Partners in Care

2015 DoNUTTs PEARLS

South Island Division of Family Practice

Victoria Division of Family Practice

SharedCare
Partners for Patients

DoNUTTs: Do No Unnecessary Testing and Treating

Using Less Expensive Alternate Necessary (LEAN) interventions

"Sometimes, the most cost-effective intervention is an early referral".

Arranged Alphabetically by Organ System, Disorder or Specialty

(Click on the Specialty to be directed to accompanying content)

Cardiology

CHEST PAIN – QUERY POSSIBLE ACUTE CORONARY SYNDROME VERSUS ATYPICAL CHEST PAIN

DoNUT ORDER OUTPATIENT TROPONIN (TN) LEVELS – Although high sensitivity troponin levels have been proposed as an all-cause-mortality prognostic tool, the main purpose of measuring Tn is to confirm or rule out an acute coronary syndrome. Typically this requires clinical, ECG and serial Tn levels. Consequently, getting a patient to go and have blood drawn as an outpatient for "one-off" Tn testing is inappropriate. The rationale often put forward for doing this is because the level of suspicion is low and to save the patient the hassle of a visit to the ER. The problem is in the interpretation of the result. Often the patient is elderly and may also have a reduced eGFR. These factors can cause the baseline Tn to be elevated and interpretation becomes difficult. The sample is processed routinely and often resulted after hours or on a weekend when the ordering physician is difficult to reach. Consequently the result is seldom usable in a timely manner. If it was a real ACS case you will likely miss it, and if it wasn't you will have wasted the test.

Clinical Biochemistry

MANAGING PATIENTS WITH INTERMEDIATE AND HIGH FRAMINGHAM SCORES

1.1 PEARL: NON-HDL CHOLESTEROL IS GOOD MARKER IN PLACE OF LDL-CHOLESTEROL

1.1.1 It is a simple calculation from the Total Cholesterol minus the HDL-C

1.1.2 It measures all the ApoB containing (i.e. atherogenic) particles.

1.1.3 It does not require pre-test fasting.

1.1.4 It is not affected by triglcerides of 2-7 mmol/L unlike calculated LDL-C).

1.1.5 **There are targets published by the Canadian Cardiovascular Society and BC Guidelines** (non-HDL-Chol $\leq$2.6 mmol/L for high risk (HR) and for intermediate risk (IR) with a non-HDL of $\geq$4.3) *(Canadian Journal of Cardiology 29 (2013) 151–167 & BC Guidelines - Cardiovascular Disease – Primary Prevention & Lipid Testing).*

1.1.6 Rx advised In Intermediate Risk patients with LDL-C <3.5 but with Non-HDL-C $\geq$4.3. *(Canadian Journal of Cardiology 29 (2013) 151–167 & BC Guidelines - Cardiovascular Disease – Primary Prevention & Lipid Testing).*

1.2 PEARL: NEW CCS GUIDELINES COMING BY 2016 WITH NON-HDL, APO-B & LDL TARGETS

1.2.1 The targets will be much lower because of the imminent availability of new PCSK9 inhibitors that lower LDL very powerfully.

1.2.2 These new guidelines are expected to be similar to those of the National Lipid Association of the USA *(Journal of Clinical Lipidology (2014) 8, 473–488)*

AST (Aspartate Amino Transferase) TEST TO BE DROPPED FROM MSP FEE LIST IN 2015/16 – This is a heads-up that the test will become a patient-pay only option for outpatients in 2016.

Testes, Male Hypogonadism, Male Low Libido, Gynecomastia

Testing for male hypogonadism

The clinical examination should emphasize decreased/loss of libido with erectile impairment, decreased energy and muscle strength and mass, and manual examination for gynecomastia and testicular size.

