

Review

When Refractory Rhinosinusitis Should Trigger Diagnostic Reassessment: A Red-Flag- and Phenotype-Guided Review of Rare and Uncommon Mimics

Eddy Ukponahunsi ^{1,†} , Eman A. Ibrahim ^{2,†} , Oziegbe A. Amhakhian ³  and Emmanuel O. Oisakede ^{4,5,6,*} 

¹ Department of Haematology, Our Lady of Lourdes Hospital, A92 VW28 Drogheda, County Louth, Ireland; edunedwin@gmail.com

² Department of General Internal Medicine, Liverpool University Hospitals NHS Foundation Trust, Liverpool L7 8XP, UK; eman.ibrahim1@nhs.net

³ Department of Radiology, Irrua Specialist Teaching Hospital, Irrua 310115, Edo State, Nigeria; andrew.dr@yahoo.com

⁴ Department of Clinical Oncology, Leeds Teaching Hospitals NHS Trust, Leeds LS9 7TF, UK

⁵ Department of Health Research, University of Leeds, Leeds LS2 9JT, UK

⁶ Department of Genomic Medicine, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London E1 2AT, UK

* Correspondence: emmanuel.oisakede@nhs.net

† These authors contributed equally to this work.

Abstract

Chronic rhinosinusitis (CRS) is common, but several rare diseases, rare sinonasal manifestations of systemic disorders, and uncommon local mimics can present as apparently refractory CRS. For terminology, this review uses the European epidemiological threshold of no more than 5 affected persons per 10,000 population for a rare disease, while conditions that do not consistently meet that threshold are described as uncommon mimics or rare sinonasal manifestations. The clinical problem is therefore not to test every patient for every rare disorder, but to recognise when routine CRS no longer explains the phenotype. This narrative review focuses on eosinophilic granulomatosis with polyangiitis (EGPA), granulomatosis with polyangiitis (GPA), primary ciliary dyskinesia (PCD), cystic fibrosis, humoral immune dysfunction, sarcoidosis, immunoglobulin G4-related disease, acute invasive fungal rhinosinusitis, sinonasal malignancy, and rhinolithiasis because they can mimic CRS yet require materially different investigation or treatment. A refractory course is not itself a diagnosis: symptoms should first be linked to objective sinonasal inflammation and treatment delivery assessed. Unilateral bleeding or a mass, tissue necrosis, facial numbness, visual or cranial neuropathy, destructive crusting, marked eosinophilia with adult-onset asthma, early-life wet cough with laterality abnormality, or recurrent bacterial respiratory infection should redirect investigation. Tests are most useful when interpreted conditionally, i.e., negative antineutrophil cytoplasmic antibody does not exclude localised vasculitis; nasal biopsy has limited sensitivity; low nasal nitric oxide is an adjunct rather than a stand-alone PCD diagnosis; and serum angiotensin-converting enzyme or immunoglobulin G4 cannot establish a tissue diagnosis. Cross-sectional imaging defines anatomy and extension but rarely determines aetiology without endoscopy and appropriately handled tissue. Biologic non-response should also trigger diagnostic reassessment before treatment escalation. The proposed red-flag framework is a pragmatic expert synthesis, not a validated diagnostic prediction rule, and is intended to facilitate earlier recognition of consequential mimics while reducing indiscriminate testing and serial empirical therapy.



Academic Editor: Adam J. Sybilski

Received: 8 August 2026

Revised: 9 September 2026

Accepted: 23 September 2026

Published: 25 September 2026

Copyright: © 2026 by the authors.

Licensee MDPI, Basel, Switzerland.

This article is an open access article distributed under the terms and

conditions of the [Creative Commons](https://creativecommons.org/licenses/by/4.0/)

[Attribution \(CC BY\)](https://creativecommons.org/licenses/by/4.0/) license.

Keywords: chronic rhinosinusitis; diagnostic delay; eosinophilic granulomatosis with polyangiitis; granulomatosis with polyangiitis; primary ciliary dyskinesia; sarcoidosis; sinonasal tumour; invasive fungal rhinosinusitis; rhinolith; biologic therapy

1. Introduction

Chronic rhinosinusitis is defined by compatible symptoms persisting for at least 12 weeks together with objective evidence of sinonasal inflammation on nasal endoscopy or computed tomography (CT). Population estimates vary with the definition used, and symptom-only surveys overestimate disease when objective confirmation is absent [1]. This distinction matters most in patients labelled “refractory.” Persistent facial pain, headache, or nasal symptoms after treatment may reflect uncontrolled Chronic rhinosinusitis (CRS), incorrect phenotype assignment, poor drug delivery, structural obstruction, neuropathic pain, or an alternative systemic or local disorder. Failure of a treatment course is therefore evidence that the diagnostic model should be re-examined, not proof of a rare disease.

For scope, “rare” requires epidemiological precision. In Europe, rare diseases are generally defined as conditions affecting no more than 5 per 10,000 people [2]. That disease-level definition does not map perfectly onto sinonasal practice: some entities considered here are rare disorders in their own right, some are more prevalent systemic diseases with rare sinonasal involvement, and others are uncommon local mimics whose prevalence may not satisfy a formal rare-disease threshold. We therefore distinguish three clinically relevant situations: (1) rare systemic or genetic diseases that involve the upper airway; (2) rare sinonasal manifestations of systemic disease; and (3) uncommon local or invasive mimics, which were included because omitting them has major clinical consequences. The purpose is clinical triage rather than construction of an exhaustive orphan-disease catalogue.

The disorders considered here are uncommon, but the cost of omitting them is disproportionate. Delayed recognition of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis can permit renal, neurological, cardiac, or pulmonary injury; delayed PCD or cystic fibrosis care allows progressive suppurative lung disease; and delayed diagnosis of invasive infection or malignancy may be immediately life-threatening. Conversely, broad laboratory panels applied to low-risk CRS produce incidental abnormalities and false-positive diagnoses. The clinically relevant question is therefore which combination of features raises the pre-test probability sufficiently to warrant targeted serology, physiological testing, imaging, or biopsy.

Broader reviews have already catalogued orphan and rare disorders of the nose and paranasal sinuses [3,4]. The present review is positioned differently: it uses the patient labelled with “refractory CRS” as the starting clinical problem and asks when that label should be questioned, which phenotype or red flag should redirect the work-up, and what the next discriminating investigation should be. Its intended contribution is therefore a decision-focused red-flag- and phenotype-guided framework rather than a comprehensive inventory of rare rhinological disease.

2. Methods

A targeted narrative review was conducted using PubMed/MEDLINE and searches of relevant professional-society and guideline websites. Searches combined terms for chronic rhinosinusitis, refractory, unilateral sinus disease, nasal polyps, and sinonasal with EGPA, GPA, ANCA, primary ciliary dyskinesia, nasal nitric oxide, cystic fibrosis, specific antibody deficiency, sarcoidosis, IgG4-related disease, invasive fungal rhinosinusitis, malignancy, NK/T-cell lymphoma, rhinolith, and individual biologic agents. English-language publi-

cations from January 2010 to 31 July 2026 were considered; earlier seminal studies were retained when they addressed enduring diagnostic limitations, such as the yield of nasal biopsy in GPA.

Disorder selection was purposive rather than prevalence-exhaustive and was guided by four clinical-relevance criteria: (1) the ability to produce chronic or recurrent sinonasal symptoms, endoscopic abnormalities, or imaging appearances that plausibly mimic CRS; (2) a recognised risk of diagnostic delay or repeated empirical CRS treatment; (3) materially different management, irreversible organ injury, or immediate threat if the diagnosis is missed; and (4) the presence of a recognisable red-flag phenotype or targeted investigation capable of redirecting the work-up. The final set therefore spans rare systemic and genetic disorders, rare sinonasal manifestations of systemic disease, and uncommon local mimics. This clinical-consequence criterion also explains the inclusion of acute invasive fungal rhinosinusitis, despite its usually acute course, and of rhinolithiasis, despite its benignity.

Guidelines, consensus statements, randomised trials, diagnostic-accuracy studies, and cohort studies were prioritised. Case reports were used only to illustrate failure modes that are difficult to study prospectively, not to estimate prevalence or treatment effect. Reference lists of key sources were examined for additional studies. Because the purpose was clinical synthesis rather than effect estimation, no pooled analysis or formal risk-of-bias instrument was applied. This approach permits integration of heterogeneous rare-disease evidence but is vulnerable to publication, language, and selection bias; recommendations supported mainly by small retrospective series are identified as such.

