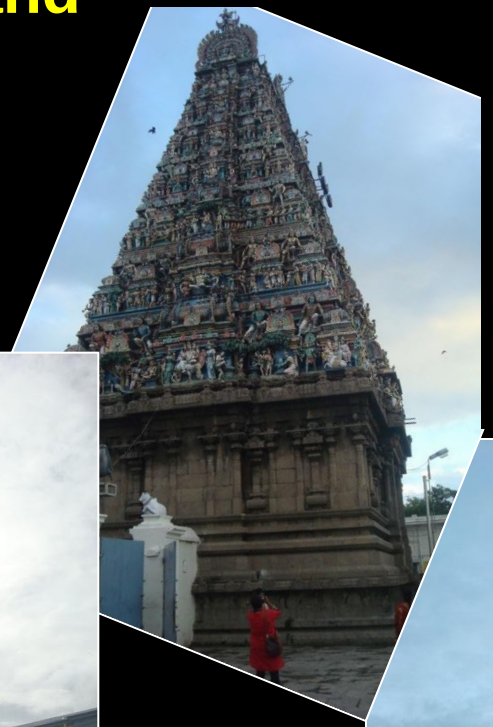
WAO WISC Hyderabad 6 December 2012

PG2: ASTHMA AND LOWER AIRWAY DISEASE TRACK

- Biomarkers, Lung Function and Bronchial Provocation Tests of Asthma

"Biomarkers Such as Exhaled NO and Sputum Eosinophils"

Peter Le Souëf
School of Paediatrics and Child Health
University of Western Australia



Asthma monitoring

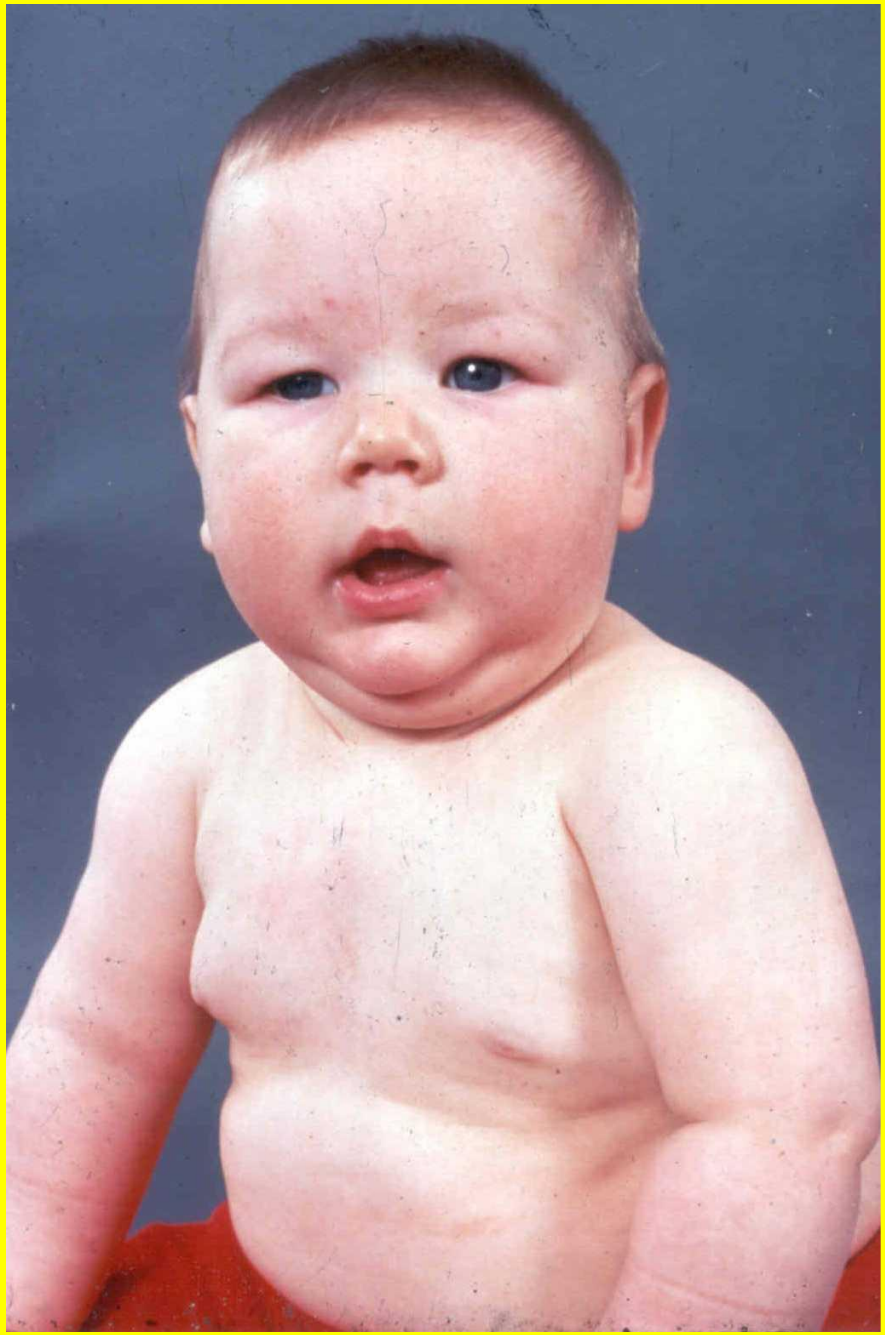
- **Clinical monitoring**
- **Biological monitoring**

Asthma monitoring

- **Clinical monitoring**
- **Biological monitoring**

Asthma monitoring

- **Clinical monitoring**
  - confirm diagnosis



History

Clinical examination

Dr Theophile Laennec listens to a patient through the precursor of the stethoscope at Necker Hospital in Paris.

Children with recurrent wheezing
Clinical index & RR asthma

Tucson longitudinal study n = 1,246 Castro-Rodrigez JA et al AJRCCM 2000;162:1403-6

Wheezing history freq wheeze < 3yrs

Major criteria ***asthma in parents*** (doctor diagnosed)
eczema in child (doctor diagnosed)

Minor criteria ***allergic rhinitis*** (doctor diagnosed)
wheezing apart from colds
eosinophils > 4%

+ve index: wheezing history + 1 major or 2 minor criteria

RR asthma 6 - 13 yrs with +ve index 4.3 - 9.8
with –ve index 95% never asthma

Asthma monitoring

- **Clinical monitoring**
  - confirm diagnosis
  - establish classification

Asthma classification guidelines:

BTS

GINA

NIH NHLBI NAEPP

PRACTALL

SIGN

TSANZ

etc

National Heart, Lung,
and Blood Institute

National Asthma Education
and Prevention Program

Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma

Full Report 2007

NIH – NHLBI NAEPP 3
2007 report – 440 pages

U.S. Department of Health and Human Services
National Institutes of Health
National Heart, Lung, and Blood Institute

National Institutes of Health – National Heart, Lung and Blood Institute
National Asthma Education and Prevention Program 3 2007 report

CLASSIFY ASTHMA SEVERITY

The Expert Panel recommends that clinicians classify asthma severity by using the domains of current impairment and future risk (Evidence B—secondary analyses of clinical trials, and Evidence C—observational studies, for assessing impairment; Evidence C, for distinguishing intermittent versus persistent asthma by risk of exacerbations; Evidence D, for distinguishing different categories of persistent asthma by varying frequencies of exacerbations).

Asthma severity is the intrinsic intensity of disease. Initial assessment of patients who have confirmed asthma begins with a severity classification because the selection of type, amount, and scheduling of therapy should then correspond to the level of asthma severity. This initial assessment of asthma severity is made immediately after diagnosis, or when the patient is first encountered, generally before the patient is taking some form of long-term control medication. Assessment is made on the basis of current spirometry and the patient's recall of symptoms over the previous 2–4 weeks, because detailed recall of symptoms decreases over time. If the assessment is made during a visit in which the patient is treated for an acute exacerbation, then asking the patient to recall symptoms in the period before the onset of the current exacerbation will suffice until a followup visit can be made.

For population-based evaluations, clinical research, or subsequent characterization of the patient's overall severity, asthma severity can be inferred after optimal therapy is established by correlating levels of severity with the lowest level of treatment required to maintain control. For clinical management, however, the emphasis is to assess asthma severity prior to initiating therapy and, then, assess control for monitoring and adjusting therapy.

National Institutes of Health – Nat
National Asthma Education and

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therapy and, then, assess control for monitoring

FIGURE 3–1. SUGGESTED ITEMS FOR MEDICAL HISTORY*

A detailed medical history of the new patient who is known or thought to have asthma should address the following items:

1. **Symptoms**
   - Cough
   - Wheezing
   - Shortness of breath
   - Chest tightness
   - Sputum production
2. **Pattern of symptoms**
   - Perennial, seasonal, or both
   - Continual, episodic, or both
   - Onset, duration, frequency (number of days or nights, per week or month)
   - Diurnal variations, especially nocturnal and on awakening in early morning
3. **Precipitating and/or aggravating factors**
   - Viral respiratory infections
   - Environmental allergens, indoor (e.g., mold, house-dust mite, cockroach, animal dander or secretory products) and outdoor (e.g., pollen)
   - Characteristics of home including age, location, cooling and heating system, wood-burning stove, humidifier, carpeting over concrete, presence of molds or mildew, characteristics of rooms where patient spends time (e.g., bedroom and living room with attention to bedding, floor covering, stuffed furniture)
   - Smoking (patient and others in home or daycare)
   - Exercise
   - Occupational chemicals or allergens
   - Environmental change (e.g., moving to new home; going on vacation; and/or alterations in workplace, work processes, or materials used)
   - Irritants (e.g., tobacco smoke, strong odors, air pollutants, occupational chemicals, dusts and particulates, vapors, gases, and aerosols)
   - Emotions (e.g., fear, anger, frustration, hard crying or laughing)
   - Stress (e.g., fear, anger, frustration)
   - Drugs (e.g., aspirin; and other nonsteroidal anti-inflammatory drugs, beta-blockers including eye drops, others)
   - Food, food additives, and preservatives (e.g., sulfites)
   - Changes in weather, exposure to cold air
   - Endocrine factors (e.g., menses, pregnancy, thyroid disease)
   - Comorbid conditions (e.g. sinusitis, rhinitis, GERD)
4. **Development of disease and treatment**
   - Age of onset and diagnosis
   - History of early-life injury to airways (e.g., bronchopulmonary dysplasia, pneumonia, parental smoking)
   - Progression of disease (better or worse)
   - Present management and response, including plans for managing exacerbations
   - Frequency of using SABA
   - Need for oral corticosteroids and frequency of use
5. **Family history**
   - History of asthma, allergy, sinusitis, rhinitis, eczema, or nasal polyps in close relatives
6. **Social history**
   - Daycare, workplace, and school characteristics that may interfere with adherence
   - Social factors that interfere with adherence, such as substance abuse
   - Social support/social networks
   - Level of education completed
   - Employment
7. **History of exacerbations**
   - Usual prodromal signs and symptoms
   - Rapidity of onset
   - Duration
   - Frequency
   - Severity (need for urgent care, hospitalization, ICU admission)
   - Life-threatening exacerbations (e.g., intubation, intensive care unit admission)
   - Number and severity of exacerbations in the past year.
   - Usual patterns and management (what works?)
8. **Impact of asthma on patient and family**
   - Episodes of unscheduled care (ED, urgent care, hospitalization)
   - Number of days missed from school/work
   - Limitation of activity, especially sports and strenuous work
   - History of nocturnal awakening
   - Effect on growth, development, behavior, school or work performance, and lifestyle
   - Impact on family routines, activities, or dynamics
   - Economic impact
9. **Assessment of patient's and family's perceptions of disease**
   - Patient's, parents', and spouse's or partner's knowledge of asthma and belief in the chronicity of asthma and in the efficacy of treatment
   - Patient's perception and beliefs regarding use and long-term effects of medications
   - Ability of patient and parents, spouse, or partner to cope with disease
   - Level of family support and patient's and parents', spouse's, or partner's capacity to recognize severity of an exacerbation
   - Economic resources
   - Sociocultural beliefs

*This list does not represent a standardized assessment or diagnostic instrument. The validity and reliability of this list have not been assessed.

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	Term	Definition
Temporal pattern	episodic (viral) wheeze	wheezing during discrete periods with clinical evidence of a viral cold, absence of wheeze between episodes
	multiple-trigger wheeze	wheezing shows discrete exacerbations, but also symptoms between episodes

Aim: To determine whether recently proposed phenotypes of preschool wheeze are stable over time

Methods: 132 2 to 6 yr old asthmatic children classified at screening as:

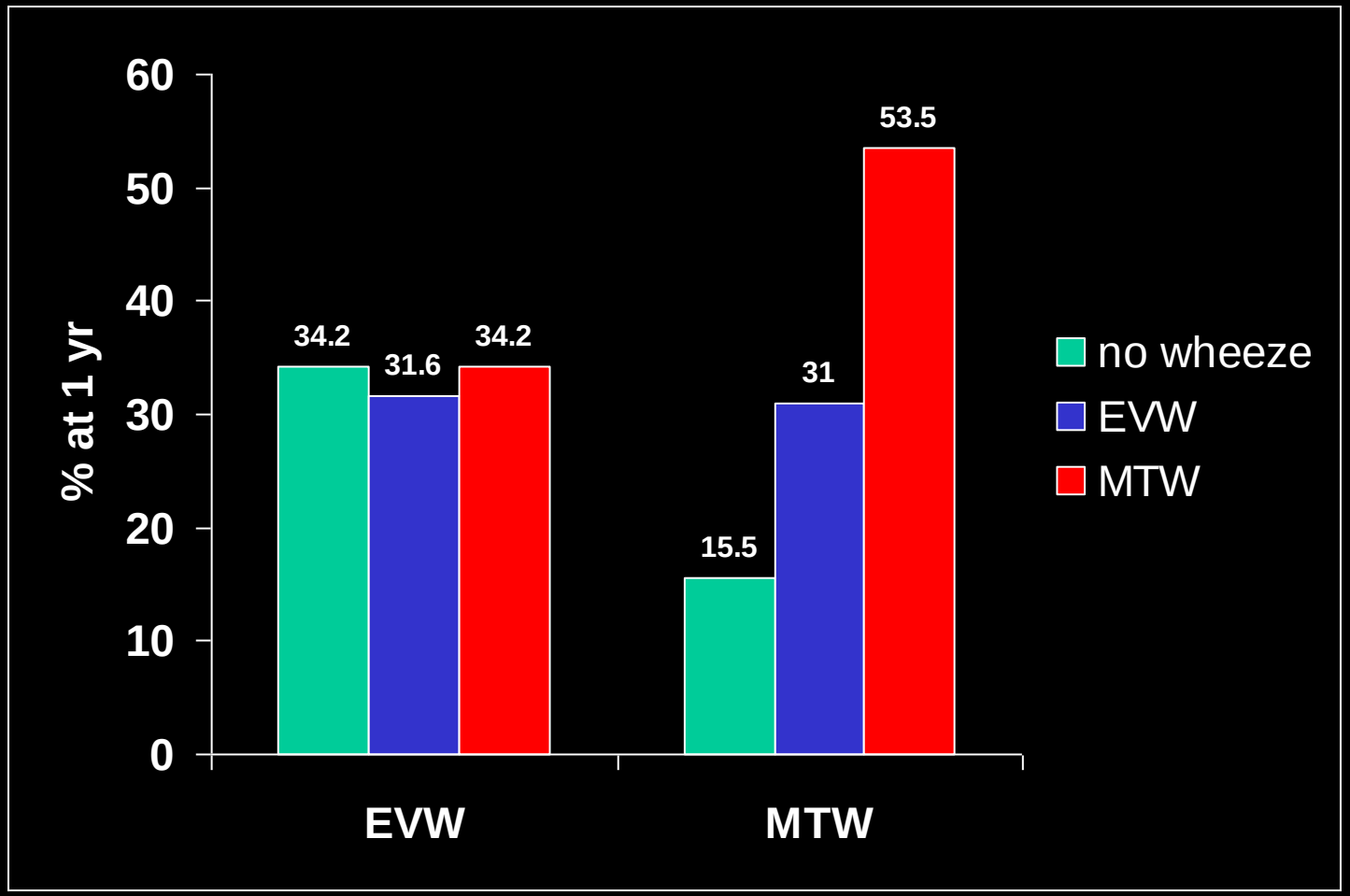
- episodic (viral) wheeze or
- multiple trigger wheeze

