Endocrine Investigations

A/Prof Shane Hamblin

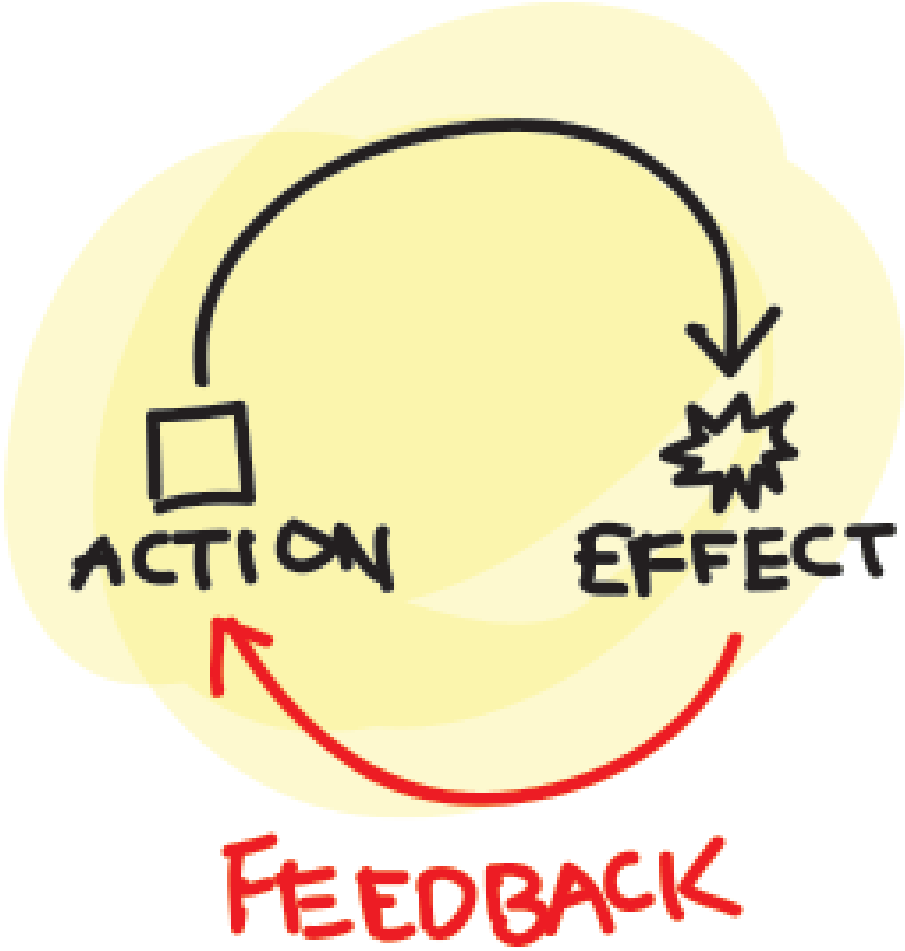
Head of Endocrinology & Diabetes

Western Health

Areas to be covered

- Diabetes
- Thyroid
- Adrenal
- Pituitary
- Osteoporosis

Endocrinology Investigations 101



Principles of endocrine investigations

- Clinical suspicion first
- Repeat abnormal tests to confirm
- Biochemical interference is not uncommon
- Speak to the lab if tests are unusual / confusing
- Only then proceed to localisation (e.g. MRI pituitary)

Diabetes

Traditional laboratory diagnostic screening tests

1. Measurement of fasting plasma glucose

   2 tests glucose >7 mmol/L

2. Random BGL ≥11.0 mmol/L with diabetic symptoms

3. Oral glucose tolerance test (oGTT) only if:

   fasting glucose in grey zone:

   5.5-6.9 mmol/L

   or

   pregnancy (Gestational DM screen)

NB Fingerprick BGL must be confirmed with laboratory BGL tests because of coefficient of variation/accuracy

Oral GTT has poor reproducibility

Only 65% people will have a similar result if a second oGTT is repeated 6 weeks after the first

Ko G et al, Ann Clin Biochem 1998 Jan;35 (Pt 1):62-7

HbA1c for *diagnosis* of diabetes

Interpretation of HbA1c for diagnosis

Diabetes status	HbA1c level
Non-diabetic	< 6.1% (43 mmol/mol)
Impaired glucose metabolism	6.1 – 6.4% (43-46 mmol/mol)
Diabetes mellitus	>= 6.5% (48 mmol/mol)

MEDICARE: HbA1c for diagnosis

HbA1c has now been recognised by Medicare as a diagnostic test.

MEDICARE: Frequency of HbA1c testing

As a diagnostic test, up to 1 test in a 12 month period is rebatable by Medicare. For monitoring established diabetes the limit of 4 tests per year remains unchanged.

WHO 2011
HbA1c

A value less than 6.5% does not exclude diabetes diagnosed using glucose tests. The expert group concluded that there is currently insufficient evidence to make any formal recommendation on the interpretation of HbA1c levels below 6.5%.

HbA1c 6.5% = 48 mmol/mol

GRADE quality of evidence: moderate
GRADE strength of recommendation: conditional

Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus

Abbreviated Report of a WHO Consultation

Some of the factors that influence HbA1c and its measurement*. Adapted from Gallagher et al (*24*)

1. Erythropoiesis Increased HbA1c: iron, vitamin B12 deficiency, decreased erythropoiesis. Decreased HbA1c: administration of erythropoietin, iron, vitamin B12, reticulocytosis, chronic liver disease.
2. Altered Haemoglobin Genetic or chemical alterations in haemoglobin: haemoglobinopathies, HbF, methaemoglobin, may increase or decrease HbA1c.
3. Glycation Increased HbA1c: alcoholism, chronic renal failure, decreased intra-erythrocyte pH. Decreased HbA1c: aspirin, vitamin C and E, certain haemoglobinopathies, increased intra-erythrocyte pH. Variable HbA1c: genetic determinants.
4. Erythrocyte destruction Increased HbA1c: increased erythrocyte life span: Splenectomy. Decreased A1c: decreased erythrocyte life span: haemoglobinopathies, splenomegaly, rheumatoid arthritis or drugs such as antiretrovirals, ribavirin and dapsone.
5. Assays Increased HbA1c: hyperbilirubinaemia, carbamylated haemoglobin, alcoholism, large doses of aspirin, chronic opiate use. Variable HbA1c: haemoglobinopathies. Decreased HbA1c: hypertriglyceridaemia.

* Some of the above interfering factors are "invisible" in certain of the available assays

Western Health

Situations where HbA1c is not appropriate for diagnosis of diabetes:

- ALL children and young people
- Patients of any age suspected of having Type 1 diabetes
- Patients with symptoms of diabetes for less than 2 months
- Patients at high diabetes risk who are acutely ill (e.g. those requiring hospital admission)
- Patients taking medication that may cause rapid glucose rise e.g. steroids, antipsychotics
- Patients with acute pancreatic damage, including pancreatic surgery
- In pregnancy
- Presence of genetic, haematologic and illness-related factors that influence HbA1c and its measurement - see Annex 1 from WHO report

http://www.diabetes.org.uk/

Correlation between HbA1c & oGTT

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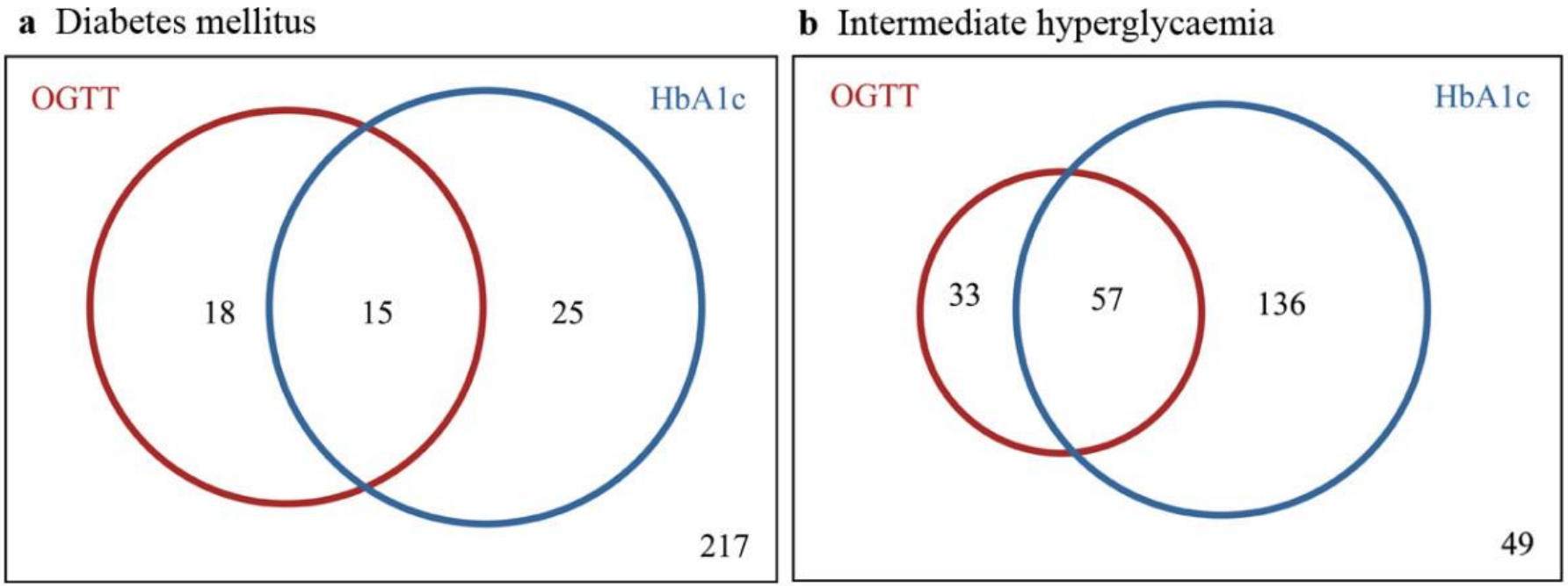

Hjellestad ID et al, *Cardiovascular Diabetology* 2013, 12:79

Antibodies and Type 1 diabetes

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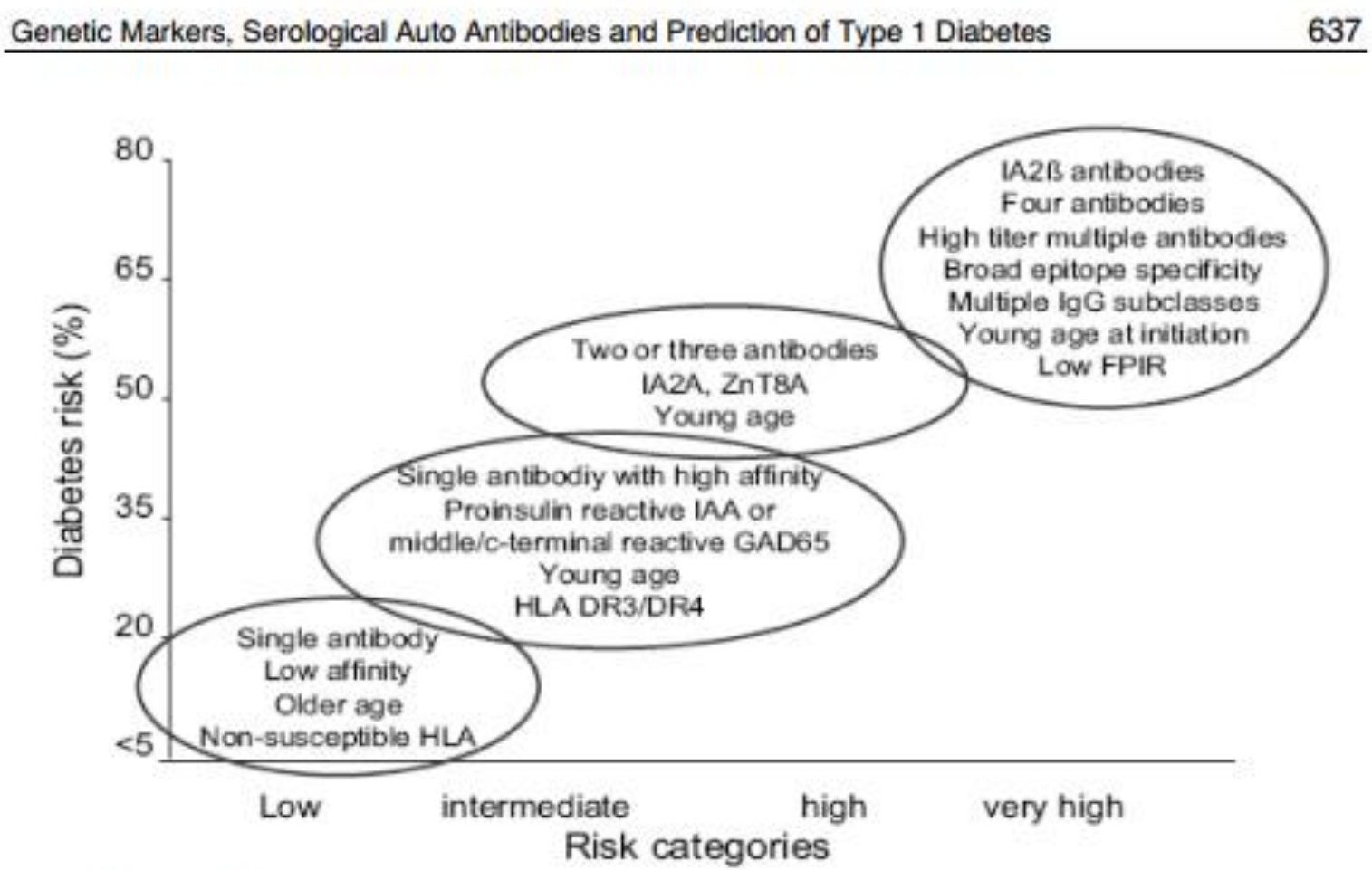


Fig. 2. Type 1 diabetes (T1D) risk stratification by islet autoantibody characteristics.

