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DOI: 10.1111/all.13793

Impact of immune work-up on outcomes and the cost of care in patients with Chronic Rhinosinusitis

To the Editor,

Chronic sinusitis (CRS) is a global medical problem afflicting 5%-15% of the world's population depending on the geographical location, accounting for billions of dollars annually in healthcare expenditures. CRS is broadly divided into two subsets defined by the presence or absence of nasal polyps (NPs): CRS with NP (CRSwNP) and CRS without NP (CRSsNP). The main factor that drives this distinction is the association between NPs and tissue eosinophilia, that defines a distinct disease phenotype, predicting clinical responses and prognosis. Although medical therapy is effective in many cases, a significant number of patients continue to have recurrence and persistence of CRS. Uncontrolled disease in CRS has been reported to reach 40% of all CRS patients treated in academic referral centers, underscoring the need for novel and better strategies of care for CRS (Figure S1, reference 8). Over 50% of patients with CRS do not respond to surgery and up to 15% require follow-up surgery in the 3 years following the initial procedure.¹ Since CRS is a multifactorial disorder with diverse and overlapping endotypes, a "one size fits all" treatment approach remains unsatisfactory clinically (Figure S1). The true incidence of immune defects in patients presenting with CRS is unknown, with the exception of antibody deficiencies seen in 10% of refractory CRS.² The only comprehensive study looking at both the cellular and humoral immunity was published 18 years ago and showed immune defects in over 50% of patients with refractory CRS,³ indicating the need to screen for immune deficiencies in CRS.

We reviewed the records of 1665 adult patients (18-88 years/old with a M:F ratio of 2:1.6) referred to our immunology clinic between January 2010, and August 2015, with the diagnosis of CRS without nasal polyposis. Patients had documented two or more new sinus infections per year for three consecutive years as well as objective criteria for CRS diagnosis based on American Otolaryngology Society definition with endoscopic findings of sinus disease and/or CT evidence.⁴ Environmental allergies were identified in 37% of the patients based on skin prick testing and 88% of these patients had been on allergen immunotherapy for

over 3 years with no significant change in CRS symptoms. At least one surgical procedure was performed in 92% of these patients, with a mean of 2.2 surgeries in the past 3 years before referral. All patients had complete immune evaluation: CBC with differential, serum total quantitative antibody levels (IgG, IgA, IgM and IgE), IgG to *Streptococcus pneumoniae*, *Hemophilus influenza B* (HiB) and tetanus, and immune profiling by flow cytometry as a part of immune curbside consultation (iCurb). In the iCurb process, physicians were provided warning signs for immune deficiencies and a predefined set of immune tests (Table S1 and Figure S1). CRSsNP was a subcategory of patients evaluated as a part of iCurb. A total of 370 control subjects with no CRS were enrolled with similar age and sex distribution. Western Institutional Review Board approved the study (Protocol: 1-824462-1).

Immune test results outside the normal range with at least one test value below or above the 10th and 90th percentiles were found in 73% of the CRS patients (Table 1), with over 70% of patients showing multiple abnormalities. The generally accepted basic immune work-up and CBC with a differential and serum quantitative antibodies were abnormal in 28% of CRS patients. Poor vaccine responses or loss of an initial response to the polysaccharide vaccines (specific antibody deficiency memory type) were observed in 38% of patients, which is slightly higher than previously published data.² Of these poor vaccine responders, 18% had a normal basic immune work-up as indicated above. Immune phenotyping of T, B, NK, and dendritic cells showed results that were out of range in 69% of the patients. The distribution of the findings to each subset is shown in Table 1. An immune deficiency was diagnosed in 67% of patients with abnormal immune phenotyping results. Immunoglobulin replacement therapy was initiated in 4%, and long- or short-term topical and/or systemic antibiotic prophylaxis was administered to 19% of these patients. Sinus infection episodes were included in the data analysis if records indicated rhinosinusitis symptoms lasting 7 days or more with maxillary pain or tenderness in the face or

