

EDITORIAL

A modest proposal for a new way forward for clinical research: Involve insurance companies

1 | THE CURRENT APPROACH AND ITS LIMITATIONS

Before a drug can be commercially distributed in the United States, it must undergo review by the U.S. Food and Drug Administration (FDA). The function of such a review is to scrutinize the clinical trial data submitted by the pharmaceutical company (herein, pharma) in order to independently verify the drug's efficacy and safety. Medical devices undergo an analogous pathway.

The FDA review, although important, does not consider appropriate application of the new drug within an established treatment paradigm. Instead, clinicians must rely on personal knowledge and preference when determining the application of a new drug. In practice, such determination is significantly influenced by the patient's health insurance companies' (HICs's) formulary of approved treatments and their tier ratings (a higher tier necessitates a higher co-pay). The development and maintenance of treatment formularies is typically outsourced to third-party organizations known as pharmacy benefit managers (PBMs).¹ PBMs rely on a variety of factors in their determination of whether to add a drug to their formulary and determining its tier, including the FDA-approved indication, literature reviews, claims data, and price rebates negotiated with pharma. Criticism has been directed at PBMs for sometimes favoring rebated expensive drugs with a high co-pay over drugs that provide better value to patients.¹ Consequently, clinical management is frequently decided based on clinician preference and the PBMs coverage rubric as opposed to validated outcome data.

The high drug-to-market cost and the narrow window of patent protection motivates pharma to further its investment on factors likely to ensure a favorable return. Researching the drug's efficacy within established treatment paradigms is of relatively low priority, especially given such research might demonstrate unfavorable data. Instead, pharma prioritizes factors known to drive com-

mercial success: marketing, low cost, ease of administration, additional indications, and clinician/patient education. Pharma frequently provides funding support to investigator-initiated research relating to new dosing, delivery mechanisms, or additional indications.

An example of this approach can currently be seen in rhinology with the introduction of biologics for the management of chronic rhinosinusitis with nasal polyps (CRSwNP). Biologics have been hailed as a major advancement in the management of patients with severe CRSwNP that is resistant to traditional treatments.² Their application within established CRSwNP treatment paradigms, however, remains poorly understood (Figure 1). First-line CRSwNP treatment, consisting of topical nasal steroids (oral steroids for episodes of exacerbations), is cost effective at \$2000 annually and achieves adequate disease control in a high percentage of patients.^{2,3} Few would argue, therefore, that patients adequately managed with first-line treatment would benefit from a biologic.

The management of patients resistant to first-line treatment is less clear. The data submitted to the FDA for review related to the biologics efficacy in patients demonstrating severe polyp disease despite first-line medical management and/or surgical intervention.⁴ Given the many variables that influence clinical decision making (treatment risk, patient preference, and varying definitions of treatment failure), we suspect that biologics will be used in patients not meeting the above criteria.

Ad hoc practices such as this could significantly impact the distribution of biologics. For instance, in the United States, an estimated 43,835 CRSwNP patients resistant to first-line treatment undergo endoscopic sinus surgery (ESS) (Figure 1).² The literature suggests that ~3% of these patients will undergo revision ESS within 12 months and ~10% within 60 months.⁵ Extending the indication to include those undergoing revision ESS within 60 months could result in roughly an additional 3000 patients now

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial License](https://creativecommons.org/licenses/by-nc/4.0/), which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2022 The Authors. *International Forum of Allergy & Rhinology* published by Wiley Periodicals LLC on behalf of American Academy of Otolaryngic Allergy and American Rhinologic Society

