

Table 1. Commonly used patient-reported outcome measures for chronic rhinosinusitis with nasal polyps.

PROM	No. of questions	Response scale	Score range	MCID
CRS-specific QOL				
Chronic sinusitis survey ⁽¹⁴⁾	6	5-item Likert scale	0 – 100	—
31-item Rhinosinusitis Outcome Measure ⁽¹⁸⁾	31	6-point Likert scale	0 – 155	30% change ⁽¹⁵⁾
Rhinosinusitis Disability Index ⁽¹⁸⁾	30	5-point Likert scale	0 – 120	—
20-item Sinonasal Outcome Test ⁽²²⁾	20	6-point Likert scale	0 – 100	16 for total score ⁽²²⁾ 0.8 for standardized score ⁽²²⁾
22-item Sinonasal Outcome Test ⁽²⁸⁾	22	6-point Likert scale	0 – 110	8.9 in surgically managed patients ⁽²⁸⁾ 12 in medically managed patients ⁽⁷⁴⁾
CRS symptom severity				
Overall symptom severity score ⁽²⁾	1	VAS	0 – 10	—
Nasal congestion/obstruction score	1	VAS 4-point Likert scale	0 – 10 (for visual analogue scale) 0 – 3 (for Likert scale)	1 point (for 4-point Likert scale)
General health-related QOL				
SF-36 ⁽¹⁰⁴⁾	36	2-, 3-, 5- and 6-item Likert scales	Item score: 0 – 100 Domain score: 0 – 100 Physical component summary score: 0 – 100 Mental component summary score: 0 – 100	2 – 5 for physical and mental component summary scores ⁽¹⁰⁵⁾
SF-36v2 ⁽¹¹⁵⁾	36	3-, 5-, and 6-item Likert scales	Item score: 0 – 100 Domain score: 0 – 100 Physical component summary score: 0 – 100 Mental component summary score: 0 – 100	2 – 5 for physical and mental component summary scores ⁽¹⁰⁵⁾
SF-6D ⁽¹¹⁸⁾	6	4-, 5- or 6-item Likert scales		0.010 to 0.066 for HUV ⁽¹²¹⁾
EQ-5D-5L ⁽¹²⁷⁾	6	5-item Likert VAS	HUV: 0.000 – 1.000 VAS: 0 – 100	0.4 for EQ-5D HUV ⁽¹³²⁾ 8 for EQ-5D VAS ⁽¹³²⁾
Asthma-specific				
Asthma control test ⁽¹⁵³⁾	5	5-point Likert scale	5 – 25	3
Asthma Control Questionnaire ⁽¹⁶⁶⁾	7	7-point Likert scale	0 – 6	0.5
Asthma Quality of Life Questionnaire ⁽¹⁵²⁾	32	7-point Likert scale	1 – 7	0.5

Abbreviations: HUV – health utility value; MCID – minimal clinically important difference; PROM – patient-reported outcome measure; QOL – quality of life; VAS – visual analogue scale.

bance, craniofacial discomfort, emotional disturbance, and functional impairment. Formal study of the subdomain structure of the SNOT-22 has yielded different results. Two studies have proposed two different 5-subdomain organization structures ^(59,60), while the study with the largest cohort consisting of 800 patients from the eastern and western United States that included formal confirmatory factor analysis validation identified a 4-subdomain structure reflecting nasal symptoms, sleep quality/disturbance, craniofacial pain, emotional disturbance ⁽⁶¹⁾. This four subdomain structure was validated separately in

the cohorts from the eastern and western United States (400 patients in each) showing consistency of these results across the two distinct populations ⁽⁶¹⁾.

More recently, data from clinical trials of two different biologics for CRSwNP have been used for post-hoc analyses of the SNOT-22 subdomain structure in patients with CRSwNP. One study of pooled data from randomized controlled trials of dupilumab has proposed the possibility of CRSwNP-specific SNOT-22 subdomains related to nasal symptoms, craniofacial pain/pressure, sleep disturbance, emotional disturbance and functional

Individual symptom severity scores

Although individual CRS symptom severities have been measured as PROMs for many years^(2,80), there has been a recent renewed interest in individual symptom severity scores, in particular for CRSwNP, due to the use of these outcome measures in clinical trials of biologics for the treatment of CRSwNP^(9,86,87). While individual symptom severities have been traditionally used for cardinal symptoms of CRS (nasal obstruction, discharge, smell loss and facial pain)^(9,86,87), other symptoms of CRS such as headache and fatigue have also been measured in this way⁽⁸⁸⁾. The nasal congestion score (sometimes referred to as the nasal blockage score) is a particularly important individual symptom severity score as it is often used as a co-primary endpoint for registration trials of CRSwNP treatments⁽⁸⁹⁾. Previous study has shown that for individual symptom VAS scores, a score cut-off of >3.5 (out of 10) identifies when patients recognize the symptom to be burdensome or uncontrolled⁽⁹⁰⁾. In some studies, the sum of individual symptom severity scores is referred to as a total nasal symptom score or total symptom score^(91,92); this is not the same as the overall symptom severity score which is measured using one question.

A post-hoc analysis of PROM data from a subset of time points from the SYNAPSE trial has provided evidence for the psychometric performance of individual symptom VAS scores⁽⁶³⁾. Strong correlations between individual nasal symptom (nasal obstruction, nasal discharge, mucus in the throat, loss of sense of smell) and facial pain VAS scores and their corresponding SNOT-22 items were provided as evidence of construct validity. These VAS scores, considered together, also demonstrated good internal consistency (Cronbach's alpha >0.7) and test-retest reliability (intraclass correlation coefficient >0.9), although the latter was based on specific assumptions related to which patients to include in the reliability calculation. A post-hoc analysis of the SINUS-24 and SINUS-52 trials data, which collected individual symptom scores with an ordinal scale ranging from 0 to 3 (0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, and 3 = severe symptoms) reported that the MCIDs of the nasal congestion/obstruction score and loss of smell score were 1 point⁽⁹³⁾. However, these MCIDs were calculated based on reliance on change in other PROMs rather than a gold standard anchor.

Acute exacerbations of chronic rhinosinusitis

Previous studies have reported that the frequency of acute exacerbations of CRS (AECRS) may be a distinct outcome and driver of decreased QOL and morbidity in patients, independent of baseline CRS symptom severity^(94,95). At present, however, exact methods for identifying and quantifying AECRS have not yet been validated⁽⁹⁶⁾, in part because the historic definitions of AECRS have been vague, such as an "acute worsening of symptoms"^(1,29). In the past, AECRS have been studied using surrogate measures, such as frequency of patient-reported sinus

infections or frequency rescue medication usage^(95,97), which has also been validated as a reflection CRS burden on QOL⁽⁹⁸⁾. More recent qualitative studies of patients' experiences and perceptions of AECRS have led to a proposed definition of AECRS as "a flare up of symptoms beyond day-to-day variation, lasting at least 3 days, and to which a distinct negative impact on a patient's QOL or functionality can be attributed"^(99,100). This definition of AECRS has also been adopted in an EPOS2020/EUFOREA expert opinion on disease states in CRSwNP⁽¹⁰¹⁾. However, this definition has not yet been validated.

General health-related quality of life*Short-form (SF) instruments*

General-health related QOL is a measure of QOL and functional status that is comparable across different conditions and diseases^(102,103). The 36-item Short Form (SF-36) is the most commonly used instrument to measure general health-related QOL, has been translated into over 170 different languages and has been used to measure general health-related QOL in CRSwNP⁽¹⁰⁴⁻¹⁰⁶⁾. The SF-36 was developed for individuals aged 14 years or older to measure health status for the Medical Outcomes Study, which was a multi-year study of chronic diseases by the Rand Corporation^(104,105). It contains questions that survey 8 domains of health: 1) limitations in physical activities due to health problems, 2) limitations in social activities because of physical or emotional problems, 3) limitations in usual activities because of physical health problems, 4) bodily pain, 5) general mental health (psychological distress and well-being), 6) limitations in usual role activities because of emotional problems, 7) vitality (energy and fatigue), and 8) general health perceptions⁽¹⁰⁷⁾. These 8 health domains were chosen as the dimensions of health that are most commonly affected by disease and treatment and each represents a domain of the SF-36, amongst which 35 of the items of the SF-36 are divided (with the remaining item, "Compared to one year ago, how would you rate your health in general now?" not included in scoring). Half of SF-36 items measure these 8 health concepts in the present state while the other half assess them over the last 4 weeks. The score for each item of the SF-36 is transformed to a score on a scale of 0 to 100, with lower score indicating greater disability, for any subsequent score calculation. There is no "total" or "global" SF-36 score⁽¹⁰⁸⁾. Instead, item scores are used to calculate domain scores, which are equal to the mean score of the items that comprise them⁽¹⁰⁹⁾. Domain scores of the SF-36 are then used to calculate the Physical Component Summary (PCS) and Mental Component Summary (MCS) scores⁽¹¹⁰⁾, which have been shown to capture up 85% of the variance in the domain scores and allow the content of the 8 SF-36 domains to be reduced into two scores. The PCS and MCS were derived through principal component analysis of SF-36 domain scores, so the PCS and MCS are each calculated as a linear combination of the domain scores (with the domain scores each

normalized to scores of the general U.S. population)⁽¹¹⁰⁾. The PCS and MCS are calculated in a manner such that their scores in the general U.S. population have a mean of 50 and standard deviation of 10. The PCS and MCS scores have been shown to have high validity and reliability⁽¹¹⁰⁾. The MCIDs of the PCS and MCS scores has been reported to be different across a variety of conditions but never calculated directly for CRS⁽¹¹¹⁻¹¹⁴⁾. However, based on “effect size” assumptions with the known standard deviation of 10 for the PCS and MCS in the general U.S. population, the MCID for these two summary scores can also be considered as ranging from 2 – 5 (small to medium effect size).

Alternative versions of the SF-36 have subsequently been developed⁽¹⁰⁵⁾. The SF36v2 was derived as a refinement of the SF-36 to improve wording of certain items and response choices as well as to update normative data⁽¹¹⁵⁾. Like the SF-36, the SF-36v2 provides scores for each of the eight individual domains as well as PCS and MCS scores. In comparison to the SF-36, the SF36v2 is described by its vendor as having improved psychometric performance with greater precision as well as reduced floor and ceiling effects⁽¹¹⁵⁾. The SF-8 and SF-12 were derived to reduce the burden of response as shorter versions of the SF-36^(116,117). In comparison to the SF-36, the SF-8 and SF-12 assess the same 8 domains of general health but are faster to complete (1-2 minutes for SF-8 vs. 2-3 minutes for SF-12 vs. 5-6 minutes for SF-36, on average) and require less space in print⁽¹¹⁵⁾. The SF-8 and SF-12, however, provide only PCS and MCS scores but not scores for individual SF-36 domains and they have lower validity, reliability, and precision with decreasing number of included items compared to the SF-36. The SF-8 and SF-12 (and its subsequent revision, the SF-12v2) are frequently used when necessary to assess all domains of the SF-36 but with priority placed on speed and compactness.

