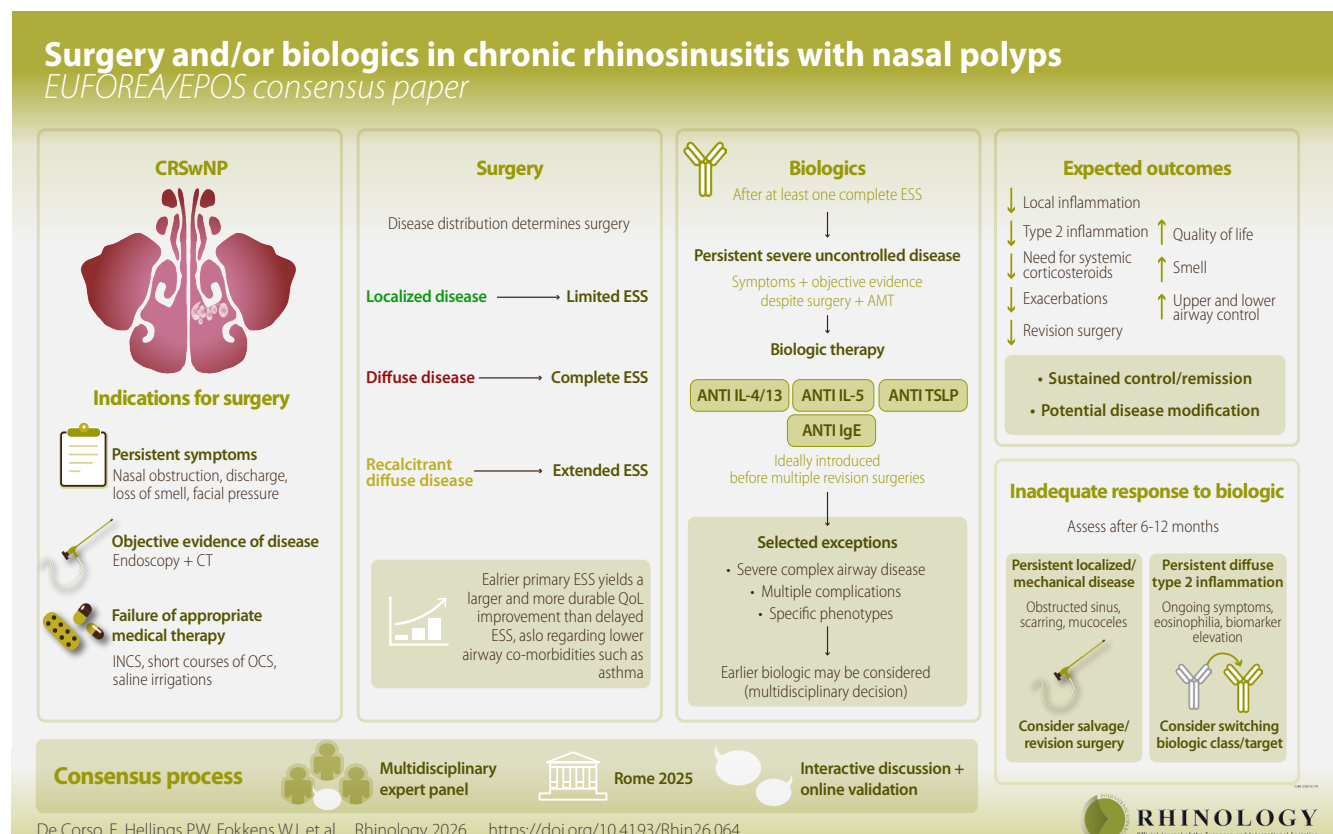


Surgery and/or biologics in chronic rhinosinusitis with nasal polyps: EUFOREA/EPOS consensus paper

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Abstract

The therapeutic landscape of chronic rhinosinusitis with nasal polyps (CRSwNP) has rapidly evolved over the past 6 years with the arrival of biologics, prompting a re-evaluation of the traditional stepwise management centred on corticosteroids and endoscopic sinus surgery (ESS). Although both ESS and biologics have proven efficacy, the optimal sequence, extent and timing of ESS relative to biologics remains a matter of debate. The international multidisciplinary panel of experts of EUFOREA/EPOS reached consensus on the aims, indications, timing, and therapeutic positioning of ESS, and biologics in CRSwNP. Evidence from pivotal RCTs, real-life studies and recent guidelines was critically reviewed. Consensus statements were drafted and refined through multiple rounds of discussion and voting. This EUFOREA/EPOS report provides key definitions and clinical criteria for ESS and biologics

in CRSwNP, offering a unified framework for personalized, evidence-based care with the aim to achieve the best outcomes for patients. The expert group agreed that patients with diffuse disease should have at least a primary complete ESS, that concurrent initiation of sinus surgery and biologic therapy is not recommended with current evidence, and the indication for biologic therapy as established by earlier guidelines were enforced. It was emphasized that with the current knowledge on side effects of systemic corticosteroids, their long-term use is no longer accepted especially where biologics are available. By emphasizing complementary and disease-modifying effects of novel care strategies, this initiative aims at optimizing outcomes across the entire airway continuum in line with EPOS/EUFOREA's mission.

Key words: biological treatment, chronic rhinosinusitis, nasal polyps, nasal surgical procedures, type-2 inflammation

Introduction

The management of severe primary diffuse chronic rhinosinusitis with nasal polyps (CRSwNP) or nasal polyp syndrome has been revolutionized during the last 6 years. The management paradigm has progressively shifted from a reactive, symptom-oriented approach toward a disease-modifying, multimodal strategy that integrates endoscopic sinus surgery (ESS) and, more recently, biologic therapies for patients with severe, refractory disease ⁽¹⁻⁴⁾. The EUFOREA/EPOS group emphasized over the past years that optimal care is achieved through an individualized, stepwise approach integrating medical, surgical, and biologic options to reduce both local and systemic inflammation, minimize systemic corticosteroid (SCS) use, and aiming for a sustained control or, if possible, a remission state even in most severe cases ⁽⁵⁻⁷⁾.

Since their introduction to the market, biologics for severe CRSwNP have been registered and reimbursed in most Western countries and continents. Consequently, the number of real-world efficacy (RWE) studies has steadily increased, reflecting their outcomes in everyday clinical practice. Following the current EUFOREA/EPOS recommendations and in line with most national health reimbursement criteria, biologics are mainly recommended after (at least) 1 ESS procedure ⁽⁷⁾. Only in a minority of surgical naïve patients, being unfit for surgery or general anaesthesia, biologics are started without prior ESS ⁽⁷⁾.