3. Refractoriness Is a Phenotype, Not a Diagnosis

Before expanding the differential diagnosis, clinicians should verify that symptoms satisfy a CRS definition, that inflammation is objectively present, and that apparently appropriate treatment was actually delivered. Intranasal corticosteroid technique, adherence, saline-irrigation method, exposure to tobacco or occupational irritants, dental disease, and the relationship between symptoms and imaging all require review. A normal endoscopy and CT during persistent “sinus” pain should prompt reconsideration of a rhinological diagnosis rather than escalation to antibiotics, systemic corticosteroids, surgery, or a biologic [1].

There is no single treatment-duration threshold that reliably separates uncontrolled inflammatory CRS from a mimic. Moreover, repeated antibiotics are not a diagnostic test, and temporary corticosteroid response is non-specific: lymphoma, sarcoidosis, EGPA, GPA, and IgG4-related disease may all improve transiently. Red flags should therefore override a routine step-care pathway (Table 1). Urgency is determined by the possible consequence of delay, not by the statistical frequency of the condition.

Table 1. Red-flag phenotypes and the first decision they should trigger.

Red-Flag Phenotype	Important Alternatives	Immediate Assessment	Why Delay Matters
Unilateral obstruction or discharge with epistaxis, visible mass, facial or dental pain, paraesthesia, or cranial neuropathy	Sinonasal tumour; extranodal NK/T-cell lymphoma; complicated inflammatory disease	Urgent nasal endoscopy and contrast-enhanced CT; MRI for orbital, skull-base, intracranial, or perineural extension; plan biopsy after imaging	Tumour stage and resectability can change; a superficial necrotic sample may be falsely non-diagnostic [5–9]

Table 1. Cont.

Red-Flag Phenotype	Important Alternatives	Immediate Assessment	Why Delay Matters
Rapid progression, severe pain, black or pale insensate mucosa, orbital signs, fever, or neurological change in diabetes, neutropenia, transplantation, or immunosuppression	Acute invasive fungal rhinosinusitis	Same-day ENT assessment, endoscopy, contrast imaging, and urgent tissue for frozen/permanent histology and fungal studies	Angioinvasion can cause orbital, cerebral, or vascular catastrophe; medical therapy alone is inadequate [10]
Persistent crusting, bloody discharge, septal perforation, saddle-nose change, pulmonary symptoms, haematuria, or neuropathy	GPA; EGPA; infection; cocaine/vasoconstrictor injury; malignancy	Full blood count, C-reactive protein/erythrocyte sedimentation rate, ANCA, urinalysis, creatinine, chest assessment, CT, and targeted biopsy	Localised ANCA-negative disease occurs; renal or pulmonary injury may be clinically silent [11–13]
Adult-onset asthma, recurrent polyps, marked or rising eosinophilia, pulmonary infiltrates, neuropathic symptoms, rash, cardiac symptoms, or constitutional illness	EGPA; parasitic/drug-related eosinophilia; hypereosinophilic syndrome	Repeat eosinophil count, medication and travel review, ANCA, urinalysis/creatinine, chest imaging when indicated, and organ-directed assessment	Systemic involvement, especially cardiac or neurological disease, changes both urgency and treatment [11,14–17]
Daily wet cough and nasal symptoms from infancy, neonatal respiratory distress, chronic otitis, laterality defect, infertility, or bronchiectasis	PCD; cystic fibrosis; other causes of bronchiectasis	Refer to a PCD/bronchiectasis service; nasal nitric oxide under standardised conditions plus confirmatory reference tests; exclude cystic fibrosis	Diagnostic delay permits avoidable airway injury and misses hearing-, fertility-, and laterality-related needs [18–20]
Nasal polyps in a young child, failure to thrive, malabsorption, recurrent lower-respiratory infection, or bronchiectasis	Cystic fibrosis; PCD; immune dysfunction	Sweat chloride with CFTR evaluation as indicated; quantitative immunoglobulins; PCD pathway guided by phenotype	“Idiopathic” paediatric polyposis is uncommon; the pulmonary diagnosis may be more consequential than the polyp [19,21,22]
Recurrent bacterial sinus and chest infections, poor antibiotic response, unusual organisms, or autoimmune/lymphoproliferative features	Humoral immunodeficiency or specific antibody deficiency	IgG, IgA, IgM; vaccine and infection history; specialist assessment of specific antibody responses	Abnormal titres require clinical context, and indiscriminate testing risks overdiagnosis [23]

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; CFTR, cystic fibrosis transmembrane conductance regulator; CT, computed tomography; EGPA, eosinophilic granulomatosis with polyangiitis; ENT, ear, nose and throat; GPA, granulomatosis with polyangiitis; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; MRI, magnetic resonance imaging; NK, natural killer; PCD, primary ciliary dyskinesia.

4. ANCA-Associated Vasculitis

4.1. Eosinophilic Granulomatosis with Polyangiitis

EGPA is characterised by asthma, eosinophilic inflammation, and small-to-medium-vessel vasculitis, but the components need not appear in a fixed sequence. Chronic rhinosinusitis with nasal polyps (CRSwNP) may precede overt vasculitis by years. That interval creates both an opportunity and a trap: adult-onset asthma, recurrent polyps, and

eosinophilia should prompt a systemic review, but these common type 2 inflammatory features do not by themselves establish EGPA.

The 2022 American College of Rheumatology /European Alliance of Associations for Rheumatology criteria assign high weights to eosinophilia, obstructive airway disease, and nasal polyps [14]. They are classification criteria for research after a diagnosis of small- or medium-vessel vasculitis has been made and mimics have been excluded; using them as a stand-alone diagnostic checklist in a general rhinology population would inflate false positives. Peripheral eosinophilia is similarly conditional. Systemic corticosteroids and anti-interleukin (IL)-5 treatment may suppress it, whereas allergy, parasitic infection, drug reactions, and other eosinophilic disorders may raise it. ANCA is absent in most patients with EGPA, and ANCA status does not map perfectly onto phenotype.

The work-up should therefore search actively for vasculitic or eosinophilic organ injury: mononeuritis multiplex, purpura, glomerular disease, pulmonary infiltrates or haemorrhage, gastrointestinal ischaemia, and cardiac disease. Nasal tissue frequently shows eosinophilic inflammation without diagnostic vasculitis, so biopsy should target the safest active organ and be interpreted alongside the clinical pattern. Absence of vasculitis in a polyp specimen does not exclude EGPA.

Treatment is determined by systemic severity, not the polyp burden. Organ- or life-threatening disease generally requires high-dose glucocorticoids with rituximab or cyclophosphamide, whereas non-severe relapsing disease may be treated with glucocorticoid-sparing agents under vasculitis specialist care [11]. In the MIRRA randomised trial, mepolizumab 300 mg subcutaneously every four weeks increased accrued remission time and reduced relapse in relapsing or refractory EGPA, but almost half of treated participants did not achieve protocol-defined remission [15]. MANDARA subsequently showed that benralizumab 30 mg every four weeks was non-inferior to mepolizumab 300 mg every four weeks for remission in this population [15]. These EGPA regimens should not be confused with the 100 mg mepolizumab regimen studied in CRSwNP.

Dupilumab may improve residual CRSwNP in patients whose vasculitis is otherwise controlled, but the evidence is materially weaker than for approved CRSwNP populations. A small prospective cohort reported sinonasal improvement [16], while a European retrospective series found complete or partial response in many patients but also recorded EGPA relapse in 31%; most relapses were preceded by eosinophilia [17]. Confounding by indication and corticosteroid withdrawal prevent causal attribution, yet the signal justifies monitoring blood eosinophils and systemic symptoms rather than assuming that improved nasal obstruction equals controlled vasculitis.

4.2. *Granulomatosis with Polyangiitis*

Upper-airway disease is often prominent in GPA. Persistent crusting, friable mucosa, bloody discharge, septal perforation, subglottic symptoms, or progressive saddle-nose deformity is more discriminating than simple congestion. Even so, destructive findings are not specific. For example, invasive fungal infection, extranodal NK/T-cell lymphoma, sarcoidosis, relapsing polychondritis, and intranasal cocaine or vasoconstrictor injury can overlap clinically and histologically.

Clinically, EGPA is favoured when chronic rhinosinusitis occurs in an adult with asthma, nasal polyposis and marked blood eosinophilia, particularly when accompanied by migratory pulmonary infiltrates, mononeuritis multiplex, purpura, eosinophilic tissue inflammation or cardiac and gastrointestinal involvement. Granulomatosis with polyangiitis (GPA), by contrast, more often produces destructive upper-airway disease characterised by bloody nasal discharge, crusting, ulceration, septal perforation, saddle-nose deformity, otitis or subglottic stenosis, together with pulmonary nodules, cavitation or pauci-immune

glomerulonephritis [12,14]. Serology is supportive rather than definitive. MPO-ANCA is the more characteristic EGPA specificity, although most patients in a 383-patient cohort were ANCA-negative, whereas PR3/c-ANCA strongly favours GPA, but its absence does not exclude localised disease [24]. Rarely, EGPA may initially manifest as eosinophilic myocarditis, cardiogenic shock or coronary vasospasm mimicking acute myocardial infarction [25], while GPA may present with an orbital inflammatory mass, hypertrophic pachymeningitis or pituitary disease-causing central diabetes insipidus. Pituitary involvement was identified in only 1.1% of 819 patients in a French GPA cohort [26]. The absence of a classic phenotype or positive ANCA therefore cannot exclude either disorder, and differentiation should integrate the longitudinal clinical pattern, eosinophil count, urinalysis, chest and sinonasal imaging, and tissue biopsy where feasible.