In contrast to the preceding short-form questionnaires, the SF-6D (and more recently the SF-6Dv2) was developed as a means to calculate health utility value (HUV) for the calculation of quality adjusted life-years (QALYs), which are needed for cost effectiveness and health economics studies⁽¹¹⁸⁻¹²⁰⁾. The SF-6D assesses 6 dimensions using 11 items of the SF-36 (reflecting 7 of the domains of the SF-36) to provide a single index value (i.e., the HUV), which ranges from 0 (worst health state) to 1 (best health state). The MCID of the SF-6D HUV has been measured for a variety of conditions, although not for CRS, with one summary review reporting MCID estimates ranging from 0.010 to 0.066⁽¹²¹⁾. Previous studies have shown that the SF-6D HUV correlates with CRS-specific QOL measures⁽¹²²⁾ and is responsive to treatment of CRS^(123,124).

EuroQol instruments

Like the SF-6D, the EuroQol (EQ-5D) instrument was designed and reported in 1991 as an instrument capturing five dimensions of general health - mobility, self-care, ability to perform usu-

al activities, pain/discomfort and anxiety/depression - that could be used to measure HUV and therefore used for health economic analyses^(125,126). In the original design of the EQ-5D, each dimension was assessed by a single item that was measured on a 3-level scale (EQ-5D-3L). The EQ-5D-3L was subsequently revised so that each dimension was measured with 5 levels and the EQ-5D-5L was introduced in 2009^(125,127). Compared to the EQ-5D-3L, the EQ-5D-5L was shown to have greater increased feasibility, reliability, sensitivity to change in general health. The EQ-5D-3L and EQ-5D-5L also include a VAS that is used as a self-reported, unbiased global measure of health. Although the VAS is not used to measure HUV, the EQ-5D VAS has been shown to possibly reflect a broader underlying construct of general health compared to the EQ-5D HUV in CRS and other conditions since it likely reflects dimensions of health - such as sleep disturbance - that are not included in the calculation of EQ-5D HUV^(128,129). In the study of CRS, the EQ-5D-5L HUV and VAS have been shown to be correlated with CRS-specific QOL, with changes in EQ-5D-5L HUV and VAS also correlated with change in CRS-specific QOL⁽¹³⁰⁻¹³²⁾. The MCID of the EQ-5D-5L HUV in CRS has been reported to be 0.04 and the MCID of EQ-5D VAS in CRS reported to be 8⁽¹³²⁾.

Comparison of the EQ-5D and SF-6D has shown that these measures have moderate agreement but with the EQ-5D having more ceiling effects and the SF-6D having more floor effects^(133,134). For the same condition, the SF-6D has generally been shown to report lower HUV compared to the EQ-5D⁽¹³⁴⁻¹³⁶⁾. Therefore, when there is a need to measure HUV, the psychometric performance of these instruments and specific needs of the investigation should inform choice of utilizing the SF-6D vs. EQ-5D.

Need for treatment as an outcome measure

The need for systemic, rescue or advanced treatments have been previously considered as outcome measures for CRS. For example, the need for systemic antibiotics or systemic corticosteroids is frequently used to indicate poorly controlled disease, including by the EPOS guidelines⁽¹³⁷⁻¹³⁹⁾, and therefore as a component of CRS disease control assessment⁽¹⁴⁰⁾. Importantly, the number of courses of CRS-related systemic antibiotics and corticosteroids needed in the past 3 or 12 months have been shown to be correlated with QOL⁽⁹⁷⁾ and validated as metrics of CRS disease burden⁽⁹⁸⁾. Courses of CRS-related systemic antibiotics and corticosteroids have been used as outcomes in clinical studies of both medical⁽¹⁴¹⁾ and surgical treatment of CRS^(142,143), including in recent clinical trials of biologics for CRSwNP^(10,56,58,144,145).

The need for more advanced treatments of CRS may also be used as an outcome measure indicative of current treatment failure or uncontrolled disease. Although biologics have been approved as an add-on treatment of CRSwNP, their recommen-

ation for use in severe and uncontrolled CRS is an indication of an unsuccessful outcome for the preceding treatment regimen⁽¹⁴⁶⁾. The need for ESS, by guideline recommendations, is well-recognized to reflect a poor or unsuccessful outcome for the preceding medical treatment regimen^(1,29). Unsurprisingly, the need for ESS been used as an outcome measure reflecting poor control for CRS⁽¹⁴⁷⁾ and as an endpoint indicative of treatment failure in clinical trials for medical treatments of CRSwNP^(10,56,145,148). Moreover, having revision ESS within 3 years of the last surgery is predictive of needing additional surgery in the future⁽¹⁴⁹⁾.

However, it should be noted that the need for - or provision of - a specific treatment may be biased by the healthcare provider's preferences and attitude towards that treatment⁽¹⁵⁰⁾. Patients' own preferences may also influence whether they undergo ESS or accept treatment with systemic rescue medications (e.g. corticosteroids) or biologics⁽¹⁵¹⁾.

Lower airway (asthma) outcomes

The Asthma Control Test (ACT), Asthma Control Questionnaire (ACQ), and Asthma Quality of Life Questionnaire (AQLQ) are integral PROMs offering insights into therapeutic effectiveness and patient experience of asthma⁽¹⁵²⁻¹⁵⁴⁾. The ACT, ACQ and AQLQ have been identified as important outcome measures for asthma⁽¹⁵⁵⁾.

Asthma control test (ACT)

The ACT, which was developed to serve as a questionnaire used by both healthcare professionals and patients to assess asthma control, consists of five simple questions that assess different domains of asthma control (activity impairment, shortness of breath, sleep disturbance, rescue inhaler usage and overall disease control). Each ACT item is scored on a 5-point Likert scale ranging from 1 (denoting poor control) to 5 (denoting optimal control) and the total ACT score ranges from 5 to 25, with an MCID of 3 points⁽¹⁵⁶⁾. An ACT score of ≤ 19 defines inadequately controlled asthma and therefore indicates necessity for reconsideration of the treatment regimen⁽¹⁵³⁾. The ACT was originally developed in English but it has been subsequently translated into at least 29 languages. The ACT has been widely used in various research studies and clinical settings, including as an outcome measure to assess the efficacy of a combination therapy for asthma⁽¹⁵⁷⁾ and the patients' perception of asthma control and attitudes toward treatment⁽¹⁵⁸⁾. Validation of the ACT in adult asthmatics has demonstrated it to be a valid reflection of asthma control through correlations with pulmonary function and symptom scores, as well as physician-rated control^(153,154). Validation of the ACT has also demonstrated it to have good internal consistency and test-retest reliability⁽¹⁵³⁾. The ACT has similarly been validated in the pediatric population as well⁽¹⁵⁹⁾. The ACT has been shown to have excellent responsive-

ness, with high sensitivity to changes in overall asthma control⁽¹⁶⁰⁾. Another study analyzing data from multiple clinical trials concluded that the ACT was responsive to changes in asthma control across different age groups and cultural backgrounds⁽¹⁶¹⁾. The ACT has been used in multiple studies to investigate the impact of CRS on asthma, with studies generally demonstrating that worse CRS disease severity or poor CRS control is a driver of uncontrolled asthma⁽¹⁶²⁻¹⁶⁵⁾.

Asthma control questionnaire (ACQ)

The ACQ was developed in 1999 by Juniper and colleagues as a short and easy-to-use questionnaire to assess asthma control⁽¹⁶⁶⁾. The ACQ consists of 7 items, of which 5 reflect the burden of symptoms (night-time awakening, limitation of normal daily activities, awakening in the morning with symptoms, dyspnea and wheezing), 1 reflects short-acting bronchodilator usage and 1 reflects airway caliber (prebronchodilator forced expiratory volume in one second [FEV1] percent predicted from pulmonary function testing), each of which are assessed on a 7-point Likert scale (item scores ranging from 0 to 6) and with a recall period of 1 week. These specific 7 items were chosen from surveying 100 asthma clinicians representing 18 countries for their opinions about the most important criteria in the domain of asthma symptoms and the most important criterion to assess airway caliber. The ACQ score is calculated as the mean of all item scores and therefore ranges from 0 (well controlled) to 6 (extremely poorly controlled). The ACQ has been shown to be correlated with measures of general health-related QOL (SF-36), asthma-specific QOL (AQLQ), pulmonary function testing^(166,167), and generally serve as a valid, reliable and responsive endpoint in clinical trials⁽¹⁶⁸⁾. The ACQ has also been shortened to include just the items reflecting asthma symptoms (ACQ-5) or the items reflecting asthma symptoms and bronchodilator use (ACQ-6)⁽¹⁶⁹⁾, with all versions having excellent psychometric performance and all versions having an MCID of 0.5.

Asthma Quality of Life Questionnaire (AQLQ)

The AQLQ is a 32-item questionnaire that quantifies the multifarious impact of asthma on patients' QOL^(152,170). It was developed in the late 1980s by Juniper and colleagues at McMaster University in Canada. The development team aimed to create a comprehensive questionnaire that could capture the multidimensional impact of asthma on a person's QOL across the domains of health (asthma symptoms), emotion, environment, and activity. Each item is scored on a 7-point Likert scale ranging from 1 (maximal impairment) to 7 (no impairment) and the AQLQ score is calculated as the mean score of all items, with the MCID previously calculated to be 0.5⁽¹⁷¹⁾. Although the AQLQ was originally developed in English and validated in English-speaking populations, it has been translated into at least 89 languages and has been extensively used in various research

Table 2. Score interpretation of the Lund-Kennedy endoscopic scoring system (LKS) to be documented on each side separately ⁽²⁾.

LKS	0	1	2
Polyps*	Absence	Polyps in middle meatus only	Polyps beyond middle meatus
Oedema*	Absent	Mild	Severe
Discharge*	No discharge	Clear, thin discharge	Thick, purulent discharge
Scarring	Absent	Mild	Severe
Crusting	Absent	Mild	Severe

*These items are retained in the modified Lund-Kennedy staging system ⁽¹⁸⁵⁾.

studies and clinical trials to measure the asthma-specific QOL in adults and the pediatric population ^(152,172,173). The AQLQ has undergone extensive validation studies to assess its reliability, validity, and responsiveness as a reflection of asthma-specific QOL in both adults and children ^(152,172). The AQLQ has also been used in many studies to measure asthma-specific QOL in CRS patients. For example, comorbid CRS have been shown to be associated with worse asthma-specific QOL in asthmatic patients ⁽¹⁷⁴⁾. Multiple studies have also used the AQLQ to show that both biologics and ESS in asthmatic patients with medically recalcitrant CRSwNP can improve asthma-specific QOL ⁽¹⁷⁵⁻¹⁷⁸⁾.