Although international position papers have extensively discussed the role of ESS and/or biologics in the treatment pathway in severe uncontrolled CRSwNP ⁽⁴⁾, several key aspects remain open to debate ⁽⁵⁻⁷⁾. There is still controversy regarding the ideal timing and the extent of primary ESS, the number of ESS needed before initiation of biologics, the extent of ESS in relation to endoscopic and radiological findings and its positioning in relation to available biologics ⁽⁶⁾.

Taking into account these considerations and the major unmet need to discuss and agree on the best care for CRSwNP, the EUFOREA/EPOS CRS Expert Panel convened an expert meeting

in Rome in October 2025 to revisit the purpose, indications, and ideal timing of ESS and biologic therapy in the modern treatment algorithm of CRSwNP patients. The discussion also included the extent of primary ESS, the place of biologics relative to surgery, and the exploration of their combined use. The potentially disease-modifying effects of both treatments, in the light of the natural history of CRSwNP, were reviewed.

Methodology

In a preliminary phase, a 4-member board of the EUFOREA group (EDC, PWH, ATP, CM) developed and pre-specified the consensus methodology, including the definition of key topics, the structure of the consensus process, and the criteria for agreement. The topics to be addressed were identified based on a targeted review of the current literature and expert prioritization.

Based on this framework, the co-chairs (EDC, ATP) independently drafted preliminary statements on surgery and biologic therapy, according to their respective areas of expertise. These statements constituted the initial material for the consensus process.

The consensus development followed a structured, multi-step approach: 1) initial statement generation, 2) face-to-face discussion and iterative refinement, and 3) external validation through an extended expert panel.

At the EUFOREA/EPOS consensus meeting held in Rome in October 2025, introductory lectures summarized the available evidence and established a shared scientific framework. Each statement was subsequently presented and discussed in a moderated session. Agreement was assessed using a structured voting process, and consensus was defined a priori as $\geq 70\%$ agreement among participants. Statements not reaching consensus were revised and re-discussed iteratively until the predefined agreement threshold was achieved.

The expert panel included specialists in otorhinolaryngology, allergology, pulmonology, epidemiology, and immunology. Patient representatives were also involved to ensure that patient perspectives were incorporated into the discussion.

In a subsequent phase, an extended panel of experts partici-

pated in a second round of evaluation conducted online. Each expert independently reviewed the statements and provided structured feedback. Responses were collected and analysed to identify areas of agreement and divergence, which informed further refinement of the statements. The revised manuscript was then circulated to all authors for final approval. Although not designed as a formal Delphi process, this methodology incorporated key elements of structured consensus development, including predefined agreement criteria, iterative feedback, and multi-round validation. The authors of this work wish to emphasize that this initiative is not intended to provide evidence-based medicine (EBM) recommendations or graded levels of recommendation; rather, its purpose was to develop an expert opinion document aimed at offering, on the basis of the authors' clinical and research experience in the field, a consensus on treatment approaches and strategies to improve patient outcomes and quality of care. This consensus aims to complement previous EUFOREA/EPOS documents ^(6,7) by specifically addressing the integration of biologics and surgery in the management of CRSwNP.

Results and Discussion

Aim of surgery and/or biologics in severe uncontrolled CRSwNP

The objective of ESS in CRSwNP is to alleviate symptoms, improve quality of life (QoL), remove the pathological and remodelled tissue, reduce the inflammatory burden, reduce the negative impact of CRSwNP on co-morbidities, restore sinus ventilation and drainage, facilitate penetration of topical therapies (e.g. intranasal corticosteroids (INCS), saline irrigations), and finally reduce the need for SCS and antibiotics ⁽⁵⁾. Randomized controlled trials (RCTs) and meta-analyses ⁽⁸⁻¹⁶⁾ consistently demonstrate that ESS results in significant and durable improvement in symptom burden and health-related QoL, as measured by Sinonasal Outcome Test (SNOT)-22, with parallel reductions in SCS use. ESS also results in olfactory improvements, which are both achievable and measurable following ESS, particularly during the early postoperative period ^(17,18).

Histologic and biomarker studies further suggest that ESS reduces local and systemic type-2 inflammatory load, translating into lower systemic inflammation and improved asthma control ⁽¹⁹⁻²³⁾. Collectively, these findings position surgery as both an anatomical and biological intervention capable of resetting local homeostasis and optimizing the response to ongoing and subsequent medical therapy (INCS and saline rinse).

Long-term data of ESS confirm sustained benefits in a large proportion of patients, estimated at approximately 60%, although symptom reappearance remains frequent, especially in cases with severe type-2 inflammation and respiratory comorbidities

⁽²⁴⁻³⁴⁾. Accordingly, maintenance of olfactory improvement over time is heterogeneous and primarily dictated by the underlying inflammatory endotype and adherence to topical therapy ⁽¹³⁾. This is particularly pronounced in type 2–dominant CRS, where olfactory recovery closely correlates with inflammatory severity and eosinophilic burden, highlighting persistent type 2 inflammation as a central determinant of incomplete ⁽¹⁷⁾ or non-durable olfaction recovery ⁽¹⁸⁾.

In this context, biologic therapies have emerged as a targeted approach addressing the underlying pathophysiology of CRSwNP, particularly type 2 inflammation. Indeed, monoclonal antibodies directed against the interleukin (IL)-4/IL-13 receptor (dupilumab, stapokibart), IL-5 (mepolizumab, depemokimab), Immunoglobulin (Ig)E (omalizumab), and Thymic Stromal Lymphopoietin (TSLP, tezepelumab), have been shown to be effective in the treatment of CRSwNP in RCTs ⁽³⁵⁻³⁸⁾. Real-world cohort studies of approved biologics demonstrated their significant improvements in symptoms and QoL, reduced pathological tissue burden and reduced need for further surgery and SCS ⁽³⁹⁻⁴⁸⁾. Literature evidence also demonstrates that biologics uniquely target the inflammatory and neuro-immunomodulatory mechanisms underlying olfactory dysfunction, positioning them as a critical therapeutic strategy when sustained or complete olfactory recovery is a primary treatment goal and a key determinant of disease severity ⁽⁴⁹⁻⁵¹⁾.

Finally, biologic therapies have been shown to significantly improve clinical outcomes not only in patients with CRSwNP alone but also in those with associated relevant comorbidities (asthma ⁽⁵²⁻⁵⁹⁾, non-steroidal anti-inflammatory-exacerbated respiratory disease (N-ERD) ⁽⁶⁰⁻⁶²⁾, eosinophilic otitis media ⁽⁶³⁾, eosinophilic esophagitis ⁽⁶⁴⁾) and frequently observing concomitant improvement in these conditions, highlighting their broader therapeutic impact across the spectrum of type 2 inflammatory diseases ^(1,65).

Together, these data underscore the complementary roles and therapeutic objectives of surgery and/or biologics in the continuum of CRSwNP care ⁽⁶⁶⁻⁷⁰⁾. Based on this premise, the expert panel discussed and exchanged views on the main objectives of surgery and the new biologic therapies, identifying many common goals between these treatment approaches, and reaching consensus on the definitions reported below.

