臺大醫院
代謝內分泌
檢查工作手冊

NTUH Endocrine/Metabolism
Dynamic Test Manual

臺灣大學醫學院附設醫院
代謝內分泌科 著

臺大醫院代謝內分泌檢查工作手冊

NTUH Endocrine / Metabolism Dynamic Test Manual

發行單位 / 臺灣大學醫學院附設醫院代謝內分泌科

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C. 腎上腺（Adrenal gland）

- Cushing syndrome
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  - Overnight dexamethasone suppression test
  - Low dose dexamethasone suppression test (LDDST)
- Adrenal insufficiency
  - Insulin tolerance test (ITT)
  - ACTH stimulation test.
- Primary aldosteronism
  - Guideline for primary aldosteronism (PA)
  - Aldosterone renin ratio (ARR)
  - Saline infusion test (SIT)
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D. 血糖與代謝（Glucose & Metabolism）

- Diabetes mellitus (DM)
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E. 其他（Miscellaneous）

- Hypophosphatemic osteomalacia
- Genetic test for endocrine disorders

序

內分泌與代謝疾病，臨床上並不罕見，一般靠著病史與身體檢查，就可以做出臨床診斷，然而要進一步做鑑別診斷，往往需要實驗室之幫忙來加以確診，也因此患者在初步荷爾蒙之檢測後，常需要再住院進行相關之檢查。由於身體荷爾蒙之分泌常為動態性，許多測試方法較為複雜，且安排也較為精密，需要特別加以注意。也因此，當我們的年輕醫師 fellows 提出要將在本科訓練所參考之手冊印製成書，本人樂觀其成，並得科內許多前輩之同意，將其在台大服務期間所建立的方法，無私的傳承下來。而且藉這個機會，也承蒙同仁，特別感謝施翔蓉助教授、李弘元副教授加以鼎正翻新，與林家宏醫師的熱心奔波，而得以讓更多的醫師參考使用，來嘉惠病患，對他們在繁重的臨床服務與研究工作之餘貢獻本書之心力，也致上最大感謝。

也要特別感謝黃天祥教授與翁遠基金會，在本書之付梓給予很大之鼓勵與經費之協助，而可同步以電子書以及口袋書的方式呈現，達到知識共享之最大效益。

本手冊提供實用之內分泌與代謝常見疾病與檢查，包括不同內分泌系統檢查之流程和結果之判讀，也提列可能影響結果判讀之因素，和在執行這些測驗時該注意之事項，以減少干擾並保護病人之器官功能。本手冊可做為臨床醫師診療時的參考，但於實際應用時，也需依病人的個別情況做適度的個別考量。

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導言

這一本書，小歸小，卻是不折不扣的內分泌和新陳代謝學的武功祕笈，在處理住院病人和門診跟教授看診時，特別可以發揮其功能。因為內容網羅了遇到各式各樣情況的處理方法，也就是所謂的套餐。此外，本書也提示遇到了各種疾病時要做甚麼檢查，如何做等。何況本書雖小， 鉅細靡遺，例如畫族譜圖的規定，到抽血時間因應一例一休的規定，都有考慮，可說十分用心。

最棒的是除了採用紙本印刷，可以放在口袋隨時參閱外，也將出電子書版，方便開檢查單時，Copy and Paste。當然版本也會不斷推陳出新，以不斷的更正到最正確、最新穎為原則。

最後要恭喜此書的出版，也希望本書能跟得上時代潮流，日後能以雙語出版 (加上英語)，以達到世界性普遍採用為終極目標。

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「臺大醫院代謝內分泌檢查工作手冊」是由「台大內科手冊」新陳代謝及內分泌專章演化而來，此手冊將代謝內分泌病房常用的檢查及治療流程做成專書出版。首先要感謝施翔蓉醫師的整理與考證，使得此書所列的檢查更有實證。

近年來參與專科醫師口試發現很多代謝內分泌訓練醫師因為病例的關係，很少接觸到傳統的內分泌疾病，因而對於內分泌動態試驗的原理、作法、判讀及注意事項不熟悉，此書之出版可補足此一缺憾。內分泌疾病常因症狀的不特定性及激素的正常範圍很廣，以致被忽略甚至誤診，內分泌動態試驗常是診斷利器。

本書包含了大部分常用的代謝內分泌檢查，但內分泌範圍甚廣，本書未包含全部檢查，也許可待後續加以補全。

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內分泌系統包含腦下垂體、甲狀腺、副甲狀腺、腎上腺、胰臟、睪丸、卵巢等分泌荷爾蒙經血液運送至身體各處產生作用，這些荷爾蒙的分泌受到許多因素的調控與影響。臨床上我們診斷內分泌新陳代謝疾病時，常常需要以「生理回饋」的概念做診斷思考的依據，也需要注意是否有其他系統疾病或藥物影響了荷爾蒙的分泌與檢測，荷爾蒙基礎值 (basal level) 以及對於動態檢查 (dynamic test) 的反應是診斷內分泌疾病不可或缺的依據。

