

## Research Article

# Cost-Effectiveness of Laboratory Testing for Uveitis

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Received: April 24, 2015; Accepted: June 30, 2015;

Published: July 07, 2015

## Abstract

**Purpose:** Lab tests are often required to reach a definitive diagnosis in uveitis and guide management. The purpose of this study is to evaluate the diagnostic value of these tests in an incremental cost perspective.

**Methods:** A revised Bayes' theorem statistical analysis was performed to determine the most cost-effective testing based on review of the rheumatologic literature of 16 common causes of uveitis for epidemiological data, laboratory testing, sensitivities and specificities, positive and negative predictive values, pretest probability for disease, and Medicare/Medicaid reimbursements. Etiologies were subsequently ranked by Cost-Effectiveness Units (CEU).

**Results:** For Medicare patients, Rheumatoid Arthritis (RA) was the most cost-effective diagnostic evaluation, average 10.4 CEU, followed by syphilis, Bartonella, granulomatosis with polyangiitis, and polyarteritis nodosa. For Medicaid patients, (HLA-A29) was the most effective initial investigation, average 5.5 CEU, followed by HLA-B27, RA, toxoplasmosis and toxocariasis.

**Conclusions:** Stepwise process of elimination of lab tests based on CEU may enable the ophthalmologists to arrive at a diagnosis within resource constraints.

**Keywords:** Uveitis diagnostic tests; Cost effectiveness; Laboratory tests

## Abbreviations

CEU: Cost-Effectiveness Units; CMS: Centers for Medicare and Medicaid Services; SLE: Systemic Lupus Erythematosus; ESR: Erythrocyte Sedimentation Rate; CRP: C-reactive Protein; ANA: Antinuclear Antibody; RF: Rheumatoid Factor; GPA: Granulomatosis with Polyangiitis; PAN: Polyarteritis Nodosa; BSCR: Birdshot Chorooretinopathy; RA: Rheumatoid Arthritis

## Introduction

Uveitis has an extensive differential, including inflammatory and infectious etiologies [1]. It can be vision-threatening and accounts for an estimated 10% of legal blindness in the United States [1,2]. Significant morbidity exists as children and working young adults are often affected. Some cases of uveitis represent isolated ocular disease, while others may present as ocular manifestations of systemic illnesses [3].

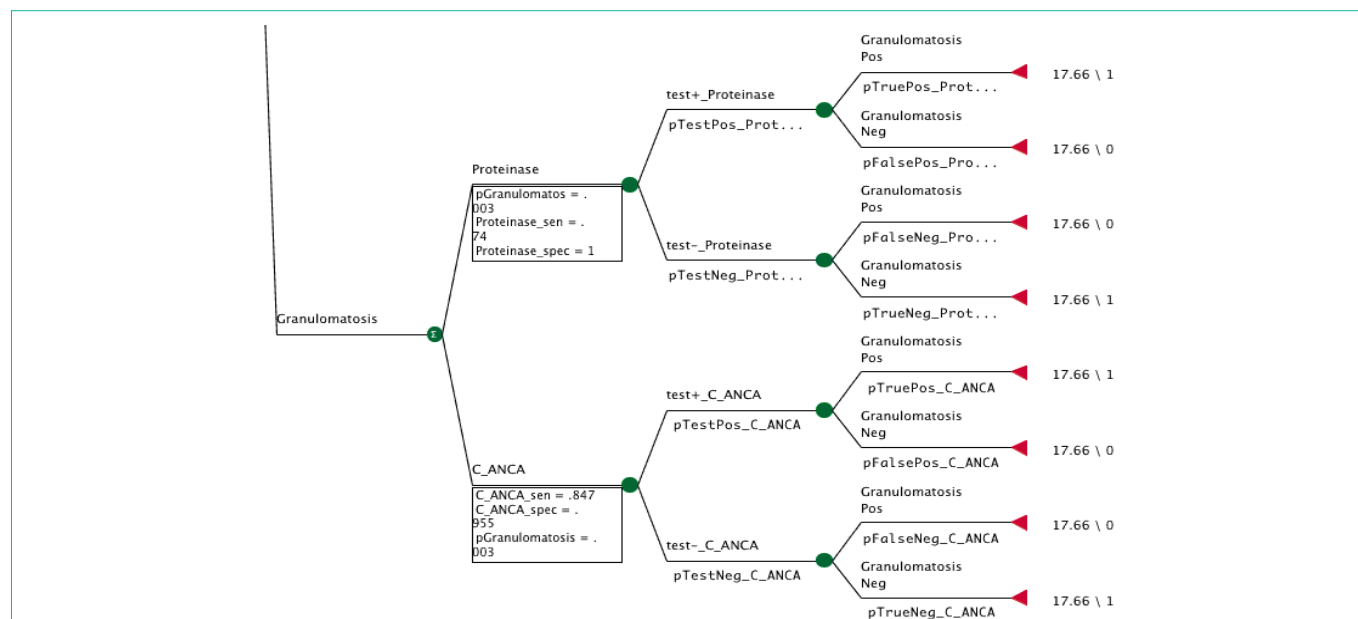
Uveitis can be classified by location, based on the structure(s) of the eye most affected (anterior uveitis, intermediate uveitis, posterior uveitis, or panuveitis) or based on the presence or absence of granulomatous disease [4]. Anterior uveitis constitutes a significant proportion of the morbidity experienced by uveitis patients, with HLA-B27 associated uveitis accounting for the majority of these diagnoses, both in community-based and university referral settings [4,5]. Many of the HLA-B27 associated cases may also present with systemic findings attributable to the seronegative spondyloarthropathies; however, this is not always the case. In certain instances, anterior uveitis may be the sentinel presentation of a seronegative spondyloarthropathy [6]. Less commonly, other autoimmune diseases, such as systemic lupus erythematosus (SLE),