Statements that reached consensus:

- **Aim of surgery in CRSwNP:** the primary aim of ESS is to improve symptom control and quality of life (QoL), while reducing the need for SCS and other systemic medications. The secondary aims are to reduce the inflammatory burden (removal of pathological tissue), aid delivery of topical intranasal therapy (INCS, saline), restore sinus ventilation and drainage,



Indications for primary ESS in CRSwNP

Aims	Indications/Criteria	Contraindications	Expected Outcomes	Considerations
The primary aim of surgery is to improve symptom control and QoL, while reducing the need for SCS and further surgical interventions The other aims are to reduce inflammatory burden (removal of pathological tissue), aid delivery of topical therapy, restore sinus ventilation and drainage, improve co-morbidities and prevent disease progression	ESS is indicated in CRSwNP patients with persistent symptoms negatively impacting QoL and objective evidence of disease despite appropriate medical treatment for at least 3 months Patient fit for surgery	Medical/surgical contraindications for anaesthesia/surgery	Short-term outcome (first year): Significant clinical improvement, topical INCS (rinses/sprays) should be continued Mid-term outcome (1-5 years): Moderate improvements, topical INCS should be continued Long-term outcome (> 5 yr): Recurrence rates depend on endotype, presence of lower airway comorbidities, and environmental/occupational exposure; topical INCS should be continued. Beneficial effects on lower airway comorbidities	Risk of serious complications Nasal polypectomy without complete ESS is not recommended Impact on direct postoperative QoL and work impairment Continued use of topical INCS (rinses/sprays) needed to maintain the surgical outcomes (risks of ocular complications)

Figure 1. Indications for primary endoscopic sinus surgery. Note: modified by the previous EUFOREA document ⁽⁶⁾. Abbreviations: QoL: quality of life; SCS: systemic corticosteroids; ESS: endoscopic sinus surgery; CRSwNP: chronic rhinosinusitis with nasal polyps; INCS: intranasal corticosteroids; ocular complications ⁽⁷⁶⁾.

improve lower airway co-morbidities, and prevent disease progression.

- **Aim of biologics in CRSwNP:** The primary aim of biologics is to improve symptom control and QoL, while reducing the need for SCS and further surgeries. Further aims are to reduce the inflammatory burden, restore sinus ventilation and drainage, improve lower airway co-morbidities and other type 2 comorbidities, prevent disease progression, and promote disease remission.

Indications for primary ESS

ESS remains a cornerstone of treatment of CRSwNP as it cost-effectively treats persistent symptoms and objective evidence of disease despite appropriate medical treatment (AMT) ^(5-7,9,12). In the stepwise approach in the treatment of CRSwNP ⁽¹⁾, ESS is considered after failure of medical therapy: this includes at least 3 months of regular maintenance therapy with nasal irrigation and INCS, and short courses of SCS with or without oral antibiotics ^(5-7,8,9,12).

Expected short-term outcomes of ESS include rapid and significant improvement in symptoms and QoL. Expected mid- and long-term outcomes include symptom control and reduced SCS use. Published data indicate that clinical control may remain favorable after ESS, particularly when appropriate postoperative medical therapy, including INCS, is maintained, even in the presence of endoscopic evidence of polyps, which does not necessarily correlate with symptom severity or loss of disease control ^(9-11,71-72). A RCT demonstrated that ESS combined with medical therapy was more effective than medical therapy

alone in patients with CRSwNP, although the minimal clinically important difference in SNOT-22 scores was not achieved at 12 months. Interestingly, a lower proportion of patients in the ESS plus medical therapy group experienced exacerbations of CRS and required fewer courses of SCS than those in the medical therapy-only group ⁽⁸⁾. Long-term data beyond 5 years indicate sustained benefit in a large group of patients, though symptomatic disease may recur especially in type 2 patients with comorbid asthma and N-ERD ^(15,24-32,73-75).

The expert panel revised and discussed the indications for surgery in primary diffuse CRSwNP and agreed that these rely on persistent, clinically significant symptoms coexisting with objective evidence of mucosal disease (endoscopic and radiologic), despite maintenance treatment (saline irrigations/INCS for a minimum of 3 months) and short cycles of SCS (possibly no more than 1-2 short courses per year ^(6,7)). This confirms the position of ESS in patients who remain uncontrolled with first-line care. The panel also recognized that shared decision-making is important in treatment selection: they agreed that surgery should be offered to individuals who are willing and fit to undergo anaesthesia and adhere to post-operative care schedules. The panel revised and updated the indication for primary ESS published by EUFOREA in 2024 ⁽⁶⁾, as reported in Figure 1.

Consensus reached statement:

- ESS is indicated in CRSwNP patients (patients fit for surgery) with persistent symptoms and objective evidence of disease despite AMT, including INCS for at least 3 months.

Ideal timing of primary ESS

The timing of ESS in CRSwNP is increasingly recognized as a critical determinant of long-term outcome. Accumulating evidence suggests that earlier surgical intervention after medical failure results in superior clinical and QoL outcomes as compared with delayed procedures⁽⁷⁷⁾. A large-scale, nation-wide survey demonstrated that patients who underwent surgery earlier in their disease course achieved greater and more sustained improvements in SNOT-22 scores than those with longer symptom duration prior to ESS⁽²³⁾. Furthermore, postponing surgery may not only diminish the degree of long-term improvement but also increase the likelihood of lower airway comorbidities, such as asthma and N-ERD, suggesting that persistent sinonasal inflammation may contribute to secondary lower airway involvement through a unified airway mechanism^(78,79). In addition, ESS after medical therapy failure results in significantly greater improvement in QoL and symptom burden than continued medical therapy, supporting the value of early intervention after adequate conservative management^(8,12). RCTs^(1,8,16) further corroborated these findings, demonstrating that patients randomized to surgery rather than medical treatment reported more improvement in SNOT-22, olfaction, and daily activities. Long-term follow-up data^(26,28) also highlight that earlier, comprehensive surgical treatment confers better disease control and lower revision rates over time, particularly in type-2 endotypes. In this context, the expert panel agreed during discussion that the decision to proceed with ESS should follow the failure of AMT but avoid unnecessary postponement and recurrent SCS use^(32,80).

Earlier ESS—within 12 months of symptom onset—maximizes the likelihood of durable benefit, improves QoL, and may contribute to improved lower airway outcomes, particularly in patients with comorbid or at-risk asthma development⁽²³⁾. Delaying surgery beyond this period appears to attenuate long-term outcomes, with diminishing returns even after technically adequate procedures⁽²³⁾.