臺大內分泌新陳代謝科在陳芳武教授、林瑞祥教授、戴東原教授、張慶忠教授、黃天祥教授、張天鈞教授、蔡克嵩教授、莊立民教授的指導下建立了很好的內分泌新陳代謝疾病檢查工作手冊。此工作手冊包括病人住院應注意事項、內分泌新陳代謝疾病與檢查、甲狀腺腫分級、眼病變患者住院流程，以及低磷骨軟化症、庫欣氏症候群、腎上腺功能不全、原發性高醛固酮症、腦下垂體腫瘤、腦下垂體功能低下、尿崩症、低血糖等之鑑別診斷及相關動態檢查之標準流程，是臨床診斷與教學的重要工具，在內分泌科病房輪訓的住院醫師可以依據手冊中所建議的流程替病人安排適當的內分泌檢查並加以判讀。此手冊由內分泌新陳代謝科研修醫師負責，每年再邀集所有內分泌新陳代謝科主治醫師提供意見並參考最新的醫學證據重新印製，是本科經驗的匯集及傳承。

臺灣各醫院使用的內分泌檢查不盡相同，我們在內分泌新陳代謝科的專科醫師考試時也看到不同醫院的內分泌研修醫師對於內分泌動態檢查的熟稔度不同，內分泌學會希望可以建立共同的診斷流程以助於臺灣內分泌學界的學術交流與研究。感謝施翔蓉醫師發起，我們徵得臺大老師教授們的同意，在所有主治醫師及林家宏、嚴愛文、陳柔合、周璠、陳思潔、黃則穎等研修醫師的共同努力之下將此本工作手冊出版，希望可以對於臺灣的內分泌疾病診斷與研究有所幫助。

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這本手冊有助於醫學生、實習醫師與住院醫師執行代謝內分泌學檢查參考。現在是個人化醫學的時代，因人制宜，有幾點說明如下：

第一：Insulin 低血糖試驗：老年人或心臟病人，不宜作 Insulin 低血糖試驗。 Insulin 劑量一般病人 Regular Insulin 0.1U/Kg 體重；席漢氏症 (Sheehan syndrome)、腦垂腺低能症 (hypopituitarism) 或腎上腺皮質低能症 (adrenal cortical insufficiency) 病人給 InsulinI 0.05U/Kg 體重;肢端肥大症 (acromegaly)、庫欣氏 (Cushing) 症 / 病 或肥胖病人可給 Insulin 0.15U/Kg 體重。 檢查期間注意病人狀況，若血壓下降、心搏過速或劇烈頭痛，先抽血一支，然後中斷試驗並給予 5% 葡萄糖液點滴。

第二：Clomiphene 刺激試驗：女病人前後 19 天；男病人前後 11 天。判讀結果：女病人 LH 上升 2 倍為陽性反應，第 19 天 progesterone 上升大於正常 luteal phase 表示有排卵。男病人第 11 天 testosterone 上升至少 50%, LH 與 FSH 分別增加 75% 與 50% 為陽性反應。

第三：檢體時間及數目 : cortisol 8AM，4PM 檢體當天送檢； 11PM 檢體放 4°C 冰箱，隔天送檢。ACTH 8AM，4PM 檢體當天送檢； 不抽 11PM，因 ACTH 胜肽易被酶分解。檢體數目 : TRH test, 公勞保時代，3 小時內 7-8 支檢體。健保 2 小時內 4 支檢體 : 0、30、60 與 120 分鐘。

第四：尿崩症病人，前人檢查要作 24 小時。台大 8AM-12noon 作 water deprivation test，中午 12 時注射 DDAVP, 12 時 -4PM DDAVP test, 檢體立刻送生化科檢查。

第五：Skull X-ray 照 PA and Lateral，不是 AP and Lateral。 腎上腺要勾 Adrenal CT，不要勾 Abdominal CT。嗜鉻細胞瘤 (pheochromocytoma) 病人若要作 Adrenal MRI，註明請作 T2- weighted image； 若要檢查 24h urine VMA、catecholamines 要註明 24h 尿的總量。