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Measure the 'early morning' Total Testosterone and LH (to differentiate testicular from central cause). Free and 'bioavailable testosterone' adds nothing to little diagnostic value. Repeat "Borderline" Total Testosterone.
Note: DHEA plays no direct role in androgen status. The response to testosterone is clinical assessment: on treatment only measure Total Testosterone if inadequate response or concern of over-replacemrnt.
Additional cost of also measuring DHEA $18.55

Ultrasound determination for presence of gynecomastia
The clinical examination takes at most 3 minutes and provides additional information about firmness, tenderness and surrounding structures. Normal males may have a small 'button' of breast tissue not exceeding 1 cm in diameter (size of a dime).
Cost of ultrasound examination of both breasts $101.23

Ultrasound determination of testicular size
The clinical examination takes at most 3 minutes and provides additional information about firmness, tenderness and surrounding structures.
Cost of ultrasound examination of the testes $105.60

Endocrinology

Adrenals

Hypercortisolism (Cushing's)
24-hr Urinary Free Cortisol, corrected for creatinine excretion. **Early Referral.**

Hypocortisolism (Addison's)
Early Morning Plasma Cortisol *and* ACTH (Cortisol/ACTH Ratio). **Early Referral.**

Hyperaldosteronism (Conn's)
Simultaneous Aldosterone and Renin levels (Aldosterone/Renin Ratio). **Early Referral.**

Pheochromocytoma
24-hr Urinary Catecholamines. **Early Referral.**

Diabetes mellitus

NOTE: Home blood glucose monitoring is the single largest expense for BC Pharmacare
Insulin-dependent diabetics on multiple daily doses of insulin test up to 7 times daily by adding after meal tests to the ones before meals and at bedtime. Without the meter and lancets it is $1.00 per glucose stick as on average there is a 'dud' of 1 in 7 measurements. Insulin-dependent diabetics on average use between 4 and 8 sticks daily.
Annual cost of glucose-sticks of up to $3,500, depending on number used.

Should diabetics on multiple daily insulins test blood sugars both before and after meal?
In well-motivated, compliant patients the need for testing after meals may be substituted with a system of standardized meals of which the patient has determined the blood sugar elevating effect (SEE).
Savings per year $1,100.

Should all diabetics use 'home blood glucose monitoring' and if so at what frequency?
Randomized controlled trials have shown no benefit from HBGM in *diabetics not on insulin* and the Canadian and American Diabetes Associations support that position. However, many

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such patients want to test. A reasonable compromise is to obtain a 24-hr blood sugar profile (*before breakfast, lunch, supper, bedtime and next morning*) one day per week or even every fortnight, and daily fasting levels if sick (for early warning of hyperglycemia and possible volume depletion).

Savings per year from 10 glucose-sticks per week to 5 every two weeks $390.

Limiting 'white starches' instead of adding a DPP-4 inhibitor ("gliptin") in diabetics.

Type 2 diabetics not requiring insulin whose blood sugar levels are deemed too high benefit markedly from reducing their use of 'white starches' (all cereals and foods derived from them, bread, potatoes, rice, corn and bananas) to no more than 15 grams at a time [15 grams (half cup) dry cereal, 1 slice of bread, 15 grams of potatoes, 15 grams (half ounce) of dry rice (= 67 grams (2 ounces cooked), half an average banana]. As patients vary in their blood 'sugar elevating effect' (SEE) to various starches and sugar, which is also affected by other constituents of the meal or snack, they can 'see' for themselves what their body will tolerate by measuring their SEE of whatever they eat: the difference in the blood sugar immediately before and 1 hour after finishing the meal/snack should not exceed 2). Improvement in glycohemoglobin (HbA1c) after 3 months is more than 1% 'absolute', double that achieved by adding a DPP-4 "gliptin" inhibitor.

Cost of gliptin for 1 year $820 to $1100 depending on dose.

Start with the cheapest insulin preparations until need for more expensive ones is proven

The published results of studies using newer, more expensive insulins suffer from three drawbacks:

1. They use surrogate (HbA1c) measures as the main outcomes,
2. The trials are done in 'efficacy', i.e. ideal settings, not 'effectiveness' real life situations,
3. The only 'clinical outcome' measured (modest hypoglycemia) is not 'clinically very important'.

Annual savings vary with dose and insulin used, up to $350 to $1000

Thyroid

THYROID FUNCTION TESTS

1.1 MONITORING levo-Thyroxine REPLACEMENT FOR HYPOTHYROIDISM

1.2.3 DoNUT ORDER TSH WITHIN THE FIRST 45d OF INITIATING Rx OR CHANGING DOSE – The TSH takes up to 90 days to stabilize. Use clinical judgment. (If you are concerned about compliance, order a FT4 instead).

1.2.4 DoNUT TICK "Suspect Hypothyroidism" when you suspect under-dosing, because if TSH is raised , a reflex FT4 is ordered unnecessarily. Tick "Monitor Replacement Rx" instead.

