	FP	<ul style="list-style-type: none"> • Text from HPI and Assessment/Plan only. Exclude negation, FH, templates, etc.
			<ul style="list-style-type: none"> • The timeframe of within 1 year may miss cases that have issues years apart (more mild, controlled cases) 	FN	<ul style="list-style-type: none"> • Expand timeframe to avoid missing intermittent asthma with infrequent exacerbations
4	Exclusion Criteria	CAPriCORN PheKB	<ul style="list-style-type: none"> • Diagnoses that should be excluded • Unnecessary exclusion criteria 	FP FN	See Appendix Table 5 for details

FP=false positive; FN=false negative; DRG=diagnosis-related group; ER=emergency room; EHR=electronic health record; NLP=natural language processing; dx=diagnosis; med=medication; HPI=history of present illness; FH=family history

Appendix Table 5. Chicago and PheKB Exclusion Criteria, Error Analysis

Exclusion criteria to potentially include - Chicago and PheKB algorithm
Chiari malformation; cerebellar hypoplasia and related disorders; chronic fatigue syndrome; dysautonomia; Fabry disease; fibromyalgia; grey matter anomalies; hiatal hernia; hypotonia; immunodeficiency; inflammatory bowel disease; intractable seizure disorder; myasthenia gravis; nephrotic syndrome; pacemaker; pectus excavatum; periodic fever syndrome; postural orthostatic tachycardia syndrome; Prader-Willi syndrome; scoliosis; supraventricular tachycardia; Trisomy 21 Syndrome
Exclusion criteria to potentially remove - CAPriCORN
Vocal cord dysfunction; disorders of the diaphragm; chronic respiratory disease arising in the perinatal period; other acute and subacute respiratory conditions due to fumes and vapors; foreign body in other specified parts of trachea bronchus and lung
Exclusion criteria to potentially remove – PheKB
Bronchitis and bronchitis not specified as acute or chronic