TABLE 1 Immune test results in patient with CRS and controls

	Control (ranges)	CRS (ranges)	Low (%)	High (%)
CBC with diff (cells/mcL)				
White blood cells	5.9 (3.9-7.5)	5.1 (3.2-7.9)	3	9
Lymphocyte	1667 (850-3900)	1332 (566-4700)	5	12
Neutrophil	3843 (1500-7800)	2255 (778-6300)	2	9
Eosinophil	560 (320-750)	880 (340-1600)	1	5
Monocyte	551 (200-950)	122 (16-377)	2	9
Antibody levels (mg/dL)				
IgG	889 (700-1200)	522 (355-778)	9	3
IgM	155 (26-217)	110 (12-210)	3	9
IgA	120 (87-352)	43 (19-201)	4	2
IgE	80 (13-139)	580 (120-1223)	1	11
Anti-pneumococcal IgG (>1.3 mcg/mL/14 serotypes)				
Baseline	7.3 (5.2-9.5)	4.2 (2.2-7.9)	59	—
Post-Pneumovax23	12.3 (7.3-13.3)	6.0 (3.1-8.4)	38	—
% Anti-tetanus IgG >0.15 IU/mL				
Baseline	89%	55%	45	—
Tetanus post-vaccine	n/a	73%	27	—
T and NK cells (cells/mcL or %*)				
CD3	1.81 (1.33-2.45)	1.32 (1.0-1.8)	2	8
CD3CD4	0.81 (0.53-1.45)	0.72 (0.10-2.1)	9	4
CD3CD8	0.51 (0.29-1.05)	0.42 (0.25-1.92)	8	5
CD3 $\gamma\delta$	55 (22-160)	122 (12-199)	14	9
CD3 $\alpha\beta$	1099 (770-1932)	1388 (554-2015)	3	2
CD3HLA-DR*	5.5 (0.8-7.3)	7.9 (0.5-10.5)	9	9
CD3CD25*	55 (30.7-61.1)	63.3 (22.2-91.1)	2	8
CD3CD56CD16	125 (79-223)	102 (59-433)	9	9
CD4CCR7CD45ROTh17*	5.4 (3.1-6.9)	4.6 (2.9-7.8)	1	6
CD4IFN γ *	18.9 (12.7-28.6)	16.6 (9.6-34.4)	9	7
CD8IFN γ *	29.5 (19.4-43.3)	24 (14.2-67.6)	8	2
B cells (cells/mcL or %*)				
CD20	290 (199-306)	233 (78-601)	16	12
CD20CD5*	18.5 (10.3-29.7)	32.6 (14.4-48.7)	0	3
CD20CD27*	20.2 (15-24.4)	27.8 (8.3-42.1)	11	14
CD20CD27IgM*	21.2 (12.4-28)	29.5 (16.4-33.4)	1	11
CD20IgG*	10.5 (7-12.2)	8.2 (4-19.2)	12	13
CD20IgM*	80.5 (69.5-93.3)	87 (76-95.5)	3	8
CD20IgA*	7.7 (4.9-11.2)	5 (3.2-9.2)	6	0
CD20IgD*	87.6 (80.5-94.4)	93.3 (85.5-95.7)	2	0
CD20CD21dim*	5.4 (2.2-8.4)	14.4 (9.4-17.9)	1	9
Dendritic cells				
mDC/pDC ratio	1.9 (1.1-2.3)	3.5 (1.0-5.5)	2	49

Values are the percentages (*) or absolute counts of the cells expressing the indicated markers for the lymphocyte population and presented as medians (10th and 90th percentiles). Antibody concentrations are presented as mg/dL or mcg/mL for specific antibodies. Only 3.4% of control subjects had laboratory values outside the normal range. Over 70% of the patients showed multiple laboratory value abnormalities. Therefore, the overall contribution of each laboratory test group (eg, CBC with differential) is not the sum of its components, due to an individual patient having multiple out of range results within the CBC components.

