ISSN: 0300-0729

INTERNATIONAL RHINOLOGIC SOCIETY

RHINOLOGY

Official Journal of the European and International Societies

VOLUME 62 | SUPPLEMENT 34 | AUGUST 2024

Outcome measures for chronic rhinosinusitis with nasal polyps

Ahmad R. Sedaghat, Raewyn G. Campbell, Richard G. Douglas, Wytske J. Fokkens, Aneeza W. Hamizan, Zeina R. Korban, Victoria S. Lee, Luis Macias-Valle, Fabrizio R. Romano, Kornkiat Snidvongs, Saad Alsaleh

2024

RHINOLOGY

Official Journal of the European and International Rhinologic Societies

Address
Journal Rhinology, c/o AMC, Mrs. J. Kosman / A2-234, PO Box 22 660,
1100 DD Amsterdam, the Netherlands.
Tel: +31-20-566 4534
Fax: +31-20-566 9662
E-mail: assistant@rhinology.org
Website: www.rhinologyjournal.com

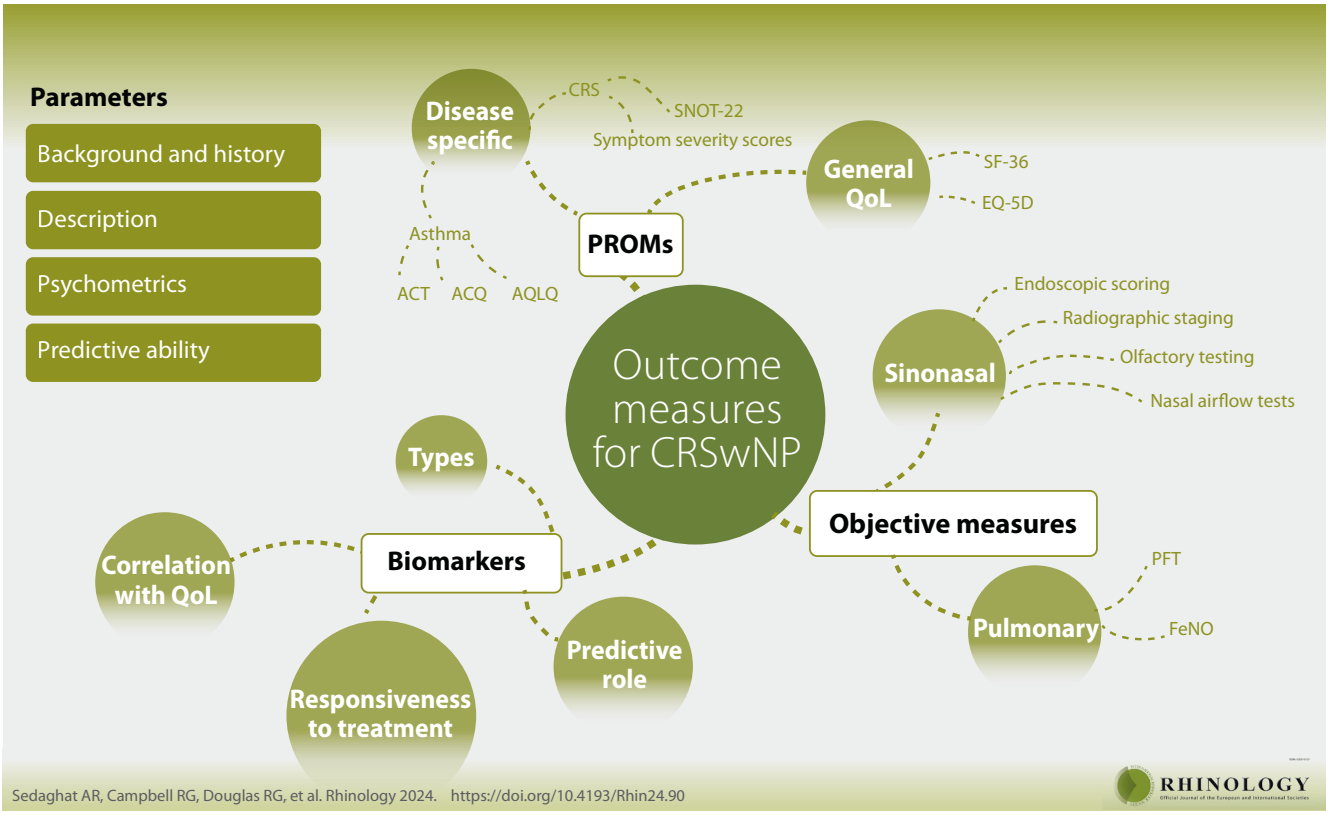
Rhinology (ISSN 0300-0729) is the official Journal of the European and International Rhinologic Societies and appears bimonthly in February, April, June, August, October and December. Cited in Pubmed, Current Contents, Index Medicus, Exerpta Medica and Embase.

Founded in 1963 by H.A.E. van Dishoeck, Rhinology is a worldwide non-profit making journal. The journal publishes original papers on basic research as well as clinical studies in the major field of *rhinology*, including physiology, diagnostics, pathology, immunology, medical therapy and surgery of both the nose and paranasal sinuses. Review articles and short communications are also pulished, but no Case reports. All papers are peer-reviewed. Letters-to-the-editor provide a forum for comments on published papers, and are not subject to editorial revision except for correction of English language.
In-depth studies that are too long to be included into a regular issue can be published as a supplement. Supplements are not subject to peer-review.

Outcome measures for chronic rhinosinusitis with nasal polyps

Ahmad R. Sedaghat[1], Raewyn G. Campbell[2], Richard G. Douglas[3], Wytske J. Fokkens[4], Aneeza W. Hamizan[5], Zeina R. Korban[6], Victoria S. Lee[7], Luis Macias-Valle[8], Fabrizio R. Romano[9], Kornkiat Snidvongs[10], Saad Alsaleh[11]

Rhinology 62:
Supplement 34; 4, 1 - 31, 2024
https://doi.org/10.4193/Rhin24.090



Abstract

Background: With the recent proliferation of novel therapeutics for chronic rhinosinusitis with nasal polyps (CRSwNP), there is an immediate need for comprehensive means to assess CRSwNP disease status as well as to determine treatment efficacy. Outcome measures exist in different forms. Patient-reported outcome measures (PROMs) allow patients to provide direct input about their condition that is not possible to obtain in any other way. Common constructs that are measured using PROMs include quality of life or the burden of disease manifestations (e.g., symptom severity). Outcomes may also include the results of objective diagnostic testing/measurement of clinical signs or measured using psychophysical tests. Biomarkers represent an emerging class of outcome measures for CRSwNP and are chosen to directly reflect the active pathophysiologic processes of CRSwNP in the peripheral blood, sinus/polyp tissues, and sinonasal mucus. **Methods**: Narrative review of the literature, identifying and describing outcome measures that may be used in the evaluation of CRSwNP and for assessment of treatment responses. **Results**: In this review, we identify many different outcome measures for CRSwNP that fall under the categories of PROM, objective test, psychophysical test or biomarker. We describe the history of each - including seminal studies - and demonstrate the formal validation, psychometric performance, and limitations of each. **Conclusions**: PROMs, objective tests, psychophysical tests and biomarkers represent different classes of outcome measures that are complementary means of assessing CRSwNP disease status and treatment efficacy. The choice or interpretation of a CRSwNP outcome measure should be undertaken with full knowledge of its formal validation, psychometric performance, and limitations.

Key words: chronic rhinosinusitis, nasal polyps, outcome measures, symptom severity, SNOT-22, asthma, nasal polyp score, Lund-Kennedy endoscopy score, control, UPSIT, Sniffin' Sticks, Connecticut Chemosensory Clinical Research Center, biomarkers, eosinophils, type-2, biologics

Introduction

The assessment of disease status as well as how that disease state changes with treatment requires specific outcome measures that are reflective of the disease and how it impacts patients. Outcome measures can consist of directly observable and measurable disease characteristics as well as those aspects of the disease, which only the patient can describe and report - known as patient-reported outcome measures (PROMs). For decades, the need for reliable outcome measures that accurately reflect chronic rhinosinusitis (CRS) disease burden and how it impacts patients has been well-recognized [1]. Outcome measures have been the cornerstone for our ability to quantify and understand the many impacts of CRS as well as to assess the efficacy of treatments that have been developed [2].

Recently, a spotlight has been cast upon CRS with nasal polyps (CRSwNP) due to the development of various novel therapeutics [3,4]. CRSwNP represents approximately one third of all CRS patients and has an overall population prevalence of approximately 2% [5-8]. The need to study the efficacy of new treatments for CRSwNP has highlighted the need for proper choices of outcome measures in clinical trials as well as the need for the greater otolaryngology community to be able to interpret those outcome measures and what they represent [9-13]. The objective of this article is to review the most prominent outcome measures relevant to CRSwNP. With an authorship representing diverse backgrounds and experiences of practitioners from around the world, our specific goal was to focus on providing a transparent discussion for the development and validity of these outcome measures, their psychometric performance and limitations, their predictive abilities, as well as how to interpret change in these outcome measures.

Methods

The objective of this article is to provide a review on outcome measures for CRS with nasal polyps (CRSwNP) with a specific focus on the most prevalent outcome measures to maximize applicability and utility. Specific outcome measures to focus on were determined through a 2-step process. The organizing authors (ARS and SA) first compiled a proposed list of outcome measures that were deemed to be commonly used in clinical studies and registration trials identified by searching the MEDLINE and PubMed Central databases. The proposed list of outcome measures was then presented to the entire authorship group for feedback and discussion, from which a final list of outcome measures for inclusion was determined. For each outcome measure discussed, the MEDLINE and PubMed Central databases were queried using PubMed for studies pertinent to the psychometric function and predictive ability of the corresponding outcome measure. The references of identified articles were also searched for pertinent articles. Emphasis was placed on including seminal studies, e.g. the studies that first and most comprehensively determined/reported the specific detail being discussed.

Patient-reported outcome measures

Because decreased quality of life (QOL) is the primary impact of CRS [1], (PROMs) have long been established as central to the assessment of CRS. PROMs that have been developed and used for CRS outcomes have included instruments that measure disease-specific QOL, CRS symptom severity and general health-related QOL (Table 1).

Disease-specific quality of life

The first widely used instruments to CRS-specific QOL were the "Chronic Sinusitis Survey" (CSS) [14] and the "31-item Rhinosinusitis Outcome Measure" (RSOM-31) [15], both described almost three decades ago. Since then, many different CRS-specific QOL instruments have been developed and validated [16,17]. These include, but are not limited to, the Rhinosinusitis Disability Index (RSDI) [18], Rhinosinusitis Quality of Life Survey (RhinoQOL) [19,20], 16-item Sinonasal Outcome Test [21], 20-item Sinonasal Outcome Test [22], and Sinonasal Questionnaire (SNQ) [23,24]. At present the 22-item Sinonasal Outcome Test (SNOT-22) [25-28], which assesses the burden of CRS with a recall period of 2 weeks, is the most widely used and generally preferred CRS-specific QOL PROM [1,29,30].

The SNOT-22 was developed by the addition of specific items for "Sense of taste/smell" and "Blockage/congestion of nose" to the preceding 20-item Sinonasal Outcome Test (SNOT-20) [25,28], which itself was derived from the RSOM-31 [22]. The burden of each of the 22 items/symptoms represented on the SNOT-22 is scored with a six-item Likert scale corresponding to numerical scores ranging from 0 – 5, respectively. The SNOT-22 total score therefore ranges from 0 – 110, with one previous study proposing a classification of CRS severity based on the SNOT-22 score as mild (SNOT-22: 8 – 20), moderate (SNOT-22: >20 – 50), and severe (SNOT-22: >50) [31].

The SNOT-22 has been validated for CRS and allergic rhinitis but no other conditions [28,32]. It has also been translated and cross-culturally adapted to at least 20 languages [28,33-51]. While the SNOT-22 has been well-validated in adults, it has been used in children and adolescents without formal validation in those age groups [52,53]. Moreover, the SNOT-22 has been used for measurement of sinonasal symptom burden or sinonasal-specific QOL in numerous conditions other than CRS and allergic rhinitis without formal validation.

The SNOT-22 score has been used in a multitude of studies, including clinical trials of ESS efficacy [27,54] and biologics for CRSwNP [55-58], and has been recommended to be a standard PROM used to assess CRS outcomes [30]. The SNOT-22 reflects CRS-specific impairment that patients feel across multiple domains, which include nasal symptoms, sleep quality/distur-

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

impairment [62]. In contrast, a post-hoc analysis of data from the SYNAPSE trial of mepolizumab for CRS has proposed the possibility of CRSwNP-specific SNOT-22 subdomains related to "nasal symptoms", "ear/facial symptoms", "non-nasal symptoms", "fatigue", "impact on sleep" and "emotional impact" [63]. It is yet unclear whether a generalizable CRSwNP-specific SNOT-22 subdomain structure exists.

The SNOT-22 is also predictive of patients' perspectives of their own disease and predictive of treatment response. A prior study has shown that a SNOT-22 score of greater than or equal to 35 is predictive of CRS patients who would rate their CRS symptom as poorly controlled with 71.4% sensitivity and 85.5% specificity [64]. The SNOT-22 has also been shown to be predictive of treatment response. As observed with other PROMs, a higher SNOT-22 score has been shown in multiple studies to be predictive of a larger improvement in SNOT-22 score with treatment [65,66]. SNOT-22 score has also be shown be predictive of ESS outcomes with greater than 70% of CRS patients having a pre-operative SNOT-22 score of greater than 30 experiencing clinically meaningful improvement after ESS [67,68].

The psychometric performance of the SNOT-22 has largely been shown to be excellent based on metrics of classical test theory. The SNOT-22 has been shown to have excellent construct validity, with previous studies showing strong correlation of SNOT-22 score with measures of general health-related QOL as well as the ability of the SNOT-22 to discriminate between patients with and without CRS. Numerous studies have also shown the SNOT-22 to have a high degree of internal consistency (Cronbach's alpha >0.9) as well as test-retest reliability (correlation coefficient >0.9) [28]. The SNOT-22 has also demonstrated excellent responsiveness with large effect size (d= 0.81 for all CRS, d = 0.90 for CRSwNP, d = 0.63 for CRS without nasal polyps [CRSsNP]) after treatment of CRS with ESS [28]. More recent study of SNOT-22 psychometric performance using item response theory (IRT), which focuses on the performance of individual survey items rather than the survey as a whole, has revealed considerable heterogeneity in the performance of individual items [69]. The "sense of taste/smell" item had the lowest reliability of any item on the entire SNOT-22 [69], a problem that was not solved by separating this item into two distinct items for sense of smell and sense of taste [70]. The SNOT-22 items for "sense of taste/smell", "cough" and "dizziness" also were found to contribute the least amount of information, functioning as the least essential items [69,71].

Different values have been reported for the minimal clinically important difference (MCID) of the SNOT-22. The MCID of the SNOT-22 was originally calculated to be 8.9 using a single anchor-based method applied to a large cohort of 2284 CRS patients undergoing ESS in the United Kingdom [28]. A subsequent study of 276 CRS patient undergoing ESS in the United States reported the MCID of the SNOT-22 to be 9, which was calculated as the mean of calculations from 4 distribution-based methods [72]. Another study of 430 medically managed CRS patients used both anchor-based and distribution-based methods to calculate the MCID of the SNOT-22 to be 12 [73,74]. This latter study reported that the MCID of the SNOT-22 had 57% sensitivity and 81% specificity for identifying patients who experienced clinically meaningful improvement [74]. The MCID of SNOT-22 subdomains has also been calculated using a combination of anchor-based and distribution-based methods for the 4-subdomain model [75].