1.2.5 DoNUT TICK "Suspect Hyperthyroidism" if you are concerned the patient's dose is too high, as this will cause a TSH to be ordered first and a FT4 only if the TSH is too low. If clinically suspicious of over-Rx, order FT4 by writing "FT4 only" on the requisition.

1.2.6 DoNUT RESIST INCREASING DOSE JUST BECAUSE TSH IS NORMAL – Increase dose of Synthroid if patient still clinically hypothyroid, provided TSH remains $\geq$0.02 mIU/L. The precision of the assay at 0.02 is good but may be $\pm$0.01 on occasion.
TSH <0.01 has increased risk of AF especially in older patients.

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1.3 <u>THYROID ANTIBODY TESTING</u>

1.3.1 DoNUT ORDER THYROID ANTIBODIES, PERIOD – Thyroglobulin abs are only ordered to help interpret thyroglobulin test results in patients with Thyroid CA. Peroxisomal abs (TPO-Abs) are increased in most cases of hypothyroidism, and ~70% of Graves disease. They provide some prognostic value for development of hypothyroidism (some also say Thyroid Ca), but don't change management. **DEFINITELY DoNUT REPEAT TPO-ABS**

1.4 <u>THYROTOXICOSIS DUE TO HYPERTHYROIDISM</u>

1.4.1 <u>IF CLINICAL PRESENTATION SUGGESTS AUTOIMMUNE THYROIDITIS AS THE CAUSE ("PARRY", "GRAVE'S" OR VON BASEDOW'S" DISEASE) THEN DoNUT ORDER TSH-R-ABS.</u> The fast majority of thyrotoxic patients have increased Radionucleotide Neck Uptake, but a small number may have decreased uptake when due to Viral (de Quirvain's) Subacute Thyroiditis, which is nearly always evident clinically.

1.4.2 TSH-R-Abs have some predictive value for Thyroid Eye Disease and Risk of Intrauterine fetal Thyrotoxicosis. **Early Referral.**

Thyroid Ultrasound Scans in Hypothyroidism and Thyrotoxicosis are not needed.

- The diagnoses of both these disorders depends on a combination of clinical – history, family history and physical examination – and biochemical indicants. Nearly all are caused by Hashimoto's autoimmune thyroiditis, a clue to which is frequently found through a positive family history.
- The thyroid gland may be of normal size or enlarged, either diffusely or irregularly, neither of which is of help to make the diagnosis or in identifying the cause. A gland that remains enlarged after 2 years of appropriate treatment, or gets larger during treatment is a candidate for an ultrasound.
- **Cost of thyroid ultrasound examination is $ 66.00.**

Thyroid Radio-nucleotide Scan in Hypothyroidism and Thyrotoxicosis are not needed

- The diagnoses of both these disorders depends on a combination of clinical – history, family history and physical examination – and biochemical indicants. Nearly all are caused by Hashimoto's autoimmune thyroiditis, a clue to which is frequently found through a positive family history.
- The thyroid gland may be of normal size or enlarged, either diffusely or irregularly, neither of which is of help to make the diagnosis or in identifying the cause.
- **Cost of thyroid ^{123}Iodide radio-nucleotide scan $ 181.00; Pertechnate scan $ 72.00.**

Parathyroids/Mineral metabolism

<u>INVESTIGATING POSSIBLE HYPERCALCEMIA OR HYPOCALCEMIA</u>

Hypercalcemia may be due to primary hyperparathyroidism, as part of a paraneoplastic syndrome (eg myeloma or PTHrP elaboration by breast or lung Ca) or overdosing with VitD. All these etiologies are more common in an aging population. The initial presentation is nausea, vomiting and weakness but mental changes can also occur.

1.1 DoNUT INTERPRET A TOTAL CALCIUM LEVEL WITHOUT THE ALBUMIN LEVEL

1.2 A calcium order is for plasma Total-Calcium. The active calcium in the blood is ionized and the remainder (~50%) is bound mainly to albumin. Thus, a total calcium in the normal range may actually be increased if the albumin is low (which is more common in the elderly). Example: Total Calcium 2.50 mmol/L (N) with Albumin of

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25 g/L (L) is the equivalent of a Total-calcium of ~2.86 (H) in a patient with an albumin of 43 (normal mean). By the same token, a Total-Calcium of 2.00 (L) and an albumin of 25 g/L (L), is the equivalent of a Total-Calcium of ~2.50 mmol/L (N) and not an indication of hypocalcemia. **Early Referral.**

1.3 **PEARL: CORRECTD CALCIUM = MEASURED CALCIUM + (43-ALBUMIN)x0.02 mmol/L** This equation is an estimate and the calculated corrected calcium is not necessarily accurate. It is recommended to confirm **abnormal** corrected Calcium results with an ionized calcium & PTH.