Raouia Fakhfakh (2011).http://www.intechopen.com/books/type-1-diabetes

C-peptide

- Useful in cases where uncertainty exists whether Type 1 or Type 2 diabetes

  eg LADA: latent autoimmune diabetes of adults

- Not a diagnostic test for diabetes

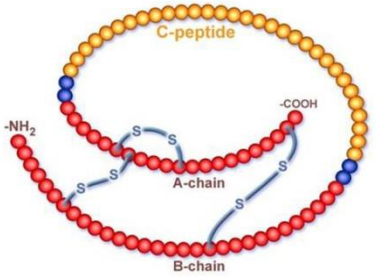
- Not to be used as a routine test

- Usually ordered in combination with

  GAD antibodies

  Ia-2 antibodies

  ZnT8 antibodies



Investigation of hypoglycemia (non-diabetic)

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- Confirm Whipple's Triad
  - Hypoglycemic Symptoms
  - Documented low BGL at time of symptoms
  - Resolution of symptoms when the glucose is raised to normal
- Capture episode of hypoglycemia
  - Assess insulin & C-peptide
  - May be done co-incidentally or with a 72 hour fast

Date Time	24th April 0815	29th April 1600	29th April 2200	30th April 0400	30th April 0505
Blood glucose mmol/L	**2.6**	5.2	3.3	**2.2**	**1.8**
Insulin mIU/L (2.5-11.1)	**40.3**		**16.9**	**27.2**	**29.8**
C-peptide nmol/L (0.33-1.47)	**2.29**	**3.26**	1.47	**1.74**	**1.81**

Thyroid

Thyroid Investigations

1. Clinical examination still important (nodules, goitre, signs of obstruction, nodes, thyroid eye signs, reflexes etc etc)
2. CXR/CT Thoracic inlet
3. Thyroid Ultrasound
4. Technetium (Tc-99m) pertechnetate thyroid nuclear scan
5. Other: I131 scans and PET scans for thyroid cancer
6. TFTs, thyroid antibodies, TSH receptor antibodies(TRABs), Thyroid Stimulating Immunoglobulins (TSI)
7. FNA cytology

Positive Pemberton's sign

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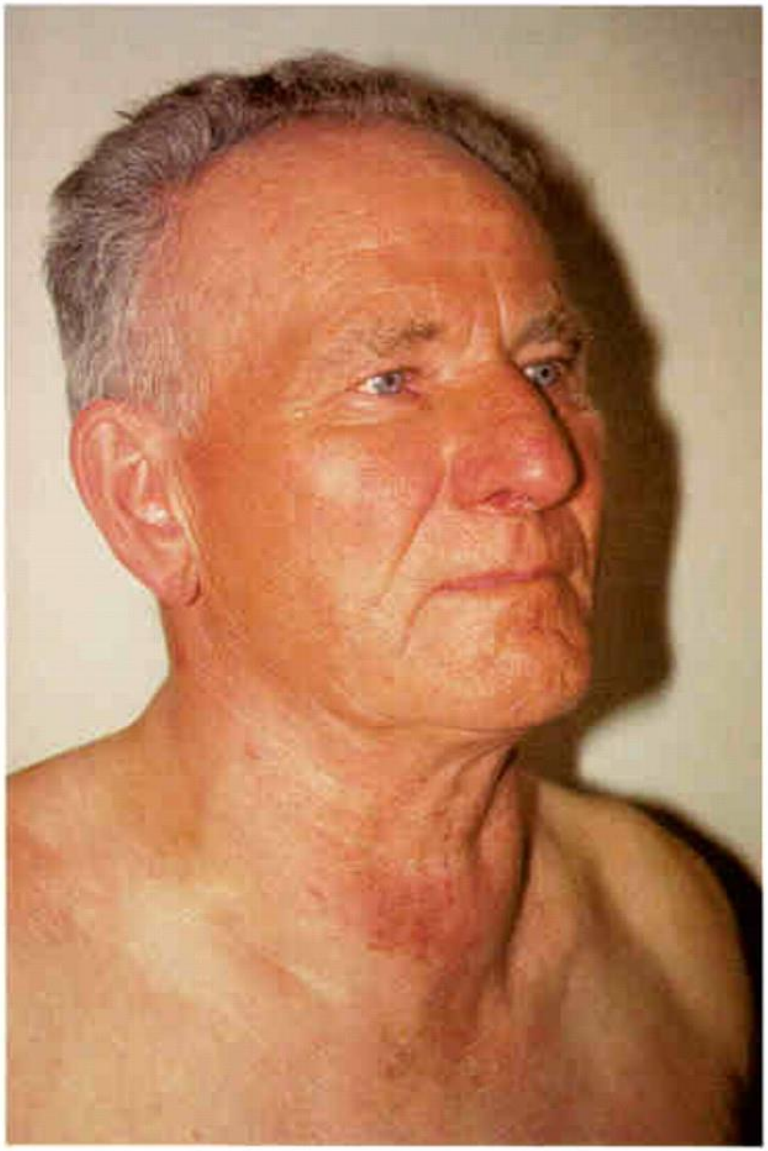
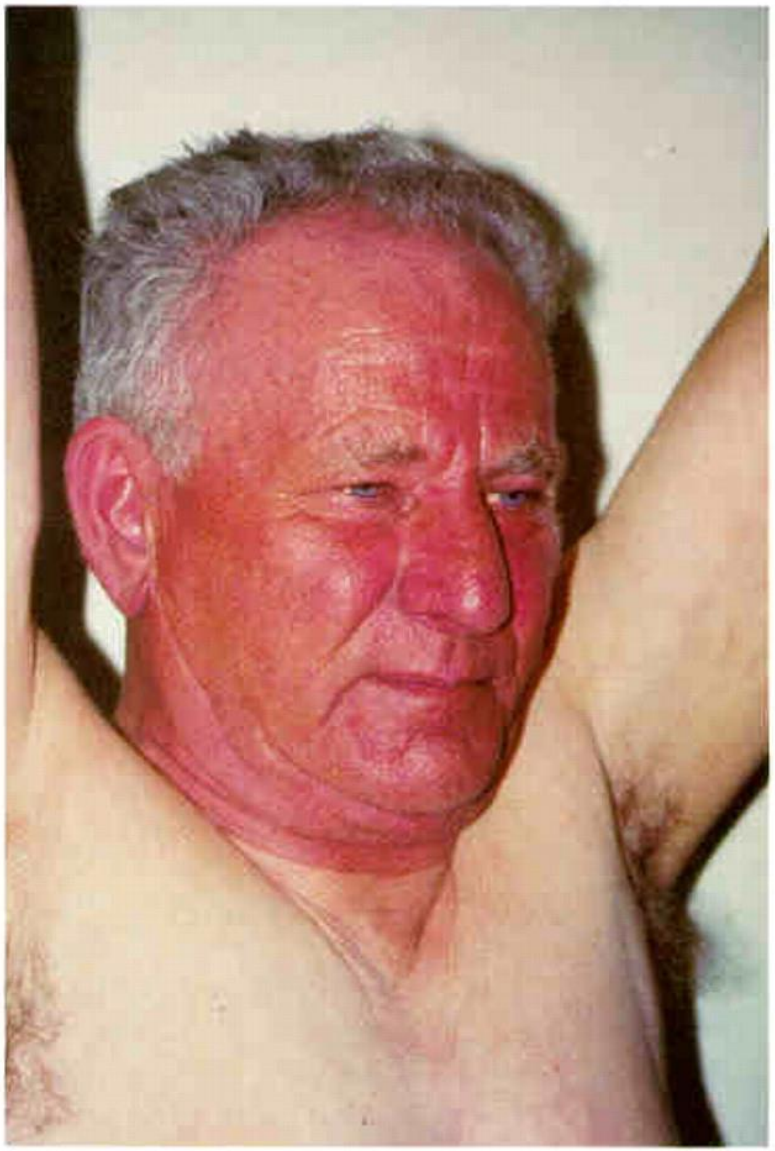
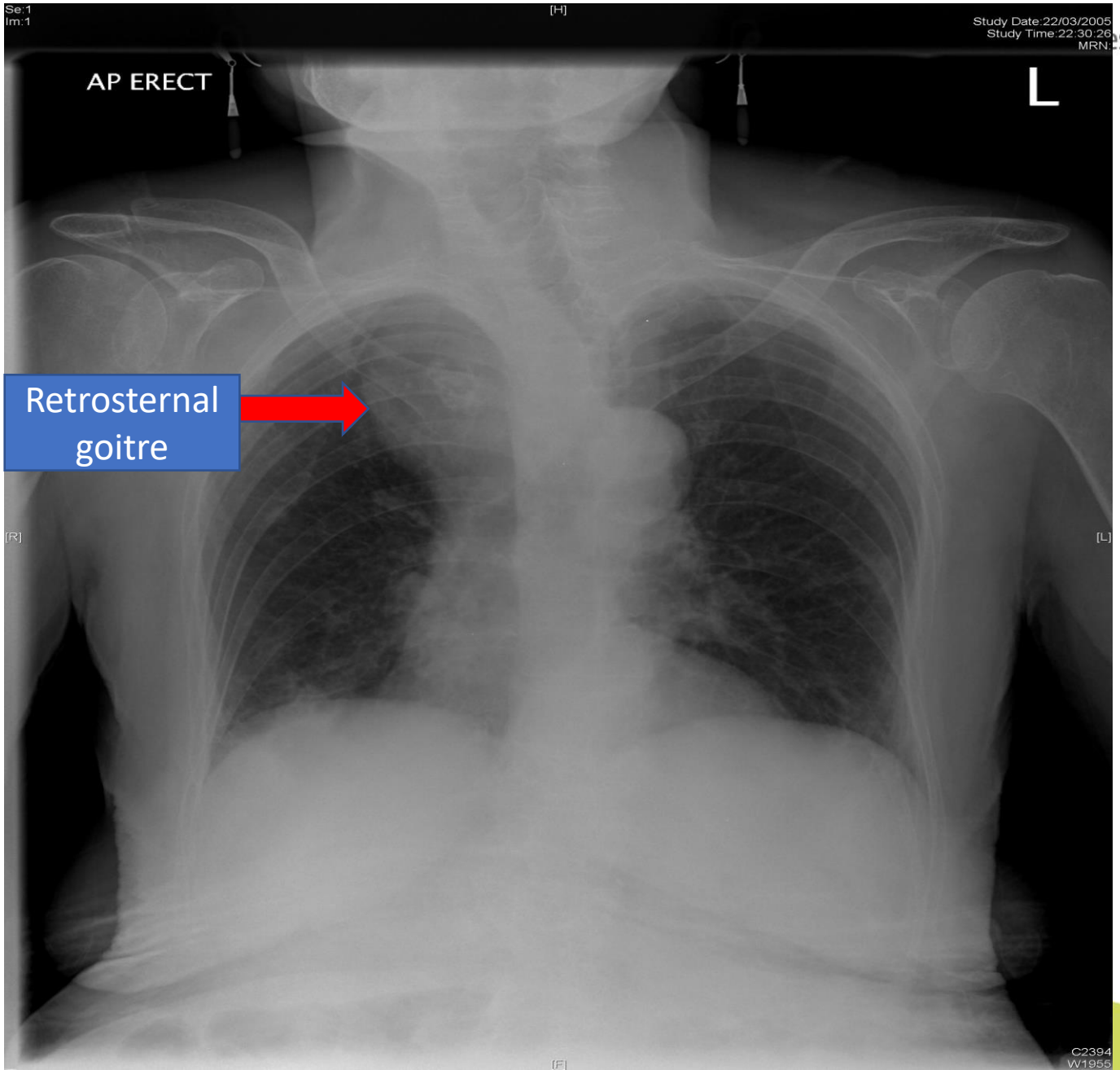
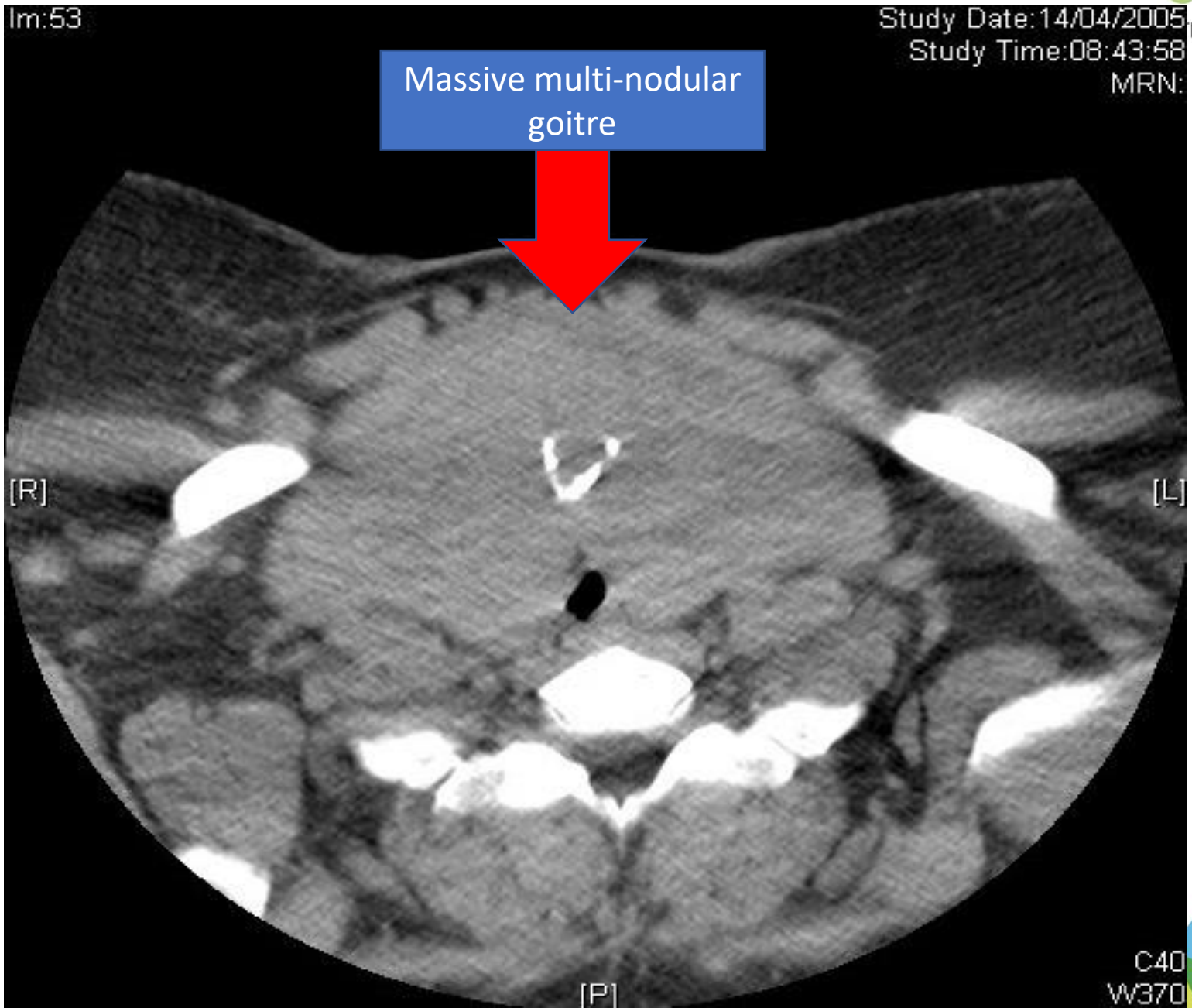




