Prior Authorization Review Panel  
MCO Policy Submission

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<table>
<thead>
<tr>
<th>Plan: Aetna Better Health</th>
<th>Submission Date: 11/01/2018</th>
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</thead>
<tbody>
<tr>
<td>Policy Number: 0694</td>
<td>Effective Date:</td>
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<tr>
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<td>Revision Date:</td>
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<tr>
<td>Policy Name: Paranasal Sinus Ultrasound for the Evaluation of Sinusitis</td>
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</tbody>
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Type of Submission – Check all that apply:

- ☑ New Policy*
- ☐ Revised Policy
- ☐ Annual Review – No Revisions

*All revisions to the policy must be highlighted using track changes throughout the document. Please provide any clarifying information for the policy below:

**CPB 0694 Paranasal Sinus Ultrasound for the Evaluation of Sinusitis**

Policy is new to Aetna Better Health of Pennsylvania.

Name of Authorized Individual (Please type or print):  
Dr. Bernard Lewin, M.D.  

Signature of Authorized Individual:
Aetna considers the following experimental and investigational because of insufficient evidence:

- Detection of IgG4-positive plasma cells in the nasal cavity or para-nasal sinuses for diagnosis of chronic rhino-sinusitis (CRS)
- Examination of tissue eosinophilia for prediction of disease severity in individuals with CRS
- Examination of tissue eosinophilia for evaluation of CRS-associated olfactory loss
- Examination of tissue epidermal growth factor receptor (EGFR) ligands (e.g., epiregulin) and matrix metalloproteinases for evaluation of CRS
- Microarray DNA testing for the evaluation of chronic rhinosinusitis; and (viii) type 2 cytokines (e.g., interleukine-4 (IL-4), IL-5, and IL-13) as biomarkers for evaluation of CRS
- Para-nasal sinus ultrasound for the evaluation of sinusitis.
Background

Para-Nasal Sinus Ultrasound for the Evaluation of Sinusitis

Sinusitis is a common disorder that affects over 30 million individuals each year in the United States and approximately 90% of these patients will visit their physician to seek treatment. Symptoms of sinusitis can include nasal congestion, purulent nasal discharge, maxillary tooth discomfort, cough, headache, fever, malaise, and facial pain or pressure that is worsened by bending forward.

The gold standard for the diagnosis of acute bacterial sinusitis is the recovery of bacteria in high density from the cavity of a paranasal sinus. However, sinus aspiration is an invasive, time-consuming, and potentially painful procedure that should only be performed by an otolaryngologist. It is not a feasible method of diagnosis for the primary care practitioner and is not recommended for the routine diagnosis of bacterial sinus infections in children.

The American Academy of Pediatrics Clinical Practice Guideline on the Management of Sinusitis for children, aged 1 to 21 years (2001), has not taken a position on the use of ultrasound as a diagnostic measure of uncomplicated sinusitis. The guidelines stated that imaging (either radiographs, computed tomography [CT] or magnetic resonance imaging [MRI]) can serve only as confirmatory measures of sinus disease in patients whose clinical histories are supportive of the diagnosis.

The American Academy of Allergy, Asthma and Immunology published parameters on the diagnosis and management of sinusitis (Spector et al, 1998), stated that computed tomography is the preferred imaging technique for pre-operative evaluation of the paranasal sinuses and that
ultrasonography has limited utility, but may be applicable in pregnant women and for determining the amount of retained secretions.

In a Cochrane review of 57 randomized trials, Ahovuo-Saloranta et al (2008) evaluated clinical response to antibiotic therapy to control or antibiotics from different classes for acute sinusitis. The methods used to establish a diagnosis of acute sinusitis were: clinical examination, radiograph, computed tomography, fiber-optic examination, or culture taken by nasal swab or sinus puncture. None of these trials reported using ultrasound to establish a diagnosis of acute sinusitis.

The Agency for Health Care Policy and Research (AHCPR) evidence report (Lau et al, 1999) on the Diagnosis and Treatment of Acute Bacterial Rhinosinusitis stated: "Compared with sinus puncture, the reference standard for diagnosing acute bacterial rhinosinusitis, sinus radiography has moderate sensitivity (76 %) and specificity (79 %). Sinus ultrasonography has similar test characteristics, but the results are more variable and the procedure is not commonly used in the United States. Limited evidence suggests that diagnoses based on clinical criteria may be as accurate as those using sinus radiography."

