Approach to the Laboratory, Imaging, and Molecular Work-up for Uveitis

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Introduction

The work-up and diagnosis of uveitic diseases can be a challenge. Evolving nomenclature and classifications as well as a limited understanding of the utility and limitations of diagnostic tests may lead to confusion, unnecessary testing, and inaccurate or delayed diagnosis. In this chapter, we hope to clarify the goals of diagnosis and present a systematic approach for the diagnostic work-up in patients with uveitis. In order to appropriately discuss this work-up, we will briefly review current nomenclature, emphasize the importance of history, present a few important discriminating exam findings, and highlight the utilization of an anatomic classification system. In addition, we will highlight the utility, indications, and complementary role of laboratory, radiographic, and molecular testing. With this review, we hope to remove some of the uncertainty that comes when approaching these often complicated patients.

Goal of Testing

There is little consensus among providers about which testing should be ordered for a uveitic evaluation. This fact highlights the importance of defining specific goals for initiating a work-up. It may be helpful to ask the questions: Will the results of this test affect my clinical decision making and change my management? Will the results affect the patient's visual or systemic prognosis? Traditionally, when defining uveitic disease, there has been an emphasis on the search for the "etiologic diagnosis" of the inflammation [1, 2]. One problem with this approach, is that even after exhaustive testing, many uveitic disorders do not have a known systemic association and are ultimately termed "idiopathic" or "undifferentiated" [1, 3]. Thus, this search may lead to "shot-gun" testing that may not affect treatment or prognosis. Jabs et al. suggest that except for infectious diseases, Mendelian genetic disorders, and toxic or allergic reactions, most uveitic disorders are not amenable to a simple unifying "etiology" [4]. With this in mind, our diagnostic philosophy places a strong emphasis on history and physical examination findings. This is to be followed by focused, complementary testing with the primary goal of ruling out diseases not treated

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with immunomodulators (i.e., infections—particularly those that cannot be identified by unique exam features, and masquerade syndromes) and systemic diseases that may have an impact on the patient's systemic health, prognosis, or treatment plan. This approach helps to limit unnecessary testing and facilitates critical treatment decisions early in the disease course. As a secondary concern, each clinician should further consider the cost of each test and try to improve the financial burden on the patient and the health care system. Finally, it is best for the examining ophthalmologist to order and interpret the appropriate testing. The primary care provider or rheumatologist will not be familiar with the ocular differential diagnosis, so a referral for testing may lead to inappropriate testing. An unnecessary or incomplete work-up can cloud the clinical picture further and ultimately lead to testing results that are misleading.

Nomenclature and Classification

In 1996, Rosenbaum et al. highlighted the gross inconsistencies in the use of vocabulary among uveitis specialists. In this editorial, members of the American Uveitis Society were given clinical vignettes and informally surveyed about terms that were deemed appropriate in describing the vignette. Only one-third of specialists agreed on descriptive terminology [5]. Some of this confusion invariably contributes to the uncertainty that many clinicians have when approaching patients with uveitis. The International Uveitis Study Group (IUSG) and the Standardization of Uveitis Nomenclature (SUN) Working Group have worked to unify inflammatory grading, outcome measurements, and disease classification. The classification established by the IUSG in 1987 [6] is based on the anatomic location of inflammation (see Table 2.1). This includes anterior uveitis (iritis, iridocyclitis, and anterior cyclitis), intermediate uveitis (pars planitis, posterior cyclitis, hyalitis/vitritis), posterior uveitis (focal, multifocal, or diffuse choroiditis, chorioretinitis, retinitis, and neuroretinitis), and panuveitis (anterior, vitreous, retina, and choroid). In 2005, the SUN Working Group came to the consensus that this IUSG anatomic classification should be used as a global standard [7]. In 2008, the IUSG designed an additional clinical classification system for uveitis based on disease etiology [8]. This was defined in 3 main categories: Infectious (bacterial, viral, fungal, parasitic, and others), non-infectious (with known systemic association, or no known systemic association), and masquerade syndromes (neoplastic, non-neoplastic). Between 2009 and 2013, the SUN Working group continued to further unify classification criteria by "mapping" terms into the description of 28 major uveitic diseases [9, 10]. Other proposed dimensions in characterizing uveitis include course (acute, monophasic vs. recurrent acute vs. chronic), laterality (unilateral vs. unilateral alternating vs. bilateral asynchronous vs. bilateral simultaneous), morphology (retinitis vs. choroiditis, paucifocal vs. multifocal), host (child vs. adult)

Table 2.1 Uveitic diseases by anatomic classification

Classification	Related conditions
Anatomic	• Anterior—iritis, iridocyclitis, anterior cyclitis • Intermediate—pars planitis, posterior cyclitis, vitritis/hyalitis • Posterior—focal, multifocal, or diffuse choroiditis, chorioretinitis, retinitis, neuroretinitis • Panuveitis—anterior, vitreous, retina, and choroid
Etiology	• Infectious—bacterial, viral, fungal, parasitic, and others • Non-infectious—known versus unknown systemic association • *Masquerade syndromes*—neoplastic, non-neoplastic
Additional dimensions	• *Course*—acute monophasic versus recurrent acute versus chronic • *Laterality*—unilateral versus unilateral alternating versus bilateral asynchronous versus bilateral simultaneous • *Morphology*—retinitis versus choroiditis paucifocal versus multifocal • *Host*—child versus adult immunocompromised versus immunocompetent

and immune status (immunocompromised vs. immunocompetent) [10].

In summary, based on the uveitis working groups described above each patient with uveitis should have a descriptive diagnosis based on anatomic location. Then using standardized examination reporting, additional disease dimensions (course, laterality, morphology, host, and immune status) should be assigned to create a differential of major uveitic diseases. Narrowing the possible diagnosis in this way will lead to a focused laboratory evaluation and greatly increase the utility of each test ordered.

The Importance of History and Examination

One cannot emphasize enough that ancillary testing should only be a supplement to the most important initial components of the uveitis work-up, the history and physical examination. In a busy ophthalmology practice it may be tempting to marginalize these steps and even have a reflex "uveitis panel" of testing regardless of the history and exam. This approach is costly, exposes patients to unnecessary testing, and may also produce testing results that confuse the diagnostic picture with false positives or negatives.

History: As with all aspects of clinical medicine, an essential first step when establishing a differential diagnosis is a thorough history [11, 12]. This becomes increasingly essential in our modern world of wide spread travel and globalization. We suggest utilizing a questionnaire for new patients with uveitis. This provides a thorough and time affective way to elicit important historical details that may otherwise be missed. An example of one such questionnaire is seen in Fig. 2.1a–d. To date, there has not been a standardized questionnaire established. Details such as age, gender, race, social history (residence, occupation, diet, travel, sexual history, drug abuse), past medical history, family history, and review of systems will help to narrow the differential diagnosis [13–20] (see Table 2.2).

Exam Findings: There is a tremendous amount of cross-over in exam findings between uveitic diseases. However, some diseases are clinically identifiable, and specific exam findings provide important clues into the possible diagnosis limiting the need for additional work-up. Particularly, a combination of specific findings may be syndromic for a specific diagnosis. For example, a patient with anterior uveitis, elevated intraocular pressure, and sectoral iris atrophy makes a diagnosis of herpetic uveitis very likely. Below, we highlight a few key exam findings that may help to further focus the work-up.

Intraocular Pressure: Both ocular hypertension and hypotony can result from intraocular inflammation. Elevated intraocular pressure in uveitis has been estimated to occur in nearly 42 % of patients [21]. Diseases thought to have a higher rate of ocular hypertension include Fuch's heterochromic iridocyclitis (FHIC), glaucomatocyclitic crisis or Posner-Schlossman syndrome, sarcoidosis, juvenile rheumatoid arthritis, VKH, toxoplasmosis, and herpetic keratouveitis.

Keratic precipitates—The presence of keratic precipitates may be helpful in defining between acute versus chronic inflammation, and based on the appearance, may also give clues into the pathogenesis [1]. Fine precipitates are thought to be more common in spondyloarthropathies and juvenile arthropathies. Stellate precipitates that may be seen involving the superior cornea (as opposed to the typical inferior corneal base down triangular appearance of most precipitates) are often seen with Fuch's heterochromic iridocyclitis. "Mutton fat" prescipitates are larger and are formed from macrophages and epithelioid cells. These may be indicative of a granulomatous disease (see Table 2.3).