The primary limitation of the SNOT-22 is that it can be confounded by other comorbidities. This limitation arises because the majority of individual items on the SNOT-22 reflect extra-nasal symptoms reflecting sleep disturbance, mood disturbance, craniofacial discomfort and functional limitations. It is therefore not surprising that comorbidities such as obstructive sleep apnea, migraine headaches, depression and anxiety can artificially inflate SNOT-22 scores [76-78].

Symptom severity scores

Chronic rhinosinusitis symptom severity scores have been recorded and used as PROMs in clinical studies for over three decades [79]. Early CRS staging guidelines recommended use of individual symptom severity scores and an overall (or total) symptom severity score as CRS PROMs measured with a visual analogue scale (VAS) [2,80]. However, individual symptom severities and overall symptom severity of CRS have also been measured using both VAS and ordinal scales.

Overall symptom severity score

Overall symptom severity of CRS, measured with a VAS, was proposed by the 2005 EPOS as a means to distinguish patients with mild (VAS: 0 – 4) from moderate/severe (VAS: 5 – 10) symptoms [81]. This scheme was developed as a preliminary attempt for better classification of CRS patients to aid treatment decisions but suffered from three limitations: it was arbitrarily derived and not based on epidemiologic data, it did not distinguish between moderate and severe symptoms and there was no clear classification for patients whose symptom severity score was between 4 and 5. A subsequent study addressed these limitations and determined an evidence-based classification scheme for overall symptom severity score as mild (VAS: 0 – 3), moderate (>3 – 7), and severe (>7 – 10) [82]. This classification scheme for the overall symptom severity VAS score continues to be adopted by the EPOS guidelines [1]. The overall symptom severity score—both as a VAS and on an ordinal scale of "mild", "moderate", and "severe"— has also been shown to be well correlated with the SNOT-22 [31,83]. The overall symptom severity score has been used in clinical trials studying both medical and surgical treatments of CRS and has demonstrated excellent responsiveness reflecting a large effect size [54,84,85].

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 usual 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-

dation 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 Questionaire (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 responsiveness, 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 dyfunction [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 wit 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 significant 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 (FEV_1) or forced vital capacity (FVC) measured in Litres (L), FEV_1/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 FEV_1 (L) or percentage of FEV_1 from predicted (FEV_1 % pred) are preferred in studies as measures of treatment response [302,303,305-307]. The FEV_1 % 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]. FEV_1 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, FEV_1, $MEF_{25-75\%}$ and $D_{L,CO}$ [308]. For example, for FEV_1, 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 ≥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 (GRβ)	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	• 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)	• Serum EDN found to correlate positively with disease severity in eosinophilic CRS [398].
Eosinophil peroxidase (EPX)	• Tissue EPX levels correlate positively but weakly with SNOT-22 scores in eosinophilic CRSwNP [400].
Neutrophils	• Conflicting results as to whether high tissue neutrophil count is associated with uncontrolled CRSwNP [381,432,433].
Nasal nitric oxide	• A significant inverse relationship was found between nasal nitric oxide levels and severity of nasal obstruction and purulent rhinorrhea [434].
Interleukins	• 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	• 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	• Serum total IgE of >400IU/L was an independent risk factor for olfactory dysfunction in eosinophilic CRSwNP patients [439].
Periostin	• Tissue and serum periostin values correlate with CRSwNP disease severity and post-operative SNOT-22 scores [440-442].
P-glycoprotein	• 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-5Rα, 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-5Rα - 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)	• 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	• 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	After ESS: • 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	• May be used as a biomarker for predicting post-operative recurrence [449,450]
Glucocorticoid Receptor β (GRβ)	• Expression of GRβ by T-cells and eosinophils in NP is predictive of corticosteroid resistance/insensitivity [451-453]
IL-5	• 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	• 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	• 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	• 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	• 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	• 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)	• 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 [465,4670]. 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/ μL 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 ≥3.7% in all CRSwNP patients and a peripheral blood eosinophil percentage of ≥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 ≥150 cells/μL 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.

Acknowledgements

None.

Authorship contribution

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

The authors declare that there are no conflicts of interests regarding the publication of this paper.

Funding

No funding.

References

1. Fokkens WJ, Lund VJ, Hopkins C, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. Rhinology 2020; 58:1-464.
2. Lund VJ, Kennedy DW. Quantification for staging sinusitis. The Staging and Therapy Group. Annals Otol, Rhinol Laryngol. Supplement 1995; 167:17-21.
3. Fokkens WJ, Viskens AS, Backer V, et al. EPOS/EUFOREA update on indication and evaluation of Biologics in Chronic Rhinosinusitis with Nasal Polyps 2023. Rhinology 2023; 61:194-202.
4. Hellings PW, Verhoeven E, Fokkens WJ. State-of-the-art overview on biological treatment for CRSwNP. Rhinology 2021; 59:151-163.
5. Sedaghat AR, Kuan EC, Scadding GK. Epidemiology of Chronic Rhinosinusitis: Prevalence and Risk Factors. J Allergy Clin Immunol Pract 2022; 10:1395-1403.
6. Sánchez-Collado I, Mora T, Muñoz-Cano R, Ribó P, Mullol J, Valero A. Prevalence of Chronic Rhinosinusitis with Nasal Polyps in Catalonia (Spain): a retrospective, large-scale population-based study. Rhinology 2022.
7. Johansson L, Akerlund A, Holmberg K, Melen I, Bende M. Prevalence of nasal polyps in adults: the Skovde population-based study. Ann Otol Rhinol Laryngol 2003; 112:625-629.
8. Klossek JM, Neukirch F, Pribil C, et al. Prevalence of nasal polyposis in France: a cross-sectional, case-control study. Allergy 2005; 60:233-237.
9. Kariyawasam HH, Chandrasekharan DP, Jacques T, et al. Biologic treatment for severe chronic rhinosinusitis with nasal polyps: a systematic review and meta-analysis. Rhinology 2023; 61:98-107.
10. Hopkins C, Han JK, Lund VJ, et al. Evaluating treatment response to mepolizumab in patients with severe CRSwNP. Rhinology 2023; 61:108-117.
11. Boscke R, Heidemann M, Bruchhage KL. Dupilumab for chronic rhinosinusitis with nasal polyps: real-life retrospective 12-month effectiveness data. Rhinology 2023; 61:203-213.
12. Boechat JL, Sousa-Pinto B, Delgado L, Silva D. Biologicals in severe chronic rhinosinusitis with nasal polyps: translation to clinical practice while waiting for head-to-head studies. Rhinology 2023; 61:283-286.
13. Brkic FF, Liu DT, Klimbacher R, et al. Efficacy and safety of switching between biologics in chronic rhinosinusitis with nasal polyps or N-ERD. Rhinology 2023; 61:320-327.
14. Gliklich RE, Metson R. Techniques for outcomes research in chronic sinusitis. The Laryngoscope 1995; 105:387-390.
15. Piccirillo JF, Edwards D, Haiduk A, Yonan C, Thawley SE. Psychometric and Clinimetric Validity of the 31-Item Rhinosinusitis Outcome Measure (RSOM-31). Am J Rhinol 1995; 9:297 - 306.
16. Rudmik L, Hopkins C, Peters A, Smith TL, Schlosser RJ, Soler ZM. Patient-reported outcome measures for adult chronic rhinosinusitis: A systematic review and quality assessment. J allergy clinical immunology 2015; 136:2.
17. Mullol J, Azar A, Buchheit KM, Hopkins C, Bernstein JA. Chronic Rhinosinusitis With Nasal Polyps: Quality of Life in the Biologics Era. J Allergy Clin Immunol Pract 2022; 10:1434-1453 e1439.
18. Benninger MS, Senior BA. The development of the Rhinosinusitis Disability Index. Arch Otolaryngol Head Neck Surg 1997; 123:1175-1179.
19. Atlas SJ, Gallagher PM, Wu YA, et al. Development and validation of a new health-related quality of life instrument for patients with sinusitis. Qual Life Res 2005; 14:1375-1386.
20. Atlas SJ, Metson RB, Singer DE, Wu YA, Gliklich RE. Validity of a new health-related quality of life instrument for patients with chronic sinusitis. Laryngoscope 2005; 115:846-854.
21. Anderson ER, Murphy MP, Weymuller EA, Jr. Clinimetric evaluation of the Sinonasal Outcome Test-16. Student Research Award 1998. Otolaryngol Head Neck Surg 1999; 121:702-707.
22. Piccirillo JF, Merritt MG, Jr., Richards ML. Psychometric and clinimetric validity of the 20-Item Sino-Nasal Outcome Test (SNOT-20). Otolaryngology-head and neck surgery. 2002; 126:41-47.
23. Dixon AE, Sugar EA, Zinreich SJ, et al. Criteria to screen for chronic sinonasal disease. Chest 2009; 136:1324-1332.
24. Rizk HG, Ferguson BJ. Categorizing nasal polyps by severity and controller therapy. Arch Otolaryngol Head Neck Surg 2012; 138:846-853.
25. Clinical Effectiveness Unit. The National Comparative Audit of Surgery for Nasal Polyposis and Chronic Rhinosinusitis: The Royal College of Surgeons of England, 2003.
26. Buckland JR, Thomas S, Harries PG. Can the Sino-nasal Outcome Test (SNOT-22) be used as a reliable outcome measure for successful septal surgery? Clin Otolaryngol Allied Sci 2003; 28:43-47.
27. Hopkins C, Browne JP, Slack R, et al. The national comparative audit of surgery for nasal polyposis and chronic rhinosinusitis. Clin Otolaryngol 2006; 31:390-398.
28. Hopkins C, Gillett S, Slack R, Lund VJ, Browne JP. Psychometric validity of the 22-item Sinonasal Outcome Test. Clin Otolaryngol. 2009; 34:447-454.
29. Orlandi RR, Kingdom TT, Smith TL, et al. International consensus statement on allergy and rhinology: rhinosinusitis 2021. Int Forum Allergy Rhinol 2021; 11:213-739.
30. Hopkins C, Hettige R, Soni-Jaiswal A, et al. CHronic Rhinosinusitis Outcome MEasures (CHROME), developing a core outcome set for trials of interventions in chronic rhinosinusitis. Rhinology 2018; 56:22-32.
31. Toma S, Hopkins C. Stratification of SNOT-22 scores into mild, moderate or severe and relationship with other subjective instruments. Rhinology 2016; 54:129-133.
32. Husain Q, Hoehle L, Phillips K, Caradonna DS, Gray ST, Sedaghat AR. The 22-Item Sinonasal Outcome Test as a Tool for the Assessment of Quality of Life and Symptom Control in Allergic Rhinitis. Am J Rhinol Allergy 2020; 34:209-216.
33. Lachanas VA, Tsea M, Tsiouvaka S, Hajiioannou JK, Skoulakis CE, Bizakis JG. The sino-nasal outcome test (SNOT)-22: validation for Greek patients. Eur Arch Otorhinolaryngol 2014; 271:2723-2728.
34. Vaitkus S, Padervinskis E, Balsevicius T, et al. Translation, cross-cultural adaptation, and validation of the sino-nasal outcome test (SNOT)-22 for Lithuanian patients. Eur Arch Otorhinolaryngol 2013; 270:1843-1848.
35. Kosugi EM, Chen VG, Fonseca VM, Cursino MM, Mendes Neto JA, Gregorio LC. Translation, cross-cultural adaptation and validation of SinoNasal Outcome Test (SNOT): 22 to Brazilian Portuguese. Braz J Otorhinolaryngol 2011; 77:663-669.
36. Caminha GP, Melo Junior JT, Hopkins C, Pizzichini E, Pizzichini MM. SNOT-22: psychometric properties and cross-cultural adaptation into the Portuguese language spoken in Brazil. Braz J Otorhinolaryngol 2012; 78:34-39.
37. Schalek P, Otruba L, Hahn A. Quality of life in patients with chronic rhinosinusitis: a validation of the Czech version of SNOT-22 questionnaire. Eur Arch Otorhinolaryngol 2010; 267:473-475.
38. Shapira Galitz Y, Halperin D, Bavnik Y,