TABLE 2 Cost comparison for the care of patients with CRS before and after a complete immune work-up

Impact of immune work-up on cost of CRS management						
Patient workup	Preimmune	Postimmune				
No. of patients	1665	1665	33	157	636	815
Procedures	2.2 surgeries over 3 y \$10 000 ea Maintenance therapy × 3 y \$1000 ea/y	Immune Testing \$1500 ea	IVIG over 3 y \$20 000 ea/y	Antibiotics over 3 y \$600 ea/y	Maintenance Therapy × 3 y \$1000 ea/y	0.9 surgeries over 3 y \$10 000 ea \$10 000 ea
Cost of procedure	\$41.6M	\$2.5M	\$2.0M	\$0.3M	\$1.9M	\$3.6M
Total cost	\$41.6M	\$11.1M				
Overall total cost savings = \$25.5M (70%)						

2010/15 data. In post-immune work-up, 49% of patients diagnosed with immune deficiency (ID). Of those with abnormal results but no ID diagnosed ($n = 400$), surgeries were 0.9/3 y. Remaining CRS with no abnormal labs ($n = 449$) was not followed. If we assume the surgery rate was the same as pre-immune, the cost savings is still above 50%. The cost analysis did not account for number of office visits, as the numbers were similar pre- and postimmune

The cost of specific procedures was determined by published data as well as United States Centers for Medicare & Medicaid Services 2018 fee schedule.

teeth, purulent nasal secretions, and antibiotic treatment initiated. Cultures were not obtained in all instances. There was a reduction in acute sinus infections as to 1.4 per year compared to 3.7 per year before starting treatment in patients with immune deficiency. Acute sinusitis was defined as thick yellow or green discharge from the nose or postnasally, nasal congestion and facial pain leading to prescribing oral antibiotics.

There are several important aspects to our study. First, the traditional stepwise diagnostic approach clearly results in significant underdiagnosis of immune deficiencies in CRS as abnormalities in each immune compartment can be independent of one another. In the setting of CRS, demonstrating the presence of immune abnormalities that no treatments are available is as important as showing defects that are treatable, as it will explain surgical failures.^{5,6} Perhaps, such abnormalities suggest the presence of mild or sub-clinic immune deficiency. Arguments against cost of an immune work-up are not a valid one, as the cost of CRS management without clear understanding of the presence of an immune disorder is clearly higher.⁷ To our knowledge, there is no such analysis published, incorporating the outcomes of an immune evaluation to the cost of care in CRS (Table 2). Second, the presence of allergies on testing should not deter the practitioner from completing an immune work-up as both atopy and immune deficiency may pose independent risk factors for CRS. Third, the presence of an immune defect does not correlate with the number of surgeries or the duration of the CRS, arguing against the erroneous notion that an immune work-up should be considered after multiple failed surgeries/therapies. The mean number of surgical procedures performed in the 3 years following the diagnosis of an immune deficiency dropped to 0.1 from 2.2 prediagnosis with significant cost savings of 70% between pre- and postimmune patient work-up as illustrated in Table 2.

Surgical management of CRS has improved significantly in the last decade, leading to increase in numbers of surgeries performed by almost 5-fold, despite the incidence of CRS staying the same⁸. As we understand the link between immune disorders and CRS, the type of the immune deficiency may very well prove to be a useful biomarker to decide the timing, type, frequency of surgical procedures and improve outcomes. We see similar trends in other branches of medicine, such as using serum cholesterol level as a biomarker before coronary artery bypass surgery to predict mid-term mortality.⁹ Basic immunology of CRS has advanced far more than its application to the clinical management of this disorder. Improving access to complete immune work-up in a meaningful way as well as insurer mandates on incorporating a complete immune evaluation (Table 1) early on in the diagnosis and management of patients with CRS will allow for better patient care, improved outcomes, and reduced cost of health care.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