Hypopyon—This layering of leukocytes is indicative of not only the number of cells in the anterior chamber, but also the presence of enough fibrin to cause the cells to clump. A limited number of etiologies may present with a hypopyon. The most common etiologies include infectious (both bacterial and viral), HLA-B27 associated uveitis, and Behcet's disease. With infectious endophthalmitis the patient will typically have a history of recent surgery, trauma, or

Fig. 2.1 **a–d** Example questionnaire. Modified from questionnaire created by Dr. Stephen Foster at the Massachusetts eye and ear infirmary. Available at http://www.uveitis.org/uveitis-questionnaire

(a)

Example Questionnaire

Modified from Questionnaire created by Dr. Stephen Foster at the Massachusetts Eye and Ear Infirmary. Available at http://www.uveitis.org/uveitis-questionnaire

FAMILY HISTORY

These questions refer to your grandparents, parents, aunts, uncles, brothers, and sisters, children, or grandchildren

Has anyone in your family had any of the following? PLEASE CIRCLE YES or NO

Cancer	Y/N	Diabetes	Y/N
Allergies	Y/N	Arthritis or rheumatism	Y/N
Syphilis	Y/N	Tuberculosis	Y/N
Sickle Cell disease or trait	Y/N	Lyme disease	Y/N

Has anyone in your family had medical problems listed below? PLEASE ANSWER YES or NO

Eyes
Skin
Kidneys
Lungs
Stomach or bowel
Nervous system or brain

SOCIAL HISTORY

Age:_____ Current
Job:_____

Where were you born?_____
Have you lived outside of the USA?
If yes, where?_____
Have you ever owned a dog?_____ a cat?_____
Have you ever eaten raw meat or uncooked sausage?
Have you ever had unpasteurized mild or cheese?
Have you ever been exposed to sick animals?
Do you drink untreated stream, well or lake water?
Do you smoke cigarettes?
Have you ever used intravenous drugs?
Have you ever had a bisexual or homosexual relationship?
Have you ever taken birth control pills?

have risk factors for endogenous infection (e.g., intravenous drug use). Ocular involvement in these patients will typically be diffuse. Very fibrinous aqueous exudate and dense hypopyon are more commonly seen with infections and HLA-B27-associated disease. In contrast, the hypopyon seen with Behcet's typically has much less fibrin and may shift with the patient's head position. A hypopyon may also be seen in patients with rifabutin toxicity [22, 23]. Pseudohypopyon, composed of tumor cells and debris can occur in some of the masquerade syndromes. Triamcinolone layering may also present as a pseudohypopyon.

Iris Changes—Sectoral iris atrophy is more commonly seen with herpes simplex, varicella zoster, and cytomegalovirus infections. As mentioned above, if accompanied by elevated intraocular pressure one should be suspicious of a herpetic etiology. Nodule formation from the

Fig. 2.1 (continued)

(b) PERSONAL MEDICAL HISTORY

Are you allergic to any medications?
If yes, which medications?_____
Please list your current medications including non-prescription drugs such as aspirin, Advil, antihistamines etc.

_____
_____
_____
_____
_____
_____
_____
_____

PAST MEDICAL HISTORY

Please list all surgeries you have had (including laser surgery)

_____
_Date_____
_____
_ Date_____
_____
_ Date_____
_____
_Date_____

(c) Have you ever had any of the following conditions? PLEASE CIRCLE YES or NO

Anemia (low blood counts)	Y/N	Cancer	Y/N
Diabetes	Y/N	Hepatitis	Y/N
High Blood pressure	Y/N	Pleurisy	Y/N
Pneumonia	Y/N	Ulcers	Y/N
Herpes (cold sores)	Y/N	Chicken pox	Y/N
Shingles (Zoster)	Y/N	German measeles (Rubella)	Y/N
Mumps	Y/N	Chlamydia or Trachoma	Y/N
Syphilis	Y/N	Gonorrhea	Y/N
Any other sexually transmitted disease	Y/N	Tuberculosis	Y/N
Leprosy	Y/N	Leptospirosis	Y/N
Lyme disease	Y/N	Histoplasmosis	Y/N
Candida or Moniliasis	Y/N	Coccidiomycosis	Y/N
Sporotrichosis	Y/N	Toxoplasmosis	Y/N
Toxocariasis	Y/N	Cysticercosis	Y/N
Trichinosis	Y/N	Whipples disease	Y/N
AIDS	Y/N	Hay Fever	Y/N
Allergies	Y/N	Vasculitis	Y/N
Arthritis	Y/N	Rheumatoid arthritis	Y/N
Lupus (Systemic Lupus Erythematosus)	Y/N	Scleroderma	Y/N

Have you ever had any of the following illnesses? PLEASE ANSWER YES or NO

Reiter's Syndrome	Y/N	Colitis	Y/N
Crohn's disease	Y/N	Ulcerative Colitis	Y/N
Behcet's disease	Y/N	Sarcoidosis	Y/N
Ankylosing spondylitis	Y/N	Erythema Nodosa	Y/N
Temporal Arteritis	Y/N	Multiple Sclerosis	Y/N
Serpiginous Choroidopathy	Y/N	Fuchs' Heterochoromic iridocyclitis	Y/N
Vogt/Koyanagi-Harada Syndrome	Y/N		

Fig. 2.1 (continued)

(d) Have you had any of the following symptoms in the past year? PLEASE CIRCLE YES or NO

GENERAL			
Chills	Y/N	Fevers (persistent or recurrent)	Y/N
Night Sweats	Y/N	Fatigue	Y/N
Poor appetite	Y/N	Unexplained weight loss	Y/N
HEAD			
Frequent headaches	Y/N	Fainting	Y/N
Numbness/tingling	Y/N	Paralysis in parts of your body	Y/N
Seizures or convulsions	Y/N		
EARS			
Hard of hearing or deafness	Y/N	Ringing or noises in your ears	Y/N
Frequent or severe ear infections	Y/N	Painful or swollen ear lobes	Y/N
NOSE AND THROAT			
Sores in your nose or mouth	Y/N	Severe or recurrent nosebleeds	Y/N
Frequent sneezing	Y/N	Sinus trouble	Y/N
Persistent hoarseness	Y/N	Tooth and gum infections	Y/N
SKIN			
Rashes	Y/N	Skin Sores	Y/N
Sunburn Easily	Y/N	White patches of skin or hair	Y/N
Loss of hair	Y/N	Tick or insect bites	Y/N
Painfully cold fingers	Y/N	Severe Itching	Y/N

RESPIRATORY			
Severe or frequent colds	Y/N	Constant coughing	Y/N
Coughing up blood	Y/N	Recent flu or viral infection	Y/N
Wheezing or asthma attacks	Y/N	Difficulty breathing	Y/N
BLOOD			
Frequent or easy bruising	Y/N	Frequent or easy bleeding	Y/N
Have you had a blood transfusion?	Y/N		
GASTROINTESTINAL			
Trouble swallowing	Y/N	Diarrhea	Y/N
Bloody stools	Y/N	Stomach ulcers	Y/N
Jaundice or yellow skin	Y/N		
BONES AND JOINTS			
Stiff joints	Y/N	Painful or swollen joints	Y/N
Stiff lower back	Y/N	Stiff lower back	Y/N
Other back pain	Y/N	Musde aches	Y/N
GENITOURINARY			
Kidney problems	Y/N	Bladder trouble	Y/N
Blood in your urine	Y/N	Urinary discharge	Y/N
Genital sores or ulcers	Y/N	Prostatitis	Y/N
Testicular pain	Y/N		

Table 2.2 Uveitic diseases by demographics

History	Related conditions
Age	
• Age < 5	• Juvenile arthropathies, masquerade (retinoblastoma, juvenile xanthogranuloma)
• Age 5–25	• Juvenile arthropathies, post-viral neuroretinitis, parasitic (e.g., toxocariasis), TINU, masquerade (retinoblastoma, juvenile xanthogranuloma), sarcoidosis, acute retinal necrosis, HLA-B27, toxoplasmosis, Fuch's uveitis
• 25–45	• HLA-B27, CMV retinitis, acute retinal necrosis, ankylosing spondylitis, Behcet's, Vogt Koyanagi Harada's (VKH), sarcoidosis, toxoplasmosis, serpiginous choroidopathy, white dot syndromes, idiopathic
• 45–65	• HLA-B27, Behcet's, birdshot retinochoroiditis, serpiginous choroidopathy, idiopathic
• >65	• Serpiginous choroidopathy, masquerade syndromes (lymphoma), herpes zoster, idiopathic
Gender	
• Male	• Ankylosing spondylitis, reactive arthritis, Behcet's, sympathetic ophthalmia
• Female	• Juvenile arthropathies
Race/ancestry	
• Caucasian	• Ankylosing spondylitis, reactive arthritis
• African American	• Sarcoidosis
• Asian	• VKH, Bechet's
• Central/South America	• Toxoplasmosis, cysticercosis, onchocerciasis
Social history	
• Endemic location	• Histoplasmosis, tuberculosis, toxoplasmosis, Lyme
• Tick/insect or water borne	• Leptospirosis, treamtode granulomas, Lyme
• Animal exposure	• Toxoplasmosis, toxocariasis, leptospirosis, cysticercosis
• Immunosuppresion	• HIV, opportunistic infections

Table 2.3 Conditions causing granulomatous inflammation

Sarcoidosis
Sympathetic ophthalmia
Vogt-Koyanagi-Harada syndrome
Syphilis
Tuberculosis
Herpetic
Uveitis associated with multiple sclerosis
Intraocular foreign body

accumulation of inflammatory cells on or within the iris is more commonly seen with diseases causing granulomatous inflammation (see Table 2.3). Heterochromic iris changes are often, but not always, observed in Fuch's heterochromic uveitis.