Warman M. Sino-Nasal Outcome Test-22: Translation, Cross-cultural Adaptation, and Validation in Hebrew-Speaking Patients. Otolaryngol Head Neck Surg 2016; 154:951-956.
39. Lange B, Thilsing T, Al-kalemji A, Baelum J, Martinussen T, Kjeldsen A. The Sino-Nasal Outcome Test 22 validated for Danish patients. Dan Med Bull 2011; 58:A4235.
40. Albrecht T, Beule AG, Hildenbrand T, et al. Cross-cultural adaptation and validation of the 22-item sinonasal outcome test (SNOT-22) in German-speaking patients: a prospective, multicenter cohort study. Eur Arch Otorhinolaryngol 2022; 279:2433-2439.
41. de Dorlodot C, Horoi M, Lefebvre P, et al. French adaptation and validation of the sino-nasal outcome test-22: a prospective cohort study on quality of life among 422 subjects. Clin Otolaryngol 2015; 40:29-35.
42. Alanazy F, Dousary SA, Albosaily A, Aldriweesh T, Alsaleh S, Aldrees T. Psychometric Arabic Sino-Nasal Outcome Test-22: validation and translation in chronic rhinosinusitis patients. Ann Saudi Med 2018; 38:22-27.
43. Adnane C, Adouly T, Oubahmane T, et al. Psychometric Validation of a Moroccan Version of the 22-Item Sino-Nasal Outcome Test. Otolaryngol Head Neck Surg 2016; 155:681-687.
44. Mozzanica F, Preti A, Gera R, et al. Cross-cultural adaptation and validation of the SNOT-22 into Italian. Eur Arch Otorhinolaryngol 2017; 274:887-895.
45. Eisenbach N, Matot S, Nemet A, Sela E, Marshak T, Ronen O. Sino-nasal outcome test-22: Cross-cultural adaptation and validation in Russian speaking patients. Clin Otolaryngol 2020; 45:350-356.
46. Numthavaj P, Bhongmakapat T, Roongpuwabaht B, Ingsathit A, Thakkinstian A. The validity and reliability of Thai Sinonasal Outcome Test-22. Eur Arch Otorhinolaryngol 2017; 274:289-295.
47. Thakur P, Gupta V, Nanda MS, Bhatia S. Psychometric Validation of Hindi Version of Sino-Nasal Outcome Test-22. Indian J Otolaryngol Head Neck Surg 2022; 74:1651-1660.
48. Jalessi M, Farhadi M, Kamrava SK, et al. The reliability and validity of the persian version of sinonasal outcome test 22 (snot 22) questionnaires. Iran Red Crescent Med J 2013; 15:404-408.
49. de los Santos G, Reyes P, del Castillo R, Fragola C, Royuela A. Cross-cultural adaptation and validation of the sino-nasal outcome test (SNOT-22) for Spanish-speaking patients. Eur Arch Otorhinolaryngol 2015; 272:3335-3340.
50. Koskinen A, Hammaren-Malmi S, Myller J, et al. Translation, cross-cultural adaptation, and validation of the sino-nasal outcome test (snot)-22 for Finnish patients. Eur Arch Otorhinolaryngol 2021; 278:405-410.
51. Dietz de Loos DAE, Cornet ME, Fokkens WJ, Reitsma S. Validation of the Dutch version of the 22-item Sino-Nasal Outcome Test (SNOT-22). Rhinology Online 2022; 5:128 - 132.
52. Soler ZM, Rosenbloom JS, Skarada D, Gutman M, Hoy MJ, Nguyen SA. Prospective, multicenter evaluation of balloon sinus dilation for treatment of pediatric chronic rhinosinusitis. Int Forum Allergy Rhinol 2017; 7:221-229.
53. Thamboo A, Santos RC, Naidoo L, Rahmanian R, Chilvers MA, Chadha NK. Use of the SNOT-22 and UPSIT to appropriately select pediatric patients with cystic fibrosis who should be referred to an otolaryngologist: cross-sectional study. JAMA Otolaryngol Head Neck Surg 2014; 140:934-939.
54. Lourijsen ES, Reitsma S, Vleming M, et al. Endoscopic sinus surgery with medical therapy versus medical therapy for chronic rhinosinusitis with nasal polyps: a multicentre, randomised, controlled trial. Lancet Respir Med 2022; 10:337-346.
55. Bachert C, Mannent L, Naclerio RM, et al. Effect of Subcutaneous Dupilumab on Nasal Polyp Burden in Patients With Chronic Sinusitis and Nasal Polyposis: A Randomized Clinical Trial. Jama 2016; 315:469-479.
56. Bachert C, Han JK, Desrosiers M, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. Lancet 2019; 394:1638-1650.
57. Bachert C, Han JK, Desrosiers MY, et al. Efficacy and safety of benralizumab in chronic rhinosinusitis with nasal polyps: A randomized, placebo-controlled trial. J Allergy Clin Immunol 2022; 149:1309-1317 e1312.
58. Han JK, Bachert C, Fokkens W, et al. Mepolizumab for chronic rhinosinusitis with nasal polyps (SYNAPSE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med 2021; 9:1141-1153.
59. DeConde AS, Bodner TE, Mace JC, Smith TL. Response shift in quality of life after endoscopic sinus surgery for chronic rhinosinusitis. JAMA otolaryngology-- head & neck surgery 2014; 140:712-719.
60. Crump RT, Liu G, Janjua A, Sutherland JM. Analyzing the 22-item Sino-Nasal Outcome Test using item response theory. Int Forum Allergy Rhinol 2016; 6:914-920.
61. Feng AL, Wesely NC, Hoehle LP, et al. A validated model for the 22-item Sino-Nasal Outcome Test subdomain structure in chronic rhinosinusitis. Int Forum Allergy Rhinol 2017; 7:1140-1148.
62. Khan AH, Reaney M, Guillemin I, et al. Development of Sinonasal Outcome Test (SNOT-22) Domains in Chronic Rhinosinusitis With Nasal Polyps. Laryngoscope 2022; 132:933-941.
63. Fokkens W, Trigg A, Lee SE, et al. Mepolizumab improvements in health-related quality of life and disease symptoms in a patient population with very severe chronic rhinosinusitis with nasal polyps: psychometric and efficacy analyses from the SYNAPSE study. J Patient Rep Outcomes 2023; 7:4.
64. Gray ST, Phillips KM, Hoehle LP, Caradonna DS, Sedaghat AR. The 22-item Sino-Nasal Outcome Test accurately reflects patient-reported control of chronic rhinosinusitis symptomatology. Int Forum Allergy Rhinol 2017; 7:945-951.
65. Epperson MV, Phillips KM, Caradonna DS, Gray ST, Sedaghat AR. Predictors of efficacy for combination oral and topical corticosteroids to treat patients with chronic rhinosinusitis with nasal polyps. Int Forum Allergy Rhinol 2019; 9:1436-1442.
66. Gallo S, Russo F, Mozzanica F, et al. Prognostic value of the Sinonasal Outcome Test 22 (SNOT-22) in chronic rhinosinusitis. Acta Otorhinolaryngol Ital 2020; 40:113-121.
67. Hopkins C, Rudmik L, Lund VJ. The predictive value of the preoperative Sinonasal Outcome Test-22 score in patients undergoing endoscopic sinus surgery for chronic rhinosinusitis. Laryngoscope 2015; 125:1779-1784.
68. Rudmik L, Soler ZM, Mace JC, DeConde AS, Schlosser RJ, Smith TL. Using preoperative SNOT-22 score to inform patient decision for Endoscopic sinus surgery. Laryngoscope 2015; 125:1517-1522.
69. Liu DT, Philips KM, Speth MM, Besser G, Mueller CA, Sedaghat AR. Item Response Theory for Psychometric Properties of the SNOT-22 (22-Item Sinonasal Outcome Test). Otolaryngol Head Neck Surg 2021; 166:580-588.
70. Liu DT, Phillips KM, Houssein FA, et al. Dedicated Olfaction and Taste Items do not Improve Psychometric Performance of the SNOT-22. Laryngoscope 2022; 132:1644-1651.
71. Liu DT, Phillips KM, Speth MM, Besser G, Mueller CA, Sedaghat AR. Exploring possibilities for shortening the 22-item Sino-Nasal Outcome Test (SNOT-22) using item response theory. Int Forum Allergy Rhinol 2022; 12:191-199.
72. Chowdhury NI, Mace JC, Bodner TE, et al. Investigating the minimal clinically important difference for SNOT-22 symptom domains in surgically managed chronic rhinosinusitis. Int Forum Allergy Rhinol 2017; 7:1149-1155.
73. Phillips KM, Hoehle LP, Caradonna DS, Gray ST, Sedaghat AR. Minimal clinically important difference for the 22-item Sinonasal Outcome Test in medically managed patients with chronic rhinosinusitis. Clin Otolaryngol 2018; 43:1328-1334.
74. Phillips KM, Houssein FA, Boeckermann LM, Singerman KW, Liu DT, Sedaghat AR. Multi-institutional minimal clinically important difference of the 22-item Sinonasal Outcome Test in medically managed chronic rhinosinusitis. Rhinology. 2021;59(6):552-559.
75. Singerman KW, Phillips KM, Sedaghat AR. Minimal clinically important difference

for subdomains of the 22-item Sino-Nasal Outcome Test in medically managed chronic rhinosinusitis patients. Int Forum Allergy Rhinol 2022; 12:1196-1199.
76. Ji K, Risoli TJ, Kuchibhatla M, Chan L, Hachem RA, Jang DW. Symptom Profile of Chronic Rhinosinusitis Versus Obstructive Sleep Apnea in a Tertiary Rhinology Clinic. Ann Otol Rhinol Laryngol 2019; 128:963-969.
77. Derbarsegian A, Adams SM, Phillips KM, Sedaghat AR. The Burden of Migraine on Quality of Life in Chronic Rhinosinusitis. Laryngoscope 2023; 133:3279-3284..
78. Phillips KM, Sedaghat AR. Depression and Anxiety: Considerations for Interpretation of the SNOT-22 (22-Item Sinonasal Outcome Test). Otolaryngol Head Neck Surg 2022; 166:985-992.
79. Lund VJ, Holmstrom M, Scadding GK. Functional endoscopic sinus surgery in the management of chronic rhinosinusitis. An objective assessment. J Laryngol Otol 1991; 105:832-835.
80. Lund VJ, Kennedy DW. Staging for rhinosinusitis. Otolaryngology--head and neck surgery. 1997; 117:35.
81. Fokkens W, Lund V, Bachert C, et al. EAACI position paper on rhinosinusitis and nasal polyps executive summary. Allergy 2005; 60:583-601.
82. Lim M, Lew-Gor S, Darby Y, Brookes N, Scadding G, Lund VJ. The relationship between subjective assessment instruments in chronic rhinosinusitis. Rhinology 2007; 45:144-147.
83. Doulaptsi M, Prokopakis E, Seys S, Pugin B, Steelant B, Hellings P. Visual analogue scale for sino-nasal symptoms severity correlates with sino-nasal outcome test 22: paving the way for a simple outcome tool of CRS burden. Clin Transl Allergy 2018; 8:32.
84. Ragab SM, Lund VJ, Scadding G. Evaluation of the medical and surgical treatment of chronic rhinosinusitis: a prospective, randomised, controlled trial. Laryngoscope 2004; 114:923-930.
85. Rowe-Jones JM, Medcalf M, Durham SR, Richards DH, Mackay IS. Functional endoscopic sinus surgery: 5 year follow up and results of a prospective, randomised, stratified, double-blind, placebo controlled study of postoperative fluticasone propionate aqueous nasal spray. Rhinology 2005; 43:2-10.
86. Borish L, Cohen NA, Chupp G, et al. Evaluating enrollment and outcome criteria in trials of biologics for chronic rhinosinusitis with nasal polyps. Ann Allergy Asthma Immunol 2022; 129:160-168.
87. Oykhman P, Paramo FA, Bousquet J, Kennedy DW, Brignardello-Petersen R, Chu DK. Comparative efficacy and safety of monoclonal antibodies and aspirin desensitization for chronic rhinosinusitis with nasal polyposis: A systematic review and network meta-analysis. J Allergy Clin Immunol 2022; 149:1286-1295.
88. van der Veen J, Seys SF, Timmermans M, et al. Real-life study showing uncontrolled rhinosinusitis after sinus surgery in a tertiary referral centre. Allergy 2017; 72:282-290.
89. U.S. Food and Drug Administration. Chronic Rhinosinusitis With Nasal Polyps: Developing Drugs for Treatment; Draft Guidance for Industry; Availability 2023. June 2023. Available at: https://www.fda.gov/media/154724/download. Accessed 1/22/2024.
90. Phillips KM, Singerman KW, Sedaghat AR. Individual symptom visual analogue scale severity scores for determining EPOS guideline-based chronic rhinosinusitis disease control. Rhinology 2022; 60:229-235.
91. Chuang CC, Guillemin I, Bachert C, et al. Dupilumab in CRSwNP: Responder Analysis Using Clinically Meaningful Efficacy Outcome Thresholds. Laryngoscope 2022; 132:259-264.
92. Damask C, Chen M, Holweg CTJ, Yoo B, Millette LA, Franzese C. Defining the Efficacy of Omalizumab in Nasal Polyposis: A POLYP 1 and POLYP 2 Subgroup Analysis. Am J Rhinol Allergy 2022; 36:135-141.
93. Han JK, Bachert C, Lee SE, et al. Estimating Clinically Meaningful Change of Efficacy Outcomes in Inadequately Controlled Chronic Rhinosinusitis with Nasal Polyposis. Laryngoscope 2022; 132:265-271.
94. Banoub RG, Phillips KM, Hoehle LP, Caradonna DS, Gray ST, Sedaghat AR. Relationship between chronic rhinosinusitis exacerbation frequency and asthma control. Laryngoscope 2018; 128:1033-1038.
95. Phillips KM, Hoehle LP, Bergmark RW, Caradonna DS, Gray ST, Sedaghat AR. Acute Exacerbations Mediate Quality of Life Impairment in Chronic Rhinosinusitis. J Allergy Clin Immunol Pract 2017; 5:422-426.
96. Walters ZA, Sedaghat AR, Phillips KM. Acute exacerbations of chronic rhinosinusitis: The current state of knowledge. Laryngoscope Investig Otolaryngol 2022; 7:935-942.
97. Yamasaki A, Hoehle LP, Phillips KM, et al. Association between systemic antibiotic and corticosteroid use for chronic rhinosinusitis and quality of life. Laryngoscope 2018; 128:37-42.
98. Phillips KM, Speth MM, Shu ET, et al. Validity of systemic antibiotics and systemic corticosteroid usage for chronic rhinosinusitis as metrics of disease burden. Rhinology 2020; 58:194-199.
99. Walker V, Trope M, Tichavakunda AA, Speth MM, Sedaghat AR, Phillips KM. Patient Perspectives on Acute Exacerbations of Chronic Rhinosinusitis: A Qualitative Study. Otolaryngol Head Neck Surg 2023; 168:862-867.
100. Walters ZA, Sedaghat AR, Phillips KM. Establishment of a duration criterion for acute exacerbations of chronic rhinosinusitis through qualitative analysis of patient experiences. Int Forum Allergy Rhinol 2023; 13:1805-1807.
101. Fokkens WJ, De Corso E, Backer V, et al. EPOS2020/EUFOREA expert opinion on defining disease states and therapeutic goals in CRSwNP. Rhinology 2024. 62;3: 287-298.
102. Guyatt GH, Feeny DH, Patrick DL. Measuring health-related quality of life. Ann Intern Med 1993; 118:622-629.
103. Kaplan RM, Hays RD. Health-Related Quality of Life Measurement in Public Health. Annu Rev Public Health 2022; 43:355-373.
104. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Medical care 1992; 30:473-483.
105. Laucis NC, Hays RD, Bhattacharyya T. Scoring the SF-36 in Orthopaedics: A Brief Guide. J Bone Joint Surg Am 2015; 97:1628-1634.
106. Arancibia C, Langdon C, Mullol J, Alobid I. Twelve-year long-term postoperative outcomes in patients with chronic rhinosinusitis with nasal polyps. Rhinology 2022; 60:261-269.
107. Ware JE, Jr., Gandek B. Overview of the SF-36 Health Survey and the International Quality of Life Assessment (IQOLA) Project. J Clin Epidemiol 1998; 51:903-912.
108. Lins L, Carvalho FM. SF-36 total score as a single measure of health-related quality of life: Scoping review. SAGE Open Med 2016; 4:2050312116671725.
109. Rand Corportation. 36-Item Short Form Survey (SF-36) Scoring Instructions. Available at: https://www.rand.org/health-care/surveys_tools/mos/36-item-short-form/scoring.html. Accessed May 25, 2023.
110. Ware JE, Jr., Kosinski M, Bayliss MS, McHorney CA, Rogers WH, Raczek A. Comparison of methods for the scoring and statistical analysis of SF-36 health profile and summary measures: summary of results from the Medical Outcomes Study. Med Care 1995; 33:AS264-279.
111. Ogura K, Yakoub MA, Christ AB, et al. What Are the Minimum Clinically Important Differences in SF-36 Scores in Patients with Orthopaedic Oncologic Conditions? Clin Orthop Relat Res 2020; 478:2148-2158.
112. Escobar A, Quintana JM, Bilbao A, Arostegui I, Lafuente I, Vidaurreta I. Responsiveness and clinically important differences for the WOMAC and SF-36 after total knee replacement. Osteoarthritis Cartilage 2007; 15:273-280.
113. Badhiwala JH, Witiw CD, Nassiri F, et al. Minimum Clinically Important Difference in SF-36 Scores for Use in Degenerative Cervical Myelopathy. Spine (Phila Pa 1976) 2018; 43:E1260-E1266.
114. Carreon LY, Bratcher KR, Canan CE, Burke LO, Djurasovic M, Glassman SD. Differentiating minimum clinically important difference for primary and revision lumbar fusion surgeries. J Neurosurg Spine 2013; 18:102-106.
115. Maruish ME. User's Manual for the SF-36v2 Health Survey. Quality Metric Incorporated, 2011.
116. Ware J, Jr., Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996; 34:220-233.