Retrosternal Goitre

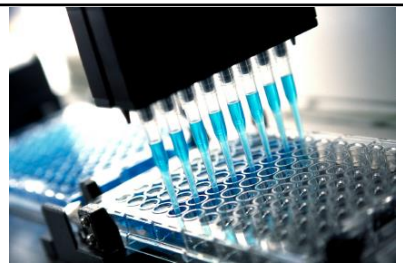


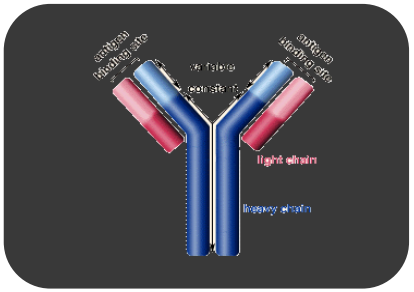
Thoracic Inlet CT Scan

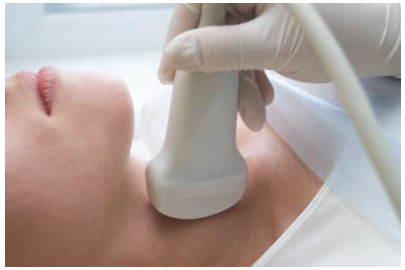


Investigation of goitre

- Thyroid Function Tests
- Thyroid antibodies
- Thyroid ultrasound





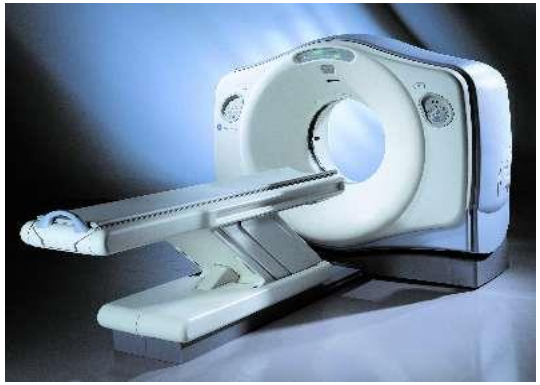


Investigation of goitre

Other imaging
in selected cases:

CT scan
(no contrast if TSH low)

Nuclear scan



Thyroid nodules

Palpable 5% [1] **Ultrasound 25% [1]**
Much higher in older age groups [2]
Much higher in iodine deficient areas [2]

[1]McKenzie E et al Med J Aust 2004, 180 (5) : 242-247

[2]Guth S et al Eur J Clin Invest 2009; 39 (8):699-706

Thyroid abnormalities by ultrasound

(German population: marginal iodine sufficiency)

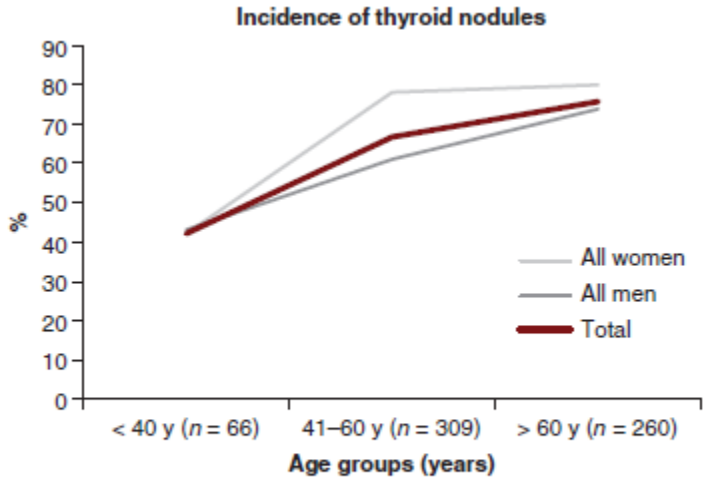


Figure 3 Increasing occurrence of thyroid nodules with age by gender and in total.

Guth S et al Eur J Clin Invest 2009; 39 (8):699-706

Thyroid Ultrasounds & Nuclear Scans:
will the result make a clinical difference?

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Ultrasound	Nuclear scan
Is this clinical nodule a simple cyst or not?	Is this a 'hot' nodule? (done when TSH low)
Is this a solitary nodule or part of a MNG?	Can I use I^{131} treatment?
Has this nodule increased in size over time?	Specialist thyroid cancer management
Amiodarone (blood flow)	Amiodarone (uptake)

Practical Points

Check if patient has been exposed to contrast agents within past month before ordering a thyroid nuclear scan (as tracer may not get into the thyroid)

Avoid i.v. contrast (if possible) where a patient is known to have:

- Multinodular goitre
- Suppressed TSH
- Thyrotoxicosis history

as hyperthyroidism may be triggered (iv contrast has lots of iodine)

Thyroid Nodule Investigation: Suggested Approach

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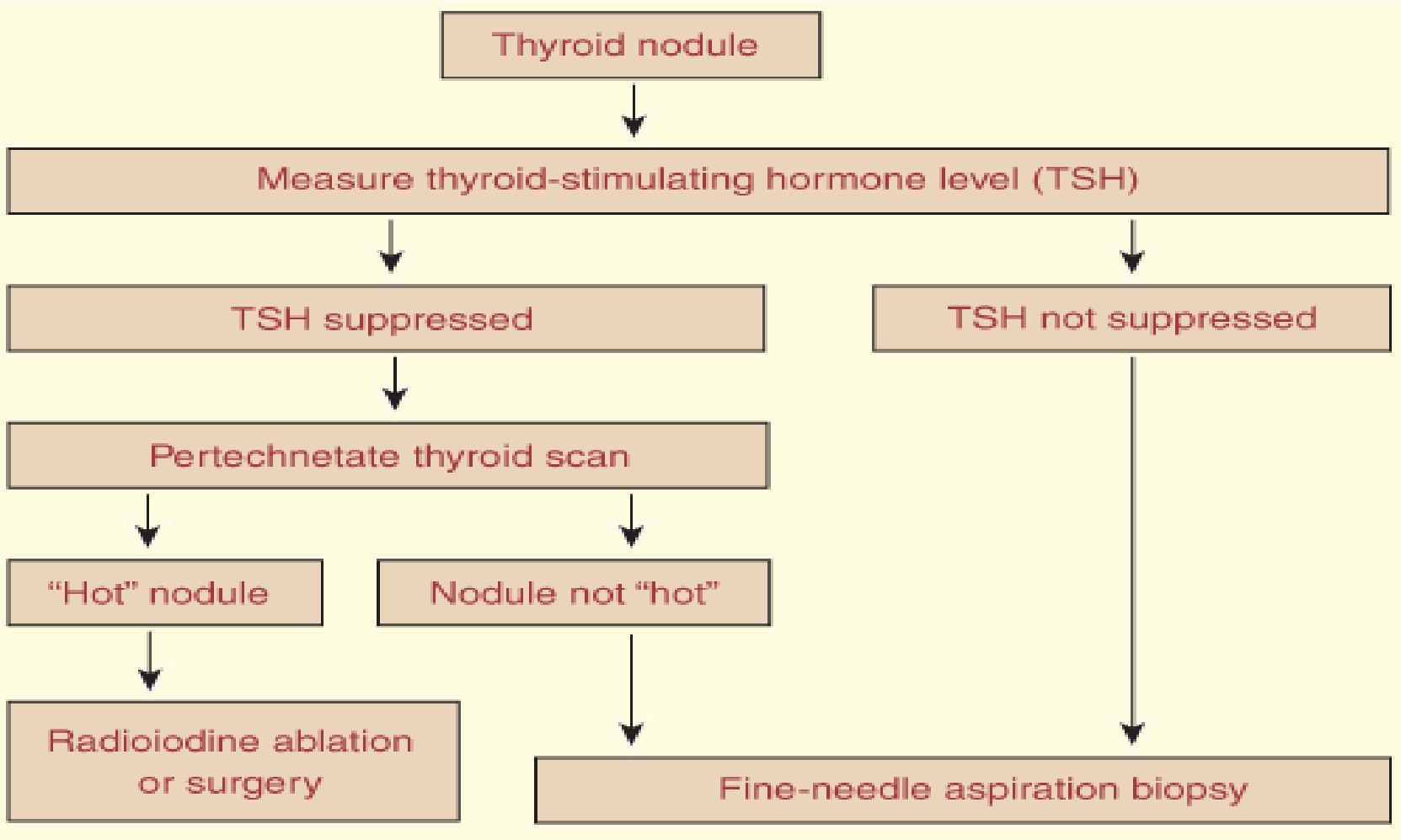