Objective outcome measures and psychophysical testing

Endoscopic scoring of chronic rhinosinusitis with nasal polyps

Sinonasal endoscopy is an essential in-office tool used by otolaryngologists for managing patients with rhinological diseases ^(1,179). With the advent of high-definition cameras, screens, and endoscopes, physicians can easily diagnose and follow patients with CRS with an accuracy comparable to that of computed tomography (CT) ⁽¹⁸⁰⁾. Compared with PROMs, sinonasal endoscopy documents different aspects of the extent of CRS disease and is recommended for use in routine clinical practice and research ⁽¹⁸¹⁾. Several sinonasal endoscopic scoring systems have been proposed to objectively quantify and standardise the appearance of the sinonasal cavity, particularly after sinus surgery. The most widely used endoscopic scoring systems in CRS literature are outlined below.

Lund-Kennedy Score (LKS)

In 1993, Lund and Kennedy led a group discussing CRS terminology, staging and therapy at the International Conference on Sinus Disease. The group outlined and developed multiple staging systems for symptoms, endoscopic appearance, radiological findings, and surgical extent scoring, all of which were described in a later publication ⁽²⁾. The recommended endoscopic staging system (known now as the Lund-Kennedy endoscopy score [LKS], which has been recommended as a core outcome

measure for CRS ⁽³⁰⁾) quantifies five elements - polyps, oedema, discharge, scarring/adhesions, and crusting - on a 0- to 2-point scale on each side (Table 2) ⁽²⁾. The LKS was developed specifically to assess clinical outcomes after ESS. After ESS, patients with CRSwNP who achieved near-perfect endoscopy (LKS of 0-2) had similar SNOT-22 total and subdomain scores at 6 months post-operatively as compared to healthy controls ⁽¹⁸²⁾. Moreover, oral corticosteroid use in patients with CRSwNP also decreased with improved postoperative LKS. However, no significant association was found between LKS and missed productivity in the patients ⁽¹⁸²⁾. In fact, one limitation of the LKS is that it does not correlate with many CRS outcome measures, most prominently with PROMs and QOL, with which it has poor correlation ⁽¹⁸³⁻¹⁸⁶⁾. Another limitation of the LKS is that it was developed specifically for endoscopic staging of patients who have undergone ESS so it cannot be used to compare endoscopic staging between patients with previous ESS and non-operated patients. To simplify the LKS, improve its consistency and reliability, as well as applicability to both patients with prior ESS as well as non-operated patients, Psaltis et al. proposed a modification to remove the scarring and crusting components from the scoring system ⁽¹⁸⁵⁾. The modified LKS (mLK) demonstrates higher inter-rater (intraclass correlation coefficient [ICC] = 0.663) and test-retest reliabilities (ICC = 0.881) than other endoscopic scoring systems ^(185,187). While the mLK did not correlate with the SNOT-22 score, it did have a weak to moderate correlation with sinonasal symptom severities in both patients with and without a history of ESS ⁽¹⁸⁵⁾. The discriminant validity of the mLK has been demonstrated through significant difference in the mean mLK scores between the symptomatic and symptomless sides of 32 patients with unilateral CRS ⁽¹⁸⁷⁾. Although correlating with PROMs to a greater extent than the LKS, the major limitation of the mLK is that it still generally does not correlate well with PROMs and QOL metrics ^(185,187).

Olfactory Cleft Endoscopy Scale (OCES)

While the LKS focuses primarily on the middle meatus, the olfactory cleft endoscopy scale (OCES) was proposed to separately grade the olfactory cleft using the LKS system elements (polyps,

Table 3. The Nasal Polyp Score (NPS): the total NPS is sum of scores from both sides.

Nasal Polyp Score*		Notes**
0	No nasal polyps	
1	Small nasal polyps in the middle meatus not reaching below the inferior border of the middle turbinate	
2	Nasal polyps reaching below the lower border of the middle turbinate	To accommodate patients with resected middle turbinates, the nasal polyp must reach the top of the inferior turbinate to be scored as a 2
3	Large nasal polyps reaching the lower border of the inferior turbinate or nasal polyps medial to the middle turbinate	If medial to the middle turbinate, the polyp must reach the lower border of the middle turbinate (or top of inferior turbinate if the middle turbinate is absent)
4	Large nasal polyps causing complete obstruction of the inferior nasal cavity	Large nasal polyps touching the floor of the nose

*Original NPS described by Gevaert et al. ⁽¹⁹³⁾. **Modifications proposed by European Academy of Allergy and Clinical Immunology taskforce ⁽¹⁹²⁾.

oedema, discharge, scarring, and crusting on a 0–2-point basis) ⁽¹⁸⁸⁾. In postoperative CRSwNP cases, the OCES demonstrated stronger correlation with the total Sniffin' Stick score ($r = -0.482$, $p < 0.001$) and Questionnaire of Olfactory Dysfunction-Negative Statement total score ($r = 0.401$, $p = 0.001$), which is a reflection of olfaction-specific QOL, compared to the correlation of these outcome measures with the LKS ($r = -0.368$, $p = 0.003$ and $r = 0.305$, $p = 0.010$ respectively) ⁽¹⁸⁹⁾. As an olfactory-specific endoscopic measure, the OCES may complement olfactory testing in patients with chemosensory dysfunction ^(189,190). However, as the OCES uses the same criteria as the LKS, it is seemingly limited in the same way as the LKS to patients who have had ESS.

Nasal Polyp Score (NPS)

Since the early 1990s, the volume and extent of nasal polyps have been graded using various scoring systems that use the lower edges of the middle and inferior turbinates as vertical landmarks. Although the various nasal polyp scoring systems have been comprehensively reviewed and compared previously ⁽¹⁹¹⁾, it is worth noting that all nasal polyp scoring systems have certain limitations. Most prominently, the nonlinear and ordinal nature of these systems creates an inherent lack of detection of minor changes in nasal polyp size ^(191,192). This is most clearly noticeable in the LKS where polyps beyond the middle meatus (e.g. extending to top of the inferior turbinate or completely filling the nasal passage) are grouped into a single category and scored the same ⁽²⁾.

In the last decade, following advances in the medical management of CRSwNP, grading the response to treatment in both clinical practice and research has become the standard of care ⁽¹⁾. Endoscopic nasal polyp scoring has served as a simple co-primary endpoint in several trials assessing the effectiveness of biologics in patients with CRSwNP. In 2006, Gevaert et al. introduced the NPS (Table 3) as an outcome measure in a randomised controlled trial to study the efficacy of reslizumab in CRSwNP ⁽¹⁹³⁾. The NPS is currently the most used scoring system

for nasal polyp size and ranges from 0 to 4 points on each side. The NPS has been used in several recent phase II and III trials of biologics for CRSwNP ⁽⁹⁾. The NPS has shown high intra-rater reliability (ICC = 0.88) and moderate to substantial inter-rater reliability (kappa value of 0.61 and 0.59 in POLYP 1 and POLYP 2 trials, respectively) ^(5,18). Recently, the NPS was endorsed by a task force from the European Academy of Allergy and Clinical Immunology, and minor modifications, such as instructions on how to accommodate patients with resected middle turbinates, were suggested (Table 3) ⁽¹⁹²⁾.

A recent systematic review has demonstrated that changes in NPS did not correlate with any CRS PROM (such as the SNOT-22) or olfactory measure, which is a limitation like the LKS ^(194,195). However, analysis of pooled data from the LIBERTY NP SINUS-24 and SINUS-52 trials ⁽⁵⁶⁾ has shown a moderate correlation between changes in the SNOT-22 rhinologic symptoms and the changes in the total NPS ($r = 0.51$), reflecting responsiveness of the NPS to nasal symptoms of CRS ⁽⁹³⁾. Another study has shown that greater nasal polyp burden (using a scale closely related to the NPS) is also predictive of greater improvement in olfaction after ESS for CRSwNP ⁽¹⁹⁶⁾. The MCID of the NPS has been previously proposed to be 1-point but was not determined based on best-practices for MCID calculation, because this MCID was calculated based on correlation with change in SNOT-22 (total and rhinologic domain) score rather than a gold-standard ⁽⁹³⁾.

Radiographic staging

Role of computed tomography (CT) imaging

Imaging with CT is considered the gold standard for radiographic evaluation of CRS ⁽¹⁹⁷⁾. It is an objective marker for assessing the presence, severity, localization, and patterns of sinus disease, including CRSwNP ⁽¹⁹⁸⁾. These findings may influence both medical and surgical management, as well as prognosticate outcomes. Commonly used outcome measures for CRSwNP that are assessed radiographically include the Lund-Mackay Score (LMS) and olfactory cleft opacification.

Lund-Mackay Score (LMS)

Although used in various forms initially, the Lund-Mackay staging system as it is now used was formalized during an international multidisciplinary consensus meeting on rhinosinusitis in 1993, during which symptom, radiographic, and endoscopic staging/scoring systems were developed⁽²⁾. The radiographic Lund-Mackay staging system was subsequently first reported in the literature by Lund and Mackay in 1993⁽¹⁹⁹⁾. Although subsequent modifications of the Lund-Mackay staging system including finer gradations in scoring of sinus opacification even to the extent of measuring individual millimeters of thickness of mucosal thickening have been reported^(200,201), the LMS is the most commonly used CT staging system owing to its simplicity and high inter-rater and intra-rater agreement⁽²⁰²⁾.

The LMS is calculated based on scoring for each sinus that depends on the degree of its opacification (0 = none, 1 = partial, and 2 = complete). The ostiomeatal complex, as the sixth component of the score, is scored as either 0 or 2 depending on whether it was patent or obstructed. LMS therefore generates a total score that ranges from 0 to 24 (0 to 12 for each side), with higher scores indicative of greater radiographic disease burden. Previous studies have shown that asymptomatic adult individuals may be incidentally found to have an LMS of up to 3 or 4^(201,203,204), while asymptomatic children may be incidentally found to have an LMS of under 3⁽²⁰⁵⁾. In addition to serving as an objective metric of disease burden, the LMS is also predictive of the need for more extensive ESS, higher surgical complication rates and higher rates of needing revision surgery^(206,207). Although LMS has been shown to not predict post-operative symptom improvement in at least one study⁽²⁰⁸⁾, several other studies have indicated that higher LMS before ESS may be a predictor of greater improvement in symptoms after surgery, even at up to 5 years^(206,209,210).

The LMS has several limitations, including its application to patients who have aplastic/non-existent sinuses (e.g. frontal sinus aplasia) or have had surgery that eliminates bilaterality (e.g. frontal sinus drill-out), in which cases the LMS may not tally up to a maximum of 24 and therefore not be comparable to LMS of standard patients. The LMS also correlates poorly or not at all with PROMs and the severity of symptoms that patients feel⁽²¹¹⁻²¹⁴⁾.