117. Ware JEJ, Kosinski M, Dewey JE, et al. How to score and interpret single-item health status measures: a manual for users of the SF-8™ Health Survey, 2001.
118. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. J Health Econ 2002; 21:271-292.
119. Craig BM, Pickard AS, Stolk E, Brazier JE. US valuation of the SF-6D. Med Decis Making 2013; 33:793-803.
120. Brazier JE, Mulhern BJ, Bjorner JB, et al. Developing a New Version of the SF-6D Health State Classification System From the SF-36v2: SF-6Dv2. Med Care 2020; 58:557-565.
121. Walters SJ, Brazier JE. What is the relationship between the minimally important difference and health state utility values? The case of the SF-6D. Health Qual Life Outcomes 2003; 1:4.
122. Ference EH, Stubbs V, Lidder AK, et al. Measurement and comparison of health utility assessments in chronic rhinosinusitis. International forum of allergy & rhinology 2015; 5:929-936.
123. Luk LJ, Steele TO, Mace JC, Soler ZM, Rudmik L, Smith TL. Health utility outcomes in patients undergoing medical management for chronic rhinosinusitis: a prospective multiinstitutional study. International forum of allergy & rhinology 2015; 5:1018-1027.
124. Soler ZM, Colman S, Velez FF, Schlosser RJ. Exhalation delivery system with fluticasone improves quality of life and health status: pooled analysis of phase 3 trials NAVIGATE I and II. Int Forum Allergy Rhinol 2020; 10:848-855.
125. Devlin NJ, Brooks R. EQ-5D and the EuroQol Group: Past, Present and Future. Applied health economics and health policy 2017; 15:127-137.
126. EuroQol G. EuroQol--a new facility for the measurement of health-related quality of life. Health policy (Amsterdam, Netherlands) 1990; 16:199-208.
127. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011; 20:1727-1736.
128. Feng Y, Parkin D, Devlin NJ. Assessing the performance of the EQ-VAS in the NHS PROMs programme. Qual Life Res 2014; 23:977-989.
129. Epperson MV, McCann AC, Phillips KM, Caradonna DS, Gray ST, Sedaghat AR. Unbiased Measure of General Quality of Life in Chronic Rhinosinusitis Reveals Disease Modifiers. Laryngoscope 2021; 131:1206-1211.
130. Hoehle LP, Phillips KM, Bergmark RW, Caradonna DS, Gray ST, Sedaghat AR. Symptoms of chronic rhinosinusitis differentially impact general health-related quality of life. Rhinology 2016; 54:316-322.
131. Speth MM, Hoehle LP, Phillips KM, Caradonna DS, Gray ST, Sedaghat AR. Changes in chronic rhinosinusitis symptoms differentially associate with improvement in general health-related quality of life. Ann Allergy Asthma Immunol 2018; 121:195-199.
132. Hoehle LP, Phillips KM, Speth MM, Caradonna DS, Gray ST, Sedaghat AR. Responsiveness and minimal clinically important difference for the EQ-5D in chronic rhinosinusitis. Rhinology 2019; 57:110-116.
133. Brazier J, Roberts J, Tsuchiya A, Busschbach J. A comparison of the EQ-5D and SF-6D across seven patient groups. Health Econ 2004; 13:873-884.
134. Whitehurst DG, Bryan S, Lewis M. Systematic review and empirical comparison of contemporaneous EQ-5D and SF-6D group mean scores. Med Decis Making 2011; 31:E34-44.
135. Whitehurst DG, Norman R, Brazier JE, Viney R. Comparison of contemporaneous EQ-5D and SF-6D responses using scoring algorithms derived from similar valuation exercises. Value Health 2014; 17:570-577.
136. Zhang A, Mao Z, Wang Z, Wu J, Luo N, Wang P. Comparing measurement properties of EQ-5D and SF-6D in East and South-East Asian populations: a scoping review. Expert Rev Pharmacoecon Outcomes Res 2023; 23:449-468.
137. Fokkens WJ, Lund VJ, Hopkins C, et al. Executive summary of EPOS 2020 including integrated care pathways. Rhinology 2020; 58:82-111.
138. Fokkens WJ, Lund VJ, Mullol J, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2012. RhinologySupplement 2012; (23):298.
139. Sedaghat AR, Phillips KM. Defining 'control' of chronic rhinosinusitis. Curr Opin Otolaryngol Head Neck Surg 2023; 31:17-23.
140. Ali A, Fakunle DR, Yu V, et al. Heterogeneity in the definition of chronic rhinosinusitis disease control: a systematic review of the scientific literature. Eur Arch Otorhinolaryngol 2023; 280:5345-5352.
141. Speth MM, M. PK, P. HL, S. CD, T. GS, R. SA. Appropriate medical management of chronic rhinosinusitis reduces use of antibiotics and oral corticosteroids. Laryngoscope 2020; 130:E709-E714.
142. Bhandarkar ND, Mace JC, Smith TL. Endoscopic sinus surgery reduces antibiotic utilization in rhinosinusitis. International forum of allergy & rhinology 2011; 1:18-22.
143. Ho J, Li W, Grayson JW, et al. Systemic medication requirement in post-surgical patients with eosinophilic chronic rhinosinusitis. Rhinology 2021; 59:59-65.
144. Desrosiers M, Mannent LP, Amin N, et al. Dupilumab reduces systemic corticosteroid use and sinonasal surgery rate in CRSwNP. Rhinology 2021; 59:301-311.
145. Desrosiers M, Diamant Z, Castelnuovo P, et al. Sustained efficacy of mepolizumab in patients with severe chronic rhinosinusitis with nasal polyps: SYNAPSE 24-week treatment-free follow-up. Int Forum Allergy Rhinol 2023.
146. Bachert C, Han JK, Wagenmann M, et al. EUFOREA expert board meeting on uncontrolled severe chronic rhinosinusitis with nasal polyps (CRSwNP) and biologics: Definitions and management. J Allergy Clin Immunol 2021; 147:29-36.
147. Dietz de Loos DAE, Ronsmans S, Cornet ME, et al. Occupational exposure influences control of disease in patients with chronic rhinosinusitis. Rhinology 2021; 59:380-386.
148. Sindwani R, Han JK, Soteres DF, et al. NAVIGATE I: Randomized, Placebo-Controlled, Double-Blind Trial of the Exhalation Delivery System With Fluticasone for Chronic Rhinosinusitis With Nasal Polyps. Am J Rhinol Allergy 2019; 33:69-82.
149. Hopkins C, Lund V. Does time from previous surgery predict subsequent treatment failure in Chronic Rhinosinusitis with Nasal Polyps? Rhinology 2021; 59:277-283.
150. De Corso E, Pipolo C, Cantone E, et al. Survey on Use of Local and Systemic Corticosteroids in the Management of Chronic Rhinosinusitis with Nasal Polyps: Identification of Unmet Clinical Needs. J Pers Med 2022; 12.
151. Saydy N, Moubayed SP, Desrosiers M. Patient perspectives on endoscopic sinus surgery for chronic rhinosinusitis. J Otolaryngol Head Neck Surg 2021; 50:34.
152. Juniper EF, Guyatt GH, Epstein RS, Ferrie PJ, Jaeschke R, Hiller TK. Evaluation of impairment of health related quality of life in asthma: development of a questionnaire for use in clinical trials. Thorax 1992; 47:76-83.
153. Nathan RA, Sorkness CA, Kosinski M, et al. Development of the asthma control test: a survey for assessing asthma control. The Journal of allergy and clinical immunology 2004; 113:59-65.
154. Schatz M, Sorkness CA, Li JT, et al. Asthma Control Test: reliability, validity, and responsiveness in patients not previously followed by asthma specialists. The Journal of allergy and clinical immunology 2006; 117:549-556.
155. Khaleva E, Rattu A, Brightling C, et al. Development of Core Outcome Measures sets for paediatric and adult Severe Asthma (COMSA). Eur Respir J 2023; 61.
156. Schatz M, Kosinski M, Yarlas AS, Hanlon J, Watson ME, Jhingran P. The minimally important difference of the Asthma Control Test. J Allergy Clin Immunol 2009; 124:719-723 e711.
157. Bateman ED, Harrison TW, Quirce S, et al. Overall asthma control achieved with budesonide/formoterol maintenance and reliever therapy for patients on different treatment steps. Respir Res 2011; 12:38.
158. Price D, David-Wang A, Cho SH, et al. Time for a new language for asthma control: results from REALISE Asia. J Asthma Allergy 2015; 8:93-103.
159. Liu AH, Zeiger R, Sorkness C, et al. Development and cross-sectional validation of the Childhood Asthma Control Test. J Allergy Clin Immunol 2007; 119:817-825.
160. Schatz M, Zeiger RS, Mosen D, Vollmer WM.

Asthma-specific quality of life and subsequent asthma emergency hospital care. Am J Manag Care 2008; 14:206-211.
161. Juniper EF, Gruffydd-Jones K, Ward S, Svensson K. Asthma Control Questionnaire in children: validation, measurement properties, interpretation. Eur Respir J 2010; 36:1410-1416.
162. Phillips KM, Hoehle LP, Caradonna DS, Gray ST, Sedaghat AR. Association of severity of chronic rhinosinusitis with degree of comorbid asthma control. Ann Allergy Asthma Immunol 2016; 117:651-654.
163. Campbell AP, Phillips KM, Hoehle LP, et al. Association between Asthma and Chronic Rhinosinusitis Severity in the Context of Asthma Control. Otolaryngol Head Neck Surg 2018; 158:386-390.
164. Forster-Ruhrmann U, Stergioudi D, Szczepek AJ, et al. A real-life comparison of pulmonary and nasal outcomes in patients with severe asthma and nasal polyposis treated with T2-biologics. World Allergy Organ J 2023; 16:100746.
165. Gelardi M, Giancaspro R, Ronca G, et al. Correlation between chronic rhinosinusitis with nasal polyposis (CRSwNP) severity and asthma control. Am J Otolaryngol 2023; 44:103701.
166. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J 1999; 14:902-907.
167. Sullivan PW, Ghushchyan VH, Marvel J, Barrett YC, Fuhlbrigge AL. Association Between Pulmonary Function and Asthma Symptoms. J Allergy Clin Immunol Pract 2019; 7:2319-2325.
168. Barnes PJ, Casale TB, Dahl R, Pavord ID, Wechsler ME. The Asthma Control Questionnaire as a clinical trial endpoint: past experience and recommendations for future use. Allergy 2014; 69:1119-1140.
169. Juniper EF, Svensson K, Mork AC, Stahl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. Respir Med 2005; 99:553-558.
170. Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR. Development and validation of the Mini Asthma Quality of Life Questionnaire. Eur Respir J 1999; 14:32-38.
171. Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific Quality of Life Questionnaire. J Clin Epidemiol 1994; 47:81-87.
172. Juniper EF, Guyatt GH, Feeny DH, Ferrie PJ, Griffith LE, Townsend M. Measuring quality of life in children with asthma. Qual Life Res 1996; 5:35-46.
173. Lanario JW, Burns L. Use of Health Related Quality of Life in Clinical Trials for Severe Asthma: A Systematic Review. J Asthma Allergy 2021; 14:999-1010.
174. Ek A, Middelveld RJ, Bertilsson H, et al. Chronic rhinosinusitis in asthma is a negative predictor of quality of life: results from the Swedish GA(2)LEN survey. Allergy 2013; 68:1314-1321.
175. Schlosser RJ, Smith TL, Mace J, Soler ZM. Asthma quality of life and control after sinus surgery in patients with chronic rhinosinusitis. Allergy 2017; 72:483-491.
176. Sujatha S, Suja V. Evaluation of Quality of Life and Pattern of Improvement of Bronchial Asthma in Chronic Rhinosinusitis Patients Treated by Functional Endoscopic Sinus Surgery. Indian J Otolaryngol Head Neck Surg 2019; 71:2176-2181.
177. Nettis E, Brussino L, Patella V, et al. Effectiveness and safety of dupilumab in patients with chronic rhinosinusitis with nasal polyps and associated comorbidities: a multicentric prospective study in real life. Clin Mol Allergy 2022; 20:6.
178. Gevaert P, Saenz R, Corren J, et al. Long-term efficacy and safety of omalizumab for nasal polyposis in an open-label extension study. J Allergy Clin Immunol 2022; 149:957-965 e953.
179. Rimmer J, Hellings P, Lund VJ, et al. European position paper on diagnostic tools in rhinology. Rhinology 2019; 57:1-41.
180. Kim DH, Seo Y, Kim KM, Lee S, Hwang SH. Usefulness of Nasal Endoscopy for Diagnosing Patients With Chronic Rhinosinusitis: A Meta-Analysis. Am J Rhinol Allergy 2020; 34:306-314.
181. Ta NH, Gao J, Philpott C. A systematic review to examine the relationship between objective and patient-reported outcome measures in sinonasal disorders: recommendations for use in research and clinical practice. Int Forum Allergy Rhinol 2021; 11:910-923.
182. Schlosser RJ, Storck K, Smith TL, et al. Impact of postoperative endoscopy upon clinical outcomes after endoscopic sinus surgery. Int Forum Allergy Rhinol 2016; 6:115-123.
183. Smith TL, Rhee JS, Loehrl TA, Burzynski ML, Laud PW, Nattinger AB. Objective testing and quality-of-life evaluation in surgical candidates with chronic rhinosinusitis. Am J Rhinol 2003; 17:351-356.
184. Ryan WR, Ramachandra T, Hwang PH. Correlations between symptoms, nasal endoscopy, and in-office computed tomography in post-surgical chronic rhinosinusitis patients. Laryngoscope 2011; 121:674-678.
185. Psaltis AJ, Li G, Vaezeafshar R, Cho KS, Hwang PH. Modification of the Lund-Kennedy endoscopic scoring system improves its reliability and correlation with patient-reported outcome measures. Laryngoscope 2014; 124:2216-2223.
186. DeConde AS, Bodner TE, Mace JC, Alt JA, Rudmik L, Smith TL. Development of a clinically relevant endoscopic grading system for chronic rhinosinusitis using canonical correlation analysis. Int Forum Allergy Rhinol 2016; 6:478-485.
187. Zhang L, Zhang LH. Comparison of different endoscopic scoring systems in patients with chronic rhinosinusitis: reliability, validity, responsiveness and correlation. Rhinology 2017; 55:363-368.
188. Soler ZM, Hyer JM, Karnezis TT, Schlosser RJ. The Olfactory Cleft Endoscopy Scale correlates with olfactory metrics in patients with chronic rhinosinusitis. Int Forum Allergy Rhinol 2016; 6:293-298.
189. Schlosser RJ, Smith TL, Mace JC, et al. The Olfactory Cleft Endoscopy Scale: a multi-institutional validation study in chronic rhinosinusitis. Rhinology 2021; 59:181-190.
190. Poletti SC, Murta G, Hahner A, Hummel T. Olfactory cleft evaluation: a predictor for olfactory function in smell-impaired patients? Eur Arch Otorhinolaryngol 2018; 275:1129-1137.
191. Djupesland PG, Reitsma S, Hopkins C, Sedaghat AR, Peters A, Fokkens WJ. Endoscopic grading systems for nasal polyps: are we comparing apples to oranges? Rhinology 2022.
192. Gevaert P, De Craemer J, Bachert C, et al. European Academy of Allergy and Clinical Immunology position paper on endoscopic scoring of nasal polyposis. Allergy 2023; 78:912-922.
193. Gevaert P, Lang-Loidolt D, Lackner A, et al. Nasal IL-5 levels determine the response to anti-IL-5 treatment in patients with nasal polyps. J Allergy Clin Immunol 2006; 118:1133-1141.
194. Jeong SS, Chen T, Nguyen SA, Edwards TS, Schlosser RJ. Correlation of polyp grading scales with patient symptom scores and olfaction in chronic rhinosinusitis: a systematic review and meta-analysis. Rhinology 2022; 60:322-334.
195. Sedaghat AR. Treating objective outcome measures of chronic rhinosinusitis: are we making the patient or ourselves feel better? Rhinology 2022; 60:321.
196. Haxel BR, Fischer L, Pade J, Reden J, Hummel T. Nasal polyp load determines the recovery of olfaction after surgery for chronic rhinosinusitis. Rhinology 2022; 60:102-108.
197. Cornelius RS, Martin J, Wippold FJ, 2nd, et al. ACR appropriateness criteria sinonasal disease. Journal of the American College of Radiology : JACR 2013; 10:241-246.
198. Zhu KZ, He C, Li Z, et al. Development and multicenter validation of a novel radiomics-based model for identifying eosinophilic chronic rhinosinusitis with nasal polyps. Rhinology 2023; 61:132-143.
199. Lund VJ, Mackay IS. Staging in rhinosinusitus. Rhinology 1993; 31:183-184.
200. Zinreich SJ. Imaging for staging of rhinosinusitis. Ann Otol Rhinol Laryngol Suppl 2004; 193:19-23.
201. Razi B, Perkovic A, Alvarado R, et al. Sinus Radiological Findings in General Asymptomatic Populations: A Systematic Review of Incidental Mucosal Changes. Otolaryngol Head Neck Surg 2022; 167:16-24.
202. Oluwole M, Russell N, Tan L, Gardiner Q, White P. A comparison of computerized tomographic staging systems in chronic sinusitis. Clin Otolaryngol Allied Sci 1996; 21:91-95.
203. Ashraf N, Bhattacharyya N. Determination