sarcoidosis, Sjogren's syndrome, and juvenile idiopathic arthritis may also be diagnosed based on laboratory testing [4,7,8].

Investigational testing can be useful in determining the etiology of uveitis; however, each test has associated costs, specificity, and sensitivity. In cases without pathognomonic clinical features to guide testing, a costly and inefficient patient work-up may result. Furthermore, non-specific testing practices may result in inaccuracies and false-positives and introduce delay to diagnosis and potential harm to patients [2]. As healthcare providers are increasingly encouraged to approach uveitis efficiently and economically, we developed an interest in evaluating commonly ordered testing in terms of diagnostic value and cost-effectiveness. Based on disease prevalence in the United States, available sensitivity and specificity data for individual tests, pretest likelihood of disease, and available Medicare and Medicaid cost data, we aimed to evaluate the laboratory and imaging investigational methods frequently ordered in the work-up of uveitis and create a cost-analysis to determine practices which promote the highest yield and lowest costs for patients [9-12].

## Methods

Institutional Review Board approval was not required for this study as it did not involve the examination or treatment of patients or a review of patient records. Diagnostic testing for classic and common etiologies of uveitis was specified by a uveitis specialist (AKR). A systematic literature review for the prevalence of each disease entity in the United States was conducted utilizing MEDLINE, the online bibliographical database, using the search terms "uveitis," "prevalence," "United States," and individual disease entities. The bibliographies of these articles were reviewed and epidemiological data were extracted. A systematic literature review of the diagnostic



**Figure 1:** The formulas for the probability of a false negative using C\_ANCA (pFalseNeg\_C\_ANCA), false positive (pFalsePos\_C\_ANCA), true negative (pTrueNeg\_C\_ANCA), and true positive (pTruePos\_C\_ANCA) are provided below. The probability of granulomatosis with polyangiitis (pGranulomatosis) and the sensitivity (C\_ANCA\_sen) and specificity (C\_ANCA\_spec) of C\_ANCA were identified from the literature.