The American College of Radiology (ACR) task force on appropriateness criteria and its expert panel (McAlister et al, 2000) have developed criteria for determining appropriate imaging examinations for the diagnosis and treatment of sinusitis in the pediatric population. The ACR guidelines recommended: (i) the diagnosis of acute and chronic sinusitis should be made clinically, not on the basis of imaging findings alone; (ii) when acute sinusitis is diagnosed and appropriately treated, no imaging studies are indicated if full clinical resolution occurs; (iii) patients with acute sinusitis persisting after 10 days of appropriate therapy, or with chronic sinusitis, and in whom imaging
evaluation is desired, should undergo coronal CT scans of the sinuses regardless of their age; and (iv) the use of plain films in the evaluation of sinusitis should be discouraged unless exceptional circumstances warrant it.

In addition, the ACR gave paranasal sinus ultrasound an appropriateness rating of 1 to 2 on a scale of 1 to 9 for 8 variant presentations (1 being the least appropriate). The task force reports that control studies using ultrasound of the sinuses have shown that this modality lacks sufficient sensitivity and specificity and is not recommended.

The German Agency for Health Technology Assessment (Perleth et al, 1999) conducted a systematic review and meta-analysis of the diagnosis of acute maxillary sinusitis in adults. The assessment concluded that x-rays in patients with suspected sinusitis appears to be the most accurate diagnostic method. The assessment found that ultrasound was less accurate and depends more on the examiner.

Ioannidis and Lau (2001) reported on the results of a systematic evidence review of diagnostic modalities for acute sinusitis in children and adolescents. The authors stated that the reference standard for the diagnosis of acute uncomplicated bacterial sinusitis is sinus aspiration and culture; this is infrequently used because it is invasive, cumbersome to perform and time-consuming. Included studies using other diagnostic parameters (e.g., clinical presentation, plain film and ultrasound) were compared to assess concordance rather than proof of diagnostic accuracy. The authors identified one study that found that 68 of 72 sinuses with ultrasonographic abnormalities yielded fluid on aspiration. The conclusions that can be drawn from the study were limited, however, because aspiration was not attempted in any control group without ultrasonographic abnormalities. In addition, cultures of the aspirate from 59 sinuses yielded microbial pathogens in less than 50 % of the cases (26 out of
The authors reported that the only study to compare ultrasonography with plain film radiography and sinus fluid abnormalities, among children with a clinical picture of sinusitis, found very low concordance between these diagnostic techniques.

In a guideline on appropriate antibiotic use in sinusitis endorsed by the Centers for Disease Control and Prevention, American Academy of Family Physicians, the American College of Physicians-American Society of Internal Medicine, and the Infectious Diseases Society of America (Snow et al, 2001), radiography is not recommended for the diagnosis of acute sinusitis. The guideline recommended that clinicians rely on duration of illness (at least 7 days) and severity of symptoms to make an accurate diagnosis of sinusitis. These guidelines make no recommendation for the use of paranasal sinus ultrasound in the diagnosis of either acute or chronic sinusitis.

Neher (2003) systematically reviewed the evidence supporting the use of various imaging studies in acute sinusitis. The author stated that "[t]here is no role for imaging in the diagnosis of acute sinusitis. For patients who have persistent symptoms, or those for whom surgery is being considered, some guidelines suggest that coronal CT scan of the paranasal sinuses be considered." The author noted that the great variability of test performance of diagnostic ultrasound in acute sinusitis, citing a systematic evidence review by Varonen et al (2000). Neher noted that, since the cost of diagnostic ultrasound is similar to that of a sinus CT, ultrasound is not indicated in the diagnostic evaluation of the sinuses. Nether concluded that "[a]ccurate diagnosis of acute sinusitis in both children and adults depends on the history and clinical examination of the patient." The author explained that, "[w]hile the clinical signs and symptoms of acute sinusitis are often difficult to distinguish from viral upper respiratory infection, such an assessment remains the best approach to diagnosing acute sinusitis."
Triulzi and Zirpoli (2007) stated that the diagnosis of both acute as well as chronic rhinosinusitis in the pediatric population should be made clinically, and not on the basis of imaging findings alone. Plain radiography may be used as a screening method for various pathological conditions of sinuses, but CT remains the study of choice for the imaging evaluation of acute and chronic rhinosinusitis. In acute sinusitis, CT is indicated in patients with symptoms persisting after 10 days of appropriate therapy and in patients with suspected complications (especially in the brain and in the orbit). In addition to CT scanning, magnetic resonance imaging of the sinuses, orbits, and brain should be performed whenever extensive or multiple complications of sinusitis are suspected. In chronic sinusitis, CT scanning is the "gold standard" for the diagnosis and the management, because it also provides an anatomical road map, when surgery is necessary. Nuclear medicine studies and ultrasound are rarely indicated in acute and chronic rhinosinusitis.