Proteinase-3 ANCA supports GPA in the appropriate setting, but a negative test cannot exclude localised disease. The 2022 ACR/EULAR GPA criteria are, again, classification rather than diagnostic criteria [12]. Urinalysis and renal function are low-cost, high-consequence tests because glomerulonephritis may be initially asymptomatic. Chest imaging is guided by respiratory symptoms and systemic suspicion.

Biopsy is valuable when it demonstrates necrotizing granulomatous inflammation or vasculitis and when it identifies an alternative diagnosis. Its sensitivity is limited by small, superficial, necrotic, or previously treated specimens. In a classic series, nasal biopsy was diagnostic in only 9 of 17 patients, with larger samples performing better [13]. A negative nasal biopsy should therefore reduce confidence only modestly when the phenotype is strong. Endoscopic targeting of viable active margins, adequate depth, communication with pathology, and parallel microbiological studies improve yield; repeat or extra-nasal biopsy may be necessary.

Induction and maintenance therapy should follow systemic AAV guidance and be coordinated across rheumatology, nephrology, respiratory medicine, and otolaryngology [11]. Local surgery can restore ventilation, manage complications, or reconstruct stable damage, but surgery during active destructive inflammation risks poor healing and does not treat the vascular disease.

5. Mucociliary Disease and Humoral Immune Dysfunction

5.1. Primary Ciliary Dyskinesia

PCD should be suspected from a life-course phenotype rather than adult CT findings alone. Daily wet cough and nasal congestion beginning in infancy, unexplained neonatal respiratory distress in a term infant, chronic otitis with hearing impairment, organ laterality abnormality, and bronchiectasis are the most useful clues. Approximately half of affected patients have a laterality defect, so normal situs does not exclude PCD [18–20]. Adult referral based only on bronchiectasis or CRS has lower specificity because both have many acquired causes.

No single test confirms or excludes PCD. The 2025 joint European Respiratory Society / American Thoracic Society guideline recommends nasal nitric oxide (nNO), high-speed video microscopy, and immunofluorescence as adjuncts to transmission electron microscopy and/or genetic testing [18]. In cooperative patients with a compatible phenotype, nNO below 77 nL/min using an accepted manoeuvre is a useful threshold, but viral upper-respiratory infection, recent epistaxis, poor technique, device differences, and cystic fibrosis can produce low values; some PCD genotypes produce normal values. An unexpectedly low result should be repeated when clinically stable, and the measured production rate, not an unstandardized device concentration, must be interpreted [20].

Transmission electron microscopy misses genetically confirmed disease without a hallmark ultrastructural defect. Gene panels do not identify all causal variants and may

return variants of uncertain significance. High-speed video microscopy is operator- and protocol-dependent. The correct diagnostic model is concordance among phenotype and complementary reference tests at an experienced centre, not a hierarchy in which one negative test ends the evaluation [18–20]. Management requires coordinated airway-clearance therapy, culture-directed treatment of exacerbations, hearing surveillance, vaccination, and fertility counselling; sinus surgery may improve local access or symptoms but cannot correct the generalised clearance defect.

5.2. Cystic Fibrosis and Paediatric Nasal Polyps

Nasal polyps are uncommon in young children and should prompt evaluation for systemic disease, particularly when accompanied by chronic wet cough, bronchiectasis, poor growth, malabsorption, or recurrent infection [22]. Sweat chloride testing is the usual starting point for cystic fibrosis, followed by CFTR genetic and/or functional assessment when results are intermediate, or the phenotype remains compelling. A sweat chloride concentration of at least 60 mmol/L supports cystic fibrosis in the appropriate clinical context, whereas 30–59 mmol/L is intermediate and requires further evaluation; laboratory quality and diagnostic-centre interpretation are essential [21]. Normal newborn screening does not exclude every later diagnosis.

The clinical error is to treat the polyp as the whole disease. Cystic fibrosis transmembrane conductance regulator modulators can substantially alter systemic and sinonasal disease in eligible genotypes, while endoscopic treatment remains adjunctive. In a child with early nasal polyposis, pulmonary, nutritional, microbiological, and genetic implications take precedence over repeated local procedures.

5.3. Humoral Immune Dysfunction

Humoral immune defects are enriched in selected cohorts referred for recurrent or difficult-to-treat CRS, but estimates cannot be generalised to all CRS. In one adult cohort selected for immunological evaluation, 24% met the study definition of specific antibody deficiency; impaired responses were also found in 11% of healthy controls, illustrating how assay thresholds and referral selection affect apparent prevalence [23].

Quantitative IgG, IgA, and IgM are reasonable when recurrent bacterial sinusitis coexists with pneumonia, bronchiectasis, unusually frequent antibiotic use, autoimmune disease, lymphoproliferation, or infection with encapsulated organisms. Specific antibody responses to pneumococcal vaccination should be interpreted by an immunologist with the vaccine type, baseline titres, laboratory method, age, infection history, and medication exposure in view. An isolated “low response” is not equivalent to clinically important immune deficiency. Treatment ranges from vaccination and optimised early antimicrobial therapy to prophylactic antibiotics and, in selected well-characterised cases, immunoglobulin replacement. This is a decision about the whole infection phenotype, not the sinus CT score.

6. Granulomatous, Infiltrative, and Invasive Infective Disorders

6.1. Sinonasal Sarcoidosis

Sinonasal sarcoidosis may cause obstruction, crusting, epistaxis, anosmia, mucosal nodularity, septal perforation, or external deformity. CT commonly shows mucosal thickening or opacification, findings that cannot separate sarcoidosis from inflammatory CRS. The broader diagnosis rests on a compatible clinical-radiological pattern, non-necrotizing granulomatous inflammation in tissue, and exclusion of alternative causes [27]. Mycobacterial and fungal infection, GPA, foreign-body reaction, common

variable immunodeficiency-associated granulomatous disease, and malignancy must be considered before immunosuppression.

Serum angiotensin-converting enzyme (ACE) is neither sufficiently sensitive nor specific to confirm or exclude sinonasal sarcoidosis. It may support a coherent multisystem assessment but should not be presented as a first-line diagnostic arbiter. Biopsy should be directed to the safest accessible active site and specimens handled for appropriate stains and cultures. Evidence for sinonasal treatment is mostly observational. In a 12-patient biopsy-proven series, relapse and repeated sinus procedures occurred despite systemic and local treatment, underscoring that surgery can relieve obstruction but does not reliably control the granulomatous disease [28]. Systemic glucocorticoid and steroid-sparing decisions should be based on symptom burden, threatened function, and extra-nasal involvement.

6.2. Immunoglobulin G4-Related Disease

IgG4-related disease (IgG4-RD) is an uncommon systemic fibroinflammatory disorder that can produce sinonasal mucosal thickening, a tumefactive lesion, or destructive change. Sinonasal involvement is itself exceptionally uncommon and may be isolated. In a seven-patient sinonasal series, presentations reflected mass effect or tissue destruction resulting in obstruction, facial swelling or pain, orbital symptoms, and septal or palatal loss, and CT often raised concern for malignancy or infection [29]. Accordingly, a patient with a progressive infiltrative or erosive lesion should not be labelled as having IgG4-RD on serology alone.

Raised serum IgG4 is supportive but neither necessary nor specific, and abundant IgG4-positive plasma cells can appear in other inflammatory disorders. The 2019 ACR/EULAR criteria were designed for classification and integrate clinical, serological, radiological, pathological, and exclusion domains [30]. Sinonasal disease has no universally accepted organ-specific diagnostic criteria. A normal serum IgG4 therefore does not exclude disease, while an isolated elevation should not trigger immunosuppression without a coherent clinicopathological picture [29,30].