then followed up 3 monthly for a year

Results: Phenotypic classification

45.9% unchanged

54.1% changed



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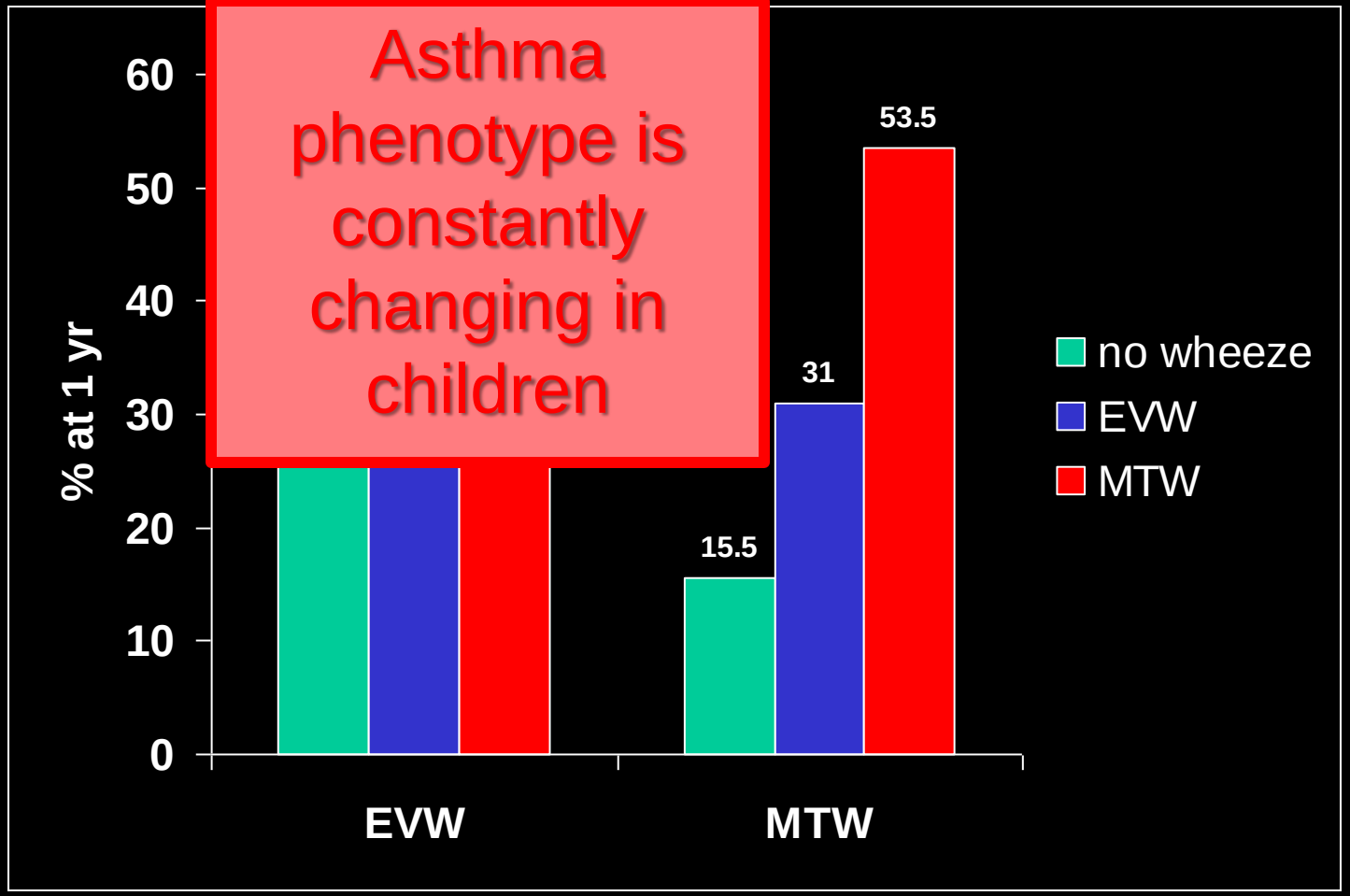

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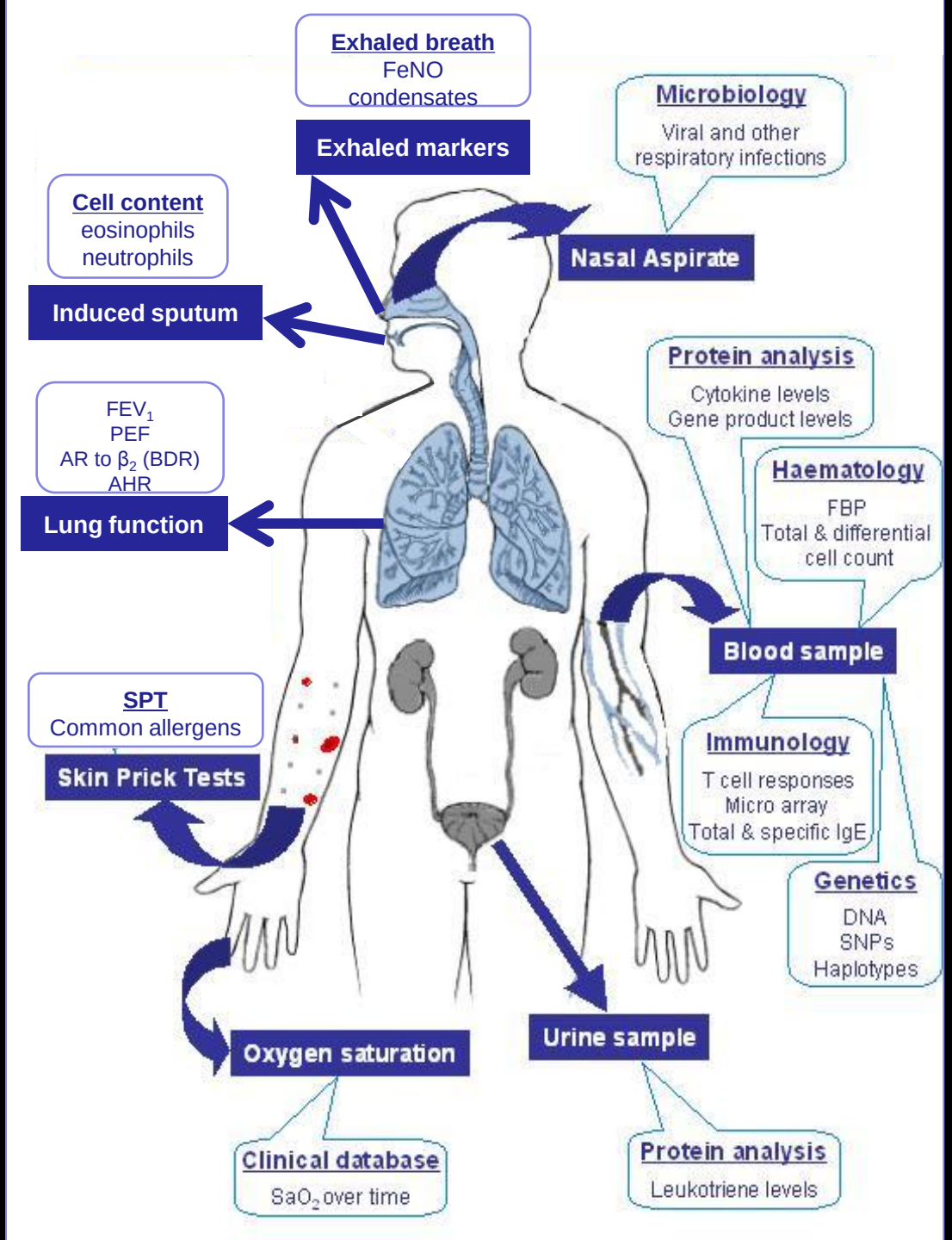
Asthma monitoring

- **Clinical monitoring**
  - confirm diagnosis
  - establish classification
  - re-evaluate every consultation

Asthma monitoring

- Clinical monitoring
- **Biological monitoring**

Biological markers of asthma



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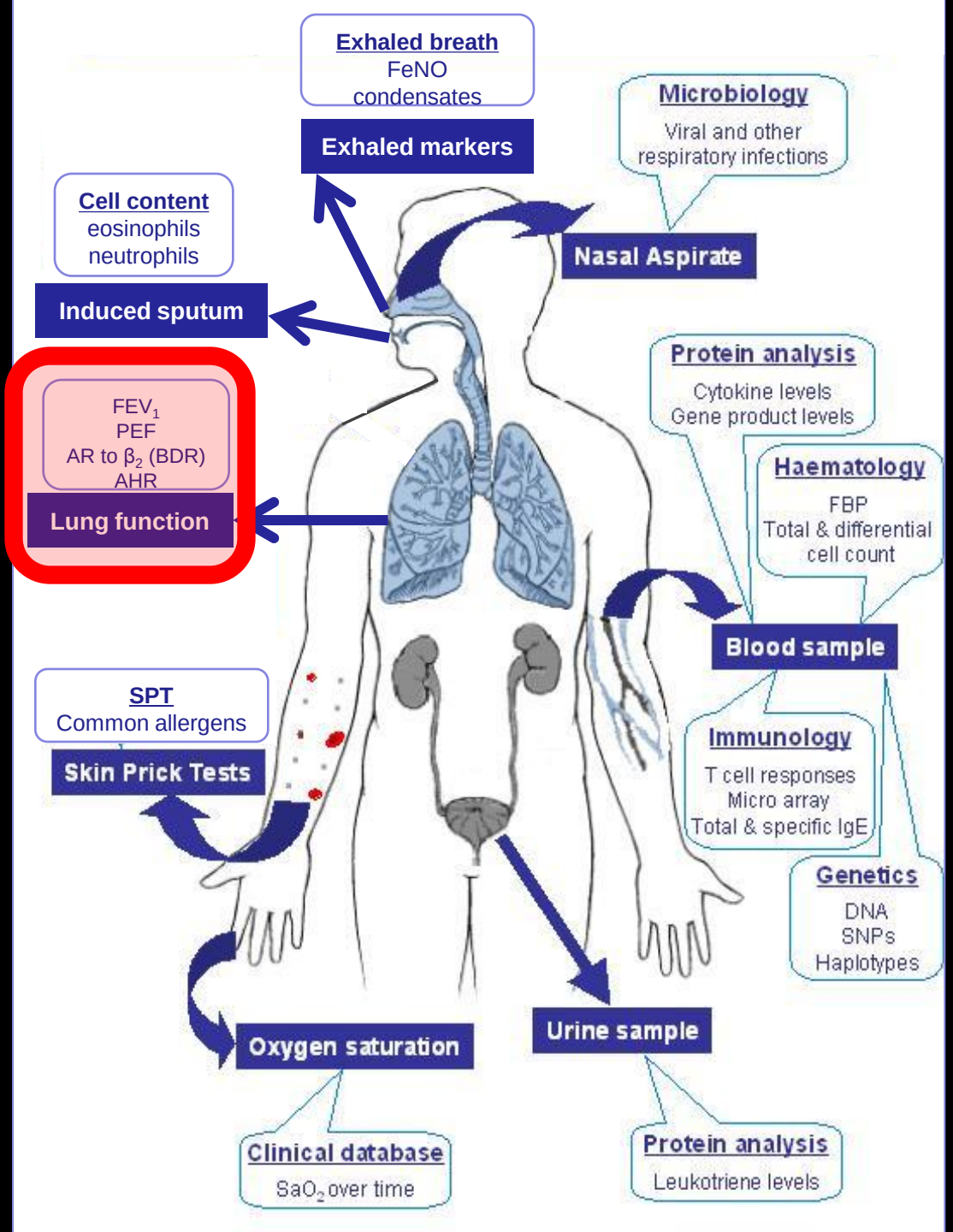