Consensus reached statement:

- *After failure of at least 3 months of AMT, earlier primary ESS (preferably within 12 months of symptom onset) yields a larger and more durable QoL improvement than delayed ESS. Delay of ESS likely diminishes long-term benefit, including increased risk of developing lower airway co-morbidities such as asthma.*

Extent of primary ESS in the treatment of CRSwNP

The extent of ESS in CRSwNP represents one of the most discussed surgical variables in rhinology, especially after the introduction of biological therapy for CRSwNP and remains matter of debate in the literature⁽⁸¹⁻¹⁰⁰⁾. Over the years, the authors have tailored the extent of surgery by considering multiple factors

(disease distribution, type-2 inflammatory burden, anatomical variations, surgeons' expertise and prior interventions), rather than by adherence to a standardized template^(81,82) favoring a complete ESS when type 2 is implicated⁽⁸³⁾.

When approached from a functional perspective, ESS aims to establish a stable, open sinonasal cavity by complete removal of the diseased mucosa and bony partitions in all affected sinuses while maintaining physiological mucosal function in the unaffected areas. Emerging evidence suggests a possible relationship between the completeness of surgery and clinical durability in patients with diffuse disease^(26,28). This is primarily attributable to adequate opening of the paranasal sinuses, which facilitates effective drainage of secretions, prevents mucus plugging, and enhances the penetration and efficacy of topical corticosteroids. Indeed, larger sinus openings improve topical INCS penetration, hence facilitating long-term disease control when good adherence to postoperative medical therapy is maintained⁽⁸⁴⁻⁸⁷⁾. These findings support the concept that, in patients with diffuse CRSwNP requiring surgery, achieving complete treatment of all diseased sinuses at the index procedure may provide more durable disease control than leaving residual untreated disease (Incomplete surgery)⁽⁹⁷⁾. Accordingly, throughout this manuscript, the term "complete ESS" refers to complete treatment of all diseased sinuses according to disease extent, whereas "limited ESS" refers to an intentionally conservative procedure performed for localized disease and should not be considered synonymous with an incomplete procedure.

Extended procedures, including Draf III, middle turbinectomy, or wide maxillary antrostomy, have been taken into consideration mainly for patients with extensive or recalcitrant disease supposing its superiority in terms of long-term control compared to standard procedures^(85,88,99). Radical ESS, nasalization, or reboot surgery was also previously advocated as extended surgical approaches for recalcitrant patients⁽¹⁰⁰⁾. Nevertheless, these interventions require highly specialized expertise and carry a higher risk of complications, particularly when performed by less experienced surgeons. The experts comprehensively approached the topic of extended procedures largely discussing the risk and benefits, aiming to reconcile current evidence from the literature with the evolving therapeutic landscape shaped by the availability of biologics. The majority agreed that, in an era characterized by the availability of novel and innovative therapeutic options, the limited incremental benefits offered by this type of extended approach should be carefully weighed against the increased risk of complications in less experienced hands, longer operative times, and the lack of randomized controlled comparative studies.

Whether the completeness/extent of previous ESS influences the response to biologic therapy remains a matter of debate. Champion et al. demonstrated that disease control in biologic-treated type 2 dominant patients was significantly associated



Definitions of ESS in CRSwNP

Limited ESS	Complete ESS	Extended ESS
ESS restricted to a small number of diseased sinuses Indicated in cases of localized disease	Complete sinus opening, including anterior and posterior ethmoidectomy, middle meatal antrostomy (likely large), sphenoidotomy and frontal sinusotomy (e.g. Draft II a/b) Indicated in cases of diffuse disease	Complete ESS plus middle turbinectomy and/or Draf III and/or wide middle meatal antrostomy and/or sphenoidotomy (type 2B or above) Indicated in cases of recalcitrant diffuse disease or surgery naive patients with high risk of being recalcitrant or if anatomical variations suggest standard surgery may not achieve long term patency

Figure 2. Proposed definitions of ESS in CRSwNP. The figure refers only to surgical classification and indications, without implying a specific treatment algorithm or hierarchy. Note: Within complete ESS, maxillary sinus surgery consists of an adequately enlarged middle meatal antrostomy incorporating natural and accessory (if present) maxillary ostium and providing sufficient ventilation, visualization, drainage, and surgical access, without extending inferiorly to the nasal floor. Within extended ESS, a wide middle meatal antrostomy is considered an extended procedure because the antrostomy is enlarged substantially in the inferior direction toward, or down to, the nasal floor, potentially including additional posterior enlargement and partial resection of the inferior turbinate.

with the extent of prior surgery, with extended surgical approaches associated with improved disease control⁽⁸⁸⁾. Similarly, authors reported improved outcomes during dupilumab therapy in patients who had undergone more extensive prior ESS⁽⁸⁹⁻⁹⁰⁾. Conversely, other studies have suggested that the impact of previous surgery may be limited to specific clinical outcomes, particularly olfactory recovery. Indeed, more extensive surgical approaches have been associated with a suboptimal olfactory recovery in patients subsequently treated with biologics⁽⁹¹⁻⁹⁵⁾. Finally, other manuscripts documented efficacy of biologics irrespective of previous surgery^(39,98).

The heterogeneous findings reported in the literature, together with the inconsistent use of terms such as limited, complete, extended, and incomplete ESS, highlight the need for clearer and more consistent terminology describing the currently adopted surgical approaches in CRSwNP. To address this issue, an extensive discussion was undertaken among the ENT surgeons participating in the panel, with the aim of reviewing and refining these definitions. The agreed definitions are reported below and summarized in Figure 2.

A consensus was reached also for indications. Limited procedures are indicated only for localized disease and complete ESS for diffuse inflammation. Extended approaches are to be reserved for recalcitrant diffuse disease unresponsive to standard surgery, surgery-naïve patients at high risk of recalcitrant disease, or presence of anatomical variations in which standard surgery may not achieve long term patency. The agreed definitions are summarized in Figure 2. It should be specified that localised disease refers to mainly unilateral involvement of one or more sinuses, whereas diffuse disease generally refers to involvement of multiple sinuses (not necessarily all together) bilaterally.

The overarching goal should always be to achieve maximal surgical efficacy with minimal morbidity and minimal risk of complications, including permanent smell loss. Finally, balancing all these aspects, the panel agreed that in patients with diffuse disease, the primary surgical intervention should ideally be a complete ESS. Furthermore, limited nasal polypectomy without ESS is not recommended, as it fails to restore sinus ventilation, is associated with higher recurrence rates^(9,84) and less improvement in olfaction⁽¹⁰¹⁾.

Consensus was reached on the following definitions:

- ESS should be defined as “limited” if surgery was restricted to a small number of diseased sinuses.
- ESS should be defined as “complete” if surgery encompasses a complete sinus opening including bilateral anterior and posterior ethmoidectomy, middle meatal antrostomy, sphenoidotomy and frontal sinusotomy (e.g. Draft IIa/b).
- ESS should be defined as “extended” if surgery included complete ESS with/without the following: middle turbinectomy, Draf III, wide middle meatal antrostomy, sphenoidotomy 2b or above.
- Patients with diffuse primary CRSwNP should have at least a primary complete ESS.