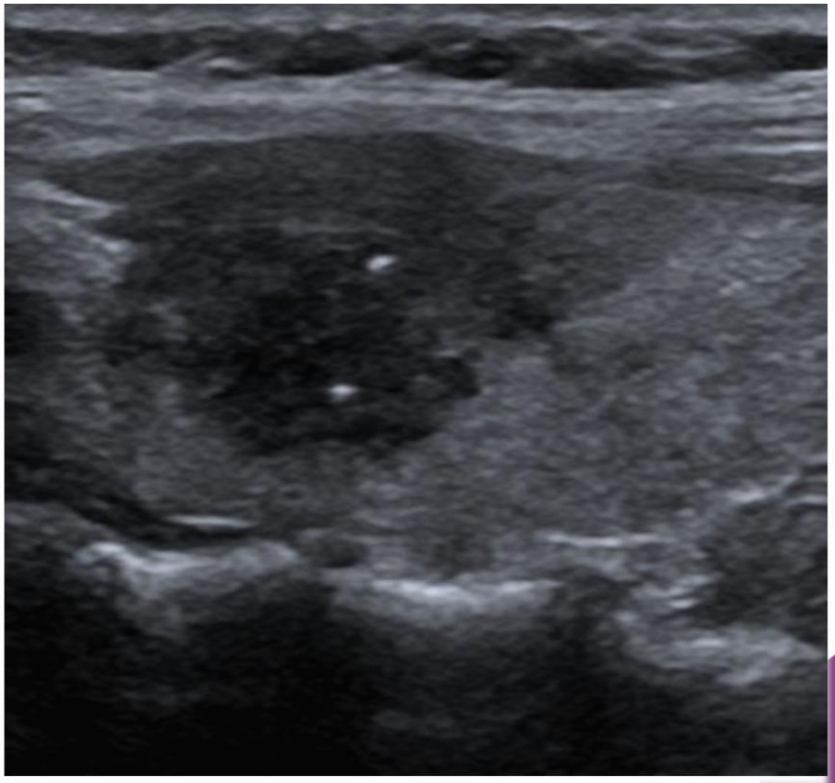
Mackenzie E. & Mortimer R. MJA 2004; 180 (5): 242-247

Thyroid Ultrasound: “Concerning” features in a nodule

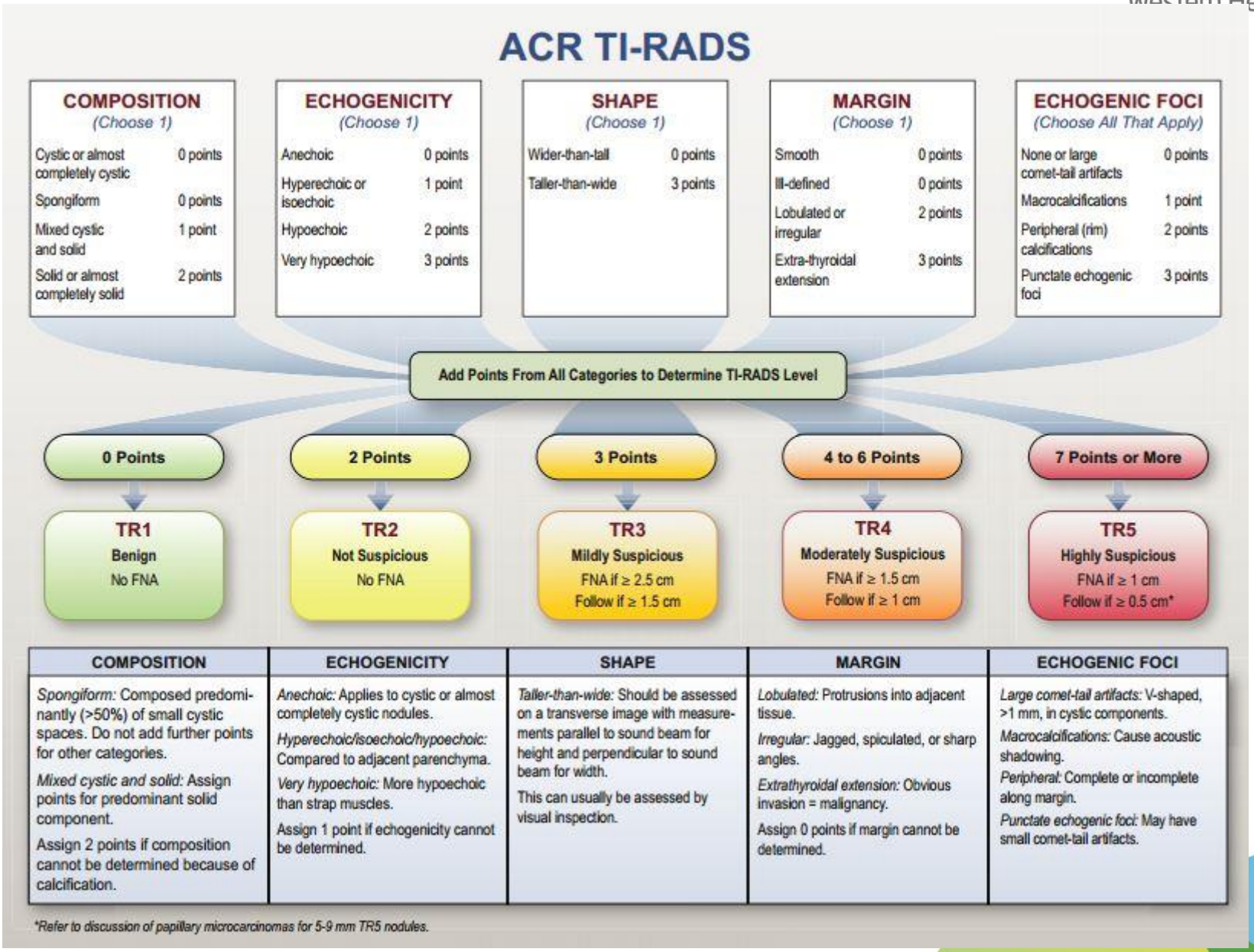
Punctate calcification, hypoechoic,and irregular or blurred margins suggestive of thyroid papillary carcinoma

Ultrasound unlikely to differentiate benign from malignant

Dominant thyroid nodule in a multi-nodular goitre is probably as likely to harbour a malignancy as a solitary nodule (approx. 5% chance)



Thyroid Imaging Reporting and Data System: TIRADS



Hypothyroidism Investigations

Free T4, Free T3, TSH

Anti-TPO (thyroid peroxidase) antibodies

Anti-thyroglobulin antibodies

.....and that's it for the vast majority of cases

Western Health

Thyroid ultrasound for a patient with hypothyroidism or positive anti thyroid antibodies is *NOT* needed in most cases

Subclinical Hypothyroidism is Common

Whickham study [1]

TSH > 6mU/L (Excluded overt hypothyroidism)

7.5% in women 2.8% in men

Detroit [2]

8.5% in women 4.4% in men

Framingham [3] [>60yo]

16.9% in women 8.2% in men

Colorado Health Fair [4]

8.5% overall: women > men in all decades

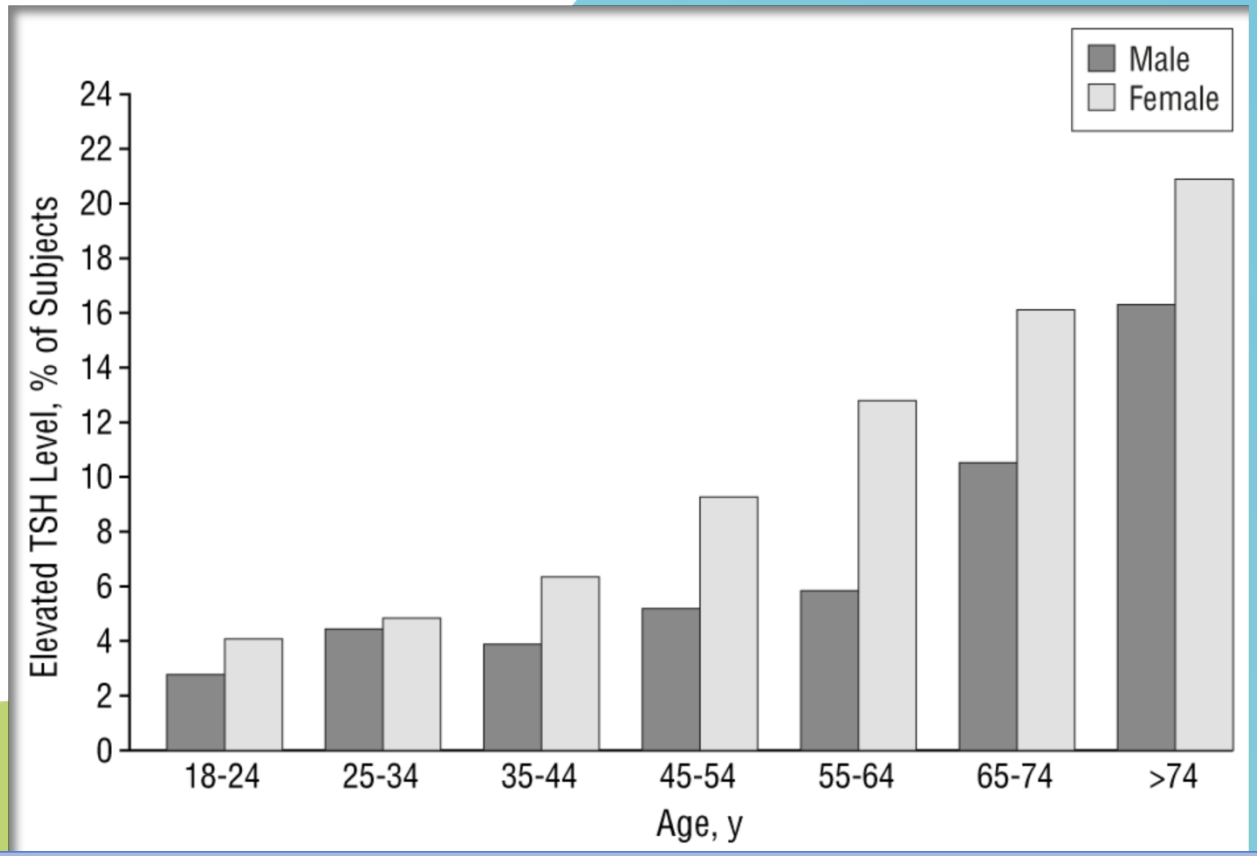
[1] *Tunbridge et al Clin Endocrinol 1977*

[2] *Bagchi et al Arch Int Med 1990*

[3] *Sawin et al JAMA 1979*

[4] *Canaris et al Arch Int Med 2000*

The Colorado Thyroid Disease Prevalence Study: 'Hypothyroidism'



Hypothyroidism (defined by a single high TSH in this study) ranged from 4% to 21% in women and from 3% to 16% in men

Canaris G et al Arch Intern Med. 2000;160(4):526-534

Subclinical Hypothyroidism

Whickham study follow-up

Overt hypothyroidism risk over 20 years of follow-up

TSH mU/L	TPOAb[-]	TPOAb[+]
2	3%	17%
5	17%	55%
10	44%	83%

Vanderpump M et al Clin Endocrinol 1995 Jul;43(1)

Prevalence of thyroid antibodies

	Thyro-peroxidase autoantibodies (anti TPO)	**Thyroglobulin autoantibodies (anti Tg)**	**TSH receptor antibody (TRAB)**
General population	8–27% (11% without history of thyroid disease in an Australian cohort[1])	5–20% (5% without history of thyroid disease in an Australian cohort[1])	1–2% (significance of these positive values remains to be determined)
Graves' disease	50–80%	50–70%	90–99%[2]
Chronic autoimmune thyroiditis	90–100%	80–90%	10–20%

[1]The Busselton Thyroid Study O'Leary PC, et al. Clin Endo (Oxf) 2006;64:97–104

[2]Second generation TSH receptor antibody assays using human TSH receptor coated tubes have a sensitivity of 90–99% and specificity of 95–100% for Graves' disease Matthews DC et al Eur J Intern Med 2011;22:213–6

Adapted from Campbell K et al, Aust Family Physician 2012 Vol 41 No 8

Role of thyroid auto-antibody testing

- Auto-immune thyroiditis – Hashimoto's thyroiditis (Anti-Thyroid Peroxidase and Anti-Thyroglobulin antibodies)
- TSH receptor antibodies: stimulatory (Graves'), but can also rarely act as blocking antibodies (Hashimoto's)
- Spectrum of disease from hypothyroidism to hyperthyroidism (& back again!)