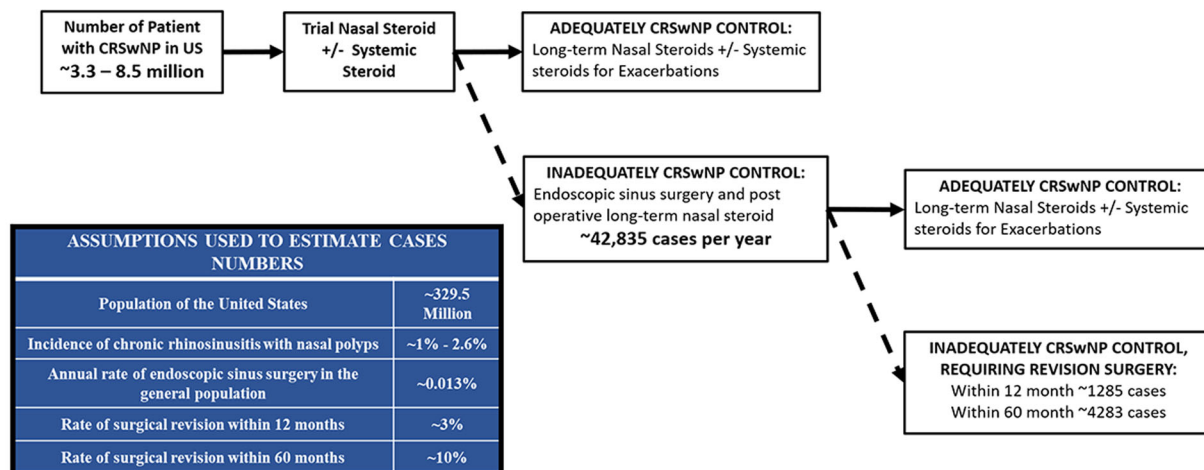


FIGURE 1 The established treatment paradigm for CRSwNP before the introduction of biologics. Applying this treatment paradigm to data reported in the literature, the number of ESSs performed annually in the United States for the management of CRSwNP can be calculated (~42,835 cases). Using reported rates of revision surgery, approximately 1285 (~3%) revision cases will be performed within 12 months and 4283 (~10%) revision cases within 60 months. Abbreviations: CRSwNP, chronic rhinosinusitis with nasal polyps; ESS, endoscopic sinus surgery

eligible for treatment with a biologic, which is more than a three-fold increase.

The timing of treatment initiation remains ill defined. Clinicians are left questioning whether to initiate biologic treatment immediately after surgery to prevent polyp recurrence or wait until recurrent polyp disease is evident. In the first scenario, all patients undergoing ESS would be required to be treated with a biologic, resulting in significant overtreatment, because most will not receive additional benefits from this treatment. In the second scenario, the literature suggests that an average of 40% of ESS patients have recurrent polyp disease by 18 months, yet only 10% undergo revision surgery within 60 months.⁵ Prescribing a biologic in all patients with recurrent disease will, therefore, likely result in considerable biologic overtreatment.

2 | THE VALUE OF A TREATMENT PARADIGM

The benefits of establishing treatment paradigms based on clinical outcomes and cost-effectiveness data become clear when considering the \$30,000–\$40,000 (mean \$35,000) wholesale cost to treat CRSwNP with a biologic for 12 months.⁶ This is more than 17.5 times the cost of first-line treatment and 3.5 times the cost of ESS (\$8200–\$10,500).⁶ Figure 2 demonstrates that extending management with a biologic to all cases undergoing revision surgery within 60 months as opposed to within 12 months, could result in a \$60 million increase in annual treatment cost. As shown in Figure 3, restricting the biologic treatment trial period in nonrespondents, which occurs at an estimated rate of

between 35% and 50%, also presents an opportunity to save on costs. In the clinical scenario where all patients undergoing revision surgery within 60 months are treated with a biologic, an estimated \$102–\$146 million could be saved by limiting the treatment trial duration from 12 months to 1 month. Although health economists are likely to cringe at these crude assumptions and calculations, we believe that such numbers effectively illustrate that even a small shift in the long-term management of CRSwNP with biologics can have a substantial impact on cost.

