

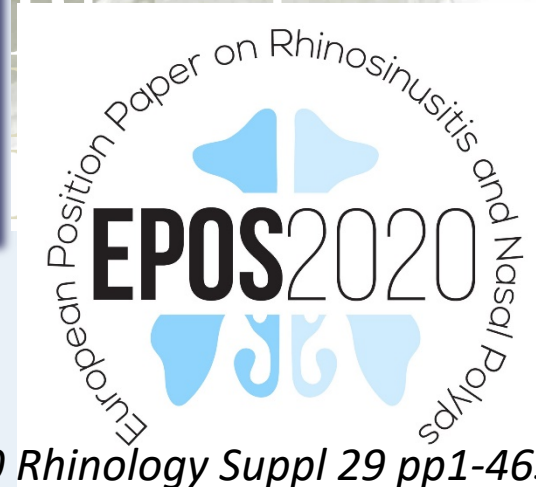
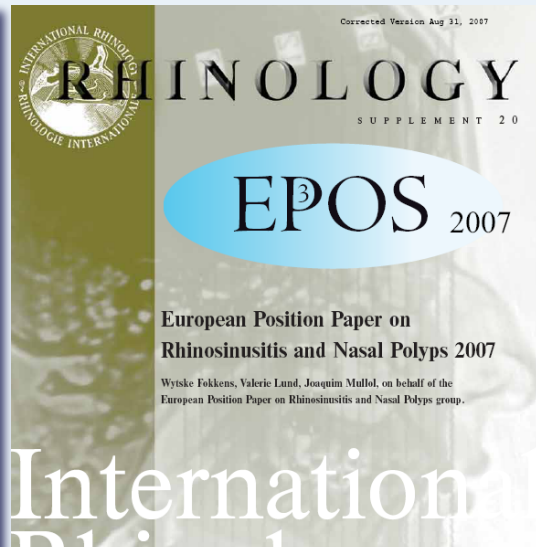
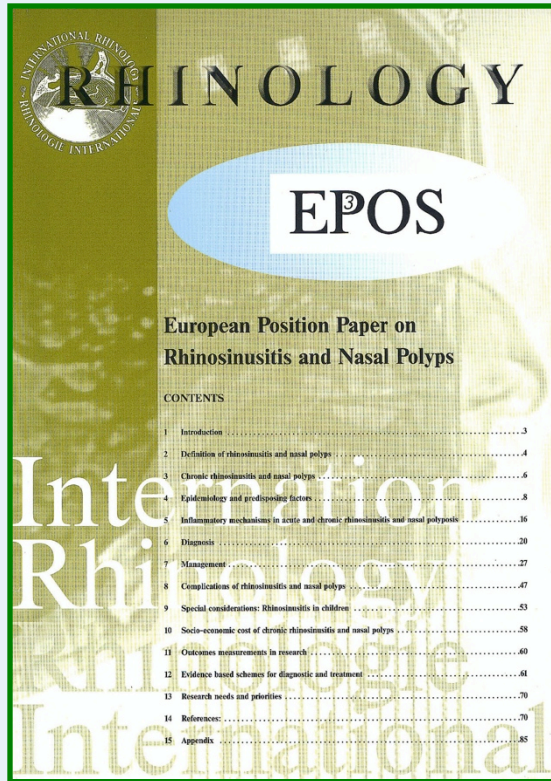


EPOS2020 from bench to bedside

Professor Valerie J LUND CBE
University College London

EPOS 2005-2007-2012-2020

Evidence-based review of rhinosinusitis

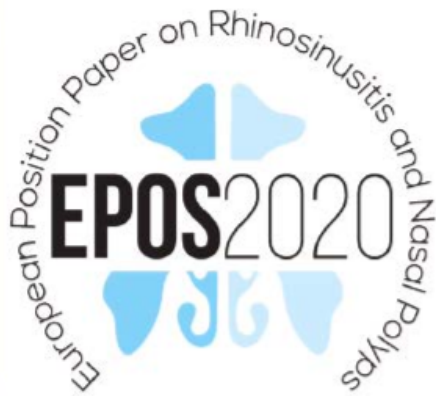




RHINOLOGY

Official Journal of the European and International Rhinologic Societies
and of the Confederation of European ORL-HNS

VOLUME 58 | SUPPLEMENT 29 | FEBRUARY 2020



European Position Paper on Rhinosinusitis and Nasal Polyps 2020

W.J. Fokkens, V.J. Lund,
C. Hopkins, P.W. Hellings,
R. Kern, S. Reitsma,
M. Bernal-Sprekelsen,
J. Mullol
et al.

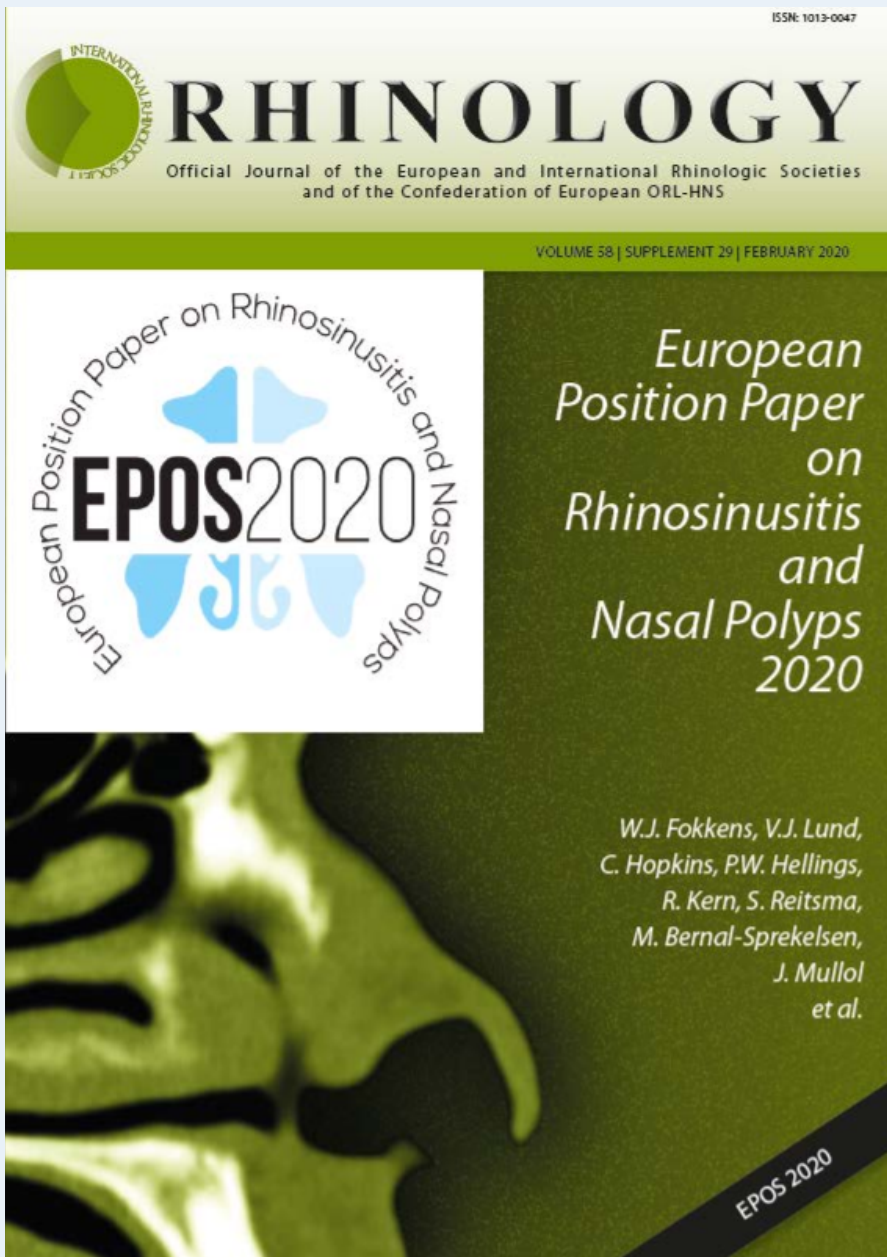
EPOS 2020

FOKKENS, LUND et al EPOPS2020
Rhinology Suppl 29 pp1-465

FOKKENS W, LUND V, HOPKINS C, HELLINGS P,
KERN R, REITSMA S, TOPPILA-SAMI S, BERNAL-
SPREKELSEN M, MULLOL J et al. Executive
summary of EPOS200 including integrated
care pathways. Rhinology 2020;58:82-111.

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FOKKENS, LUND et al EPOPS2020
Rhinology Suppl 29 pp1-465

Steering group of 47 international
experts/stakeholders:

Rhinology
Basic science
Pulmonology
Allergy
Paediatrics
Primary care
Pharmacy
Nursing
& PATIENTS



Then reviewed by another 104 experts
Overall from 69 countries in 5
continents



What's new in EPOS2020

Update and expansion on

- Classification, definitions & preferred terminology
- Concepts of pathophysiology
- Control v cure
- Paediatric CRS
- Concepts for surgery
- Integrated care pathways
- Research needs



EPOS2020 from bench to bedside

Update and expansion on

- Classification, definitions
- Preferred terminology
- Burden
- Concepts of pathophysiology and inflammation
- Control v cure

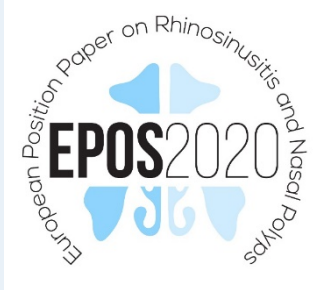


What's new in EPOS2020

Used:

- AGREE II framework for 6 key areas
- Mixed methodologies eg EB Systematic review and Delphi if no evidence available
- 30,000 references (published RCTs, SRs) provided by a medical information expert, reviewed by WF & VJL - reduced to ~>3500
- Only published literature accepted
- 3 face-to-face meetings of full Steering group (Netherlands, Belgium, USA)

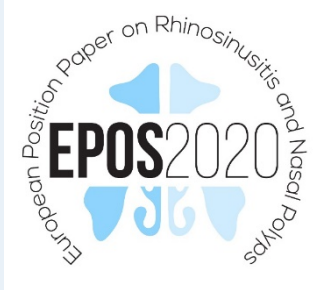
FOKKENS W, DESROSIERS M, HARVEY R, et al EPOS2020: Development Strategy And Goals For The Latest European Position Paper On Rhinosinusitis Rhinology 2019;57:162-168



Definitions

Sinusitis v Rhinosinusitis

- Since 1990s 'rhinosinusitis' recognised - rhinitis and sinusitis co-exist and difficult to distinguish physiologically and pathophysiologically
- In primary care, GPs may distinguish between rhinosinusitis and rhinitis
- In secondary care ENT surgeons may distinguish between phenotypes of rhinosinusitis
- In tertiary care, rhinologists may distinguish between rhinosinusitis endotypes



Clinical definition in adults

Rhinosinusitis (acute and chronic, including nasal polyps)
is defined as:

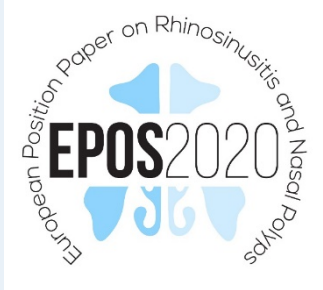
Inflammation of the nose and the paranasal sinuses
resulting in:

Two symptoms, one of which is:

- Blockage/congestion/obstruction
- Discharge anterior/post nasal drip

+/-

- **Reduction or loss of sense of smell**
- Facial pain/pressure



Clinical definition in children

Rhinosinusitis (includes ARS, CRSw/s NP) is defined as:

Inflammation of the nose and the paranasal sinuses
resulting in:

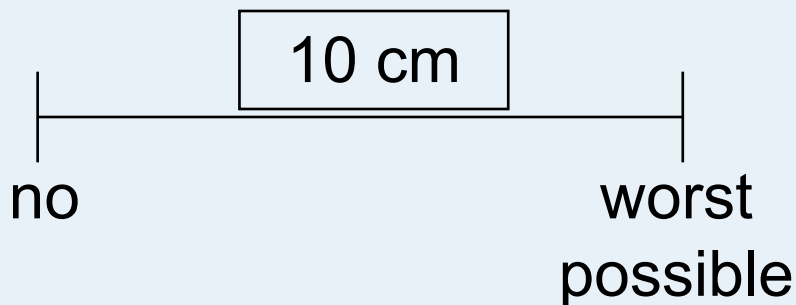
Two symptoms, one of which is:

- Blockage/congestion/obstruction
- Discharge anterior/post nasal drip
+/-
- **Cough (day & night time)**
- Facial pain/pressure

Clinical definition

Severity*

- MILD = VAS 0-3
- MODERATE VAS >3-7
- SEVERE = VAS >7-10
(for at least one symptom)



Duration

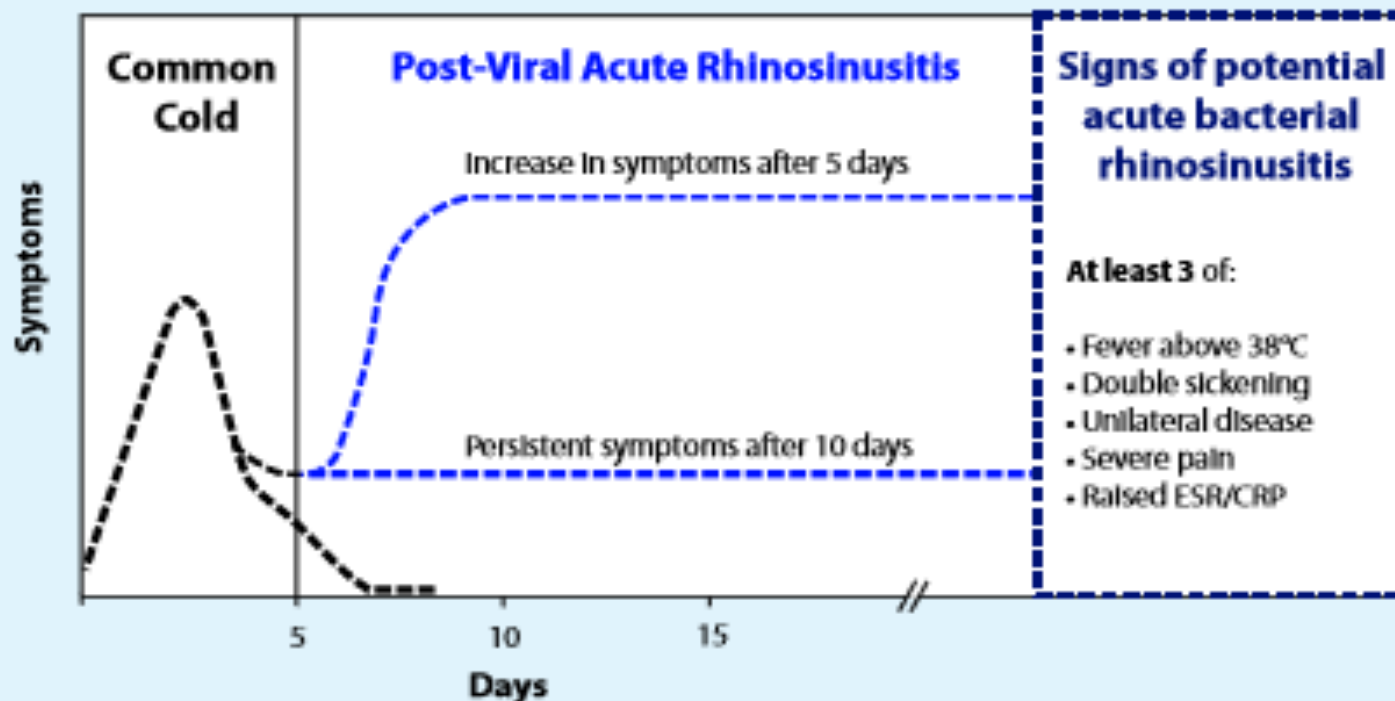
- **ACUTE**
 - < 12 weeks
 - Sudden onset & complete resolution of symptoms
- **CHRONIC**
 - >12 weeks symptoms
 - no complete resolution of symptoms

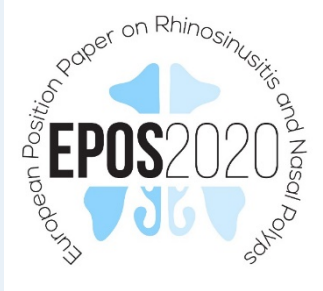
*Lim, LewGor ...Lund Rhinology 2007,45;144



Definition of Acute Rhinosinusitis

Increase in symptoms after 5 days, or persistent symptoms after 10 days
with less than 12 weeks duration





Clinical definition

Rhinosinusitis (includes ARS, CRSw/SNP) is defined as:

Inflammation of the nose and the paranasal sinuses
resulting in

- Two symptoms, one of which is:
- Blockage/congestion/obstruction
- Discharge anterior/post nasal drip
+/-
- Smell/cough
- Facial pain/pressure

AND either
ENDOSCOPIC SIGNS of

- Polyps or
- Mucopurulent discharge from middle meatus
- Oedema/mucosal obstruction primarily in middle meatus

AND/OR CT CHANGES

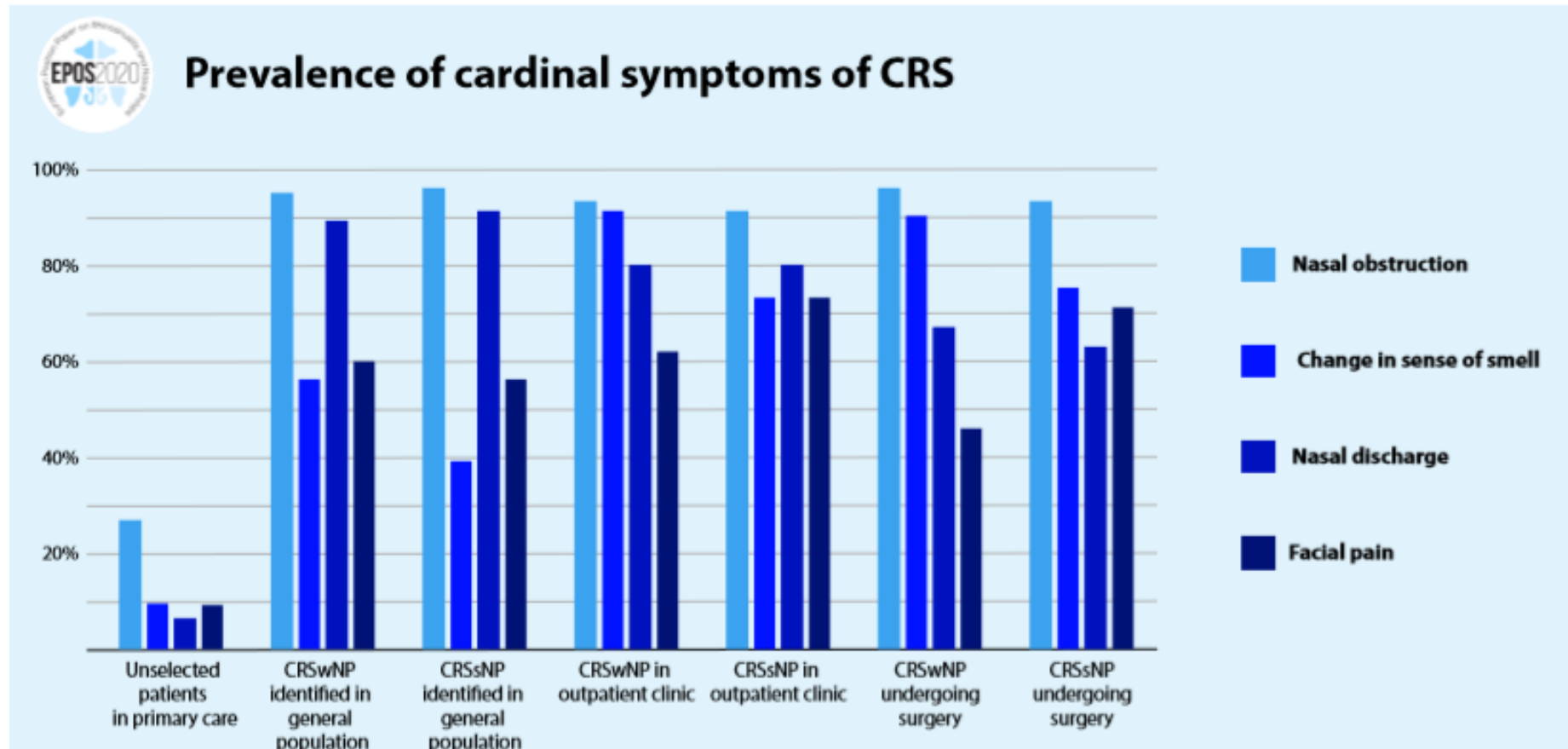
- Mucosal changes within ostiomeatal complex and/or sinuses

[Minimal thickening, involving only 1 or 2 walls and not the ostial area is unlikely to represent rhinosinusitis]