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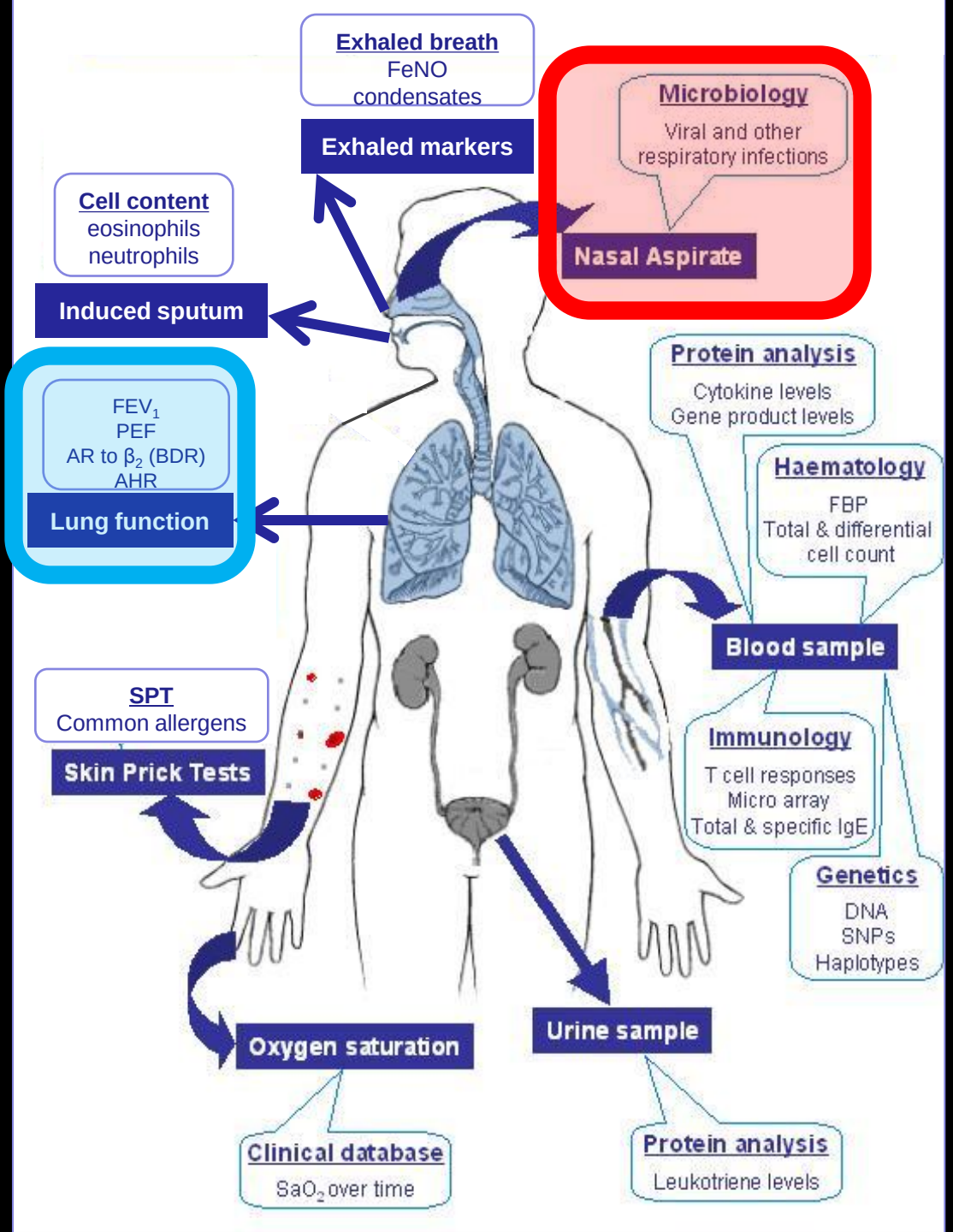
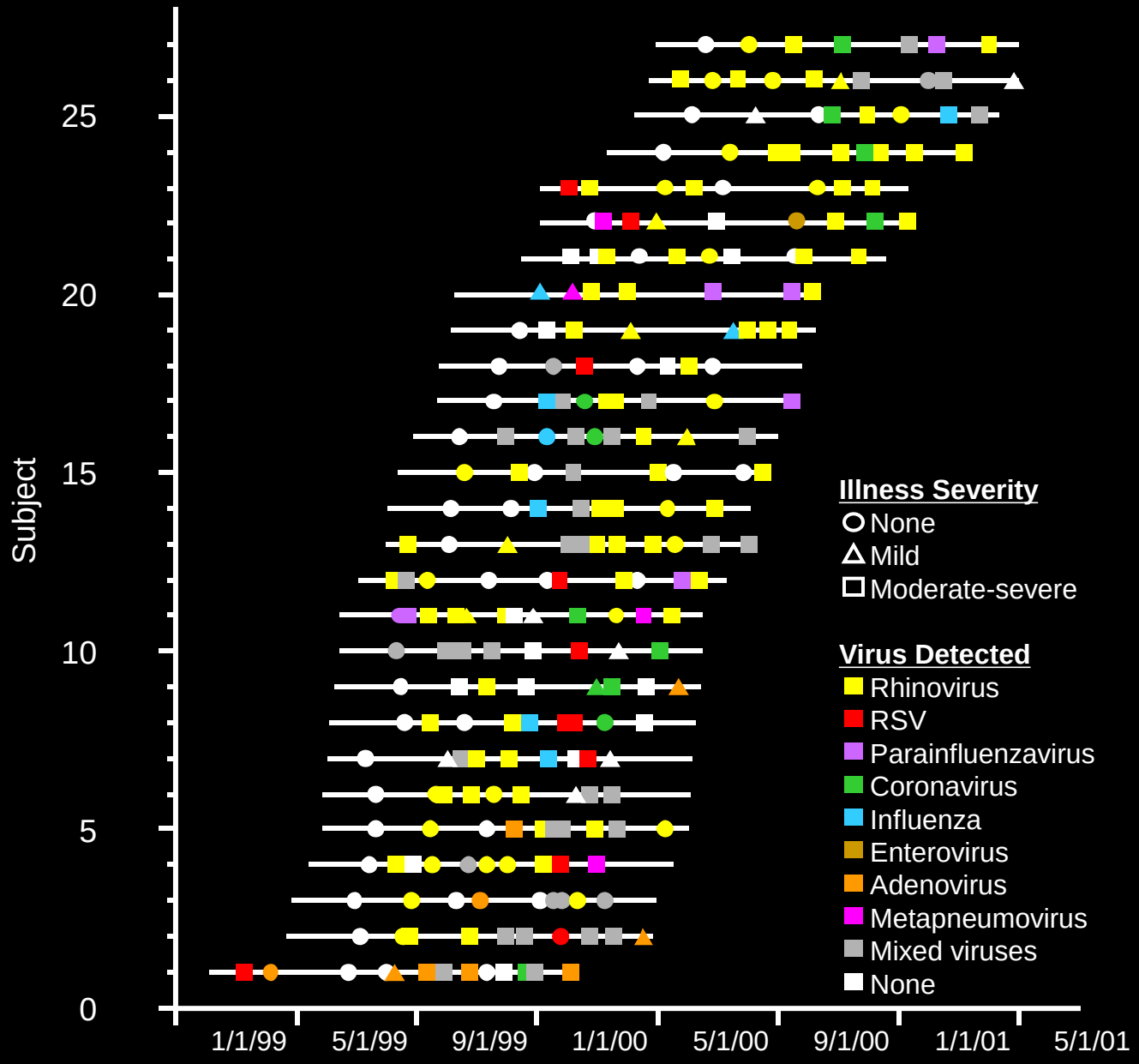


Serial viral infections in infants with recurrent respiratory illnesses

COAST study



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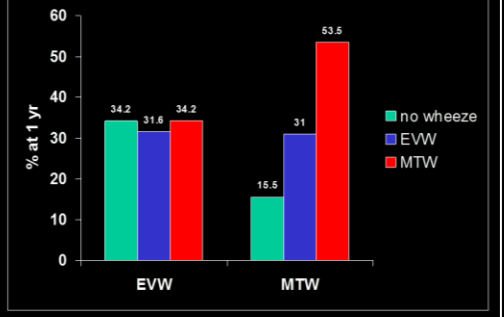

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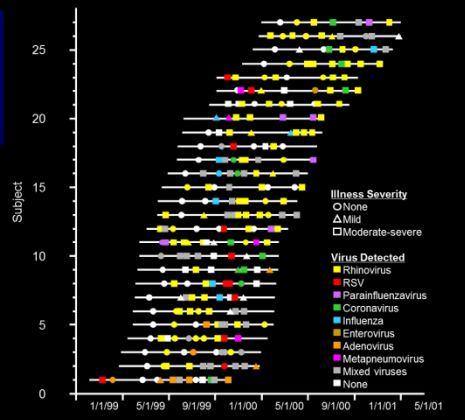

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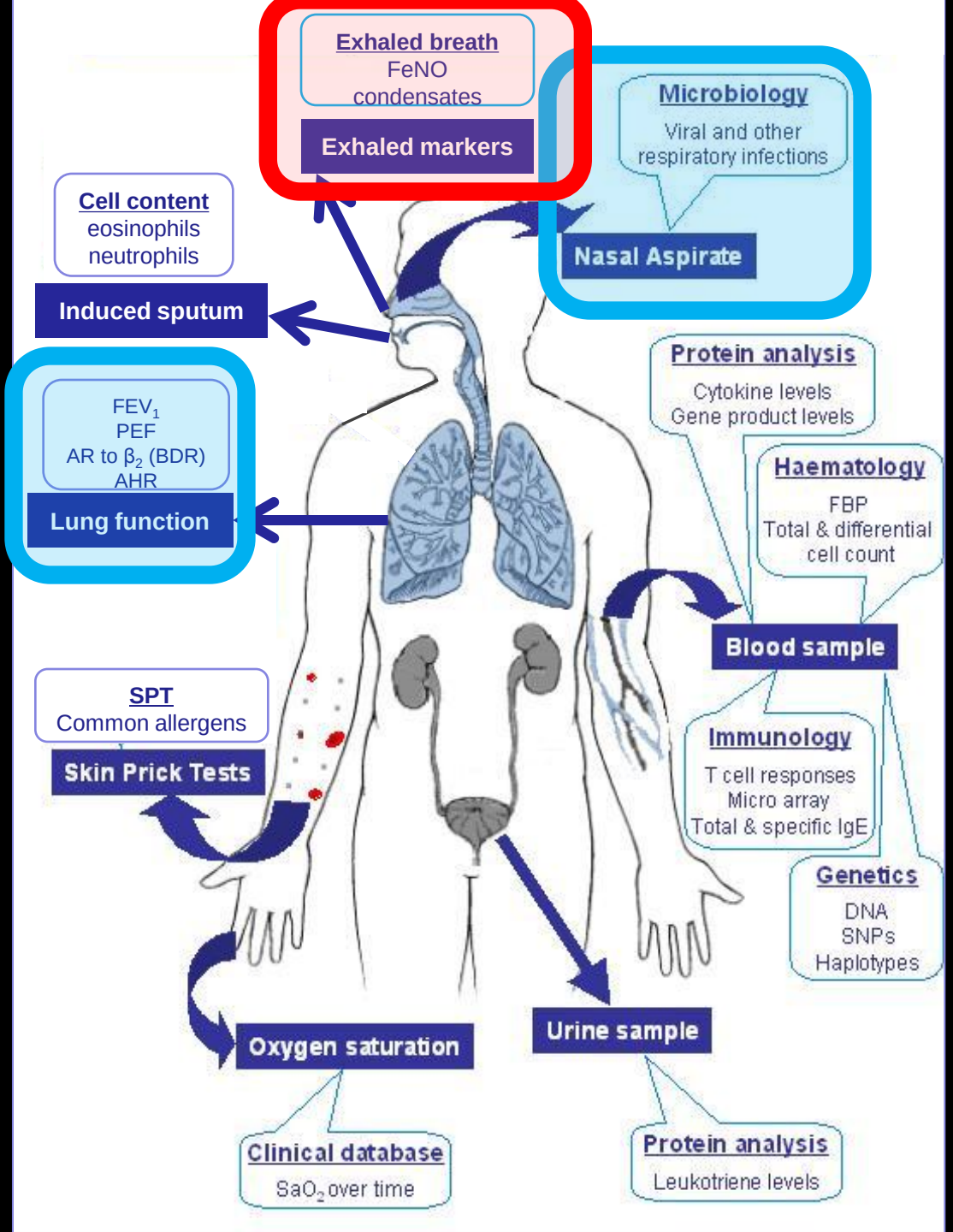
Classification must be re-evaluated at every clinic visit

Biological markers of asthma



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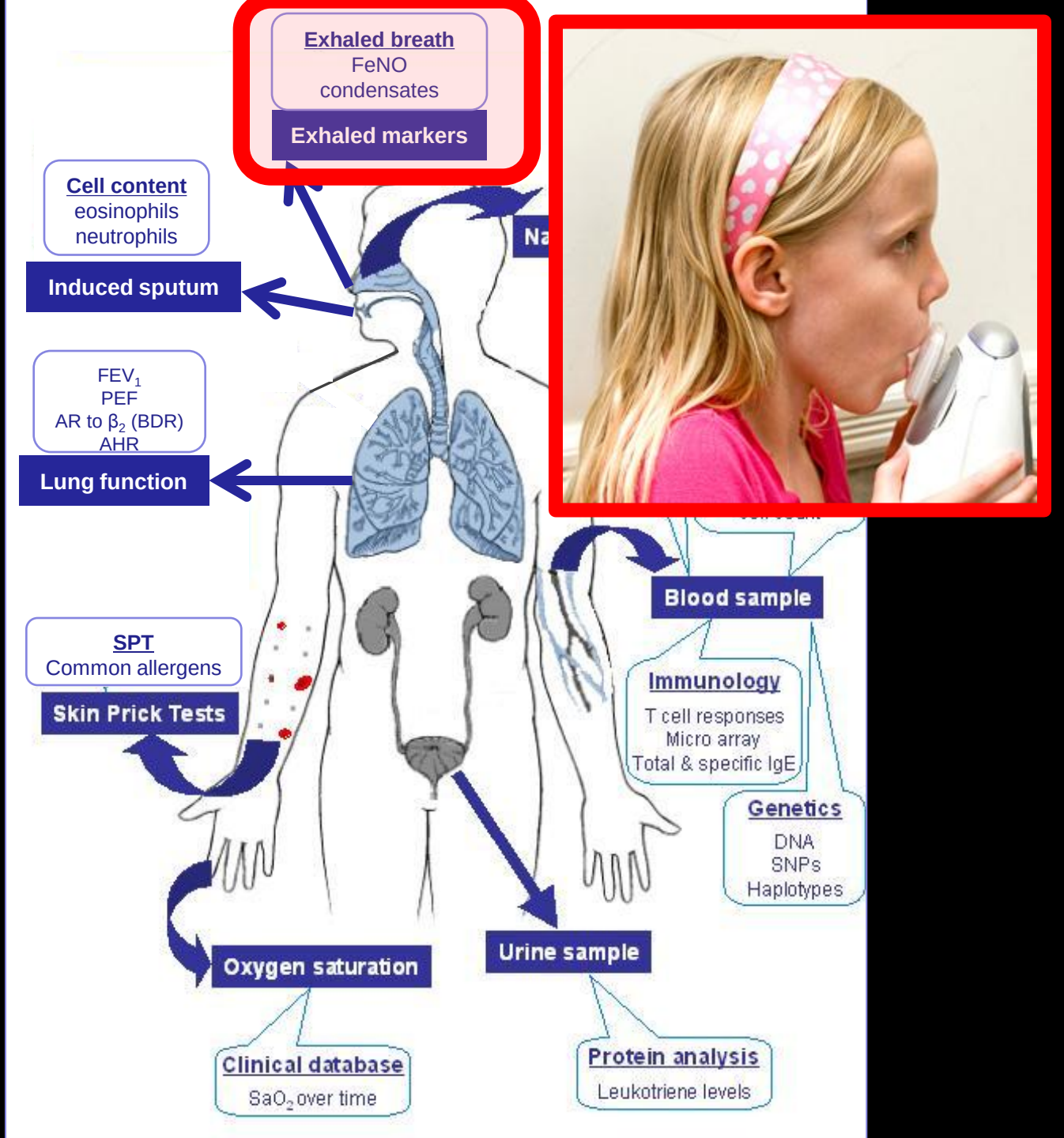
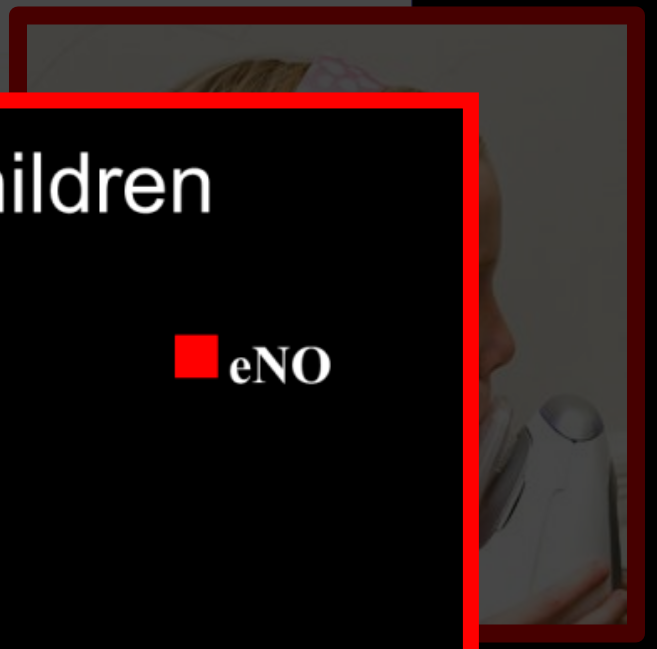