We recognize that any decision to initiate treatment with a biologic should not be based simply on cost. Yet it is important that treatment with a biologic is discouraged in cases when equally effective, but more cost-effective treatments are available. In the absence of a validated treatment paradigm for the treatment of CRSwNP with biologics, organizations such as the European Forum for Research and Education (EUFOREA) and the European Position Paper on Rhinosinusitis (EPOS) issued statements on its application based on expert opinion and data, where available.^{7,8} Similarly, the National Institutes of Health (NIH) sponsored a workshop to design clinical trials to address questions of the comparative effectiveness of biologics to current treatment paradigms.² These efforts demonstrate that there is a clear desire to address the uncertainties pertaining to the use of biologics in CRSwNP patients to ensure delivery of care that is not only high-quality but also cost-effective. Such work will assist in lowering healthcare costs, benefiting both employers (who pay HICs for coverage) and patients (who are responsible for co-pays and may indirectly suffer lower salaries or higher premiums not covered by their employers).

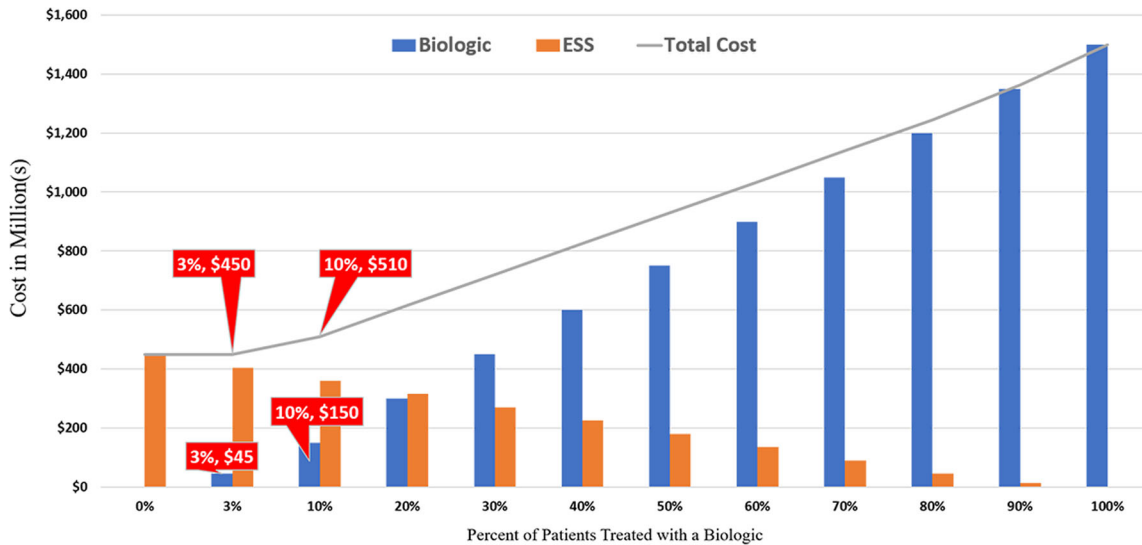
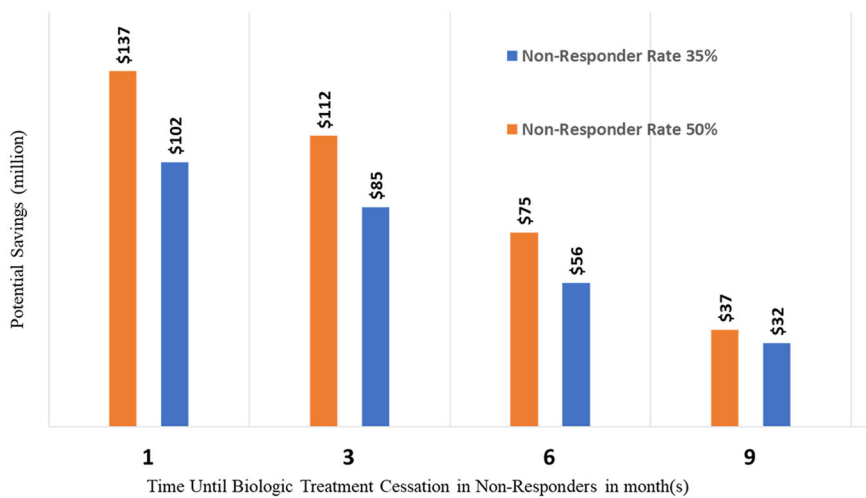