Varonen et al (2003) conducted a randomized controlled clinical study to compare antibiotics and placebo in patients with clinically diagnosed acute maxillary sinusitis, and to study whether sinus ultrasound examination would help to detect those patients who benefit from antibiotic therapy. The study included 150 adult patients with a clinical diagnosis of sinusitis at nine primary care sites in Finland. Subjects received antibiotics or placebo for one week after diagnosis; all patients were examined with sinus ultrasound after randomization. The authors found that only half of patients with a clinical diagnosis of acute maxillary sinusitis had sinusitis in ultrasound examination.

A review on management of acute sinusitis in Drug and Therapeutics Bulletin (2009) stated that ultrasound is only of moderate value, adds little to radiology, and is seldom used in the management of acute sinusitis. Furthermore, the
University of Michigan Health System's clinical guideline on "Acute rhinosinusitis in adults" (2011) did not mention the use of ultrasonography for the diagnosis of rhinosinusitis.

An UpToDate review on “Clinical manifestations, pathophysiology, and diagnosis of chronic rhinosinusitis” (Hamilos, 2013) states that “Transillumination and ultrasound imaging of the sinuses are considered outmoded and have not been recommended for diagnostic purposes by consensus groups due to lack of sensitivity and specificity for rhinosinusitis”. Also, an UpToDate review on “Acute sinusitis and rhinosinusitis in adults: Clinical manifestations and diagnosis” (Hwang and Getz, 2013) states that “Ultrasonography is of limited use in the diagnosis of ABRS [acute bacterial rhinosinusitis], due to its high operator variability and inferior accuracy relative to other modalities”.

Karosi et al (2013) stated that microbial biofilms have been implicated in the pathogenesis of chronic rhinosinusitis with nasal polyposis (CRSwNP). Although biofilms are characterized by an extremely high resistance against chemical and physical agents, low-frequency ultrasound (LFU) treatment has been suspected to be an efficient and safe method for biofilm disruption. In a basic science experimental study, these researchers examined the effectiveness of LFU for biofilm disruption in chronic rhinosinusitis with nasal polyposis. A total of 10 patients with CRSwNP undergoing endoscopic sinus surgery were analyzed. Two series of identical nasal polyps (n = 20) were processed to hematoxylin-eosin and Gram staining and to continuous-wave LFU treatment (5 minutes, 0.4 MHz, 37°C), respectively. Presence of microbial biofilms was confirmed in all patients with CRSwNP. Hematoxylin-eosin staining showed a strong correlation with the results of Gram protocol in biofilm detection. In the LFU-treated group (n = 10), a significantly decreased inflammatory cell count was found in the subepithelial layer of nasal polyps (p < 0.001). In addition, bacterial biofilms were completely removed from the surface of
the epithelial layer. Microscopic tissue injuries or significant temperature changes were not detected due to LFU treatment. The authors concluded that between in-vitro conditions, LFU treatment appeared to be a reliable and microscopically safe method for the disruption of microbial biofilms in CRSwNP. They stated that these findings may provide a basis for a prospective human study investigating the safety and effectiveness of this therapeutic modality alone or in combination with antibiotics or topical steroids in biofilm-positive cases of CRSwNP.

D'Anza and colleagues (2017) stated that granulomatosis with polyangiiitis (GPA) (Wegener granulomatosis) frequently presents in the head and neck, and the sinonasal cavity is among the most common areas affected. Although the clinical findings, histologic appearance, and laboratory work-up have been described, characteristic findings and the distribution of disease on sinonasal imaging are not well established. The appropriate imaging modality to evaluate for sinonasal involvement is also unclear. These investigators described the imaging characteristics, distribution, and location of sinonasal pathology in patients with GPA as noted on CT and MRI modalities. These researches performed a systematic review of English language articles, by using appropriate search terms, which reported the CT and MRI findings specific to sinonasal disease in adult subjects with GPA. Studies were included only when they focused primarily on specific imaging results in patients with GPA. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed. A total of 50 articles were identified on an initial search of medical literature data bases. There were 7 articles that comprised 224 patients who met inclusion criteria. All the articles were retrospective case series and descriptive in nature. A high incidence of patients with GPA who were imaged showed evidence of pathologic findings. The prevalence of key radiographic findings in patients with GPA were the following: mucosal thickening (87.7 % of patients), bony destruction (59.9 %), and septal erosion (59.4 %).
were no randomized or prospective studies that compared imaging findings between patients with GPA and the controls, and no studies that correlated imaging findings with prognosis. The authors concluded that sinus imaging in GPA revealed a spectrum of nonspecific findings. The constellation of septal erosion, mucosal thickening, and bony changes should raise suspicion for GPA. The current literature was insufficient to make any comments on the time course of sinonasal disease and imaging manifestations. They stated that further comparative studies are needed to determine a role for sinonasal imaging in the diagnosis and prognosis of GPA.