Pathology is most persuasive when dense lymphoplasmacytic inflammation is accompanied by storiform fibrosis and obliterative phlebitis, with IgG4-positive plasma-cell density and the IgG4/IgG ratio interpreted in an organ- and specimen-specific context. Small superficial samples may show plasma-cell enrichment without the characteristic architecture, and storiform fibrosis or obliterative phlebitis may be absent on the first biopsy [29]. When suspicion persists, deeper repeat sampling and expert pathology review may be required. Granulomas, necrotising vasculitis, prominent neutrophilic inflammation, organisms, or clonal lymphoid features should redirect attention to alternatives such as GPA, fungal disease, Rosai–Dorfman disease, or lymphoma. The overlap is clinically important: a recent sinonasal series described a patient ultimately diagnosed with GPA despite both raised serum IgG4 and increased tissue IgG4-positive cells [31].

Once tissue and clinical findings support IgG4-RD, assessment should look for extra-sinonasal disease in the orbit, lacrimal or salivary glands and other commonly affected systems according to symptoms and specialist judgement. Treatment is specialist-directed; systemic glucocorticoids are commonly used for active symptomatic disease, while rituximab may be considered for relapsing, refractory, or organ-threatening disease [29,30]. Surgery is mainly diagnostic or used to address obstruction and structural complications rather than as stand-alone disease control. Neither treatment response nor serum IgG4 normalisation retrospectively proves the diagnosis.

6.3. Acute Invasive Fungal Rhinosinusitis

Acute invasive fungal rhinosinusitis is not a chronic refractory phenotype, but it is a crucial mimic when symptoms evolve rapidly in a patient with neutropenia, haematological malignancy, transplantation, poorly controlled diabetes, or other major immunosuppression. Severe or escalating pain; fever; facial swelling; cranial neuropathy; visual change; or pale, dusky, black, ulcerated, or insensate mucosa warrants emergency assessment. Early CT may be subtle; MRI better evaluates orbital, intracranial, skull-base, and vascular extension when suspected [10].

Diagnosis depends on urgent endoscopy and tissue demonstrating invasion, ideally sampled from viable tissue at the margin rather than the necrotic centre. Management combines prompt surgical debridement, systemic antifungal therapy tailored to the suspected or identified organism, reversal of immunosuppression or metabolic derangement where possible, and repeated multidisciplinary reassessment [10]. Waiting for culture confirmation before treating a high-probability case is unsafe. Equally, a positive non-invasive fungal culture without tissue invasion does not establish invasive disease. Table 2. provides an overview of CRS mimics with distinctive clinicopathological signatures as well as their investigative modalities and treatment options.

Table 2. Distinctive clinicopathological signatures of uncommon CRS mimics.

Condition	Clinical/ Pathophysiological Signature	Laboratory and Pathology	Imaging/Endoscopy	Treatment Implication
EGPA	Adult-onset asthma and CRSwNP with eosinophilic disease; neuropathy, pulmonary infiltrates, purpura, renal, gastrointestinal, or cardiac involvement suggests systemic vasculitis	Eosinophilia is supportive but treatment-sensitive and non-specific; ANCA often negative; polyp tissue may show eosinophilia without vasculitis	Bilateral polyps/CRS are common but non-specific; chest and organ-directed imaging according to symptoms	Systemic severity determines immunosuppression; mepolizumab 300 mg every four weeks or benralizumab 30 mg every four weeks has randomised EGPA evidence [11,14–17,32]
GPA	Destructive granulomatous small-vessel vasculitis; crusting, bleeding, septal loss, saddle nose, subglottic or renal-pulmonary disease	PR3-ANCA supports but does not exclude when negative; urinalysis/creatinine are essential; nasal biopsy sensitivity is limited	CT maps bony/cartilaginous damage; chest imaging may show nodules, cavities, or infiltrates	Rituximab- or cyclophosphamide-based systemic therapy for severe disease; operates mainly for function/complications once inflammation is controlled [11–13]
PCD	Congenital mucociliary clearance failure: neonatal distress, daily early-life wet cough/nasal symptoms, otitis, laterality defect, infertility, bronchiectasis	Low nNO is an adjunct; TEM, genetics, high-speed video microscopy, and immunofluorescence are complementary; no single test excludes disease	Pan-sinus inflammation; chest CT may show bronchiectasis; laterality abnormality is supportive, not obligatory	Lifelong airway clearance, microbiology-led infection care, hearing and fertility support; sinus surgery is adjunctive [18–20]
Cystic fibrosis	CFTR dysfunction with viscous secretions; paediatric polyps plus bronchiectasis, poor growth, malabsorption, or characteristic infection	Sweat chloride ≥ 60 mmol/L supports diagnosis; intermediate values require CFTR genetic/functional evaluation	Chronic sinus hypoplasia/opacification may occur; chest disease and nutritional phenotype guide suspicion	CF-centre care and genotype-eligible modulator therapy; local treatment alone is inadequate [9,21]

Table 2. Cont.

Condition	Clinical/ Pathophysiological Signature	Laboratory and Pathology	Imaging/Endoscopy	Treatment Implication
Humoral immune dysfunction	Recurrent bacterial upper- and lower-airway infection, bronchiectasis, encapsulated organisms, autoimmunity, or lymphoproliferation	Quantitative immunoglobulins and vaccine responses interpreted with infection phenotype; abnormal titres occur in some controls	CRS imaging is non-specific; chest imaging may show bronchiectasis	Vaccination and infection plan; prophylaxis or immunoglobulin only in selected specialist-confirmed disease [23]
Sarcoidosis	Multisystem granulomatous disease; crusting, nodular or violaceous mucosa, epistaxis, anosmia, septal or external deformity	Non-necrotising granulomas plus exclusion of infection and other causes; serum ACE is supportive at most	Mucosal thickening/opacification is non-specific; systemic imaging may supply safer biopsy targets	Local/systemic corticosteroid or steroid-sparing therapy according to organ threat; surgery relieves obstruction, but relapse occurs [27,28]
IgG4-RD	Fibroinflammatory tumefactive or destructive disease, sometimes with salivary, lacrimal, orbital, pancreatic, renal, or retroperitoneal involvement	Serum/tissue IgG4 alone is insufficient; storiform fibrosis and obliterative phlebitis strengthen diagnosis after exclusions	Mass-like mucosal/soft-tissue disease; systemic pattern supports coherence	Specialist systemic glucocorticoid; rituximab in selected relapsing/refractory disease; exclude infection and lymphoma first [30,31]
Acute invasive fungal rhinosinusitis	Angioinvasion in major immunocompromise or uncontrolled diabetes; rapid pain, necrosis, orbital/neurological signs	Urgent tissue invasion on histology; fungal stains/culture aid identification, but treatment should not await culture	CT for anatomy; MRI for orbital, intracranial, skull-base, or vascular spread; serial endoscopy is important	Emergency debridement plus systemic antifungal and reversal of host risk where possible [10]
Sinonasal malignancy/NK-T lymphoma	Persistent unilateral obstruction, epistaxis, pain, numbness, mass, cranial or visual deficit; NK/T lymphoma may be highly necrotic	Histological typing is mandatory; deep/repeat viable-margin biopsy and Epstein–Barr virus studies may be needed for NK/T lymphoma	Contrast CT stages bone; MRI defines soft tissue, orbit, skull base, intracranial and perineural spread	Tumour-specific multidisciplinary care; do not allow temporary steroid/antibiotic response to delay biopsy [5–8]
Rhinolith	Mineralised concretion around endogenous/exogenous nidus; unilateral foetid discharge, obstruction, epistaxis, or halitosis	No characteristic systemic laboratory abnormality; diagnosis usually endoscopic/radiological	Hard irregular intranasal mass, often calcified on CT; surrounding inflammation may obscure it	Endoscopic removal is usually definitive; inspect for retained nidus and alternative unilateral pathology [33]

Abbreviations: CRS, chronic rhinosinusitis; CT, computed tomography; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; IgG4, immunoglobulin G4; IgG4-RD, immunoglobulin G4-related disease; MRI, magnetic resonance imaging; NK/T, natural killer/T-cell; PCD, primary ciliary dyskinesia.

7. Neoplastic and Structural Mimics

7.1. Sinonasal Tumours

Unilateral disease is neither synonymous with cancer nor safe to observe without objective assessment. Persistent unilateral obstruction or discharge, recurrent epistaxis, facial or dental pain, facial numbness, trismus, orbital symptoms, cranial neuropathy, neck nodes, or a visible mass should prompt specialist endoscopy and imaging [5–7,9]. In retrospective unilateral-disease cohorts, inflammatory causes remain common, but neoplasia is sufficiently consequential that a structured pathway is justified [6].

CT best defines bone and surgical anatomy; contrast-enhanced MRI better characterises soft-tissue extent, orbit, dura, brain, marrow, skull base, and perineural spread. Bone erosion is an important warning but is not pathognomonic: pressure remodelling and aggressive inflammation can erode bone, while early malignancy may not. Imaging should precede office biopsy when vascular tumour, skull-base defect, orbital or intracranial communication, or extensive necrosis is possible [5,7].