1.4 **DoNUT HESITATE TO REFER UNEXPECTED CORRECTED CA ≥3.00 IMMEDIATELY**

1.5 **DoNUT REPEAT CORRECTED CALCIUMS <3.00. ORDER PTH AND IONIZED CA.** Most corrected calciums >3.00 should be urgently referred for confirmation & management. Lower levels may be repeated with a PTH and ionized calcium: In primary hyperparathyroidism the PTH & the iCa are elevated (PTH may be normal, i.e. not suppressed);

1.6 In paraneoplastic disease and VitD toxicity the PTH is suppressed and iCa raised.

Don't measure parathyroid hormone level without first having an abnormal calcium
The diagnostic value of PTH is in established the cause of hypercalcemia, hypocalcemia or in renal failure (leave that to the nephrologist!). Having found an initial abnormal total calcium level repeat it and add a phosphate, alkaline phosphate, creatinine and PTH. **Refer if abnormality confirmed. Ionized calcium: for specialists.**
Cost of PTH measurement $ 17.52, Total Calcium...$1.55; Ionized Calcium…$15.81

Gastroenterology

Stool FIT testing

- intended for screening asymptomatic patients between 50-74 years of age, who are appropriate candidates for endoscopy
- should be repeated in average risk asymptomatic patients every 2 years
- should not be performed in patients that have a history of inflammatory bowel disease or who are already on a surveillance colonoscopy schedule

Ammonia

-the diagnosis of hepatic encephalopathy is a clinical diagnosis in the appropriate clinic context and should not require ammonia level testing

Patients with liver conditions

- complete panel of liver enzymes (AST, ALT, AlkPhos, GGT) and liver function studies (INR, Total and direct bilirubin, albumin) should be performed

Screening Gastroscopy for Barrett's

- the yield of a onetime screening gastroscopy in patients with chronic GERD is extremely low and no longer recommended. Screening for Barrett's should be targeted towards patients with multiple factors: **Male gender, Caucasian, >10-year history, Increased BMI, Smoking history.**

CT colonography

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- Should not be used for screening – patients should be enrolled in the Colon Cancer Screening Program with FIT testing if they are appropriate
- CTC is not an appropriate investigation for inflammatory bowel disease, diarrhea, etc.
- CTC can be used for patients who have had an incomplete colonoscopy

Hematology

INVESTIGATING POSSIBLE B12 DEFICIENCY & FOLLOW-UP

Seldom a problem in patients with obvious anemia, oval macrocytes (MCV>105), lemon yellow tinge, high LDH etc. Problem is with anemia of uncertain etiology and/or vague neurological symptoms/signs. Early Rx for neurological sequelae is recommended. Even pernicious anemia patients will respond to high dose oral replacement.

1.1 PEARL: ~20% B12 IS CARRIED ON TRANSCOBALAMIN II AND IS BIOAVAILABLE – ~80% ON TC-1 IS UNAVAILABLE. - Thus a low B12 does not always mean B12 deficiency and a normal B12 does not exclude deficiency. Active-B12 assay to measure TC-11-B12 may be coming.

1.2 DoNUT ORDER MMA (Methyl Malonic Acid) WHERE TOTAL B12 IS BORDERLINE OR DEFICIENCY STILL SUSPECTED (Total B12 150-220 pmol/L). Order Homocysteine (HCYST): MMA and Homocysteine are about equally sensitive in this setting and HCYST is done on the island. MMA is a time consuming mass spectrometry test only available on the lower mainland. HCYST is increased in both folate & B12 deficiency whereas MMA is specific for B12 deficiency. However folate deficiency is very rare in our non-pregnant population because of supplements in basic foodstuffs. MMA and HCYST are both increased in CKD (low eGFR). If HCYST is equivocal MMA or ActiveB12 test may be added.