Biological markers

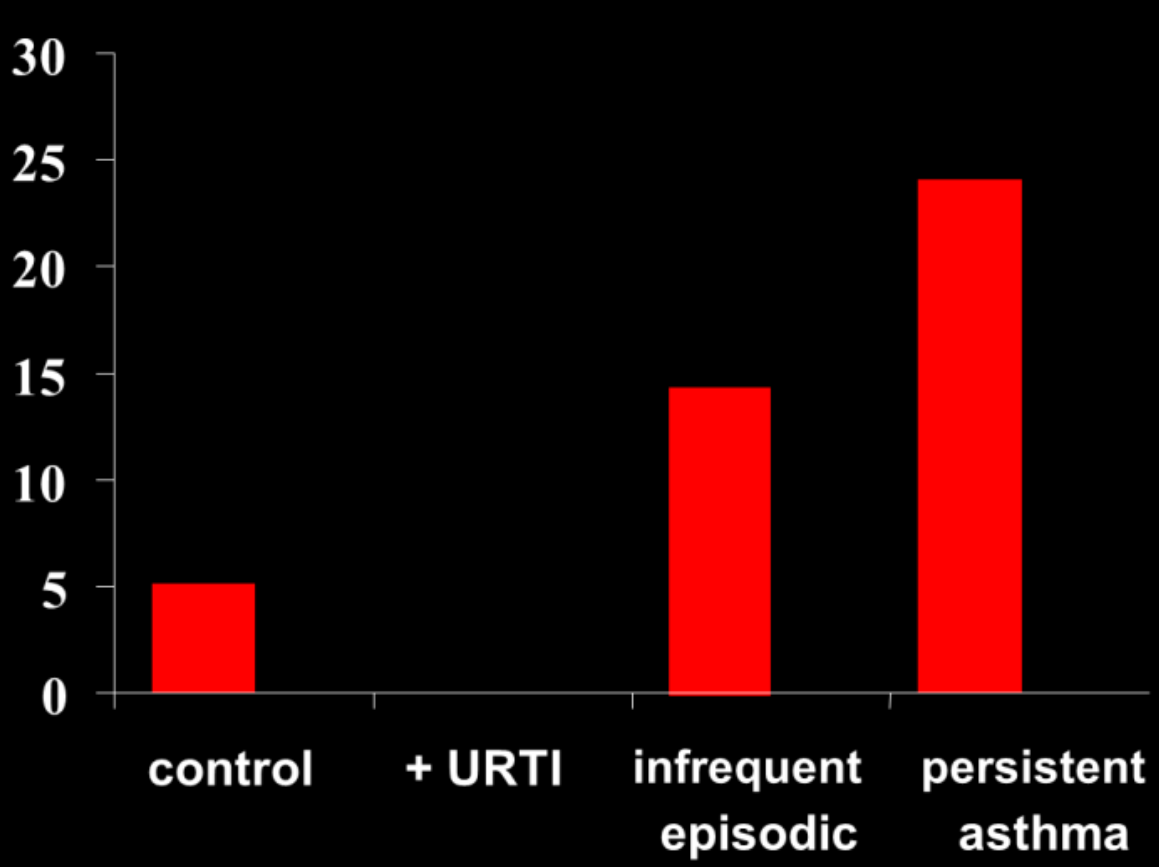
Exhaled breath
FeNO



SaO2 over time

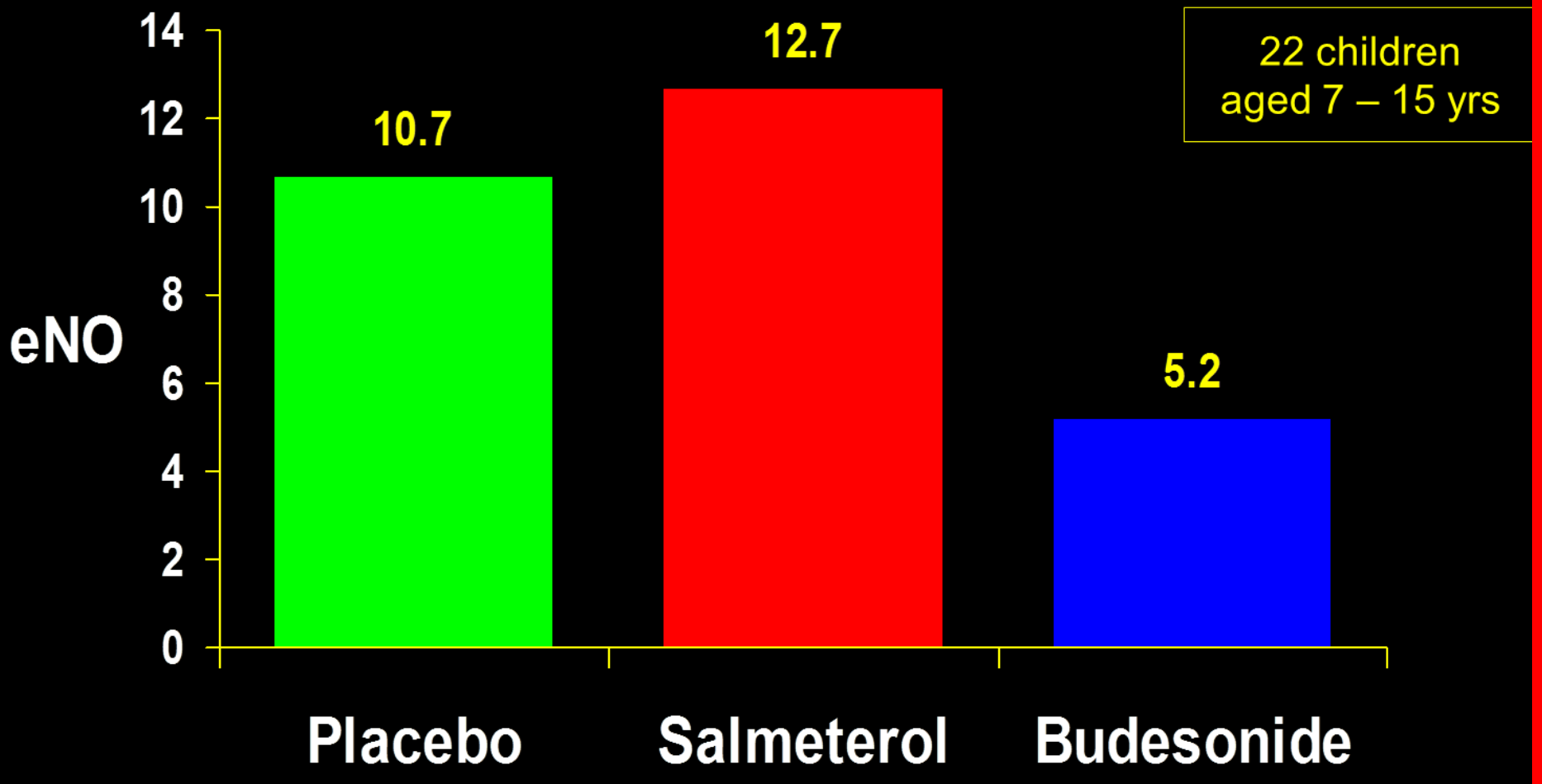
Leukotriene levels

eNO: asthma severity in children



Uasuf GG et al J Pediatr 1999; 135:569-74

eNO: Effect of drugs in mild childhood asthma



Fuglsang G et al Ped Pulmonol 1998;25:314-21

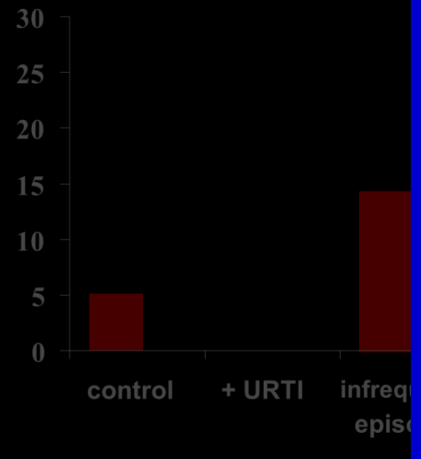
Biological markers of asthma

Exhaled breath
FeNO
condensates

Exhaled markers

Cell content

eNO: asthma sev



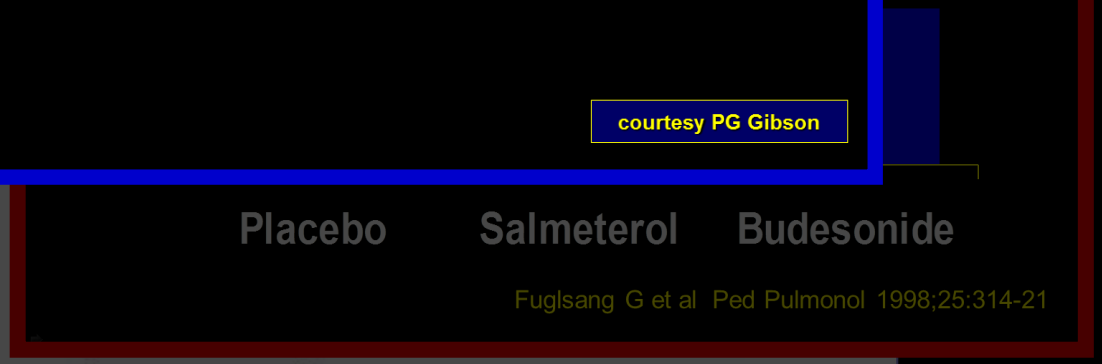
Nitric oxide - children

INCREASE	DECREASE
asthma	corticosteroid
age	montelukast
atopy	sputum induction
domestic formaldehyde	allergic avoidance
domestic allergen	cystic fibrosis
β2-agonists	
URTI	

courtesy PG Gibson

sthma

22 children
ged 7 – 15 yrs



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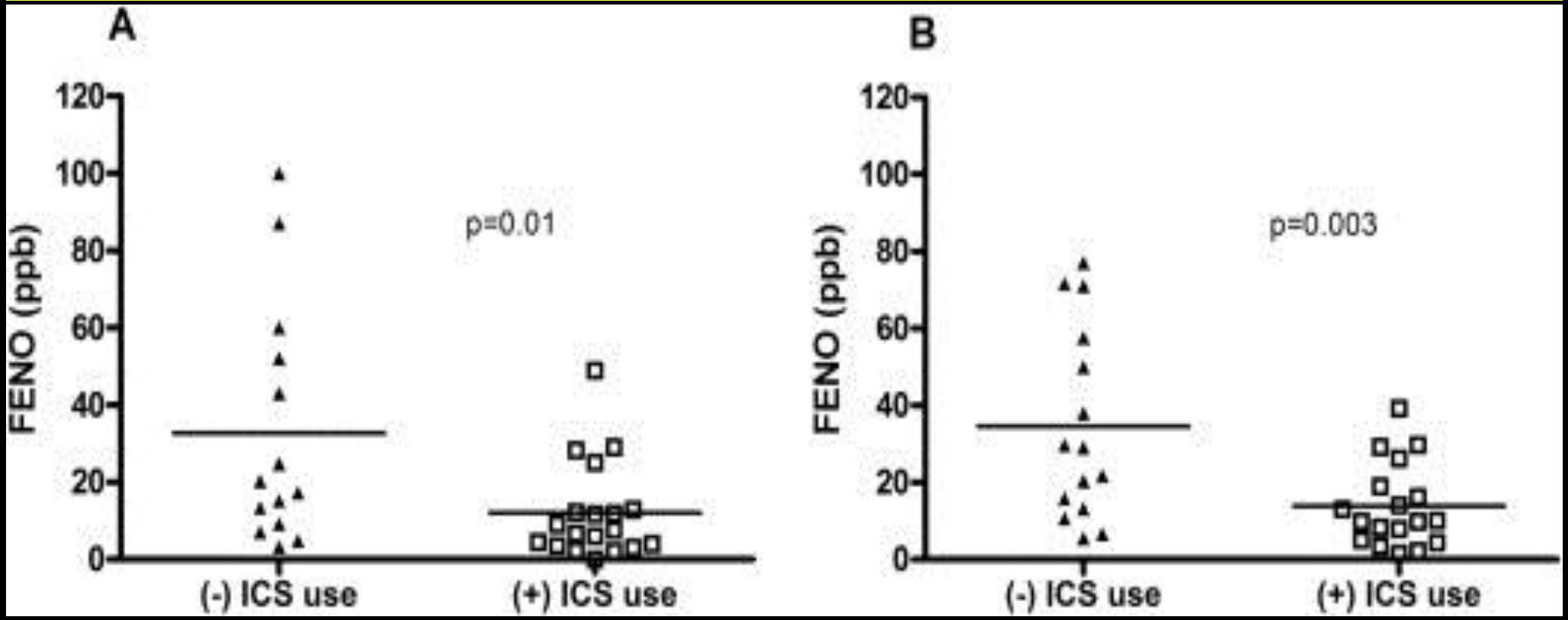
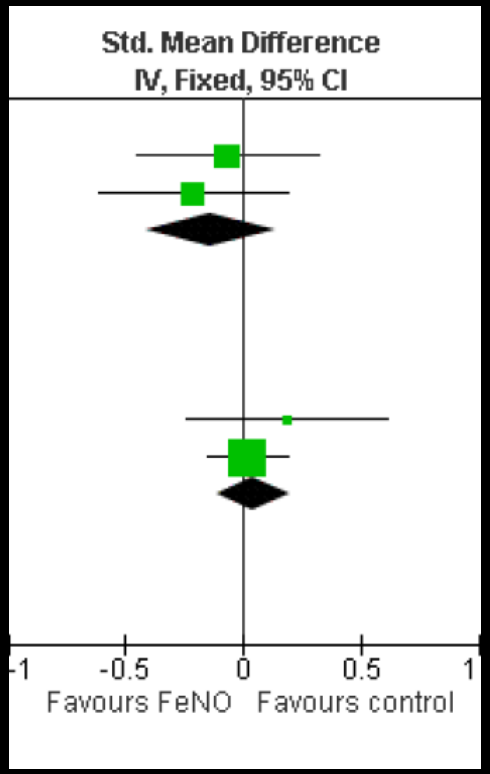
FENO 2 and 4 weeks after viral-induced asthma exacerbation in children with and without inhaled corticosteroids



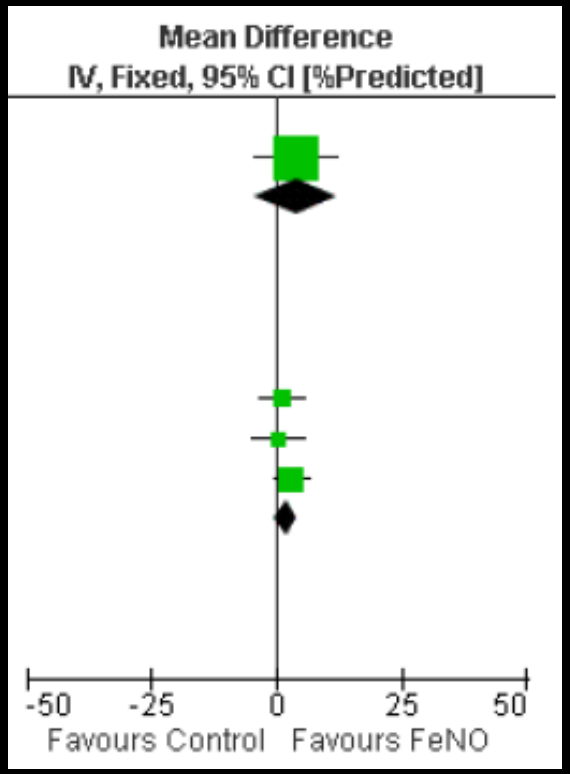
Debley et al Ann Allergy Asthma Immunol 2012;109:114-120

Tailored interventions based on FENO vs clinical symptoms in children and adults

symptom score



FEV_1



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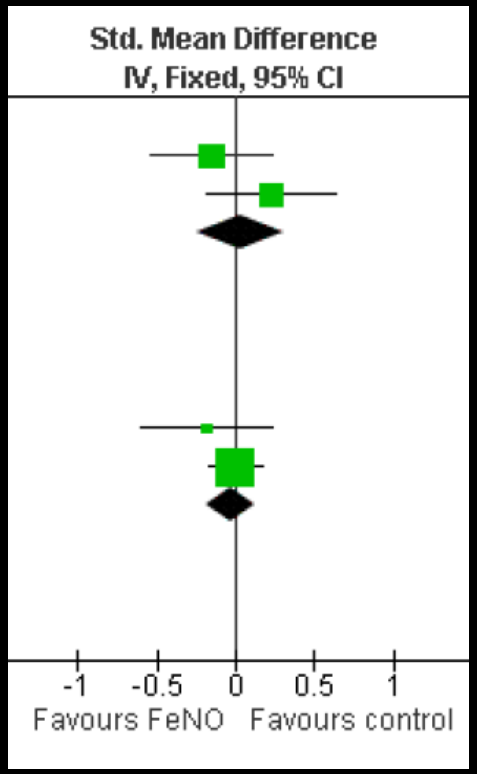


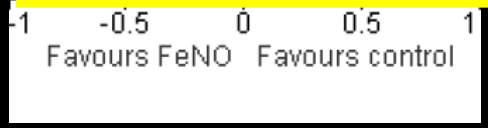
Petsky et al Cochrane Database Syst Rev 2009 Oct 7;(4):CD006340

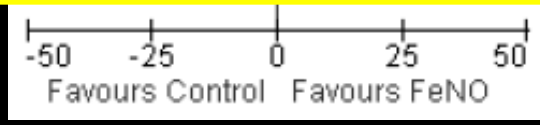
Tailored interventions based on FENO vs clinical symptoms in children and adults

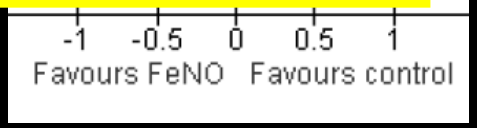
symptom score	FEV_1	FENO

Implications for practice

The studies included in this review highlight the difficulties involved in tailoring the dose of inhaled corticosteroids based on exhaled nitric oxide, instead of primarily on clinical symptoms. At present this approach cannot be advocated as routine clinical practice.