Tissue quality is a recurrent source of delay. Extranodal NK/T-cell lymphoma and nasal type can be masked by necrosis and inflammation; superficial samples may contain no viable diagnostic tissue. The appropriate response to a non-diagnostic specimen with a progressive, discordant phenotype is radiology-pathology review and a deeper or differently targeted biopsy, not reassurance. Epstein–Barr virus-encoded RNA testing is part of the pathological assessment when NK/T-cell lymphoma is suspected [8]. Empirical corticosteroids before secure tissue diagnosis can further reduce yield.

7.2. Rhinolithiasis and Other Structural Disease

Rhinolithiasis is a benign but distinctive cause of chronic unilateral foetid rhinorrhoea, obstruction, epistaxis, or halitosis. A hard irregular mass may be visible on rigid endoscopy, and CT demonstrates calcification and surrounding disease [33]. Removal is usually curative. Its benignity does not justify assuming that all calcified or unilateral lesions are rhinoliths; fungal concretions, odontogenic material, osteoma, retained foreign bodies, and calcified tumours remain alternatives.

Odontogenic sinusitis, a retained foreign body, mucocele, postoperative stenosis, or anatomical obstruction can also sustain unilateral symptoms. Dental history and focused maxillary imaging are particularly important because repeated “sinus” antibiotics without source control will predictably fail. The diagnostic principle is anatomical concordance: the lesion should plausibly account for the symptoms and distribution of inflammation.

8. Diagnostic Tests: What a Result Can and Cannot Establish

The usefulness of a test depends on the clinical question, pre-test probability, specimen, timing, and downstream action. Table 3 summarises common overinterpretations. The central distinction is between supporting evidence and diagnostic sufficiency. Positive serology may be incidental; negative serology may be falsely reassuring; and histology can be non-diagnostic when the wrong site or tissue compartment is sampled.

Table 3. Strengths and limitations of commonly used investigations.

Test	Best Use	Important Limitation	Rational Next Step When Discordant
Nasal endoscopy	Confirms polyps, crusting, bleeding, necrosis, mass, foreign body, or a target for culture/biopsy	A normal limited examination does not exclude deeper sinus or skull-base disease	Cross-sectional imaging or repeat expert examination when symptoms/red flags persist [9]
CT of paranasal sinuses	Confirms objective inflammation; maps bone, calcification, dental source, and surgical anatomy	Opacification is a pattern, not an aetiology; erosion can be benign or malignant	Add contrast MRI for soft-tissue, orbital, skull-base, intracranial, or perineural questions; obtain tissue when indicated [5–7]
ANCA (PR3/MPO)	Supports AAV in a compatible systemic phenotype and assists classification	Negative localised GPA and ANCA-negative EGPA occur; a positive result does not replace exclusion of infection/drug mimics	Repeat/confirm when appropriate; urinalysis, creatinine, organ assessment, and targeted biopsy [11,12,14]

Table 3. Cont.

Test	Best Use	Important Limitation	Rational Next Step When Discordant
Peripheral eosinophil count	Identifies eosinophilic phenotype and raises suspicion for EGPA when combined with asthma/systemic features	Altered by corticosteroids and biologics; allergy, parasites, drugs, malignancy, and other syndromes overlap	Review longitudinal counts and exposures; evaluate organ involvement and alternative eosinophilic disorders
Nasal biopsy	Can diagnose tumour, granulomatous disease, invasive infection, or vasculitis and permit microbiology/molecular tests	Superficial, necrotic, small, or pretreated samples have low yield; GPA sensitivity is modest	Target viable active margin, obtain adequate depth, alert pathology, send parallel cultures, and repeat/choose another organ if needed [5,8,10,13]
Nasal nitric oxide	Sensitive adjunct in cooperative patients with a strong PCD phenotype under standardised conditions	Viral illness, epistaxis, technique, device, and CF can lower values; some PCD genotypes have normal values	Repeat when stable and proceed to complementary reference testing at a PCD Centre [18,20]
TEM/genetic PCD testing	Demonstrates hallmark ultrastructure or pathogenic variants	Normal TEM does not exclude PCD; panels are incomplete, and variants of uncertain significance are not diagnostic	Integrate phenotype, nNO, high-speed video microscopy/immunofluorescence, and expert variant review [18–20]
Serum ACE	May support an already coherent multisystem sarcoidosis assessment	Limited sensitivity and specificity; affected by genotype, medicines, and other diseases	Seek tissue and exclude infectious/non-infectious granulomatous mimics [27]
Serum IgG4 and tissue IgG4-positive cells	Supports IgG4-RD when morphology, organ pattern, and exclusions align	May be normal in disease or elevated in allergy, infection, GPA, and lymphoma; counts without morphology mislead	Expert pathology review for storiform fibrosis/obliterative phlebitis and systemic evaluation [30,31]
Quantitative immunoglobulins and pneumococcal responses	Evaluates recurrent bacterial infection with a suggestive systemic phenotype	Assays and thresholds vary; abnormal responses occur in some healthy controls	Immunology review integrating vaccine type, baseline/post-vaccine titres, age, infection burden, and secondary causes [23]

Abbreviations: AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; CF, cystic fibrosis; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; IgG4-RD, immunoglobulin G4-related disease; MPO, myeloperoxidase; PCD, primary ciliary dyskinesia; PR3, proteinase 3; TEM, transmission electron microscopy.

Genetic and Molecular Context: When Biomarkers Add Value

Genetic testing has direct diagnostic value in the inherited mucociliary disorders considered here. PCD is genetically heterogeneous, with pathogenic variants in more than 55 genes; most forms are autosomal recessive, although X-linked and dominant forms occur. Contemporary comprehensive testing identifies a causative genotype in more than 70% of people with PCD, but variants of uncertain significance and a negative panel require correlation with phenotype and complementary ciliary tests [18]. Cystic fibrosis is an autosomal-recessive CFTR-related disorder; identification of disease-causing CFTR variants can resolve equivocal sweat testing and also has therapeutic implications because modulator eligibility is genotype-dependent [21]. Thus, genetics is not merely a research adjunct in PCD or cystic fibrosis, but part of the clinical diagnostic pathway.

In contrast, EGPA/GPA, sarcoidosis, and IgG4-RD have immunogenetic or polygenic susceptibility, but germline genetic testing is not currently a stand-alone diagnostic test and is not incorporated as a routine discriminator in the cited clinical or classification frameworks [11,12,14,27,30]. Similarly, molecular testing in sinonasal malignancy is usually

performed after tissue diagnosis to refine tumour classification or treatment rather than as a screening test for undifferentiated “refractory CRS”. This distinction is important: the existence of genetic predisposition does not automatically make broad genetic screening clinically useful in a low-pre-test-probability CRS population.

Inflammatory biomarkers require the same conditional interpretation. C-reactive protein and erythrocyte sedimentation rate can support the presence and trajectory of systemic inflammation, but they are nonspecific and may be normal in localised disease. Blood eosinophils and total IgE are clinically accessible markers of type 2 inflammation and can help phenotype CRSwNP, but they do not distinguish routine CRS from EGPA by themselves [14,34]. Cytokines and related markers, including IL-4, IL-5, IL-13, periostin, and eosinophil granule proteins are being studied for CRS endotyping and prognostication, yet no validated plasma or nasal biomarker panel currently separates the rare systemic, infective, neoplastic, and structural mimics reviewed here with sufficient accuracy for routine use [35]. Their most useful research role is therefore as part of prospectively validated multi-domain models combining phenotype, imaging, standard laboratory tests, and tissue findings.

9. Biologic Non-Response as a Diagnostic Checkpoint

Biologics are relevant to this review primarily because escalation of type 2 therapy can delay recognition of a mimic if the underlying diagnosis is insecure. Dupilumab, mepolizumab, omalizumab, and tezepelumab have positive phase 3 evidence in selected patients with severe bilateral CRSwNP, and benralizumab improved key polyp and block-age outcomes in OSTRO [36–40]. EVEREST provides direct evidence that dupilumab outperformed omalizumab at 24 weeks for the co-primary polyp and smell outcomes in patients with severe CRSwNP and coexisting asthma [41]. These trial populations do not justify biologic treatment of an unexplained unilateral mass, untreated infection, structural obstruction, destructive granulomatous disease, or active systemic vasculitis. EGPA-specific biologic regimens and endpoints also differ from those used for CRSwNP [15,32].

Accordingly, apparent biologic failure should be treated as a diagnostic checkpoint before cycling or intensifying treatment. Clinicians should reconfirm objective inflammation, adherence and intranasal drug delivery; reassess whether disease is bilateral and phenotypically consistent with CRSwNP; and actively reconsider structural disease, infection, malignancy, AAV/EGPA, IgG4-RD, or another systemic process when the course is discordant. Improvement in nasal obstruction or polyp size likewise does not prove that a coexisting systemic disorder is controlled. The practical message is diagnostic: biologics are appropriate only after the phenotype and competing explanations are sufficiently secure.