Greschus et al (20170 noted that due to the complex anatomy of the anterior skull base and paranasal sinuses, radiologic diagnostics in this area are challenging; MRI and CT are the primary indicated modalities. Guidelines helping to select the appropriate modality have been published by the German Society of Head and Neck Radiology and the Society of Otorhinolaryngology. These investigators presented an overview of the current radiologic procedures and their optimized implementation using clinical examples. These examples highlighted the fact that a combination of at least CT and MRI is frequently needed. Use of CT for intra-operative navigation is everyday practice in clinical routine. Occasionally, additional procedures such as angiography or myelography are required, especially in cases of pre-operative vascular diagnostics or embolization. The authors concluded that evaluation of radiologic diagnostics in this area is complex; it requires experience and knowledge of the disease, as well as an understanding of the diagnostic procedures. Ultrasonography is not mentioned as an imaging modality for paranasal sinuses.

Detection of IgG4-Positive Plasma Cells in the Nasal Cavity or Para-Nasal Sinuses for Diagnosis of Chronic Rhino-Sinusitis
Ohno and colleagues (2017) clarified the clinicopathological characteristics of IgG4-positive plasma cells in patients with CRS. These investigators examined nasal mucosal specimens from 35 patients and assigned them to high-IgG4 and low-IgG4 groups based on infiltration of IgG4-positive plasma cells. They compared the pathological characteristics of the 2 groups, including the presence of fibrosis, phlebitis, hyperplasia of the nasal glands and infiltration of inflammatory cells. No cases of CRS showed storiform fibrosis or obliterative phlebitis. The mean number of IgG4-positive plasma cells in samples from all patients was 29.8 ± 40.3/high-power field; 11 of the 35 cases (31.4 %) were classified as high-IgG4. Hyperplasia of the nasal glands was observed significantly more frequently in the high-IgG4 group than in the low-IgG4 group (p = 0.03). The authors concluded that high levels of IgG4-positive plasma cells were observed in tissue samples from approximately 30 % of patients with CRS who satisfied the comprehensive diagnostic criteria for IgG4-related disease. They stated that detection of increased numbers of IgG4-positive plasma cells in the nasal cavity or paranasal sinuses might not be sufficient to make a diagnosis of IgG4-related rhino-sinusitis, and a comprehensive evaluation is needed.

Examination of Blood Eosinophil for Diagnosis of Eosinophilic Chronic Rhino-Sinusitis

Li and co-workers (2016) evaluated the practice of peripheral blood eosinophil in the diagnosis of eosinophilic CRS (ECRS). The correlation between eosinophil count and percentage in peripheral blood and that in topic tissue in 787 patients (January 2013 to June 2016) with CRS were retrospectively analyzed. The optimal cut-off value of blood eosinophil count and percentage as predictors for ECRS was determined by receiver operating characteristic curves (ROC) and their diagnostic ability was compared. The positive correlation between eosinophil count and percentage in blood and that in tissue was found in 787 patients with CRS (r = 0.450, 0.499,
0.463, 0.465, respectively, p < 0.01). Although the significant correlation between blood eosinophil count and its count and percentage in tissue was not found after blood leukocyte and tissue eosinophilic inflammation was controlled (r = 0.041, p = 0.380; r = 0.046, p = 0.329 and r = 0.023, p = 0.618; r = 0.032, p = 0.499, respectively), blood eosinophil percentage still showed significant correlation with tissue eosinophil count and percentage, but reduced unequally after that (r = 0.383, 0.436 and r = 0.153, 0.169, p < 0.01). With ROC analysis, the diagnostic ability of optimal cut-off values of eosinophil count and percentage varied as the histological criteria for ECRS differed. The authors concluded that eosinophil in peripheral blood showed significant positive correlation with its tissue infiltration, which may be not strong and easily effected by individual factors. They stated that theoretically, blood eosinophil may have a diagnostic significance as a predictor for ECRS; but not practically.