DOI: 10.1111/all.13794

The contribution made by skin-infiltrating basophils to the development of alpha-gal syndrome

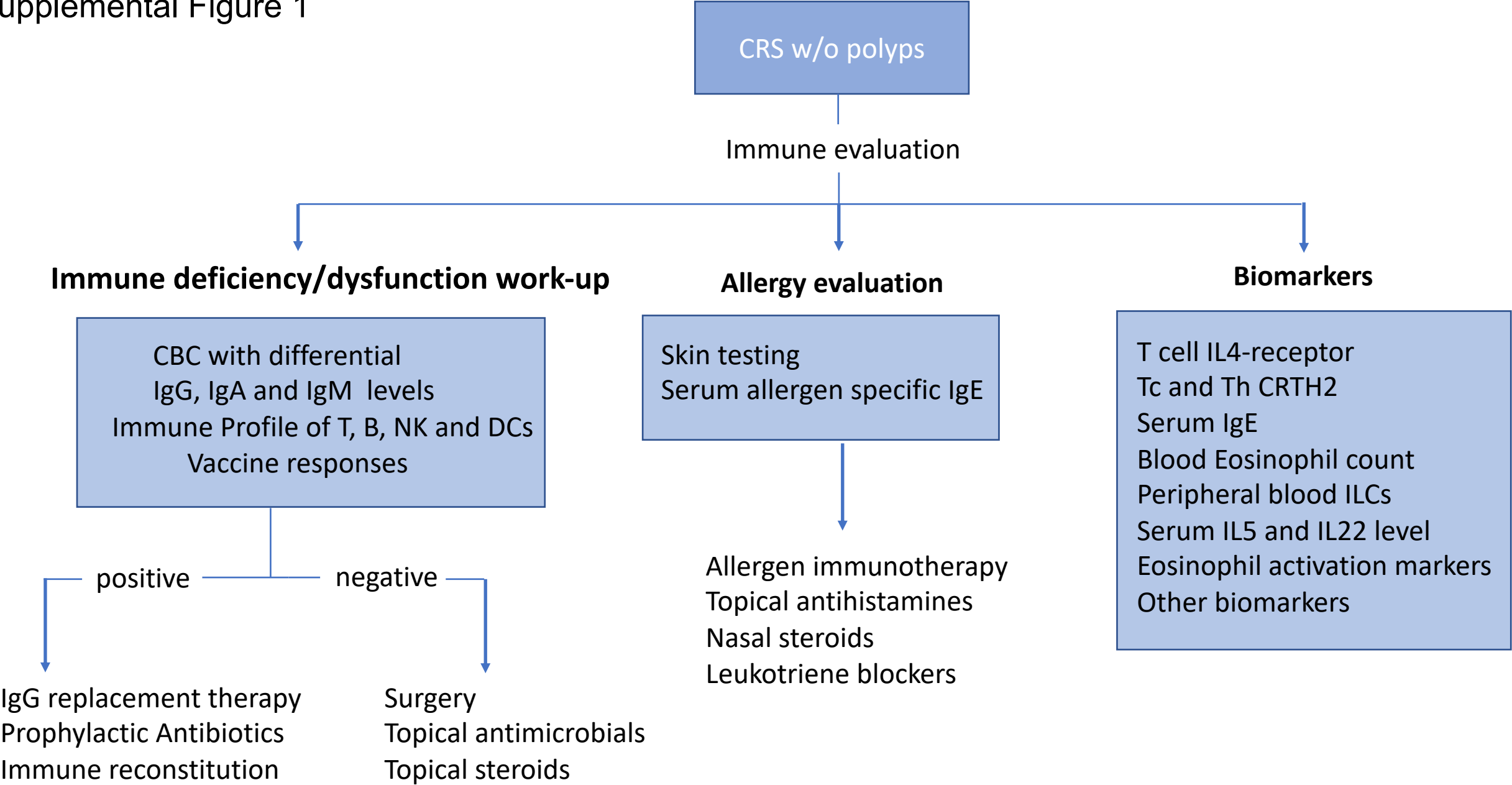
To the Editor,

The galactose-alpha-1,3-galactose (alpha-gal) disaccharide is a typical glycoprotein component in mammals. Nevertheless, over evolutionary time, primates such as humans have lost this because of loss of galactosyltransferase, the enzyme required for its production and large amounts of IgM and IgG, but not IgE, antibodies specific to this molecule are naturally produced in healthy individuals; however, certain patients that have been bitten by ticks that harbor this carbohydrate¹ and may develop alpha-gal syndrome, an immediate-type hypersensitivity to red meat and drugs containing alpha-gal,² which is mediated by anti-alpha-gal IgE antibody. Although we and others have recently reported that a recurrent tick bite history is associated with the development of alpha-gal syndrome,^{3,4} little is known about how tick bites are involved in the development of alpha-gal syndrome. To investigate this in more detail, we stratified the patients visiting our hospital with new tick bites according to their past tick bite histories, where the historical number of bites they had received was added to the new one (1 tick bite [1°], 2 tick bites [2°], or ≥3 tick bites [≥3°]). One hundred and twelve patients with new tick bites, who presented at our hospital, were enrolled in

this study after informed consent was provided. More than 80% of the ticks were identified as *Amblyomma testudinarium* (most are nymphs; a few are adults and no larvae). The study was performed according to the Declaration of Helsinki, and the study protocol was approved by the Shimada Municipal Hospital Ethical Committee.