Other clinical definitions

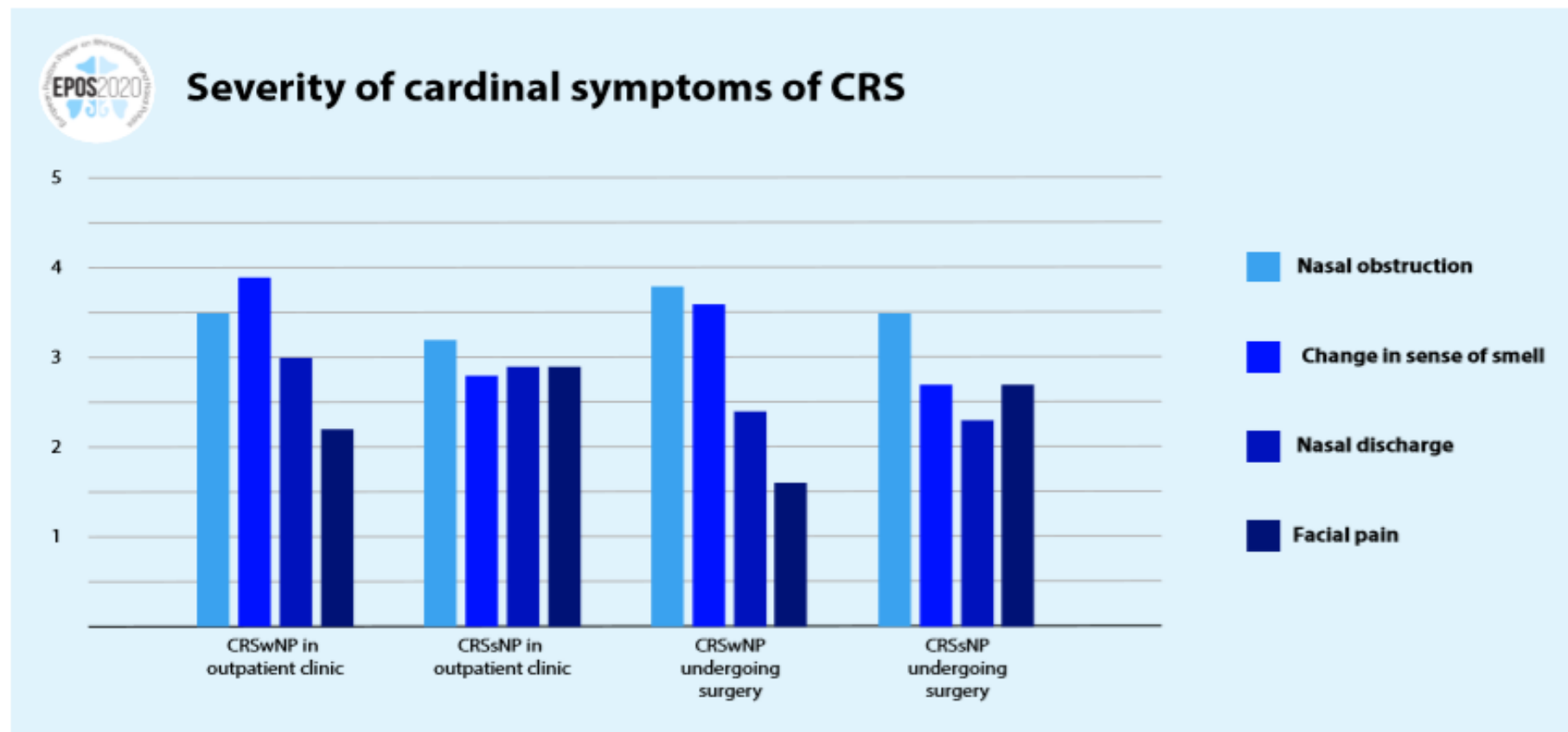
- **Recurrent acute rhinosinusitis (RARS)** is defined as ≥ 4 episodes per year with symptom free intervals (ideally ≥ 1 episode confirmed with endoscopy and/or CT)
- **Acute exacerbation of chronic rhinosinusitis (AECRS)** is defined as worsening of symptom intensity with return to baseline CRS symptom intensity, often after intervention with corticosteroids and/or antibiotics

Figure 1.3.1. Prevalence of cardinal symptoms of CRS ^(25, 26).



CRS, chronic rhinosinusitis; CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps.

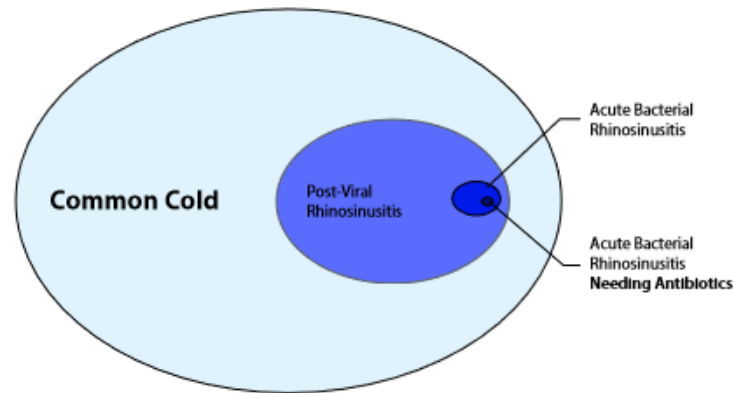
Figure 1.3.2. Severity of cardinal symptoms of CRS. (25, 26)



CRS, chronic rhinosinusitis; CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps.

ARS Epidemiology

Fig 4.1.2. The incidence of different forms of ARS: Common cold, postviral rhinosinusitis and acute bacterial rhinosinusitis (ABRS). Antibiotics are only indicated in a small part of the patients with ABRS.



Viral : 2-5 episodes/yr in adults
 7-10 episodes/yr in school children

Post-viral/ABRS : 18% (17-21%) prevalence

0.5-2% → ABRS



ABRS

Predisposing factors

- **Dental:** infections and procedures
- **Iatrogenic causes:** sinus surgery, nasogastric tubes, nasal packing, mechanical ventilation
- **Immunodeficiency:** human immunodeficiency virus infection, immunoglobulin deficiencies Impaired ciliary motility: smoking, cystic fibrosis, Kartagener syndrome, immotile cilia syndrome
- **Mechanical obstruction:** anatomic eg deviated nasal septum/concha bullosa (RARS), nasal polyps, tumour, trauma, foreign body, granulomatosis with polyangiitis
- **Mucosal oedema:** preceding viral upper respiratory infection, allergic rhinitis, vasomotor rhinitis

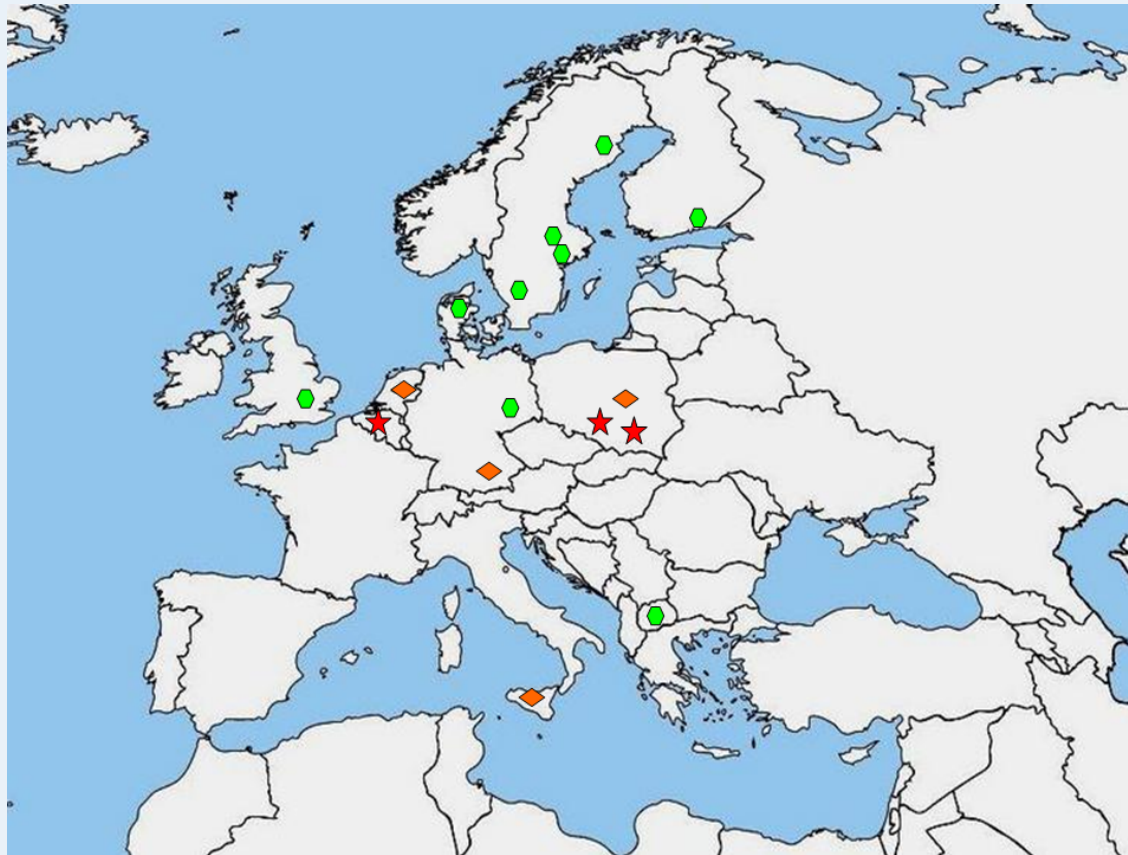


CRS Epidemiology

- 5.5-28% prevalence based on symptoms
- 5.5% Brazil; 8% China; 11% S Korea; 12% USA; 16% Netherlands; 28% Iran
- 3-6% on symptoms + endoscopy +/- CT
- GA2LEN: adults 15-75 yrs, 19 European centres, 12 countries, n=57,128
6.95% Finland – 27.1% Portugal

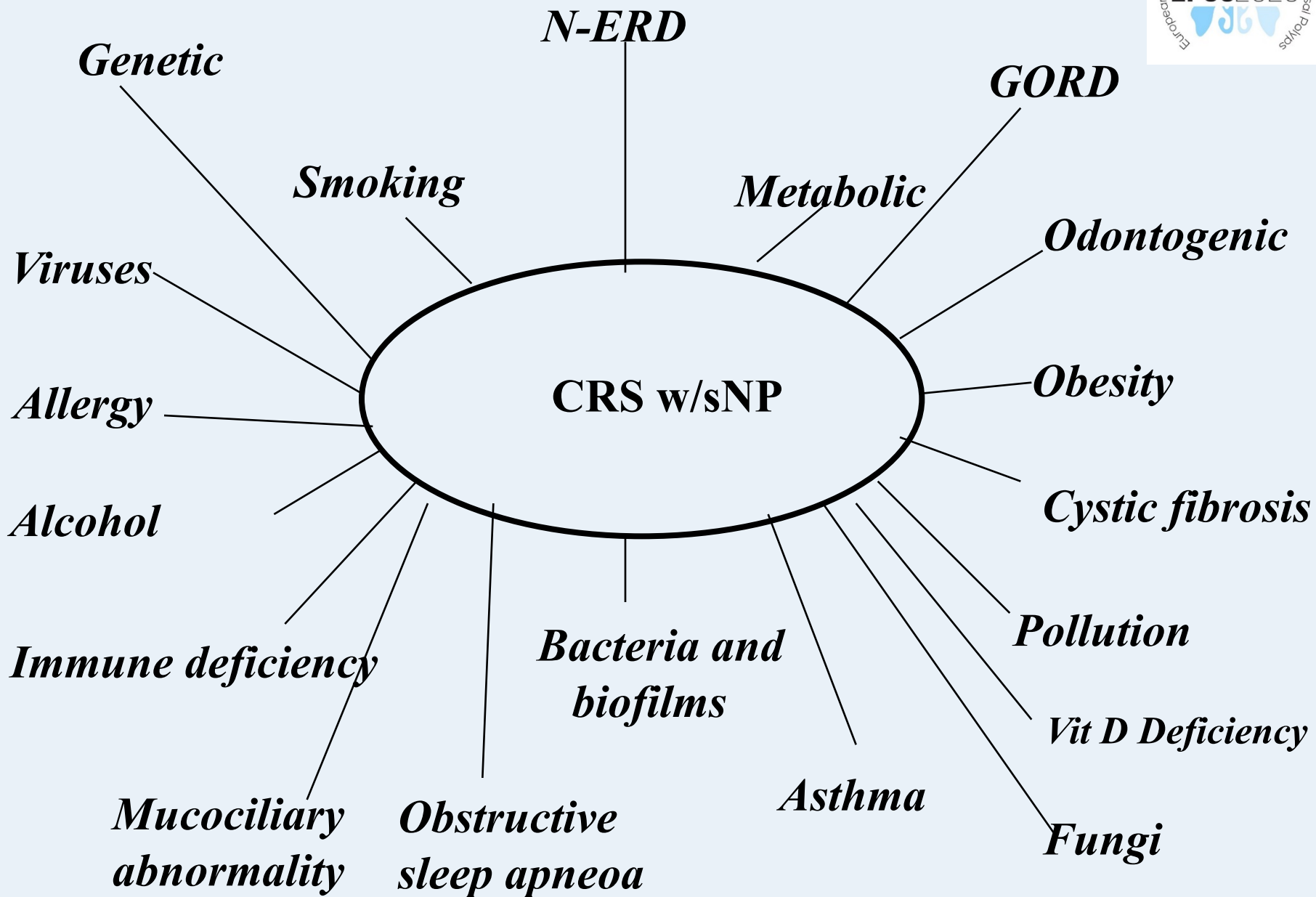
GALEN study

Mean Prevalence of CRSw/sNP ~ 10.9% (5-12%)
(2% CRSwNP)