第六：Cushing 氏症 / 病，從前無法測量 plasma ACTH，要作 1mg overnight、Low dose 2mg/d、high dose 8mg/d Dexamethasone suppression test. 以區別病變在腎上腺或腦垂腺。現今 plasma ACTH 已是常規檢查，且影像學進步又 Adrenal CT、MRI of sella turcica 足以區別病變所在，又 Dexamethasone suppression test 結果常有偽陽性與偽陰性，因此可以不作此 suppression test。

第七：嗜鉻細胞瘤、副神經節瘤與副甲狀腺低能症病人及其親屬要作基因蛋白質學檢查。

最後，檢查期間請停用所有其它藥物；最近門診已檢查項目，不必重覆作。

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檢測血液和尿液中的各種生化物質，是內分泌科醫師診治病人的首要工具。醫師們除了需要了解環境，如晨昏、進食對正常生理機機能之影響，了解自己使用的實驗室的精確度，並使用正確的血液和尿液容器之外，最重要的是安排正確的施檢流程，以得到正確的診斷，避免更多的檢查和重覆，造成病人的傷害及資源的浪費。

內分泌檢查常使用刺激性和抑制性的介入，以動態與系列性的驗血和驗尿方式，使正常狀態與病理狀態能夠清楚分別。這些介入性的方法數目繁多且細節複雜，也時常隨著醫療的進展而改變 ，醫師們很需要一個方便的手冊供時時查閱。這一次的改版就是提供一本充分考慮目前世界及台灣醫療現況，具高度實用性的新手冊，敬請各位醫師多加利用。

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Endocrine and Metabolism 病人入院注意事項

A. Admission note 需詳細記載

- Current medications(dosage & duration)
- 正確的家族病史及 pedigree(可參考 Bennett RL et al, Am J Hum Genet. 1995 Mar; 56(3):745-52.)
- 職業
- 月經與懷孕史
- 相關理學檢查重點 (如 BMI、central obesity、hyperpigmentation、goiter、hirsutism、striae, acanthosis nigicans, etc.)

B. New patients with DM

- DM diet (use IBW to calculate daily calorie intake)
- Consult dietitian if indicated for DM diet education
- Consult ophthalmologist if indicated for retinopathy screening
- U/A : protein (-) → Check 24 hr albumin excretion rate or spot urine microalbumin/creatinine (UACR)
- U/A : protein (+) → Check 24 hr protein excretion rate or spot urine total proein/creatinine (UPCR)
- Monofilament test and tuning fork test
- Arrange NCV if symptoms of neuropathy
- Patients with DM foot: measure 4 limbs BP (ABI: 0.9-1.3), check pulsations
- DM patients 應有 6 個月內的 lipid profile (T-CHO, TG, LDL, HDL)

C. Endocrine dynamic test 注意事項

- 注意抽血、打藥以及送檢查的時間。(大部分檢查週末以及晚上不能做)。
- 開檢驗單時，請務必備註是何種 test 以及是幾分鐘時抽的血。
- 如：ACTH (rapid ACTH stimulation test 30 mins)
- 病歷中須註明 Endocrine dynamic test 使用的藥物劑量，和時間對應之檢驗值。
- 有些檢查 test 會受某些藥物影響，要開藥及檢查前請務必釐清。
- 若需反覆抽多次血，可開 heparin lock 醫囑：heparin 0.1 ml + N/S 10 ml, 抽 1 ml for IV lock，每次抽血前需先抽掉廢血。

D. Image

- Pituitary MRI 要特別註明部位並且**要打顯影劑。**
- Adrenal CT 要註明部位並且**要打顯影劑。**
- Orbital CT 要註明部位，**不需打顯影劑。**
- 需打顯影劑患者需注意用藥與腎功能之可能惡化。

Endocrine and Metabolism 常見疾病與檢查

以下是以 Endocrine and Metabolism 常見的疾病為主軸，列出診斷不同疾病時經常使用的檢查，其中有 (※) 的部份，可參考此本手冊中的 protocol 以供使用。

※***Thyroid***

A. Graves' disease

- Lab: fT4, hsTSH (EIA/RIA), TBII (thyrotropin binding inhibitory immunoglobulin) , anti-TPO antibody, anti-thyroglobulin antibody (ATA)
- Thyroid echography
- Graves' orbitopathy : non-contrast orbital CT, TBII

B. Hashimoto's thyroiditis

- Lab: fT4, hsTSH (EIA/RIA), anti-TPO antibody, anti-thyroglobulin antibody(ATA)
- Thyroid echography

C. Thyroid nodule

- Lab: fT4, hsTSH → toxic/nontoxic
- Thyroid echo (single/multiple/size/echogenicity/border/calcification/cyst)
- Fine needle aspiration cytology
- Radioiodine scan

D. Thyroid cancer：papillary/follicular/medullary/anaplastic

- CEA and calcitonin for medullary thyroid cancer
- Thyroglobulin (post-total thyroidectomy and 131I treatment) for PTC/FTC