Because the alpha-gal epitope is structurally related to the blood type B antigen, specific IgE antibody production is reportedly suppressed in patients who have this antigen.⁵ We reassure that the levels of specific IgE antibodies were significantly higher in the A and O blood type patients who had recurrent tick bite histories, compared with only a marginal increase in the B and AB blood type patients (Figure S1 and Table S1); and thus, we excluded the patients with B and AB blood types from any further investigations to delineate clearly the relationships between anti-alpha-gal IgE production and immune cell infiltration. We compared the chronological variations (1-5 days, the early period and ≥6 days after the bite, the late period) in the antibody levels among these three groups (Figure 1A). In the 1° group (N = 32), the IgE-specific antibody levels were constantly below detectable levels (<0.1 U_A/

Supplemental Figure 1



Guided Panel Request Form

Patient Name: _____ DOB: _____ Sex: _____
Address: _____
City: _____ State: _____ Zip: _____
Phone: _____ Email: _____

Physician Name: _____ Draw Date: _____
Physician Signature: _____ Draw Time: _____
Fax: _____ Phone: _____

Test Panels Based on Clinical Presentation Check relevant box.
CBC and differential required with all tests. All shaded tests require 4 ml purple top.

☐ **RECURRENT SINUS & EAR INFECTIONS**
CBC&diff, IgG, IgA, IgM, IgE, CH50, IgG subclasses
IgG to S.pneumococcus serotypes and HiB
Lymphocyte Monitoring, B cell panel and memory
ICD-10: D84.9 Z87.01, J32.9, H65.20

☐ **PYOGENIC INFECTIONS AND SEPSIS**
CBC&diff, IgG, IgA, IgM, IgE, CH50, C3, C4
IgG to S.pneumococcus serotypes
Lymphocyte Monitoring, CD62L, DHR
ICD-10: D84.9, A41.9, Z87.01

☐ **FAILURE TO THRIVE**
CBC&diff, IgG, IgA, IgM, IgE
IgG to S. pneumococcus serotypes
Lymphocyte Monitoring, B cell and memory
ICD-10: D84.9, R62.51

☐ **LOW SERUM ANTIBODIES**
CBC&diff, IgG, IgA, IgM, IgE, IgG subclasses
IgG to S. pneumococcus serotypes
Lymphocyte Monitoring, B cell panel and memory
ICD-10: D80.1, D84.9