Retinal/Choroidal findings—The diagnosis of posterior uveitis may be recognizable clinically based on vascular and chorioretinal lesion characteristics. Ocular imaging techniques such as fluorescein angiogram are essential in characterizing these changes. Pattern recognition is important and a few key findings may be seen more commonly with specific diagnosis. Serous retinal detachments are classically associated with VKH syndrome (particularly if bilateral). Dalen-Fuchs nodules (small, discrete, deep, yellow-white chorioretinal lesions) may be associated with VKH and sympathetic ophthalmia. Acute retinal necrosis (ARN) is a type of necrotizing retinitis most commonly caused by herpetic viruses (HSV, VZV). The classic posterior appearance includes vitritis, retinal vascular arteriolitis, and peripheral retinitis. Typically, the retinitis begins as peripheral areas of multifocal retinal yellowing, often flat with scalloped edges. This can eventually progress into confluent whitening extending into the posterior pole. Cytomegalovirus (CMV) retinitis may also be identified clinically and should be suspected in patients that are immunosuppressed. The classic exam findings in CMV retinitis are peripheral or posterior yellow-white lesions that follow the retinal vasculature centripetally, vasculitis with a "frosted branch" appearance, and retinal hemorrhages. This constellation of findings has been described as a "scrambled eggs or cottage cheese with ketchup" appearance. There may be little to no vitritis, given the immunocompromised state of these patients. Classic toxoplasmosis lesions present as focal and white with overlying vitritis with a "headlight in the fog" appearance, often with adjacent pigmented retinochoroidal scarring. Other diagnosis that may be clinically identifiable include white dot syndromes, ocular histoplasmosis syndrome, and serpiginous choroidopathy.

Optic Nerve—Disc hyperemia, papillitis or papilledema can occur in many uveitic disorders, However, classically prominent disc hyperemia is noted in VKH.

Principles of Diagnostic Testing

As emphasized above, all testing should be complementary to the history and exam, not an alternative. Patient work-up should focus on ruling out infectious diseases that may respond to antimicrobial therapy and systemic disorders that may affect the patients overall health.

It is important to understand several key concepts when discussing diagnostic testing. Knowing how pre- and post-test probabilities and predictive values change based on Bayesian principles can help direct when a test should be ordered. Additionally, the utility of each test can be clarified by acknowledging the difference between targeted versus screening tests as well as understanding when different tests are helpful for ruling in disease versus ruling out disease.

Pre-test probability is defined as the likelihood that a patient has the disease in question prior to testing. It can be estimated based on history, exam, the incidence of disease in the population, and the sensitivity and specificity of the test (see Fig. 2.2). To illustrate how this value changes from patient to patient we will use the example of a male patient with no risk factors, from a non-endemic area presenting with intermediate uveitis. The clinician is considering sending Lyme testing (specificity 50–95 %, sensitivity 99–100 % [24, 25]). For purposes of

$$\text{Post-test probability} = \frac{\text{Pretest probability x sensitivity}}{\text{(Pre-test probability x sensitivity) + (1-pretest probability)(1-specificity)}}$$

Fig. 2.2 Post-test probability formula

this illustration we will say the overall incidence for the patient's geographic location is 1:1000. The patient has no risk factors on history and no other findings on exam so we would estimate the pre-test probability to be approximately 1:1000 (0.1 %). Using a specificity and sensitivity of 90 %, we can calculate the post-test probability using the formula in Fig. 2.2. This calculation estimates the post-test probability as only 0.9 %. In other words, if this patient's serology testing came back positive, there would still only be a 0.9 % chance of having Lyme disease and ultimately a positive value may be misleading. Testing may likewise be unhelpful if the pre-test probability is very high (i.e., the patient recently went hiking in the northeast, was bitten by a tick, and has a new "bulls-eye" rash). In this case, the post-test probability would nearly equal the pre-test probability. This also makes the test minimally useful as the patient would likely receive treatment regardless of the results.

Positive predictive value defines the likelihood that a person with a positive test has the disease in question. It is a function of the test itself and is also dependent on disease prevalence in the population being tested. Thus, if a test is performed on a population with a very low prevalence of disease, the positive predictive value declines substantially. The alternative is true, the more prevalent the disease, the more likely a positive test accurately indicates that the patient has the disease in question (high positive predictive value). An example of this can be demonstrated with tuberculosis testing. In the general population of the United States, tuberculosis accounts for 0.1–0.5 % of uveitis cases [26–29]. The reported sensitivity and specificity of purified protein derivative (PPD) ranges from 75–89 % and 85–86 %, and for Quantiferon-gold 70–81 %, 97–99 % [27–30], respectively. If all patients are screened for tuberculosis, the positive predictive value is 1 % for the PPD test and 11 % for Quantiferon-gold [26, 27]. However, in a patient from an endemic area with exam findings concerning for possible tuberculosis (e.g., differential of serpiginous choroiditis vs. serpiginous-like choroiditis) the positive predictive value of the PPD and Quantiferon-gold increase to 82 and 96 %, respectively [1, 31]. Thus the utility of each test can vary remarkably based on which patients are tested. The same concept applies when defining disease by anatomical location of the inflammation (see below). For example, the utility of HLA-B27 testing in a patient with bilateral posterior uveitis is poor and a positive test would confuse the diagnostic picture and likely represent a false positive (can be positive in up to 8 % of Caucasians and 4 % of African Americans [32]) and should, in general, be performed only in patients with acute, recurrent anterior uveitis. Likewise, positive HLA-A29 or toxoplasmosis testing will likely represent false positivity in a patient with anterior uveitis and should generally be restricted to selective cases with posterior uveitis. Table 2.4 illustrates how positive predictive values are affected by disease prevalence.

Targeted versus Screening tests—After addressing the importance of a focused or targeted laboratory work-up, it is important to acknowledge that there are a few infectious uveitic diseases that cannot be defined by their clinical findings and may present in various anatomical locations. These are important to

Table 2.4 The affect of disease prevalence on positive predictive value

Disease prevalence (%)	Positive predictive value (%)
1	16
10	68
20	83
50	95

Modified from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2636062/

highlight as they are not treated with immunomodulators, and if left untreated can lead to a poor visual and in some cases systemic prognosis. Generally, these diseases include Lyme disease, syphilis, and tuberculosis. The appropriate timing for Lyme testing can be elicited by the patient's history and risk factors, and thus should not be ordered on every patient. We do, however, suggest that it may be warranted to send a screening syphilis test on all patients requiring laboratory work-up. Although this infection is rare, the incidence of primary and secondary disease has doubled in the US since 2000 [33]. Screening is warranted given that risk factors may be difficult to illicit, testing is inexpensive and very sensitive and specific, it is easily treatable, and there is significant morbidity associated if left untreated. There are differing opinions on whether or not tuberculosis testing should be sent as a screening test on all patients. Rosenbaum et al. [26] concluded that routine screening in the general US population with purified protein derivative (PPD) is not warranted based on the low positive predictive value. Hong et al. [34] more recently suggested that screening in certain geographic areas in the US that are known to have a large immigrant population (such as the Los Angeles County hospital cited in the study) may be useful. It is important to highlight that in the latter study the only risk factor found to significantly predict PPD positivity was a history of being born outside of the United States. Thus, a thorough history may help guide the decision about screening for tuberculosis. In practice, many uveitis specialists advocate for screening tuberculosis testing citing the importance of confirming negativity prior to starting systemic immune modulation therapy, especially if an anti-TNF (anti-Tissue Necrosis Factor) medication may be utilized [35].

Several non-specific tests may also be appropriate as screening tools. A complete blood count (CBC) with differential may be useful for identifying more urgent diagnosis such as patients with systemic infection (leukocytosis or eosinophilia), malignancy (leukemia), or who are immunocompromised. Likewise, a comprehensive metabolic panel (CMP) and urinalysis (UA) may reveal renal or hepatic dysfunction or hyperglycemia. This information may also be important when making decisions about starting oral immunomodulators.

Tests that rule in disease versus ruling out disease—In some cases, a test being negative may be just as important as positive testing. An example is seen with toxoplasmosis titers. A positive value does not mean a patient has toxoplasma retinochoroiditis, since nearly 30 % of the population may have been exposed to toxoplasma at some point in their life. Specifically, seropositivity in the US has been reported as >20 % (higher in males, nonhispanic blacks, those not born in the US, elderly) [36, 37]. In contrast, a negative test is sensitive for the exclusion of toxoplasmosis. HLA-A29 is another test that, if negative, may be helpful in ruling out Birdshot chorioretinopathy in patients with multiple white chorioretinal lesions.

Individual Tests

We will now briefly review the sensitivities and specificities of commonly ordered diagnostic testing. It is important to keep in mind the above concepts that despite sensitivity and specificity, the utility of each test may vary greatly dependent on the patient's risk factors, population prevalence, and exam findings. A summary of the discussed tests including their estimated costs, sensitivities, and specificities can be found in Table 2.5. Additionally, it is important to note that much of the research regarding sensitivity and specificities of the following tests are based on non-ophthalmologic literature.