- $pFalseNeg\_C\_ANCA = (pGranulomatosis * (1 - C\_ANCA\_sen)) / ((pGranulomatosis * (1 - C\_ANCA\_sen)) + ((1 - pGranulomatosis) * C\_ANCA\_spec))$
- $pFalsePos\_C\_ANCA = ((1 - pGranulomatosis) * (1 - C\_ANCA\_spec)) / ((pGranulomatosis * C\_ANCA\_sen) + ((1 - pGranulomatosis) * (1 - C\_ANCA\_spec)))$
- $pTrueNeg\_C\_ANCA = ((1 - pGranulomatosis) * C\_ANCA\_spec) / ((pGranulomatosis * (1 - C\_ANCA\_sen)) + ((1 - pGranulomatosis) * C\_ANCA\_spec))$
- $pTruePos\_C\_ANCA = (pGranulomatosis * C\_ANCA\_sen) / ((pGranulomatosis * C\_ANCA\_sen) + ((1 - pGranulomatosis) * (1 - C\_ANCA\_spec)))$
- The formula for the probability that the test came back negative (pTestNeg\_C\_ANCA) and positive (pTestPos\_C\_ANCA) is given by the following formulas:
- $pTestNeg\_C\_ANCA = ((pGranulomatosis * (1 - C\_ANCA\_sen)) + ((1 - pGranulomatosis) * C\_ANCA\_spec))$
- $pTestPos\_C\_ANCA = ((pGranulomatosis * C\_ANCA\_sen) + ((1 - pGranulomatosis) * (1 - C\_ANCA\_spec)))$

The CEU was calculated for each etiology and subsequently ranked from lowest to highest CEU (the lower the cost and the higher the accuracy, the more cost-effective the test).

value of each testing modality as well as sensitivity and specificity, was conducted utilizing the search terms, “uveitis,” “sensitivity,” and “specificity,” for each disease entity and the diagnostic test. English language articles were selected. The bibliographies of these articles were reviewed and diagnostic accuracy and values for tests were recorded [13-51].

A cost determination was made for Medicare and Medicaid reimbursement. Medicare reimbursement cost structures of diagnostic tests in Virginia for fiscal year 2014 were obtained from the 2000 American Medical Association Current Procedural Terminology (CPT) codebook and the Centers for Medicare and Medicaid Services (CMS) Searchable Medicare Physician Fee Schedule via the CMS website [11]. Medicaid reimbursement cost structures were determined using Virginia’s Department of Medical Assistance Services online searchable database [12].

Cost Effectiveness Units (CEU) were determined by dividing the total cost by the total effectiveness. To obtain the CEU, each etiology was paired with its appropriate diagnostic studies. The measure of effectiveness was constructed using each diagnostic test’s sensitivity and specificity for detecting disease as well as the disease prevalence in the United States as a measure of disease probability.

Figure 1 provides an example of one branch of the decision tree used to calculate and compare CEUs. There are two test procedures that could be used to test for Granulomatosis with polyangiitis,

C\_ANCA (anti neutrophilic cytoplasmic antibody) and PR-3 (anti proteinase-3 antibody). Each test procedure has a sensitivity and specificity and there is also a probability that the patient has granulomatosis with polyangiitis. The end of each branch includes the cost, in this case the Medicare cost is \$17.66, and the effectiveness, which is either 1 if the test gave a correct result and 0 if the test gave an incorrect result (Figure 1).

## Results

A total of 16 diagnoses were considered for this analysis. The average cost effectiveness for each diagnosis was determined and the diagnoses were ranked by most cost-effective. The rankings for Medicare payments are demonstrated in Table 1 and Medicaid payments are demonstrated in Table 2.

For Medicare patients, Rheumatoid Arthritis (RA) was the most effective first diagnostic evaluation, with an average cost effectiveness of 10.4 CEU. This was followed by syphilis (14.5 CEU), Bartonella infection (15.6 CEU), granulomatosis with polyangiitis (18.1 CEU), and polyarteritis nodosa (19.0 CEU).

For Medicaid patients, birdshot chorioretinopathy (HLA-A29) was the most effective initial investigation, with an average cost effectiveness of 5.5 CEU. This was followed by HLA-B27-positive anterior uveitis (5.7 CEU), RA (10.1 CEU), toxoplasmosis (11.1 CEU), and toxocariasis (11.9 CEU).