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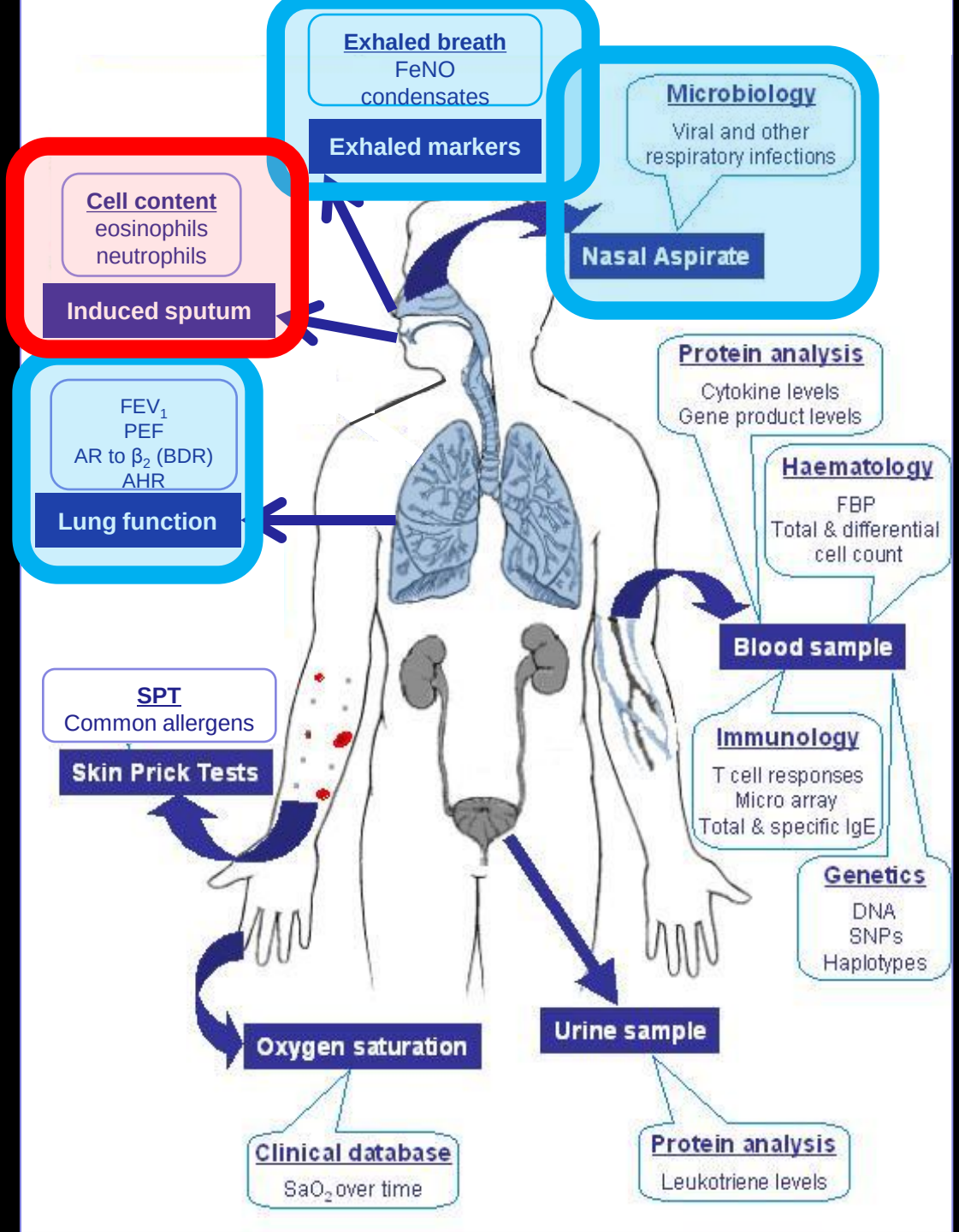
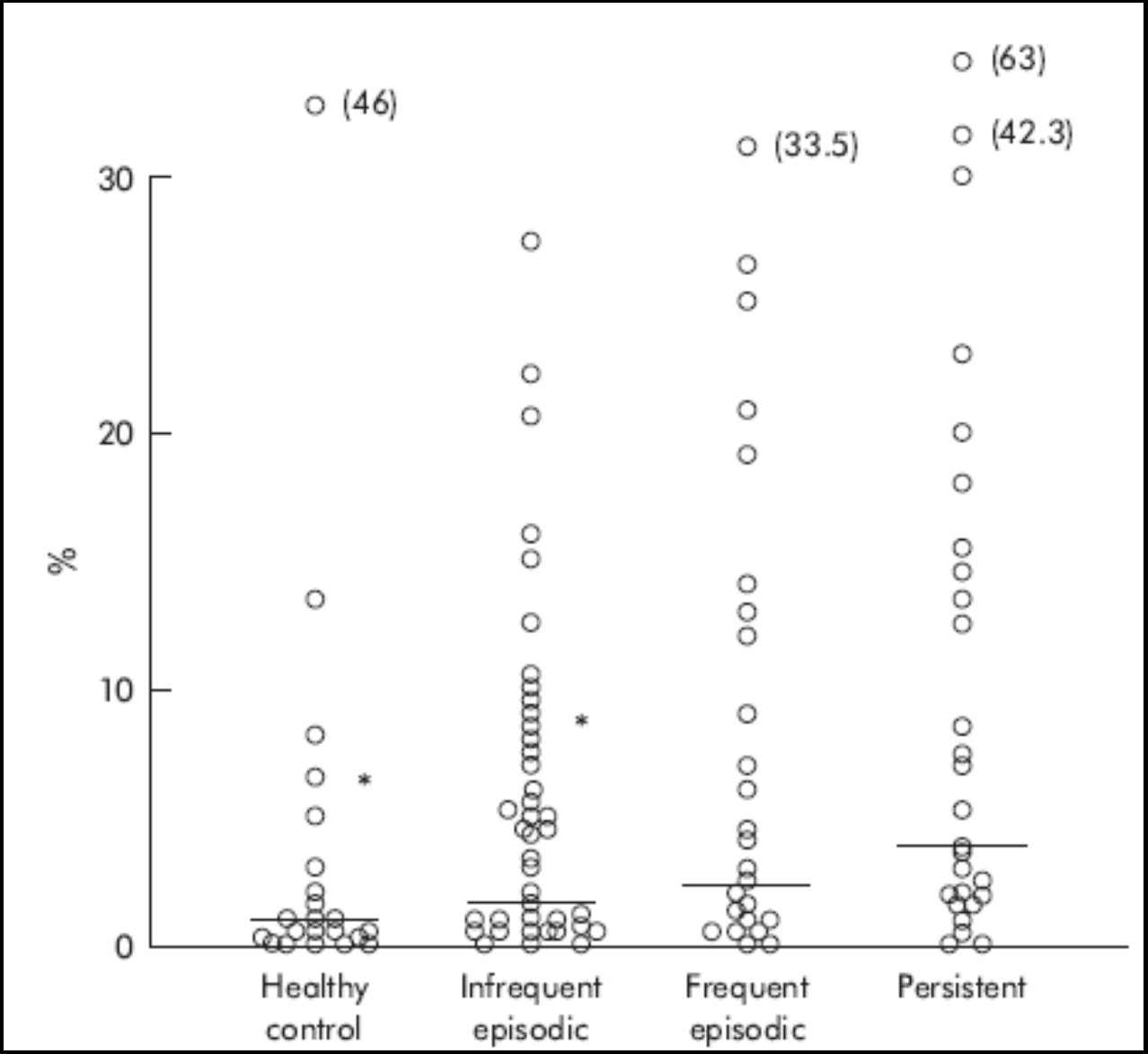
Breath condensate

- H_2O_2 asthma, CF
- Nitrite CF
- 8-isoprostane asthma, CF

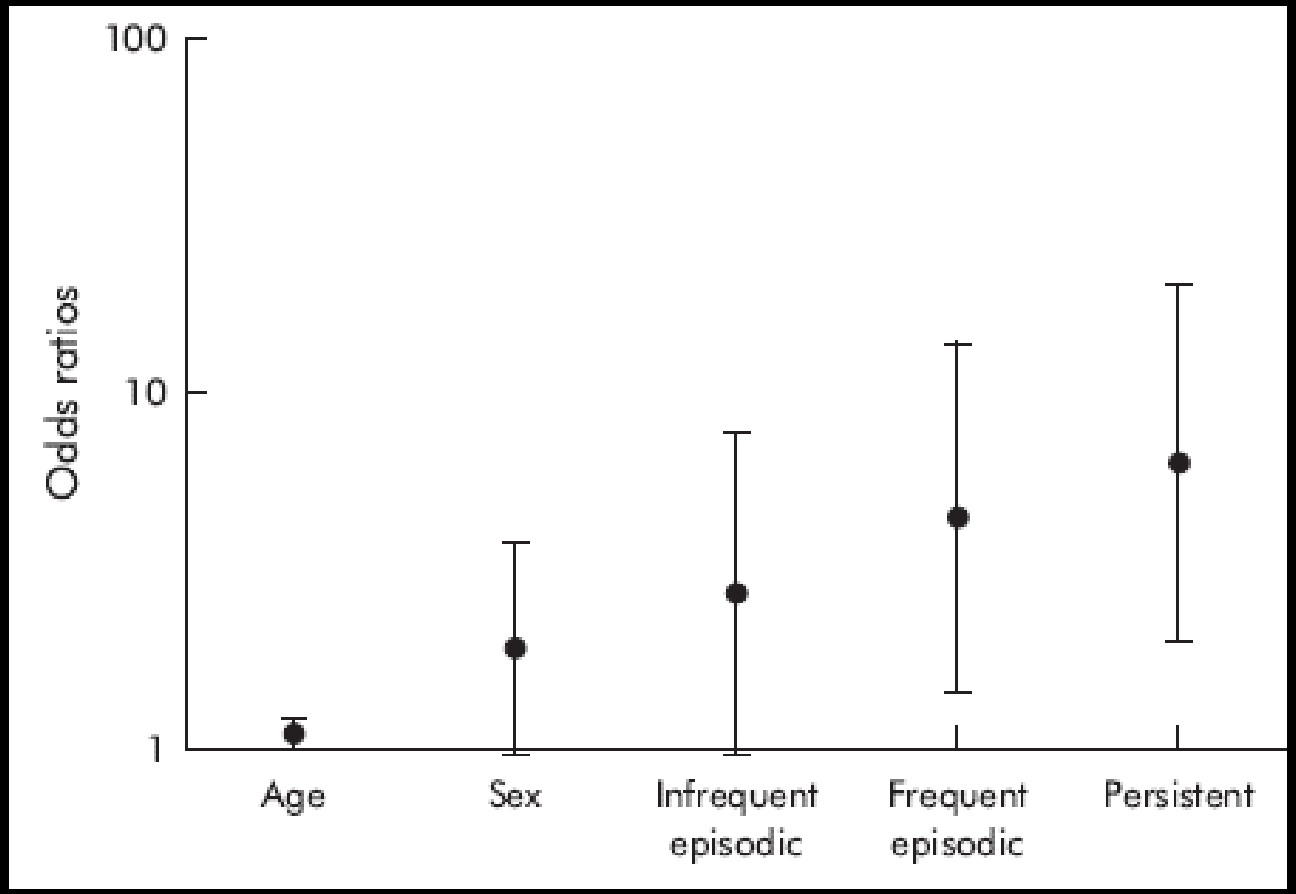
Biological markers of asthma





Sputum eosinophils vs clinical asthma patterns in 146 asthmatic children and 47 controls

Gibson PG et al Thorax 2003;58:116-21

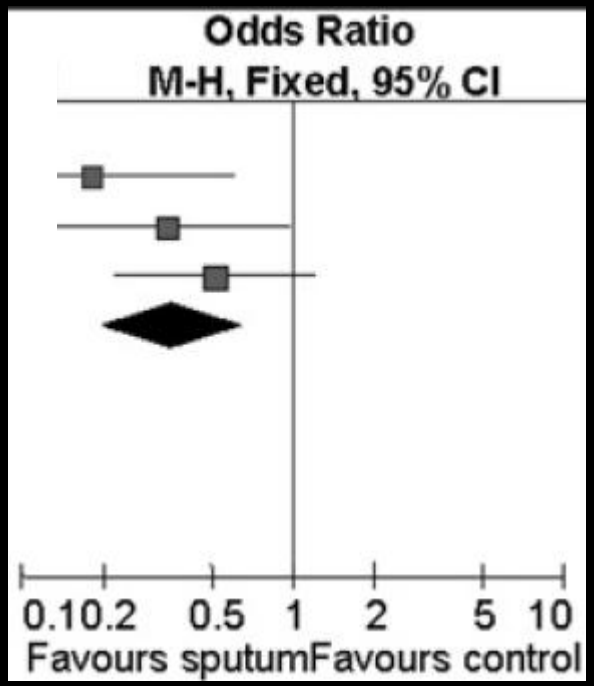


Log odds (95% CI) of increased eosinophils for asthma pattern in 146 asthmatic children