Laboratory

Tuberculin Skin Test and Interferon Gamma Release Assays

Tuberculin is a glycerol extract derived from the precipitate of sterilized, concentrated cultures of the tubercle bacillus. The skin test, also known as the purified protein derivative (PPD), or Mantoux

Table 2.5 Summary of important testing modalities

Test	% Positivity (in uveitis patients)	[a]Estimated cost	Sensitivity/specificity disease prevalence dependent	Possible indications
Tuberculin skin test	0.2–1 %	$18	75–89 %/85–86 %	Tuberculosis, immunomodulatory therapy
Interferon gamma release assay—*Quantiferon-gold*		$243	70–81 %/97–99 %	Tuberculosis, immunomodulatory therapy
Lyme serology	Geographic dependent	$56-screening $193-confirmatory	59–99 %/81–100 %[b]	Lyme disease
Angiotensin converting enzyme	3-7 %	$56	60–90 %/83–95 %[d]	Sarcoidosis
Lysozyme		$75	60 %/76 %	Sarcoidosis
Antinuclear antibodies	0.1–1 %	$48	95 %/68–97 %[e]	JIA, vasculitis, connective tissue disease
VDRL	1.6–4.5 %	$27	Primary 78–86 %/85–99 % Secondary 100 %/85–99 % Tertiary 95–98 %/85–99 % Neurosyphilis/ocular 69 %/85–99 %	Syphilis
FTA-ABS		$60	Primary 84 %/96 % Other stages 100 %/96 %	Syphilis
HLA-B27	50–80 % of acute anterior uveitis	$105	99 %/99 %	Seronegative spondyloarthropathy
Complete blood count		$27		Overall health, immunomodulatory therapy, masquerade syndromes
Complete metabolic panel		$92		Overall health, immunomodulatory therapy, sarcoidosis, masquerade syndromes
Urinalysis		$40		Vasculitis, TINU
Chest X-ray—*Sarcoidosis*		$156[c]	79 %/99 %	Sarcoidosis, tuberculosis, Wegener's
Chest X-ray—*Tuberculosis*		$156[c]	86.8 %/89.4 %	
Chest computed tomography—*Sarcoidosis*		$975[c]	85–95 %/53 %	Sarcoidosis
Magnetic resonance imaging—head		$2,785[c]		Multiple sclerosis, CNS lymphoma, cysticercosis
Gallium scan		$695[c]		Sarcoidosis

[a]Estimated from the Lahey clinic laboratories 2009–2014. These are charges and do not reflect what may be collected. Radiologic datat from 2009

[b]Dependent on when in the disease course the tests were done

[c]Professional fee included

[d]Depdendent on active versus inactive disease

[e]Dependent on titer values used—note very low positive predictive value (<1 %)

Table 2.6 Positivity classification of the tuberculin skin test reaction

Diameter of induration	Persons for whom reaction is considered positive
Induration of ≥5 mm	HIV infected, recent contact of person with TB, fibrotic changes on X-ray consistent with prior TB, immunosuppressed (history of organ transplant, taking the equivalent of >15 mg/day of prednisone for ≥1 month; taking TNF-α antagonists)
Induration of ≥10 mm	Recent immigrants (<5 years) from high prevalence countries, Injection drug users, Nursing home/correctional facility residents and employees, healthcare workers, Mycobacteriology laboratory personnel, Age >70 or <18 years old, medical condition associated with increased TB risk (diabetes, corticosteroid use, gastrectomy, malabsorption, silicosis, malnutrition)
Induration of ≥15 mm	All others

Modified from Centers for disease control, tuberculosis, publications and products, fact sheets testing & diagnosis, tuberculin skin testing, classification of the tuberculin skin test reaction. Available at http://www.cdc.gov/tb/publications/factsheets/testing/skintesting.htm

skin test, is performed when tuberculin is injected intradermally and then skin induration is measured at 24–48 h based on a host type IV Hypersensitivity reaction. The extent of skin induration indicates test positivity (see Table 2.6). It is important to note that certain conditions can suppress this reaction leading to false negative results (see Table 2.7). The test was established in 1908 and remained the foremost means of screening for tuberculosis for nearly a century. In 2005, the CDC released guidelines for use of FDA approved interferon gamma release assays. These tests are ELISA assays that measure the interferon gamma produced when the patient's peripheral blood leukocytes are purified and mixed with three different tuberculosis antigens from a whole blood sample. There are currently two FDA approved tests, the Quantiferon TB-gold test, and the T-SPOT TB test. A recent head-to-head prospective study demonstrated the Quantiferon TB-gold test to be more specific but slightly less sensitive than the T-SPOT TB [38, 39]. However, the Quantiferon test was significantly more accurate in identifying true-positive tuberculous uveitis than T-SPOT TB in discordant cases (98 % vs. 76 %) [39]. The Quantiferon-gold is more readily available and used more extensively in the US. Latent versus active TB cannot be differentiated from a positive result for skin testing or for ELISA assays. It is not recommended that these be used as the sole method for diagnosis. Microbiologic sampling remains the gold standard for diagnosis. However, culture or tissue sampling is often difficult to obtain in an ocular specimen and analysis may be limited in its availability.

Table 2.7 Conditions that suppress PPD hypersensitivity reaction

Infectious mononucleosis
Live virus vaccine—if given within 3 weeks of testing
Sarcoidosis
Hodgkin's disease
Corticosteroids/immune suppression
Malnutrition
Upper respiratory tract infection

There are certain limitations to both the tuberculin skin test and ELISA assays. Skin testing is limited by poor inter-reader reliability (e.g., 9 mm negative vs. 10 mm positive), low specificity (e.g., prior BCG vaccination), poor predictive value in low prevalence populations (see example mentioned above), and it requires patient reliability to return to read the test. Thus, interferon gamma release assays may be more useful for poorly reliable patients or immigrants from endemic areas that may have a false positive PPD from previous BCG vaccination. There

are conflicting reports about the sensitivities and specificities of purified protein derivative versus Quantiferon-gold. Reported sensitivities and specificities range from 75–89 % and 85–86 % for the PPD test and 70–81 %, 97–99 % for Quantiferon-gold, respectively [27–30]. Another recent study by McMullen et al. indicates that in the correct population, PPD screening is still highly specific with a specificity of 99.7 % versus 91.4 % for Quantiferon-gold ($p < 0.0001$) [40]. Cost continues to be an important disparity between these two screening methods. One study focusing on the cost-effectiveness of Quantiferon versus PPD measured the number of averted TB cases in two years. This study estimated the cost for the screening of latent TB and treatment of a hypothetical cohort to be $16,021 per averted case for PPD versus $227,977 per averted TB case for Quantiferon [41].

As mentioned above, the role of tuberculosis testing as a screening tool for all patients is debated among uveitis specialists. Given the varied population presenting at our clinic, it is generally our practice to selectively send this as a screening test for patients with intermediate or posterior/panuveitis, any patient with suggestive exposure history or risk, and those we are anticipating the initiation of systemic immune modulation therapy (especially with TNF alpha inhibitors).

Syphilis Testing (Non-specific and Specific)

Syphilis is rarely diagnosed by dark field microscopy or immunofluorescence from a tissue biopsy. Thus, the mainstays of testing are specific (direct) and non-specific (indirect) treponemal antibody tests. Indirect tests such as the Venereal Disease Research Laboratory (VDRL) and rapid plasma reagin (RPR) measure IgG and IgM antibodies directed to cardiolipin that is released during cellular damage that occurs during active infection. These antibodies are not specific for *Treponemal pallidum*. These tests typically become non-reactive with time and following adequate treatment. The sensitivities for the indirect tests for syphilis are reported to be 78–86 % for detecting primary syphilis, 100 % for detecting secondary syphilis, and 95–98 % for detecting tertiary syphilis [42]. Sensitivity, however, decreases significantly for detection of neurosyphilis to 69 % [43]. Specificity ranges from 85 to 99 %. False positives can be seen with systemic lupus erythematosus, biliary cirrhosis, rheumatoid arthritis, pregnancy, intravenous drug use, advanced malignancy, tuberculosis, malaria, Lyme, HIV, hepatitis, viral diseases. Confirmation for any positive or equivocal non-treponemal test result are traditionally followed with a specific or direct treponemal test, such as the fluorescent treponemal antibody absorption (FTA-ABS), quantitative VDRL/RPR, microhemagglutination assay *T. pallidum* (MHA-TP), *T. pallidum* hemagglutination (TPHA), or *T. pallidum* particle agglutination (TPPA) test. Direct treponemal tests detect antibodies specific to *T. pallidum* (and a few other treponemal subspecies that are rarely seen in the US). This test stays reactive for life and indicates that infection has occurred but does not distinguish active versus latent or treated infection. Thus, a positive direct test will indicate whether the patient has been exposed to syphilis in the past and a positive indirect test such as the RPR or VDRL will indicate active untreated infection. FTA-ABS is the most commonly used confirmatory test following positive VDRL or RPR test findings. FTA-ABS has a sensitivity of 84 % for detecting primary syphilis infection and almost 100 % sensitivity for detecting syphilis infection in other stages. Its specificity is 96 % [42]. Possible causes for a positive direct test and negative indirect are latent syphilis, previously treated infection, neurosyphilis, or false positive direct test.