☐ **PULMONARY PANEL**
CBC&diff, IgG, IgA, IgM, IgE, CRP
Northeastern Panel, alpha1-antitrypsin, C3, C4
IgG to S.pneumococcus serotypes, p-ANCA, c-ANCA
Lymphocyte & B cell panel and memory
ICD-10: D84.9, J18.9

☐ **PERSISTENT ECZEMA/DERMATITIS**
CBC&diff, IgG, IgA, IgM, IgE
Lymphocyte Monitoring, B cell and memory
ICD-10: D84.9, J18.9

☐ **ANAPHYLAXIS/URTICARIA**
CBC&diff, IgG, IgA, IgM, IgE
Tryptase, ANA, Anti-IgE receptor antibody
Anti-thyroglobulin antibodies, C3, C4
Anti-thyroid peroxidase antibodies
Lymphocyte Monitoring, B cell and memory
ICD-10: D84.9, T78.2, L50.1

☐ **EOSINOPHILIC GASTROINTESTINAL DISORDERS**
CBC&diff, IgG, IgA, IgM, IgE
Lymphocyte Monitoring and B cell panel
ICD-10: D84.9, K20.0

CUSTOM PROBLEM:

☐ _____
Specific Tests Required:

ADDITIONAL CLINICAL INFORMATION

ANTIBODIES USED IN IMMUNE PHENOTYPING

Lymphocyte Monitoring:
CD3, CD4, CD8, CD45, CD56/16, CD20
αβ, γδ, HLA-DR, CD25, CD57, CD14

B Cell Panel:
CD20, CD5, CD27, CD21, IgG, IgM, IgD, IgA

T Cell Memory Panel:
CD3, CD4, CD8, CD45RO, CD45RA

PLEASE TAKE NOTE:

All shaded tests will be sent to Amerimmune. All other tests can be performed at the local lab or draw location. Samples must be received at the Amerimmune lab in Fairfax, VA within 24 hours of draw. Please call (703) 459-5869 for questions. Depending on location, FedEx, UPS and courier services are available.
Please send insurance information and demographics. Patients with HMO plans: Please call Amerimmune to confirm whether your insurance is accepted.

Amerimmune Lab Address: 11212 Waples Mill Rd., Suite 100, Fairfax, VA 22030

	ENT	Pulmonary	Pediatric Cardiology	Primary Care	Infectious Disease	Gastroenterology	Pediatrics
Total number of patients	3112	1569	635	1613	408	1364	945
Patients with abnormal results: n (%)							
CBC with differential	1060 (34%)	889 (57%)	155 (24%)	285 (18%)	84 (21%)	349 (26)	211 (22%)
Serum antibodies	1274 (41%)	450 (29%)	45 (7%)	40 (2%)	185 (45%)	157 (19)	101 (11%)
Immune phenotyping	1775 (57%)	1242 (79%)	302 (48%)	993 (62%)	289 (71%)	1099 (81)	455 (48%)
Diagnosis of a defined immune disorder: n (%)	899 (29%)	601 (38%)	90 (14%)	177 (11%)	99 (24%)	309 (23%)	96 (10%)
Male : Female ratio	1:1.2	3:1	1:10	1.5:1	2:1	1:1.3	1:1.4
Established Immune disorder diagnosis at referral: n (%)	30 (1%)	55 (4%)	2 (0.3%)	10 (0.6%)	55 (13%)	17 (1%)	19 (2%)

Supplemental Table 1. *Patients with immune work up using iCurb between 2011-2017.* Abnormal results indicate ranges below or above the 10% confidence interval, as described in Table 1 of paper. A Defined immune disorder is an immunological disease with established definition in the literature (1, 2). Immune work up was performed on patients based on warning signs for immune deficiencies or disease states that require an immune evaluation. The immune work-up consisted of assays outlined in the manuscript.