of the "incidental" Lund score for the staging of chronic rhinosinusitis. Otolaryngology--head and neck surgery . 2001; 125:483-486.
204. Dietz de Loos D, Lourijsen ES, Wildeman MAM, et al. Prevalence of chronic rhinosinusitis in the general population based on sinus radiology and symptomatology. J Allergy Clin Immunol 2019; 143:1207-1214.
205. Hill M, Bhattacharyya N, Hall TR, Lufkin R, Shapiro NL. Incidental paranasal sinus imaging abnormalities and the normal Lund score in children. Otolaryngol Head Neck Surg 2004; 130:171-175.
206. Hopkins C, Browne JP, Slack R, Lund V, Brown P. The Lund-Mackay staging system for chronic rhinosinusitis: how is it used and what does it predict? Otolaryngol Head Neck Surg 2007; 137:555-561.
207. Hopkins C, Browne JP, Slack R, et al. Complications of surgery for nasal polyposis and chronic rhinosinusitis: the results of a national audit in England and Wales. The Laryngoscope 2006; 116:1494-1499.
208. Kennedy JL, Hubbard MA, Huyett P, Patrie JT, Borish L, Payne SC. Sino-nasal outcome test (SNOT-22): a predictor of postsurgical improvement in patients with chronic sinusitis. Ann Allergy Asthma Immunol 2013; 111:246-251 e242.
209. Brooks SG, Trope M, Blasetti M, et al. Preoperative Lund-Mackay computed tomography score is associated with preoperative symptom severity and predicts quality-of-life outcome trajectories after sinus surgery. Int Forum Allergy Rhinol 2018; 8:668-675.
210. Simmonds JC, Paz-Lansberg M, Scangas G, Metson R. Endoscopic sinus surgery for chronic rhinosinusitis: 22-item Sino-Nasal Outcome Test 5-year results. Int Forum Allergy Rhinol 2022; 12:257-265.
211. Chen T, Chidarala S, Young G, et al. Association of Sinonasal Computed Tomography Scores to Patient-Reported Outcome Measures: A Systematic Review and Meta-analysis. Otolaryngol Head Neck Surg 2023; 168:628-634.
212. Holbrook EH, Brown CL, Lyden ER, Leopold DA. Lack of significant correlation between rhinosinusitis symptoms and specific regions of sinus computer tomography scans. Am J Rhinol 2005; 19:382-387.
213. Wabnitz DA, Nair S, Wormald PJ. Correlation between preoperative symptom scores, quality-of-life questionnaires, and staging with computed tomography in patients with chronic rhinosinusitis. Am J Rhinol 2005; 19:91-96.
214. Stewart MG, Sicard MW, Piccirillo JF, Diaz-Marchan PJ. Severity staging in chronic sinusitis: are CT scan findings related to patient symptoms? Am J Rhinol 1999; 13:161-167.
215. Kohli P, Naik AN, Harruff EE, Nguyen SA, Schlosser RJ, Soler ZM. The prevalence of olfactory dysfunction in chronic rhinosinusitis. Laryngoscope 2017; 127:309-320.
216. Kohli P, Schlosser RJ, Storck K, Soler ZM. Olfactory cleft computed tomography analysis and olfaction in chronic rhinosinusitis. Am J Rhinol Allergy 2016; 30:402-406.
217. Reitsma S, Adriaensen G, Cornet ME, van Haastert RM, Raftopulos MH, Fokkens WJ. The Amsterdam Classification of Completeness of Endoscopic Sinus Surgery (ACCESS): a new CT-based scoring system grading the extent of surgery. Rhinology 2020; 58:538-543.
218. Hopkins C. Two years of COVID-19 aeuro" smell is still stealing the spotlight on the rhinology stage. Rhinology 2022; 60:81.
219. Fokkens WJ. Smell is the sense of memory and desire. Rhinology 2021; 59:113.
220. Hellings PW. Smell dysfunction in the center of Rhinology care during the covid-19 pandemic. Rhinology 2021; 59:1.
221. Han P, Su T, Qin M, Chen H, Hummel T. A systematic review of olfactory related questionnaires and scales. Rhinology 2021; 59:133-143.
222. Philpott C, Kumaresan K, Fjaeldstad AW, et al. Developing a core outcome set for clinical trials in olfactory disorders: a COMET initiative. Rhinology 2023; 61:312-319.
223. Haxel BR, Bertz-Duffy S, Fruth K, Letzel S, Mann WJ, Muttray A. Comparison of subjective olfaction ratings in patients with and without olfactory disorders. J Laryngol Otol 2012; 126:692-697.
224. Hannum ME, Ramirez VA, Lipson SJ, et al. Objective Sensory Testing Methods Reveal a Higher Prevalence of Olfactory Loss in COVID-19-Positive Patients Compared to Subjective Methods: A Systematic Review and Meta-Analysis. Chem Senses 2020; 45:865-874.
225. Saniasiaya J, Islam MA, Abdullah B. Prevalence of Olfactory Dysfunction in Coronavirus Disease 2019 (COVID-19): A Meta-analysis of 27,492 Patients. Laryngoscope 2021; 131:865-878.
226. Deems DA, Doty RL, Settle RG, et al. Smell and taste disorders, a study of 750 patients from the University of Pennsylvania Smell and Taste Center. Arch Otolaryngol Head Neck Surg 1991; 117:519-528.
227. Cain WS, Gent J, Catalanotto FA, Goodspeed RB. Clinical evaluation of olfaction. Am J Otolaryngol 1983; 4:252-256.
228. Cain WS, Gent JF, Goodspeed RB, Leonard G. Evaluation of olfactory dysfunction in the Connecticut Chemosensory Clinical Research Center. Laryngoscope 1988; 98:83-88.
229. Kobal G, Hummel T, Sekinger B, Barz S, Roscher S, Wolf S. "Sniffin' sticks": screening of olfactory performance. Rhinology 1996; 34:222-226.
230. Hummel T, Sekinger B, Wolf SR, Pauli E, Kobal G. 'Sniffin' sticks': olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold. Chem Senses 1997; 22:39-52.
231. Cain WS, Rabin MD. Comparability of two tests of olfactory functioning. Chem Senses 1989; 14:479-485.
232. Wolfensberger M, Schnieper I, Welge-Lussen A. Sniffin'Sticks: a new olfactory test battery. Acta Otolaryngol 2000; 120:303-306.
233. 233. Doty RL, Smith R, McKeown DA, Raj J. Tests of human olfactory function: principal components analysis suggests that most measure a common source of variance. Percept Psychophys 1994; 56:701-707.
234. Welge-Lussen A, Wille C, Renner B, Kobal G. Anesthesia affects olfaction and chemosensory event-related potentials. Clin Neurophysiol 2004; 115:1384-1391.
235. Doty RL. Office procedures for quantitative assessment of olfactory function. Am J Rhinol 2007; 21:460-473.
236. Doty RL, Frye RE, Agrawal U. Internal consistency reliability of the fractionated and whole University of Pennsylvania Smell Identification Test. Percept Psychophys 1989; 45:381-384.
237. Doy RL, Newhouse MG, Azzalina JD. Internal consistency and short-term test-retest reliability of the University of Pennsylvania Smell Identification Test. Chemical Senses 1985; 10:297-300.
238. Schlosser RJ, Storck KA, Rudmik L, et al. Association of olfactory dysfunction in chronic rhinosinusitis with economic productivity and medication usage. International forum of allergy & rhinology 2016.
239. Andrews PJ, Poirrier AL, Lund VJ, Choi D. Outcomes in endoscopic sinus surgery: olfaction, nose scale and quality of life in a prospective cohort study. Clin Otolaryngol 2016; 41:798-803.
240. Yousem DM, Geckle RJ, Bilker WB, Doty RL. Olfactory bulb and tract and temporal lobe volumes. Normative data across decades. Ann N Y Acad Sci 1998; 855:546-555.
241. Doty RL, Yousem DM, Pham LT, Kreshak AA, Geckle R, Lee WW. Olfactory dysfunction in patients with head trauma. Arch Neurol 1997; 54:1131-1140.
242. Doty RL, Marcus A, Lee WW. Development of the 12-item Cross-Cultural Smell Identification Test (CC-SIT). Laryngoscope 1996; 106:353-356.
243. El Rassi E, Mace JC, Steele TO, et al. Sensitivity analysis and diagnostic accuracy of the Brief Smell Identification Test in patients with chronic rhinosinusitis. Int Forum Allergy Rhinol 2016; 6:287-292.
244. Levy JM, Mace JC, Bodner TE, Alt JA, Smith TL. Defining the minimal clinically important difference for olfactory outcomes in the surgical treatment of chronic rhinosinusitis. Int Forum Allergy Rhinol 2017; 7:821-826.
245. Tripathi SH, Min S, Cody AS, et al. Variability in Minimal Clinically Important Difference Calculation and Reporting in the Otolaryngology Literature. Laryngoscope 2024; 134:2059-2069.
246. Fenolio GHM, Anselmo-Lima WT, Tomazini GC, et al. Validation of the Connecticut olfactory test (CCCRC) adapted to Brazil. Braz J Otorhinolaryngol 2022; 88:725-732.

247. Rumeau C, Nguyen DT, Jankowski R. How to assess olfactory performance with the Sniffin' Sticks test((R)). Eur Ann Otorhinolaryngol Head Neck Dis 2016; 133:203-206.
248. Hox V, Bobic S, Callebaux I, Jorissen M, Hellings PW. Nasal obstruction and smell impairment in nasal polyp disease: correlation between objective and subjective parameters. Rhinology 2010; 48:426-432.
249. Simopoulos E, Katotomichelakis M, Gouveris H, Tripsianis G, Livaditis M, Danielides V. Olfaction-associated quality of life in chronic rhinosinusitis: adaptation and validation of an olfaction-specific questionnaire. Laryngoscope 2012; 122:1450-1454.
250. Nguyen DT, Nguyen-Thi PL, Jankowski R. How does measured olfactory function correlate with self-ratings of the sense of smell in patients with nasal polyposis? Laryngoscope 2012; 122:947-952.
251. Gudziol V, Lotsch J, Hahner A, Zahnert T, Hummel T. Clinical significance of results from olfactory testing. Laryngoscope 2006; 116:1858-1863.
252. Wright BM, McKerrow CB. Maximum forced expiratory flow rate as a measure of ventilatory capacity: with a description of a new portable instrument for measuring it. Br Med J 1959; 2:1041-1046.
253. Taylor G, Macneil AR, Freed DL. Assessing degree of nasal patency by measuring peak expiratory flow rate through the nose. J Allergy Clin Immunol 1973; 52:193-198.
254. Youlten LJF. The peak nasal inspiratory flow meter: a new instrument for the assessment of the response to immunotherapy in seasonal allergic rhinitis. Allergol Immunopathol 1980; 8:344.
255. Ottaviano G, Scadding GK, Coles S, Lund VJ. Peak nasal inspiratory flow; normal range in adult population. Rhinology 2006; 44:32-35.
256. Van Zele T, Gevaert P, Holtappels G, et al. Oral steroids and doxycycline: two different approaches to treat nasal polyps. J Allergy Clin Immunol 2010; 125:1069-1076 e1064.
257. Aukema AA, Mulder PG, Fokkens WJ. Treatment of nasal polyposis and chronic rhinosinusitis with fluticasone propionate nasal drops reduces need for sinus surgery. J Allergy Clin Immunol 2005; 115:1017-1023.
258. Holmberg K, Juliusson S, Balder B, Smith DL, Richards DH, Karlsson G. Fluticasone propionate aqueous nasal spray in the treatment of nasal polyposis. Ann Allergy Asthma Immunol 1997; 78:270-276.
259. Jankowski R, Schrewelius C, Bonfils P, et al. Efficacy and tolerability of budesonide aqueous nasal spray treatment in patients with nasal polyps. Arch Otolaryngol Head Neck Surg 2001; 127:447-452.
260. Penttila M, Poulsen P, Hollingworth K, Holmstrom M. Dose-related efficacy and tolerability of fluticasone propionate nasal drops 400 microg once daily and twice daily in the treatment of bilateral nasal polyposis: a placebo-controlled randomized study in adult patients. Clin Exp Allergy 2000; 30:94-102.
261. Ruhno J, Andersson B, Denburg J, et al. A double-blind comparison of intranasal budesonide with placebo for nasal polyposis. J Allergy Clin Immunol 1990; 86:946-953.
262. Small CB, Stryszak P, Danzig M, Damiano A. Onset of symptomatic effect of mometasone furoate nasal spray in the treatment of nasal polyposis. J Allergy Clin Immunol 2008; 121:928-932.
263. Stjarne P, Blomgren K, Caye-Thomasen P, Salo S, Soderstrom T. The efficacy and safety of once-daily mometasone furoate nasal spray in nasal polyposis: a randomized, double-blind, placebo-controlled study. Acta Otolaryngol 2006; 126:606-612.
264. Raghavan U, Jones NS. A prospective randomized blinded cross-over trial using nasal drops in patients with nasal polyposis: an evaluation of effectiveness and comfort level of two head positions. Am J Rhinol 2006; 20:397-400.
265. Lund VJ, Flood J, Sykes AP, Richards DH. Effect of fluticasone in severe polyposis. Arch Otolaryngol Head Neck Surg 1998; 124:513-518.
266. Kirtsreesakul V, Khanuengkitkong T, Ruttanaphol S. Does oxymetazoline increase the efficacy of nasal steroids in treating nasal polyposis? Am J Rhinol Allergy 2016; 30:195-200.
267. Wallwork B, Coman W, Mackay-Sim A, Greiff L, Cervin A. A double-blind, randomized, placebo-controlled trial of macrolide in the treatment of chronic rhinosinusitis. Laryngoscope 2006; 116:189-193.
268. Mullol J, Laidlaw TM, Bachert C, et al. Efficacy and safety of dupilumab in patients with uncontrolled severe chronic rhinosinusitis with nasal polyps and a clinical diagnosis of NSAID-ERD: Results from two randomized placebo-controlled phase 3 trials. Allergy 2022; 77:1231-1244.
269. Ottaviano G, De Corso E, Cantone E, et al. Measuring Nasal Patency and the Sense of Smell in CRSwNP Patients Treated with Dupilumab. J Pers Med 2023; 13.
270. Ogata N, Darby Y, Scadding G. Intranasal lysine-aspirin administration decreases polyp volume in patients with aspirin-intolerant asthma. J Laryngol Otol 2007; 121:1156-1160.
271. Ragab S, Parikh A, Darby YC, Scadding GK. An open audit of montelukast, a leukotriene receptor antagonist, in nasal polyposis associated with asthma. Clin Exp Allergy 2001; 31:1385-1391.
272. Ecevit MC, Erdag TK, Dogan E, Sutay S. Effect of steroids for nasal polyposis surgery: A placebo-controlled, randomized, double-blind study. Laryngoscope 2015; 125:2041-2045.
273. Bermuller C, Kirsche H, Rettinger G, Riechelmann H. Diagnostic accuracy of peak nasal inspiratory flow and rhinomanometry in functional rhinosurgery. Laryngoscope 2008; 118:605-610.
274. Mo S, Gupta SS, Stroud A, et al. Nasal Peak Inspiratory Flow in Healthy and Obstructed Patients: Systematic Review and Meta-Analysis. Laryngoscope 2021; 131:260-267.
275. Araujo-Martins J, Bras-Geraldes C, Neuparth N. The potential role of peak nasal inspiratory flow to evaluate active sinonasal inflammation and disease severity. Sci Rep 2020; 10:12674.
276. Johansson L, Bramerson A, Holmberg K, Melen I, Akerlund A, Bende M. Clinical relevance of nasal polyps in individuals recruited from a general population-based study. Acta Otolaryngol 2004; 124:77-81.
277. Koo Ng NK, Young D, McGarry GW. Reversible nasal airway obstruction: does change in nasal peak inspiratory flow following decongestion predict response to topical steroids in chronic rhinosinusitis patients? J Laryngol Otol 2012; 126:1238-1240.
278. Ghadersohi S, Price CPE, Beaumont JL, et al. Responsiveness and Convergent Validity of a New Patient-Reported Outcome Measure for Chronic Rhinosinusitis (CRS-PRO). J Allergy Clin Immunol Pract 2020; 8:2351-2359 e2352.
279. Jose J, Ell SR. The association of subjective nasal patency with peak inspiratory nasal flow in a large healthy population. Clin Otolaryngol Allied Sci 2003; 28:352-354.
280. Proimos EK, Kiagiadaki DE, Chimona TS, Seferlis FG, Maroudias NJ, Papadakis CE. Comparison of acoustic rhinometry and nasal inspiratory peak flow as objective tools for nasal obstruction assessment in patients with chronic rhinosinusitis. Rhinology 2015; 53:66-74.
281. Dor-Wojnarowska A, Radlinska A, Rabski M, et al. Investigation of Repeatability of Peak Nasal Inspiratory Flow Rate Measurements Under Baseline Conditions and After Administration of 0.05% Oxymetazoline. Am J Rhinol Allergy 2022; 36:41-46.
282. Timperley D, Srubisky A, Stow N, Marcells GN, Harvey RJ. Minimal clinically important differences in nasal peak inspiratory flow. Rhinology 2011; 49:37-40.
283. Chin D, Marcells G, Malek J, et al. Nasal peak inspiratory flow (NPIF) as a diagnostic tool for differentiating decongestable from structural nasal obstruction. Rhinology 2014; 52:116-121.
284. Auge J, Vent J, Agache I, et al. EAACI Position paper on the standardization of nasal allergen challenges. Allergy 2018; 73:1597-1608.
285. Ottaviano G, Scadding GK, Scarpa B, Accordi D, Staffieri A, Lund VJ. Unilateral peak nasal inspiratory flow, normal values in adult population. Rhinology 2012; 50:386-392.
286. Ottaviano G, Lund VJ, Nardello E, et al. Comparison between unilateral PNIF and rhinomanometry in healthy and obstructed noses. Rhinology 2014; 52:25-30.
287. Volstad I, Olafsson T, Steinsvik EA, Dahl FA, Skrindo I, Bachmann-Harildstad G. Minimal unilateral peak nasal inspiratory flow correlates with patient reported nasal obstruction. Rhinology 2019; 57:436-443.
288. Ottaviano G, Fokkens WJ. Measurements of nasal airflow and patency: a critical review