※Parathyroid

A. Hyperparathyroidism:

- Lab: Ca, P, Cl, iPTH, Alb, ALP, Cre
- Thyroid echo
- 99mTc sestamibi scan (parathyroid SPECT/CT)

※Cushing's syndrome

- Lab: serum ACTH (8AM, 4PM), cortisol (8 AM, 4 PM, 11 PM), glucose, electrolytes, CBC+D/C
- Screen: Overnight 1mg dexamethasone suppression test, 24H urine free cortisol (※)
- Confirmation test: Low dose dexamethasone suppression test (※)
- Etiology: plasma ACTH, High dose dexamethasone suppression test (※) , Bilateral inferior petrosal sinus sampling (BIPSS)
- Skull X ray (PA+lateral), pituitary MRI, adrenal CT (according to the origin)
- Ectopic ACTH syndrome: K, VBG, tumor markers, chest+abdominal CT

※Adrenal gland

A. Adrenal insufficiency

- Lab: Cortisol/ACTH (8 am/4 pm), electrolytes, glucose, CBC+D/C
- Confirm test: Cortrosyn test (※), Insulin tolerance test (ITT) (※)

B. Primary aldosteronism

- Lab: K, Na, TTKG, VBG
- Screen: ARR (aldosterone / plasma renin activity ratio) (※)
- Confirm test: Saline infusion test (※), Captopril suppression test (※)
- Postural stimulation test (※)
- Adrenal CT with/without contrast medium
- Bilateral adrenal venous sampling (AVS)
- I-131 NP59 scintigraphy

C. Pheochromocytoma

- Lab: 24 hours urine VMA + catecholamine (dopamine, epinephrine)
- Consider MEN-2 survey:
  - Thyroid echography for MTC
  - Albumin, Ca, P, Cl, iPTH for hyperparathyroidism
  - Consider genetic testing
- Plasma free normetanephrines/metanephrines (if available)
- Chromogranin A (CgA) (if available)
- Adrenal CT with/without contrast medium
- I-131 MIBG (if available), F-DOPA PET (if available)

- 可能會干擾 catecholamine/metanephrine 結果的因子 : (William 13e, Chap. 16)

Table 16-5
Medications That May Increase Measured Levels of Fractionated Catecholamines and Metanephrines
♦ Tricyclic antidepressants (including cyclobenzaprine) ♦ Levodopa ♦ Drugs containing adrenergic receptor agonists (e.g., decongestants) ♦ Amphetamines ♦ Buspirone and antipsychotic agents ♦ Prochlorperazine ♦ Reserpine ♦ Withdrawal from clonidine and other drugs (e.g., illicit drugs) ♦ Illicit drugs (e.g., cocaine, heroin) ♦ Ethanol

Food: (Greenspan's 9e, Chap. 11)
♦ Caffeine ♦ Bananas ♦ Coffee ♦ Peppers

※Pituitary gland

A. Pituritary function reserve

整套 : Prolactin , GH, IGF-1, FSH/LH, E2+P4/Testosterone, TSH/fT4, ACTH/Cortisol(8 AM/4 PM)

- TRH test (※): TSH, Prolactin
- LHRH test (※): LH, FSH
- ITT(insulin tolerance test) (※): GH, ACTH/Cortisol
- Consider MEN-1 survey
  - Albumin, Ca, P, Cl, iPTH for hyperparathyroidism
  - Abdominal image for pancreatic tumor
  - Consider genetic testing (MENIN gene)

B. Prolactinoma

- Prolactin (consider dilution if Hook effect is suspected)
- Detailed medication screen for drug-induced hyperprolactinemia
- Pituitary MRI: microadenoma/macroadenoma

C. Acromegaly

- Lab: GH, IGF-1, serum glucose
- OGTT (oral glucose tolerance test or GH suppression test) (※)
- Bromocriptine test (※)
- Confrontation test, consider visual field exam
- Image: skull X ray (PA + lateral), bilateral hands/feet X ray, pituitary MRI with/without contrast medium

D. Diabetes insipitus

- Lab: serum Na, urine/serum osmolality, urine analysis for special gravity
- Water deprivation test (※)
- Skull X ray, pituitary MRI if central DI

※Sex hormone

A. Male hypogonadism

- Lab: LH/FSH, testosterone, prolactin
- LHRH test (※)
- Clomifene test (※) (可在 Outpatient clinic 做)

B. Amenorrhea

- Lab: Beta HCG, FSH/LH, E2, (P4), Prolactin, hsTSH/fT4, cortisol/ACTH, renal/hepatic function
- Gynecologic echography
- LHRH test (※)
- Clomifene test (※) (可在 Outpatient clinic 做)