Indications for biologic treatment in CRSwNP

Biologic therapy has emerged as a key pillar in the management of severe CRSwNP that remains uncontrolled despite surgery and AMT. Randomized trials consistently demonstrated clinically significant reductions in nasal polyp size, nasal congestion, and SNOT-22 scores, with parallel improvements in olfactory and asthma outcomes. Meta-analyses and real-world cohorts corro-



Indications for biologic treatment in CRSwNP

Aims	Indications/Criteria	Contraindications	Expected Outcomes	Considerations
The primary aim of biologics is to improve sinonasal symptom control including LoS and QoL, while reducing the need for SCS and further surgical interventions. The other aims are to reduce inflammatory burden, restore sinus ventilation and drainage, improve comorbidities, improve disease remission, and prevent disease progression.	Bilateral severe CRSwNP in patient who had FESS*, with ≥ 3 of 5 criteria: Evidence of Type 2 inflammation Need for SCS or contraindication to SCS[^] Significantly impaired QoL Significant LoS (anosmic or severely hyposmic on smell test) Diagnosis of co-morbid asthma or N-ERD	Hypersensitivity to monoclonal antibodies Pregnancy (except for omalizumab) Hypereosinophilic syndrome for dupilumab	Short-term outcome (16w-24w): Significant improvement of sinonasal symptoms, including LoS Mid-term - long-term outcomes (> 6 months-24 months therapy): Significant improvement of sinonasal symptoms, QoL, including LoS, and significant reduction of pathological tissue and improving disease remission Beneficial effects on comorbidities Long-term outcome (> 2 yr): high rate of sustained disease control and remission.	High direct cost Patient preference Safe treatment, with some relative medical contraindications, and product-dependent. Potential long-term safety data (not available for all biologics). Self-administration Comorbidity treatment benefits Reduced need for SCS and ESS Local availability/affordability/insurance policies in different regions

Figure 3. Indications for biologic treatment in CRSwNP. * Exceptional circumstances excluded (e.g. not fit for surgery). ° Ideally after one complete ESS but before the patient undergoes multiple revision procedures if permitted by regulatory authorities. ^ Long term low dose use of SCS is no longer accepted. Abbreviations: LoS: loss of smell; QoL: quality of life; SCS: systemic corticosteroids; CRSwNP: chronic rhinosinusitis with nasal polyps; FESS: Functional Endoscopic Sinus Surgery; N-ERD: non-steroidal anti-inflammatory drug- exacerbated respiratory disease; ESS: endoscopic sinus surgery.

borate these findings, showing sustained benefit over 1–2 years and marked decreases in the need for SCS and revision surgery (35-58,93-95,102-104).

Based on EUFOREA/EPOS guidelines, biologics are indicated in patients with bilateral, severe CRSwNP who have undergone prior ESS, and who fulfil at least three of five criteria including: evidence of type 2 inflammation, need for or contraindication to SCS, significantly impaired QoL, significant loss of smell, and presence of comorbid asthma (7). These criteria have been applied mainly for indications for biologics in routine clinical practice, and for selecting a population in which the biologics have been demonstrated to be highly effective (35-48). During the discussion the authors confirmed the criteria. In relation to surgery, it has been only specified that primary surgery should be at least a complete ESS and that long term use of SCS is no longer accepted especially where biologics are available and accessible (Figure 3).

Concerning smell loss, current evidence supports biologics as a highly effective strategy for restoring and maintaining olfactory function in severe CRSwNP, with specific advantages in long-term stability, reduced reliance on SCS, and potential neurosensory benefits (51) beyond the mechanical improvements achievable with surgery (13,14,17,18). Indeed, evidence from pivotal (80,103) RCTs and real-world studies consistently shows that biologic therapies induce rapid, clinically meaningful, and sustained improvements in olfactory function. Progressive and durable improvement is maintained up to 1–2 years without

the need for SCS (35-58,93-95,102-104). Very little evidence is available in comparing biologics and surgery for olfactory outcomes. Some authors (48,105) reported superior olfactory outcomes with dupilumab compared with ESS, whereas Chen et al. (47) observed that ESS and mepolizumab or omalizumab achieved broadly similar results. Head-to-head randomized trials are missing to confirm this data.

The use of biologic therapies has demonstrated efficacy in the management of comorbid patients with both upper and lower airway inflammation. In these cases, biologics have been shown to significantly reduce dependence on SCS, improve markedly impaired QoL, and enhance the functional status of both upper and lower airways. Biologics have been demonstrated to offer advantages even in the presence of other coexisting comorbidities—such as atopic dermatitis, chronic urticaria, eosinophilic otitis media and eosinophilic esophagitis—which are also known to benefit from some of these targeted therapies (65). This added therapeutic value underscores the role of biologics as a cornerstone in the comprehensive and multidisciplinary management of patients with complex type 2 clinical profiles (65).

In the short-term, the use of biologic therapies is expected to lead to significant symptom improvement, with achievement of disease control and sustained control, as defined in the consensus document about disease states (106). In the medium term (6–12 months), a marked reduction in pathological tissue and

disease activity is anticipated, with the potential attainment of a state of remission⁽¹⁰⁶⁾. In the long term, a high rate of sustained control and remission is expected (Figure 3).

Safety profiles across biologics remain favourable, with mostly mild, transient adverse events—such as arthralgia or injection-site reactions. In some of them non-harmful alteration in blood parameters may be observed such as a temporary eosinophilia with dupilumab or an increase for total IgE with omalizumab⁽¹⁰⁷⁻¹¹¹⁾. Specific eosinophilic side effect has been observed only rarely with dupilumab⁽¹¹²⁻¹¹³⁾. Finally, although their short-term safety profile is considered safe, data on potential adverse effects associated with long-term use of biologics are currently lacking, highlighting an urgent need for long-term safety studies⁽¹¹⁴⁾.

Data regarding the safety and efficacy of biologic therapies for CRSwNP during pregnancy and nursing are limited, as pregnant women were excluded from CRSwNP clinical trials. Most available evidence is extrapolated from literature and experience in pregnant women with severe asthma. A Delphi consensus addressing the use of biologics during pregnancy and lactation emphasized the importance of shared decision-making and discussion of the potential risks and benefits⁽¹¹⁵⁾. The panel supported the continued use of biologics in pregnant and breastfeeding patients with severe asthma, noting that the large molecular size of these agents likely limits infant exposure⁽¹¹⁶⁾. Ongoing pregnancy registries are evaluating the safety of dupilumab and mepolizumab during pregnancy^(116,117). Tezepelumab and depemokimab have the least pregnancy data as they are the latest biologics approved for airway diseases. Among currently available biologics, omalizumab has the most extensive pregnancy safety data⁽¹¹⁸⁻¹²¹⁾. Given the shared underlying type 2 inflammatory mechanisms in asthma and CRSwNP, these findings can reasonably inform treatment decisions for pregnant patients with CRSwNP.