**Table 1:** Diagnoses ranked by average cost-effectiveness for Medicare.

Rank	Etiology	Testing	Cost [11,12]	Prevalence (per 100,000)	Average Cost Effectiveness	Sensitivities	Specificities	Effectiveness
1	Rheumatoid arthritis [29]	Rheumatoid factor	\$7.74	397	10.46	75%	74%	0.74
2	Syphilis [34-37]	Syphilis IgG	\$41.68	2.4	14.49	91%	99%	2.88
		VDRL				78-86% primary, 100% secondary, 95-98% latent	85-99%	
		RPR				78-86% primary, 100% secondary, 95-98% latent	85-100	
		MHATP				95%	99%	
		FTA-ABS				84% primary, 100% other stages	96%	
3	Bartonella [52]	Bartonella Henslae serological antigen	\$13.89	7100	15.62	2-50% IgM	86-100% IgM	0.89
						14-100% IgG	34-100% IgG	
4	Granulomatosis with polyangiitis [28]	C-ANCA	\$35.32	3	18.07	85%	95%	1.95
		Proteinase-3				74% ELISA/ 87.5% capture ELISA	100%	
5	Polyarteritis Nodosa [31-33]	P-ANCA	\$35.32	3.3-6.3	19.01	19%	92%	1.86
		MPO				20%	94%	
6	Toxocariasis [49,50]	Toxacara Antigen serological test	\$17.75	14000	20.29	91%	86%	0.87
7	HIV/AIDS [47,48]	HIV ELISA	\$59.66	355	20.65	100%	100%	2.89
		HIV Western Blot				100%	89%	
		Rapid HIV				100%	100%	
8	Toxoplasmosis [41-43]	Toxoplasma IgM	\$39.29	10,8000-22,500	20.79	93-100%	78-99%	1.89
		Toxoplasma IgG				97%	98%	
9	Lyme Disease [44-46]	ELISA	\$44.37	78	22.31	100%	99%	1.99
		Western Blot				32% IgM	100% IgM	
10	SLE [13-15]	Anti-nuclear antibody (ANA)	\$35.23	52	23.18	83% IgG	95% IgG	1.52
		Anti-double-stranded DNA (DSDNA)				93%	57%	
11	Sjogren syndrome [13-16]	SSA	\$48.92	420	25.24	70-96%	100%	1.94
		SSB				60-91%	94%	
12	Birdshot Chorioretinopathy [26,27]	HLA-A29 Molecular typing	\$35.21	0.14	37.06	97%	95%	0.95
13	HLA B27 Uveitis [24,25]	HLA-B27 Molecular typing	\$35.21	100	38.27	90%	92%	0.92
14	Tuberculosis [38-40]	Quantiferon	\$316.69	3617	89.7	70%	92%	3.53
		Purified Protein Derivative				67%	79%	
		Chest X-Ray				78%	51%	
		Chest CT				88%	88%	
15	Sarcoidosis [21-23]	ACE	\$269.76	48	176.16	73%	83%	1.53
		Lysozyme				60%	70%	
		Chest X-Ray				70%	NA	
		Chest CT				78%	NA	
16	Multiple Sclerosis [30]	MRI Scan	\$336.73	159.8	387.56	53%	87%	0.87

**Abbreviations:** VDRL: Venereal Disease Research Laboratory; RPR: Rapid Plasmin Reagin; MHATP: Microhemagglutination assay for Treponema Pallidum; FTA-ABS: fluorescent treponemal antibody absorption test; C-ANCA: Cytoplasmic anti-neutrophil cytoplasmic antibodies; P-ANCA: Perinuclear Anti-neutrophil antibody test; MPO: Myeloperoxidase; ELISA: Enzyme linked immunosorbent assay; SSA: Sjogren's Syndrome antigen A; SSB: Sjogren's Syndrome antigen B; HLA: Human Leukocyte Antigen; ACE: Angiotensin Converting Enzyme

## Discussion

Uveitis represents a significant portion of ophthalmology clinic visits to both community-based and academic centers [2,4,5]. The diagnostic evaluation for patients presenting with uveitis can be

challenging and costly, and the approach to patients can be highly variable [3]. Determining the etiology of uveitis is of great importance as treatment regimens can be distinct for certain entities, and delay to appropriate therapy may lead to further morbidity for the patient