Olfactory cleft opacification

Although hyposmia affects up to 80% of CRS patients⁽²¹⁵⁾, LMS does not consider the olfactory cleft (OC) as a discrete anatomical subsite. Volumetric analysis of the OC on sinus CT scans of CRS patients has found that the degree of OC opacification is correlated with olfaction as measured with psychophysical testing⁽²¹⁶⁾. However, a meta-analysis of 37 studies suggested that this correlation mainly applies to the CRSwNP patient population⁽²¹¹⁾.

Completeness of endoscopic sinus surgery

The Amsterdam Classification of Completeness of Endoscopic Sinus Surgery (ACCESS) is a standardized radiographic scoring system that can be used to assess the completeness of ESS based on bony boundaries⁽²¹⁷⁾. The ACCESS score is calculated like the LMS on a scale of 0, 1 or 2 for each of the ostiomeatal complex, and frontal, anterior ethmoid, posterior ethmoid, sphenoid and maxillary sinuses, where 0 indicates the sinus/site is functionally opened (no further surgery is warranted), 1 indicates that the sinus was operated on previously but inadequately opened, and 2 indicates that the sinus/site has not been operated on. The ostiomeatal complex can only be graded as a 0 or 2. Thus the ACCESS score ranges from 0 to 24, with higher scores indicative of less complete previous ESS. ACCESS has been shown to have excellent inter-rater reliability (intraclass correlation coefficient >0.950) for all degrees of sinus opacification and for all forms of CRS, including CRSwNP⁽²¹⁷⁾.

Olfactory testing

Olfaction is an important area of clinical and research focus⁽²¹⁸⁻²²¹⁾, and a recently reported COMET (Core Outcome Measures in Effectiveness Trials) initiative has included psychophysical testing of olfaction in their proposed core outcome measures for clinical trials in olfactory disorders⁽²²²⁾. Olfactory function includes three domains: identification (the ability to accurately identify an odor), threshold (the minimum concentration of an odorant required to accurately identify an odor), and discrimination (the ability to identify the difference between two odors). In addition to PROMs, culturally validated psychophysical testing can provide additional complementary information in the evaluation of olfactory impairment, especially since patients may underestimate their degree of olfactory impairment⁽²²³⁻²²⁵⁾. Although many psychophysical tests of olfaction have been developed and validated worldwide, the most frequently used are the University of Pennsylvania Smell Identification Test (UPSIT)⁽²²⁶⁾, the Connecticut Chemosensory Clinical Research Center (CCCRC) test^(227,228), and the Sniffin' Sticks^(229,230). A systematic review of olfactory dysfunction in patients with CRS found the UPSIT, CCCRC test and Sniffin' Sticks are all commonly used psychophysical tests⁽²¹⁵⁾, with each test shown to correlate with the others⁽²³⁰⁻²³³⁾. Each test has distinct advantages and disadvantages (Table 4), and the decision to use one test or the other in clinical practice and/or research should consider price, availability, cultural aspects, time to perform the test, use of an examiner, and the domains of olfaction desired to be tested. In the consideration of when to perform these tests during a patient evaluation, it should also be noted that topical anesthetics associated with nasal endoscopy that may affect psychophysical testing results⁽²³⁴⁾.

Table 4. Comparison between olfactory tests.

Test	Threshold	Identification	Discrimination	Need for Examiner	Duration
UPSIT	No	Yes	No	No	10-15 min ⁽²³⁵⁾
CCCRC	Yes	Yes	No	Yes	15-30 min ^(231,246)
Sniffin' Sticks	Yes	Yes	Yes	Yes	10-60 min ^(230,235)

Abbreviations: UPSIT – University of Pennsylvania Smell Identification Test; CCCRC – Connecticut Chemosensory Clinical Research Center.

The University of Pennsylvania Smell Identification Test (UPSIT)

The North American version of the UPSIT ⁽²²⁶⁾ (UPSIT-NA) is one of the most widely used olfactory tests but only tests the identification domain of olfaction - not threshold or discrimination domains. It has undergone at least 10 different cross-cultural adaptations (e.g. British English, Dutch, French, Italian, German, Japanese, Korean, Portuguese, and Spanish). In the course of cross-cultural adaptation, some UPSIT items or response alternatives have been modified from the UPSIT-NA to account for cultural differences ⁽²³⁵⁾. Most recently, the UPSIT has been used in many clinical trials, including phase-3 studies of biologics for the treatment of CRSwNP ^(56,178). The popularity of the UPSIT reflects, in large part, its high internal consistency ⁽²³⁶⁾, high test-retest reliability ($r=0.94$) ⁽²³⁷⁾ and practicality, since it can be performed by the patients themselves or with the help of an examiner, and usually takes between 10 and 15 minutes ⁽²³⁵⁾.

The UPSIT must be purchased commercially and is composed of four cards of ten pages each. Each page of the UPSIT contains an odor that is released by scraping a brown strip at the bottom of the page, and the patient is instructed to identify the odor using a 4-option multiple choice response. The patient must answer what each odor is; if they cannot smell anything or cannot tell, they must at least randomly guess. The UPSIT score is calculated as the number of odors that the patient guesses correctly and therefore ranges from 0 to 40. Interestingly, the UPSIT score has been previously found to correlate with patient-reported smell loss either weakly ⁽²³⁸⁾ or not at all ⁽²³⁹⁾.

Olfactory function is classified based on the UPSIT score as normosmia, hyposmia - which can also be classified as mild, moderate or severe - and anosmia most accurately in an age-dependent manner ⁽²⁴⁰⁾. However, in a general manner, olfactory function can also be classified based on the UPSIT score as normosmia (34 – 40), hyposmia (20 – 33) or anosmia (6 – 19) ⁽²³⁵⁾. Age-based norms have been reported, which more specifically classify olfactory function based on UPSIT score and depending on the patient's age. A score of 5 or below indicates possible malingering or simulation of olfactory loss for personal benefit, for example, in labour lawsuits ⁽²³⁵⁾. In the longitudinal assessment of olfaction, the MCID of the UPSIT has previously been reported to be 4 points ⁽²⁴¹⁾, although it is unclear how exactly this was calculated.

An abbreviated 12-item version of the UPSIT has also been developed, referred to as the Brief Smell Identification Test (B-SIT), in which a score of ≤ 8 is considered to reflect abnormal/decreased sense of smell ⁽²⁴²⁾. In one study of CRS patients, the B-SIT score has been shown to be strongly correlated with UPSIT score ($r=0.893$) ⁽²⁴³⁾. However, the B-SIT was found to underestimate the prevalence of decreased sense of smell compared to the UPSIT ⁽²⁴³⁾. The MCID of the B-SIT in surgically managed CRS patients has also been reported to be 1 point ⁽²⁴⁴⁾, although this MCID value was determined using a smell PROM in the anchor-based calculation, inconsistent with best practice for MCID calculation ⁽²⁴⁵⁾.

The Connecticut Chemosensory Clinical Research Center (CCCRC) test

The CCCRC test assesses the threshold and odor identification domains of olfaction ^(227,228). This test independently examines each nasal cavity and therefore can discriminate the laterality of olfactory loss. During the threshold testing portion, at least 7 concentrations of n-butyl alcohol are used - with the highest concentration a 4% solution and subsequent 3-fold dilutions. Starting with the lowest concentration, the patient is asked to occlude one nostril, presented with the butanol as well as an odorless bottle containing distilled water, and then asked to choose the which bottle contains the butanol. If the patient chooses incorrectly, the next highest concentration of butanol is used. If the patient chooses correctly, the test is repeated for that same concentration 3 more times; after 4 correct choices in a row, the testing is stopped for that nostril. The threshold test is scored separately for each nostril on a scale of 0 – 7, with a score of 0 assigned for inability to smell the highest concentration of the butanol and 7 assigned for detecting the 7th (or greater) dilution of the butanol. For the identification portion of the test, 7 odors (along with 3 trigeminal stimuli - such as ammonia, menthol or wintergreen - which are not scored as part of the identification test) are presented individually to the patient, one nostril at a time, and the patient asked to identify the odor from a list of 20 possible options (10 of which represent the 7 odors and 3 trigeminal stimuli, and 10 which present “distractors” [some of which are chosen to represent common sensations in dysosmia]). The identification test is scored separately for each

nostril on a scale of 0 – 7 to reflect the number of odors that the patient identified correctly. A composite score, ranging from 0 – 7, for the CCCRC is calculated as the mean score of the threshold and identification tests from each nostril (i.e., the mean of 4 tests).

Olfactory function is classified based on the composite CCCRC score⁽²²⁸⁾. Normosmia is classified by a score of ≥ 6 , mild hyposmia by a score ≥ 5 but < 6 , moderate hyposmia by a score of ≥ 4 but < 5 , severe hyposmia by a score of ≥ 2 but < 4 and anosmia by a score of < 2 ⁽²²⁸⁾. For persons over the age of 65 years, this classification scheme is changed by decreasing the lower ends of normosmia, mild hyposmia, and moderate hyposmia by one point⁽²²⁸⁾.

The CCCRC test has excellent discriminant validity with approximately 90% of healthy control patients having a composite score of 6 or greater and 90% of patients with olfactory impairment having a composite score of less than 6⁽²²⁸⁾. However, the CCCRC has been found to have variable test-retest reliability, from low ($r=0.36$ for the threshold and $r=0.60$ for the identification components)⁽²³⁰⁾ to moderate (for the overall composite score)⁽²⁴⁶⁾.

To date, no MCID has been reported for the CCCRC.

Variations may be introduced into the CCCRC to suit specific diagnostic and investigative needs. For example, the inclusion and substitutions of specific odors in the identification test can be made for cultural adaptation⁽²⁴⁶⁾. The number of serial dilutions in the threshold test may also be increased beyond 7 to test supra-normal threshold ability, although the detection of odors in dilutions greater than the seventh are still scored as 7^(227,228).

The number of consecutive correct answers on the threshold test may also be varied to minimize type 1 error (for example, 4 consecutive correct answers with $p=0.0625$ vs. 5 consecutive correct answers with $p=0.0313$). One significant advantage of the CCCRC test is its low cost. The CCCRC test can be homemade using ingredients readily available at many grocery stores. However, the CCCRC test is limited by its time requirement (mean time for completion is 30 minutes) and the necessity for an examiner^(231,246).