However, cost and accessibility remain key practical considerations; biologic initiation should be individualized through shared decision-making in a multidisciplinary setting, balancing disease severity, comorbidity control, patient preference, and health-system sustainability⁽¹²²⁾.

Ideal timing for biologics (after surgery, before surgery or in combination)

The optimal timing for initiating biologic therapy in CRSwNP remains a matter of clinical debate. The most recent EUFOREA/EPOS publications recommend that biologics are indicated after failure of AMT and primary ESS (unless contra-indicated)⁽⁵⁻⁷⁾. Consequently, biologics are typically positioned after at least one ESS, though the current global landscape remains highly heterogeneous. Regulatory authorities across different countries

have adopted divergent approaches, with biologic therapies being initiated in most cases after a first surgical intervention, only after a second revision surgery in others, and—albeit rarely—even prior to any surgical intervention. Notwithstanding these differences, real-world evidence consistently supports the effectiveness of biologic therapies across these clinical scenarios, as demonstrated by several real-life studies^(39,41,51,123). Nonetheless there was an extensive discussion within the panel regarding the optimal timing of biologic therapy in relation to the number of prior sinus surgeries. Concerns have been raised about multiple repeated ESS, based on evidence from the literature supporting their association with potentially detrimental outcomes. Indeed, some authors⁽⁸⁰⁾ have observed that major CRS symptoms are not significantly reduced in patients undergoing multiple ESS, while others observed that the durability of surgical benefit decreases progressively with each subsequent revision procedure, with this trend evident from the second surgery onward and persisting across multiple revision interventions⁽³²⁾. Furthermore, emerging literature^(32,80) highlights the risk of suboptimal outcomes with biologic therapies following multiple repeated surgeries, particularly with respect to olfactory recovery, likely due to surgical damage to the olfactory region^(92,93). Taken together, these findings suggest that an excessive number of revision surgeries may limit the maximal therapeutic benefit achievable with biologic therapy^(91,124). For these reasons, when permitted by regulatory authorities and/or insurance policies, the expert panel considered the optimal positioning of biologic therapies to be after one complete ESS but before the patient undergoes multiple revision procedures. This approach is even more strongly advised in patients presenting with well-recognized risk factors for revision surgery failure, including early recurrence within three years⁽¹²⁵⁾, the presence of comorbidities such as asthma and N-ERD⁽¹²⁶⁾, evidence of significant local eosinophilia⁽¹²⁷⁾, and high requirement for SCS^(128,129).

The panel also agreed that exceptions to the post-surgical initiation strategy include patients with relevant comorbidities, for whom earlier biologic therapy may be considered appropriate. From a broader airway perspective, initiating biologic therapy earlier in the disease course may improve lower airway outcomes, prevent long-term morbidity, and prevent progressive airway remodelling⁽¹³⁰⁻¹³⁹⁾. The expert panel felt that biologics should be considered alongside or before surgery only in selected cases of severe complex airway disease (severe asthma and CRSwNP), with the decision made in a multidisciplinary setting.

There has been limited investigation of the concurrent use of biologics with primary and revision surgery. Such a combined approach refers to initiating biologic treatment simultaneously, which in some cases may involve starting the biologic 2-8 weeks before primary or revision surgery. The rationale behind

this strategy is to optimize postoperative healing processes, achieving superior results compared to a single procedure. Unfortunately, the evidence from the literature remains poor with few articles exploring a potential incremental benefit of using dupilumab in pre-, peri- and post- surgery adjuvant treatment⁽¹⁴⁰⁻¹⁴⁴⁾ or adding surgery to mepolizumab in selected contexts (macropolyps)⁽¹⁴⁵⁾.

The expert panel considers that current data on the optimal timing of biologic therapy initiation relative to ESS remain preliminary, and further studies are needed to outline evidence-based initiation strategies. Given the importance of this topic, the authors believe that further evidence is required to determine the comparative clinical and economic benefits of different strategies, to formulate a definitive statement on this issue.

Considering combined therapy with biologics and primary/revision ESS, the panel considered the available data insufficient to support concomitant approaches. Furthermore, in the absence of a clear benefit for the patients, concomitant initiation of biologics and/or surgery can obscure attribution of benefit, complicate decisions about continuation, and reduce the response criteria, leaving the need for the next step unclear. Other factors supporting a sequential rather than a combined treatment approach should also be considered. First, failure after surgery itself has been regarded as a useful predictor of disease severity and may aid in identifying the most severe cases. Second, health-economic considerations play a relevant role, particularly regarding the cost of biologics. Finally, the panel considers it is important to allow a sufficient period (>6 months) to adequately assess the clinical effectiveness of biologic therapy before considering revision surgery or switching to an alternative biologic.

Consensus reached definition:

- *Concurrent initiation of sinus surgery and biologic therapy is not recommended with current evidence.*

Options for non-responders: salvage surgery versus switching biologics

Despite the substantial efficacy demonstrated by biologic agents in severe type-2 CRSwNP, a small proportion of patients fail to achieve satisfactory disease control, highlighting the need for structured management pathways for non-responders. According to EPOS/EUFOREA 2023 updates⁽⁷⁾, non-response should be assessed after an adequate therapeutic trial of 6–12 months, using a multidimensional evaluation that incorporates different criteria (QoL, smell recovery, reduction in nasal polyp size, improvement of lower airway comorbidities and no need for SCS).

After discussion the consensus group agreed that salvage surgery during biologic treatment is appropriate for patients

who, after an adequate course of therapy (6–12 months), remain severely symptomatic due to localized disease rather than persistent diffuse inflammatory activity. Salvage ESS indeed should aim to correct anatomic factors or post-operative sequelae limiting topical drug access or ventilation, rather than to replace systemic anti-inflammatory control.

Conversely, in patients who remain significantly symptomatic with persistent bilateral diffuse disease and evidence of ongoing type-2 inflammation, a switch in biologic class or target is favoured^(146,147). The decision to switch should always be preceded by objective verification of adherence, comorbidity management, and optimization of topical therapy. Safety-related switching should incorporate an appropriate time interval to allow adequate management and resolution of adverse events. Switching should be to another class of biologics, switching to the same class (e.g. IL-5 to IL-5 receptor) is not useful⁽¹⁴⁶⁾.

