Investigating Uveitis
A Tailored Approach

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Pattern recognition:

• includes ALL aspects of the patient and their environment, not just the eye:
  - Age, sex, race
  - Country, latitude, season, epidemics
  - Travel, sexual behaviour
  - Concurrent or preceding systemic disease
  - Previous medical/surgical history, ametropia
Investigating uveitis is usually to support or confirm a suspicion

- ie targeted investigation after pattern recognition
But sometimes more “inquisitive” testing is needed:

- Unusual eye signs; pattern recognition difficult
- Concurrent systemic symptoms/signs
- Possibility of infection or malignancy
A tailored approach

• ‘The “shotgun” approach to diagnostic tests is costly and intellectually bankrupt’
  – R Nussenblatt

• “shotgun” means inquisitive, untargeted testing
• Untargeted tests have low pre-test probability
  – so relative risk of positive test is often very low
  – and false positives are not uncommon

• Increase pre-test probabilities by examining the patient (under the collar!) and restricting tests
Examining the patient (properly!)
Know your test!

• Why are you asking for it?:
  – To confirm a suspected diagnosis?
  – To exclude an important differential?
  – It just seemed like a good idea?

• Do you understand what the test can do?
  – Can this test answer the question you have set?
  – Can you interpret all possible test results?
  – Do you know the range of normality for your patient, in terms of age, sex, race
  – Will you over-interpret a test result?
Know your test!

• Do you understand the sensitivity and specificity of this test?
  – What are the rates of false positivity and negativity for this test?
  – How do these alter the relative risks of a +ve test, for the disease under investigation, in the subject population?

• Can you make the diagnosis without this test?
Know your test!

- Is this test invasive? If so:
- Is the risk of this test justified for this particular patient?
- Is the test expensive?

- Can you make the diagnosis without this test?
Definitions

- Sensitivity = \( \frac{A}{A+C} \)%
- Specificity = \( \frac{D}{D+B} \)%
- Positive predictive value = \( \frac{A}{A+B} \)%
Relative risk

- eg what is the relative risk of ankylosing spondylitis in somebody who is HLA-B27 positive, compared with somebody who is HLA-B27 negative?
  - 5% of a population are HLA-B27 +ve
  - 80% of those with AS are HLA-B27 +ve
  - 1% of those who are HLA-B27 +ve develop AS
  - 0.011% of those who are HLA-B27 –ve develop AS

- \( RR = \frac{1}{0.011} = 90 \)
Find out about the test!

• Read the basics
• Speak to your laboratory
  – Local decisions on testing parameters
  – They welcome it!
• Place the text into the clinical context
  – Before asking for it
  – After you get the answer
P(A|B) = \frac{P(B|A) P(A)}{P(B)}
Informal Bayesian analysis: (“experience-based-medicine”)

• Starting point: a patient of known age, sex, race in a known region, with a known pattern of uveitis, with known systemic symptoms

• Knowledge of the relative risk of a positive test result

• Knowledge of the pre-test risk for:
  – the general population
  – the particular patient

• Knowledge of the pre-test risk of other diseases (untested)

• Experience of pattern recognition, in the context of all the above
Example 1

- 30 year-old black woman with:
  - bilateral granulomatous anterior uveitis
  - no systemic symptoms or signs
  - CXR normal, ACE 125

- Probable diagnosis: sarcoidosis

- Is any other investigation necessary?
Example 1

• The pre-test probability of sarcoidosis is high
  – it is the most common cause of granulomatosus uveitis in this population

• ACE >100 IU usually indicates sarcoidosis
  – all other diseases causing raised ACE (including TB and lymphoma) are very unlikely to raise it to >100 IU
Do you know about ACE?