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Supplemental Table 1 Expanded Figure Legend: iCurb – connecting the dots in diagnosing immune disorders.

Although healthcare reform is generating pressure for the U.S. healthcare system to provide better care at a lower cost, accomplishing this goal has to start with diagnosing diseases quickly and correctly. There are numerous initiatives to improve the speed of diagnosis, such as the eReferral system started at San Francisco General Hospital, to improve the supply/demand mismatch between primary and specialty care (1). Rare disorders are a significant burden to the healthcare system as delays in diagnosis is still very common. For example, diagnosis of immune deficiencies is delayed over 10 years in 45% of the cases (2). Rare disorders are seen across multiple specialties, require a strong laboratory diagnostic component and with a referral base that may not exist in the hospital system, and create a very different/supply demand mismatch depending on the geographic location and institution.

Building on eReferral, we designed a new diagnostic process called immune curbside consultation (iCurb) and offered it to primary care and specialist in Northern Virginia, with a population of approximately 3 million people. We hypothesized that physicians lack understanding of immune disorders, the components of an immune deficiency evaluation, and its interpretation are the three main obstacles in identifying immune deficiencies. We provided physicians warning signs for immune deficiencies or disease states that require an immune evaluation and a pre-defined set of immune tests without the need for the ordering physician to have a comprehensive understanding of test selection (Supplemental Figure 2) (3). Patient blood specimens were collected either in physicians office or through mobile phlebotomy. Then they

are submitted to the accredited in-office central immunology laboratory along with a form that is populated with patient and physician information, the reason for consultation, and relevant history and exam findings. Testing includes the commonly ordered serum total and specific antibodies, but supplemented with immune phenotyping, thus providing a complete evaluation (4). Interpretation of the results and recommendations unique to the patient are given by an expert immunologist, providing expedient guidance to the ordering provider. Patients with abnormal results were referred for further immunological evaluation. The iCurb system is in compliance with current laboratory regulations in the United States, as the consultative nature of the interaction differentiates it from a moderate to high complexity laboratory (5).

Records of a total of 9646 patients that went through iCurb between 2011-2017 were included in the analysis (Table 1). There were significant differences between specialties in the percentage of patients diagnosed with an immune disease as well as the contribution of each immune test to the diagnosis. After three years we applied this model nationally. Blood specimens and clinical history were either shipped to the central diagnostic immune laboratory in Northern Virginia linked with iCurbConsult to complete the predefined laboratory workup, or to the clinical immunology practices with replicated companion labs in other states. There was a total of 544 patients from 12 states referred through iCurbConsult between 2014-2017. The national referral base was a similar mixture of physicians and results were consistent with that of our local experience. Patients diagnosed with immune disorders were then referred to immunologists in the cities and states in which they reside. The feedback from the physicians using iCurbConsult has been incredibly positive, as over the course of the 6 years the utility per physician went up

from 0.4 iCurbConsults/month to 1.9 iCurbConsults/month. Having a financial assistance program in place further helped decrease burden on patients.

This new process of access to specialty expertise has had several benefits. First, it offers greater efficiency in the referral process, reducing unnecessary referrals and the wait time associated with seeing specialists. Further, it eliminates redundancy in laboratory testing and provides interpretation of the complete immunophenotyping in the context of the patient's clinical history, in contrast to an imprecise stepwise approach to testing by multiple providers. Components of an immune workup have a non-overlapping contribution to diagnosis, hence the importance of performing a more comprehensive evaluation when patients present with a possible immune dysfunction. Improvements in flow cytometry-based immunophenotyping have helped us design these comprehensive panels while lowering costs.