FIGURE 2 In patients with CRSwNP who are resistant to first-line treatment, there is a considerable increase in cost of treatment when an increasing percentage are treated with a biologic instead of ESS plus nasal corticosteroids. Simply by increasing the percent of patients treated with a biologic from 3% (remaining 97% treated with ESS) to 10% (remaining 90% treated with ESS) the cost of care increases by ~\$60 million annually. Abbreviations: CRSwNP, chronic rhinosinusitis with nasal polyps; ESS, endoscopic sinus surgery

FIGURE 3 There is potential for considerable savings if treatment is stopped in nonresponders after 1 month as opposed to a full 12-month treatment



3 | MOTIVATING THE DEVELOPMENT OF VALIDATED TREATMENT PATHWAYS

We believe that HICs should fund research programs aimed at establishing validated treatment paradigms, because such investment is in their long-term interest. The creation of validated treatment pathways can be achieved using well-designed clinical trials. A crude estimate of the cost for such a trial would be about \$35 million over the 3 years required for completion. By considering the added cost of \$180 million, over a 3-year period, of treating the 10% of CRSwNP patients requiring revision ESS with a biologic versus 3%, the benefit to HICs is apparent. This scenario would also benefit patients, as it encourages best practice of care.

In the current ad hoc approach, practitioners perform their own individual trials to ascertain how biologics fit within their practice. For example, a practitioner might substitute postoperative corticosteroids with a biologic to see if recurrence is minimized. Although understandable, this approach greatly increases healthcare costs and is likely not necessary for most patients. The introduction of standardized research protocols would allow information to be collected into a central registry, generating powerful data on a scale that can be reviewed by a systematic and comprehensive approach.

In addition to cost savings, the development of clinically validated treatment paradigms could mitigate the risk of lawsuits, because it provides payors with clear proof of providing treatment coverage according to best practices.

Had such an approach been in place in 1992, it might have impacted the lawsuit faced by Health Net, which was successfully sued for \$89 million for refusing to provide coverage for a bone marrow transplant in a patient suffering from metastatic breast cancer. At the time of the case, a bone marrow transplant was hypothesized to improve patient outcomes but was later proven to have no benefit on survival by rigorous clinical trials, defying prior expert consensus.⁹

Although HICs lack the expertise needed to conduct clinical trials, this could be overcome by partner with the NIH and/or academic institutions. Examples of such partnerships include UnitedHealth Group (Optum Labs) and the Mayo Clinic.¹⁰ However, a major drawback to conducting clinical trials is the time needed for results. So, while we consider which clinical trials to conduct, what can we do to advance our knowledge in the meantime?

One approach would be to develop a registry in which all physicians using biologics for the treatment of CRSwNP would be required to enter data (e.g., computed tomography [CT] scans, endoscopies, quality of life assessments, symptoms, comorbidities, and prior treatments) before prescribing the biologic. This registry could be run by the representatives of a group of insurers, or by an external organization funded by all insurers. These insurers would need to participate to comprehensively capture the use of biologics. The registry would also provide data for other potential indications and usage schedules. Clinicians may object because of the burden of uploading data; however, we feel the burden would lead to faster acquisition of knowledge and would have long-term benefits to patients.


Pharma already funds incremental innovation related to new dosing, delivery mechanisms, and discovering additional indications. Thus, HICs would benefit from reducing such unorganized research. The registry would also provide data for other potential indications and usage schedules.

HICs agree that research can improve patient outcomes; therefore, we strongly believe that HICs should join with each other and with clinicians, scientists, and public health leaders to contribute financially to the acquisition of knowledge. This approach would not only benefit patients but also would eventually provide cost saving for HICs, businesses, the government, and society. How to convince HICs of the merits of this idea is a challenge for the future.