Examination of Serum / Tissue Eosinophilia in Patients with Chronic Rhino-Sinusitis

In a case-series study, Gitomer and colleagues (2016) described clinical and histopathologic findings in patients with CRSwNP. These investigators also examined if tissue and serum eosinophilia predicts disease severity in CRSwNP. Clinical data were collected; sinus CT scans were scored according to the Lund-Mackay system; and surgical specimens were evaluated for degree of tissue eosinophilia. Statistical analysis was performed to compare eosinophilia with indicators of disease severity. A total of 70 CRSwNP patients were included, with a mean Lund-Mackay score of 16.7; 62.1 % of patients had severe asthma, and 62.9 % were aspirin-sensitive. Elevated tissue eosinophil level did not correlate with medication usage, olfactory symptoms, or Lund-Mackay scores, nor did it correlate with presence of asthma or aspirin-sensitivity (p = 0.09). Patients with mild asthma had significantly more tissue eosinophils versus patients with severe asthma, possibly because of the high amount of
chronic corticosteroid use in severe asthmatics. There was no correlation between tissue and serum eosinophil counts (p = 0.97), however, there was a significant positive correlation between CT score and peripheral eosinophil level (p < 0.05). The authors concluded that higher serum eosinophil levels may indicate more extensive mucosal disease as measured on CT scan. They stated that neither serum nor tissue eosinophilia predicted disease severity in their retrospective analysis of CRSwNP patients, and serum eosinophil level did not serve as a marker of tissue eosinophilia.

Examination of Serum Immunoglobulin E (IgE) Levels for Prediction of Outcomes of Medical Therapy in Patients with Chronic Rhino-Sinusitis

In a prospective, cohort study, Lemos-Rodriguez and colleagues (2017) evaluated the impact of immunoglobulin E (IgE) levels on outcomes in patients with CRS who received maximal medical therapy (MMT). A total of 38 patients who underwent MMT for CRS were assigned to 3 different cohorts based on their IgE levels: low IgE (less than 25 IU), moderate (greater than 25 to less than 149 IU), and high (greater than or equal to 150 IU). The primary outcome evaluated was MMT failure with a surgical recommendation within each IgE cohort. Secondary outcomes included changes in pre- and post-MMT scores for the Rhinosinusitis Disability Index, Chronic Sinusitis Survey, and CT-based Lund-Mackay evaluation. The cohorts were sub-stratified based on the presence of NPs and nasal allergies. No significant difference was found when MMT failure was compared between the cohorts in terms of quality of life (QOL). When sub-stratified based on the presence of NPs and nasal allergic disease, there was no significant difference between the cohorts. In the high-IgE cohort, all patients regardless of presence of NPs and nasal allergic disease, frequently failed MMT and were recommended for surgery. The authors concluded that overall, IgE levels did not appear to have a significant effect on the QOL or outcomes of MMT in the patients with CRS. However, the presence of nasal
allergies regardless of IgE levels appeared to result in more frequent recommendations for surgery after MMT. In the patients with higher-IgE levels (greater than or equal to 150 IU), MMT seemed to fail at high rates with or without the presence of NPs or allergic disease.

The authors stated that this study had several drawbacks. The most important was the small sample size (n = 38) in the 3 different cohorts. Several pre-trial power calculations were performed; however, the clinical impact and effect size of differing levels of serum IgE among the cohorts was unknown and no comparative studies exist. For a pre-trial power calculation, an effect size of 0.5 was used to determine a cohort of 192 patients needed to achieve 80% power. However, the standard error of non-binary outcomes was unknown because such comparative studies do not exist and, therefore, pre-trial power calculations were at best an educated guess in such a situation. In addition, the power calculations mentioned were made by using standardize tables that greatly under-estimated the true sample size needed to achieve appropriate power based on the actual effect size. Thus, these researchers were unable to make a robust a priori calculation of the sample size. They stated that future studies with larger sample sizes would likely provide a more-effective estimate of the effect size because there was no previous literature that evaluated the clinical difference between subjects that could be implemented. Also, immunohistochemical analysis of sino-nasal tissue could provide useful data to assist stratifying patients based on the presence of local tissue eosinophils and/or IgE.

Examination of Tissue Eosinophilia for Evaluation of CRS-Associated Olfactory Loss