with emphasis on the use of peak nasal inspiratory flow in daily practice. Allergy 2016; 71:162-174.
289. Bouzgarou MD, Ben Saad H, Chouchane A, et al. North African reference equation for peak nasal inspiratory flow. J Laryngol Otol 2011; 125:595-602.
290. Gleadhill C, Speth MM, Gengler I, et al. Chronic rhinosinusitis disease burden is associated with asthma-related emergency department usage. Eur Arch Otorhinolaryngol 2021; 278:93-99.
291. Phillips KM, Hoehle LP, Bergmark RW, et al. Chronic rhinosinusitis severity is associated with need for asthma-related systemic corticosteroids. Rhinology 2017; 55:211-217.
292. Larsen K. The clinical relationship of nasal polyps to asthma. Allergy Asthma Proc 1996; 17:243-249.
293. Enright PL, Lebowitz MD, Cockroft DW. Physiologic measures: pulmonary function tests. Asthma outcome. Am J Respir Crit Care Med 1994; 149:S9-18; discussion S19-20.
294. Abdulghany A, Surda P, Hopkins C. Core Outcome Measures in Chronic Rhinosinusitis With Nasal Polyps: In Practice and Research. Am J Rhinol Allergy 2023; 37:232-239.
295. Jain P, Kavuru MS, Emerman CL, Ahmad M. Utility of peak expiratory flow monitoring. Chest 1998; 114:861-876.
296. Vashishta R, Soler ZM, Nguyen SA, Schlosser RJ. A systematic review and meta-analysis of asthma outcomes following endoscopic sinus surgery for chronic rhinosinusitis. Int Forum Allergy Rhinol 2013; 3:788-794.
297. Cao Y, Hong H, Sun Y, et al. The effects of endoscopic sinus surgery on pulmonary function in chronic rhinosinusitis patients with asthma: a systematic review and meta-analysis. Eur Arch Otorhinolaryngol 2019; 276:1405-1411.
298. Rix I, Hakansson K, Larsen CG, Frendo M, von Buchwald C. Management of chronic rhinosinusitis with nasal polyps and coexisting asthma: A systematic review. Am J Rhinol Allergy 2015; 29:193-201.
299. Harrison TW, Chanez P, Menzella F, et al. Onset of effect and impact on health-related quality of life, exacerbation rate, lung function, and nasal polyposis symptoms for patients with severe eosinophilic asthma treated with benralizumab (ANDHI): a randomised, controlled, phase 3b trial. Lancet Respir Med 2021; 9:260-274.
300. Bachert C, Sousa AR, Lund VJ, et al. Reduced need for surgery in severe nasal polyposis with mepolizumab: Randomized trial. The Journal of allergy and clinical immunology 2017; 140:1031.e1014.
301. Gevaert P, Calus L, Van Zele T, et al. Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. J Allergy Clin Immunol 2013; 131:110-116 e111.
302. Detoraki A, Tremante E, D'Amato M, et al. Mepolizumab improves sino-nasal symptoms and asthma control in severe eosinophilic asthma patients with chronic rhinosinusitis and nasal polyps: a 12-month real-life study. Ther Adv Respir Dis 2021; 15:17534666211009398.
303. Heffler E, Saccheri F, Bartezaghi M, Canonica GW. Effectiveness of omalizumab in patients with severe allergic asthma with and without chronic rhinosinusitis with nasal polyps: a PROXIMA study post hoc analysis. Clin Transl Allergy 2020; 10:25.
304. Koegelenberg CF, Swart F, Irusen EM. Guideline for office spirometry in adults, 2012. S Afr Med J 2012; 103:52-62.
305. Chen FH, Zuo KJ, Guo YB, et al. Long-term results of endoscopic sinus surgery-oriented treatment for chronic rhinosinusitis with asthma. Laryngoscope 2014; 124:24-28.
306. Dhong HJ, Jung YS, Chung SK, Choi DC. Effect of endoscopic sinus surgery on asthmatic patients with chronic rhinosinusitis. Otolaryngol Head Neck Surg 2001; 124:99-104.
307. Ehnhage A, Olsson P, Kolbeck KG, et al. Functional endoscopic sinus surgery improved asthma symptoms as well as PEFR and olfaction in patients with nasal polyposis. Allergy 2009; 64:762-769.
308. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. Eur Respir J 2005; 26:948-968.
309. Enright PL, Johnson LR, Connett JE, Voelker H, Buist AS. Spirometry in the Lung Health Study. 1. Methods and quality control. Am Rev Respir Dis 1991; 143:1215-1223.
310. Crimi C, Impellizzeri P, Campisi R, Nolasco S, Spanevello A, Crimi N. Practical considerations for spirometry during the COVID-19 outbreak: Literature review and insights. Pulmonology 2021; 27:438-447.
311. Yawn BP. Factors accounting for asthma variability: achieving optimal symptom control for individual patients. Prim Care Respir J 2008; 17:138-147.
312. Escamilla-Gil JM, Fernandez-Nieto M, Acevedo N. Understanding the Cellular Sources of the Fractional Exhaled Nitric Oxide (FeNO) and Its Role as a Biomarker of Type 2 Inflammation in Asthma. Biomed Res Int 2022; 2022:5753524.
313. Maniscalco M, Fuschillo S, Mormile I, et al. Exhaled Nitric Oxide as Biomarker of Type 2 Diseases. Cells 2023; 12.
314. Yatera K, Mukae H. Possible pathogenic roles of nitric oxide in asthma. Respir Investig 2019; 57:295-297.
315. Lipworth B, Kuo CR, Chan R. 2020 Updated Asthma Guidelines: Clinical utility of fractional exhaled nitric oxide (Feno) in asthma management. J Allergy Clin Immunol 2020; 146:1281-1282.
316. Dweik RA, Boggs PB, Erzurum SC, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. Am J Resp Crit Care Med 2011; 184:602-615.
317. American Thoracic S, European Respiratory S. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. Am J Respir Crit Care Med 2005; 171:912-930.
318. Lugogo N, Green CL, Agada N, et al. Obesity's effect on asthma extends to diagnostic criteria. J Allergy Clin Immunol 2018; 141:1096-1104.
319. Dressel H, de la Motte D, Reichert J, et al. Exhaled nitric oxide: independent effects of atopy, smoking, respiratory tract infection, gender and height. Respir Med 2008; 102:962-969.
320. Anderson WJ, Short PM, Williamson PA, Lipworth BJ. Inhaled corticosteroid dose response using domiciliary exhaled nitric oxide in persistent asthma: the FENOtype trial. Chest 2012; 142:1553-1561.
321. Buchvald F, Baraldi E, Carraro S, et al. Measurements of exhaled nitric oxide in healthy subjects age 4 to 17 years. J Allergy Clin Immunol 2005; 115:1130-1136.
322. Gratziou C, Lignos M, Dassiou M, Roussos C. Influence of atopy on exhaled nitric oxide in patients with stable asthma and rhinitis. Eur Respir J 1999; 14:897-901.
323. Galli J, Montuschi P, Passali GC, Laruffa M, Parrilla C, Paludetti G. Exhaled nitric oxide measurement in patients affected by nasal polyposis. Otolaryngol Head Neck Surg 2012; 147:351-356.
324. Karrasch S, Linde K, Rucker G, et al. Accuracy of FENO for diagnosing asthma: a systematic review. Thorax 2017; 72:109-116.
325. Busse WW, Wenzel SE, Casale TB, et al. Baseline FeNO as a prognostic biomarker for subsequent severe asthma exacerbations in patients with uncontrolled, moderate-to-severe asthma receiving placebo in the LIBERTY ASTHMA QUEST study: a post-hoc analysis. Lancet Respir Med 2021; 9:1165-1173.
326. Loewenthal L, Menzies-Gow A. FeNO in Asthma. Semin Respir Crit Care Med 2022; 43:635-645.
327. McNicholl DM, Stevenson M, McGarvey LP, Heaney LG. The utility of fractional exhaled nitric oxide suppression in the identification of nonadherence in difficult asthma. Am J Respir Crit Care Med 2012; 186:1102-1108.
328. Couillard S, Shrimanker R, Chaudhuri R, et al. Fractional Exhaled Nitric Oxide Nonsuppression Identifies Corticosteroid-Resistant Type 2 Signaling in Severe Asthma. Am J Respir Crit Care Med 2021; 204:731-734.
329. Butler CA, McMichael AJ, Honeyford K, et al. Utility of fractional exhaled nitric oxide suppression as a prediction tool for progression to biologic therapy. ERJ Open Res 2021; 7.
330. Pianigiani T, Alderighi L, Meocci M, et al. Exploring the Interaction between Fractional Exhaled Nitric Oxide and Biologic Treatment in Severe Asthma: A Systematic Review. Antioxidants (Basel) 2023; 12.
331. Park JA, Cha H, Yang SK, et al. The Role of Fractional Exhaled Nitric Oxide in Diagnosing Asthmatic Type 2 Chronic Rhinosinusitis With Nasal Polyps. Am J Rhinol Allergy 2023; 37:524-530.
332. Kambara R, Minami T, Akazawa H, et al.