Map of prevalence of CRS. Symbols indicate prevalence categories of $\geq 15\%$ (red stars), $\geq 10\%$ and $< 15\%$ (orange diamonds) and $< 10\%$ (green hexagons)

Predisposing factors in CRS





BURDEN OF ARS

- Quality of life impact (MARS & SNOT16)¹ show sig impact v controls though with SF36 less impact than CRS²

1. Garbutt J, Spitznagel E, Piccirillo J. Use of the modified SNOT-16 in primary care patients with clinically diagnosed acute rhinosinusitis. *Arch Otolaryngol Head Neck Surg.* 2011;137:792-7

2. Teul I, Zbislowski W, Baran S, Czerwinski F, Lorkowski J. Quality of life of patients with diseases of sinuses. *J Physiol Pharmacol* 2007;58 Suppl 5:691-7..



DIRECT MEDICAL COSTS OF ABRS

In US, 20 million cases/yr ABRS¹, 1:3000 adults RARS²
RARS: 5.6 OPDs/yr + 9.4 prescription → mean \$1091/yr³

1. Orlandi et al. *ICOR Int Forum Allergy Rhinol* 2016;6:S22-S209.
2. Anand. *Epidemiology and economic impact of rhinosinusitis. Ann Otol Rhinol Laryngol* 2004;113:3-5.
3. Bhattacharyya et al. *Recurrent Acute Rhinosinusitis: Epidemiology and Health Care Cost Burden Otolaryngol Head Neck Surg* 2012;146:30712. .



BURDEN OF CRS

- Quality of life impact greater than angina, chronic heart and lung disease¹
- Mean SNOT22: 42 v 9.3 for controls²
(pre-op Th1/CRSsNP 44.2, Th2/CRSwNP 41)

1. Gliklich RE, Metson R. The health impact of chronic sinusitis in patients seeking otolaryngologic care. *Otolaryngol Head Neck Surg.* 1995;113:104-9
2. Hopkins C, Browne JP, Slack R, Lund V et al. The national comparative audit of surgery for nasal polyposis and chronic rhinosinusitis. *Clinical Otolaryngol.* 2006;31:390-8.



DIRECT MEDICAL COSTS OF CRS

In US the total cost of treating a patient with CRS was \$2609/year (\$10-13 billion)

In Europe the direct costs of 2500E/year

Cost of surgery ranges from \$11,000 (USA) to \$1100 (India) and results in decrease in direct costs in next two post-op years¹

Health care spending was significantly greater in CRS than in other chronic diseases such as ulcer disease, asthma and hay fever²

1. Blackwell DL, Collins JG, Coles R. Summary health statistics for U.S. adults. *Vital Health Stat.* 10 2002:1-109.
2. Bhattacharyya N. Contemporary assessment of the disease burden of sinusitis. *Am J Rhinol Allergy.* 2009;23:392-5.



INDIRECT COSTS OF CRS

Indirect costs account for 40% of the total costs of rhinosinusitis

Rhinosinusitis is one of the top ten most costly health conditions to US employers

Absenteeism: missed work days: 4.8-5.7/year

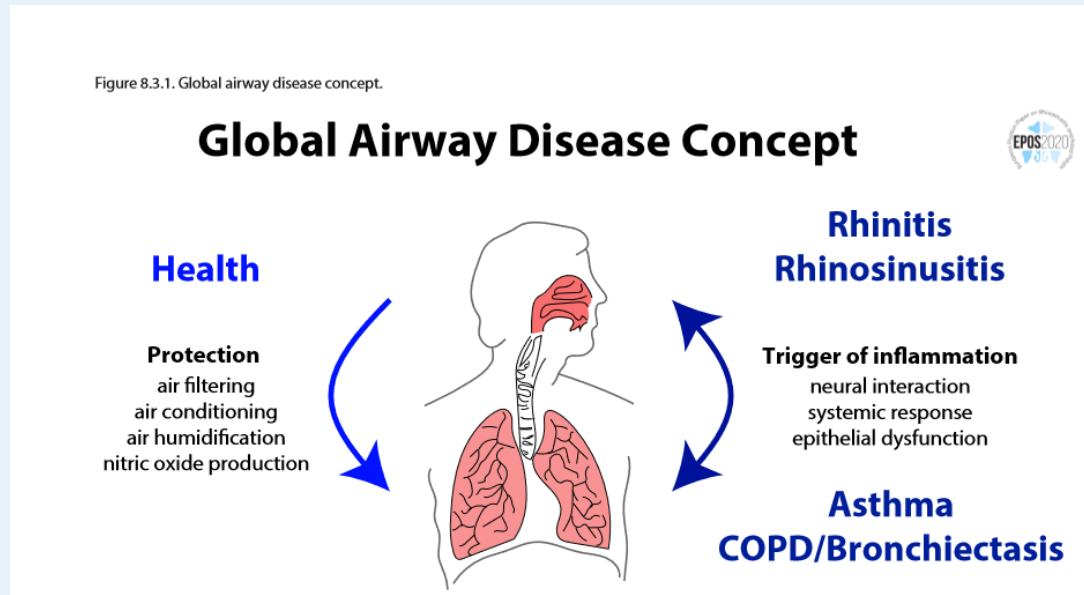
Presenteeism: decreased productivity at work because of symptoms → 38% of work productivity loss

Overall total indirect costs of CRS >\$20billion/yr in USA mainly due to presenteeism¹

1. Rudmik L. Economics of Chronic Rhinosinusitis. Curr Allergy Asthma Reports 2017;17:20.

GLOBAL AIRWAYS

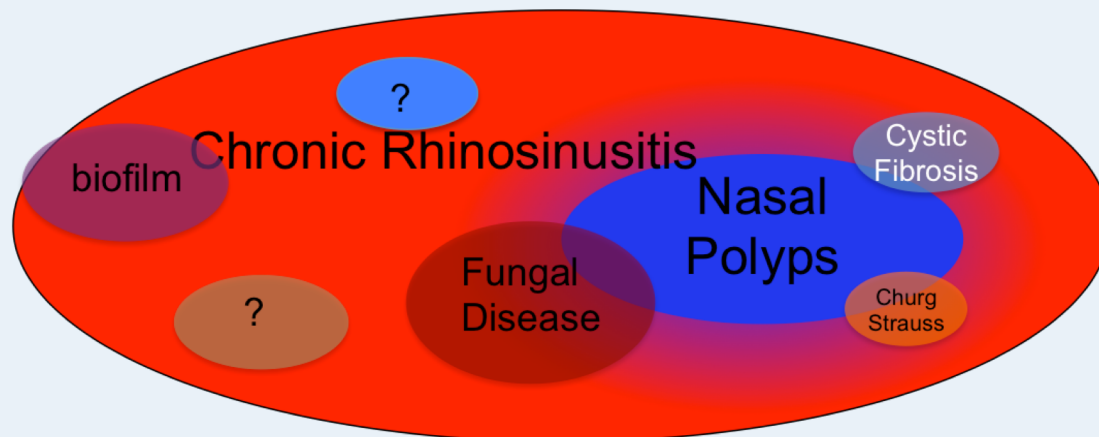
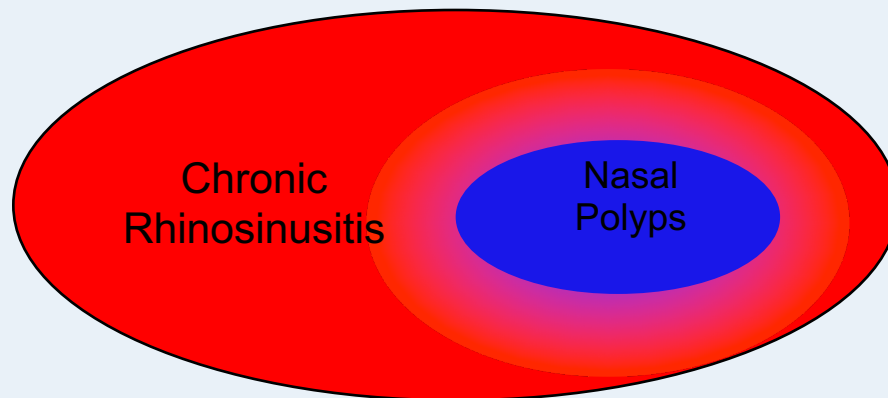
Pathological continuum ~ interaction between upper and lower airways in allergy, asthma, infection and inflammation