10. A Practical Diagnostic Framework

The proposed pathway in Figure 1 is a pragmatic expert synthesis intended to structure diagnostic reassessment; it is not a validated clinical prediction rule or a substitute for specialist judgement. It begins by confirming objective CRS and treatment delivery, but it does not require completion of every routine treatment step before urgent investigation. A patient with necrotic mucosa, a unilateral mass with cranial neuropathy, or rapidly progressive orbital symptoms exits the standard CRS pathway immediately. In stable disease, the dominant phenotype determines the next test: eosinophilic asthma directs an EGPA screen; destructive crusting directs vasculitis, infection, toxic exposure, and biopsy assessment; early-life upper- and lower-airway disease directs PCD and cystic fibrosis testing; recurrent bacterial infection directs immune evaluation; and persistent unilateral disease directs anatomical imaging and tissue diagnosis.

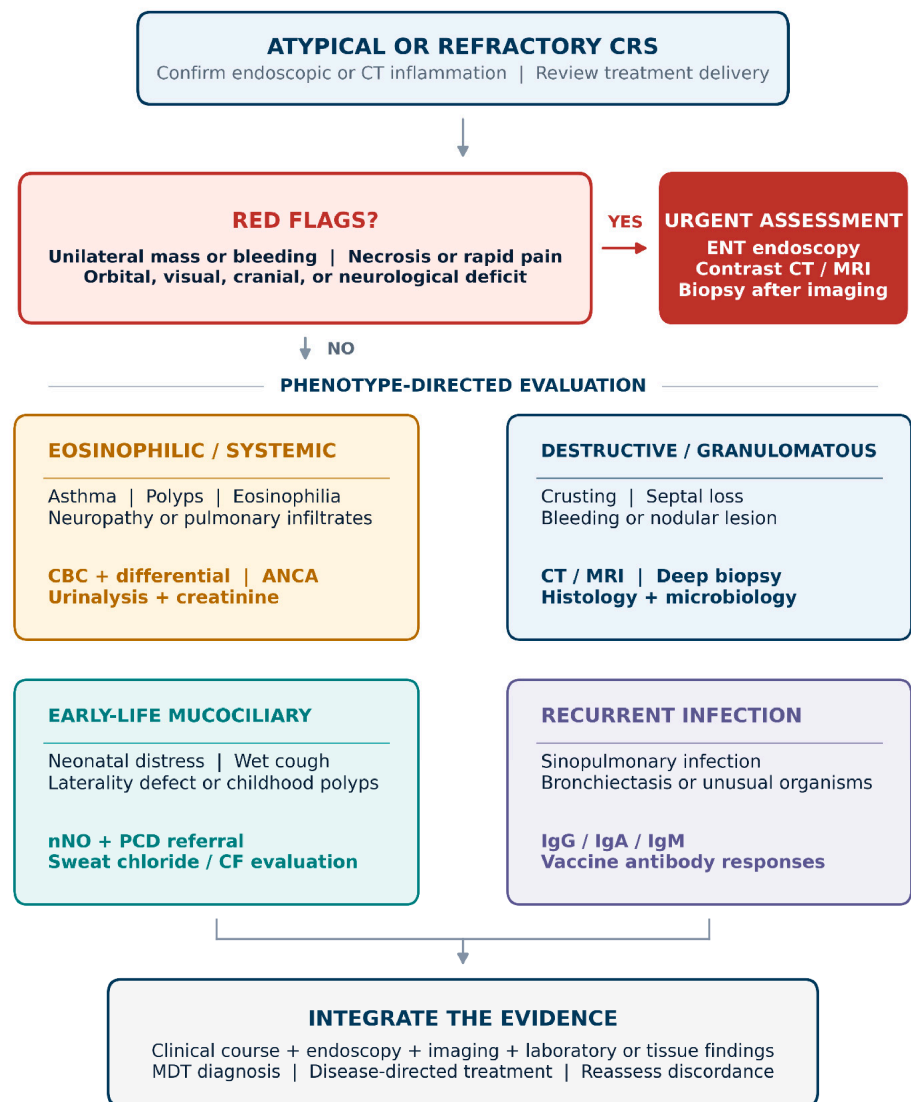


Figure 1. Proposed pragmatic red-flag-led framework for atypical or refractory chronic rhinosinusitis. This expert synthesis is intended to structure diagnostic reassessment and has not been prospectively validated as a clinical prediction rule. Urgent features bypass sequential empirical treatment and prompt endoscopy, appropriate contrast-enhanced imaging, and tissue diagnosis. In the absence of red flags, investigations are selected according to the dominant clinical phenotype. Abbreviations: ANCA, antineutrophil cytoplasmic antibody; CF, cystic fibrosis; CRS, chronic rhinosinusitis; CBC, complete blood count; CT, computed tomography; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; MRI, magnetic resonance imaging; MDT, multidisciplinary team; nNO, nasal nitric oxide; PCD, primary ciliary dyskinesia.

Multidisciplinary discussion is most valuable when data disagree. For example, a progressive destructive lesion with negative ANCA and a non-diagnostic superficial biopsy, or a strong PCD phenotype with normal ultrastructure. The purpose is not to generate more tests indiscriminately, but to decide which result may be falsely reassuring, and which organ or tissue can answer the question safely.

11. Positioning, Evidence Gaps, and Research Priorities

The key contribution of this review is not a new catalogue of rare rhinological diseases. Broad orphan-disease reviews already describe many of these entities [3,4]. Instead, the synthesis is organised around a common clinical failure point, often resulting in a patient labelled as having refractory CRS, and asks when that label should be abandoned or

provisionally suspended. The red-flag framework deliberately prioritises consequential phenotypes and the next discriminating test over exhaustive disease listing. Because it is derived from guidelines, diagnostic studies, trials, referral cohorts, and expert synthesis rather than prospective validation, it should be viewed as a pragmatic cognitive aid whose clinical performance remains to be tested.

Rare sinonasal presentations are studied mainly in referral cohorts and case series. This creates spectrum bias: red flags derived from tertiary centres may perform differently in general practice, while published dramatic cases exaggerate the apparent probability of malignancy or vasculitis. Prospective studies should test red-flag combinations against clinically relevant outcomes, including time to diagnosis, stage or organ damage at diagnosis, unnecessary biopsy, and false-positive serology.

For PCD, future diagnostic research should use genotype-aware reference standards and reproducible nNO protocols across ages and devices, because genotype can determine whether ultrastructural or physiological abnormalities are detectable [18]. For granulomatous disease and vasculitis, studies should report biopsy site, specimen size, prior corticosteroid exposure, microbial methods, and the effect of repeat sampling. The same validation principle should be applied to emerging molecular biomarkers: prospective studies should test whether combinations of acute-phase proteins, eosinophil/IgE measures, cytokines, or nasal biomarkers add discrimination beyond phenotype, imaging, standard serology, and tissue findings before they are incorporated into a red-flag pathway [35]. The term “refractory CRS” also requires tighter operationalisation; failure caused by inadequate delivery should not be pooled with objectively persistent inflammation after high-quality therapy.

Biologic trials need longer active-comparator follow-up, broader inclusion, and outcomes that matter across specialties: systemic corticosteroid burden, surgery, smell, asthma exacerbations, vasculitis relapse, organ damage, and treatment discontinuation. EVEREST is an important direct comparison, but its asthma-enriched population does not resolve sequencing for the wider CRSwNP population [41]. Rare systemic diseases will often require registries and carefully phenotyped pragmatic cohorts rather than conventional large trials.

12. Conclusions

Refractory rhinosinusitis should be treated as a trigger for diagnostic reassessment, not as a disease label or automatic indication for treatment escalation. The central contribution of this review is to identify the clinical situations in which routine CRS should be questioned: unilateral bleeding or mass effect, necrosis, cranial or visual signs, destructive crusting, systemic eosinophilic or vasculitic features, congenital mucociliary clues, and a recurrent bacterial infection phenotype. These signals matter regardless of whether the underlying entity is a formally rare disease, a rare sinonasal manifestation of a systemic disorder, or an uncommon local mimic.

Cross-sectional imaging, expert endoscopy, appropriately targeted tissue, and conditional interpretation of genetic, serological, and inflammatory markers remain the foundation of diagnosis. Negative ANCA, a superficial biopsy, normal serum IgG4, or a nondiagnostic genetic panel may be falsely reassuring, while isolated biomarker abnormalities may be misleading. Biologic response or failure should likewise prompt phenotype-aware interpretation rather than reflex escalation. The proposed red-flag framework is not yet validated; its value is as a structured prompt to reconsider the diagnosis early and to direct testing toward the most consequential alternative.