Lower Airway Inflammation in Eosinophilic Chronic Rhinosinusitis as Determined by Exhaled Nitric Oxide. Int Arch Allergy Immunol 2017; 173:225-232.
333. Kurokawa R, Kanemitsu Y, Fukumitsu K, et al. Nasal polyp eosinophilia and FeNO may predict asthma symptoms development after endoscopic sinus surgery in CRS patients without asthma. J Asthma 2022; 59:1139-1147.
334. Terada T, Inui T, Moriyama K, et al. Effects of Endoscopic Sinus Surgery for Eosinophilic Chronic Rhinosinusitis on Respiratory Functions and FeNO Production in the Lower Respiratory Tract. Ear Nose Throat J 2024; 103:49-54.
335. Paoletti G, Casini M, Malvezzi L, et al. Very Rapid Improvement in Extended Nitric Oxide Parameters Is Associated With Clinical and Functional Improvement in Patients With Chronic Rhinosinusitis With Nasal Polyps Treated With Dupilumab. J Investig Allergol Clin Immunol 2023; 33:457-463.
336. Ambrosino P, Molino A, Spedicato GA, et al. Nasal Nitric Oxide in Chronic Rhinosinusitis with or without Nasal Polyps: A Systematic Review with Meta-Analysis. J Clin Med 2020; 9.
337. Lee DJ, Yip J, Lee JM. Nasal nitric oxide as a long-term monitoring and prognostic biomarker of mucosal health in chronic rhinosinusitis. Int Forum Allergy Rhinol 2020; 10:971-977.
338. Ragab SM, Lund VJ, Saleh HA, Scadding G. Nasal nitric oxide in objective evaluation of chronic rhinosinusitis therapy. Allergy 2006; 61:717-724.
339. Shapiro AJ, Josephson M, Rosenfeld M, et al. Accuracy of Nasal Nitric Oxide Measurement as a Diagnostic Test for Primary Ciliary Dyskinesia. A Systematic Review and Meta-analysis. Ann Am Thorac Soc 2017; 14:1184-1196.
340. Sedaghat A, Hopkins C. Chronic rhinosinusitis disease control as a metric for guiding treatment. Rhinology 2020; 58:193.
341. Sedaghat AR, Phillips KM. Chronic rhinosinusitis disease control: a review of the history and the evidence. Expert Rev Clin Immunol 2023; 19:903-910.
342. Dietz de Loos DAE, Cornet ME, Hopkins C, Fokkens WJ, Reitsma S. Measuring control of disease in Chronic Rhinosinusitis; assessing the correlation between SinoNasal Outcome Test-22 and Visual Analogue Scale item scores. Rhinology 2023; 61:39-46.
343. Walker V, Trope M, Tichavakunda AA, Speth MM, Sedaghat AR, Phillips KM. Disease control in chronic rhinosinusitis: a qualitative study of patient perspectives. Rhinology 2022; 60:282-292.
344. Phillips KM, Houssein FA, Singerman K, Boeckermann LM, Sedaghat AR. Patient-reported chronic rhinosinusitis disease control is a valid measure of disease burden. Rhinology 2021; 59:545-551.
345. Sedaghat AR, Hoehle LP, Gray ST. Chronic rhinosinusitis control from the patient and physician perspectives. Laryngoscope Investig Otolaryngol 2018; 3:419-433.
346. McCann AC, Trope M, Walker VL, et al. Olfactory Dysfunction is not a Determinant Of Patient-Reported Chronic Rhinosinusitis Disease Control. Laryngoscope 2021; 131:E2116-E2120.
347. Talat R, Speth MM, Gengler I, et al. Chronic rhinosinusitis patients with and without polyps experience different symptom perception and quality of life burdens. Am J Rhinol Allergy 2020.
348. Sedaghat AR, Caradonna DS, Chandra RK, et al. Determinants of physician assessment of chronic rhinosinusitis disease control using EPOS 2020 criteria and the importance of incorporating patient perspectives of disease control. Int Forum Allergy Rhinol 2023.
349. Sedaghat AR, Fokkens WJ, Lund VJ, et al. Consensus criteria for chronic rhinosinusitis disease control: an international Delphi Study. Rhinology 2023; 61:519-530.
350. Seah JJ, Thong M, Wang Y. The Diagnostic and Prognostic Role of Biomarkers in Chronic Rhinosinusitis. Diagnostics (Basel) 2023; 13.
351. Kato A, Peters AT, Stevens WW, Schleimer RP, Tan BK, Kern RC. Endotypes of chronic rhinosinusitis: Relationships to disease phenotypes, pathogenesis, clinical findings, and treatment approaches. Allergy 2022; 77:812-826.
352. Toro MDC, Antonio MA, Alves Dos Reis MG, de Assumpcao MS, Sakano E. Achieving the best method to classify Eosinophilic Chronic Rhinosinusitis: a systematic review. Rhinology 2021; 59:330-339.
353. Lees KA, Orlandi RR, Oakley G, Alt JA. The Role of Macrolides and Doxycycline in Chronic Rhinosinusitis. Immunol Allergy Clin North Am 2020; 40:303-315.
354. Lin CF, Wang MC, Merton AT, et al. Add-on effect of clarithromycin to oral steroids as post- operative therapy for chronic rhinosinusitis with nasal polyps: a randomised controlled trial. Rhinology 2020; 58:550-558.
355. de Oliveira IS, Guimaraes AF, Arantes Pegas GF, et al. Azithromycin for chronic eosinophilic rhinosinusitis with nasal polyp: a placebo-controlled trial. Rhinology 2020; 58:610-617.
356. Varvyanskaya A, Lopatin A. Efficacy of long-term low-dose macrolide therapy in preventing early recurrence of nasal polyps after endoscopic sinus surgery. Int Forum Allergy Rhinol 2014; 4:533-541.
357. Peric A, Vojvodic D, Matkovic-Jozin S. Effect of long-term, low-dose clarithromycin on T helper 2 cytokines, eosinophilic cationic protein and the 'regulated on activation, normal T cell expressed and secreted' chemokine in the nasal secretions of patients with nasal polyposis. J Laryngol Otol 2012; 126:495-502.
358. Cervin A, Wallwork B, Mackay-Sim A, Coman WB, Greiff L. Effects of long-term clarithromycin treatment on lavage-fluid markers of inflammation in chronic rhinosinusitis. Clin Physiol Funct Imaging 2009; 29:136-142.
359. Fujita K, Shimizu T, Majima Y, Sakakura Y. Effects of macrolides on interleukin-8 secretion from human nasal epithelial cells. Eur Arch Otorhinolaryngol 2000; 257:199-204.
360. Yamada T, Fujieda S, Mori S, Yamamoto H, Saito H. Macrolide treatment decreased the size of nasal polyps and IL-8 levels in nasal lavage. American Journal of Rhinology 2000; 14:143-148.
361. Chan D, Ooi E, Khalid O. A systematic review and meta-analysis of the role of doxycycline in chronic rhinosinusitis. J Laryngol Otol 2023; 137:474-483.
362. Huvenne W, Zhang N, Tijsma E, et al. Pilot study using doxycycline-releasing stents to ameliorate postoperative healing quality after sinus surgery. Wound Repair Regen 2008; 16:757-767.
363. Barnes PJ. Molecular mechanisms of corticosteroids in allergic diseases. Allergy 2001; 56:928-936.
364. Wen W, Liu W, Zhang L, et al. Increased neutrophilia in nasal polyps reduces the response to oral corticosteroid therapy. J Allergy Clin Immunol 2012; 129:1522-1528 e1525.
365. Zhang Y, Lou H, Wang Y, Li Y, Zhang L, Wang C. Comparison of Corticosteroids by 3 Approaches to the Treatment of Chronic Rhinosinusitis With Nasal Polyps. Allergy Asthma Immunol Res 2019; 11:482-497.
366. de Borja Callejas F, Martinez-Anton A, Picado C, et al. Corticosteroid treatment regulates mucosal remodeling in chronic rhinosinusitis with nasal polyps. Laryngoscope 2015; 125:E158-167.
367. Honma A, Takagi D, Nakamaru Y, Homma A, Suzuki M, Fukuda S. Reduction of blood eosinophil counts in eosinophilic chronic rhinosinusitis after surgery. J Laryngol Otol 2016; 130:1147-1152.
368. Brescia G, Parrino D, Zanotti C, et al. Blood Eosinophil and Basophil Values Before and After Surgery for Eosinophilic-type Sinonasal Polyps. Am J Rhinol Allergy 2018; 32:194-201.
369. Yancey KL, Li P, Huang LC, et al. Longitudinal stability of chronic rhinosinusitis endotypes. Clin Exp Allergy 2019; 49:1637-1640.
370. Jonstam K, Alsharif S, Bogaert S, et al. Extent of inflammation in severe nasal polyposis and effect of sinus surgery on inflammation. Allergy 2021; 76:933-936.
371. Jonstam K, Swanson BN, Mannent LP, et al. Dupilumab reduces local type 2 pro-inflammatory biomarkers in chronic rhinosinusitis with nasal polyposis. Allergy 2019; 74:743-752.
372. Bachert C, Corren J, Lee SE, et al. Dupilumab efficacy and biomarkers in chronic rhinosinusitis with nasal polyps: Association between dupilumab treatment effect on nasal polyp score and biomarkers of type 2 inflammation in patients with chronic rhinosinusitis with nasal polyps in the phase 3 SINUS-24 and SINUS-52 trials. Int Forum Allergy Rhinol 2022; 12:1191-1195.
373. Armengot-Carceller M, Gomez-Gomez MJ, Garcia-Navalon C, et al. Effects of Omalizumab Treatment in Patients With

Recalcitrant Nasal Polyposis and Mild Asthma: A Multicenter Retrospective Study. Am J Rhinol Allergy 2021; 35:516-524.
374. De Schryver E, Derycke L, Calus L, et al. The effect of systemic treatments on periostin expression reflects their interference with the eosinophilic inflammation in chronic rhinosinusitis with nasal polyps. Rhinology 2017; 55:152-160.
375. Tai J, Han M, Kim TH. Therapeutic Strategies of Biologics in Chronic Rhinosinusitis: Current Options and Future Targets. Int J Mol Sci 2022; 23.
376. Gevaert P, Han JK, Smith SG, et al. The roles of eosinophils and interleukin-5 in the pathophysiology of chronic rhinosinusitis with nasal polyps. Int Forum Allergy Rhinol 2022; 12:1413-1423.
377. Shah SA, Ishinaga H, Takeuchi K. Pathogenesis of eosinophilic chronic rhinosinusitis. J Inflamm (Lond) 2016; 13:11.
378. Kountakis SE, Arango P, Bradley D, Wade ZK, Borish L. Molecular and cellular staging for the severity of chronic rhinosinusitis. The Laryngoscope 2004; 114:1895-1905.
379. Soler ZM, Sauer D, Mace J, Smith TL. Impact of mucosal eosinophilia and nasal polyposis on quality-of-life outcomes after sinus surgery. Otolaryngol Head Neck Surg 2010; 142:64-71.
380. Tokunaga T, Sakashita M, Haruna T, et al. Novel scoring system and algorithm for classifying chronic rhinosinusitis: the JESREC Study. Allergy 2015; 70:995-1003.
381. Lou H, Meng Y, Piao Y, Wang C, Zhang L, Bachert C. Predictive significance of tissue eosinophilia for nasal polyp recurrence in the Chinese population. Am J Rhinol Allergy 2015; 29:350-356.
382. Xu X, Seet JE, Yap QV, et al. Latent class analysis of structured histopathology in prognosticating surgical outcomes of chronic rhinosinusitis with nasal polyps in Singapore. Rhinology 2023; 61:358-367.
383. Matsuwaki Y, Ookushi T, Asaka D, et al. Chronic rhinosinusitis: risk factors for the recurrence of chronic rhinosinusitis based on 5-year follow-up after endoscopic sinus surgery. Int Arch Allergy Immunol 2008; 146 Suppl 1:77-81.
384. Brescia G, Barion U, Zanotti C, Giacomelli L, Martini A, Marioni G. The prognostic role of serum eosinophil and basophil levels in sinonasal polyposis. Int Forum Allergy Rhinol 2017; 7:261-267.
385. Shen KH, Wang YH, Hsu TW, Hsieh LC, Sun FJ, Wang YP. Differential effects of postoperative oral corticosteroid on eosinophilic vs. non-eosinophilic CRSwNP subtypes. Am J Otolaryngol 2019; 40:22-29.
386. Deng J, Wang Z, Xu Z, et al. Blood eosinophils to direct oral corticosteroid treatment for patients with nasal polyps aeuro" an open label, non-inferiority, randomized control trial. Rhinology 2023; 61:328-337.
387. Seresirikachorn K, Kerr SJ, Aeumjaturapat S, et al. Predictive factors for identifying macrolide responder in treating chronic rhinosinusitis. Rhinology 2021; 59:284-291.
388. Fujieda S, Matsune S, Takeno S, et al. Dupilumab efficacy in chronic rhinosinusitis with nasal polyps from SINUS-52 is unaffected by eosinophilic status. Allergy 2022; 77:186-196.
389. Soyka MB, Ryser FS, Bruhlmann C, et al. Predicting dupilumab treatment outcome in patients with primary diffuse type 2 chronic rhinosinusitis. Allergy 2023; 78:1036-1046.
390. Bachert C, Khan AH, Lee SE, et al. Prevalence of type 2 inflammatory signatures and efficacy of dupilumab in patients with chronic rhinosinusitis with nasal polyps from two phase 3 clinical trials: SINUS-24 and SINUS-52. Int Forum Allergy Rhinol 2023.
391. Rabin MD. Experience facilitates olfactory quality discrimination. Percept Psychophys 1988; 44:532-540.
392. Jehl C, Royet JP, Holley A. Odor discrimination and recognition memory as a function of familiarization. Percept Psychophys 1995; 57:1002-1011.
393. Rodriguez-Alcazar JF, Ataide MA, Engels G, et al. Charcot-Leyden Crystals Activate the NLRP3 Inflammasome and Cause IL-1beta Inflammation in Human Macrophages. J Immunol 2019; 202:550-558.
394. Forster-Ruhrmann U, Szczepek AJ, Pierchalla G, et al. Chemokine Expression-Based Endotype Clustering of Chronic Rhinosinusitis. J Pers Med 2022; 12.
395. Patadia M, Dixon J, Conley D, et al. Evaluation of the presence of B-cell attractant chemokines in chronic rhinosinusitis. Am J Rhinol Allergy 2010; 24:11-16.
396. Lee J, Rosenberg HF. Eosinophils in health and disease. London; Waltham, MA: Elsevier/Academic Press, 2013.
397. Watelet JB, Bachert C, Claeys C, Van Cauwenberge P. Matrix metalloproteinases MMP-7, MMP-9 and their tissue inhibitor TIMP-1: expression in chronic sinusitis vs nasal polyposis. Allergy 2004; 59:54-60.
398. Tsuda T, Maeda Y, Nishide M, et al. Eosinophil-derived neurotoxin enhances airway remodeling in eosinophilic chronic rhinosinusitis and correlates with disease severity. Int Immunol 2019; 31:33-40.
399. Barnes PJ. Reactive oxygen species and airway inflammation. Free Radic Biol Med 1990; 9:235-243.
400. Idler BM, Iijima K, Ochkur SI, et al. Eosinophil Peroxidase: A Biomarker for Eosinophilic Chronic Rhinosinusitis Agnostic of Polyp Status. Laryngoscope 2023.
401. Smith KA, Gill AS, Pollard CE, et al. An eosinophil peroxidase activity assay accurately predicts eosinophilic chronic rhinosinusitis. J Allergy Clin Immunol 2023; 152:400-407.
402. Van Zele T, Holtappels G, Gevaert P, Bachert C. Differences in initial immunoprofiles between recurrent and nonrecurrent chronic rhinosinusitis with nasal polyps. Am J Rhinol Allergy 2014; 28:192-198.
403. Bai J, Huang JH, Price CPE, et al. Prognostic factors for polyp recurrence in chronic rhinosinusitis with nasal polyps. J Allergy Clin Immunol 2022; 150:352-361 e357.
404. Bochner BS, Stevens WW. Biology and Function of Eosinophils in Chronic Rhinosinusitis With or Without Nasal Polyps. Allergy Asthma Immunol Res 2021; 13:8-22.
405. Blanchard C, Rothenberg ME. Biology of the eosinophil. Adv Immunol 2009; 101:81-121.
406. Ho J, Earls P, Harvey RJ. Systemic biomarkers of eosinophilic chronic rhinosinusitis. Curr Opin Allergy Clin Immunol 2020; 20:23-29.
407. Ramos-Ramirez P, Tliba O. Glucocorticoid Receptor beta (GRbeta): Beyond Its Dominant-Negative Function. Int J Mol Sci 2021; 22.
408. Oakley RH, Cidlowski JA. The biology of the glucocorticoid receptor: new signaling mechanisms in health and disease. J Allergy Clin Immunol 2013; 132:1033-1044.
409. Carsuzaa F, Bequignon E, Dufour X, de Bonnecaze G, Lecron JC, Favot L. Cytokine Signature and Involvement in Chronic Rhinosinusitis with Nasal Polyps. Int J Mol Sci 2021; 23.
410. Cabral-Pacheco GA, Garza-Veloz I, Castruita-De la Rosa C, et al. The Roles of Matrix Metalloproteinases and Their Inhibitors in Human Diseases. Int J Mol Sci 2020; 21.
411. Lygeros S, Danielides G, Grafanaki K, Riga M. Matrix metalloproteinases and chronic rhinosinusitis with nasal polyposis. Unravelling a puzzle through a systematic review. Rhinology 2021; 59:245-257.
412. Malinsky RR, Valera FC, Cavallari FE, et al. Matrix metalloproteinases and their impact on sinusal extension in chronic rhinosinusitis with nasal polyps. Eur Arch Otorhinolaryngol 2013; 270:1345-1348.
413. Lundberg JO. Nitric oxide and the paranasal sinuses. Anat Rec (Hoboken) 2008; 291:1479-1484.
414. Wang H, Pan L, Liu Z. Neutrophils as a Protagonist and Target in Chronic Rhinosinusitis. Clin Exp Otorhinolaryngol 2019; 12:337-347.
415. Delemarre T, Bochner BS, Simon HU, Bachert C. Rethinking neutrophils and eosinophils in chronic rhinosinusitis. J Allergy Clin Immunol 2021; 148:327-335.
416. Taha MS, Nocera A, Workman A, Amiji MM, Bleier BS. P-glycoprotein inhibition with verapamil overcomes mometasone resistance in Chronic Sinusitis with Nasal Polyps. Rhinology 2021; 59:205-211.
417. Workman AD, Kohanski MA, Cohen NA. Biomarkers in Chronic Rhinosinusitis with Nasal Polyps. Immunol Allergy Clin North Am 2018; 38:679-692.
418. Zhang W, Hubin G, Endam LM, Al-Mot S, Filali-Mouhim A, Desrosiers M. Expression of the extracellular matrix gene periostin is increased in chronic rhinosinusitis and decreases following successful endoscopic sinus surgery. Int Forum Allergy Rhinol 2012; 2:471-476.
419. Kimura Y, Tsukui D, Kono H. Uric Acid in Inflammation and the Pathogenesis of Atherosclerosis. Int J Mol Sci 2021; 22.
420. Choby G, Low CM, Levy JM, et al. Urine Leukotriene E4: Implications as a Biomarker in Chronic Rhinosinusitis. Otolaryngol Head