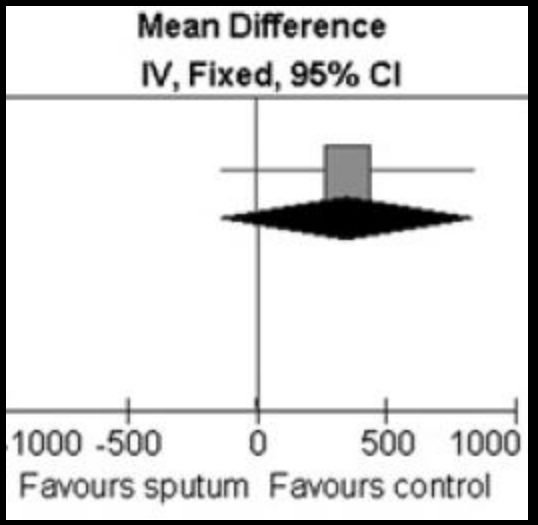
Gibson PG et al Thorax 2003;58:116-21

Tailored interventions based on sputum eosinophils vs clinical symptoms in adults

exacerbations



Inhaled corticosteroid dose

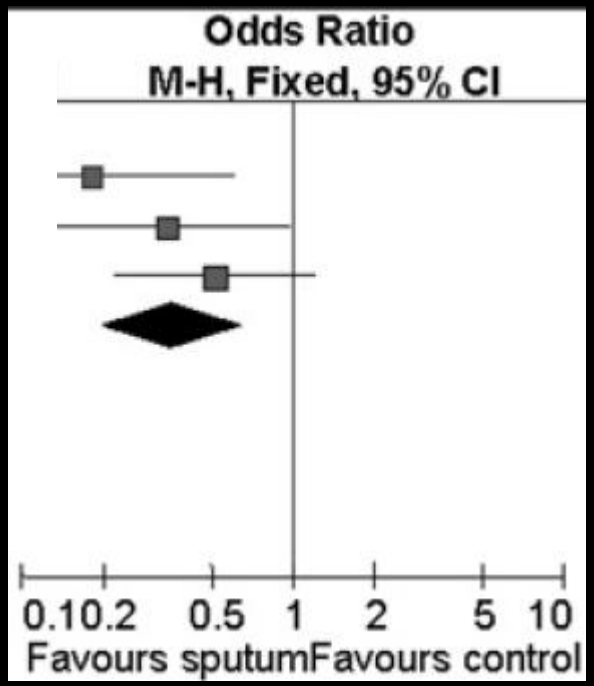


Petsky et al Thorax 2012;67:199-208

Tailored interventions based on sputum eosinophils vs clinical symptoms in adults

"At present, there is insufficient justification to advocate the routine use of sputum analysis (due to technical expertise required) in everyday clinical practice"

exacerbations



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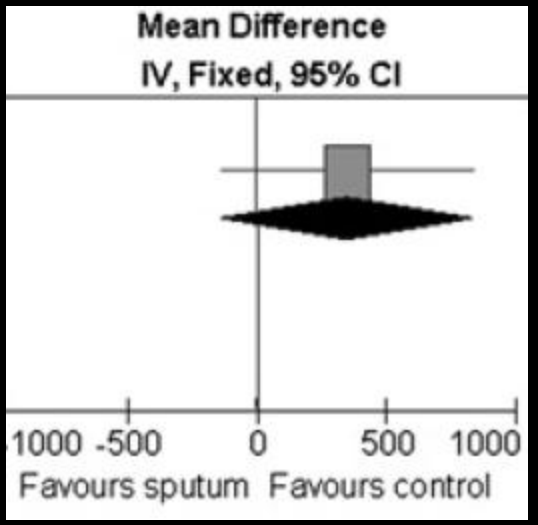

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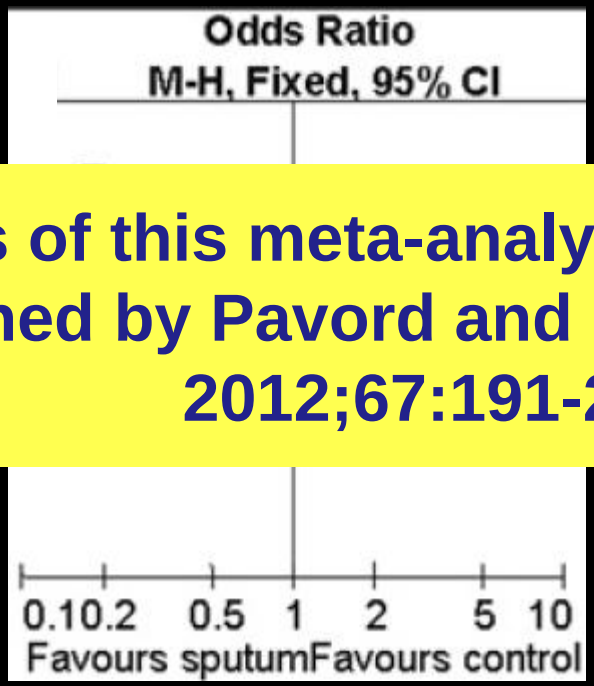

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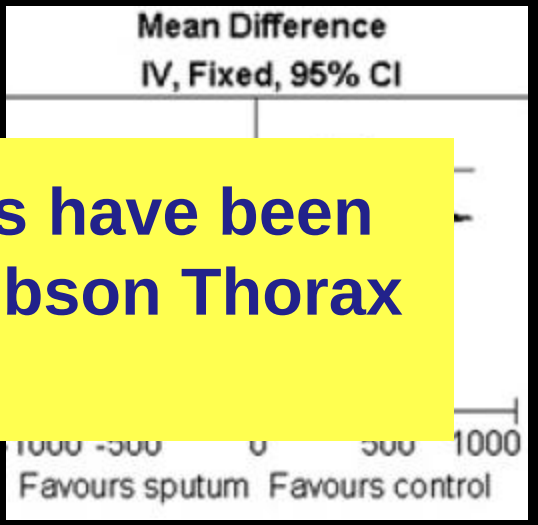


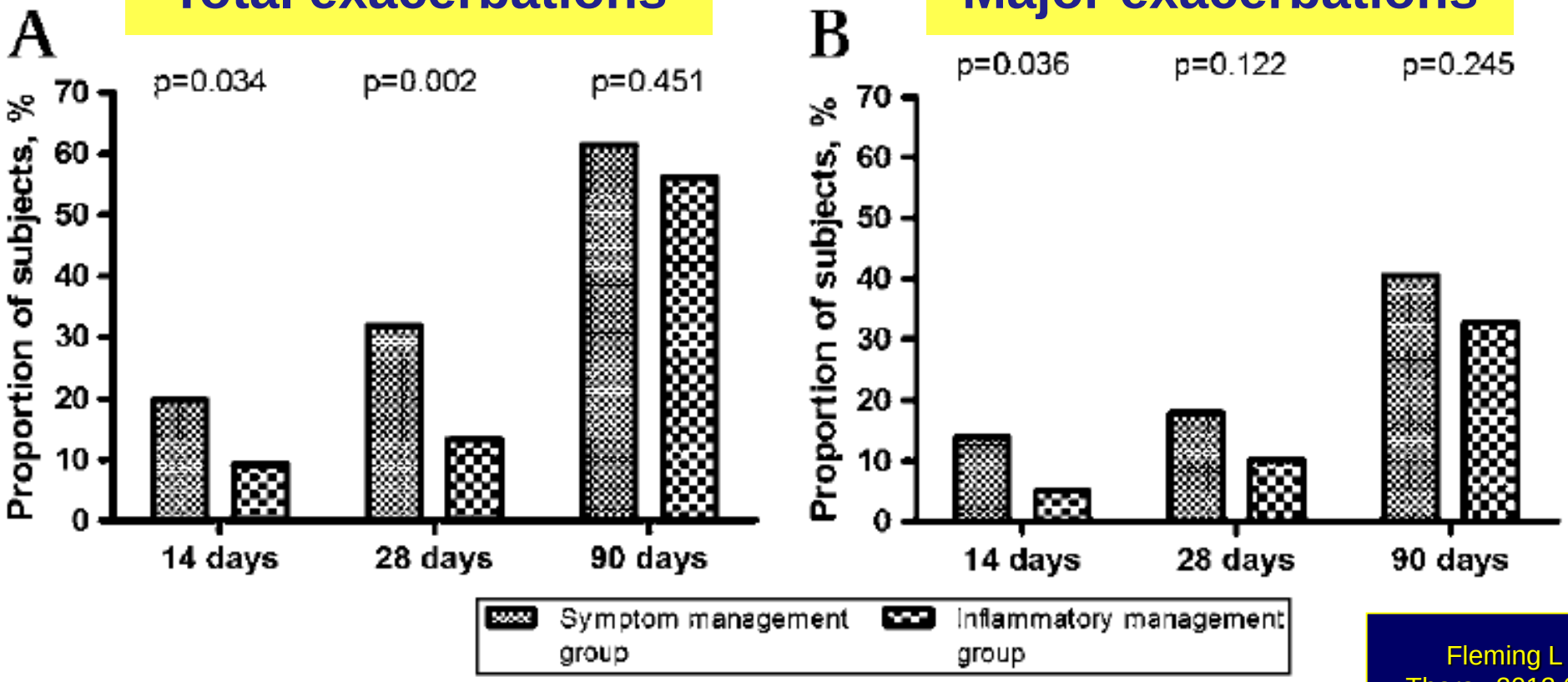
Results of this meta-analysis have been questioned by Pavord and Gibson Thorax 2012;67:191-2

Petsky et al Thorax 2012;67:199-208

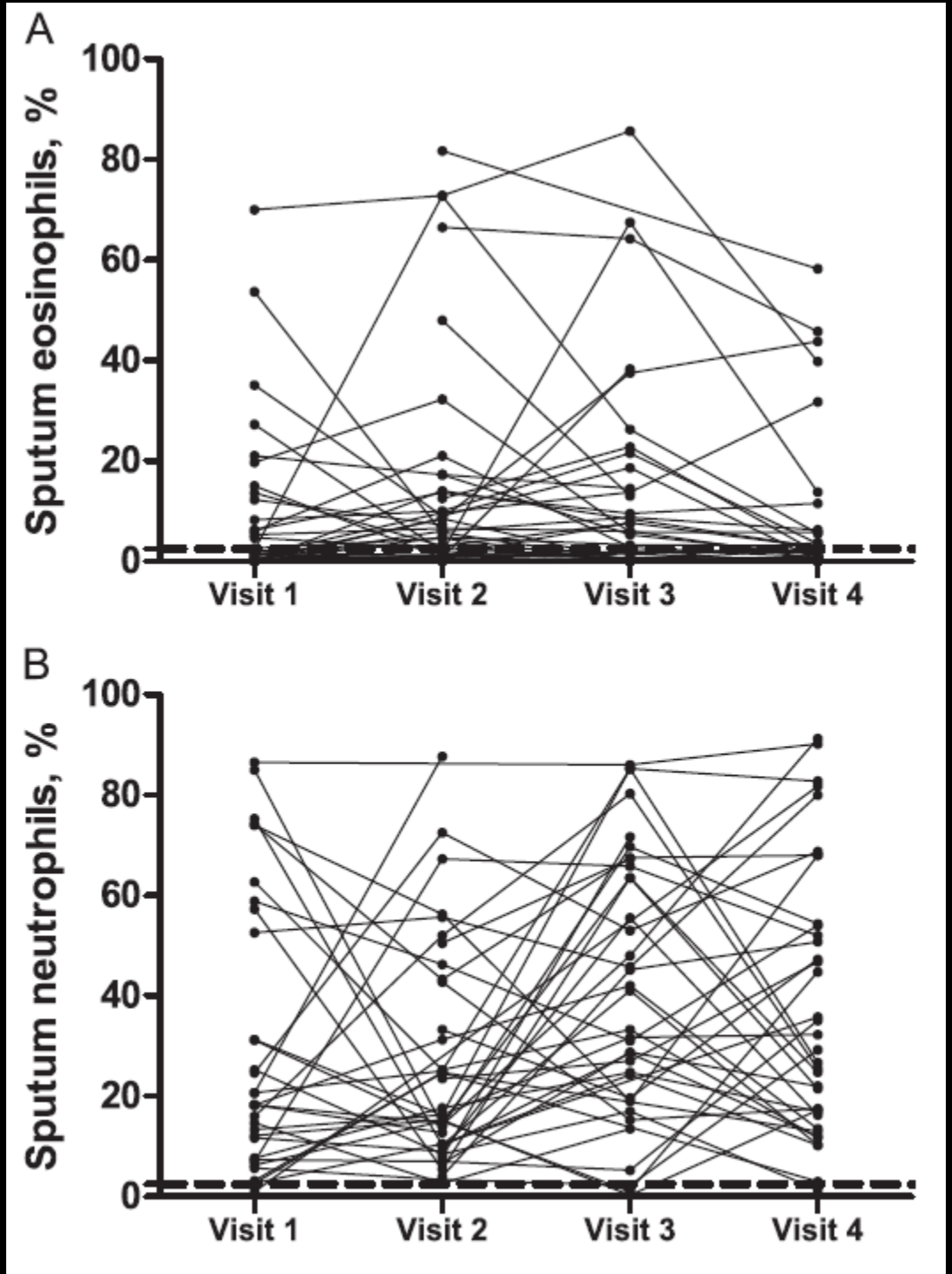
RCT in 55 children (7-17 years) with severe asthma: conventional symptom-based Rx or sputum eosinophil-based Rx Children seen 3-monthly for 1 yr

Total exacerbations

Major exacerbations



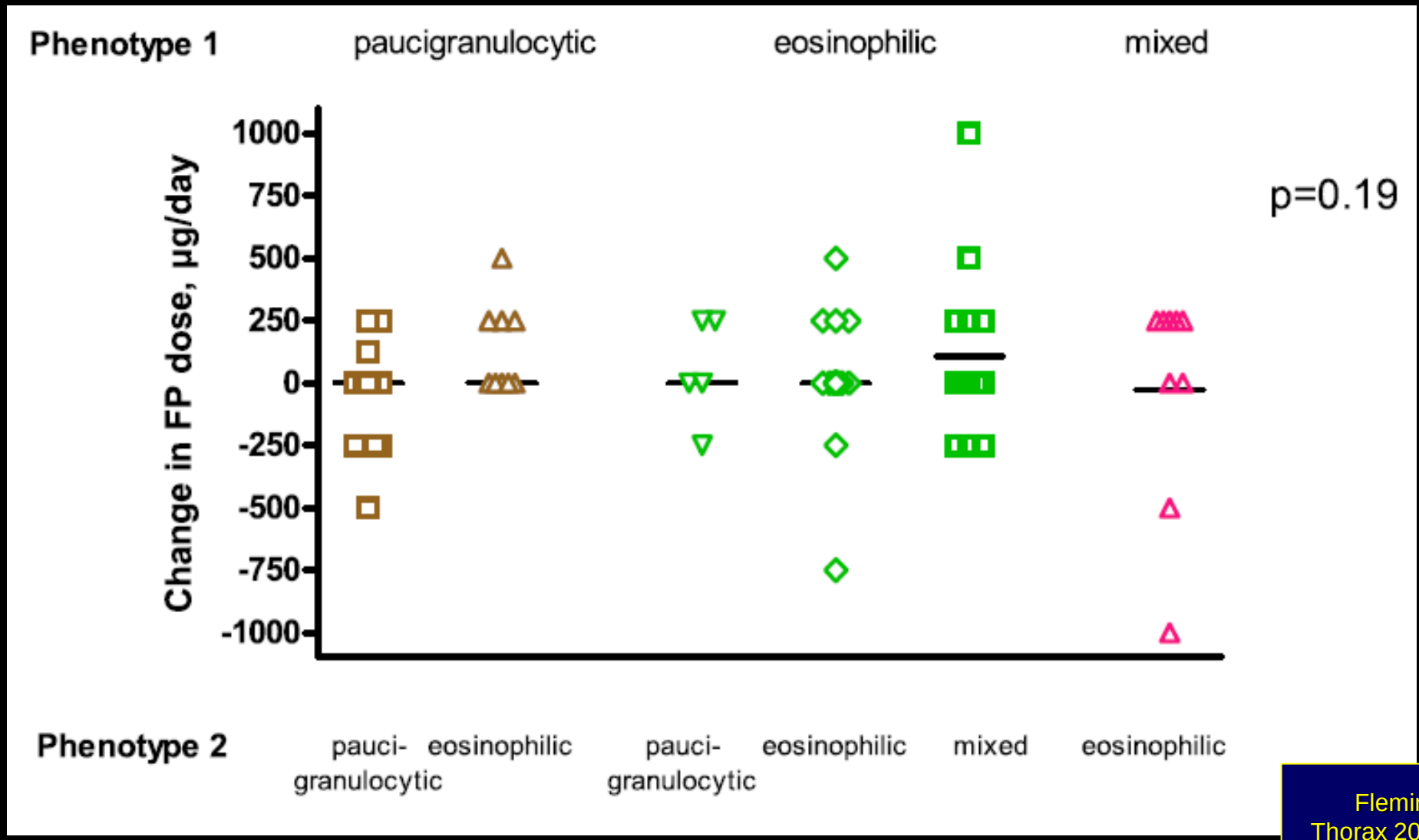
Fleming L et al
Thorax 2012;67:193-8



Sputum eosinophil and neutrophil counts in 51 severe and 28 mild asthmatics

Fleming L et al
Thorax 2012;67:675-81

Sputum eosinophil and neutrophil counts in 51 severe and 28 mild asthmatic children
No relationship between phenotype and Rx