※***Metabolism***

A. Type 1 DM

- Glucagon test (※)
- Anti-GAD-AB, anti-IA2 (自費)

B. Hypoglycemia

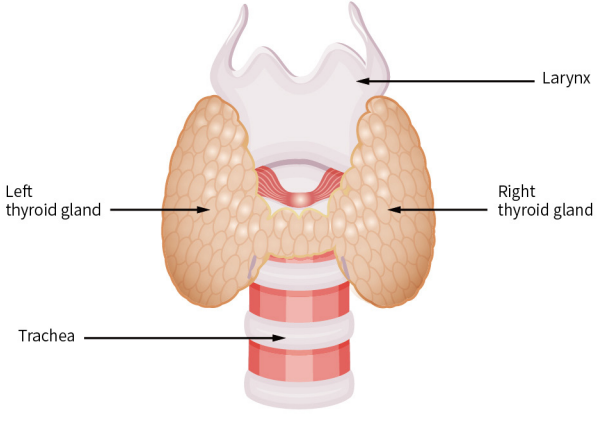
- Fasting or postprandial
- 72 hours fasting test (※)
- Mixed meal test (2-5 hours) (※)
- Octreotide test or selective arterial calcium stimulation test with venous sampling if insulinoma (※)
- Endoscopic ultrasound + FNA or abdominal image if insulinoma

Goiter Grading System

A. WHO Grading System (1994)

- Grade 0: No goiter presence is found (the thyroid impalpable and invisible)
- Grade 1: Neck thickening is present in result of enlarged thyroid, palpable, however, not visible in normal position of the neck; the thickened mass moves upwards during swallowing. Grade 1 includes also nodular goiter if thyroid enlargement remains invisible.
- Grade 2: Neck swelling, visible when the neck is in normal position, corresponding to enlarged thyroid - found in palpation

B. NTUH Goiter Grading System by Anatomy (台大老師病歷記載習慣，陳芳武教授建立的紀錄方式)



Grade 0	Thyroid palpable, but not visible.
Grade 1	Goiter visible, restricted within the medial side of sterno-cleidomastoid muscle.
Grade 2	Goiter visible, extending beyond the medial side, but still within the lateral side of sternocleidomastoid muscle.
Grade 3	Goiter visible, extending beyond the lateral side of sterno-cleidomastoid muscle.

範例：

1. No goiter. WHO grading system Grade 0.
2. Goiter: WHO grading system Grade 1, or 2.
3. Goiter: NTUH Grading system by anatomy Grade 0, 1, 2, 3.

Graves' orbitopathy 患者住院流程

1. History taking 時，須注意何時開始服藥治療，及所服用的藥物劑量。
2. 若近期內無報告，請抽血驗 free T4, TSH, TBII
3. **確認病人是否有 HBV (HBsAg) or HCV (anti-HCV) ，小心注射 steroid 可能產生的 side effect 項目的 baseline 狀況 (e.g. hepatitis, hypertension, hyperglycemia, GI bleeding, insomnia,)**
4. 確認病人是否已經做過 **non-contrast orbital CT**
5. 衛教病人 Graves' orbitopathy 注意事項 (e.g. 戒煙)
6. 紀錄 Clinical activity score，EOM，diplopia，並使用 Hertel exophthalmometer (凸眼計) 紀錄病人凸眼情形。

以上須在打 PULSE THERAPY 之前完成

7. Pulse therapy 劑量 :
   - **Methylprednisolone 500 mg in 250 ml normal saline IV**
   - **Drip for 1 hour QD x 3 days**
8. 紀錄病人打 pulse therapy 多久之後症狀自覺好轉
9. 出院前再一次紀錄 Clinical activity score， EOM，diplopia，與凸眼程度。

10. Clinical Activity score

	Right eye	Left eye
紅 Eyelid redness		
腫 Eyelid swelling		
紅 Conjunctival redness		
腫 Chemosis		
紅 Inflammation of caruncle		
痛 Pain on attempted up or dowm gaze		
痛 Spontaneous retrobulbar pain		

- EOM (extraocular movement) : 程度由 0 ~ 3 (眼球運動正常打 3，完全不動 0)
- Diplopia : 若有 , 就以 (+) 表示 , 若沒有 , 就以 (—) 表示

Right Eye

Left Eye

24-hour urine free cortisol

A. Purpose: Screening for Cushing's syndrome

B. Procedure: 24 hour urine free cortisol level. (Normal range: 4.3~176.0 μg/24hr)

註：先進行此檢查再進行 dexamethasone suppression test 避免干擾。

Overnight Dexamethasone Suppression Test

A. Purpose: Screening for Cushing's syndrome

B. Procedure

- Give 1 mg dexamethasone po at 11 pm
- Check cortisol at 8 am of the following day prior to food intake