Investigation of hyperthyroidism

- TSH Receptor antibodies (TRAB) (or TSI: thyroid stimulating immunoglobulin)

- Thyroid nuclear scan

  (not needed if clinical features of Graves' disease clearly present)

Possible findings:

- Diffusely increased uptake
- 'Hot' nodule
- Toxic multi nodular goitre
- Reduced uptake (sub-acute thyroiditis)

Therapeutic Guidelines

Interpretation matrix for thyroid function results

	High T_4	Normal T_4	Low T_4
High TSH	• *in vivo* or *in vitro* artefact • pituitary hyperthyroidism (TSHoma) • thyroid hormone resistance	• mild thyroid failure (primary) (also called subclinical hypothyroidism and diminished thyroid reserve)	• primary hypothyroidism
Normal TSH	• as above • sampling within 6 hours of thyroxine dose	• normal (in patients taking thyroxine, TSH more than 3 mU/L may indicate subtle under-replacement)	• pituitary or hypothalamic hypothyroidism • severe nonthyroidal illness
Low TSH	• hyperthyroidism (for this diagnosis, TSH must be suppressed rather than just low)	• subclinical hyperthyroidism • subtle thyroxine over-replacement • thyroid autonomy (multinodular goitre or autonomous functioning thyroid nodule) • nonthyroidal illness • pituitary or hypothalamic hypothyroidism on therapy	• pituitary or hypothalamic hypothyroidism • severe nonthyroidal illness

T_4 = serum free thyroxine; TSH = thyroid stimulating hormone

Topliss DJ, Eastman DJ. 5: Diagnosis and management of hyperthyroidism and hypothyroidism. MJA 2004;180:186-93.

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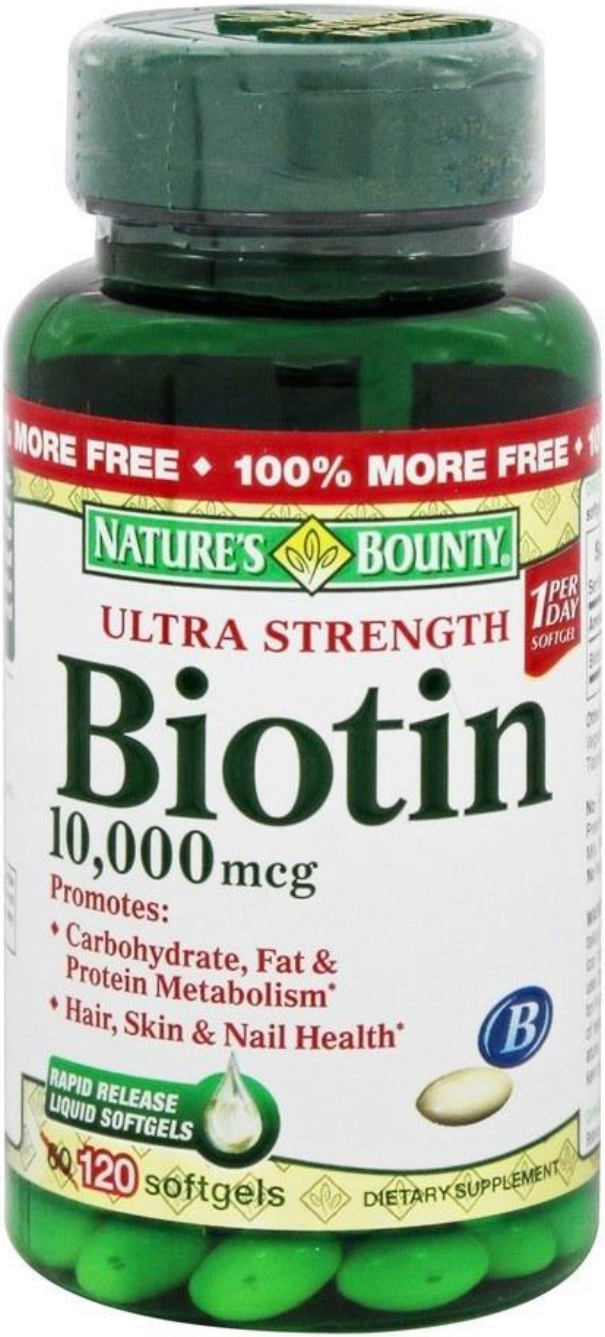
Thyroid function test interpretation -practical points

- **Always use *clinical* judgement**
- **If TSH low, check T4 and T3**
- **If TSH high, check T4 and T3**
- **Remember in severe illness:** TFTs ‘non steady state’
- **If in doubt call the laboratory**



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Multiple sclerosis

- If your patient has MS.....
- Check if they are taking high dose BIOTIN

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Biotin & TFTs

- Spurious result due to lab artefact
- Assay dependent (not all assays): Biotin interferes with the assay test performance
- May affect TSH, FT4, FT3, TSH Receptor Antibodies (LH,FSH and possibly others)
- Patient may appear to have “Graves’ disease”
- Effect disappears within 3 days of ceasing Biotin

Adrenal

Adrenal Incidentaloma

Western Health

4.4% general population high resolution CT[1]

10% older population[2]

0.4% childhood & adolescence[3]

[1]J Endocrinol Invest. 2006;29(4):298

[2]Eur J Endocrinol 2003; 149 273-285

[3]J Pediatric Surgery1997; 32 (6) 911-915

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Adrenal Incidentaloma

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Table 3. Characteristics of Adrenal Incidentalomas on Imaging (Imaging Phenotype).*

Variable	Adrenocortical Adenoma	Adrenocortical Carcinoma	Pheochromocytoma	Metastasis
Size	Small, usually ≤3 cm in diameter	Large, usually >4 cm in diameter	Large, usually >3 cm in diameter	Variable, frequently <3 cm
Shape	Round or oval, with smooth margins	Irregular, with unclear margins	Round or oval, with clear margins	Oval or irregular, with unclear margins
Texture	Homogeneous	Heterogeneous, with mixed densities	Heterogeneous, with cystic areas	Heterogeneous, with mixed densities
Laterality	Usually solitary, unilateral	Usually solitary, unilateral	Usually solitary, unilateral	Often bilateral
Attenuation (density) on unenhanced CT	≤10 Hounsfield units	>10 Hounsfield units (usually >25)	>10 Hounsfield units (usually >25)	>10 Hounsfield units (usually >25)
Vascularity on contrast-enhanced CT	Not highly vascular	Usually vascular	Usually vascular	Usually vascular
Rapidity of washout of contrast medium	≥50% at 10 minutes	<50% at 10 minutes	<50% at 10 minutes	<50% at 10 minutes
Appearance on MRI†	Isointense in relation to liver on T_2-weighted image	Hyperintense in relation to liver on T_2-weighted image	Markedly hyperintense in relation to liver on T_2-weighted image	Hyperintense in relation to liver on T_2-weighted image
Necrosis, hemorrhage, or calcifications	Rare	Common	Hemorrhage and cystic areas common	Occasional hemorrhage and cystic areas
Growth rate	Usually stable over time or very slow (<1 cm per year)	Usually rapid (>2 cm per year)	Usually slow (0.5 cm to 1.0 cm per year)	Variable, slow to rapid

Young NEJM 2007

Investigation adrenal incidentaloma

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- If Hounsfield units <10 and appearance is not worrying and size ≤ 4 cm
- Check functional status
  - ARR
  - 24h Urinary Catecholamines
  - 1 mg Dexamethasone suppression test
- Repeat adrenal CT scan in 6 months
- Then annual CT scans for 1-2 years
- Hormone re-evaluation annually for 5 years

AACE & AAES Guidelines ENDOCRINE PRACTICE Vol 15 (Suppl 1) July/August 2009

Investigation of possible primary hyperaldosteronism (Conn's syndrome)

Western Health

Use drugs which do not interfere with Aldosterone or renin if possible:

- verapamil
- prazosin
- hydralazine
- moxonidine

Case Detection, Diagnosis, and Treatment of Patients with Primary Aldosteronism: An Endocrine Society Clinical Practice Guideline

Western Health

John W. Funder, Robert M. Carey, Carlos Fardella, Celso E. Gomez-Sanchez, Franco Mantero, Michael Stowasser, William F. Young Jr., and Victor M. Montori*

J Clin Endocrinol Metab 2008;93:3266-3281

TABLE 4. Factors that may affect the ARR and thus lead to false-positive or false-negative results

Factor	Effect on aldosterone levels	Effect on renin levels	Effect on ARR
Medications			
β-Adrenergic blockers	↓	↓ ↓	↑ (FP)
Central α-2 agonists (*e.g.* clonidine and α-methyldopa)	↓	↓ ↓	↑ (FP)
NSAIDs	↓	↓ ↓	↑ (FP)
K^+-wasting diuretics	→↑	↑ ↑	↓ (FN)
K^+-sparing diuretics	↑	↑ ↑	↓ (FN)
ACE inhibitors	↓	↑ ↑	↓ (FN)
ARBs	↓	↑ ↑	↓ (FN)
Ca^{2+} blockers (DHPs)	→↓	↑	↓ (FN)
Renin inhibitors	↓	↓ ↑[a]	↑ (FP)[a] ↓ (FN)[a]