Of note, it has been reported that nearly 30 % of ocular syphilis cases test negative to non-specific testing [44]. Thus, we strongly advocate using direct testing for initial screening. Many laboratory protocols have been trending toward this approach as well. Treponemal Enzyme Immunoassays (EIA) are a type of automated direct treponemal test, where reactive results are subsequently followed by indirect

testing. Reports indicate that this approach is highly cost effective, slightly decreases the sensitivity, but improves specificity [45–47]. This protocol is now the standard at many academic laboratories, including ours. Ophthalmologists should become familiar with their local laboratory testing algorithm for syphilis, so if needed, it can be specified that you would like direct testing done first.

It is our practice to send for syphilis testing on all patients with uveitis (excluding HLA-B27 positive anterior uveitis—*see targeted versus screening* section above).

Lyme Testing

The most accepted laboratory analysis for Lyme disease is based on a two-step approach. The first screening test is a serology test looking at serum IgG and IgM antibodies. The host antibody response to *B. burgdorferi* infection develops slowly so both the IgG and IgM antibodies take weeks to appear (2–4 weeks and 4–6 weeks, respectively). Thus, if serology alone is performed early in the disease course the sensitivity and specificity are 59 and 93 %, respectively [24]. Considering this delayed response, if suspicion for infection is high, tests may need to be repeated later in the disease course for confirmation. If testing is performed after 2–4 weeks the sensitivity and specificity increases to 95 and 81 %, respectively [24]. The two-step approach recommended by the CDC describes that positive or indeterminate serologies should be followed by a Western blot test [25]. This approach increases specificity to 99–100 % [24, 25]. It is worth emphasizing again the importance of pre- and post-test probabilities with this disease in particular as there are rather well defined endemic areas within the US (see Fig. 2.3). Despite the two-step testing approach the guidelines for the diagnosis of Lyme disease as described by the American College of Physicians is based primarily on clinical findings [24]. More recent tests have been developed in an effort to obviate the need for western blot confirmatory testing. Two of these tests include the C6 and VlsE antibody tests. These detect both IgG and IgM antibodies specific to portions of the *B. burgdorferi* organism. There are several advantages to the use of these newer tests, including no interference in patients who have been vaccinated with the available Lyme antigen, detection of antibodies to the European strains of *B. burgdorferi*, and high specificity [48, 49]. These tests currently are not widely available and have limited clinical data.

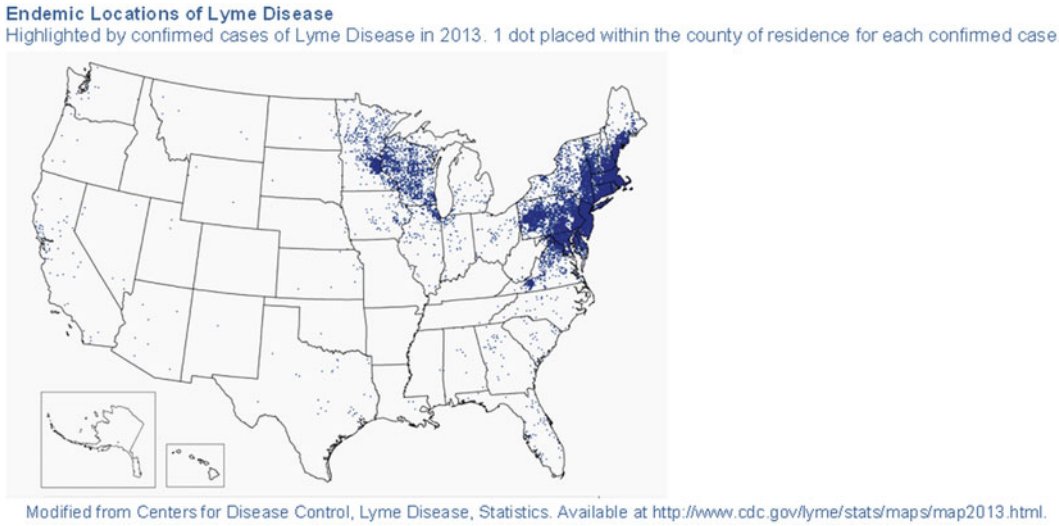

Fig. 2.3 Endemic locations of Lyme disease

Angiotensin Converting Enzyme and Lysozyme

Angiotensin converting enzyme is secreted in the lungs and kidneys by the pulmonary endothelium and activated macrophages (epithelioid cells). Measurements of serum ACE may be elevated in multiple systemic disorders (see Table 2.8). It is proposed that the elevation of ACE in sarcoidosis specifically, is related to the abundance of epithelioid cells and macrophages in sarcoid granulomas. In addition to ACE, sarcoid granulomas also secrete lysozyme, glucuronidase, collagenase and elastase. Despite certain limitations, elevated ACE levels have been found to be a useful *adjunct* to the diagnosis and assessment of disease activity and management of sarcoidosis. Reference values for serum ACE is age dependent and it is important to note that healthy children have ACE levels that are 40–50 % higher than adults [50]. The sensitivities have been reported with a rather broad range of 59 % for inactive disease and 60–90 % in active disease [51, 52]. Specificity ranges from 83 to 95 % [53, 54]. In one report, the sensitivity increases to 85.9 % when looking only at patients with a clinical suspicion of sarcoidosis and 92.1 % if only those with a known diagnosis of sarcoidosis are included [29]. Reports specifically focusing on patients with uveitis found sensitivities of 73–84 % and specificities of 83–95 % but with a predictive value of 47 % [54, 55].

Table 2.8 Conditions causing elevated serum ACE levels

Asbestosis
Beryllium disease
Coccidioidomycosis
Diabetes mellitus
Gaucher disease
Hodgkin disease
Hypersensitivity pneumonitis
Hyperthyroidism
Leprosy
Lung cancer
Primary biliary cirrhosis
Sarcoidosis
Silicosis
Tuberculosis

Lysozyme, like ACE is an enzyme produced by epithelioid cells, giant cells, and macrophages found in granulomas. It is often increased in the serum and tears of sarcoid patients. Serum levels are age dependent with levels increasing with age above 60 years. Levels may also be increased in patients with kidney dysfunction. Baarsma et al. found a sensitivity of 60 % and a specificity of 76 % and a mean predictive value of only 12 % in patients with uveitis [54]. This test should not be used in isolation, as it has poor sensitivity and specificity. However, this test may be a useful adjunctive test when combined with serum ACE, where the predictive value when both are positive will be over 70 %.

It is important to note that in patients suspected of having sarcoidosis, other than with tissue confirmation of sarcoidosis (see Tissue Sampling), there are no definitive diagnostic blood, skin, or radiologic imaging tests specific for this disorder and the diagnosis is made based on a constellation of findings [56].

Antinuclear Antibodies and Rheumatoid Factor

In our experience, antinuclear antibodies (ANA) and rheumatoid factor (RF) represent two of the most frequently ordered, and least helpful tests for a "uveitis work-up". These tests are not helpful for most uveitic diseases. The exception to this is pediatric cases where JIA is suspected (particularly female patients, typically ANA positive and RF negative). In cases of the pediatric patient with pauciarticular arthritis, a positive ANA may help assess the patient's risk for uveitis [57]. It is also important to review that rheumatoid arthritis appears to have a correlation with scleritis and episcleritis but essentially no correlation with uveitis. Thus, RF should typically not be ordered on any adult with uveitis. As with the other testing described above, the sensitivity and specificity of ANA varies greatly depending on the pre-test probability of the

Table 2.9 Conditions causing elevated serum ANA

Hashimotos thyroiditis
Graves disease
Autoimmune hepatitis
Primary biliary cirrhosis
Primary autoimmune cholangitis
Idiopathic pulmonary arterial hypertension
Infectious mononucleosis
Hepatitis C
Subacute bacterial endocarditis
Tuberculosis

population being evaluated. Levels of ANA may be elevated in a number of systemic disorders (see Table 2.9).

The specificity of ANA testing has been reported to range from 68 to 97 % (dependent on titer levels) [58]. Based on the high false positive rates among healthy individuals, ANA testing is not recommended as a *screening* test for autoimmune disorders. When applying the use of ANA testing to the disease prevalence seen in uveitis patients, Rosenbaum et al. found that patients with uveitis and a positive ANA have <1 % chance of having systemic lupus erythematosus (SLE). Thus, it is important to emphasize that even in patients with uveitis and *positive* ANA the chance of then having an underlying systemic diagnosis of SLE is <1 %. Thus, the utility of this test in the work-up of uveitis is very limited [26].