Hauser and colleagues (2017) noted that olfactory dysfunction is one of the hallmark symptoms of CRS. Eosinophilic inflammation has been implicated as a potential causative factor. However, prior studies have been limited by
retrospective study designs, concomitant use of systemic corticosteroids, and other confounding factors. In a prospective study, CRS and healthy non-CRS control subjects undergoing endoscopic sinus or skull-base surgery were enrolled and completed olfactory testing utilizing the 40-item Smell Identification Test (SIT) immediately prior to surgery. Histopathological evaluation of tissue excised from the ethmoid bulla was performed by a pathologist in a blinded fashion. Disease severity and patient-reported outcomes were measured via the Lund-Mackay CT grading system and 22-item Sino-Nasal Outcome Test (SNOT-22), respectively. The associations between olfactory function, tissue eosinophilia, and disease severity were analyzed using Spearman rank order correlation and multiple linear regression. A total of 27 subjects with CRSsNP, 32 subjects with CRSwNP, and 10 healthy non-CRS controls were enrolled. CRSwNP was associated with higher mean tissue eosinophil counts (71.6 versus 28.1 eosinophils/high-power field [HPF], p < 0.05) and lower age/sex-adjusted SIT scores (-17.4 versus -6.2, p < 0.001) when compared to CRSsNP; SIT scores were strongly negatively correlated with tissue eosinophil counts in CRSwNP (r = -0.60, p = 0.0003), but not CRSsNP (r = 0.16, p = 0.42).

The correlation between olfactory function and tissue eosinophilia in CRSwNP persisted after adjusting for disease severity. The authors concluded that tissue eosinophilia was associated with olfactory loss in CRSwNP, independent of disease severity. They stated that these findings suggested a possible role for eosinophils or eosinophil-associated cytokines in CRS-associated olfactory loss. These preliminary findings need to be validated by well-designed studies.

Examination of Tissue Epidermal Growth Factor Receptor Ligands (e.g., Epiregulin) and Matrix Metalloproteinase-1 for Evaluation of Chronic Rhino-Sinusitis

Homma and colleagues (2017) stated that CRS is a heterogeneous chronic inflammatory disease of the nose and para-nasal sinuses that presents without or with NPs. Notable
features of CRSwNP are the frequent presence of type 2 allergic inflammation and high prevalence of Staphylococcus aureus (SA) colonization. As inflammation persists, sinus tissue undergoes epithelial damage and repair along with polyp growth, despite active medical management. Because one feature of damaged tissue is enhancement of growth factor signaling, these researchers evaluated the presence of epidermal growth factor receptor (EGFR) ligands and matrix metalloproteinases (MMPs) in CRS. They analyzed the expression of EGFR ligands and MMPs in patients with CRS and examined the possible role of SA on epithelial activation. Sino-nasal tissues were collected during surgery from control subjects and patients with CRS. Tissues were processed as described previously for analysis of mRNA (RT-PCR) and proteins (ELISA) for the majority of EGFR ligands within the tissue extracts. CRS tissue was used for evaluation of the distribution of epiregulin (EREG), an EGFR ligand, and MMP-1 by immunohistochemistry. In parallel studies, expression of these genes and proteins was analyzed in cultured primary airway epithelial cells. Elevated expression of EREG and MMP-1 mRNA and protein was observed in uncinate and polyp tissue from patients with CRSwNP. Immunohistochemistry study of clinical samples revealed that airway epithelial cells expressed both of these proteins. Cultured primary human airway epithelial cells expressed MMP-1, and MMP-1 was further induced by stimulation with EREG or heat-killed SA (HKSA). The induction of MMP-1 by HKSA was blocked by an antibody against EREG, suggesting that endogenous EREG induces MMP-1 after stimulation with HKSA. EREG and MMP-1 were found to be elevated in NP and uncinate tissues in patients with CRSwNP. The authors concluded that elevated expression of EREG and MMP-1 may be related to polyp formation in CRS, and colonization of SA might further enhance this process. These preliminary findings need to be validated by well-designed studies.
Microarray DNA Testing for Evaluation of Chronic Rhinosinusitis

Orlandi and colleagues (2007) determined and compared the differential gene expression in allergic fungal sinusitis (AFS) and eosinophilic mucin rhino-sinusitis (EMRS). These researchers conducted a complementary DNA microarray analysis of prospectively gathered tissue from a tertiary rhinology practice. Compared to normal subjects, 38 genes or potential genes were differentially expressed in AFS patients, while 10 genes were differentially expressed in EMRS patients; 4 genes differentially expressed in EMRS were not differentially expressed in AFS: cathepsin B, sialyltransferase 1, GM2 ganglioside activator protein, and S100 calcium binding protein. These genes mediate lysosomal activity and are known to have differential expression in inflammatory and neoplastic states. The authors concluded that EMRS and AFS showed some similarities in gene expression profiles using microarray analysis. Significant differences in gene expression in both EMRS and AFS patients compared with normal subjects provide early clues to the pathophysiology of EMRS and AFS. This study demonstrated that complementary DNA microarray analysis is a feasible tool for studying different disease sub-classes and was the first to study these sub-classes in CRS.