Western Health

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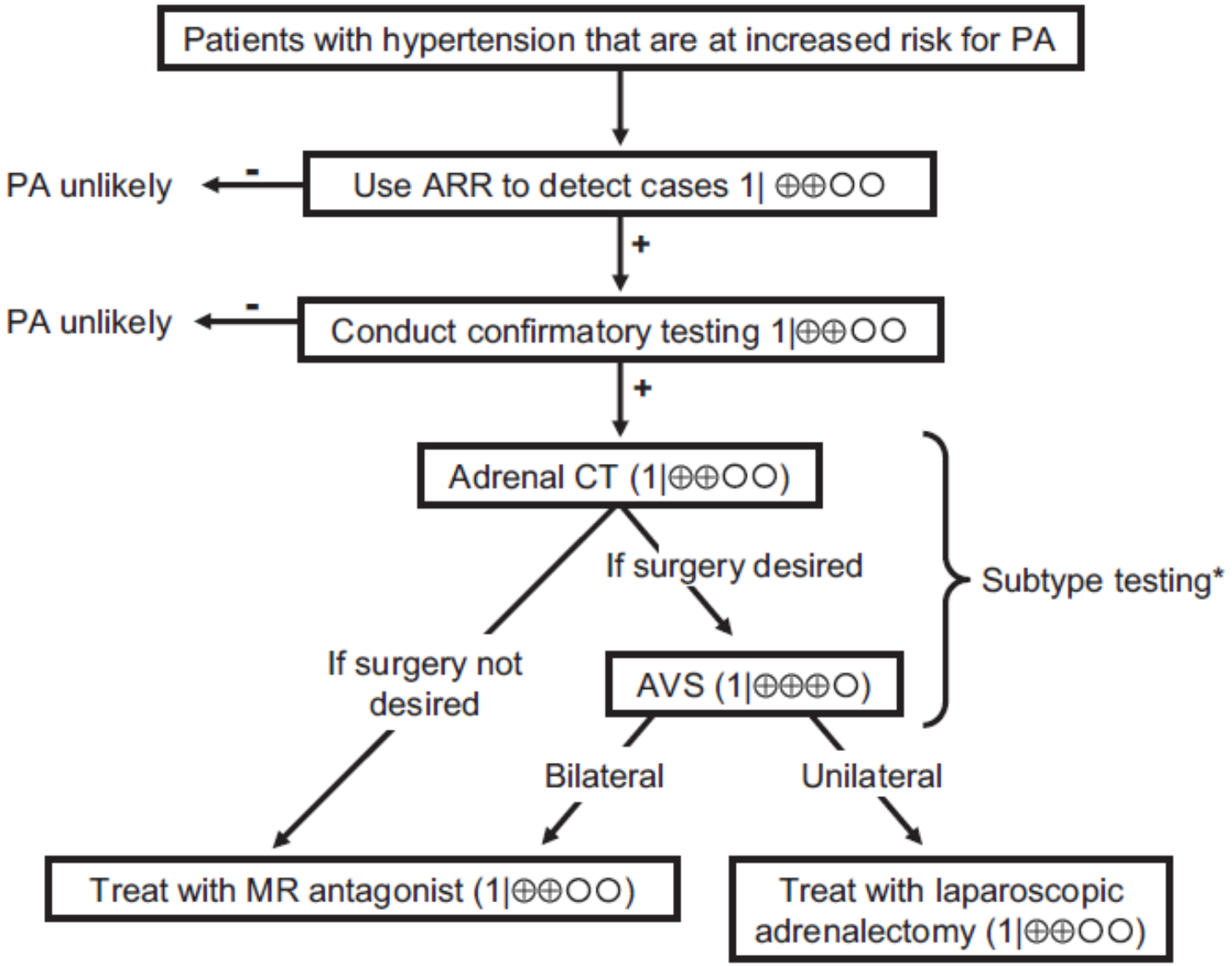
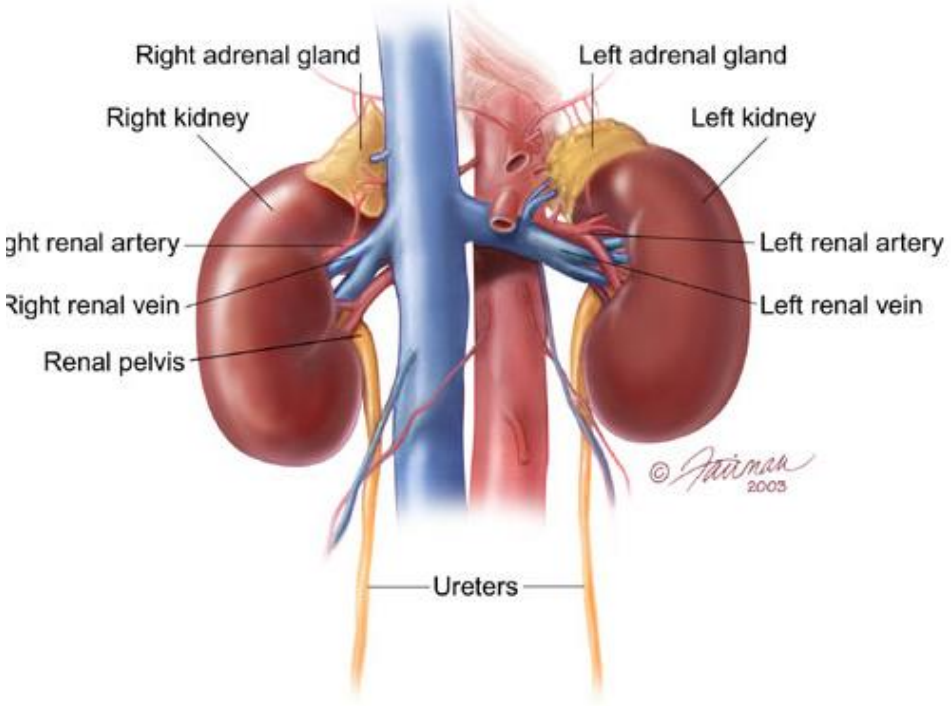
Evaluation of primary aldosteronism



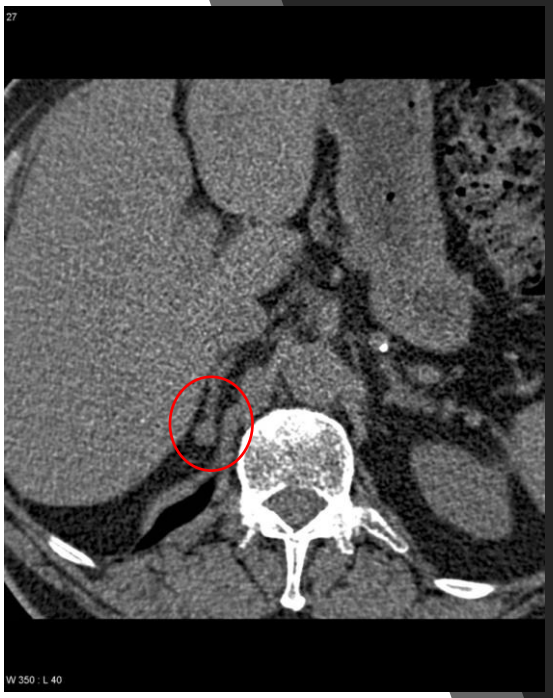
J Clin Endocrinol Metab 2007;93:3266-3281

Imaging & adrenal vein sampling



- Only request adrenal CT, if function testing confirmed to be abnormal
- Adrenal vein sampling is still required in people over age 35 even if adrenal adenoma present on CT because of incidentalomas

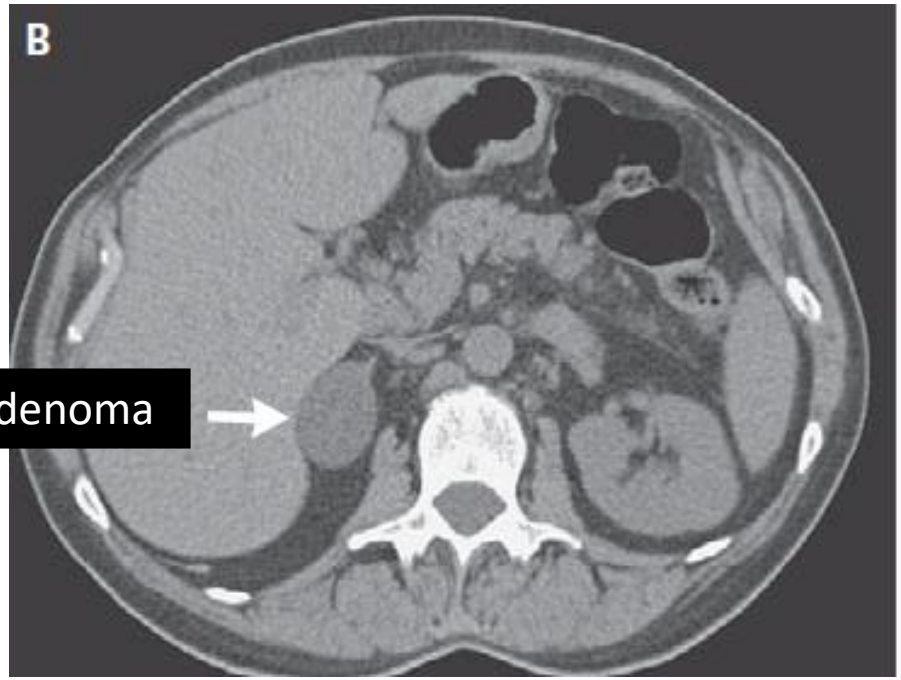
Adrenal vein sampling



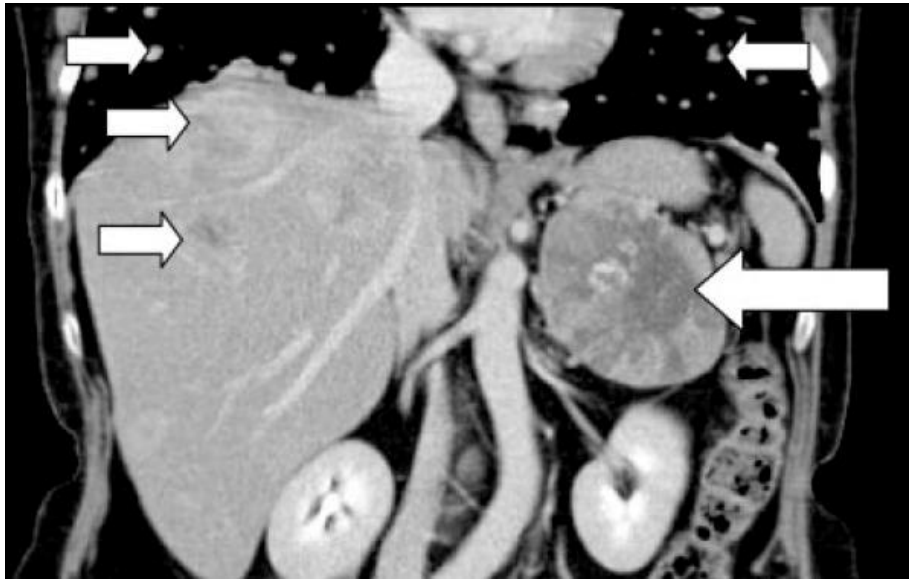
Aldosterone levels

- Right adrenal
- Left adrenal
- Periphery
- Ratios - adrenal v: periphery
- May amplify ratios by administration of synthetic ACTH

Cortisol (used as a control to ensure correct position of catheter)

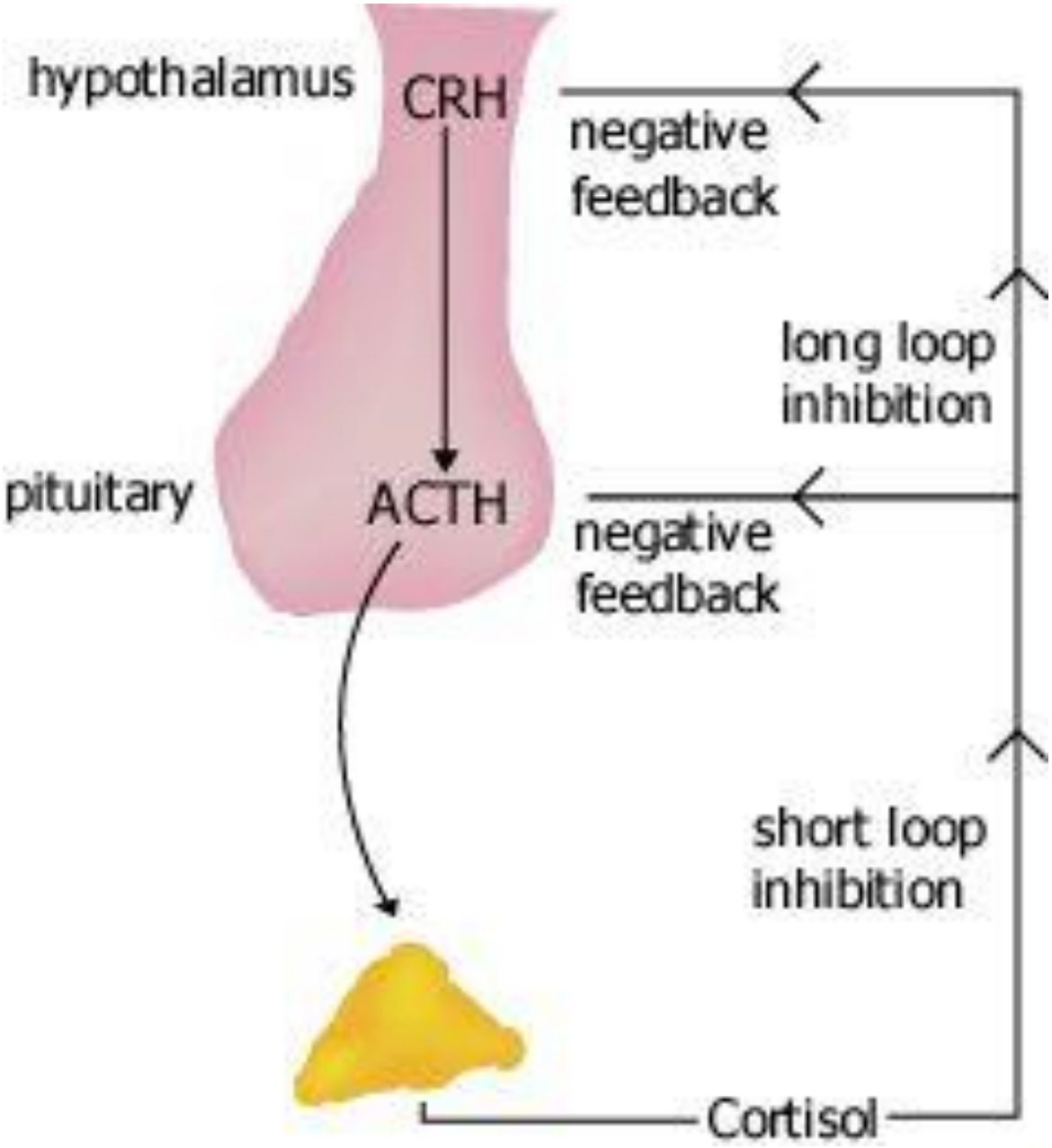


Adenoma



Carcinoma

President John F Kennedy: Addison's disease


hypothalamus
CRH
negative
feedback
long loop
inhibition
pituitary
ACTH
negative
feedback
short loop
inhibition
Cortisol