C. Interpretation

- Normally serum cortisol are suppressed to < 1.8 (2.0) μg/dL
- Depression, restless sleep, emotional or physical stress, recent heavy alcohol consumption, obesity, thyrotoxicosis, acro-megaly, pregnancy, oral contraceptives, diphenylhydantoin, phenytoin, rifampin and barbiturates → false positive

Low Dose Dexamethasone Suppression Test

A. Purpose: Confirmation of Cushing's syndrome

B. Procedure

- D1: Obtain baseline serum cortisol, ACTH at 8 am
- D1-2: Give dexamethasone 0.5 mg q6h po x 2 days
- D3: Check serum cortisol level at 8 am

Day1 8 am	Give dexamethasone 0.5 mg q6h po x 2 days (D1, D2)	Day3 8 am
ACTH, Cortisol		Cortisol

C. Interpretation: normal response → serum cortisol < 2 μg/dl at 8 am on D3

High Dose Dexamethasone Suppression Test

A. Purpose: D/D of Cushing's disease or ectopic ACTH secretion

B. Procedure

- D1: Obtain baseline serum cortisol, ACTH at 8 am
- D1-2: Give dexamethasone 2 mg q6h po x 2 days
- D3: Check serum cortisol level at 8 am

C. Interpretation

- Cushing's disease: D3 cortisol level is < 50% of D1 baseline cortisol level;
- Ectopic ACTH: non-suppressible

Reference:

1. Stewart PM, et al. Williams Textbook of Endocrinologoly, 13e, Chap. 15, p. 515-517

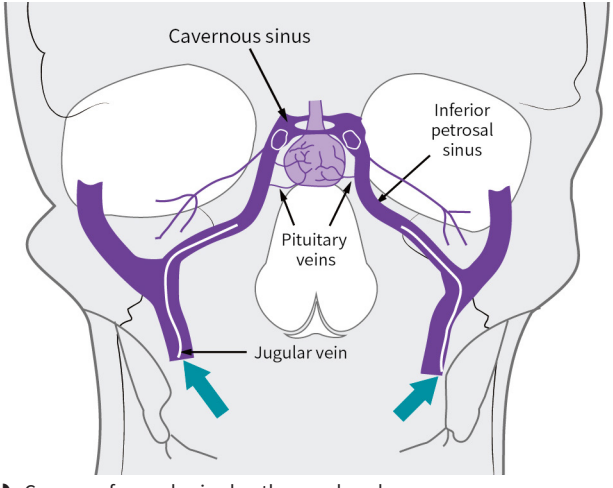
2. Ergin AB, et al. The Cleveland Clinic Manual of Dynamic Endocrine Testing, Chap. 5, 7, 8

Inferior petrosal sinus sampling (IPSS)

A. Purpose

- To distinguish pituitary from nonpituitary origin of ACTH-dependent Cushing syndrome. (The gold standard test)

B. Procedure (因為 ACTH 要冰浴急送 , 故需要一位病房醫師至放射科協助送檢)



- Common femoral vein sheaths are placed.
- Through the femoral sheath, catheters are placed into bilateral IPS.
- Blood samples are obtained for plasma ACTH measurement from each of the three ports (Peripheral, Left and Right IPS) simultane-

ously as baseline **(0 min).**

- Desmopressin (DDAVP) **10 μg peripheral IV** injection.
- Repeat blood sampling for plasma ACTH from each of the three ports simultaneously (Peripheral, Lt and Rt IPS) **at 3, 5,** and **10 min** after DDAVP IV injection.
- Bed rest for 4 hrs.

ACTH	0 min	3 min (After DDAVP)	5 min	10 min
Peripheral				
Left IPS				
Right IPS				

C. Interpretation

- Pituitary-origin of ACTH: An IPS to peripheral (IPS:P) ratio ≥ **2** at basaline **and ≥ 3** after DDAVP stimulation.
- Lateralization of pituitary adenoma: An intersinus ratio (IPS : IPS) **≥ 1.4.**

D. Complication: Groin hematoma, thromboembolic event, etc.

Reference

1. Machado MC, et al. Clin Endocrinol 2007 Jan;66:136-42

Rapid ACTH Stimulation (Cortrosyn) Test

A. Purpose

- Evaluate adrenocortical function in suspected adrenal insufficiency

B. Procedure

- Anytime, NPO is not necessary
- 1 μg Cortrosyn (商品名 : Synacthen)* slow iv push (or 5μg or 250μg，劑量需與主治醫師討論後決定)
  ※Synacthen 0.001 mg (=1 μg) 泡法：1amp 用 insulin 針筒抽 4 U (=0.04 mL=10 μg)，再用 25 mL 空針加入 normal saline 總共 dilute 成 10 mL (此時濃度 1 μg/1mL) --> 抽 1mL 即為 1 μg
- Blood sampling: 0' (ACTH, Cortisol), 30', 60' (Cortisol)

C. Interpretation

- Normal response: Peak of cortisol (≥ 20 μg/dl)
- A normal response rules out primary adrenal insufficiency; but can not exclude secondary adrenal insufficiency.