Fraczek and associates (2013) stated that the inflammatory process underlying nasal polyposis is induced and perpetuated by the enhanced activity of several agents including transcription factors. It has recently been shown that one of them, named nuclear factor-kappa B (NF-κB), is implicated in the regulation of multiple pro-inflammatory genes. These researchers identified using microarray technology which NF-κB-dependent genes are activated in nasal polyp (NP) samples compared to the control mucosa. The transcriptional activity of genes was analyzed using an oligonucleotide microarray on 15 NPs and 8 cases of normal nasal mucosa. Gene expression patterns obtained in NPs
were significantly different from those in normal mucosa. NPs and control cases clustered separately, each of them with large homogeneity in gene expression. Among 582 human NF-κB-dependent genes 25 showed a significantly higher expression in NPs compared to the control. The largest increase focused on gene encoding TFF3 (a 5-fold higher expression) followed by NOS2A (5x), SERPINA1 (4x), UCP2 (4x), OXTR (4x) and IL8 (3x) (p<0.05). In healthy mucosa, 19 genes presented increased transcription activity compared to NPs. The most significantly enhanced levels were shown LTF gene (20 fold) followed by KRT6B (7x), LYZ (7x), SD11B2 (5x) and MMP3 (4x) (p < 0.05). The authors concluded that DNA microarray technology highlighted the involvement of many unsuspected pathologic pathways, which could be involved in NP growth. They stated that the identification of novel disease-related genes may help to understand the biology of NPs and elaborate new targeted therapy. Moreover, they stated that further studies are needed to learn more about transcriptional pathways down-stream to NF-κB and the clinical usefulness of NF-κB inhibitory molecules.

Thunberg and co-workers (2015) noted that the anterior nares have been regarded as the major carriage site of Staphylococcus aureus. From here, the organism can spread to other parts of the body where it might act as harmless commensal or cause mild-to-severe infections. Nasal sinuses are normally sterile, but in patients with CRS, the finding of S. aureus in maxillary sinus cultures is common. Isolates were obtained from the nares and maxillary sinus of patients with CRS and the nares of healthy controls. A significantly higher frequency of S. aureus was found in nares samples from patients (24/42) compared to controls (16/57) (p = 0.004). There is no consensus regarding whether S. aureus is a relevant pathogen in CRS. A DNA microarray was used to investigate the prevalence of S. aureus virulence genes with focus on staphylococcal enterotoxins, toxic shock syndrome toxin-1, agr types, and cell wall-associated proteins. The genotyping of S. aureus isolates revealed only small and non-
significant differences in gene prevalence between isolates collected from patients with CRS and those collected from healthy nasal carriers. The authors concluded that the findings of this study provided an increased knowledge of the genetic pattern of virulence genes among S. aureus collected in CRS.

Zheng and colleagues (2015) stated that DNA methylation has been implicated in the pathogenesis of allergy and atopy. This study aimed to identify whether DNA methylation also plays an important role in the pathogenesis of NP. NP tissues were obtained from 32 patients with CRS with bilateral NP. Biopsies of inferior turbinate mucosa (ITM) were taken from 18 patients who underwent rhino-septoplasty (control group). The methylated genes, which were detected by DNA methylation microarray, were validated by methylation-specific polymerase chain reaction (PCR), bi-sulphite sequencing, real-time PCR (rt-PCR) and immunohistochemistry. DNA methylation microarray identified 8,008 CpG islands in 2,848 genes; 198 genes were found to have a methylated signal in the promoter region in NP samples compared with ITM samples. The 4 top genes that changed, COL18A1, EP300, GNAS and SMURF1, were selected for further study. The methylation frequency of COL18A1 was significantly higher in NP samples than in ITM samples. The authors concluded that DNA methylation might play an important role in the pathogenesis of NP. Moreover, they stated that promoter methylation of COL18A1 was found to be significantly increased in NP tissues, further studies are needed to confirm the significance of these epigenetic factors in the mechanisms underlying the development or persistence of NP.

Tokunaga and associates (2017) noted that the number of patients with eosinophilic CRS (ECRS) has been increasing in recent years in Japan. In ECRS, NPs recur immediately after endoscopic sinus surgery. The molecular biological mechanism underlying the refractoriness of ECRS is unclear. Whole-transcriptome analysis with next-generation sequencing
(RNA-seq) was conducted to examine the molecular biological mechanism of ECRS; rt-PCR, immunohistochemical staining, and immunofluorescence staining were performed to validate the results of RNA-seq. RNA-seq analysis revealed that in the NPs of ECRS, the levels of 3 transcripts were elevated significantly and those of 7 transcripts were diminished significantly. Among the genes encoding these transcripts, TRPV3 (transient receptor potential cation channel, subfamily V, member 3) was identified as the only gene that is highly expressed in ECRS NPs; but this gene's expression was not previously detected using DNA microarray analysis in peripheral blood eosinophils. TRPV3 was newly identified here as a gene transcribed in ECRS. The analysis also revealed that TRPV3 was highly expressed in the infiltrating eosinophils and mucosal epithelium of the NPs of ECRS, and further that the more severe the refractoriness was after surgery, the higher the TRPV3 expression was in NPs. The authors concluded that the TRPV3 might play a role in the refractoriness of ECRS; additional studies are needed to evaluate the function of TRPV3 in ECRS.