Testing for possible adrenal insufficiency

- Blood taken for cortisol and ACTH
- 250 ug synthetic ACTH (Synacthen) I.M.
- 30 min and 60 min cortisol

Normal response:

- Peak cortisol ≥ 550 nmol/L
- (Also supposed to increase by at least 250 nmol/L...but in maximally stressed situations, this may not occur)

60

Secondary Adrenal insufficiency

- Short Synacthen test correlates well with ACTH deficiency (90% correlation)

- "Gold standard": Insulin tolerance test ITT
  - Rarely performed. ***Must*** be very closely supervised
  - Hypoglycaemia < 2.2 mmol/L
  - Cortisol response ≥ 550 nmol/L normal
  - GH deficiency can also be assessed with ITT
  - ***Risks: Patients with IHD or epilepsy***

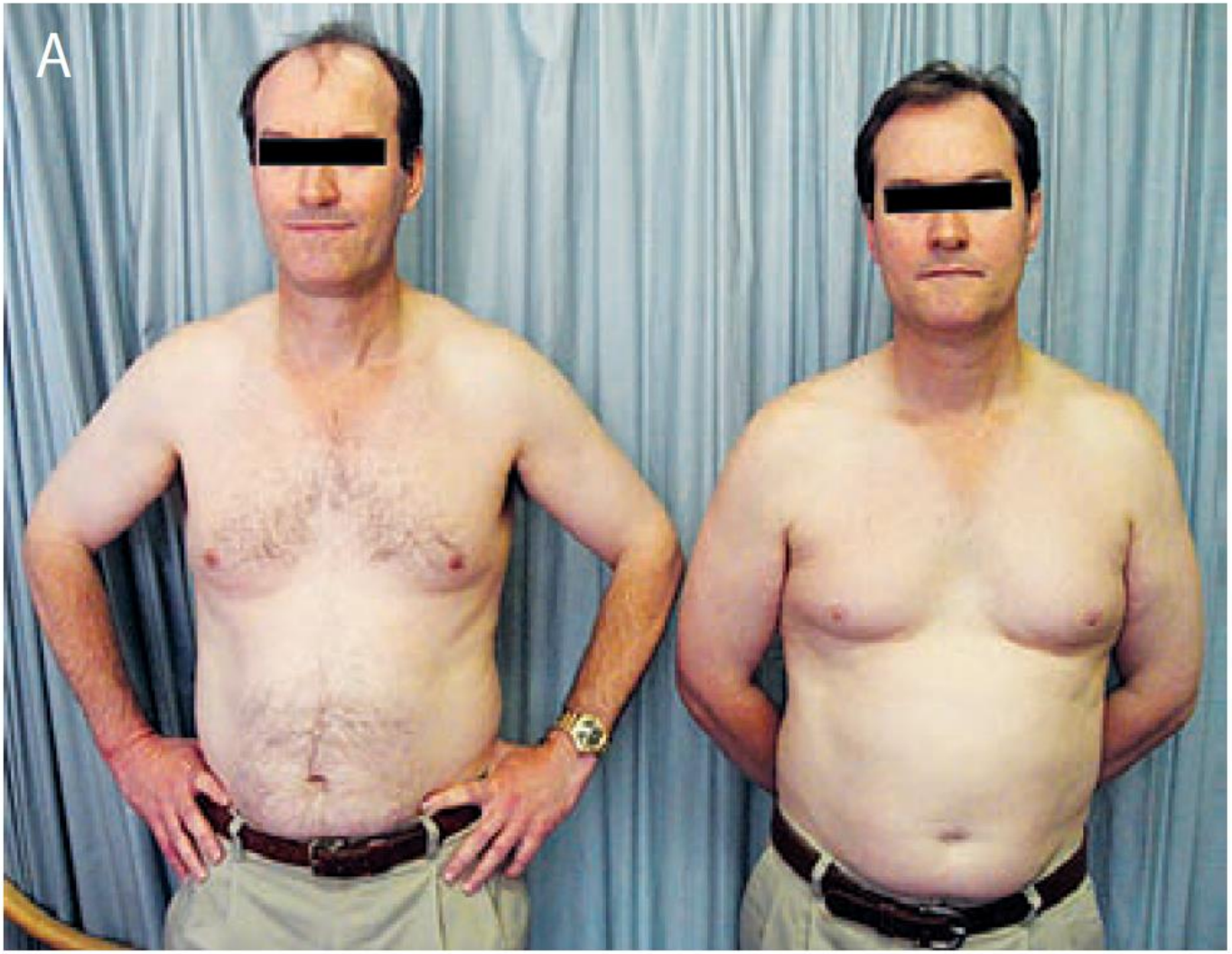
Pituitary

Incidental pituitary adenomas

- Common
- Usually less than 10 mm (microadenoam)
- Prevalence approx 10% adult MRI pituitary scans
- Assess pituitary hormone function: Prolactin, ACTH, cortisol, GH, IGF-1, LH, FSH, Testosterone/oestradiol, TSH, T4, T3
- If macroadenomas near optic apparatus: formal visual fields & Visual Acuity
- Re-scan in 12 months for microadenomas
- ?Annual scans for 3 years

Endocrine Society Clinical Guidelines

Journal of Clinical Endocrinology & Metabolism 2011, 96(4):894–904



N Engl J Med 2008; 359:2824

Testosterone assessment

- Fasting a.m.
- Total Testosterone: 4.2 nmol/L
- Repeat T: 3.8 nmol/L
- (Ref Range 10- 28 nmol/L)

Next investigation ?

A. MRI pituitary
B. Semen Analysis
C. Karyotype
D. LH/ FSH
E. SHBG/ calculated free testosterone

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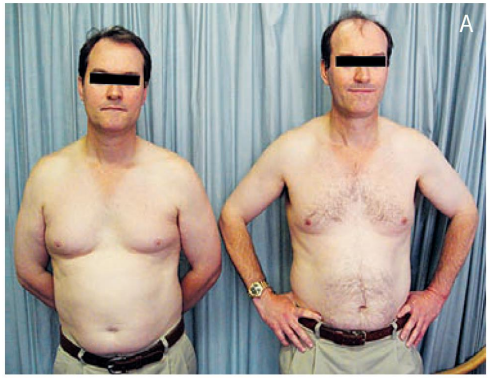
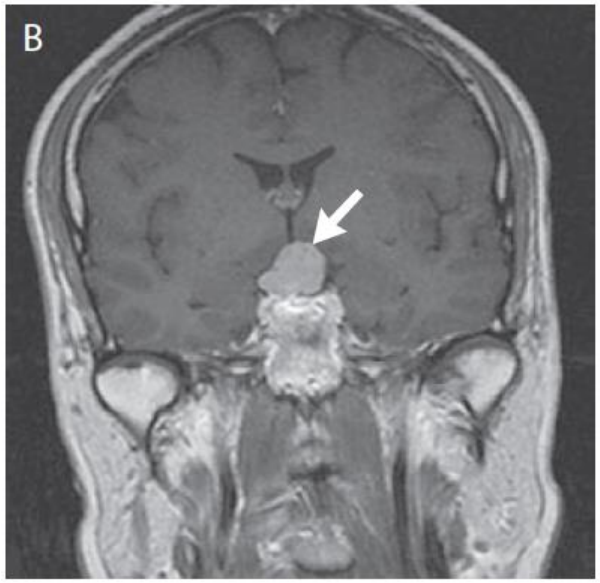
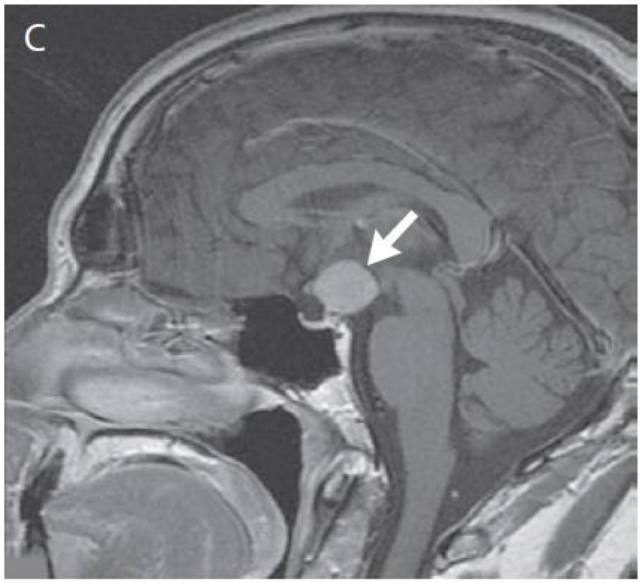
Further Assessment

- FSH 2.96 U/L (1-10); LH 2.45 U/L (1-10) ➔ ***inappropriately normal*** = hypogonadotrophic hypogonadism
- Prolactin 1250 mU/L (<500) ➔ stalk effect or prolactinoma?
- Normal fT4, TSH, am cortisol
- No headaches, visual field defects







N Engl J Med 2008; 359:2824

Causes of Androgen Deficiency

Western Health

↑LH/FSH

Testicular

- Chromosomal — Klinefelter's syndrome
- Surgery — bilateral orchidectomy
- Radiotherapy /chemotherapy/drugs (spironolactone, ketoconazole)
- Infection — mumps, orchitis
- Maldescended testes
- Trauma
- Systemic disease — haemochromatosis, thalassaemia, myotonic dystrophy

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↓ **LH/FSH** or inappropriately normal **LH/ FSH**

Hypothalamo-pituitary

- Pituitary macroadenoma (mass effect destroys gonadotropins)
- Panhypopituitarism (post surgery or radiotherapy)
- Prolactinoma (elevated prolactin levels suppress release of LH and FSH)
- Haemochromatosis
- Hypogonadotropic hypogonadism (Kallmann's syndrome)

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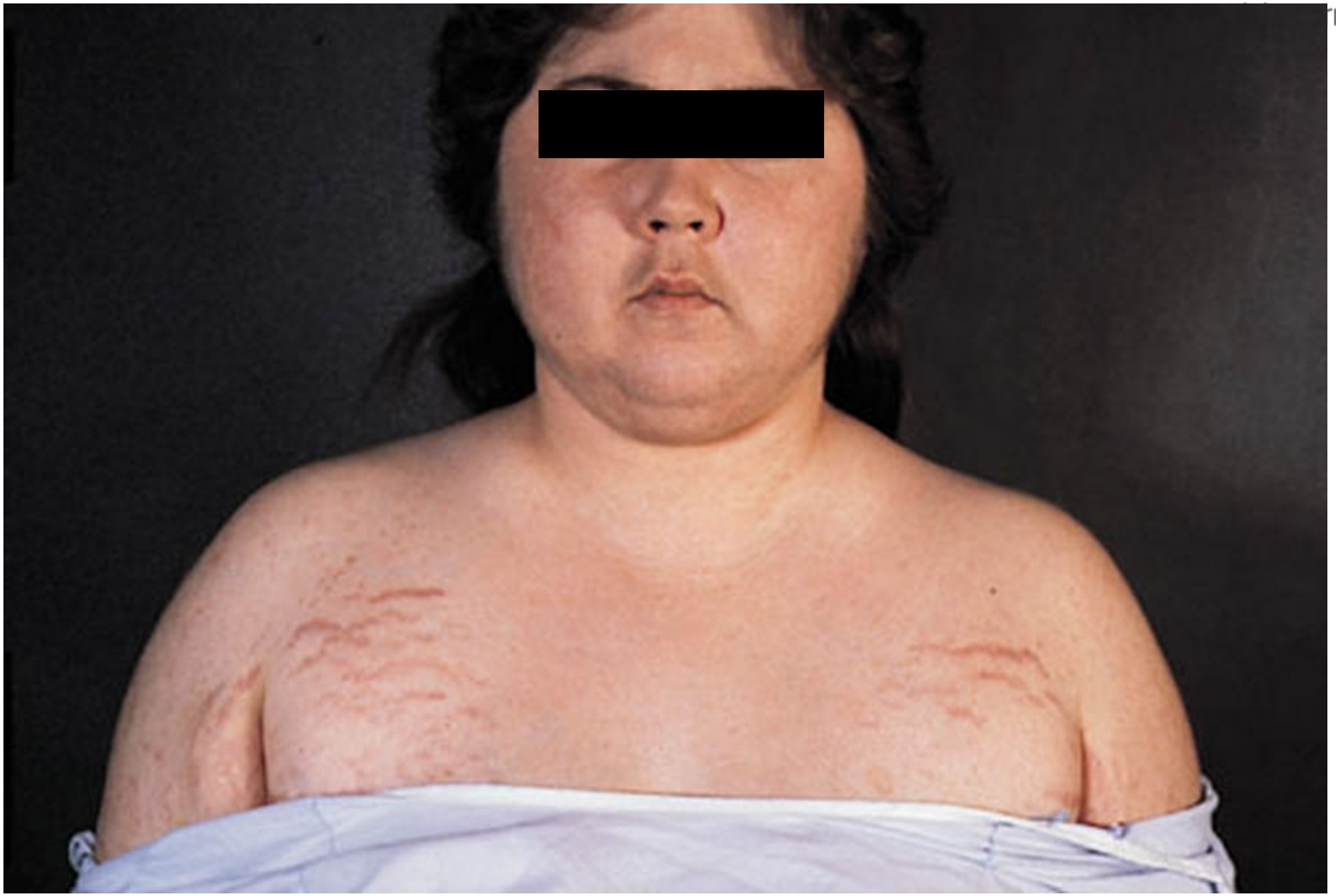
Partial or transient androgen deficiency
Constitutional delay of puberty
Acute critical illness, burns, major trauma or surgery
Drug use (eg, opiates, glucocorticoids, anabolic steroids)
Chronic disease and its treatment
Ageing ("late-onset" androgen deficiency)