Consensus reached definitions:

- *“Salvage surgery” (performed during ongoing biologic therapy) is considered appropriate for patients who, despite prior complete surgery and an adequate trial of biologic therapy (6–12 months), continue to exhibit persistent, symptomatic, and predominantly localized disease attributable to mechanical factors (e.g., frontal sinus obstruction) rather than uncontrolled systemic inflammation.*
- *A change in medical strategy, such as “switching the biologic agent”, is considered appropriate for patients who, after an adequate treatment period, continue to exhibit significant symptomatic residual disease, indicating insufficient control of systemic inflammation. In cases with comorbid lower airway disease, the decision to switch should be discussed within a multidisciplinary setting.*

Disease modification for surgery and biologics

Disease modification in CRSwNP has been defined as a treatment or intervention that affects the underlying pathophysiology of the disease and has a beneficial effect on its course or slows its progression⁽¹⁰⁶⁾.

The concept of disease modification in CRSwNP extends our ambition from symptomatic control toward altering the natural course of the disease and its lower airways/type 2 comorbidities⁽¹⁰⁶⁾. Both ESS and/or biologic therapy have demonstrated the potential to modify disease progression^(15,58).

Beyond symptom relief and improved local inflammatory control, evidence indicates that ESS exerts beneficial effects on airway inflammation, particularly in patients with comorbid asthma and N-ERD. Longitudinal data^(10,22,23) demonstrated that earlier ESS may reduce new onset as well as asthma exacerbations, improve lung function, and enhance asthma control scores, with confirmed significant postoperative improvements in FEV₁ and reduction in rescue medication use, and finally a decrease

in type-2 inflammatory markers, suggesting a broader impact beyond local disease. Timely intervention may therefore act as a disease-modifying step, restoring local function before irreversible changes occur and potentially mitigating the downstream burden on lower airways and systemic inflammation modifying the disease trajectory.

Biologic agents on the other hand may suppress type-2 inflammation across airway compartments, interrupting or attenuating mucosal remodelling suggesting that they may fundamentally alter disease progression rather than merely palliate sinonasal symptoms, including loss of smell. Accordingly, the literature on CRSwNP with asthma/N-ERD has consistently shown reductions in upper and lower airway exacerbations, decreased SCS dependence, and improvements in comorbid asthma control. Long-term data demonstrated that these effects are sustained for years and, in some patients, remain stable even with dose tapering, supporting a potential disease-modifying capacity of biologic therapy ^(35-58,93-95,102,103,106,148).

Consensus reached definition:

- *Disease modification by surgery: while ESS is aimed at relieving sinonasal symptoms, including loss of smell, it has also been shown to reduce asthma exacerbations. Earlier surgery is associated with better outcomes and decreases the risk of developing asthma.*
- *Disease modification for biologics: biologics can reduce exacerbations in upper and lower airways, reduce the need for ESS and SCS, and have the potential to alter the disease course.*

Conclusions

The experts who contributed to this project reported in this paper their opinions on relevant topics regarding the use of biologics in relation to ESS summarizing the most important statements that reached a consensus during the Rome Consensus Meeting organized by EUFOREA in 2025 and after the involvement of an extended group of authors. The present manuscript was developed with the primary aim of establishing consensus on the proposed definitions, while recognizing the limited availability of high-quality evidence, including randomized controlled trials evaluating different surgical approaches, surgery versus biologic therapy, and the optimal timing of biologic therapy in the perioperative setting. The authors considered it of primary importance to undertake this consensus initiative considering the rapid and substantial changes currently occurring in real-world clinical practice following the introduction of biological therapies. The novel definitions presented in this document may not only support clinicians in their daily practice but also provide a framework for the design of future studies aimed at generating higher-quality evidence in this evolving field. The newly proposed statements constitute an important step toward the optimization and harmonization of outcomes for

both interventions, within the framework of the modern therapeutic algorithm for chronic rhinosinusitis with nasal polyps ⁽¹⁴⁹⁾. A summary of the agreed definitions is reported in Figure 4 and the future unmet needs in Figure 5.

In this manuscript, the authors revisited the most clinically relevant definitions concerning the aims, indications, and therapeutic positioning of both surgery and/or biologic therapies. The statements approved in this consensus represent an effort to harmonize definitions and to maximize outcomes not only in the upper airways but also in the lower airways of comorbid patients, emphasizing the disease-modifying potential of both treatment modalities.

The authors of this document, on the basis of the extensive discussions held in Rome and the currently available evidence in the literature, strongly encourage researchers to generate further evidence regarding the optimal positioning of biological therapies in relation to surgery, the differences in outcomes associated with the various treatment strategies, and the potential benefits achievable through combined approaches. Particular emphasis should be placed on efforts aimed at demonstrating possible disease-modifying effects of different therapeutic strategies, with the objective of identifying the approaches most capable of altering the natural history of the disease, ultimately with the ambition of achieving disease remission and cure.

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Author contributions

All authors meet the ICMJE criteria for authorship. Most of the authors (EDC, PWH, WJF, CH, VJL, CM, XB, VB, EP, BSB, CP, MW, MBS, DMC, JH, GKS, ATP) participated in the consensus meeting held in Rome in October 2025 and contributed substantially to the conception and content of the manuscript. EDC, ATP, CM, CH, PT, and WF contributed significantly to drafting the initial version of the manuscript. JM, MC, PG, RH, LK, RCK, BNL, SL, IA, AUL, SR, SS, ARS, BS, AVT, KCW, YC, JC, AB, NHAO, SA, and MAA contributed to the two subsequent online revision rounds. All authors contributed to the critical revision of the manuscript, approved the final version, and agree to be accountable for all aspects of the work.

Conflict of interest

EDC has received honoraria for lectures and advisory boards participation for Sanofi, Regeneron, AstraZeneca, Novartis, and Firma. PWH has received grants and/or honoraria for lectures and/or advisory boards by Sanofi, Regeneron, GSK, AstraZeneca, Medtronic, Viartis. WJF The department of Otorhinolaryngology of the Amsterdam University Medical centre, location AMC received grants for research in Rhinology from: ALK, Aller-