1.3 DoNUT ORDER INTRINSIC FACTOR ABS OR GASTRIN LEVELS IN THESE PATIENTS – this is generally a waste of time and money. Only 50-70% of pernicious anemia cases have detectable IF-Abs and gastrin elevation is very non-specific so the increased risk of gastric neoplasia cannot be excluded. Some Total B12 assays were susceptible to interference from IF-Abs but not now in BC.

1.4 DoNUT RETEST B12 WITHIN 3 MONTHS OF STARTING REPLACEMENT THERAPY – Injected B12 course will raise the level usually to above the limit of detection of the assay – High dose (1-2 mg/d) oral therapy after full IM course, may justify checking level at 3m intervals to confirm compliance.

1.5 DoNUT REPLACE FOLATE WITHOUT REPLACING B12 IN SUSPECTED B12 DEFICIENCY. In patients with suspected B12 deficiency, giving folate before B12 may precipitate subacute combined degeneration of cord.

Orthopedics

Forthcoming

Rheumatology

Baker's Secret Ingredients:

- Preliminary diagnosis of a rheumatic disease always relies on an extensive history & physical exam.
- No screening test exists for arthritis.

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- A shotgun approach of ordering a number of laboratory tests with joint or muscle pain can lead to false positive results or misleading diagnoses when no rheumatic disease exists.

Baker's Half - Dozen:

1. Rheumatoid factor

- misnomer: name confers specificity that is not deserved
- present in many people at very low levels
- higher levels are present in 5-10% of the population
- percentage rises with age
- NOT useful for screening: nonspecific and insensitive
    - presence does not indicate rheumatoid arthritis
    - absence does not rule out rheumatoid arthritis
- This test should only be done if polyarticular joint inflammation is present for more than 4-6 weeks
- In rheumatoid arthritis, a higher titre can predict a more severe disease course
- ***Serial testing is NOT useful*** for RA or any other condition (it is NOT a disease-activity marker)
- Many conditions can cause an elevated rheumatoid factor:

Rheumatologic Diseases	Other Conditions
Rheumatoid Arthritis	Viral Hepatitis
Sjogren's Syndrome	Endocarditis
Scleroderma	Mycobacterial Diseases
Polymyositis and Dermatomyositis	Syphilis
Systemic Lupus Erythematosus	Advanced Age
Mixed Connective Tissue Disease	
Sarcoidosis	

2. Anti-nuclear antibody

- many autoimmune diseases are associated with a positive ANA
- a positive test is 1 criteria used in the diagnosis of SLE; a positive test by itself does not ensure a diagnosis of a connective tissue disease
- useful as a screening test if SLE is suspected because a negative test virtually rules SLE out; the ANA is positive in 98% of patients with SLE; only 0.1% of the population has SLE, so a low titre ANA is almost always of no consequence
- an ANA is positive in 40-70% of those with other connective tissue diseases
- an ANA is positive in up to 20% with autoimmune thyroid and liver disease
- an ANA is positive in 5% of healthy adults at a cutoff titre of 1:160; a cutoff titre of 1:40 is seen in 32% of the general population and 1:80 in 13%
- Only order an ANA when a history or physical exam is highly suggestive of a connective tissue disease:
    - photosensitivity, malar rash, alopecia, painless aphthous ulcers, sicca symptoms, Ray-naud's phenomenon, inflammatory arthritis, or pleuropericarditis
- Never order an ANA for fatigue alone or back pain
- The ANA is useless in monitoring disease activity, therefore, it does not need to be repeated

3. Anti-Double Stranded DNA

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- relatively specific (95%) for SLE, making it useful for diagnosis
- a negative test does not rule out disease as it only occurs in 30% of patients with SLE
- Should only be ordered when SLE is suspected by history and physical exam AND and ANA is positive
- The anti-ds DNA is 1 of the 11 diagnostic criteria for SLE and may predict renal or central nervous system involvement
- Sometimes an anti-ds DNS may be useful as a disease activity marker although most rheuma-tologists would not treat an isolated rise in the anti-dsDNA level in the absence of a clinical flare
- This test should NEVER be performed for screening in a patient with aches and pains