Author Contributions: Conceptualisation, E.U. and E.A.I.; writing—original draft preparation, E.U., E.A.I., O.A.A. and E.O.O.; writing—review and editing, E.U., E.A.I., O.A.A. and E.O.O.; visualisation, E.U., E.A.I. and O.A.A. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article; all information discussed is available in the cited sources.

Acknowledgments: During the preparation of this manuscript, the authors used OpenAI ChatGPT (GPT-5.6) exclusively to improve the English language. The authors have reviewed and edited the output and take full responsibility for the content of this publication. Figure 1 was also created with the same OpenAI model, but the idea and commands were those of the authors.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

ACE, angiotensin-converting enzyme; ANCA, antineutrophil cytoplasmic antibody; AAV, ANCA-associated vasculitis; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; CRP, C-reactive protein; CRS, chronic rhinosinusitis; CRSwNP, chronic rhinosinusitis with nasal polyps; CT, computed tomography; ECP, eosinophil cationic protein; EGPA, eosinophilic granulomatosis with polyangiitis; ESR, erythrocyte sedimentation rate; GPA, granulomatosis with polyangiitis; Ig, immunoglobulin; IgG4-RD, immunoglobulin G4-related disease; IL, interleukin; MRI, magnetic resonance imaging; nNO, nasal nitric oxide; PCD, primary ciliary dyskinesia; PR3, proteinase 3; TEM, transmission electron microscopy.

References

1. Fokkens, W.J.; Lund, V.J.; Hopkins, C.; Hellings, P.W.; Kern, R.; Reitsma, S.; Toppila-Salmi, S.; Bernal-Sprekelsen, M.; Mullol, J.; Alobid, I.; et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. *Rhinology* **2020**, *58*, 1–464. [\[CrossRef\]](#)
2. Nguengang Wakap, S.; Lambert, D.M.; Olry, A.; Rodwell, C.; Gueydan, C.; Lanneau, V.; Murphy, D.; Le Cam, Y.; Rath, A. Estimating cumulative point prevalence of rare diseases: Analysis of the Orphanet database. *Eur. J. Hum. Genet.* **2020**, *28*, 165–173. [\[CrossRef\]](#)
3. Laudien, M. Orphan diseases of the nose and paranasal sinuses: Pathogenesis-Clinic-Therapy. *GMS Curr. Top. Otorhinolaryngol. Head Neck Surg.* **2015**, *14*, Doc04. [\[CrossRef\]](#)
4. Sommer, F. Rare Diseases of the Nose, the Paranasal Sinuses, and the Anterior Skull Base. *Laryngorhinootologie* **2021**, *100*, S1–S44. [\[CrossRef\]](#)
5. Kuan, E.C.; Wang, E.W.; Adappa, N.D.; Beswick, D.M.; London, N.R.; Su, S.Y.; Wang, M.B.; Abuzeid, W.M.; Alexiev, B.; Alt, J.A.; et al. International Consensus Statement on Allergy and Rhinology: Sinonasal Tumors. *Int. Forum Allergy Rhinol.* **2024**, *14*, 149–608. [\[CrossRef\]](#)
6. Paz Silva, M.; Pinto, J.M.; Corey, J.P.; Mhoon, E.E.; Baroody, F.M.; Naclerio, R.M. Diagnostic algorithm for unilateral sinus disease: A 15-year retrospective review. *Int. Forum Allergy Rhinol.* **2015**, *5*, 590–596. [\[CrossRef\]](#)
7. Resteghini, C.; Baujat, B.; Bossi, P.; Franchi, A.; de Gabory, L.; Halamkova, J.; Haubner, F.; Hardillo, J.; Hermesen, M.; Iacovelli, N.; et al. Sinonasal malignancy: ESMO–EURACAN Clinical Practice Guideline for diagnosis, treatment and follow-up. *ESMO Open* **2025**, *10*, 104121. [\[CrossRef\]](#)
8. Christensen, B.R.; Kou Cting, J.; Lee, L.E. A Rare Case of Extranodal Natural Killer/T-cell Lymphoma, Nasal Type Associated With Hemophagocytic Lymphohistiocytosis in a Patient With Recurrent Sinusitis. *Cureus* **2024**, *16*, e56237. [\[CrossRef\]](#)
9. Oisakede, E.O. When “Sinusitis” Is Actually Cancer: Diagnostic Red Flags for Unilateral or Refractory Sinonasal Disease. *Sinusitis* **2026**, *10*, 13. [\[CrossRef\]](#)
10. Roland, L.T.; Humphreys, I.M.; Le, C.H.; Babik, J.M.; Bailey, C.E.; Ediriwickrema, L.S.; Fung, M.; Lieberman, J.A.; Magliocca, K.R.; Nam, H.H.; et al. Diagnosis, Prognosticators, and Management of Acute Invasive Fungal Rhinosinusitis: Multidisciplinary Consensus Statement and Evidence-Based Review with Recommendations. *Int. Forum Allergy Rhinol.* **2023**, *13*, 1615–1714. [\[CrossRef\]](#)