Less Frequently Used Laboratory Tests

Based on the clinical presentation, some less common laboratory tests should be considered. Urinary β2-microglobulin may be of value in detecting tubulointerstitial nephritis and uveitis syndrome (TINU) and should be considered in pediatric and young patients presenting with acute anterior uveitis [59]. Bartonella henselae should be considered in patients with a history of a cat scratch or significant cat exposure, especially when presenting with neuroretinitis [60].

Molecular

HLA-Typing

Several uveitic diseases have been found to be associated with specific human leukocyte antigen types (see Table 2.10). The most studied antigen type is HLA-B27. It has been shown that patients with recurrent, acute unilateral, alternating

Table 2.10 HLA associations in uveitic disease

Disease	HLA association
Acute anterior uveitis	HLA-B27
Reactive arthritis	HLA-B27
Juvenile idiopathic arthritis	HLA-DR, Dw2
Behcet syndrome	HLA-B51
Birdshot retinochoroiditis	HLA-A29
Intermediate uveitis	HLAB8, B51, DR2, DR15
Sympathetic ophthalmia	HLA-DR4
VKH syndrome	HLA-DR4
Sarcoidosis	HLA-BA, B13
Multiple sclerosis	HLA-B7, DR2
Ocular histoplasmosis syndrome	HLA-B7, DR2
Retinal vasculitis	HLA-B44

Modified from Intraocular inflammation and uveitis, basic and clinical science course, 2003–2004. American Academy of Ophthalmology, 2003. p. 92

anterior uveitis have nearly an 80 % chance of being HLA-B27 positive [61]. Of those patients that are positive for HLA-B27, 66–75 % will have an associated spondyloarthropathy [62–64]. It has been reported that up to 50 % of these arthropathies are either misdiagnosed or undiagnosed [65]. Thus, HLA-B27 testing may be helpful as an adjunct for the patient's systemic health. Based on the typical presentation of HLA-B27 associated anterior uveitis, this should *not* be ordered for patients with intermediate or posterior disease. As a *diagnostic* test, however, the utility of HLA-typing is limited. This is demonstrated by applying Bayes theorem when using HLA-A29 typing to diagnose Birdshot Chorioretinopathy (BSCR). HLA-A29 has one of the highest associations between HLA type and disease with nearly 85–95 % of BSCR patients being HLA-A29 positive (vs. 4–8 % of the general population) [32, 61]. However, when applied as a screening test in *all* patients with posterior uveitis the positive predictive value is only 47 % [61]. This predictive value would increase if applied to only patients with multiple white chorioretinal lesions. It does, however, and retain high sensitivity (99 %) when applied exclusively to patients with posterior uveitis [61, 66]. Thus, it may be a useful to aid in exclusion of disease. In HLA-types that are not as tightly associated to a specific uveitic disease, the utility for use as a diagnostic test is significantly decreased.

Imaging

Chest X-Ray

Chest radiography is often used as an adjunctive screening test for both sarcoidosis and tuberculosis. Important findings for sarcoidosis include hilar or mediastinal nodal enlargement, interstitial "air-space like" opacities and peripheral cavitation [67]. For tuberculosis, findings include patchy consolidation or poorly defined linear and nodular opacities often located in the posterior or superior segments of the lung [68]. Studies have estimated that 90–95 % of patients with sarcoidosis have pulmonary findings on chest X-ray [69–71]. In one representative study, 8 % of patients presented at radiologic stage zero (no visible changes on plain film chest X-ray), 40 % presented at stage 1 (bilateral hilar lymphadenopathy), and 37 % present at stage 2 (bilateral hilar lymphadenopathy and diffuse pulmonary infiltration) [69]. The utility of the chest X-ray for sarcoid has been well established and the reported sensitivity is 79 % [72, 73]. It is important to note, however, that these estimates may have a selection bias for patients that were ultimately diagnosed with pulmonary sarcoid. In our experience, it is not uncommon for patients to present with extrapulmonary sarcoidosis (uveitis) and have an unremarkable chest X-ray.

A review looking at chest X-ray as an additional screening tool for active tuberculosis (specifically reporting "abnormalities suggestive of TB"), estimated sensitivity and specificity as 86.8 and 89.4 %, respectively [74]. When comparing chest X-ray and symptoms (e.g., prolonged cough) in parallel, the sensitivity was improved by 0–9 % and specificity by 2–5 % [74]. It is important to recognize, however, that most cases of ocular TB from paucibacillary or miliary disease are not accompanied by pulmonary findings. Thus, positive testing in a patient with suspicious ocular findings but a negative chest X-ray does not rule out TB infection. In such cases appropriate tissue sampling through culture or PCR analysis (e.g., anterior chamber or vitreous sampling) should be considered.

Chest Computed Tomography

Computed tomography is a more sensitive but less specific modality for detecting mediastinal lymphadenopathy in sarcoid patients, particularly in the elderly [75]. Some studies suggest that chest computed tomography (CT) may not add significant additional clinical information for the initial diagnosis of sarcoidosis and is generally not a helpful adjunctive test [76]. However, one

study looking specifically at elderly women with chronic uveitis found a chest CT useful in identifying mediastinal lymphadenopathy and helped to guide tissue confirmation [77]. According to the American Thoracic Society, European Respiratory Society, and the World Association of Sarcoidosis and Other Granulomatous Disorders, chest CT can be justified in the following circumstances: 1—Atypical clinical and/or chest radiograph findings, 2—normal chest radiograph but a strong clinical suspicion of the disease, 3—Detection of complications of the lung disease [78, 79]. Additional limitations of this modality include significant cost and radiation exposure. The typical chest CT will expose the patient to 2 millisieverts (mSv) of radiation versus the 0.05 mSv of a chest X-ray. Thus, a chest CT should be used as an adjunctive test only if it will impact a patient's systemic health or the treatment paradigm.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) of the brain may be warranted in the work-up of uveitis in very select cases. Examples may include patients (particularly elderly) in whom CNS lymphoma is suspected. Additionally, for the evaluation of intermediate uveitis in a patient with other neurologic symptoms concerning for possible multiple sclerosis (e.g., numbness, tingling, weakness, muscle spasms), MRI of the brain and neurologic consultation should be considered. This is particularly important given recent data suggesting that early initiation of disease-modifying therapy may improve prognosis and reduce neurologic damage [80].

Tissue Sampling

Polymerase Chain Reaction

The polymerase chain reaction is an important biologic test that is used to amplify an infinitesimal amount of sampled DNA into analytic quantities. This test utilizes thermal cycling, where the nucleic acid sequence is repeatedly heated and cooled, allowing replicating enzymes and primers to exponentially amplify the sequence. This test provides a method for minimally invasive tissue sampling through aqueous and vitreous extraction. The sensitivity of PCR for the detection of DNA is astounding and estimated to be nearly 1×10^{-21} molar [81]. This sensitivity also leads to a potential pitfall of false positivity with amplification of contaminated samples. Indications for PCR testing include media opacity, irregular or unanticipated disease course, disease unresponsive to therapy, or diagnosis confirmation. This test should also be considered when viral or fungal retinitis is suspected where the typical yield of culture alone is poor or results may be delayed. Much of the utility of sampling depends on laboratory handling. Generally, approximately 0.05 cc of fluid is required for analysis, which should be placed immediately on ice, followed by freezing on dry ice, then sent to a PCR laboratory. Improper handling can lead to false negative or positive results. A list of organisms available for PCR analysis can be seen in Table 2.11. The broad utility of PCR testing is still under investigation. Rothova et al. examined the usefulness of aqueous humor analysis for the diagnosis of posterior uveitis. In their report, 29 % of patients had positive PCR results to at least one diagnostic assay and 24 % of patients required a change of treatment based on their assay findings [82]. Additional studies have shown that PCR diagnostic testing correlates with improved clinical outcomes [83, 84]. Given that PCR analysis may be costly and not widely available, alternative methods for DNA amplification are currently being explored [85].

Table 2.11 Organisms available for testing by PCR

Viral: CMV, HSV, VZV, EBV, HIV, HTLV-1, Rubella, HHV-6, HHV-8
Bacteria: All (using 16S ribosomal DNA sequencing)—including TB
Protozoans: *Toxoplasma gondii, Oncocerca*
Fungi: All (using 18S/28S ribosomal DNA sequencing)

Biopsy/Cytology

Tissue biopsy accompanied with cytologic examination plays an important role in the diagnosis of specific uveitic entities. Examples of important biopsy and sampling procedures that may be utilized include anterior chamber paracentesis, vitreous tap and diagnostic vitrectomy, iris and ciliary body biopsy, choroidal and retinochoroidal biopsy and fine needle aspiration biopsy. Given the invasive nature of this testing, indications are often limited to clinical presentations suspicious for vision or life threatening etiologies, diseases with an unanticipated course, or that are unresponsive to therapy. These may include masquerade syndromes such as leukemia, lymphoma, or metastatic disease. A ratio measurement in the aqueous humor of the cytokines IL-10 (elevated in non-Hodgkins lymphoma) and IL-6 (elevated with intraocular inflammation) show promise as an adjunctive measure for intraocular lymphoma but is currently not widely utilized. Additional indications for sampling and cytology include concern for infectious endophthalmitis, necrotizing retinitis, delayed endophthalmitis, or parasitic uveitis.