Phenotyping & Endotyping
Complex endotypes

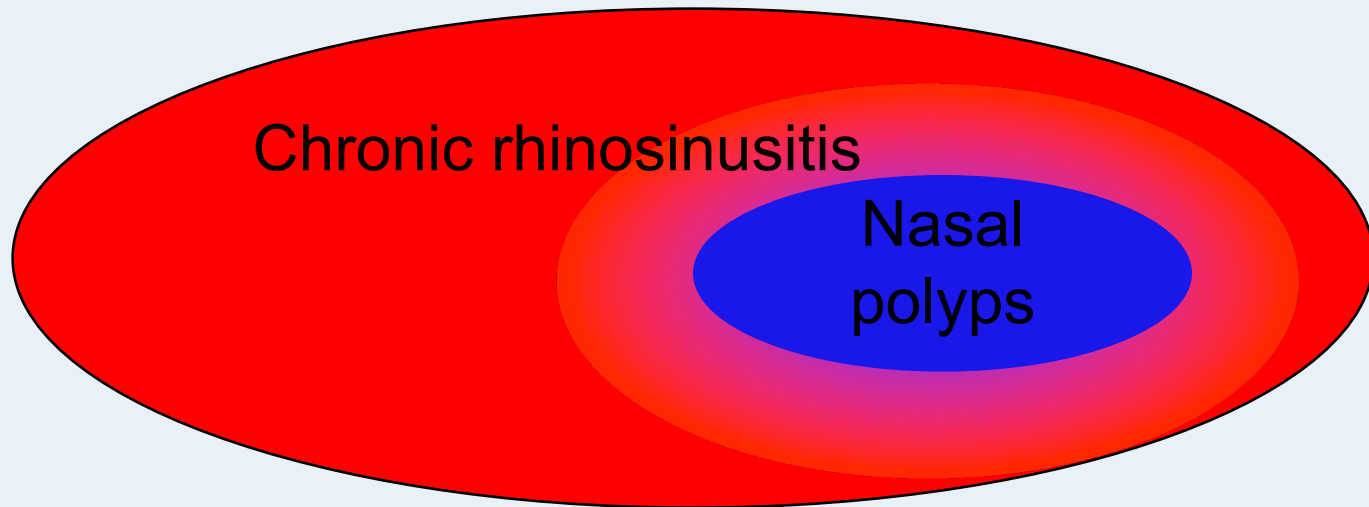
Phenotyping of CRS

EPOS 2012



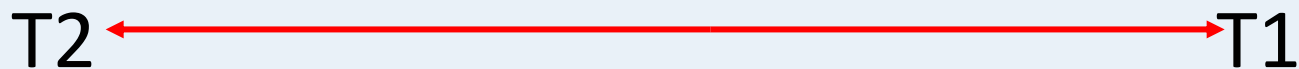
Fokkens with permission

Relationship of CRSsNP & CRSwNP



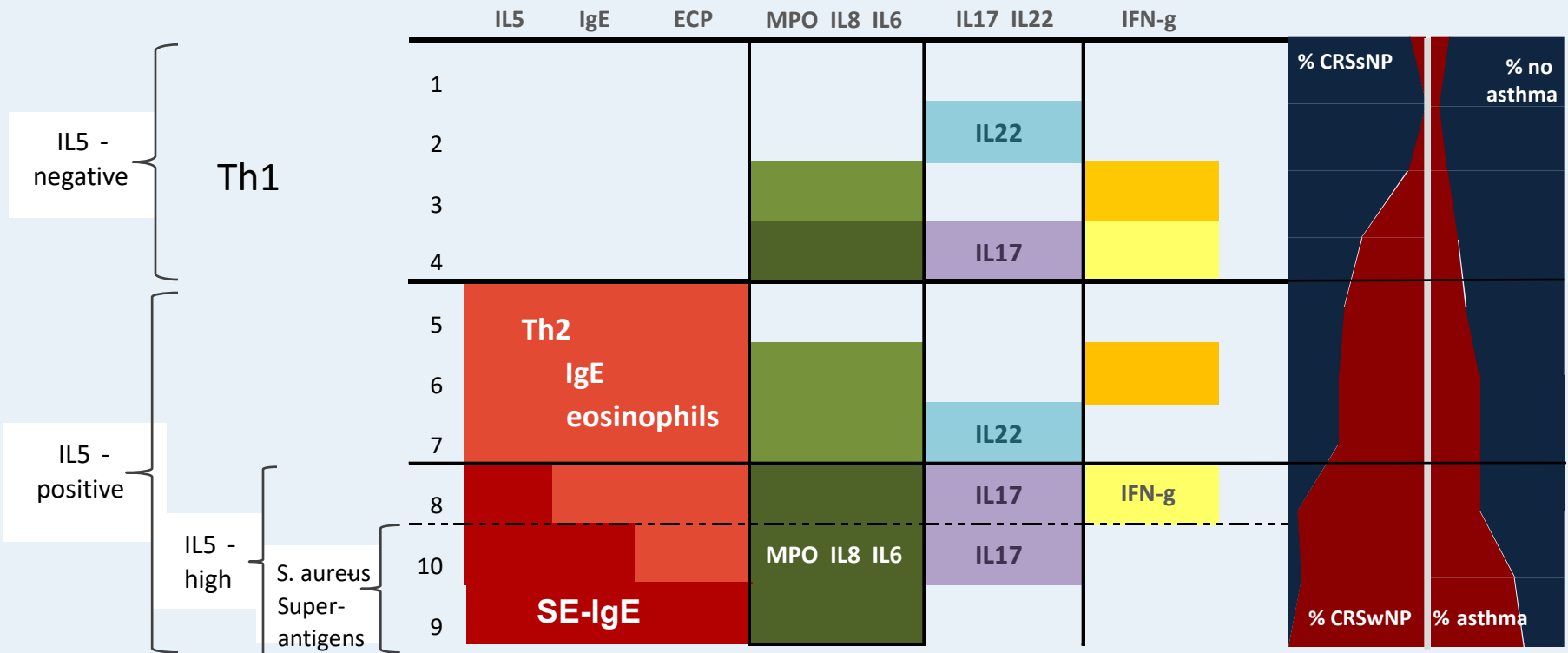
CRS with NP (CRSwNP) or without NP (CRSsNP)

Eosinophilic v 'non'-eosinophilic



(T3)

Endotyping of CRS Based on Cluster Analysis



Eosinophilia in NP- Western world view?

after *Nakayama et al Rhinology 2011;49:392-*

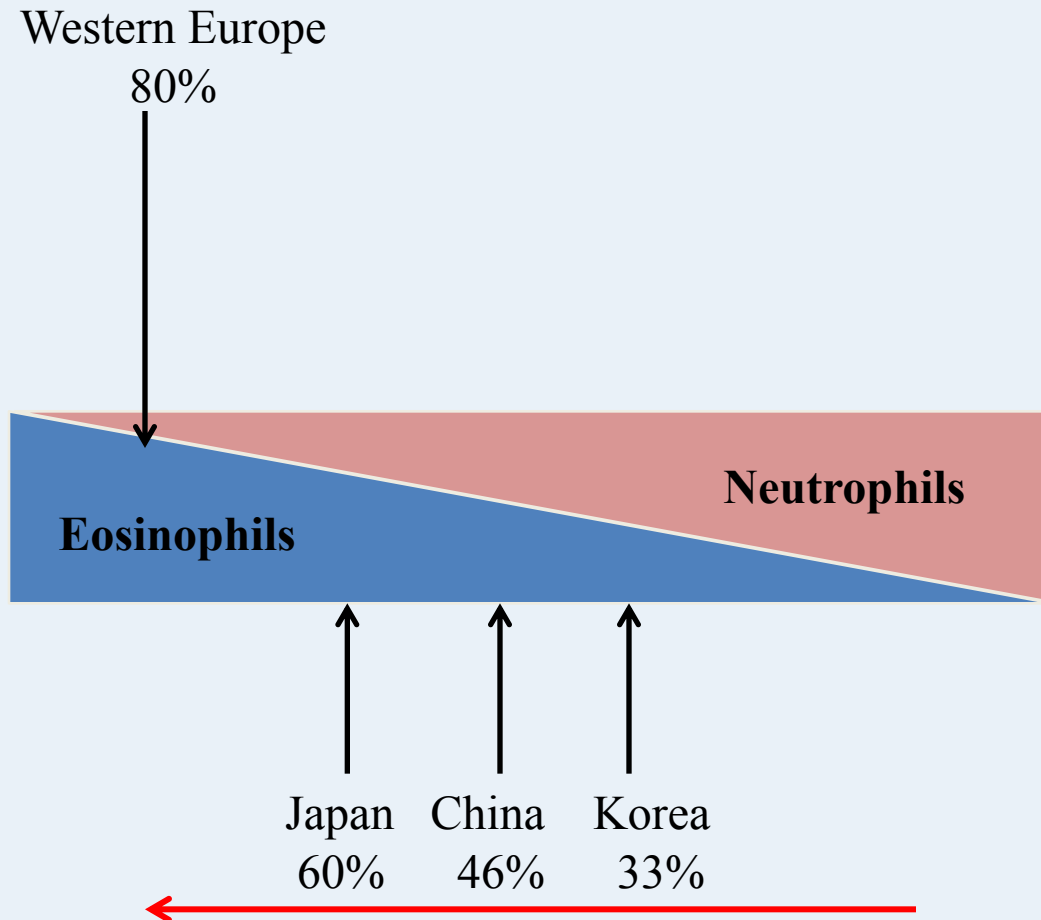
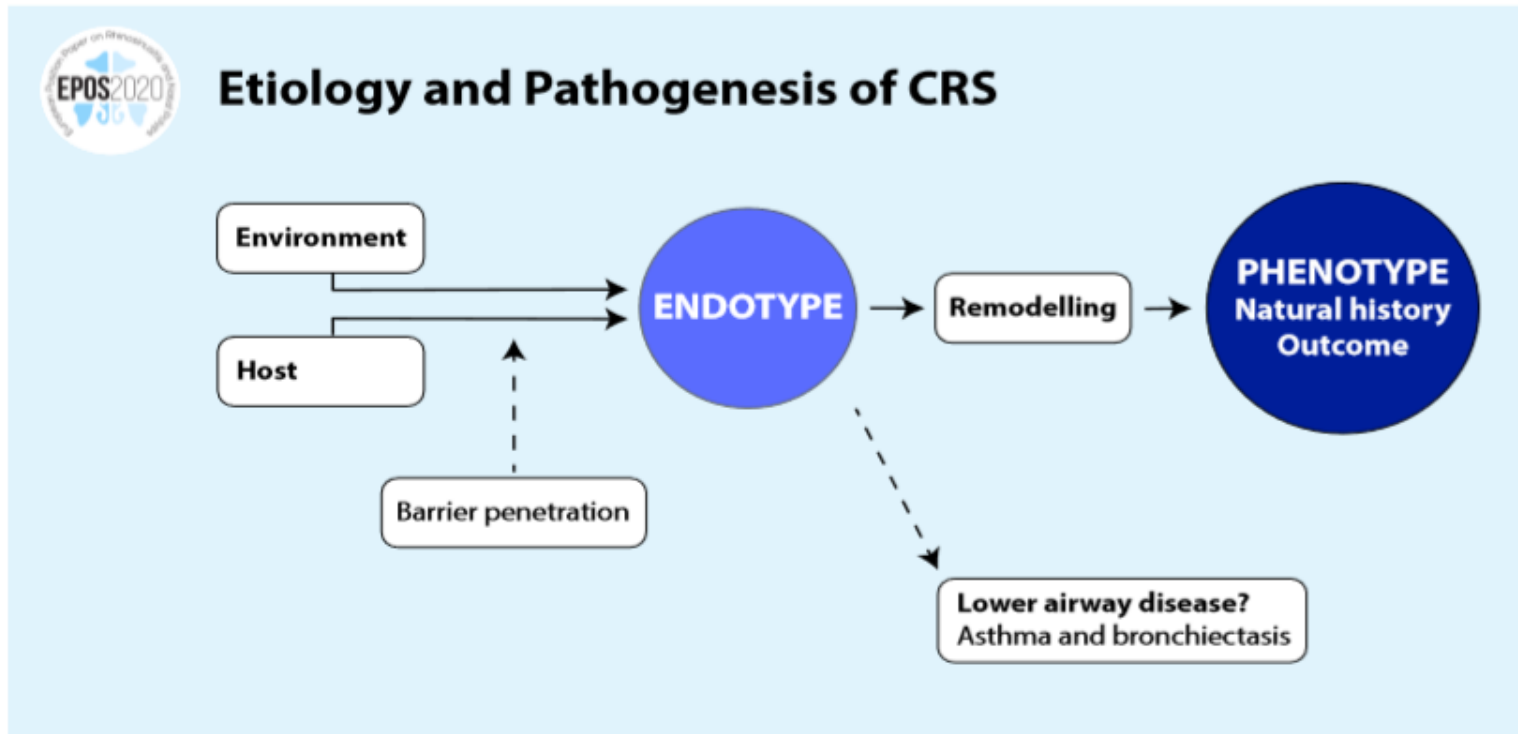


Figure 1.5.1. Aetiology and pathogenesis of CRS.