11. Chung, S.A.; Langford, C.A.; Maz, M.; Abril, A.; Gorelik, M.; Guyatt, G.; Archer, A.M.; Conn, D.L.; Full, K.A.; Grayson, P.C.; et al. 2021 American College of Rheumatology /Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody–Associated Vasculitis. *Arthritis Rheumatol.* **2021**, *73*, 1366–1383. [\[CrossRef\]](#)
12. Robson, J.C.; Grayson, P.C.; Ponte, C.; Craven, A.; Judge, A.; Khalid, S.; Hutchings, A.; Watts, R.A.; Merkel, P.A.; Luqmani, R.A.; et al. 2022 American College of Rheumatology /European Alliance of Associations for Rheumatology classification criteria for granulomatosis with polyangiitis. *Ann. Rheum. Dis.* **2022**, *81*, 315–320. [\[CrossRef\]](#)
13. Del Buono, E.A.; Flint, A. Diagnostic usefulness of nasal biopsy in Wegener’s granulomatosis. *Hum. Pathol.* **1991**, *22*, 107–110. [\[CrossRef\]](#)
14. Grayson, P.C.; Ponte, C.; Suppiah, R.; Robson, J.C.; Craven, A.; Judge, A.; Khalid, S.; Hutchings, A.; Luqmani, R.A.; Watts, R.A.; et al. 2022 American College of Rheumatology /European Alliance of Associations for Rheumatology Classification Criteria for Eosinophilic Granulomatosis with Polyangiitis. *Ann. Rheum. Dis.* **2022**, *81*, 309–314. [\[CrossRef\]](#)
15. Wechsler, M.E.; Nair, P.; Terrier, B.; Walz, B.; Bourdin, A.; Jayne, D.R.; Jackson, D.J.; Roufosse, F.; Sjö, L.B.; Fan, Y.; et al. Benralizumab versus Mepolizumab for Eosinophilic Granulomatosis with Polyangiitis. *N. Engl. J. Med.* **2024**, *390*, 911–921. [\[CrossRef\]](#)
16. Padoan, R.; Davanzo, F.; Iorio, L.; Saccardo, T.; Rocuzzo, G.; Zampollo, S.; Nicolai, P.; Doria, A.; Ottaviano, G. Dupilumab for refractory chronic rhinosinusitis in eosinophilic granulomatosis with polyangiitis. *Rheumatology* **2025**, *64*, 2892–2901. [\[CrossRef\]](#)
17. Molina, B.; Padoan, R.; Urban, M.L.; Novikov, P.; Caminati, M.; Taillé, C.; Néel, A.; Bouillet, L.; Fraticelli, P.; Schleinitz, N.; et al. Dupilumab for relapsing or refractory sinonasal and/or asthma manifestations in eosinophilic granulomatosis with polyangiitis: A European retrospective study. *Ann. Rheum. Dis.* **2023**, *82*, 1587–1593. [\[CrossRef\]](#)
18. Shoemark, A.; Goutaki, M.; Kinghorn, B.; Ardura-Garcia, C.; Baz-Redón, N.; Chilvers, M.; Davis, S.D.; De Brandt, J.; Dell, S.; Dhar, R.; et al. European Respiratory Society and American Thoracic Society guidelines for the diagnosis of primary ciliary dyskinesia. *Eur. Respir. J.* **2025**, *66*, 2500745. [\[CrossRef\]](#)
19. Lucas, J.S.; Davis, S.D.; Omran, H.; Shoemark, A. Primary ciliary dyskinesia in the genomics age. *Lancet Respir. Med.* **2020**, *8*, 202–216. [\[CrossRef\]](#)
20. Marangu-Boore, D.; Lucas, J.S.; Beydon, N. Nasal nitric oxide measurement for the diagnosis of primary ciliary dyskinesia: Summary of the European Respiratory Society technical standard. *Breathe* **2025**, *21*, 240230. [\[CrossRef\]](#)
21. Farrell, P.M.; White, T.B.; Ren, C.L.; Hempstead, S.E.; Accurso, F.; Derichs, N.; Howenstine, M.; McColley, S.A.; Rock, M.; Rosenfeld, M.; et al. Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation. *J. Pediatr.* **2017**, *181*, S4–S15.e1. [\[CrossRef\]](#)
22. Di Cicco, M.E.; Bizzoco, F.; Morelli, E.; Seccia, V.; Ragazzo, V.; Peroni, D.G.; Comberiati, P. Nasal Polyps in Children: The Early Origins of a Challenging Adulthood Condition. *Children* **2021**, *8*, 997. [\[CrossRef\]](#)
23. Keswani, A.; Dunn, N.M.; Manzur, A.; Kashani, S.; Bossuyt, X.; Grammer, L.C.; Conley, D.B.; Tan, B.K.; Kern, R.C.; Schleimer, R.P.; et al. The Clinical Significance of Specific Antibody Deficiency (SAD) Severity in Chronic Rhinosinusitis (CRS). *J. Allergy Clin. Immunol. Pract.* **2017**, *5*, 1105–1111. [\[CrossRef\]](#)
24. Comarmond, C.; Pagnoux, C.; Khellaf, M.; Cordier, J.; Hamidou, M.; Viallard, J.; Maurier, F.; Jouneau, S.; Bienvenu, B.; Puéchal, X.; et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): Clinical characteristics and long-term followup of the 383 patients enrolled in the French Vasculitis Study Group cohort. *Arthritis Rheum.* **2013**, *65*, 270–281. [\[CrossRef\]](#)
25. Schramm, M.A.; Frye, B.C.; Staudacher, D.L.; Schlett, C.L.; Thiele, F.; Voll, R.E.; Thiel, J.; Venhoff, N. Coronary vasospasms and other cardiac manifestations in Eosinophilic Granulomatosis with Polyangiitis: Clinical impact and frequency in a monocentre study of 103 patients. *RMD Open* **2025**, *11*, e005816. [\[CrossRef\]](#)
26. De Parisot, A.; Puéchal, X.; Langrand, C.; Raverot, G.; Gil, H.; Perard, L.; Le Guenno, G.; Berthier, S.; Tschirret, O.; Eschard, J.P.; et al. Pituitary Involvement in Granulomatosis With Polyangiitis: Report of 9 Patients and Review of the Literature. *Medicine* **2015**, *94*, e748. [\[CrossRef\]](#)
27. Crouser, E.D.; Maier, L.A.; Wilson, K.C.; Bonham, C.A.; Morgenthau, A.S.; Patterson, K.C.; Abston, E.; Bernstein, R.C.; Blankstein, R.; Chen, E.S.; et al. Diagnosis and Detection of Sarcoidosis. An Official American Thoracic Society Clinical Practice Guideline. *Am. J. Respir. Crit. Care Med.* **2020**, *201*, e26–e51. [\[CrossRef\]](#)
28. Kirsten, A.M.; Watz, H.; Kirsten, D. Sarcoidosis with involvement of the paranasal sinuses—A retrospective analysis of 12 biopsy-proven cases. *BMC Pulm. Med.* **2013**, *13*, 59. [\[CrossRef\]](#)
29. Hess, A.O.; Lobo, B.C.; Leon, M.E.; Duarte, E.M.; Mulligan, J.K.; Justice, J.M. Sinonasal IgG4-related sclerosing disease: A rare entity and challenging diagnosis. *Laryngoscope Invest. Otolaryngol.* **2022**, *7*, 1725–1732. [\[CrossRef\]](#)
30. Wallace, Z.S.; Naden, R.P.; Chari, S.; Choi, H.K.; Della-Torre, E.; Dicaire, J.-F.; Hart, P.A.; Inoue, D.; Kawano, M.; Khosroshahi, A.; et al. The 2019 American College of Rheumatology /European League Against Rheumatism classification criteria for IgG4-related disease. *Ann. Rheum. Dis.* **2020**, *79*, 77–87. [\[CrossRef\]](#)

31. Sato, R.; Kumai, T.; Yuasa, R.; Wakisaka, R.; Komatsuda, H.; Yamaki, H.; Ishida, Y.; Wada, T.; Takahara, M. Common Characteristics of Sinonasal Inflammation Associated with IgG4-Related Disease and Other Chronic Inflammatory Diseases: A Retrospective Observational Study. *ORL* **2024**, *86*, 95–100. [\[CrossRef\]](#)
32. Wechsler, M.E.; Akuthota, P.; Jayne, D.; Khoury, P.; Klion, A.; Langford, C.A.; Merkel, P.A.; Moosig, F.; Specks, U.; Cid, M.C.; et al. Mepolizumab or Placebo for Eosinophilic Granulomatosis with Polyangiitis. *N. Engl. J. Med.* **2017**, *376*, 1921–1932. [\[CrossRef\]](#)
33. Adib, H.; Natout, M.A.E.; Zaytoun, G.; Hadi, U.A. Rhinolithiasis: A Misleading Entity. *Allergy Rhinol.* **2018**, *9*, 2152656718783596. [\[CrossRef\]](#)
34. Fokkens, W.J.; Viskens, A.-S.; Backer, V.; Conti, D.; De Corso, E.; Gevaert, P.; Scadding, G.K.; Wagemann, M.; Bernal-Sprekelsen, M.; Chaker, A.; et al. EPOS/EUFOREA update on indication and evaluation of Biologics in Chronic Rhinosinusitis with Nasal Polyps 2023. *Rhinol. J.* **2023**, *61*, 194–202. [\[CrossRef\]](#)
35. Seah, J.J.; Thong, M.; Wang, D.Y. The Diagnostic and Prognostic Role of Biomarkers in Chronic Rhinosinusitis. *Diagnostics* **2023**, *13*, 715. [\[CrossRef\]](#)
36. Bachert, C.; Han, J.K.; Desrosiers, M.; Hellings, P.W.; Amin, N.; Lee, S.E.; Mullol, J.; Greos, L.S.; Bosso, J.V.; Laidlaw, T.M.; et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): Results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. *Lancet* **2019**, *394*, 1638–1650. [\[CrossRef\]](#)
37. Han, J.K.; Bachert, C.; Fokkens, W.; Desrosiers, M.; Wagenmann, M.; Lee, S.E.; Smith, S.G.; Martin, N.; Mayer, B.; Yancey, S.W.; et al. Mepolizumab for chronic rhinosinusitis with nasal polyps (SYNAPSE): A randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir. Med.* **2021**, *9*, 1141–1153. [\[CrossRef\]](#)
38. Gevaert, P.; Omachi, T.A.; Corren, J.; Mullol, J.; Han, J.; Lee, S.E.; Kaufman, D.; Ligueros-Saylan, M.; Howard, M.; Zhu, R.; et al. Efficacy and safety of omalizumab in nasal polyposis: 2 randomized phase 3 trials. *J. Allergy Clin. Immunol.* **2020**, *146*, 595–605. [\[CrossRef\]](#)
39. Bachert, C.; Han, J.K.; Desrosiers, M.Y.; Gevaert, P.; Heffler, E.; Hopkins, C.; Tversky, J.R.; Barker, P.; Cohen, D.; Emson, C.; et al. Efficacy and safety of benralizumab in chronic rhinosinusitis with nasal polyps: A randomized, placebo-controlled trial. *J. Allergy Clin. Immunol.* **2022**, *149*, 1309–1317.e12. [\[CrossRef\]](#)
40. Lipworth, B.J.; Han, J.K.; Desrosiers, M.; Hopkins, C.; Lee, S.E.; Mullol, J.; Pfaar, O.; Li, T.; Chen, C.; Almqvist, G.; et al. Tezepelumab in Adults with Severe Chronic Rhinosinusitis with Nasal Polyps. *N. Engl. J. Med.* **2025**, *392*, 1178–1188. [\[CrossRef\]](#)
41. De Corso, E.; Canonica, G.W.; Heffler, E.; Springer, M.; Grzegorzec, T.; Viana, M.; Horváth, Z.; Mullol, J.; Gevaert, P.; Michel, J.; et al. Dupilumab versus omalizumab in patients with chronic rhinosinusitis with nasal polyps and coexisting asthma (EVEREST): A multicentre, randomised, double-blind, head-to-head phase 4 trial. *Lancet Respir. Med.* **2025**, *13*, 1067–1077. [\[CrossRef\]](#)

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.