Sniffin' Sticks

The Sniffin' Sticks test assesses all 3 domains of olfaction: threshold, discrimination, and identification and can be performed in between 10 to 60 minutes^(230,235). The test requires an examiner and the total score, also referred to as the TDI score, has a maximum score of 48 points (16 points for each domain). The Sniffin' Sticks test kit, which must be bought commercially, consists of felt-tipped pens that release odors when the pen caps are removed and the logistical application of the test has been previously described⁽²⁴⁷⁾. Odor threshold is measured by presenting up to 16 increasing concentrations of n-butanol to the patient. Once an approximate threshold is identified, multiple rounds of presenting higher and lower concentrations of n-butanol are

performed in order to more clearly define where on the ladder of 16 n-butanol dilutions that the patient's threshold falls, which is reflected by the threshold score that falls in the range of 0 to 16 (with 0 indicating that the patient was unable to detect the highest concentration of n-butanol and 16 indicating that the patient was able to detect the lowest concentration of n-butanol)⁽²⁴⁷⁾. Odor discrimination is measured with 16 tests where for each test, the patient is presented with 3 pens - two of which have the same odor - and the patient must identify the pen with the unique odor. If the patient cannot distinguish, they must guess. The discrimination score is calculated as the number of these individual tests that the patient performs correctly and therefore ranges from 0 – 16. The odor identification test is performed by presenting the patient with 16 common odorants. For each odor, the patient must guess the identity from a multiple choice of four items given verbally. Olfactory function is classified based on the TDI score as normosmia (>30), hyposmia (15 – 30), anosmia (<15).

Beyond its correlation with other psychophysical tests, the validity of the Sniffin' Sticks has been demonstrated by correlation between the TDI and various measures of patient-reported olfactory dysfunction⁽²⁴⁸⁻²⁵⁰⁾. The test-retest reliability of the Sniffin' Sticks is moderate ($r=0.73$ for identification, $r=0.54$ for discrimination, $r=0.61$ for threshold and $r=0.72$ for the composite TDI)⁽²³⁰⁾. The MCID of the TDI has previously been reported to be 5.5⁽²⁵¹⁾. The MCID for the threshold identification (T) has been reported to be 2.5, 3 for the odor discrimination (D), and 3 for odor identification (I)⁽²⁵¹⁾.

Nasal airflow and respiratory function tests

Peak nasal inspiratory flow (PNIF)

The development of peak nasal inspiratory flow (PNIF) can be traced back to 1959 when Wright and McKerrow introduced a spirometer to measure lung capacity through forced expiration⁽²⁵²⁾. In 1973, Taylor and colleagues substituted the mouthpiece of the Wright peak expiratory flow meter with a mask to measure expiratory nasal airflow⁽²⁵³⁾. In 1980, Youlten modified the Wright flowmeter to measure inspired nasal airflow⁽²⁵⁴⁾. PNIF was felt to be advantageous over the nasal expiratory method because it does not risk expelling nasal secretions onto a mask⁽²⁵⁵⁾. PNIF is performed using the Youlten peak flow meter, which is commercially available worldwide. PNIF is determined by first asking the patient to perform a full expiration, after which the face mask of the Youlten peak flow meter is applied with an airtight seal (without occluding the nose) and the patient is asked to maximally sniff through both nostrils with the mouth closed. This procedure is repeated at least three times, and the highest value is recorded. Several clinical trials for treatment of CRSwNP have used PNIF as a secondary outcome measure for the efficacy of oral⁽²⁵⁶⁾ or intranasal steroids⁽²⁵⁷⁻²⁶⁶⁾, macrolides⁽²⁶⁷⁾, and biologics^(268,269), as well as therapies for nasal polyps in

aspirin-exacerbated respiratory disease^(270,271) and for improvements after functional ESS⁽²⁷²⁾.

There is much interest in determining a single PNIF cutoff value to identify patients with or without nasal obstruction. A cutoff value of 120 L/minute was previously reported to have 66% sensitivity and 80% specificity to identify patients with symptomatic nasal obstruction⁽²⁷³⁾. However, this cutoff may fail to detect more than a quarter of the patients with nasal obstruction⁽²⁷³⁾. In a systematic review, a pooled analysis reported that patients with normal nasal breathing had a mean PNIF value of 138 (95% CI 127.9-148.8) L/min while patients with nasal obstruction had a mean PNIF of 97.5 (95% CI 86.1-108.8) L/min. The authors recommend that a clinician can confidently classify patients as having normal nasal breathing if the PNIF value is 140 L/min or more and nasal obstruction if the PNIF value is 90 L/min or less⁽²⁷⁴⁾.

PNIF may be useful for differentiating CRS with or without nasal polyps; however, this may only be applicable to large or obstructing polyps, as smaller non-obstructing polyps may not cause significant nasal obstruction. Furthermore, other factors associated with nasal obstruction, such as mucosal oedema, inferior turbinate hypertrophy, or anatomical abnormalities, may be present in both phenotypes. This is evident in prior conflicting findings where CRSwNP was found to have worse⁽²⁷⁵⁾, similar^(276,277) or even better⁽²⁷⁸⁾ PNIF measurements compared to CRSsNP.

The validity of PNIF has been demonstrated through its correlation with both subjective and objective measures of nasal obstruction. For example, PNIF is associated with the subjective sense of nasal patency in the general population⁽²⁷⁹⁾. A moderate correlation between PNIF and VAS scores for nasal obstruction has also been reported among patients with CRSwNP ($r=-0.48$, $p<0.01$)⁽²⁴⁸⁾, with a weak inverse correlation between PNIF and the SNOT-22 blockage score ($r=-0.40$, $p<0.01$)⁽²⁴⁸⁾ and total score ($r=0.4$, $p<0.05$)⁽²⁸⁰⁾. The validity of PNIF has further been shown by demonstrating correlation between it and other objective measures of nasal obstruction (such as acoustic rhinometry and rhinomanometry)^(269,275). PNIF has been found to inversely correlate with polyp size ($r=-0.29$, $p=0.02$) and nasal resistance measured by 4 phase rhinomanometry^(248,280). PNIF has also correlated well with the nasal cavity volume on acoustic rhinometry ($r=0.61$, $p<0.01$)⁽²⁸⁰⁾. The responsiveness of PNIF has been demonstrated in clinical trials in which PNIF values were found to improve continuously with the duration of treatment in correlation with the subjective improvement in nasal blockage^(258,269) or improvement in polyp size^(256,259,264,269). Because PNIF is effort dependent, concerns have been raised regarding its repeatability but with practice and repeated measurements, the coefficient of variation is reported to be only 15%⁽²⁸¹⁾.

The MCID of PNIF has been previously reported to be 20 L/min⁽²⁸²⁾ and in clinical trials of CRSwNP treatment showing signifi-

cant changes in PNIF, the absolute value of PNIF improved by >20 L/min^(259,260,262). Beyond using the absolute value of PNIF improvement, the percentage of improvement from baseline measurement is also accepted. An increase of 20% or more in PNIF has been found to be 75% sensitive and 64% specific to detect clinically improved nasal obstruction after decongestion⁽²⁸³⁾. This is also the minimum accepted percentage decrease in PNIF to indicate a positive nasal allergen challenge⁽²⁸⁴⁾.

Unilateral PNIF has also been described as a technique for measuring unilateral nasal patency, which may be especially important for anatomic sources of obstruction that typically have one-sided affect such as nasal septal deviation⁽²⁸⁵⁾. While unilateral PNIF has not been as extensively studied as the conventional (bilateral) PNIF, normative values for unilateral PNIF in adult males and females have been reported⁽²⁸⁵⁾. Moreover, unilateral PNIF has been shown to be correlated with the corresponding unilateral rhinomanometry⁽²⁸⁶⁾ as well as with patient-reported nasal obstruction⁽²⁸⁷⁾. However, an MCID value has not yet been determined for unilateral PNIF.

General limitations of PNIF include that it may detect physical obstruction due to a myriad of etiologies - not just polyps but also nasal valve collapse, septal deviation, hypertrophied inferior turbinates, or excessive secretions - and all of these factors must be considered in interpreting the results⁽²⁸⁸⁾. PNIF is also affected by ventilatory function, and concomitant measurement of the oral peak expiratory flow rate (PEFR) is therefore suggested⁽²⁸⁸⁾. Physiological variations should be considered, as PNIF measurements also decrease with age, increase with height, and are lower in females^(255,289).

Pulmonary function testing

Previous studies have demonstrated the CRS is a risk for asthma-related morbidity^(94,162,290,291) and among patients with CRSwNP, the prevalence of asthma may range between 30 – 70%⁽²⁹²⁾. As result, pulmonary function tests—which are noninvasive tests—should be used to assess and monitor lung function in CRSwNP patients with comorbid asthma^(293,294). The most used clinical tool is spirometry, which can be performed in clinic. The term spirometer was first coined by John Hutchison in 1846, and more than a century later, it became an essential diagnostic and management tool for respiratory diseases. Other pulmonary function tests include bronchial provocation and metacholine challenge tests, but these tests are more labor-intensive and invasive to the patient. Ambulatory tests using a handheld peak expiratory flow meter are generally affordable and objective tools for measuring airflow obstruction. However, spirometry is still considered the gold standard and cannot be substituted with a handheld peak flow meter for the initial assessment of airway obstruction⁽²⁹⁵⁾.

In patients with CRSwNP and comorbid asthma, spirometry has been used to measure the impact of upper airway inflam-

mation on the lower airway and vice versa⁽²⁹⁶⁾. The effect of ESS on improving spirometry in CRSwNP has been well studied and described in three systematic reviews⁽²⁹⁶⁻²⁹⁸⁾. More recently, spirometry has been included as an outcome measure in clinical trials assessing the effects of biologics on CRSwNP in patients with severe uncontrolled asthma^(56,299-303). However, there is a notable lack of studies employing spirometry to assess the efficacy of intranasal corticosteroids to impact lower airway outcomes in CRSwNP.

In spirometry, the main outcome measures are the forced expiratory volume at 1 s (FEV₁) or forced vital capacity (FVC) measured in Litres (L), FEV₁/FVC reported as a percentage (%), and peak expiratory flow measured in L/s. Additional measures include the vital capacity, forced expiratory volume in the first x seconds (FEV_x), forced expiratory flow rate (FEF_{x%}) at the point where x% of FVC has been expired and the FEF_{25-75%} which is the average flow during the middle 50% of FVC⁽³⁰⁴⁾. The spirometry is considered valid if the volume-time curve reaches a plateau where expiration lasts at least 6 s. Interpretation is made by comparing the individual data with reference data from healthy participants (predicted values). Changes in FEV₁ (L) or percentage of FEV₁ from predicted (FEV₁ % pred) are preferred in studies as measures of treatment response^(302,303,305-307). The FEV₁ % pred may also be used to categorize the severity of lung impairment as follows: mild >70%, moderate 60 – 69%, moderately severe 50 – 59%, severe 35 – 49% and very severe <35%⁽³⁰⁸⁾. FEV₁ is also a reproducible measure with a within-subject coefficient variation of 3 to 5%⁽³⁰⁹⁾.