Neck Surg 2022; 166:224-232.
421. Rabinovitch N. Urinary leukotriene E4. Immunol Allergy Clin North Am 2007; 27:651-664; vii.
422. Fregonese L, Silvestri M, Sabatini F, Rossi GA. Cysteinyl leukotrienes induce human eosinophil locomotion and adhesion molecule expression via a CysLT1 receptor-mediated mechanism. Clin Exp Allergy 2002; 32:745-750.
423. Lee E, Robertson T, Smith J, Kilfeather S. Leukotriene receptor antagonists and synthesis inhibitors reverse survival in eosinophils of asthmatic individuals. Am J Respir Crit Care Med 2000; 161:1881-1886.
424. Snidvongs K, Lam M, Sacks R, et al. Structured histopathology profiling of chronic rhinosinusitis in routine practice. Int Forum Allergy Rhinol 2012; 2:376-385.
425. McHugh T, Snidvongs K, Xie M, Banglawala S, Sommer D. High tissue eosinophilia as a marker to predict recurrence for eosinophilic chronic rhinosinusitis: a systematic review and meta-analysis. Int Forum Allergy Rhinol 2018; 8:1421-1429.
426. Tajudeen BA, Ganti A, Kuhar HN, et al. The presence of eosinophil aggregates correlates with increased postoperative prednisone requirement. Laryngoscope 2019; 129:794-799.
427. Chowdhury NI, Chandra RK, Li P, Ely K, Turner JH. Investigating the correlation between mucus cytokine levels, inflammatory cell counts, and baseline quality-of-life measures in chronic rhinosinusitis. Int Forum Allergy Rhinol 2019; 9:538-544.
428. Soler ZM, Sauer DA, Mace J, Smith TL. Relationship between clinical measures and histopathologic findings in chronic rhinosinusitis. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery 2009; 141:454-461.
429. Hauser LJ, Chandra RK, Li P, Turner JH. Role of tissue eosinophils in chronic rhinosinusitis-associated olfactory loss. Int Forum Allergy Rhinol 2017; 7:957-962.
430. Lavin J, Min JY, Lidder AK, et al. Superior turbinate eosinophilia correlates with olfactory deficit in chronic rhinosinusitis patients. Laryngoscope 2017; 127:2210-2218.
431. Zhang L, Hu C, Sun Z, et al. Correlation of tissue eosinophil count and chemosensory functions in patients with chronic rhinosinusitis with nasal polyps after endoscopic sinus surgery. Eur Arch Otorhinolaryngol 2019; 276:1987-1994.
432. Kim DK, Kim JY, Han YE, et al. Elastase-Positive Neutrophils Are Associated With Refractoriness of Chronic Rhinosinusitis With Nasal Polyps in an Asian Population. Allergy Asthma Immunol Res 2020; 12:42-55.
433. Ikeda K, Shiozawa A, Ono N, et al. Subclassification of chronic rhinosinusitis with nasal polyp based on eosinophil and neutrophil. Laryngoscope 2013; 123:E1-9.
434. Jeong JH, Yoo HS, Lee SH, Kim KR, Yoon HJ, Kim SH. Nasal and exhaled nitric oxide in chronic rhinosinusitis with polyps. Am J Rhinol Allergy 2014; 28:e11-16.
435. Vaitkus J, Vitkauskiene A, Simuntis R, Vaitkus Z, Siupsinskiene N, Vaitkus S. Chronic Rhinosinusitis with Nasal Polyps: Age and Disease Severity Differences in the Levels of Inflammatory Markers. Medicina (Kaunas) 2021; 57.
436. Yu SE, Chiang S, Olonisakin TF, et al. Local cytokine levels associate with SNOT-22 and UPSIT scores in chronic rhinosinusitis. Int Forum Allergy Rhinol 2023.
437. Schlosser RJ, Mulligan JK, Hyer JM, Karnezis TT, Gudis DA, Soler ZM. Mucous Cytokine Levels in Chronic Rhinosinusitis-Associated Olfactory Loss. JAMA Otolaryngol Head Neck Surg 2016; 142:731-737.
438. Han X, Wu D, Sun Z, et al. Type 1/type 2 inflammatory cytokines correlate with olfactory function in patients with chronic rhinosinusitis. Am J Otolaryngol 2020; 41:102587.
439. Mori E, Matsuwaki Y, Mitsuyama C, Okushi T, Nakajima T, Moriyama H. Risk factors for olfactory dysfunction in chronic rhinosinusitis. Auris Nasus Larynx 2013; 40:465-469.
440. Yilmaz GO, Cetinkaya EA, Eyigor H, et al. The diagnostic importance of periostin as a biomarker in chronic rhinosinusitis with nasal polyp. Eur Arch Otorhinolaryngol 2022; 279:5707-5714.
441. Ninomiya T, Noguchi E, Haruna T, et al. Periostin as a novel biomarker for postoperative recurrence of chronic rhinosinitis with nasal polyps. Sci Rep 2018; 8:11450.
442. Sato T, Ikeda H, Murakami K, Murakami K, Shirane S, Ohta N. Periostin is an aggravating factor and predictive biomarker of eosinophilic chronic rhinosinusitis. Allergol Int 2023; 72:161-168.
443. Nocera AL, Meurer AT, Miyake MM, Sadow PM, Han X, Bleier BS. Secreted P-glycoprotein is a noninvasive biomarker of chronic rhinosinusitis. Laryngoscope 2017; 127:E1-E4.
444. Chen W, Bai Y, Kong W, et al. Predictive significance of Charcot-Leyden crystal structures for nasal polyp recurrence. Clin Transl Allergy 2022; 12:e12212.
445. Wu D, Yan B, Wang Y, Zhang L, Wang C. Predictive Significance of Charcot-Leyden Crystal Protein in Nasal Secretions in Recurrent Chronic Rhinosinusitis with Nasal Polyps. Int Arch Allergy Immunol 2021; 182:65-75.
446. Bystrom J, Amin K, Bishop-Bailey D. Analysing the eosinophil cationic protein--a clue to the function of the eosinophil granulocyte. Respir Res 2011; 12:10.
447. Lu PC, Lee TJ, Huang CC, Chang PH, Chen YW, Fu CH. Serum eosinophil cationic protein: a prognostic factor for early postoperative recurrence of nasal polyps. Int Forum Allergy Rhinol 2021; 11:766-772.
448. Wu PW, Chiu CH, Huang YL, et al. Tissue eosinophilia and computed tomography features in paediatric chronic rhinosinusitis with nasal polyps requiring revision surgery. Rhinology 2023; 61:348-357.
449. Yamada T, Miyabe Y, Ueki S, et al. Eotaxin-3 as a Plasma Biomarker for Mucosal Eosinophil Infiltration in Chronic Rhinosinusitis. Front Immunol 2019; 10:74.
450. Wang G, Zheng H, Chen X, et al. Exploration of Predictive Biomarkers for Postoperative Recurrence in Chronic Rhinosinusitis with Nasal Polyps Based on Serum Multiple-Cytokine Profiling. Mediators Inflamm 2022; 2022:1061658.
451. Pujols L, Mullol J, Picado C. Importance of glucocorticoid receptors in upper and lower airways. Front Biosci (Landmark Ed) 2010; 15:789-800.
452. Hamilos DL, Leung DY, Muro S, et al. GRbeta expression in nasal polyp inflammatory cells and its relationship to the anti-inflammatory effects of intranasal fluticasone. J Allergy Clin Immunol 2001; 108:59-68.
453. Valera FC, Queiroz R, Scrideli C, Tone LG, Anselmo-Lima WT. Evaluating budesonide efficacy in nasal polyposis and predicting the resistance to treatment. Clin Exp Allergy 2009; 39:81-88.
454. Calus L, Van Bruaene N, Bosteels C, et al. Twelve-year follow-up study after endoscopic sinus surgery in patients with chronic rhinosinusitis with nasal polyposis. Clin Transl Allergy 2019; 9:30.
455. Zhang Z, Liu J, Xie L, Cao W, Ma F, Zhang Y. Tissue eosinophils and mucous inflammatory cytokines for the evaluation of olfactory recovery after endoscopic sinus surgery in patients with nasal polyposis. Am J Otolaryngol 2022; 43:103561.
456. Kim DK, Kang SI, Kong IG, et al. Two-Track Medical Treatment Strategy According to the Clinical Scoring System for Chronic Rhinosinusitis. Allergy Asthma Immunol Res 2018; 10:490-502.
457. Gokani SA, Espehana A, Pratas AC, et al. Systematic Review of Protein Biomarkers in Adult Patients With Chronic Rhinosinusitis. Am J Rhinol Allergy 2023:19458924231190568.
458. Bommarito L, Guida G, Heffler E, et al. Nasal nitric oxide concentration in suspected chronic rhinosinusitis. Ann Allergy Asthma Immunol 2008; 101:358-362.
459. Vaidyanathan S, Williamson P, Anderson K, Lipworth B. Effect of systemic steroids on humming nasal nitric oxide in chronic rhinosinusitis with nasal polyposis. Ann Allergy Asthma Immunol 2010; 105:412-417.
460. Lee JM, McKnight CL, Aves T, Yip J, Grewal AS, Gupta S. Nasal nitric oxide as a marker of sinus mucosal health in patients with nasal polyposis. Int Forum Allergy Rhinol 2015; 5:894-899.
461. Colantonio D, Brouillette L, Parikh A, Scadding GK. Paradoxical low nasal nitric oxide in nasal polyposis. Clin Exp Allergy 2002; 32:698-701.
462. Deroee AF, Naraghi M, Sontou AF, Ebrahimkhani MR, Dehpour AR. Nitric oxide metabolites as biomarkers for follow-up after chronic rhinosinusitis surgery. Am J Rhinol Allergy 2009; 23:159-161.
463. Xie S, Zhang C, Xie Z, Zhang J, Zhang H,

Jiang W. Serum metabolomics identifies uric acid as a possible novel biomarker for predicting recurrence of chronic rhinosinusitis with nasal polyps. Rhinology 2023; 61:541-551.
464. Divekar R, Hagan J, Rank M, et al. Diagnostic Utility of Urinary LTE4 in Asthma, Allergic Rhinitis, Chronic Rhinosinusitis, Nasal Polyps, and Aspirin Sensitivity. J Allergy Clin Immunol Pract 2016; 4:665-670.
465. Santarelli GD, Lam KK, Han JK. Establishing Urinary Leukotriene E(4) as a Diagnostic Biomarker for Chronic Rhinosinusitis with Comorbid Asthma and Atopy. Otolaryngol Head Neck Surg 2019; 161:764-769.
466. Thorwarth RM, Scott DW, Lal D, Marino MJ. Machine learning of biomarkers and clinical observation to predict eosinophilic chronic rhinosinusitis: a pilot study. Int Forum Allergy Rhinol 2021; 11:8-15.
467. Idler BM, Lal D, Marino MJ. Urinary leukotriene E4 is a biomarker for chronic rhinosinusitis associated with leukotriene dysregulation irrespective of aspirin sensitivity status. Int Forum Allergy Rhinol 2022; 12:805-808.

Ahmad R. Sedaghat, MD, PhD
Department of Otolaryngology
Head and Neck Surgery
University of Cincinnati College of Medicine
Medical Sciences Building Room 6410
231 Albert Sabin Way
Cincinnati, OH 45267-0528
USA

Tel: +001 513-558-4152
Fax: +001 513-558-3231
E-mail: ahmad.sedaghat@uc.edu

Saad Alsaleh, MBBS FRCSC
Department of Otolaryngology
Head and Neck Surgery
College of Medicine
King Saud University
Riyadh
Saudi Arabia

E-mail: alssaad@ksu.edu.sa

Ahmad R. Sedaghat[1], Raewyn G. Campbell[2], Richard G. Douglas[3], Wytske J. Fokkens[4], Aneeza W. Hamizan[5], Zeina R. Korban[6], Victoria S. Lee[7], Luis Macias-Valle[8], Fabrizio R. Romano[9], Kornkiat Snidvongs[10], Saad Alsaleh[11]

[1] Department of Otolaryngology Head and Neck Surgery, University of Cincinnati College of Medicine, Cincinnati, OH, USA
[2] Faculty of Medicine, Health and Human Sciences, Macquarie University, Sydney, Australia; Department of Otorhinolaryngology, Head and Neck Surgery, Royal Prince Alfred Hospital, Sydney, Australia; Rhinology and Skull Base Research Group, Applied Medical Research Centre, University of New South Wales, Sydney, Australia
[3] Department of Surgery, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand
[4] Department of Otorhinolaryngology, Amsterdam University Medical Centres, location AMC, Amsterdam, The Netherlands
[5] Department of Otorhinolaryngology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia
[6] Department of Otolaryngology, Head and Neck Surgery, American University of Beirut Medical Center, Beirut, Lebanon
[7] Department of Otolaryngology, Head and Neck Surgery, University of Illinois Chicago, Chicago, IL, USA
[8] Department of Otorlaryngology Head and Neck Surgery, Hospital Español de México, La Salle University , México City, México
[9] Universidade de São Paulo (USP), Faculdade de Medicina de Ribeirão Preto (FMRP), Ribeirão Preto, SP, Brazil
[10] Department of Otolaryngology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
[11] Department of Otolaryngology-Head and Neck Surgery, College of Medicine, King Saud University, Riyadh, Saudi Arabia

Rhinology 62: 5, 0 - 0, 2024
https://doi.org/10.4193/Rhin24.090

***Received for publication:**
February 25, 2024
Accepted: May 7, 2024

Assocociate Editor: Sietze Reitsma

CONTENT