**Table 2:** Diagnoses ranked by average cost-effectiveness for Medicaid.

Rank	Etiology	Testing	Cost	Prevalence	Average Cost Effectiveness (CEU)	Sensitivities	Specificities	Effectiveness
1	Birdshot Chorioretinopathy [26,27]	HLA-A29 Molecular typing	\$5.20	0.14	5.47	97%	95%	0.95
2	HLA B27 Uveitis [24,25]	HLA-B27 Molecular typing	\$5.20	100	5.65	90%	92%	0.92
3	Rheumatoid arthritis [29]	Rheumatoid factor	\$7.46	397	10.08	75%	74%	0.74
4	Toxoplasmosis [41-43]	Toxoplasma IgM	\$20.90	10,8000-22,500	11.06	93-100%	78-99%	1.89
		Toxoplasma IgG				97%	98%	
5	Toxocariasis [49,50]	Toxacara Antigen serological test	\$10.45	14000	11.95	91%	86%	0.87
6	Bartonella [52]	Bartonella Henslae serological antigen	\$10.74	7100	12.08	2-50% IgM	86-100% IgM	0.89
						14-100% IgG	34-100% IgG	
7	Syphilis [34-37]	Syphilis IgG	\$41.15	2.4	14.3	91%	99%	2.88
		VDRL				78-86% primary, 100% secondary, 95-98% latent	85-99%	
		RPR				78-86% primary, 100% secondary, 95-98% latent	85-100	
		MHATP				95%	99%	
		FTA-ABS				84% primary, 100% other stages	96%	
8	Granulomatosis with polyangiitis [28]	C-ANCA	\$32.83	3	16.79	85%	95%	1.95
		Proteinase-3				74% ELISA/87.5% capture ELISA	100%	
9	HIV/AIDS [47,48]	HIV ELISA	\$50.82	355	17.59	100%	100%	2.89
		HIV Western Blot				100%	89%	
		Rapid HIV				100%	100%	
10	Polyarteritis Nodosa (MPA)	P-ANCA	\$33.49	3.3-6.3	18.03	19%	92%	1.86
		MPO				20%	94%	
11	Lyme Disease [44-46]	Lyme ELISA	\$41.23	78	20.73	100%	99%	1.99
		Lyme Western Blot				32% IgM	100% IgM	
						83% IgG	95% IgG	
12	Sjogren syndrome [13-16]	SSA	\$41.80	420	21.56	70-96%	100%	1.94
		SSB				60-91%	94%	
13	SLE [13-15]	Anti-nuclear antibody (ANA)	\$33.91	52	22.31	93%	57%	1.52
		Anti-double-stranded DNA (DSDNA)				70%	95%	
14	Tuberculosis [38-40]	Quantiferon	\$217.66	3617	61.65	70%	92%	3.53
		Purified Protein Derivative				67%	79%	
		Chest X-ray				78%	51%	
		Chest CT				88%	88%	
15	Sarcoidosis [21-23]	ACE	\$246.70	48	161.11	73%	83%	1.53
		Lysozyme				60%	70%	
		Chest X-Ray				70%	NA	
		Chest CT				78%	NA	
16	Multiple Sclerosis [30]	MRI Scan	\$413.46	159.8	475.87	53%	87%	0.87

**Abbreviations:** VDRL: Venereal Disease Research Laboratory; RPR: Rapid Plasmin Reagin; MHATP: Microhemagglutination assay for Treponema Pallidum; FTA-ABS: fluorescent treponemal antibody absorption test; C-ANCA: Cytoplasmic anti-neutrophil cytoplasmic antibodies; P-ANCA: Perinuclear Anti-neutrophil antibody test; MPO: Myeloperoxidase; ELISA: Enzyme linked immunosorbent assay; SSA: Sjogren's Syndrome antigen A; SSB: Sjogren's Syndrome antigen B; HLA: Human Leukocyte Antigen; ACE: Angiotensin Converting Enzyme

related both to the original uveitic disease and the adverse effects of an ineffective treatment regimen. Thus, based on the prevalence of certain conditions and associated expense, not all testing is equally cost-effective.