D. Drug-drug interaction: 如有服用 depakine，須小心 hepatotoxicity。

Reference:

1. Stewart PM, et al. Williams Textbook of Endocrinology, 13e, Chap. 15, p. 530

2. Ergin AB, et al. The Cleveland Clinic Manual of Dynamic Endocrine Testing , Chap. 5, 7, 8

3. Gardner DG, et al. Greenspan’s Basic & Clinical Endocrinology, 9e, Chap. 9

* 註：臺大醫院目前有兩種劑型

1. < 專 > Synacthen IV/IM 0.25 mg/1 mL/amp，本藥為專案進口藥品，限內分泌科限定醫師使用，適應症為腎上腺機能低下症之診斷。
2. < 專 > Synacthen Depot 1 mg/1 mL/amp (IM only)，1 mg Synacthen = 100 IU ACTH，限小兒神經部限定醫師使用，專案申請適應症為嬰兒點頭癲癇症。

ITT (Insulin Tolerance Test)

A. Purpose: 利用 hypoglycemia 造成之 stress 來刺激 hypothalamic-pituitary- adrenal axis and growth hormone 分泌；為診斷 adrenal insufficiency & growth hormone deficiency 之 gold standard

B. Contraindication: ischemic heart disease, pregnancy, cerebrovascular disease, epilepsy, severe hypopituitarism (9 am cortisol < 6.5 μg/dL)；而 elderly, critical illness 為 relative contraindication

C. Procedure:

- 問 seizure, CAD history，做 EKG，check baseline cortisol level
- (測試進行時，需有家屬陪同)
- NPO since midnight，set IV catheter (確認暢通 for D50W 備用)，可給 N/S infusion
- Give regular insulin iv，dose: 0.1-0.15 U/kg of actual BW，
- 若病人為 obese or DM/Acromegaly/Cushing's syndrome: 0.2-0.3 U/kg BW (DM 病人可算一下 dose 可否達成 hypoglycemia)
- 懷疑病人有 GH deficiency，測 GH。

- Blood sampling before adequate hypoglycemia met:

	0' (insulin iv)	15'	30'	45'	60'	90'	120'
One touch							
Plasma Glucose							
Cortisol							
GH							

- **Plasma glucose (請 key 急單 (STAT))**
- 緊追 plasma glucose 結果 , 若當次 plasma glucose 沒有小於 40 mg/dl, cortisol/GH 就不要送出 , 直到當次 plasma glucose 小於 40 mg/dl, cortisol/GH 才送出 , 且 hypoglycemia 後 30 min 的 cortisol/GH 也要送出
- Repeated dose: 若 45 min 時仍未達到 adequate hypoglycemia，可 repeat RI iv, dose 可計算一下，一般以 initial 一半的 dose 給予
- 若 one touch 接近或 <40mg/dl，可一起抽 plasma glucose + Cortisol+GH (如果懷疑 GH deficiency) ，但 Cortisol 及 GH 的管子先不要送去檢驗室，等 central plasma glucose data 確認是 <40 mg/dl，再把 hypoglycemia 那時的 Cortisol, GH 送出。(e.g. 30' one touch 42 mg/dl ⇒一起抽 plasma glucose+Cortisol+GH ⇒後來 plasma glucose 出來是 45 mg/dl ⇒ Cortisol,GH 那 2 管不送出。45' one touch 41 mg/dl ⇒一起抽 plasma glucose+Cortisol+GH ⇒後來 plasma glucose 出來是 38 mg/dl ⇒ Cortisol,GH 那 2 管送出。)

- Blood sampling after adequate hypoglycemia

	0' (hypoglycemia 當下)	30'
One touch		
Plasma Glucose		
Cortisol		
GH		

- 當有 adequate hypoglycemia 即可給糖，依嚴重度給 D50W or 食物，繼續監控血糖，Hypoglycemia 後雖然有吃東西或給 D50W，但是在 30 mins 後要抽 cortisol and GH。

D. Interpretation:

- Adequate hypoglycemia : glucose < 40 mg/dL，大部分在 insulin 打後 20-35min 發生。
- HPA axis: 正常 peak cortisol level > 18 μg/dL
- 正常 GH peak > 5 ng/mL. If GH <3 ng/mL：GH deficiency.