• The effect of age, sex and race?
  – levels in children can be much higher
  – blacks can have lower ACE with severe disease

• The localisation of symptoms affects the likelihood of raised ACE in sarcoidosis
  – pulmonary = high, neurological = low

• The effect of ACE inhibitors

• The normal range for ACE is wide (and possibly widening) – secretion is genetically affected – genes are being located – individualised normal range may become possible
Example 1

- If the patient is otherwise asymptomatic:
  - invasive tests unjustified:
    - HRCT delivers -1mSv
    - Bronchoscopy unpleasant, biopsy carries risks
- Exclude important infections:
  - syphilis serology (always)
  - gamma-interferon (almost always)
- Otherwise – presume sarcoidosis
Example 2

• 50 year-old German farmer with:
  – bilateral non-granulomatous anterior uveitis
  – no systemic symptoms or signs
  – Borrelia serology +ve (low titre)
  – All other investigations (including syphilis serology) negative

• Does he have Lyme disease?
• How should he be treated?
Example 2

• He has a low likelihood of Lyme disease:
  – the uveitis has no suggestive features
  – he has no associated systemic features
  – therefore Lyme serology is a “random” test

• Positive Lyme serology:
  – has a random +ve predictive value of <10%
  – low titre may be found in up to 40% of some European populations, particularly farmers or vets
Example 2

- His likelihood of Lyme disease is very low
- He should not undergo antibiotic treatment
- Treat as idiopathic non-infective uveitis
- Empirical antibiotic treatment is justified for some patients with possible borreliosis if there is genuinely supporting information, but the doctor is responsible to the patient for adverse drug reactions etc
Example 3

• 40 year-old man presents with:
  – bilateral subacute panuveitis
  – right diffuse retinitis
  – headache, malaise
  – treated 4 years ago for STD ? diagnosis

• Syphilis ELISA +ve
• RPR 1:4
• Does he have syphilitic uveitis?
Example 3

• Syphilis ELISA remains positive for life after an infection, so cannot diagnose active infection
  – but high specificity and sensitivity, so can “prove” infection at some time
• An RPR of only 1:4 does not support active infection
  – as long as the immune system is working properly
• But: the uveitis strongly suggests syphilis in this context
• Further investigations:
Example 3

• Repeat RPR: easy, cheap, may rise
• Do HIV serology – if +ve may cause RPR to be lower than normal – treat for syphilis
• Take CSF for syphilis testing?
  – ? justified if no focal neurology
• Take vitreous for syphilis PCR?
• Take blood for dark-field microscopy?
• Treat empirically anyway?
Tests which are useless

• Antinuclear antibody testing in adults
  – because there is no link with uveitis in fit patients
  – because a positive test will confuse

• ANCA testing in the absence of scleritis
  – because there is no link with uveitis in fit patients
  – because a positive test may lead to unnecessary investigations

• Any other auto-antibody testing as routine
  – because no uveitis is linked specifically to any one
Tests which are useless

• Toxoplasma serology when the clinical appearance is diagnostic of recurrent disease
  – because confirmation of diagnosis is not needed
  – because a false negative may lead to unnecessary further investigation
  – Different laboratories use different minimum serum titres for serology:
    • false negatives are not uncommon

• Any test for which you do not understand the significance of both +ve and −ve result
Physician Liaison

• Is a physician’s opinion important?
  – Will their opinion affect your management?
  – Will they find undiagnosed systemic disease?
  – Is shared care necessary?

• Necessary for obtaining samples elsewhere in the body

• BUT – timescale!
When is “inquisitive” testing justified?

- Travel outside, or immigration to, your area
- Coexistent systemic disease
- Sexually transmitted disease/drug abuse
- Suggestion of immune deficiency
- Suggestion of malignancy
- Suggestion of intraocular infection
- Unusual ophthalmological features
- Rapidly progressive sight-threatening or life-threatening disease
The main problems with investigations in uveitis

• The person asking for the test does not understand properly how to interpret the result

• An irrelevant test result may:
  – lead to more invasive or expensive tests
  – cause more concern to the patient
  – distract the doctor from the real diagnosis
  – delay appropriate treatment
  – therefore lead to visual loss or other illness
A test-by-test appendix

- A protocol for investigation (NPJ opinion) is available as an appendix to this talk, from:
  - nicholas.jones@cmft.nhs.uk

NPJ approach to investigation is dealt with in detail in:
In Summary:

- Recognise the spectrum of mundane uveitis, but:
- Keep a high index of suspicion for the unusual. However, when this occurs:
- Keep your investigations appropriate and:
- Know how to interpret your test!