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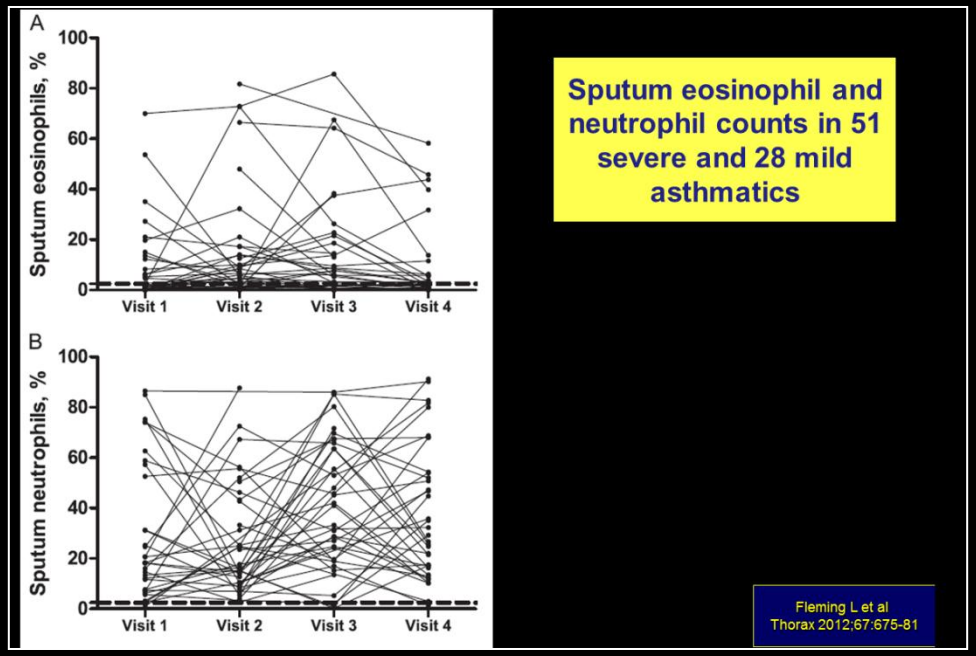

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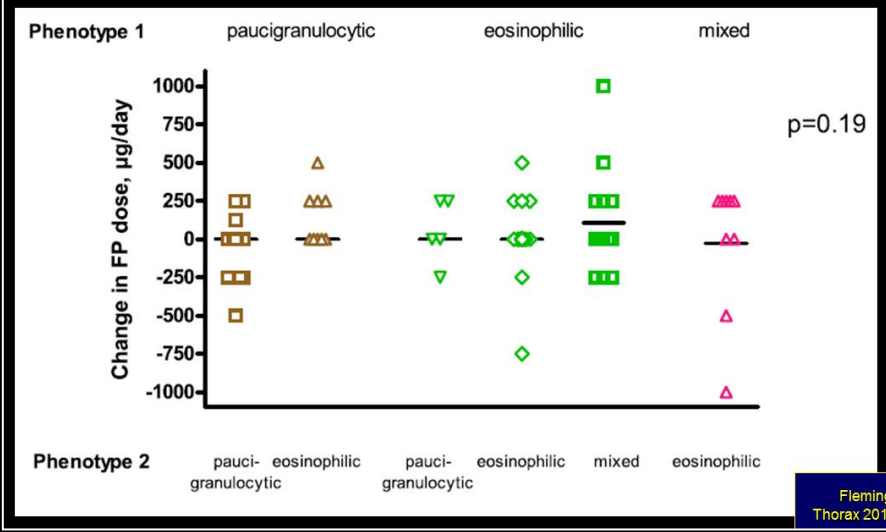
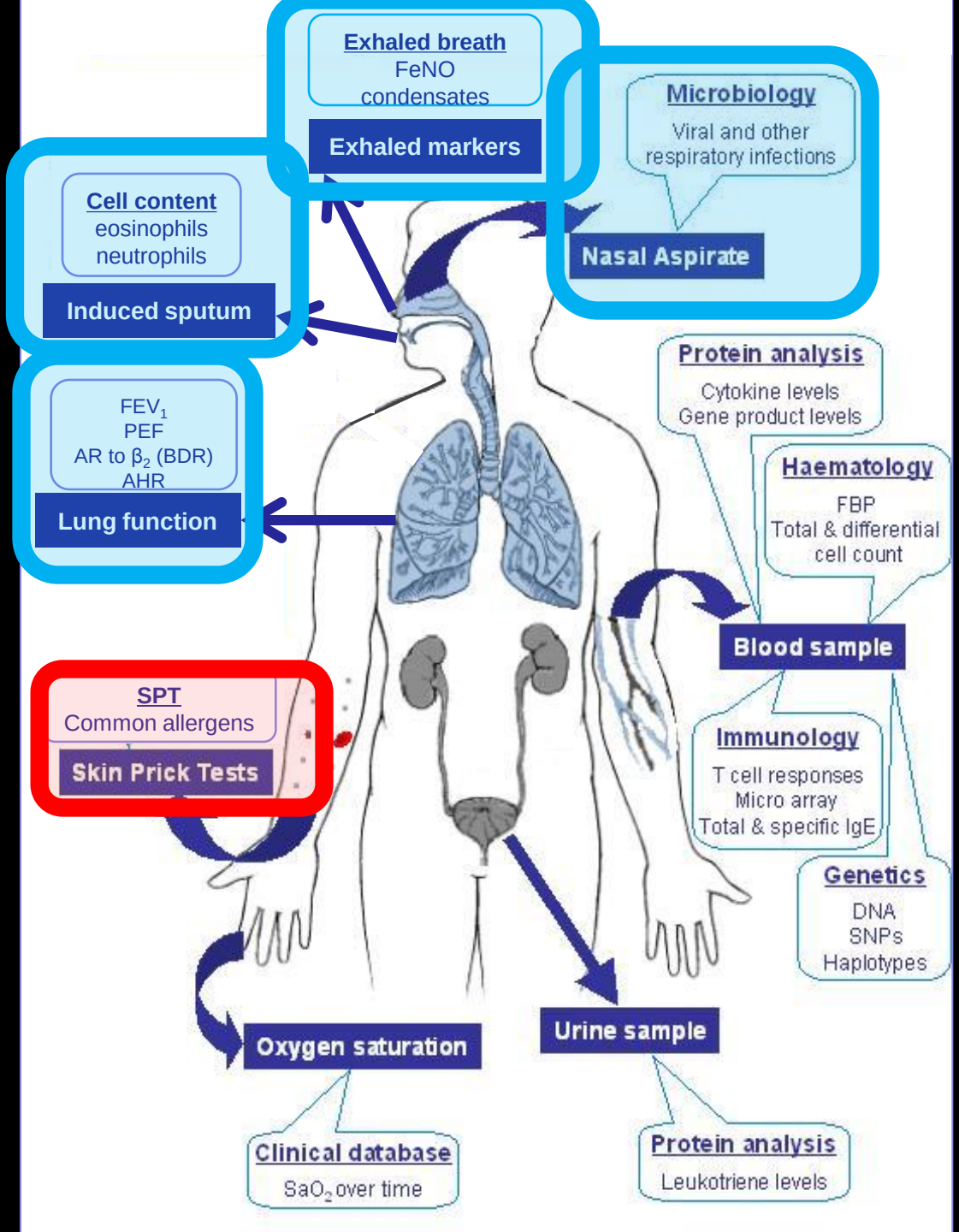


Fleming L et al
Thorax 2012;67:675-81

CONCLUSION: Raised levels of inflammatory cells were frequently found in children with asthma of all severities. Sputum inflammatory phenotype was not stable in children with asthma

Fleming L et al
Thorax 2012;67:675-81

Biological markers of asthma



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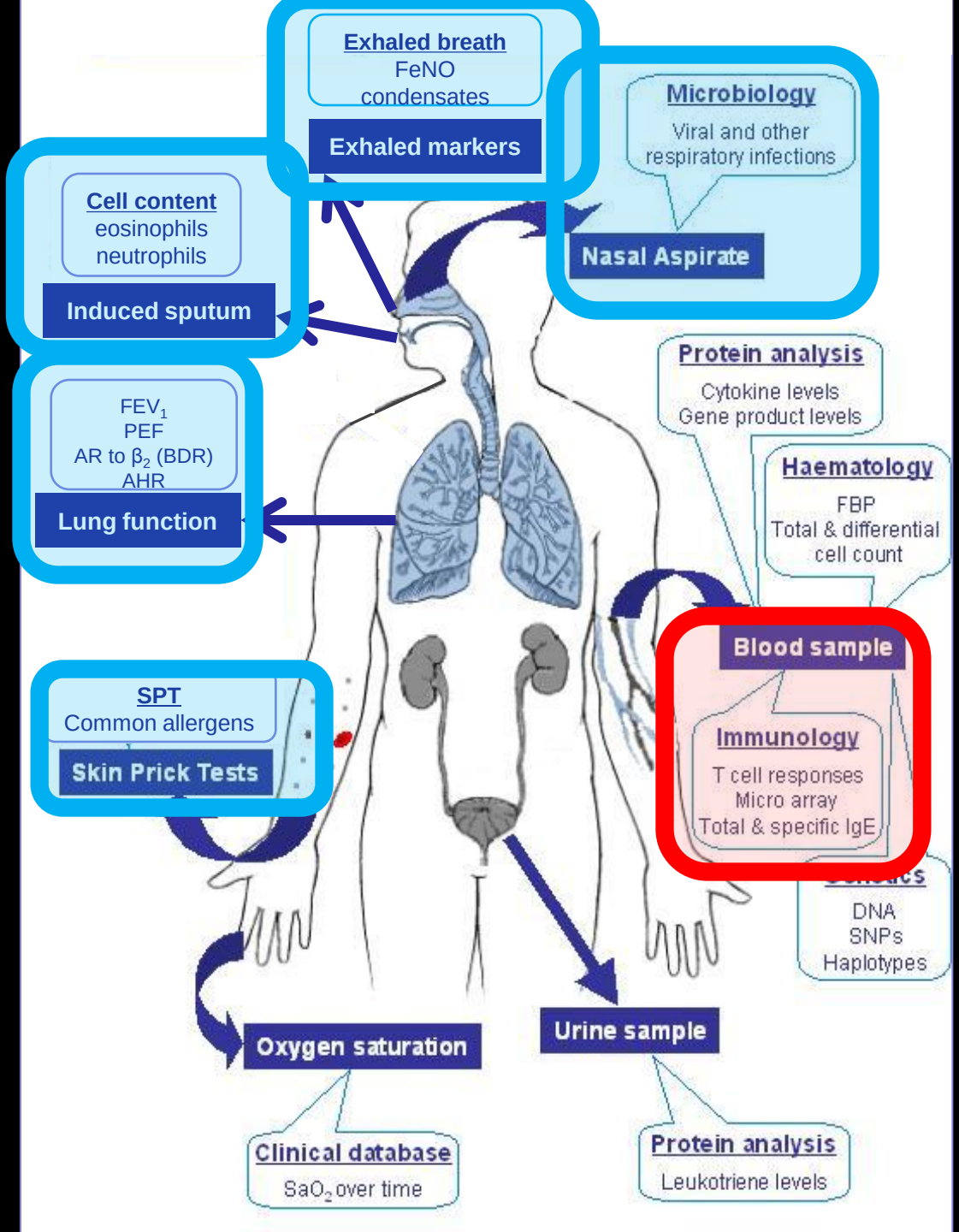