Furthermore, an UpToDate review on “Chronic rhinosinusitis: Clinical manifestations, pathophysiology, and diagnosis” (Hamilos, 2018) does not mention microarray DNA testing as a management tool.

Type 2 Cytokines as Biomarkers in the Evaluation of Chronic Rhinosinusitis

Yao and colleagues (2017) noted that CRSwNP is a group of multi-factorial and heterogeneous disorders with a significant economic strain on society, likely made up of different endotypes, each with a unique patho-mechanism. In addition to the traditional clinical measures, there is a recognized need for reliable biomarkers to provide predictive information regarding diagnosis, endotypes, therapeutic responses, and future risk of recurrence. Fueled by the advances in basic research, various biomarkers have been explored in recent
years. Biomarkers of CRSwNP can originate from a variety of sources, including nasal secretions, nasal biopsies, exhaled breath, and peripheral blood. In this review, these investigators summarized the existing and emerging biomarkers available for the evaluation and management of CRSwNP. Currently, eosinophil count in nasal mucosa has proved particularly valuable for endotyping, assessing disease severity, and predicting steroid responsiveness and surgical outcomes. Blood eosinophilia may be used as a surrogate for tissue eosinophilic inflammation, whereas its utility remains limited. Type 2 cytokines (e.g., IL-4, IL-5, and IL-13), and IgE have been identified as potential therapeutic targets.

Moreover, MMP-9 is linked to healing quality after sinus surgery. Nasal nitric oxide (nNO) appears to fill the niche as a non-invasive measure for sinus ostial patency. In addition, recent data have shown some promising biomarkers involved in corticosteroid resistance and olfactory dysfunction.

Moreover, the authors concluded that rigorous validation using large cohort studies is needed before these biomarkers can be incorporated into clinical practice.

CPT Codes / HCPCS Codes / ICD-10 Codes

*Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":*

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<thead>
<tr>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>No specific code</td>
</tr>
</tbody>
</table>

*Type 2 cytokines, microarray DNA testing, IgG4-positive plasma cells, examination of tissue eosinophilia, Examination of tissue epidermal growth factor receptor (EGFR) ligands, matrix metalloproteinases*
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>76536</td>
<td>Ultrasound, soft tissues of head and neck (e.g., thyroid, parathyroid, parotid), real time with image documentation</td>
</tr>
</tbody>
</table>

**HCPCS codes not covered for indications listed in the CPB:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>S9024</td>
<td>Paranasal sinus ultrasound</td>
</tr>
</tbody>
</table>

**ICD-10 codes not covered for indications listed in the CPB:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J01.00-J01.91</td>
<td>Acute sinusitis</td>
</tr>
<tr>
<td>J32.0-J32.9</td>
<td>Chronic sinusitis</td>
</tr>
<tr>
<td>R43.0</td>
<td>Anosmia [CRS-associated olfactory loss]</td>
</tr>
</tbody>
</table>

The above policy is based on the following references:

4. Perleth M, Jakubowski E, Busse R. Diagnosis of acute maxillary sinusitis in adults - systematic review and meta-analysis. Koln, Germany: German Agency for Health Technology Assessment at the German Institute for Medical Documentation and Information (DAHTA) (DIMDI); 1999.

http://aetnet.aetna.com/mpa/cpb/600_699/0694.html


30. Hamilos DL. Clinical manifestations, pathophysiology, and diagnosis of chronic rhinosinusitis. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed June 2013.

31. Hwang PH, Getz A. Acute sinusitis and rhinosinusitis in adults: Clinical manifestations and diagnosis. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed June 2013.


36. Orlandi RR, Thibeault SL, Ferguson BJ. Microarray analysis of allergic fungal sinusitis and eosinophilic


47. Hamilos DL. Chronic rhinosinusitis: Clinical manifestations, pathophysiology, and diagnosis. UpToDate Inc., Waltham, MA. Last reviewed May 2018.
AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number: 0694 Paranasal Sinus Ultrasound for the Evaluation of Sinusitis

There are no amendments for Medicaid.

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