4. Human Leukoctye Antigen B27 (HLA B27)

- The HLA B27 antigen is present in 8% of the general Caucasian population
- It should be positive in 95% of Caucasians with ankylosing spondylitis
- This antigen is also present in 50-80% of patients with other seronegative spondyloarthropathies (reactive arthritis, psoriatic arthritis, and spondylitis associated with inflammatory bowel disease)
- This test has NO VALUE diagnosing the usual patient with back pain
- It does not usually need to be ordered to confirm a diagnosis of ankylosing spondylitis although it can be sometimes helpful in diagnosing patients who have an atypical presentation of this condition
- Routine ordering of a HLA-B27 antigen for patients with nonspecific low-back pain will invariably result in many false positive results and erroneous diagnoses
- Asymptomatic family members of a person with ankylosing spondylitis should not be tested for HLA-B27
- a first degree relative of a person with ankylosing spondylitis only has a 10-20% chance of ever developing the disease

5. Serum Uric Acid

- Helpful in monitoring the extent of hyperuricemia in patients with gout requiring treatment
- Prevalence of asymptomatic hyperuricemia in men is 5-8% with fewer than 1 in 3 developing gout
- Asymptomatic hyperuricemia does not diagnose gout and does not need to be treated unless:
    - serum uric acid levels are persistently above 760 mmol/L for men
    - serum uric acid levels are persistently above 600mmol/L for women
    - at these levels, there is an increased risk of renal complication
    - testing a serum uric acid level during an acute monoarthritis attack is not helpful in the diagnosis of gout because of the high prevalence of asymptomatic hyperuricemia and fact that 10% of patients with acute gout have normal serum uric acid levels (renal hyperfiltration)
    - A diagnosis of acute gout can only be made with certainty by joint aspiration to confirm urate crystals

6. Synovial Fluid Testing

- examined for viscosity and tested for cell count and differential, gram stain, bacteria, and presence of crystals under polarized light

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- polymorphonuclear leukocytes in synovial fluid is essential to investigate an acute monoarthritis to diagnose septic or crystal arthritis
- A white blood cell count <2000 X 10^9/L indicates a non-inflammatory effusion
- Inflammatory effusions have a white blood cell count 2000 X 10^9/L – 50,000 X 10^9/L
- Infectious arthritis typically has a white blood cell count > 50,000 X 10^9/L
- Other tests of value in specific clinical situations are mycobacteria tuberculosis staining and culture, fungal cultures, or cytological examinations
- Ideally, a synovial fluid analysis for crystals should be carried out promptly using a fresh sample to avoid crystal degradation and a false negative analysis
- The most common pitfalls occur when synovial fluid testing is NOT done.
- it is required for the diagnosis of infectious or crystal synovitis

Characteristics of Synovial Fluid in Rheumatic Disease

Gross examination	Normal	Non-Inflammatory	Rheumatoid Arthritis	Gout or Pseudogout	Septic Arthritis	Hemorrhagic
Colour	Transparent	Transparent	Translucent or opaque	Translucent or opaque	Opaque	Bloody
Viscosity	High	High	Low	Low	Variable	Variable
Gram Stain	-	-	-	-	+	-
Bacteria Culture	-	-	-	-	+	-
WBC Count X10^9/L	<200	200-2,000	2000-10,000	2000-40,000	>50,000	200-2,000
PMNLs %total	<25	<25	>50	>50	>75	50-75
Crystals	-	-	-	+	-	-

The Krispy Kreme:
Usefulness of laboratory tests in assessing rheumatic disease after history and physical exam

Clinical Diagnosis	CBC	ESR	CRP	RF	ANA	Uric Acid	HLA-B27	Synovial Fluid Analysis
Osteoarthritis	0	1	1	0	0	0	0	2
Rheumatoid Arthritis	3	3	1	3	2	0	0	3
Connective Tissue Disease	3	3	1	2	4	0	0	2
Gout	1	1	1	1	0	2	0	4
Ankylosing Spondylitis	2	1	1	0	0	0	2	2
Mechanical Back Pain	0	0	0	0	0	0	0	0
PMR and TA	4	4	1	1	0	0	0	0

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Septic Arthritis	4	3	3	0	0	0	0	4
Fibromyalgia	0	0	0	0	0	0	0	0

0 = not useful in making a diagnosis
1 = positive or negative test is rarely helpful in investigating the condition
2 = positive or negative test is sometimes helpful
3 = a positive or negative test is often helpful
4 = a positive or negative test is always helpful in investigating the condition

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