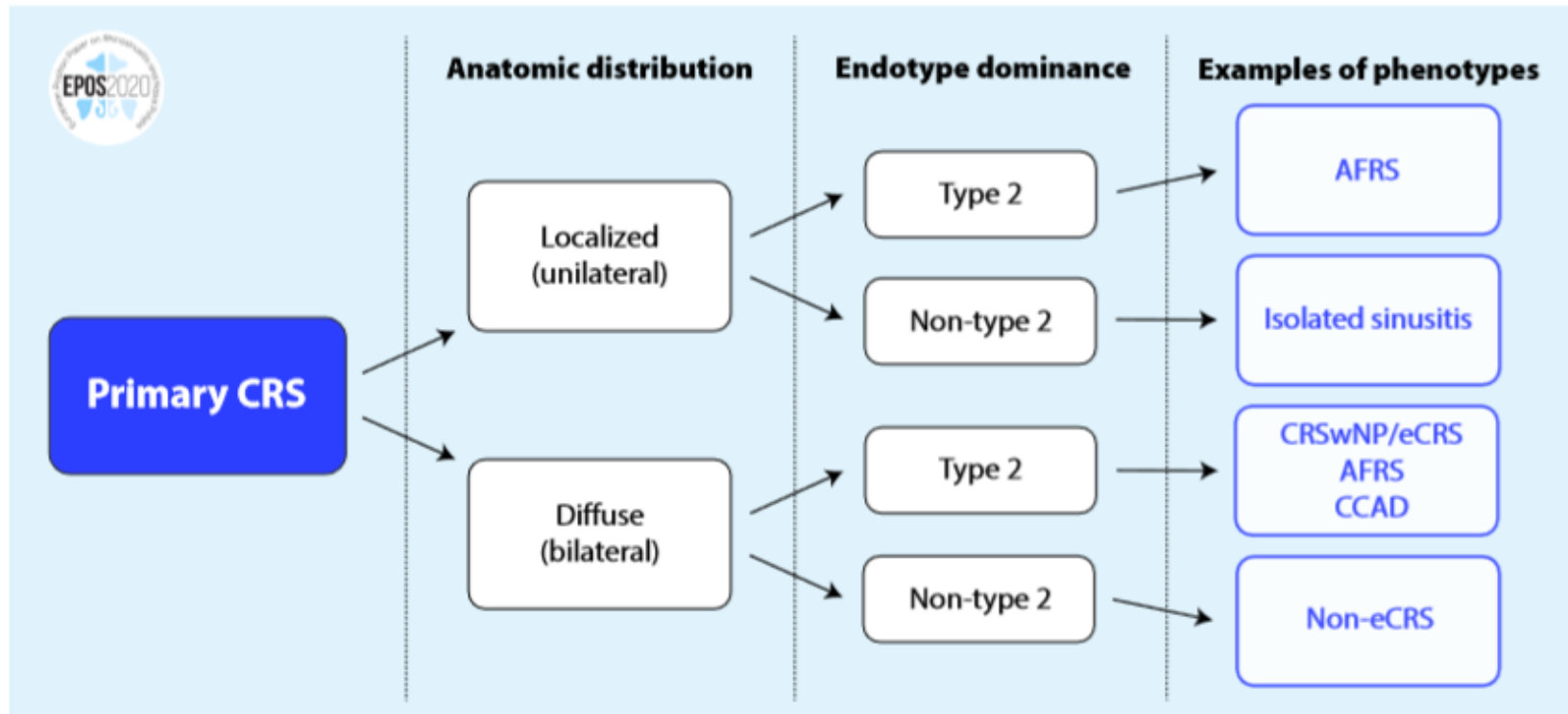


Remodelling – goblet hyperplasia,
- polyp formation
- epithelial barrier abnormalities
– greater permeability

Driven by Type 2 cytokinesmonoclonal antibodies

NEW CRS CLASSIFICATION

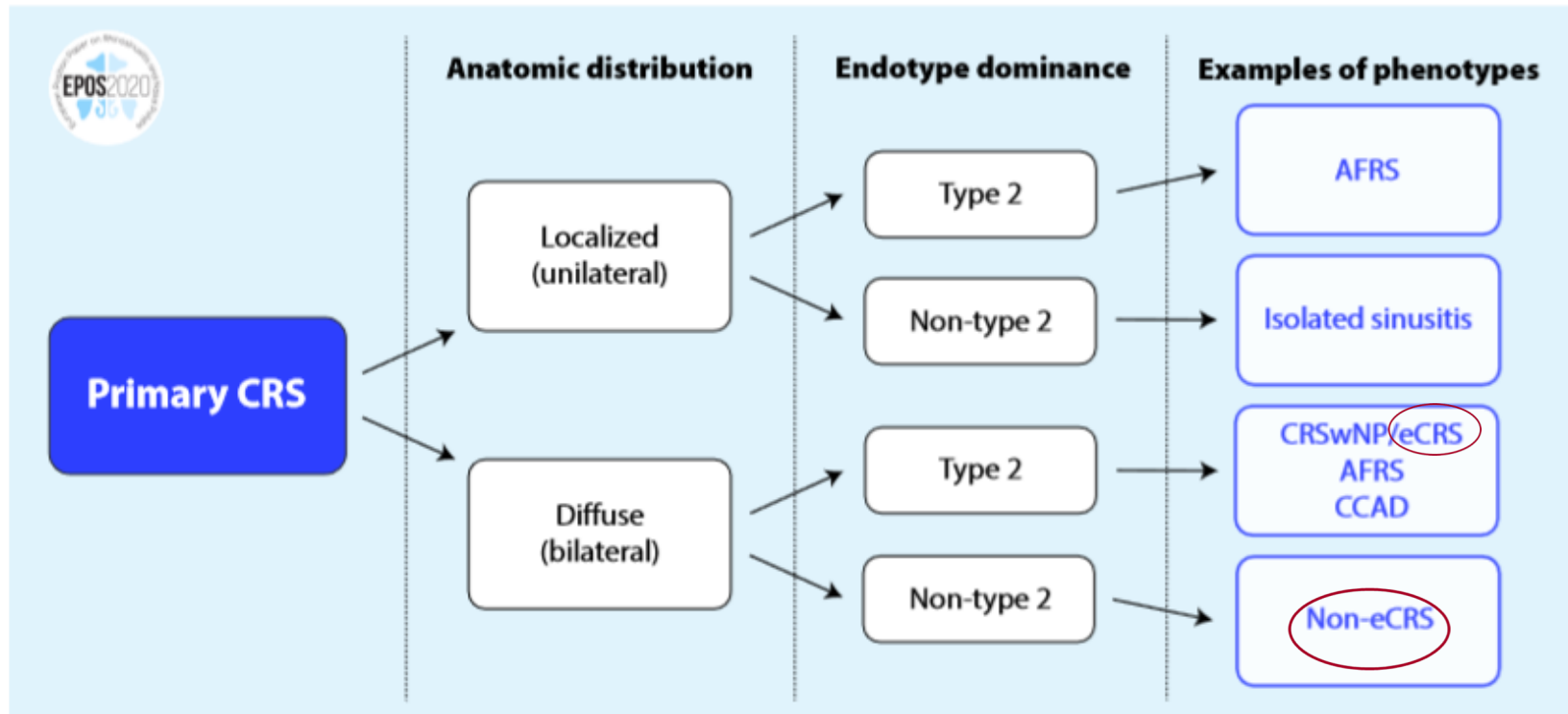
Figure 1.2.1. Classification of primary CRS (Adapted from Grayson et al⁽¹⁵⁴⁾)



AFRS, allergic fungal rhinosinusitis; CRSwNP, Chronic Rhinosinusitis with nasal polyps; CCAD, central compartment allergic disease; eCRS, eosinophilic CRS.

NEW CRS CLASSIFICATION

Figure 1.2.1. Classification of primary CRS (Adapted from Grayson et al⁽¹⁵⁰⁾)

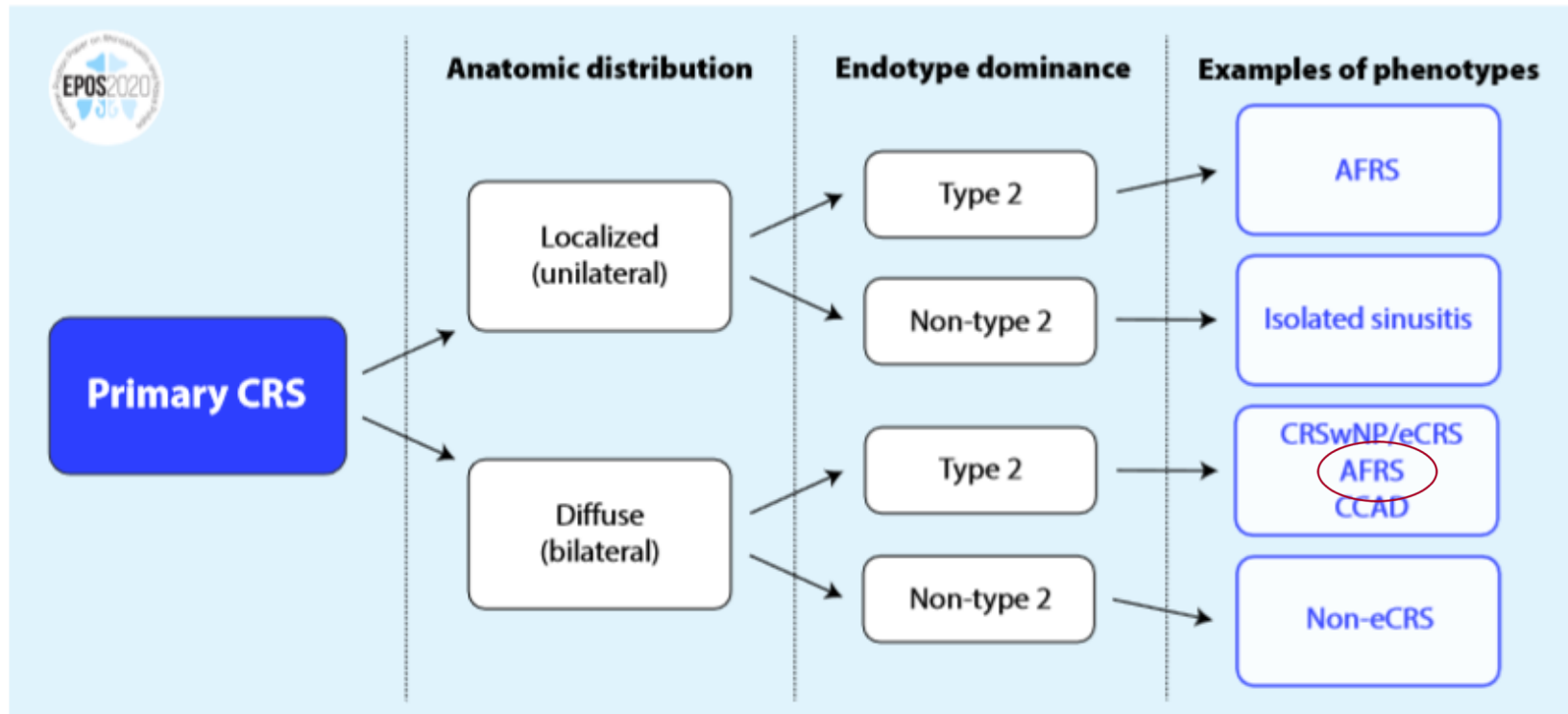


AFRS, allergic fungal rhinosinusitis; CRSwNP, Chronic Rhinosinusitis with nasal polyps; CCAD, central compartment allergic disease; eCRS, eosinophilic CRS.