One limitation of spirometry is that it is not recommended during active respiratory tract infections, which can artificially impair lung function. Pulmonary function tests should also be avoided within 1 month of myocardial infarction⁽³⁰⁴⁾. One point of concern for spirometry during the COVID-19 pandemic was the risk of transmitting infection through direct or indirect contact, although these concerns are controlled by using proper handling and disinfection procedures outlined in subsequently developed guidelines that include pandemic precautions⁽³¹⁰⁾. There is no well-accepted MCID for spirometric measurements. An increase of more than 12% and 200 ml in FEV₁ with bronchodilator treatment is the accepted definition of airway reversibility⁽²⁹³⁾ and this is used to differentiate asthma from other types of obstructive airway disease. However, considerable intra-individual change may be accepted to be within the realm of normal variation. A joint guideline by the American Thoracic Society and European Respiratory Society recognizes normal day-to-day, week-to-week and year-to-year variation in measurements of FVC, FEV₁, MEF_{25-75%} and D_{LCO}⁽³⁰⁸⁾. For example, for FEV₁, there is up to 5% accepted day-to-day variability, up to 12% week-to-week variability and up to 15% year-to-year variability for individuals with “normal” lung function; this accepted variability may be even higher for patients with pulmonary pathology

such as COPD⁽³⁰⁸⁾. Moreover, in performance of spirometry, it is important to be cognizant of factors that may further increase variability in spirometry results such as the time of testing, bronchodilator use, and recent exposure to cold weather⁽³¹¹⁾. These sources of variability may explain the lack of significant increases in PFT results after treatment despite improvements in other lower airway measures, such as the Asthma Control Test, asthma symptoms, and decreased use of bronchodilators^(296,300,301).

Fraction exhaled nitric oxide (FeNO)

Nitric oxide (NO) is a gas molecule released by bronchial epithelial cells that is synthesized by the inducible form of nitric oxide synthase (iNOS) and regulates normal pulmonary functions⁽³¹²⁾. Overexpression of IL-4 and IL-13 in type-2 airway inflammation leads to upregulation of iNOS and overproduction of nitric oxide^(312,313), which promotes bronchial eosinophilic inflammation⁽³¹⁴⁾. Hence, the concentration of NO in exhaled air, or fractional exhaled nitric oxide (FeNO) that is measured in units of parts per billion (ppb), is utilized as a biomarker of type-2 airway inflammation. Currently, FeNO is the only point-of-care test available that can aid in endotyping asthma and identifying patients with type-2 disease⁽³¹⁵⁾.

American Thoracic Society/ European Respiratory Society guidelines describe a standardized protocol for the measurement and interpretation of FeNO^(316,317). A FeNO level of >50 ppb (>35 ppb in children) indicates a high likelihood of eosinophilic airway inflammation and corticosteroid responsiveness, while a low FeNO level (<25 ppb in adults and <20 ppb in children) indicates that eosinophilic airway inflammation is unlikely. In monitoring of asthmatic patients, a clinically significant change in FeNO levels is defined as more than a 20% change from baseline FeNO levels if initial levels were above 50 ppb or a change of more than 10 ppb if initial FeNO levels were below 50 ppb⁽³¹⁶⁾. It should be noted, however, that FeNO levels may be confounded by obesity⁽³¹⁸⁾, smoking⁽³¹⁹⁾, and corticosteroid therapy⁽³²⁰⁾, which can lower FeNO levels while increasing age⁽³²¹⁾, height⁽³¹⁹⁾, and certain disease states (e.g., rhinovirus infection⁽³¹⁹⁾, allergic rhinitis⁽³²²⁾, and nasal polyps⁽³²³⁾) can increase FeNO levels.

FeNO measurement can be predictive of several clinical outcomes. A systematic review and meta-analysis of 26 studies showed that a FeNO of >50ppb had an overall sensitivity of 0.65, specificity of 0.82, and diagnostic OR of 9.23 for predicting the diagnosis of asthma⁽³²⁴⁾. FeNO can also be used as a prognostic biomarker. Post-hoc analysis of the phase 3 LIBERTY ASTHMA QUEST study showed that moderate to severe asthma patients with baseline FeNO levels \geq 50 ppb suffered a 1.54 times higher exacerbation rate than patients with baseline FeNO levels <25 ppb⁽³²⁵⁾. Persistently high FeNO levels can also predict nonadherence to inhaled corticosteroid therapy or corticosteroid resistance and severe asthma^(316,326). Demonstration of a significant fall in FeNO levels after 7 days of directly observed inhaled

corticosteroid therapy identified nonadherent patients and was introduced as the FeNO suppression test⁽³²⁷⁾. Conversely, non-suppression of FeNO levels can identify corticosteroid resistance in type 2 asthma patients and to predict the possible need for biological therapy^(328,329). The role of FeNO levels in the choice of biological therapy for severe asthma has also been investigated. A systematic review of 58 studies has concluded that a higher baseline FeNO level predicted a good response in patients treated with omalizumab, dupilumab, and tezepelumab. However, this was not clearly demonstrated with biologics targeting IL-5 and its receptor (mepolizumab, reslizumab, and benralizumab), which was mechanistically explained by the possibility that FeNO is an indirect marker of IL-4 and IL-13 activity⁽³³⁰⁾. By comparison to asthma, there is still limited scientific evidence for the role of FeNO in the evaluation and management of CRS. The role of traditionally measured (i.e., through oral exhalation) FeNO in CRS so far has focused on predicting the presence of occult asthma⁽³³¹⁻³³³⁾, as well as tracking improvement in asthma after treatment of CRS^(334,335). Nasal nitric oxide (nNO) has been described as a marker of and outcome measure for eosinophilic or type-2 CRS that can improve with treatment of CRS⁽³³⁵⁾ but its measurement is confounded by physical obstruction of sinus ostia. For example, despite the higher prevalence of type-2 inflammation, CRSwNP is associated with lower nNO levels compared to CRSsNP or control patients⁽³³⁶⁾ and ESS can increase nasal FeNO due to enlarged sinus ostia, despite the lack of obvious mucosal inflammation^(337,338). Interestingly, nNO is also found to be low in primary ciliary dyskinesia⁽³³⁹⁾. Further research is needed to better delineate the extent to which nNO reflects sinonasal mucosal type-2 inflammation vs. patency of sinus ostia.

Disease control

Control is an important concept and outcome measure for chronic, incurable diseases that can be defined as the extent to which manifestations of a disease are within acceptable limits^(139,340). Criteria for the assessment of CRS disease control were first proposed by the 2012 EPOS guidelines based on both patient-reported outcome measures as well as objective assessments of disease burden: the severity of five symptoms, the recent need for systemic corticosteroids or antibiotics, and the presence of diseased mucosa on nasal endoscopy⁽¹³⁸⁾; these control assessment criteria were largely preserved in the 2020 EPOS guidelines⁽¹⁾. While the EPOS criteria for CRS control have been used in the plurality of studies using CRS control as an outcome measure, at least 15 different definitions and criteria for CRS control have been used in the literature⁽¹⁴⁰⁾. The exact definition of CRS control - its criteria and how to measure those criteria - remains a topic of investigation^(90,341,342). Recent studies have shown that patients' and healthcare providers'

views of CRS control largely align⁽³⁴³⁾ and that patients' assessments of their own CRS control reflects their CRS disease burden⁽³⁴⁴⁾. In general, patients focus on their nasal symptoms in judging their own CRS control^(345,346), which is consistent between CRS patients with and without polyps⁽³⁴⁷⁾. While healthcare providers take broader approaches to assessing CRS control than patients⁽³⁴⁵⁾, healthcare providers nevertheless prioritize the severity of nasal symptoms as well as patients' perceptions of their own CRS control (patient-reported CRS control)⁽³⁴⁸⁾. Recently, consensus criteria for assessment of CRS disease control have been identified in an international multidisciplinary Delphi study⁽³⁴⁹⁾. These consensus criteria consisted of overall symptom severity, the severity of nasal obstruction, patient-reported CRS control and the need for oral corticosteroids with near-consensus criteria including diseased mucosa on nasal endoscopy, severity of smell loss, overall QOL impact, impairment of normal activities, and the severity of nasal discharge⁽³⁴⁹⁾. These criteria have subsequently been adopted by an EPOS2020/EUFOREA expert opinion on CRSwNP disease states in a proposed scheme for defining controlled CRSwNP that is based on patient-reported CRS control, overall symptom severity, the severity of nasal obstruction and the severity of smell loss⁽¹⁰¹⁾.

Biomarkers as outcome measures

Biomarkers are human physiologic markers that can provide information regarding a disease state. Current classification of CRS into that with and without polyps or eosinophilic and non-eosinophilic is overly simplistic⁽³⁵⁰⁾. Biomarkers in CRSwNP can be used to endotype - or classify - an individual based on molecular pathways of inflammation, determine treatment type and severity, to predict and monitor treatment response and to improve outcomes⁽³⁵⁰⁾. Although the specific categories are evolving, the broadest subdivisions are Type 2 (includes IL-4, IL-5, IL-13 biomarkers) and non-Type 2 (includes IFN and IL-17 biomarkers, associated with Type 1 and Type 3 inflammation, respectively)⁽³⁵¹⁾. Biomarkers can also reflect novel therapeutic targets. Sources of biomarkers in CRS include: serum, nasal secretions, exhaled nasal air and sinonasal tissues⁽³⁵⁰⁾. Possible biomarkers that may be of clinical significance that are currently being studied for CRSwNP are described in Table 5. However, not all these biomarkers are currently supported by data correlating them with symptoms and quality of life or showing these biomarkers to be predictive of treatment response. Moreover, CRS biomarkers and their predictive abilities may vary by geography and the genetic makeup (including CRS pathophysiology) of patients⁽³⁵²⁾. The following sections will focus on discussing biomarkers with evidence specifically showing them to have clinical relevance as a reflection of CRS symptom burden, QOL or as a predictor of treatment response.

Table 5. Putative biomarkers for CRSwNP.