With the advent of new therapies for CRSwNP, we must move beyond the status quo. For many years, we have developed clinical guidelines for asthma based on rigorous clinical trials. Now, we must think outside the box to develop new methods of acquiring useful, practical data on which to base treatments. Only then will we be positioned to treat our patients in a manner that optimizes outcomes.

CONFLICT OF INTEREST

James H. Clark has no relevant financial disclosures or conflicts of interest. Jayant M. Pinto is a member of advisory boards for GlaxoSmithKline, Sanofi/Regeneron, Genentech, and Optinose; he is also the speakers' bureau for Optinose and Sanofi-Regeneron; and he is a site PI for clinical trials for Sanofi/Regeneron and Connect Pharma. Robert M. Naclerio is a member of the Medical Advisory Board for GlaxoSmithKline, Lyra, Sanofi, Regeneron, Ismed, and AstraZeneca.

James H. Clark MD¹ 

Jayant M. Pinto MD² 

Robert M. Naclerio MD² 

¹ Department of Otolaryngology–Head and Neck Surgery, The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

² Department of Surgery, Section of Otolaryngology–Head and Neck Surgery, The University of Chicago, Chicago, Illinois, USA


Correspondence

James H. Clark, MD, Department of Otolaryngology–Head and Neck Surgery, The Johns Hopkins School of Medicine, 4940 Eastern Avenue, Baltimore, MD 21224, USA.
Email: jclark79@jhmi.edu

KEYWORDS

biologics, chronic rhinosinusitis with nasal polyps, clinical research, insurance

ORCID

James H. Clark MD  <https://orcid.org/0000-0002-8841-3402>

Jayant M. Pinto MD  <https://orcid.org/0000-0003-2838-490X>

Robert M. Naclerio MD  <https://orcid.org/0000-0003-4016-9030>

REFERENCES

1. Seeley E, Kesselheim AS. Pharmacy benefit managers: practices, controversies, and what lies ahead. *Issue Brief (Commonw Fund)*. 2019;2019:1–11.
2. Naclerio R, Baroody F, Bachert C, et al. Clinical research needs for the management of chronic rhinosinusitis with nasal polyps in the new era of biologics: a National Institute of Allergy and Infectious Diseases Workshop. *J Allergy Clin Immunol Pract*. 2020;8(5):1532–1549.e1. <https://doi.org/10.1016/j.jaip.2020.02.023>.
3. Bhattacharyya N, Villeneuve S, Joish VN, et al. Cost burden and resource utilization in patients with chronic rhinosinusi-

- tis and nasal polyps. *Laryngoscope*. 2019;129(9):1969–1975. <https://doi.org/10.1002/lary.27852>.
4. 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(5):469–479. <https://doi.org/10.1001/jama.2015.19330>.
 5. Stein NR, Jafari A, DeConde AS. Revision rates and time to revision following endoscopic sinus surgery: a large database analysis. *Laryngoscope*. 2018;128(1):31–36. <https://doi.org/10.1002/lary.26741>.
 6. Patel GB, Peters AT. The role of biologics in chronic rhinosinusitis with nasal polyps. *Ear Nose Throat J*. 2021;100(1):44–47. <https://doi.org/10.1177/0145561320964653>.
 7. Fokkens WJ, Lund V, Bachert C, et al. EUFOREA consensus on biologics for CRSwNP with or without asthma. *Allergy*. 2019;74(12):2312–2319. <https://doi.org/10.1111/all.13875>.
 8. Fokkens WJ, Lund VJ, Hopkins C, et al. European Position Paper on rhinosinusitis and nasal polyps 2020. *Rhinology*. 2020;58(Suppl S29):1–464. <https://doi.org/10.4193/Rhin20.600>.
 9. Welch HG, Mogielnicki J. Presumed benefit: lessons from the American experience with marrow transplantation for breast cancer. *BMJ*. 2002;324(7345):1088–1092.
 10. Wallace PJ, Shah ND, Dennen T, Bleicher PA, Crown WH. Optum Labs: building a novel node in the learning health care system. *Health Aff*. 2014;33(7):1187–1194. <https://doi.org/10.1377/hlthaff.2014.0038>.