Key Definitions

Aims of surgery in CRSwNP	The primary aim of ESS is to improve symptom control and QoL, while reducing the need for SCS and other systemic medications. The secondary aims are to reduce the inflammatory burden (removal of pathological tissue), aid delivery of topical intranasal therapy (INCS, saline), restore sinus ventilation and drainage, improve lower airway co-morbidities and prevent disease progression.
Aims of biologics in CRSwNP	The primary aim of biologics is to improve symptom control and QoL, while reducing the need for SCS and further surgeries. Further aims are to reduce the inflammatory burden, restore sinus ventilation and drainage, improve lower airway co-morbidities, prevent disease progression, and promote disease remission.
Indications for primary ESS	ESS is indicated in CRSwNP patients with persistent symptoms and objective evidence of disease despite appropriate medical treatment, including INCS for at least 3 months. (Patients fit for surgery).
Ideal timing of primary ESS	After failure of at least 3 months of appropriate medical therapy, earlier primary ESS (preferably within 12 months of symptom onset) yields a larger and more durable QoL improvement than delayed ESS. Delay of ESS likely diminishes long-term benefit, including increased risk of developing lower airway co-morbidities such as asthma.
Ideal extent of primary ESS	Patients with diffuse disease should have at least a primary complete ESS.
Salvage surgery	"Salvage surgery" (performed during ongoing biologic therapy) is considered appropriate for patients who, despite prior complete surgery and an adequate trial of biologic therapy (6–12 months), continue to exhibit persistent, symptomatic, and predominantly localized disease attributable to mechanical factors (e.g., frontal sinus obstruction) rather than uncontrolled systemic inflammation.
Switching	A change in medical strategy, such as "switching the biologic agent", is considered appropriate for patients who, after an adequate treatment period, continue to exhibit significant symptomatic residual disease, indicating insufficient control of systemic inflammation. In cases with comorbid lower airway disease, the decision to switch should be discussed within a multidisciplinary setting.
Disease modification in the airways	A treatment or intervention that affects the underlying pathophysiology of the disease and has a beneficial outcome on the course of the disease or slows down disease progression.
Potential disease modification with ESS	While ESS is aimed at relieving sinonasal symptoms, including LoS, it has also been shown to reduce asthma exacerbations. Earlier surgery is associated with better outcomes and decreases the risk of developing asthma.
Potential disease modification with biologics	Biologics can reduce exacerbations in upper and lower airways, reduce the need for ESS and SCS, and have the potential to alter the disease course.
Role of SCS in severe CRSwNP	It is strongly recommended to avoid SCS for the treatment of CRS.

Figure 4. Key definitions proposed in this manuscript.

gy Therapeutics, Chordate, Novartis, EU, GSK, MYLAN, Sanofi-Aventis, and Zon-MW. Wytske Fokkens received consultation and/or speaker fees from Dianosis, GSK, Novartis and Sanofi-Aventis/ Regeneron and is chair of EPOS and board member of EUFOREA. CH Ad boards - GSK, AstraZeneca, Sanofi, Regeneron, Lilly. VJL Speaker, Advisory Board member: Abbott, Astra Zeneca, GSK, Novartis, Sanofi Regeneron. VB has received personal fees from AstraZeneca, GSK, TEVA, Sanofi Genzyme, MSD, Chiesi, Boehringer-Ingelheim, Novartis, ALK-Abello, Mundipharma, BIRK NPC, Menarini and Pharmaxis. BSB: Novartis, Olympus, Karl Storz,

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Future of biologics and surgery care in CRSwNP / Nasal Polyp Syndrome

Pathophysiologic needs
Current therapeutic targets are the key drivers of Type-2 inflammation (e.g., alarmins, IL-4, IL-5, IL-13 pathways), which are common to upper and lower airways. The goal is to modify and eventually stop the progression of Type-2 airway disease, achieving remission and, potentially, a cure. Ideal biomarkers and predictors of therapeutic response, disease modification, and cure need to be identified.
Diagnostic needs
Care pathways for chronic respiratory diseases should ensure that all patients receive affordable, early, and appropriate treatment and follow-up promptly. All primary care providers should be able to recognize CRS and refer patients in a timely manner to specialized care. Treatment should focus on the whole patient rather than the disease alone, using a multidisciplinary and personalized approach. Understanding the natural course of CRS is essential to predict severity, assess control, guide prevention, and identify windows for early intervention. Regulatory agencies need to adopt unified definitions for disease modification, remission, and cure, thereby harmonizing evaluation standards. Advancing knowledge of remission and cure in both upper and lower airway diseases requires coordinated research and standardized endpoints.
Therapeutic needs
Biologics should be considered a valuable and safe treatment option for patients with severe, uncontrolled chronic respiratory disease who fail a complete ESS and AMT. Biologics may be considered before surgery in patients with other significant comorbidities that may benefit from early intervention with biologic therapy (eg, severe asthma). Early diagnosis and timely initiation of optimal therapy, including biologics, can improve disease remission and prevent disease progression, remodelling, and end-stage manifestations. We need robust data demonstrating the disease-modifying potential of biologics and whether remission can persist after treatment discontinuation.

Figure 5. Future of biologics and surgery care in CRSwNP

Germany. MC has given presentations, participated in advisory boards, and received research grants from Sanofi-Regeneron, GSK, ALK, Mylan, Stallergens Greer, and Medtronic. DMC Serves as Academic Manager at the European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA) and as Associate Editor at Frontiers in Allergy, Rhinology Section. PG Has participated in advisory boards and received speaker fees from ALK-Abelló, Argenx, AstraZeneca, Genentech, GSK, Novartis, Regeneron, Roche, Sanofi Genzyme, and Stallergens-Greer. RH Research consultant for Sanofi, Regeneron, GlaxoSmithKline and AstraZeneca. LK has received research grants from Allergy Therapeutics/Bencard, Great Britain/Germany; ALK-Abelló, Denmark; Allergopharma, Germany; Aimmune, USA; ASIT Biotech, Belgium; AstraZeneca, Sweden, Bionorica, Germany; BioNTech, Germany, Biomay, Austria, Blueprint, USA, Boehringer Ingelheim, Germany, Celltrion, South Korea, Circassia, USA; Chiesi, Italy; Cytos, Switzerland; Curalogic, Denmark; HAL, Netherlands; Lofarma, Italy; Menarini, Italy; Viartis/Mylan, USA; Novartis, Switzerland, Leti, Spain; ROXALL, Germany; GlaxoSmithKline (GSK), Great Britain; Sanofi, France; Stallergens, France; Thermofisher, USA and/or has served on the speaker's bureau or was consulting for the above mentioned pharmaceutical companies. LK is the current President of German Society of Allergology AeDA, Governance Committee Board Member and ENT Section Board Member of the European Academy for Allergy and Clinical Immunology (EAACI), Vice-President of German Academy for Allergy and Environmental Medicine and Editor-in-Chief of AllergoJournal and AllergoJournal International. RCK has received consultancy fees from Sanofi, GSK, Medtronic, and he is the CMO of Lyra Therapeutics. SL Clinical trial funding and advisory boards for AstraZeneca, Genentech, GSK, Lyra, Optinose, Sanofi Regeneron, Upstream Bio. IA has received honoraria for consultancy and conferences from AstraZeneca, Viartis, Roche, Sanofi, GSK, MSD, Menarini, Storz, Olympus, Metronic, Salvat and Novartis. AUL serves as a consultant for Lyra Therapeutics (Watertown, Massachusetts), Medtronic (Dublin, Ireland), Sanofi (Paris, France), and Stryker (Kalamazoo, Michigan), and serves on the scientific advisory board for ENTvantage Dx (Austin,

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