In many cases, patients present with pathognomonic features (i.e. panuveitis with a rash of the palms and soles in syphilis or acute, recurrent anterior uveitis in a young man with HLA-B27 uveitis), in which case a complex algorithmic approach is not indicated and generally only confirmatory testing is necessary. The cost-effectiveness of confirmatory testing in such situations is high. For patients without pathognomonic features at presentation, the analysis conducted shows that CEU can be utilized to guide a diagnostic work-up. Stepwise testing can lead to the exclusion of individual diagnoses until a positive test elucidates the origin of disease. It would be helpful to note that this step-wise approach would be particularly useful following a clinician's assessment of pre-test probability based on history and physical exam. It doesn't seem likely that the diagnosis will be reached solely based on exclusion by CEU (and may be less cost-effective overall) given the importance of the clinical exam in creating a differential diagnosis. Employing this particular method can assist ophthalmologists in preparing an effective diagnostic evaluation while remaining cognizant of costs to patients and the overall healthcare system.

As with any analysis based on literature review, limitations and weaknesses exist due to uncontrollable factors or unavailable data. One particular limitation faced at each step of the analysis was the separation of diagnostic testing from the clinical history and exam. Relevant historical data about a particular patient, such as exposure to infectious agents, family history of inflammatory conditions, demographic and racial factors, and a birth history complicated by congenital illnesses will likely lead a clinician down a more focused diagnostic path. A number of the disease processes responsible for causing uveitis may be evident from a patient's past medical history. As patients present in a myriad of ways, clinical features were not accounted for in our analysis.

Another limiting factor included the lack of available prevalence studies for particular uveitis etiologies in parts of the United States. We chose the national prevalence of these entities for our calculations because their prevalence among patients with uveitis is not well-established. A complementary analysis with calculations based on the prevalence of these conditions among patients with uveitis will be published in a subsequent paper. Much of the epidemiological data in the literature includes small population studies, which are thought to be representative of the US population as a whole. The prevalence of certain conditions (especially infections such as syphilis and tuberculosis) are more common in some parts of the country than others, which affects determination of cost-effectiveness. Although estimates may be accurate in terms of demographical data, they may limit broad application of an algorithm derived from CEU. Our conclusions are based on the best calculations possible given what is known about the prevalence of these conditions in the United States.

A specific difficulty encountered in this particular analysis was with determination of the effectiveness of testing for sarcoidosis, specifically with imaging studies. As these studies can be read and interpreted with significant inter-reporter variability [52], specificity

data for this parameter was not available and had to be inferred as zero.

A common issue facing all cost-effectiveness analyses is in the production of standardized data. Our results have been reported in cost-effectiveness units, which is a measure of total cost divided by total effectiveness. However, many other cost-effectiveness analyses performed use standardized units, such as quality-adjusted life-years. At present, no utilization data exists for this particular analysis, so we are unable to present the data as such. Etiologic differences also exist among the pediatric population versus the adult population. Our study was limited to the adult population, but further sub-group analysis should be performed for the diagnostic evaluation of uveitis in the pediatric population.

Previous studies of cost analysis have been performed for the diagnostic work-up of uveitis, but not in the United States. A Canadian study published in 2008 reported investigational patterns of Canadian ophthalmologists for anterior uveitis through survey and found that diagnostic practices varied significantly among providers. The authors concluded that ophthalmologists consistently ordered more tests than recommended by evidence-based guidelines. Furthermore, they asserted that a number of the tests ordered by ophthalmologists for diagnostic work up are non-specific and offered very little aid in determining the etiology of uveitis. The authors concluded that adherence to clinical practice guidelines and refraining from ordering extraneous tests reduced costs with no loss in sensitivity in diagnostic work-up. These tests included the Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP), Antinuclear Antibody (ANA), Rheumatoid Factor (RF). When applied to the Canadian population, adherence to clinical practice guidelines would have resulted in potential cost savings of \$600,000 per year in the Canadian Healthcare System [9]. Algorithmic approaches to uveitis have been pursued, but tend to neglect cost-utility [53,54].

## Conclusion

In conclusion, CEU can be used to guide diagnostic evaluation in uveitis to minimize costs to patients and the health economy, which is increasingly important as accountable care and economics play a larger role in medical decision making. As epidemiologic data on uveitis is collected and reported by a growing number of centers, our ability to apply CEU to guide evaluations for ocular inflammation will improve. Future studies may build on this data and explore cost-minimization models for various clinical scenarios in uveitis.

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