Biomarker	Pathophysiologic role in CRS
Charcot-Leyden Crystal (CLC)	Byproduct of eosinophilic degradation and marker of Type-2 inflammation ⁽³⁹³⁾ .
Chemokines	Peptides secreted by eosinophils. Induce eosinophil and T-cell migration/chemotaxis ^(394,395) .
Eosinophil-derived neurotoxin (EDN)	Cytotoxic properties, attracts and enhances activity of antigen presenting cells and toll-like receptors ⁽³⁹⁶⁾ . Contributes to tissue remodeling (e.g., upregulates MMP-9) ^(397,398) .
Eosinophil peroxidase (EPX)	Involved in formation of bactericidal reactive oxygen species ⁽³⁹⁹⁾ . Very sensitive for degranulated eosinophils and not associated with other leukocytes ^(400,401) .
Eosinophil cationic protein (ECP)	An eosinophil granule protein with cytotoxic and immune-regulatory functions ^(402,403) .
Eosinophils	Granulocytic leukocytes produced in bone marrow that contain & secrete inflammatory mediators. Released mediators promote further eosinophil recruitment, mucus secretion and increased vascular permeability ^(404,405) .
Eotaxin	Chemokine family (consisting of Eotaxin-1, -2, and -3) which promotes chemotaxis of eosinophils primarily but also basophils, and T-helper-2 lymphocytes ⁽⁴⁰⁶⁾ .
Glucocorticoid Receptor β (GR β)	An endogenous inhibitor of glucocorticoid action that functions as a dominant negative partner of glucocorticosteroid receptor α , the classical receptor for corticosteroids that mediates their anti-inflammatory properties ^(407,408) .
Immunoglobulin E (IgE)	An antibody produced by plasma cells involved in allergic, eosinophilic, or parasitic diseases ⁽³⁵⁰⁾ .
Interleukins	Chemical molecules that function in cell signaling. Many different categories of interleukins exist and Type-2 interleukins, which include IL-4, -5 and -13, are most associated with allergy, atopy and eosinophilic disease ^{(409)v} .
Matrix metalloproteinases (MMPs)	Proteases that are involved in various aspects of tissue remodelling ⁽⁴¹⁰⁾ . Levels of MMPs are consistently elevated in nasal polyps ^(411,412) .
Nasal nitric oxide	A pluripotent gaseous messenger involved in sinus host defence: having vasodilatory and antimicrobial activity, and improving mucociliary clearance ⁽⁴¹³⁾ .
Neutrophils	Granulocyte produced in bone marrow that is a critical component of innate immunity. It functions as a phagocyte that release proteases which coordinate and escalate inflammatory reactions ⁽⁴¹⁴⁾ . Although classically associated with non-Type-2 inflammation, an increasingly important role for neutrophils is emerging for CRSwNP ⁽⁴¹⁵⁾ .
P-glycoprotein	Known as multidrug resistance protein 1. ATP-dependent efflux protein pump in cell membranes. Pumps foreign substances out of cells, and may represent a mechanism of corticosteroid resistance ^(350,416) .
Periostin	A secretory protein and component of extracellular matrix produced by epithelial cells when stimulated by IL-4 and IL-13 ⁽⁴¹⁷⁾ . Enhances collagen cross-linking, remodeling and eosinophil recruitment ⁽⁴¹⁸⁾ .
Uric acid	Naturally-occurring metabolic by-product from breakdown of purine nucleotides. Elevated levels of uric acid may induce production of reactive oxygen species and activate inflammatory pathways ⁽⁴¹⁹⁾ .
Urine leukotriene E4 (uLTE4)	Cysteinyl leukotrienes (including LTE4) are formed during the metabolism of arachidonic acid to leukotrienes ⁽⁴²⁰⁾ . LTE4 stimulates the proliferation of eosinophils in bone marrow, eosinophil chemoattractant ^(421,422) . LTE4 may be associated with increased production of IL-5 and reduction of eosinophil apoptosis ⁽⁴²³⁾ .

Correlation of biomarkers with quality of life/symptomatology

Many studies have evaluated the association between biomarkers and CRS disease type. However, few studies have specifically investigated the association of putative CRS biomarkers with specific symptoms or QOL. A consolidation of the available evidence on the correlation of biomarkers with CRSwNP symptoms and QoL is shown in Table 6. Although there is emerging evidence for biomarkers reflecting a variety of inflammatory pathways, biomarkers of eosinophilic inflammation have so far demonstrated the greatest positive correlations with worse CRSwNP symptomatology (Table 6).

Responsiveness of biomarkers to treatment of CRSwNP

Antibiotics: macrolides and doxycycline

Both macrolides and doxycycline are presumed to have treatment effects for CRSwNP through anti-inflammatory mechanisms, which is supported by their observed modulation of inflammatory mediators ^(351,353). Macrolides, which have been shown to reduce CRSwNP symptoms and reduce nasal polyp size ^(354,355), have been shown to impact both eosinophilic and neutrophilic biomarkers. For example, studies have found significantly lower eosinophil cationic protein (ECP) in nasal secretions in those treated with oral clarithromycin daily for 8 to 24 weeks compared with no antibiotics ^(356,357). Other studies have observed anti-neutrophilic effects as reflected by lower IL-8 in nasal lavage fluid after treatment with macrolides such as roxithromycin ⁽³⁵⁸⁾ or clarithromycin ^(359,360).

Although a recent systematic review with meta-analysis did not find significant CRS treatment effects for doxycycline ⁽³⁶¹⁾, one

Table 6. Biomarkers that correlate with symptom and quality of life burden in CRSwNP.

Biomarker	Correlation with QoL/symptoms
Eosinophils	<ul style="list-style-type: none"> Tissue eosinophil count is associated with disease severity and symptoms ^(364,381,424-427). Tissue eosinophils after ESS are associated with worse chemosensory function ⁽⁴²⁸⁻⁴³¹⁾. Inverse relationship between tissue eosinophil counts and baseline physical function at work ⁽⁴²⁷⁾.
Eosinophil-derived neurotoxin (EDN)	<ul style="list-style-type: none"> Serum EDN found to correlate positively with disease severity in eosinophilic CRS ⁽³⁹⁸⁾.
Eosinophil peroxidase (EPX)	<ul style="list-style-type: none"> Tissue EPX levels correlate positively but weakly with SNOT-22 scores in eosinophilic CRSwNP ⁽⁴⁰⁰⁾.
Neutrophils	<ul style="list-style-type: none"> Conflicting results as to whether high tissue neutrophil count is associated with uncontrolled CRSwNP ^(381,432,433).
Nasal nitric oxide	<ul style="list-style-type: none"> A significant inverse relationship was found between nasal nitric oxide levels and severity of nasal obstruction and purulent rhinorrhea ⁽⁴³⁴⁾.
Interleukins	<ul style="list-style-type: none"> IL-6 and IL-12 in nasal mucus have been found to correlate with poorer baseline general health/QOL scores ⁽⁴²⁷⁾. SNOT-22 scores correlate positively with tissue concentrations of IL-2, IL-4 and IL-22 ⁽⁴³⁵⁾. Elevated IL-5 and IL-13 levels in middle meatal mucus correlated with higher SNOT-22 scores ⁽⁴³⁶⁾. IL-4 and IL-12 in nasal mucus correlate positively with sinonasal symptoms ⁽⁴²⁷⁾. Elevated IL-4 and IL-5 levels in nasal mucus inversely correlate with olfaction ^(437,438). Elevated IL-13 in nasal mucus correlates with sleep impairment ⁽⁴²⁷⁾. Elevated levels of IL-5, IL-13 and IL-33 in middle meatal mucus correlated with worse UPSIT scores ⁽⁴³⁶⁾.
Chemokines	<ul style="list-style-type: none"> Elevated levels of CCL2 in middle meatal mucus correlated with worse UPSIT scores, although, when adjusting for multiple comparisons/interactions, chemokines were not significant ⁽⁴³⁶⁾. Elevated CCL2, TNF-α and CXCL8 levels in middle meatal mucus correlated with higher SNOT-22 scores ⁽⁴³⁶⁾.
IgE	<ul style="list-style-type: none"> Serum total IgE of >400IU/L was an independent risk factor for olfactory dysfunction in eosinophilic CRSwNP patients ⁽⁴³⁹⁾.
Periostin	<ul style="list-style-type: none"> Tissue and serum periostin values correlate with CRSwNP disease severity and post-operative SNOT-22 scores ⁽⁴⁴⁰⁻⁴⁴²⁾.
P-glycoprotein	<ul style="list-style-type: none"> P-glycoprotein in nasal secretions correlates positively with SNOT-22 scores in CRSwNP ⁽⁴⁴³⁾.

Abbreviations: APC – antigen presenting cell; CCL – chemokine ligand; CLC: Charcot-Leyden crystal protein (aka Galectin 10); ECM – extracellular matrix; ECP – eosinophilic cationic protein; EDN – eosinophil-derived neurotoxin; EPX – eosinophil peroxidase; IFN- γ – interferon gamma; IL – interleukin; LTC – cysteinyl leukotriene; PGE – prostaglandin E; MBP – major basic protein; MCC – mucociliary clearance; MMP – matrix metalloproteinase; ROS – reactive oxygen species; SNOT-22 – 22-item Sinonasal Outcome Test; TNF- α – tumor necrosis factor alpha; TLR – toll-like receptor; UPSIT –University of Pennsylvania Smell Identification Test.

clinical trial did show positive treatment effects of doxycycline for CRSwNP ⁽²⁵⁶⁾. In that study, significantly lower levels of nasal secretion matrix metalloproteinase 9 (MMP-9), ECP, and myeloperoxidase (MPO), and serum soluble IL-5R α , were observed in those treated with oral doxycycline daily for 20 days compared to placebo; doxycycline had no effect on serum eosinophil or ECP or nasal secretion IL-5 ⁽²⁵⁶⁾. Another study, which investigated the efficacy of doxycycline-releasing stents delivered locally to the frontal sinus/recesses after ESS, found significantly decreased nasal secretion MMP-9 in patients receiving doxycycline-releasing stents compared to placebo stent at 3 months; nasal secretion MPO was similar between treatment groups ⁽³⁶²⁾.

Corticosteroids

Corticosteroids are strongly anti-inflammatory, particularly against Type 2 inflammation ^(351,363). Corticosteroids form the basis of treatment for CRSwNP - with topical intranasal delivery as standard of care for maintenance treatment and short course oral delivery for rescue treatment - because they have

been shown to reduce symptoms of CRSwNP and reduce polyp size ^(1,29). Concomitant with reducing symptoms and polyp size, corticosteroids have been shown to also significantly decreased Type 2 inflammatory markers - such as serum eosinophils, serum ECP and soluble IL-5R α - in the peripheral blood ⁽²⁵⁶⁾, which is accompanied by changes in levels of inflammatory biomarkers in sinus and polyp tissue, as well as nasal secretions. After treatment with oral corticosteroids for as little as 7 days, the levels of tissue eosinophils but not neutrophils are reduced ⁽³⁶⁴⁻³⁶⁶⁾, including a reduction of Type 2 inflammatory mediators such as ECP and IL-5, as well as modulation of tissue remodeling ^(365,366). This effect was also observed for treatment of CRSwNP with a topical intranasal corticosteroid ⁽³⁶⁵⁾. Similar to their effects on sinus tissue, oral corticosteroids have also been shown to significantly reduce Type 2 inflammatory markers such as IL-4, IL-5 and ECP in nasal secretions of patients with CRSwNP ^(256,364). By contrast, levels of the neutrophil chemoattractant IL-8 or the Type 3 inflammatory cytokine IL-17 in nasal secretions are not affected ⁽³⁶⁴⁾.

Table 7. Predictive ability of clinical outcomes by biomarkers of CRSwNP.