Obesity/ Insulin Resistance via low SHBG or increased E2

Practical point

Do not request LH/FSH if a woman is taking OCP

Cushing’s syndrome



The Diagnosis of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline

Lynnette K. Nieman, Beverly M. K. Biller, James W. Findling, John Newell-Price, Martin O. Savage, Paul M. Stewart, and Victor M. Montori

TABLE 1. Overlapping conditions and clinical features of Cushing's syndrome[a]

Symptoms	Signs	Overlapping conditions
Features that best discriminate Cushing's syndrome; most do not have a high sensitivity		
	Easy bruising	
	Facial plethora	
	Proximal myopathy (or proximal muscle weakness)	
	Striae (especially if reddish purple and > 1 cm wide)	
	In children, weight gain with decreasing growth velocity	
Cushing's syndrome features in the general population that are common and/or less discriminatory		
Depression	Dorsocervical fat pad ("buffalo hump")	Hypertension[b]
Fatigue	Facial fullness	Incidental adrenal mass
Weight gain	Obesity	Vertebral osteoporosis[b]
Back pain	Supraclavicular fullness	Polycystic ovary syndrome
Changes in appetite	Thin skin[b]	Type 2 diabetes[b]
Decreased concentration	Peripheral edema	Hypokalemia
Decreased libido	Acne	Kidney stones
Impaired memory (especially short term)	Hirsutism or female balding	Unusual infections
Insomnia	Poor skin healing	
Irritability		
Menstrual abnormalities		
In children, slow growth	In children, abnormal genital virilization	
	In children, short stature	
	In children, pseudoprecocious puberty or delayed puberty	

J Clin Endocrinol Metab. May 2008, 93(5):1526–1540

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Which are the 2 best screening test for Cushing's syndrome?

A. 8 am serum cortisol
B. 24 hour urinary free cortisol
C. 1 mg overnight dexamethasone suppression test
D. ACTH
E. 8 mg overnight dexamethasone suppression test

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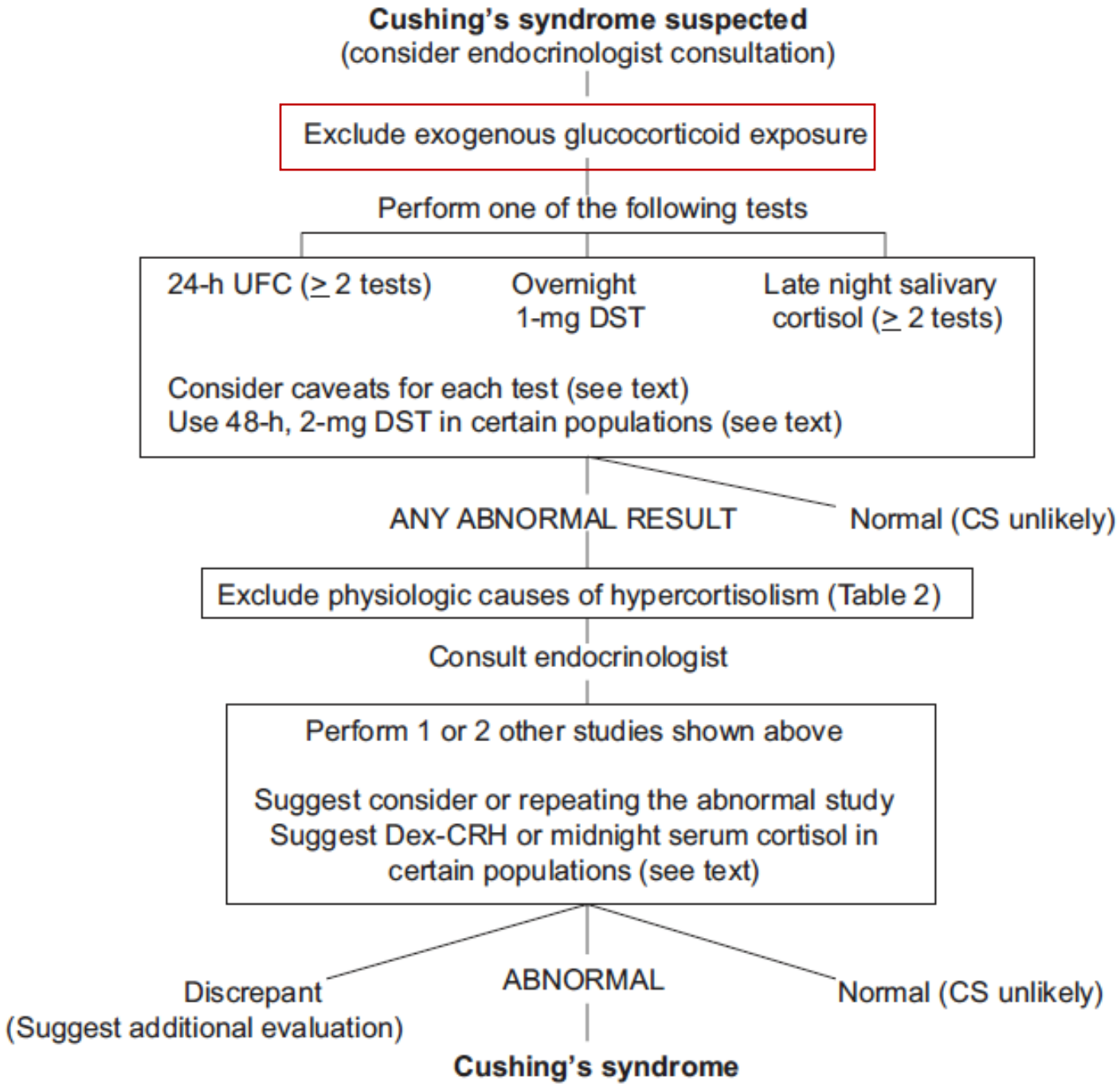
TABLE 2. Conditions associated with hypercortisolism in the absence of Cushing's syndrome[a]

Conditions
Some clinical features of Cushing's syndrome may be present
Pregnancy
Depression and other psychiatric conditions
Alcohol dependence
Glucocorticoid resistance
Morbid obesity
Poorly controlled diabetes mellitus
Unlikely to have any clinical features of Cushing's syndrome
Physical stress (hospitalization, surgery, pain)
Malnutrition, anorexia nervosa
Intense chronic exercise
Hypothalamic amenorrhea
CBG excess (increased serum but not urine cortisol)

[a] Whereas Cushing's syndrome is unlikely in these conditions, it may rarely be present. If there is a high clinical index of suspicion, the patient should undergo testing, particularly those within the first group.

Urinary free cortisol usually < 4 x ULN


Cushing's syndrome suspected
(consider endocrinologist consultation)
Exclude exogenous glucocorticoid exposure
Perform one of the following tests
24-h UFC (≥ 2 tests)
Overnight 1-mg DST
Late night salivary cortisol (≥ 2 tests)
Consider caveats for each test (see text)
Use 48-h, 2-mg DST in certain populations (see text)
ANY ABNORMAL RESULT
Normal (CS unlikely)
Exclude physiologic causes of hypercortisolism (Table 2)
Consult endocrinologist
Perform 1 or 2 other studies shown above
Suggest consider or repeating the abnormal study
Suggest Dex-CRH or midnight serum cortisol in certain populations (see text)
Discrepant
(Suggest additional evaluation)
ABNORMAL
Normal (CS unlikely)
Cushing's syndrome

ACTH-dependent or not?

< 1 pmol/L	ACTH - independent	Adrenal Source (Adrenal CT)
> 65 pmol/L	ACTH - dependent	Pituitary (more common) vs. ectopic source
1-65 pmol/L	Usually (not always) ACTH - dependent	

Prechilled EDTA tube, on ice, rapid refrigeration/ centrifugation essential

High dose dexamethasone suppression tests

Western Health

- Classic protocol: Liddles' test
- Dexamethasone 2 mg orally every 6 hours for 48 hours
- Measure plasma cortisol and ACTH; urine free cortisol

- Modern protocol
- 4 hour 1 mg/h Dexamethasone iv infusion
- Plasma cortisol, ACTH measured hourly for 4 hours and the next morning
- Normal person suppresses by at least 50% by 4 hours and remains suppressed the next day
- Cushing's disease may partially suppress, but rebounds next day[1]

[1]Jung C et al, Clin Endocrinol (Oxf). 2010 Jul;73(1):78-84

Bilateral Inferior Petrosal Sinus Sampling

- Best test to differentiate central from ectopic
- Experienced radiologist needed
- Invasive test
- A ratio of central to peripheral ACTH of more than 2 in the basal state or more than 3 after CRH stimulation is consistent with Cushing's disease

Western Health

TABLE 3. Causes of ectopic ACTH secretion from literature data (Refs. 54–58)

Localization	Frequency, % (No.)			
	Aniszewski *et al.*, 2001 (54)	Ilias *et al.*, 2005 (55)	Isidori *et al.*, 2005 (56)	Salgado *et al.*, 2006 (57)
Bronchial carcinoid	25% (26/106)	40% (35/90)	34% (12/35)	40% (10/25)
Pancreatic carcinoid	16% (17/106)	1% (1/90)	8% (3/35)	12% (3/25)
Small-cell lung cancer[a]	11% (12/106)	3% (3/90)	6% (2/35)	ND
Thymic carcinoid	5% (5/106)	5% (5/90)	6% (2/35)	16% (4/25)
Unknown/occult	7% (7/106)	19% (17/90)	14% (5/35)	8% (2/25)
Other	36% (39/106)	32% (27/90)	32% (11/35)	24% (6/25)

ND, Not done.

[a] Generally, this aggressive cancer is evident and is often recognized in patients with overt hypercortisolism. These patients are probably not referred to an endocrine expert center.

Osteoporosis

Case

- 80-year-old man recurrent falls.
- Kyphosis on examination.
- No prior fracture
- BMD
  - Lumbar spine T score +0.7
  - Femoral neck T score -2.3
- **LS BMD falsely elevated due to osteoarthritis**
- Plain thoracolumbar XR confirms crush fractures

Bone Mineral Density/DXA

- Osteoporosis T scores <-2.5
- Osteopenia T scores -2.4 to -1.0
- Look at the scout films
- When comparing scans, a significant change in BMD is only if:
  - Lumbar spine Δ3% if normal BMD, 5% if osteopenia/OP
  - Hip/Femur Δ7%

Bone turnover markers

- CTx (C-telopeptide) – bone resorption
- P1NP (Procollagen type 1 amino-terminal propeptide)–bone formation
- Fasting sample
- May be used to assess compliance with therapy
  - Expect CTx & P1NP to be suppressed on anti-resorptive therapy