Biopsy also plays an important diagnostic role in sarcoidosis with the sample exhibiting non-caseating epithelioid granulomas. The most common biopsy site is to the intrathoracic lymph nodes (transbronchial). Yield of these biopsies have been found to be 60 % in patients with a normal chest X-ray and 90 % if parenchymal disease is present [86]. Conjunctival, lacrimal gland, cutaneous lesions or extrathoracic nodes have also been utilized for diagnosis. The yield of conjunctival and lacrimal biopsies without a discrete lesion is controversial and reports of positive yield range from 10 to 55 %. This has been shown to improve in the presence of follicles, when bilateral biopsies are taken, and when multiplane sectioning techniques are utilized [87–90]. Thus, the yield for biopsy is low if there is no discrete lesion or if there is no other imaging modality indicating infiltration of that tissue (e.g., Gallium-67 scanning may show lacrimal gland uptake and can guide where to biopsy [91]). Our recommendation when considering tissue biopsy for sarcoid is to perform a thorough physical exam and consider biopsy if there is an abnormal lesion.

Suggested Testing Algorithm by Anatomic Classification

As described earlier in the chapter, the SUN working group established an anatomic classification for uveitis in 1987 that was later proposed as being the global standard in 2005. Thus, our classification scheme generally follows this standard. Grouping each uveitic patient into an anatomic class is important when deciding about what and when testing should be ordered. For example, the first episode in a patient with isolated mild to moderate acute anterior uveitis and an unremarkable history generally does not require *any* work-up. Alternatively, patients with intermediate, posterior, or panuveitis should *always* have testing done. The anatomic location will also direct what tests to order. For example, you would not send HLA-B27 testing on a patient with posterior uveitis. Likewise, you would not send HLA-A29 or Toxoplasmosis testing on a patient with isolated anterior uveitis. Possible diagnosis and associated testing based on anatomic classification can be seen in Fig. 2.4a–d and are briefly discussed below.

Anterior uveitis—This includes terms such as iritis, irdocyclitis and anterior cyclitis. We further divide these patients into acute versus chronic and unilateral versus bilateral simultaneous versus bilateral alternating. Common etiologies for anterior uveitis can be seen in Fig. 2.4a. As mentioned above, testing is not necessary in patients with a single episode of mild to moderate anterior uveitis and an unremarkable history. However, in patients with anterior uveitis that is recurrent, bilateral, chronic, granulomatous, associated with a questionable history, or are unresponsive to treatment, additional testing should be considered. Suggested work-up for these patients includes HLA-B27 (if acute unilateral or alternating bilateral). If this test is negative, additional testing may include, syphilis, PPD/Quantiferon-gold, chest X-ray, Lyme titers,

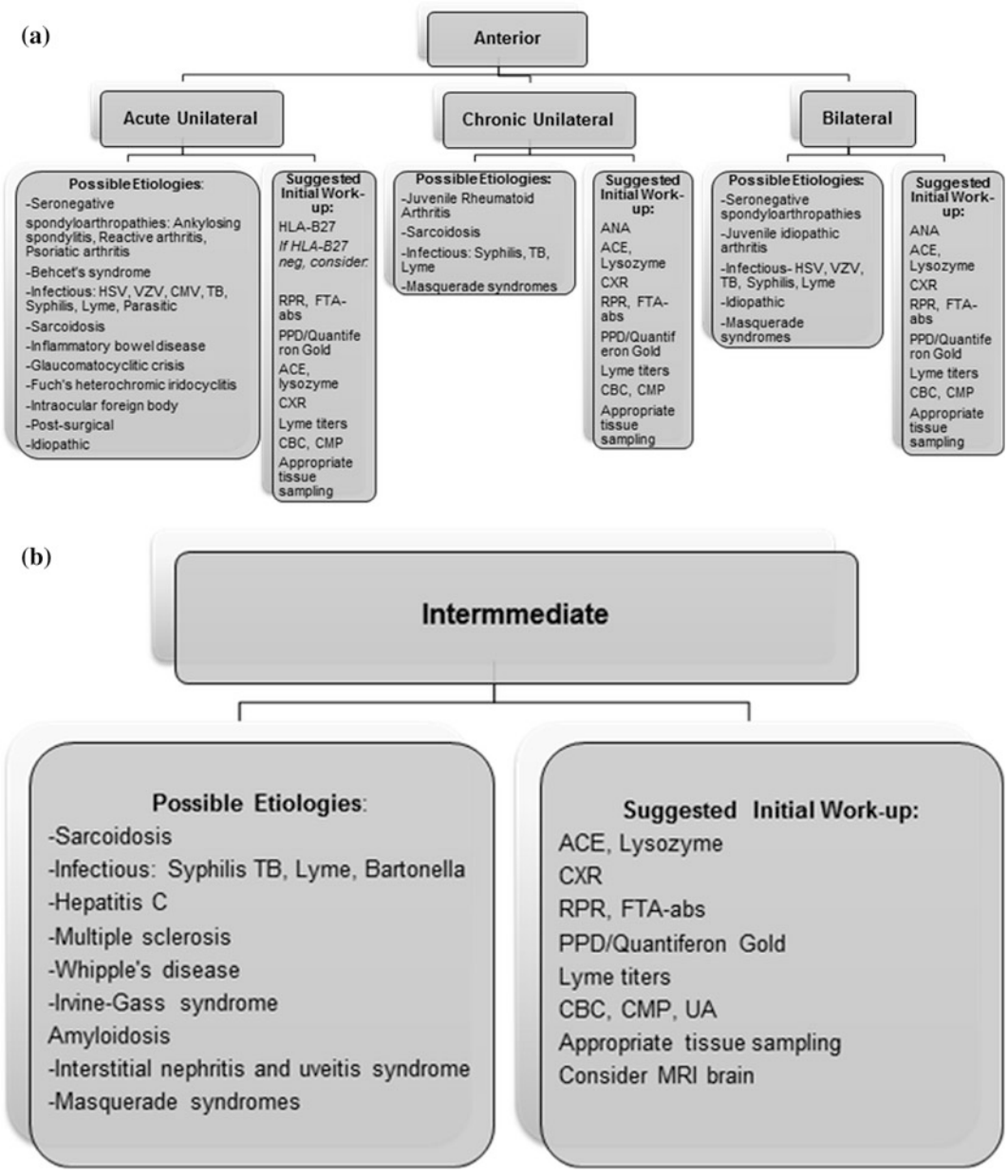

Fig. 2.4 **a–d** Note this is list by no means all-inclusive. *Abbreviations* HSV-herpes simplex virus, VZV-varicella zoster virus, CMV-cytomegalovirus, TB-tuberculosis, VKH-Vogt-Koyanagi-Harada syndrome, HLA-human leukocyte antigen, RPR-rapid plasma reagin, FTA-fluorescent treponemal antibody absorption, ACE-angiotensin converting enzyme, PPD-purified protein derivative, CXR-chest X-ray, CBC-complete blood count, CMP-complete metabolic panel