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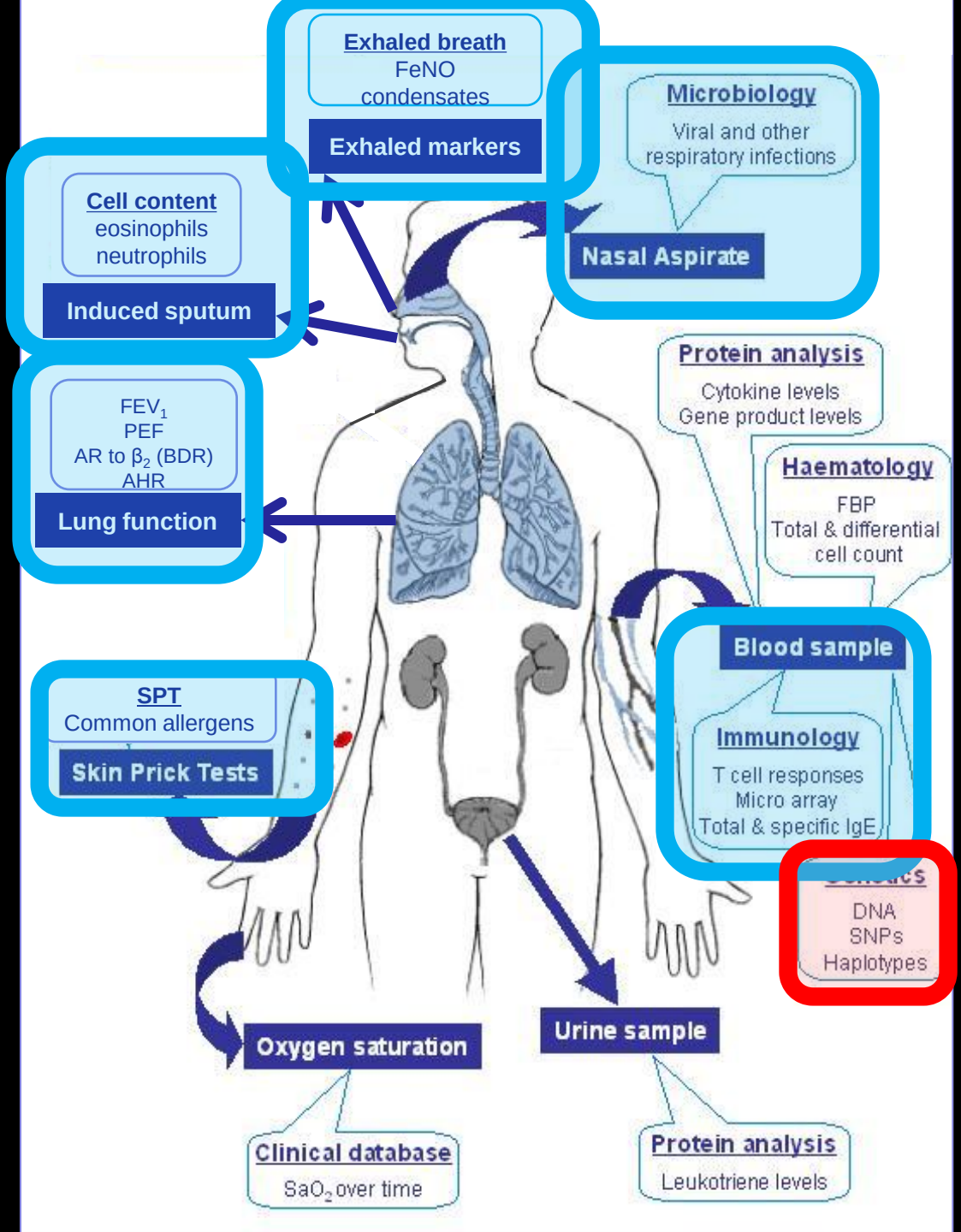
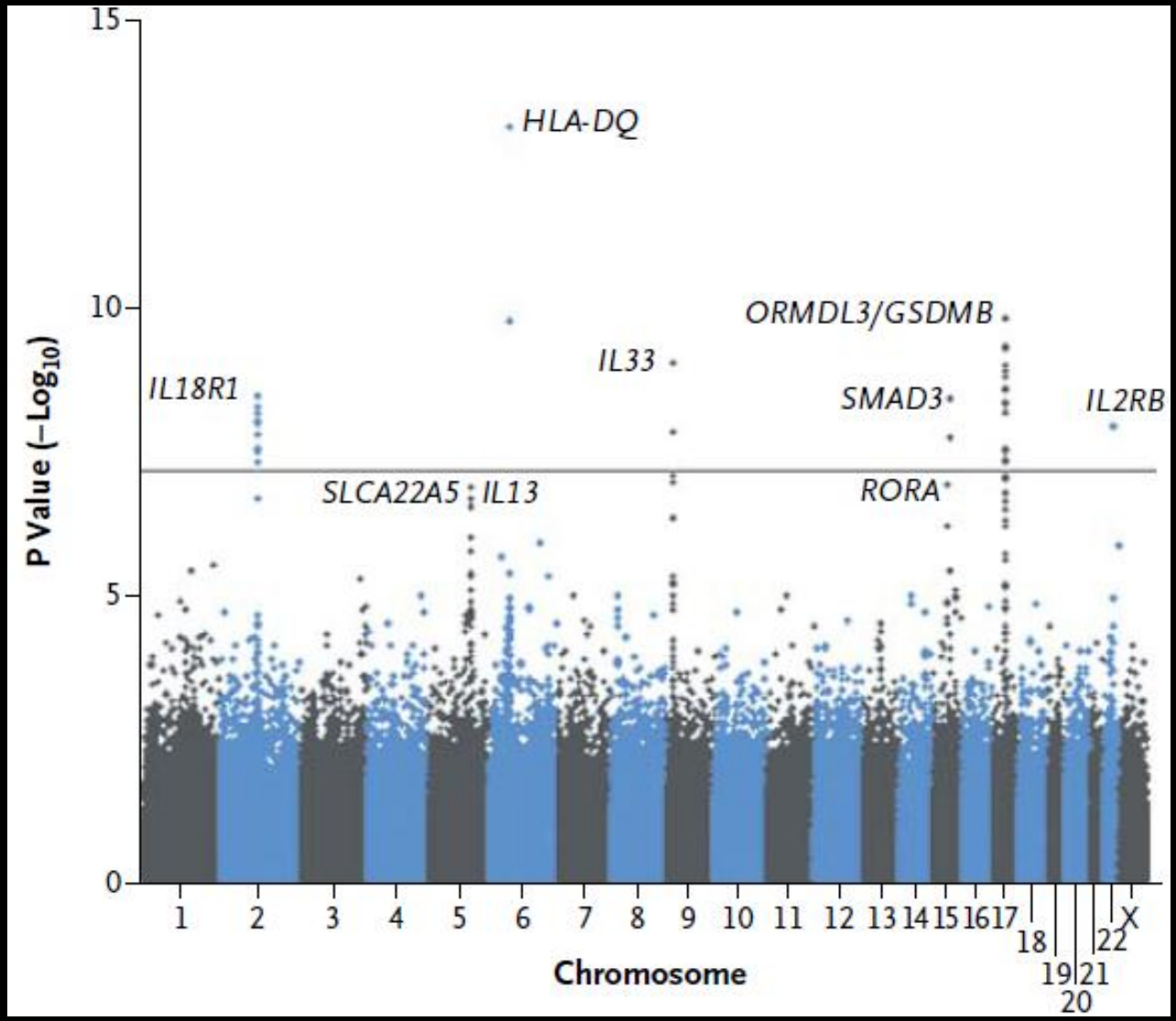
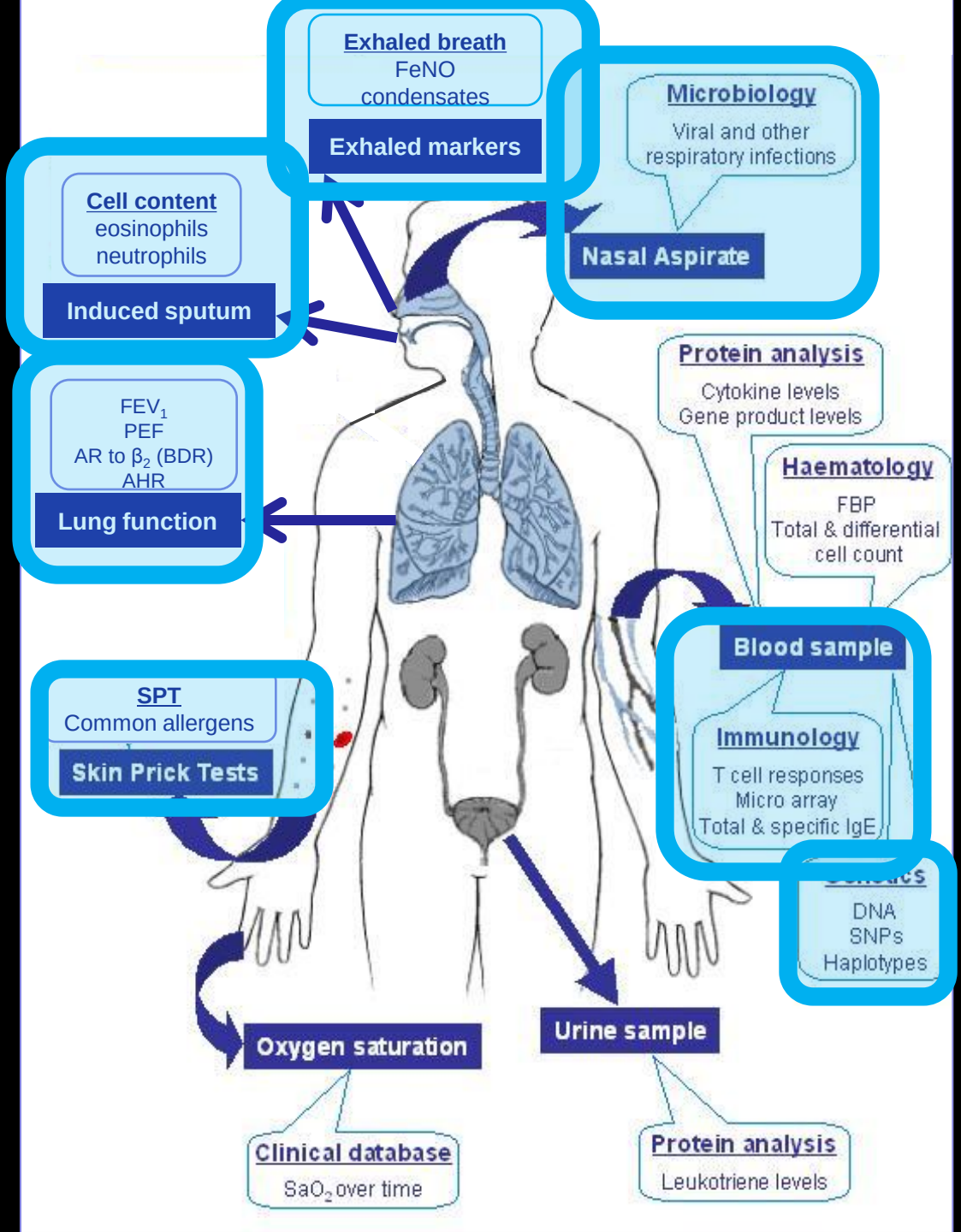


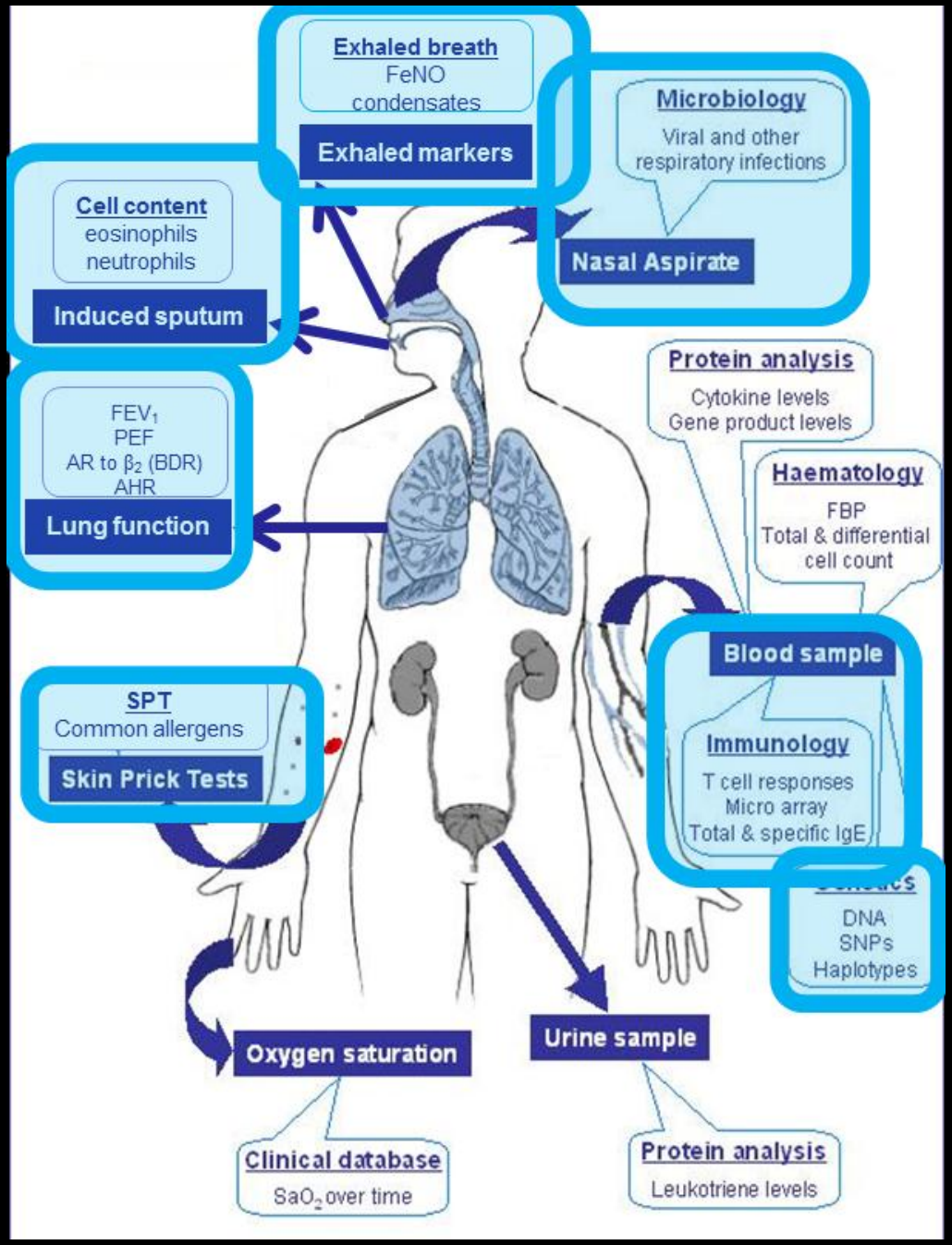
GABRIEL - GWAS

Moffatt MF et al NEJM 2010;363:1211-21



Biological markers of asthma





summary

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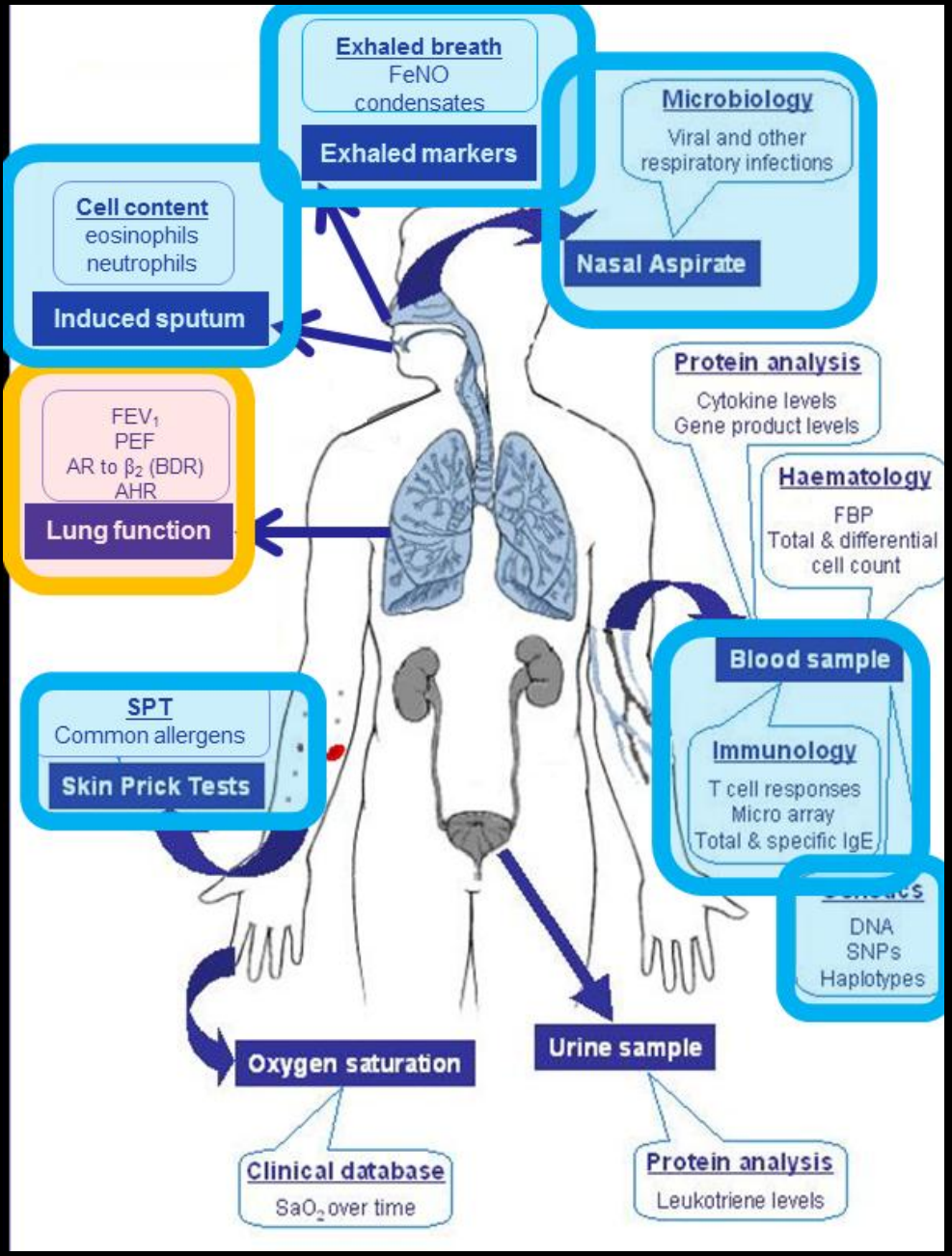
- Lung function
- Exhaled markers
- Induced sputum
- Allergy tests
- Immunology tests
- Genetics



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