Biomarker	Predictive role in CRSwNP
Charcot-Leyden Crystal (CLC)	<ul style="list-style-type: none"> Greater than 1 CLC per high power field in nasal tissue can predict nasal polyp recurrence after ESS with 84.80% sensitivity and 98.70% specificity ⁽⁴⁴⁴⁾ CLC concentration (>34.24ng/mL) in nasal secretions can predict nasal polyp recurrence with 92.6% sensitivity and 87.5% specificity ⁽⁴⁴⁵⁾
Eosinophil Cationic Protein (ECP)446	<ul style="list-style-type: none"> High tissue concentration of ECP is associated with nasal polyp recurrence ⁽⁴⁰³⁾ Serum ECP is associated with early nasal polyp recurrence after ESS ⁽⁴⁴⁷⁾
Eosinophils	<p>After ESS:</p> <ul style="list-style-type: none"> Peripheral blood eosinophil levels are predictive of nasal polyp recurrence, need for oral corticosteroids, or revision ESS ^(143,367,383,384) Tissue eosinophil levels are associated with poor QOL and nasal polyp recurrence ⁽³⁷⁸⁻³⁸²⁾, including in pediatric CRSwNP ⁽⁴⁴⁸⁾
Eotaxin-3	<ul style="list-style-type: none"> May be used as a biomarker for predicting post-operative recurrence ^(449,450)
Glucocorticoid Receptor β (GR β)	<ul style="list-style-type: none"> Expression of GRβ by T-cells and eosinophils in NP is predictive of corticosteroid resistance/insensitivity ⁽⁴⁵¹⁻⁴⁵³⁾
IL-5	<ul style="list-style-type: none"> High tissue levels of IL-5 are a significant predictor of nasal polyp recurrence and revision ESS ^(403,454) Tissue IL-5 is a predictor of poor olfactory outcomes after ESS ⁽⁴⁵⁵⁾
IL-17A	<ul style="list-style-type: none"> Lower levels predictive of severe eosinophilic CRSwNP ⁽⁴⁵⁶⁾ Conflicting findings regarding whether levels are increased or not in CRSwNP vs CRSsNP ⁽⁴⁵⁷⁾
Nasal nitric oxide	<ul style="list-style-type: none"> Cut-off of 163-442 ppb is predictive of having CRSwNP ^(434,458) Lower levels are predictive of greater CRSwNP disease severity; higher levels are predictive of a positive treatment response ⁽⁴⁵⁹⁻⁴⁶²⁾
Neutrophils	<ul style="list-style-type: none"> Neutrophilic polyps (defined as having ≥ 4 Human neutrophil elastase positive cells per hpf) have been shown to be associated with less efficacy of corticosteroids to improve symptoms or reduce polyp size ⁽³⁶⁴⁾
Periostin	<ul style="list-style-type: none"> Tissue periostin levels >115.5 ng/ml have been found to be associated with a significantly higher rate of post-operative recurrence in CRSwNP ⁽⁴⁴¹⁾ Tissue periostin levels correlate with disease severity and noted to reduce post-operatively ^(418,441)
Uric acid	<ul style="list-style-type: none"> Serum uric acid level >6.9 mg/dL at the time of ESS for CRSwNP is reported to be predictive for post-operative of NP (sensitivity: 45.1%, specificity: 85.4% ⁽⁴⁶³⁾
Urine leukotriene E4 (uLTE4)	<ul style="list-style-type: none"> Levels greater than 166pg/mg creatinine are predictive of N-ERD ⁽⁴⁶⁴⁻⁴⁶⁶⁾ Levels greater than 106pg/mg creatinine are predictive of eosinophilic CRS ⁽⁴⁶⁶⁾ Elevated levels are associated with CRSwNP with comorbid asthma ^(465,467). Values lower in AFRS vs non-AFRS patients ⁽⁴⁶⁷⁾

Abbreviations: AFRS – allergic fungal rhinosinusitis; CRSsNP – chronic rhinosinusitis without nasal polyps; CRSwNP – chronic rhinosinusitis with nasal polyps; ESS – endoscopic sinus surgery; IL – interleukin; NP – nasal polyps; hpf – high power field; QOL – quality of life; ppb – parts per billion; N-ERD – NSAID-exacerbated respiratory disease; NSAID – non-steroidal anti-inflammatory drug

Endoscopic sinus surgery

ESS is associated with substantial reductions in inflammatory mediators and biomarkers in the peripheral blood and nasal mucus of patients with CRSwNP. After ESS, significant reductions in peripheral blood eosinophils and IL-5 have been observed in patients with eosinophilic CRSwNP ^(367,368). ESS has also been shown to produce long-term reductions in Type 2 biomarkers (for example, IL-5 and IL-13) in nasal mucus ⁽³⁶⁹⁾. This has also been observed after the more extensive sinus “reboot” surgery, which is associated with reduced IgE, ECP, and IL-5 in nasal secretions for up to 12 months ⁽³⁷⁰⁾.

Biologics: monoclonal antibodies

Dupilumab, which targets the IL-4/IL-13 receptor, has been shown in two phase 3 trials to reduce Type 2 biomarkers (total

IgE, thymus and activation-regulated chemokine [TARC], eotaxin-3, ECP, and periostin) in serum, nasal secretions and polyp homogenates ^(56,371). However, the correlation between change in biomarkers with improvement in symptoms or polyp size has been found to be weak or very weak ⁽³⁷²⁾. Studies have shown that omalizumab, which targets IgE, does not reduce serum IgE or tissue eosinophils, although it may reduce serum periostin ^(301,373,374). Mepolizumab, which targets IL-5, has been shown in a phase 3 trial to reduce serum eosinophils, as have other IL-5 targeting biologic agents not yet FDA approved for CRSwNP (reslizumab, benralizumab) ^(58,375).

The predictive role of biomarkers in CRSwNP treatment outcomes

With currently available and evolving indications for biologic

(and other) treatments for CRS, biomarkers may form a vital role in treatment selection by prognosticating treatment outcomes. Several different biomarkers have been identified that may be predictive of treatment response in CRSwNP (Table 7). Of these, eosinophils have been the most widely studied⁽³⁷⁶⁾. Currently, there is no broad agreement on criteria, such as minimum level of tissue eosinophils, to define eosinophilic CRS⁽³⁵²⁾. However, eosinophilic CRS - as reflected by increased numbers of tissue eosinophils - has been recognized as a reliable predictor of greater disease severity and poorer treatment outcomes⁽³⁷⁷⁾. For example, having tissue eosinophilia of >10 eosinophils per high power field (eosinophils/hpf) was found to correlate with a poorer QOL after ESS^(378,379). Other studies have shown that having tissue eosinophils of >55-70 eosinophils/hpf is a significant predictor of recurrence after ESS⁽³⁸⁰⁻³⁸²⁾. Blood eosinophilia has also been found to be associated with CRS outcomes. Peripheral blood eosinophil counts of 240 – 520 cells/ μ L or greater have been found to predict nasal polyp recurrence after ESS, the need long-term systemic corticosteroids or revision ESS^(143,367,383,384). Nasal polyp recurrence after ESS has been associated with a peripheral blood eosinophil percentage of \geq 3.7% in all CRSwNP patients and a peripheral blood eosinophil percentage of \geq 5.9% in patients with eosinophilic CRSwNP⁽³⁸⁴⁾. Although eosinophilic CRSwNP may be indicative of long-term poorer outcomes, the presence of eosinophilia may also inform immediate treatment decisions as either a positive or negative prognostic indicator of specific treatment responses. For example, tissue eosinophilia is associated with a greater treatment effect of corticosteroids⁽³⁸⁵⁾, and blood eosinophil counts have been suggested as a biomarker to direct treatment with oral corticosteroids in CRSwNP⁽³⁸⁶⁾. However, higher levels of peripheral blood eosinophils (>2.2%) have been shown to be predictive of poor response to macrolides⁽³⁸⁷⁾. Recent clinical trials of biologics for CRSwNP have also revealed insights into biomarkers as predictors of treatment response. Higher levels of peripheral blood eosinophils has also been shown to be associated with efficacy of the anti-IL-5 biologic, mepolizumab, for the treatment of CRSwNP⁽⁵⁸⁾. In the SYNAPSE trial, which studied the efficacy of mepolizumab to treat severe CRSwNP, only the subgroup of patients with pre-treatment peripheral blood eosinophils \geq 150 cells/ μ L experienced a statistically significant benefit from mepolizumab to improve NPS and nasal obstruction VAS score. In contrast, the ability of pre-treatment peripheral blood eosinophil count to predict the efficacy of dupilumab is less clear. Several studies have shown dupilumab efficacy to be unaffected by the peripheral blood eosinophil composition^(388,389). However, another study examining the efficacy of dupilumab in the SINUS-24 and SINUS-52 trials suggests that the efficacy of dupilumab to improve NPS and symptoms may be greater in CRSwNP patients who have "type-2" inflammation based on (any one of several) clinical criteria,

which may include peripheral blood eosinophil counts, serum IgE levels or comorbid type-2 conditions⁽³⁹⁰⁾. In comparison, a proteomic analysis of CRSwNP patients' serum prior to initiation of treatment with dupilumab revealed that lower levels of pre-treatment Osteoprotegrin protein levels were predictive of positive response with high accuracy⁽³⁸⁹⁾.

Recommendations of regulatory agencies on CRSwNP outcome measures

The U.S. Food and Drug Administration (USFDA) has provided guidance for industry on outcome measures to be used in clinical trials for treatments of CRSwNP⁽⁸⁹⁾. The USFDA recommends coprimary endpoints of NPS and nasal congestion score (NCS), as a reflection both objectively measured and patient-reported assessments of clinical efficacy. Although the USFDA has not required a specific NPS or NCS, they do offer common grading scales as suggestions. For NPS, a description of the scale described by Gevaert et al. in 2006 is given⁽¹⁹³⁾, while NCS (or any individual symptom severity) is recommended to be implemented with response scales that include verbal descriptors, with a 4-level verbal rating scale (VRS) of 0 (absent symptoms), 1 (mild symptoms), 2 (moderate symptoms) and 3 (severe symptoms) described as a common examples. The USFDA also recommends secondary endpoints of smell loss, patient-reported symptom scores, the need for sinus surgery or systemic corticosteroid usage, and radiographic grading of disease burden. The USFDA specifically does not recommend the use of smell identification tests (such as the UPSIT) due to possible cultural bias^(391,392). They also do not recommend use of any version of the Sinonasal Outcome Test (such as the SNOT-22) due to its inclusion of items that can be confounded by non-rhinologic comorbidities⁽⁷⁶⁻⁷⁸⁾, as well as redundancy with the recommended primary endpoint of NCS or secondary endpoints of other individual symptom severity scores.

Conclusion

Outcome measures such as PROMs, objective measures of disease burden, psychophysical assessments and biomarkers have been developed and used for CRSwNP. These outcome measures reflect various constructs related to CRSwNP disease burden and they offer the clinician and researcher the opportunity to understand CRSwNP in different complementary ways. However, the many described CRSwNP outcome measures have been studied, characterized, and validated to various extents. It is important to understand that the use and interpretation of each outcome measure must be in the context of its formal validation, psychometric performance, and limitations.

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ARS and SA: Conceptualized, organized, performed and wrote the review. RGC: Organized, performed and wrote the review. RGD, WJF, AWH, ZRK, VSL, LM, FRR, and KS: Performed and wrote the review.

Conflict of interest

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