eCRS v non-eCRS : 10/hpf (400x) eosinophils or higher on histology

NEW CRS CLASSIFICATION

Figure 1.2.1. Classification of primary CRS (Adapted from Grayson et al⁽¹⁵⁰⁾)

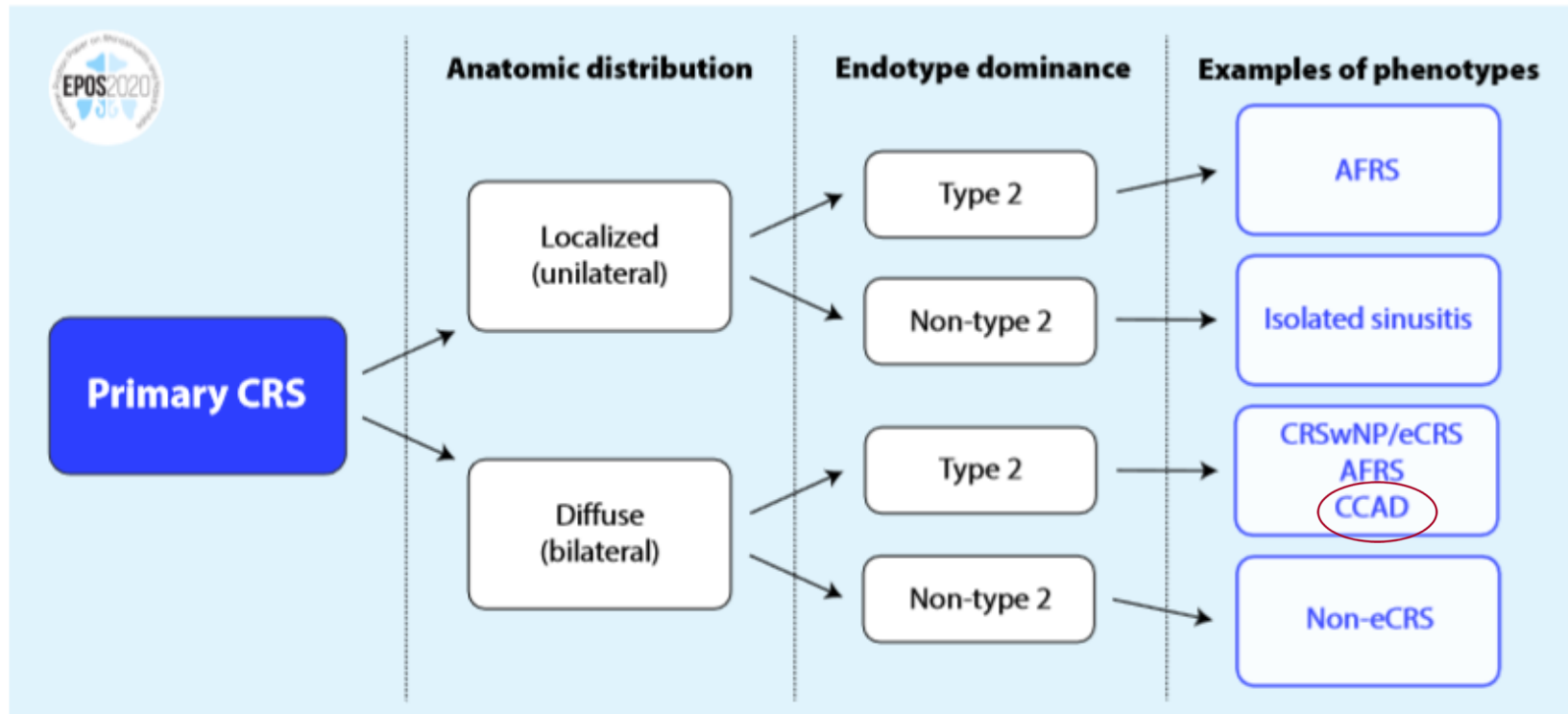


AFRS, allergic fungal rhinosinusitis; CRSwNP, Chronic Rhinosinusitis with nasal polyps; CCAD, central compartment allergic disease; eCRS, eosinophilic CRS.

‘allergic’ fungal rhinosinusitis v ‘eosinophilic fungal rhinosinusitis’
AFRS retained due to common usage, recognising that not all cases are allergic to fungi e.g. a positive skin prick and/or specific IgE

NEW CRS CLASSIFICATION

Figure 1.2.1. Classification of primary CRS (Adapted from Grayson et al⁽¹⁵⁰⁾)

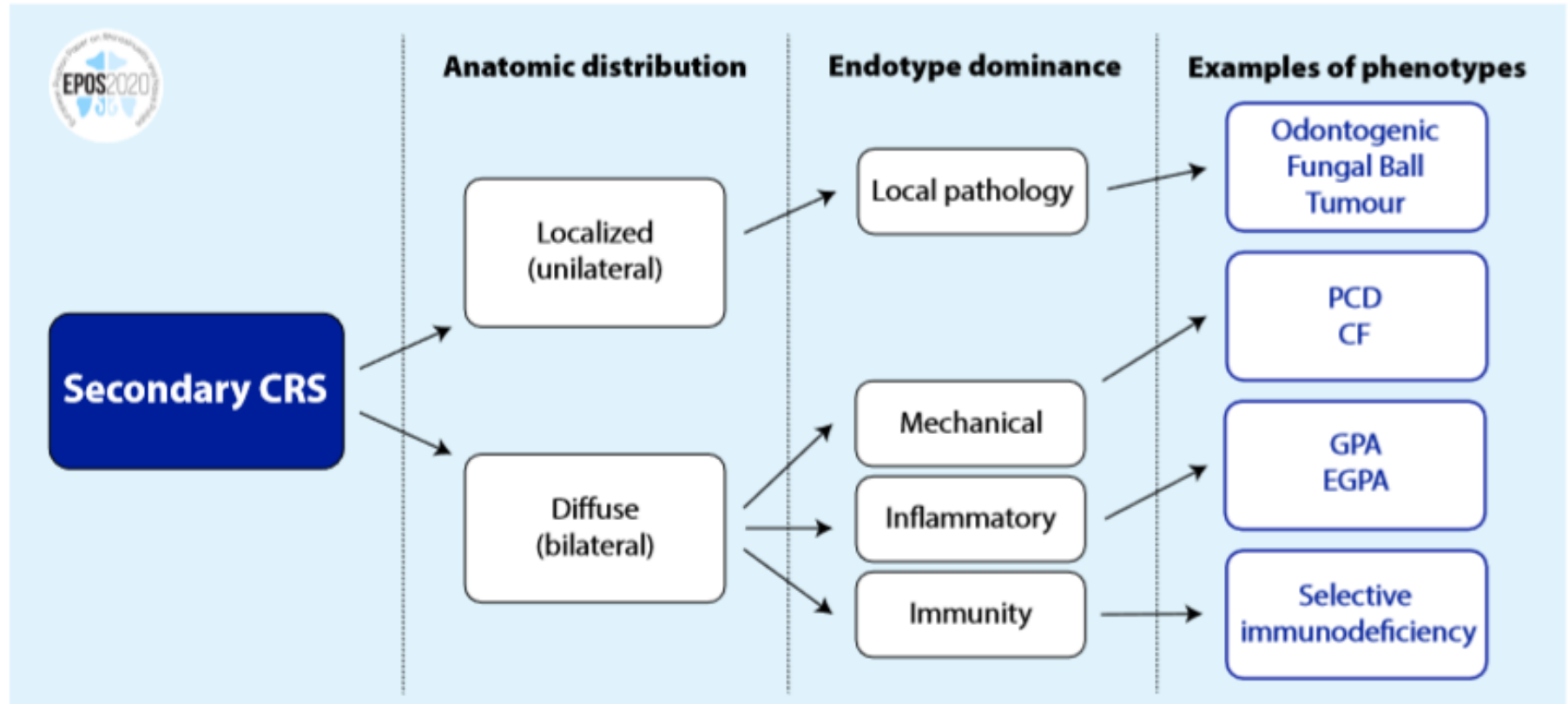


AFRS, allergic fungal rhinosinusitis; CRSwNP, Chronic Rhinosinusitis with nasal polyps; CCAD, central compartment allergic disease; eCRS, eosinophilic CRS.

CCAD: variant of CRS with polypoid changes of the entire central sinonasal compartment while the lateral sinus mucosa remains relatively normal ('black halo'), likely due to allergy

NEW CRS CLASSIFICATION

Figure 1.2.2. Classification of secondary CRS (Adapted from Grayson et al⁽¹⁵⁴⁾).



CF, cystic fibrosis; EGPA, eosinophilic granulomatosis with polyangiitis (Churg-Strauss disease); GPA, granulomatosis with polyangiitis (Wegener's disease); PCD, primary ciliary dyskinesia.

Definition of difficult-to-treat (recalcitrant) rhinosinusitis

Patients who have persistent symptoms of rhinosinusitis despite appropriate treatment (recommended medication and surgery)

Patients who do not reach **an acceptable level of control** despite adequate surgery, intranasal corticosteroid treatment and up to 2 short courses of antibiotics or systemic corticosteroids in the last year can be considered to have difficult-to-treat rhinosinusitis.

*Fokkens W, Lund V, et al. Rhinology 2020. (Suppl 29)
web: www.ep3os.org, rhinologyjournal.com*

Recurrence of disease after surgery is common, as high as 60% of patients (50% of these patients have had previous surgery) *DeConde & Soler Am J Rhinol Allergy. 2016;30:134–139*

Figure 1.2.3. Assessment of current clinical control of CRS.



EPOS 2020: Assessment of current clinical control of CRS (in the last month)

	Controlled (all of the following)	Partly controlled (at least 1 present)	Uncontrolled (3 or more present)
Nasal blockage¹	Not present or not bothersome ²	Present on most days of the week ³	Present on most days of the week ³
Rhinorrhoea / Postnasal drip¹	Little and mucous ²	Mucopurulent on most days of the week ³	Mucopurulent on most days of the week ³
Facial pain / Pressure¹	Not present or not bothersome ²	Present on most days of the week ³	Present on most days of the week ³
Smell¹	Normal or only slightly impaired ²	Impaired ³	Impaired ³
Sleep disturbance or fatigue¹	Not present ²	Present ³	Present ³
Nasal endoscopy (if available)	Healthy or almost healthy mucosa	Diseased mucosa ⁴	Diseased mucosa ⁴
Rescue treatment (in last 6 months)	Not needed	Need of 1 course of rescue treatment	Symptoms (as above) persist despite rescue treatment(s)

¹ Symptoms of CRS; ² For research VAS ≤ 5; ³ For research VAS > 5; ⁴ Showing nasal polyps, mucopurulent secretions or inflamed mucosa

CRS, chronic rhinosinusitis; VAS, visual analogue scale.