Second, with the growing shortage of physicians in certain specialties, such a referral process can be very powerful in rapid diagnosis and guidance to the referring physician. The specialist reviewer is a clinical immunologist trained in laboratory medicine, with interpretation of the results as part of the test reporting, avoiding further costs like salary support or fee-for-service based models. In the case of iCurbConsult, the cost is built into the interpretation code of the immune phenotyping performed at testing sites. Of note, the cases referred through iCurbConsult were patients with poor response to medical and/or surgical intervention, and unclear diagnoses. This streamlined consultation enabled referring providers to connect more dots in their complex patients, influencing management strategies to decrease morbidity and improve outcomes.

Third, iCurb has the potential to addressing care-coordination challenges, increasing the effectiveness of in-person specialty visits, and producing cost savings by reducing the number of specialty visits for conditions that can be managed by primary care specialists, especially in the era of spread of payment reform and federal investments in speeding the uptake of health information technology. It provides a solution to improve the gap in diagnosis as well as targeted education about immune deficiencies. The personalized interpretations and recommendations obtained with an iCurbConsult inform and enhance the referring providers' understanding of PI diseases. It reinforces meaningful longitudinal care, reduces fragmentation in patient management, reduces morbidity associated with PI, and improves patient outcomes.

Fourth, iCurb formalizes the “curbside consult” in a manner that establishes the documentation of the interaction, while preserving advantages such as case-based education, building of relationships between PCPs and specialists, identification of cases that require formal consultation, and the patient convenience and cost savings associated with avoiding a visit. Furthermore, streamlining the laboratory diagnostic process, and moving away from a step-wise approach without any clear guidelines on which step comes first or how far to progress the evaluation iCurb has improved diagnosis of immune disorders. Components of an immune work-up have a non-overlapping contribution to the diagnosing an immune disorder, hence the importance of performing a complete work-up when patients present with a possible immune disorder.

It is imperative that we remain attuned to the consequences of delayed diagnosis (i.e. quality of life, organ damage, avoidable surgeries/hospitalizations, even death), and strive to implement innovative, effective approaches to medical management that serve patients, providers, and insurers well. The burden of delayed diagnosis to the healthcare system would supersede the cost of screening a high-risk population. Value in healthcare is understood as better care at lower cost, but diagnostic testing is a critical part of patient management and should be regarded as the standard of care. While cost analysis is useful, it is limited in these circumstances, as total costs should be measured over a patient's care cycle and weighed against outcomes. Here we present an actively expanding process for identifying undiagnosed immune disorders in the U.S, and our experience validates that value improvement in healthcare is increasingly more dependent on innovation over cost-containment (6). Providing value in healthcare relies on *accurate* and *expeditious* diagnoses. Implementing the iCurbConsult model addresses inefficiencies and knowledge disparity, as providers become more informed and better equipped to diagnose and manage primary immune disorders. Utilizing iCurbConsult for earlier, more comprehensive surveillance of immune disorders realigns outcomes around the patient's entire care cycle, ultimately enhancing value, reducing cost, and benefiting all.

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Figure 1: Algorithm on immune evaluation of CRS without nasal polyps.

Precision medicine for chronic sinusitis requires a deep understanding of the immunopathology and phenotype heterogeneity in relation to clinically significant outcomes. One study identified ten CRS clusters, of which six exhibited a type 2 inflammatory profile with raised IL-5 and eosinophilia (1). Rather than the simple division of CRS into those with and without polyps, phenotypes that separate and accurately describe the disease process will ultimately prove much more valuable. CRS, in a given patients, seems to be a dynamic disease process, as the pathophysiology of these condition may change over time and this has to be taken into account in designing therapies (2) There are a number of biomarkers that can be measured with potential impact on treatment decisions (3, 4). It is important to identify co-morbid conditions as the risk of other diseases associated with CRS adds to the burden of an already highly burdensome condition (5, 6). Identification of the pathogens isolated from the nasal and/or sinus cultures and selection of proper antibiotics, especially for patients on antibiotic prophylaxis is important (7). Personalized care in the management of CRS will allow better prediction of treatment success, prevention of disease exacerbation and is expected to substantially improve the therapeutic approach (8).

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