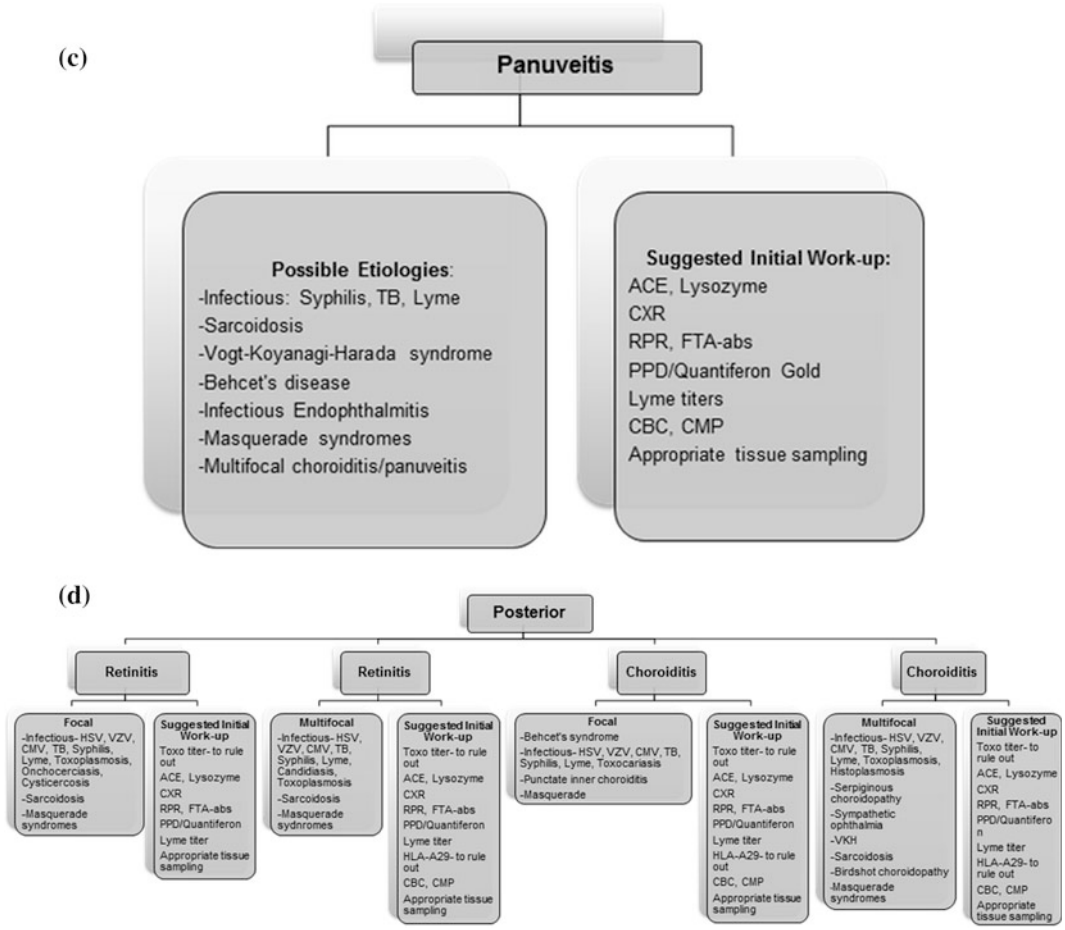

Fig. 2.4 (continued)

ACE and lysozyme levels, CBC, CMP, and appropriate tissue sampling.

Intermediate uveitis—This diagnosis often causes the most confusion among ophthalmologists but is important to identify as these patients may often have an underlying systemic disease. The inflammation in intermediate uveitis primarily affects the vitreous and at times the peripheral retina. Terminology used to describe this inflammation includes pars planitis, posterior cyclitis, vitritis, and hyalitis. Additional terms frequently used to describe aggregates of inflammatory cells in the inferior vitreous and along the pars plana/ora serrata are "snowballs" and "snowbanks", respectively. The most common etiologies are seen in Fig. 2.4b. These patients should always have a work-up that include syphilis and tuberculosis testing, ACE, lysozyme, chest X-ray, CBC, CMP. Other tests to consider based on history and exam include Lyme titers, MRI of the brain (rule out multiple sclerosis), and appropriate tissue sampling.

Posterior and Panuveitis

Many of the entities considered in posterior and panuveitis pose a unique diagnostic challenge in that most of them have no clear etiology and thus no specific applicable laboratory test. Thus, our goal of diagnosis is to rule out entities not treated with immunomodulators (infections and

masquerade syndromes) or other diagnosis that affect systemic prognosis. Pattern recognition and additional modalities such as fluorescein angiography are essential in characterization of these entities. Examples not amenable to laboratory diagnosis include Behcet's, VKH, sympathetic ophthalmia, multifocal choroiditis with panuveitis, white dot syndromes, acute posterior multifocal placoid pigment epitheliopathy, serpiginous choroiditis, punctate inner choroidopathy, and relentless placoid chorioretinitis.

Posterior uveitis—This refers to inflammation limited primarily to the retina and choroid. The potential causes are rather vast, so this category is defined as retinitis, choroiditis; then further divided into focal or multifocal disease. A list of potential causes is seen in Fig. 2.4c. Suggested work-up includes syphilis and tuberculosis testing, toxoplasma titers (primarily to rule out in atypical cases), ACE, lysozyme, chest X-ray, CBC, CMP, UA (if evidence of vasculitis), HLA-A29, and appropriate tissue sampling. Testing for Lyme may be sent based on appropriate history.

Panuveitis—This classification refers to diseases that involve inflammation of all segments of the eye. The most common entities are listed in Fig. 2.4d. Suggested work-up includes syphilis and tuberculosis testing, ACE, lysozyme, chest X-ray, CBC, CMP, UA and appropriate tissue sampling.

Testing for Masquerade Syndromes

Although much less common than other etiologies, each clinician should be vigilant for the exclusion of masquerade syndromes. Non-malignant causes that can mimic uveitic disorders include intraocular foreign body, retinal detachments, myopic degeneration, pigment dispersion syndrome, retinal degeneration, ocular ischemia and drug reactions. Malignant masqueraders include intraocular/central nervous system lymphoma, leukemia, uveal melanoma, metastasis, paraneoplastic syndromes, cancer-associated retinopathy, and retinoblastoma. These syndromes should be considered in patients with concerning systemic symptoms and chronic uveitis that shows minimal response to aggressive medical therapy. Careful history and exam coupled with screening CBC, CMP, UA and appropriate tissue sampling are important steps in appropriately diagnosing these patients.

Particularly, in elderly patient with chronic posterior or panuveitis that shows minimal response to steroid treatment, lymphoma should be considered. Intraocular lymphoma typically occurs as an extension of central nervous system (CNS) lymphoma. Thus, additional appropriate testing would include an MRI of the head and possible lumbar puncture. The gold standard for confirmation, however, is vitreous biopsy for cytology and immunohistochemistry. It is important to confirm that the pathology lab receiving the specimen is familiar with the diagnosis of intraocular lymphoma so appropriate markers can be tested. As mentioned earlier in the chapter, aqueous measurements of IL-10 and IL-6 may be sent as an adjunctive means for diagnosis.

In a child with decreased red reflex and a hypopyon or vitritis clinicians should consider seeding from retinoblastoma. This diagnosis is made primarily by clinical findings, B-mode ultrasonography, and/or CT imaging. Biopsy is contraindicated for fear of seeding the tumor systemically.

Tests of Limited Utility and Additional Testing

There are certain tests that are commonly ordered both by ophthalmologists and non-ophthalmologists that have little to no role in the diagnosis of uveitis. The confusion may lie in separating the work-up for uveitis versus scleritis and peripheral ulcerative keratitis. The latter two entities yield a different differential diagnosis and

Table 2.12 Less common testing for specific clinical scenerios

Disease	Typical findings	Testing
Toxocariasis	Unilateral posterior uveitis in child with history of dog/cat exposure. Posterior pole or peripheral granuloma, often with a grey center and adjacent retinal folds	Serology
Onchocerciasis	Unilateral panuveitis in patient from endemic region, possible visualization of microfilaria in anterior chamber. Distinct skin findings of freely mobile subcutaneous nodules over bony prominences (hips, lower limbs), dermatitis, lymphadenitis, depigmentation	Skin biopsy, Filarial screening Serology
Cysticercosis	Panuveitis with subretinal or vitreal translucent potentially mobile cyst with dense white spot in one region	CBC, Serology, CT/MRI brain
Bartonella	History of exposure to cats, tender regional lymphadenopathy, unilateral exudative optic neuritis with transudation into the macula forming a macular star	Serology, PCR, culture
TINU	Bilateral sudden-onset anterior uveitis in young patient	CBC, CMP, Urinalysis, Non-specific: Beta-2 microglobulin, ANA, Lysozyme, CXR
Isolated retinal vasculitis		CBC, CMP, ANA, complement 3 and 4 levels, urinalysis, Antiphospholipid antibodies, ESR/CRP, Anti-dsDNA, Anti-RoSSA/La/SSB, ANCA

work-up that would include testing for rheumatoid arthritis, granulomatosis with polyangiitis (GPA previously known as Wegener's Granulomatosis), polyarteritis nodosa, and relapsing polychondritis. Generally, ANA, rheumatoid factor, anti-CCP, and antineutrophil cytoplasmic antibody (ANCA) should *not* be ordered on patients with uveitis. Exceptions to this would include children, where a positive ANA may supplement the work-up for suspected JIA [57]. Additionally, ANCA may be considered in patients with retinal signs of vasculitis accompanied with other findings concerning for GPA. HLA-B27 should not be ordered on patients with intermediate, posterior, or panuveitis. Pathergy testing has been used to aid in the diagnosis of Behcet's disease. This test has poor sensitivity (35.8 %) but high specificity (98.4 %) [92]. In our experience, the diagnosis of Behcet's is based on the clinical presentation, and this test is rarely performed.

Less common testing that should be reserved for very specific patient presentations are listed in Table 2.12.

Conclusion

Making decisions about the appropriate work-up in patients with uveitis can be a challenge. In this chapter we highlighted a few key points that may help guide this process:

1. Remember the goal of testing is not necessarily to find an "etiology" but should be to rule out diseases not treated with immunomodulators (i.e., infections—particularly those that cannot be identified by unique exam features, and masquerade syndromes) and systemic diseases that may have an impact on the patient's systemic health, prognosis, or treatment plan.

2. The history and physical exam is the first and most important step in deciding which testing may be appropriate.
3. Laboratory, imaging, and molecular testing should be a supplement to and not a replacement for a thorough history and physical exam.
4. To facilitate limitation of the differential and further guide testing, each patient should be defined into an anatomic classification.
5. When deciding when to order testing, consider the pre- and post-test probabilities and potential for false positives and negatives.
6. With only a few exceptions ANA, rheumatoid factor, anti-CCP, ANCA testing should not be included in the work-up for uveitis.

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