Concept of Control v Cure

The primary goal of any treatment, especially in chronic diseases, is to achieve and maintain clinical control, which can be defined as a disease state in which the patient does not have symptoms, or the symptoms are not impacting quality of life¹

Validation studies of EPOS2012 proposal suggests it may over-estimate number of uncontrolled.²⁻⁴

Mean VAS of 5.5 for total nasal symptoms³

For research, a VAS scale for all symptoms: “not bothersome” can be substituted by ‘VAS < 5’, and ‘present/impaired’ by ‘VAS ≥ 5.

1. Fokkens W, Lund V, et al. EPOPS 2012 *Rhinology* 2012;50:1-12

2. Snidvongs (2014) prospective, n=106;

3. Van der Veen (2017) cross-sectional, n= 389;

4. Calus (2019) prospective, n=47

Reasons for lack of control in CRS

Disease-related factors ('SCUAD')*

Exogenous/endogenous/genetic factors
Global airway disease



Uncontrolled
upper airway
disease

Diagnosis-related factors

Incorrect diagnosis
Concomitant local/systemic disease



Patient-related factors

Inadequate intake of medication
Poor adherence

Treatment-related factors

Inadequate treatment
Lack of symptom-oriented treatment

*Severe Chronic Upper Airway Disease



Diagnosis related factors

Incorrect diagnosis

- Allergic & non-allergic rhinitis
- Other conditions associated with olfactory loss
- Facial pain



Diagnosis related factors Concomitant disease in CRS

- Allergy
- Immunodeficiencies
- Lower respiratory tract disease
- Cystic fibrosis
- Primary ciliary dyskinesia
- Fungal rhinosinusitis
- Vasculitis

Diagnostics and Objective Assessments in CRS

Primary

- History & symptoms
- General examination – URT & LRT
- Endoscopy

Secondary

- Quality of life assessment eg SNOT22, SF36
- Allergy tests eg skin prick, RAST
- Imaging

Tertiary

- Olfaction
- Nasal smears, swabs & biopsy for micro, eosinophils etc
- Nasal challenge eg aspirin

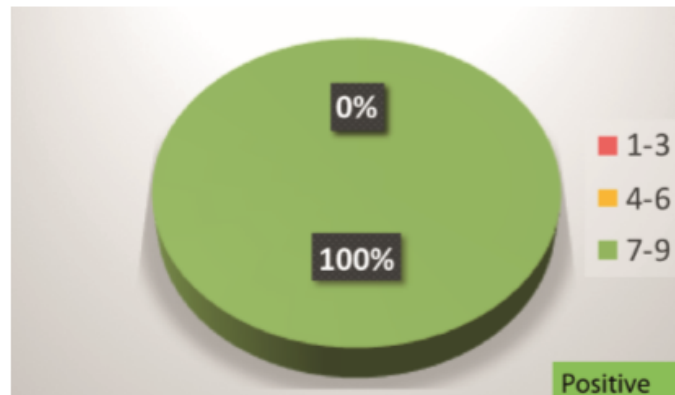
CARE

- Mucociliary function
- Nasal airway assessment
- Systemic eg haematology for eosinophils, ANCA etc

Delphi for Diagnosis

- QoL in ARS & CRS
- CT: when to perform, use of old scans, clinically relevant LM score in CRS
- When to perform other diagnostic tests

Figure 5.3.28. Delphi: Is a QoL instrument important for the management of CRS?



Only Delphi where everyone agreed but not which one!

Delphi for Diagnosis

- CT: mandatory pre-op to confirm presence + extent of disease
But can you use an old scan?

Figure 5.3.3. Delphi: Is it essential to do CT in CRS after failure of appropriate medical or surgical treatment in secondary care with continued symptoms and abnormal endoscopy?

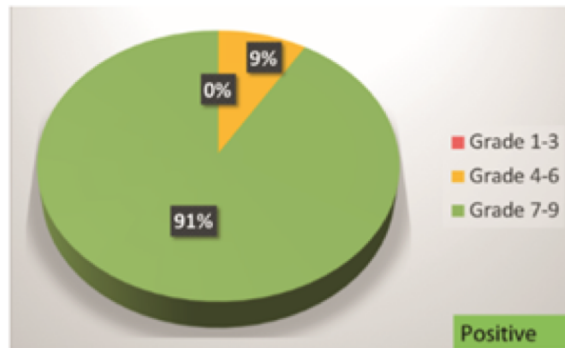


Figure 5.3.22. Delphi For the purposes of surgical treatment in secondary care/ENT is it acceptable to use the previously performed CT scan which has been done 6-12 months ago?

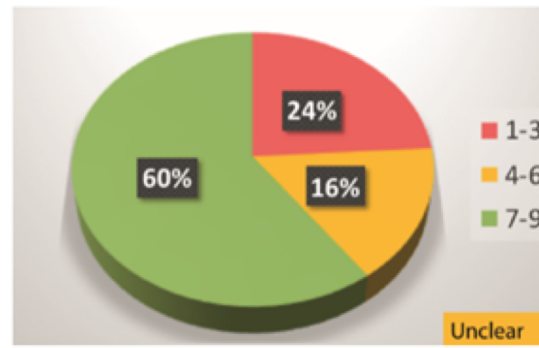
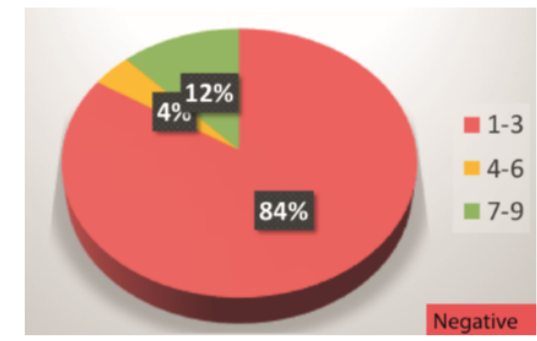



Figure 5.3.24. Delphi For the purposes of surgical treatment in secondary care/ENT is it acceptable to use the previously performed CT scan which has been done longer than 3 years ago?



Diagnostics and Objective Assessments in CRS

- 
- Primary
- History & symptoms
 - General examination – URT & LRT
 - Endoscopy
- Secondary
- Quality of life assessment eg SNOT22, SF36
 - Allergy tests eg skin prick, RAST
 - Imaging
 - Olfaction
 - **Nasal smears, swabs & biopsy for eosins, IgE, ECP etc**
- Tertiary
- Nasal challenge eg aspirin
- CARE
- Mucociliary function
 - Nasal airway assessment
 - **Systemic eg haematology for eosins, IgE, ECP, periostin etc**

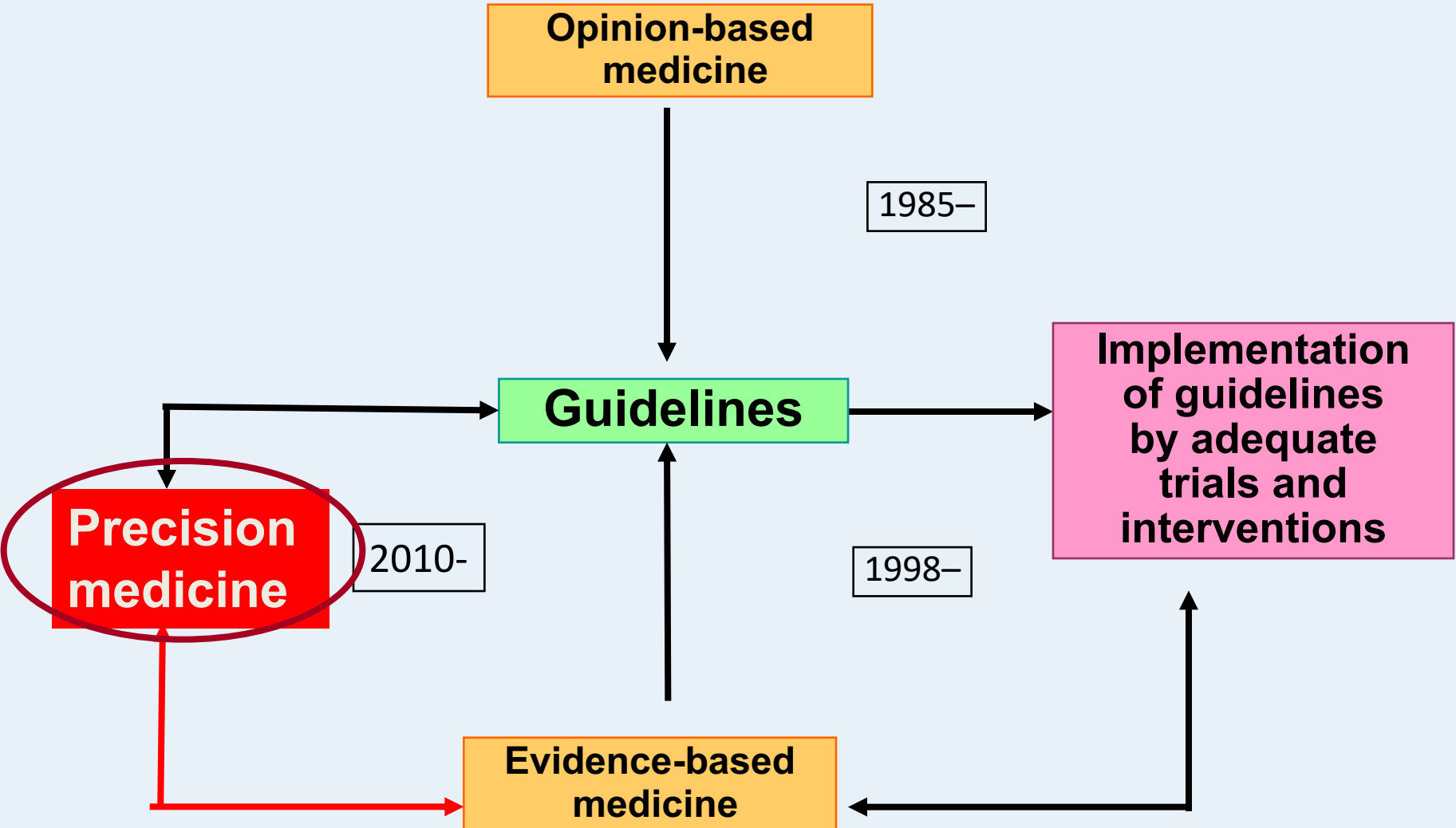


The search for the ideal biomarker!

Top research priority to find a
reliable, simple and cheap biomarker

HELLINGS P, FOKKENS W.... LUND V et al. EUFOREA Rhinology Research Forum 2016:
report of the brainstorming sessions on needs and priorities in rhinitis and rhinosinusitis.
Special Report. Rhinology 2017 <https://doi.org/10.4193/Rhino17.028>

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EPOS2020 from bench to bedside

Thank you!