References:

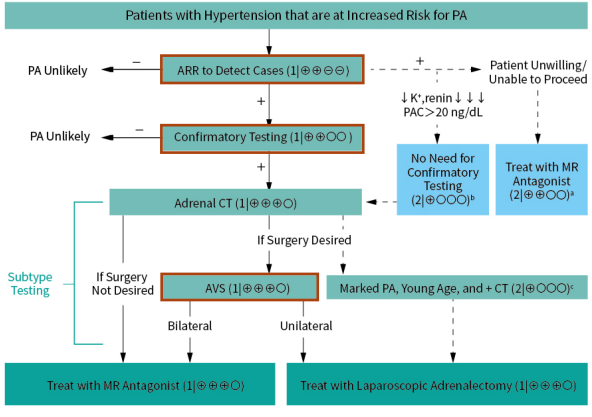
1. Kaiser UB, et al. Williams Textbook of Endocrinology, 13e, Chap.8, p. 203

2. Gardner DG, et al. Greenspan’s Basic & Clinical Endocrinology, 9e, Table 4-9, p. 86

Algorithm for Detection, Confirmation, Subtype Testing, and Treatment of Primary Aldosteronism (PA)

When to consider testing for primary aldosteronism:

- Hypertension and hypokalemia
- Resistant hypertension
- Adrenal incidentaloma and hypertension
- Onset of hypertension at a young age (<20 y)
- Severe hypertension (≥ 160 mm Hg systolic or ≥ 100 mm Hg diastolic)
- Whenever considering secondary hypertension



A. Case detection: **ARR (aldosterone – renin – ratio)**

B. Confirmatory testing

- Oral sodium loading test,
- **Saline infusion test,**
- Fludrocortisone suppression test,
- **Captopril challenge test**

C. Subtype testing: (1) Adrenal CT, **(2) AVS (adrenal venous sampling)**

References

1. *Funder JW, et al. The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab, 2016, 101: 1889-1916*
2. *Williams Textbook of Endocrinology, 13th Edition, Chapter 16, 556-88*

Aldosterone Renin Ratio (ARR)

A. Objective : Case detection for suspected primary aldosteronism (PA)

B. Principle : Plasma aldosterone concentration (PAC) ↑ + Plasma renin activity (PRA) ↓ ⇒ ARR ↑

C. Preparation:

- 矯正低血鉀，目標 serum [K+] ≥ 4.0 mmol/L。
- 放寬鈉攝取限制。
- **停用下列藥物至少 4 週 (– 6 週)：**
  - **Spironolactone,** eplerenone, amiloride, triamterene
  - Potassium-wasting diuretics
  - 甘草 (licorice root) 衍生物 (如：甘草糖果、嚼菸)
- 如果停用以上藥物後所得之 ARR 結果無法診斷，而且血壓能以替代藥物 (表格 2) 控制的狀況下，建議停止下列藥物至少 2 週：
  - β-adrenergic blockers, central α-2 agonists (e.g. clonidine, α-methyldopa), NSAIDs
  - ACE inhibitors, ARB, renin inhibitors, dihydropyridine CCB

D. Measurement:

- 在 midmorning 抽血 (最好在 8 – 10 AM)
- 抽血前身體需直立 (坐、站、或走路) 至少 2 小時且呈坐姿 5–15 分鐘

E. Interpretation:

- **PAC ↑ ≥ 15 ng/dL、PRA ↓ < 1 ng/mL/hour，加上 ARR ≥ 20** (請注意單位 !) ⇒ 疑似 PA，進入 confirmatory testing。

- 如果在服用可能導致 false – negative ARR 的藥物下，PRA 仍然被 suppressed (< 1 ng/mL/hour)，合理懷疑有 PA，可以直接進入 confirmatory testing。

References:

1. *Funder JW, et al. The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab, 2016, 101: 1889-1916*
2. *Williams Textbook of Endocrinology, 13th Edition, Chapter 16, 556-88*

表格 1

Factors that may lead to false-positive or false-negative ARR results

Factors	Effect on PAC	Effect on renin	Effect on ARR
Medications			
β-adrenergic blockers	↓	↓↓	↑ (FP)
Central agonists (clonidine, α-methyldopa)	↓	↓↓	↑ (FP)
NSAIDs	↓	↓↓	↑ (FP)
K^+-wasting diuretics	→↑	↑↑	↓ (FN)
K^+-sparing diuretics	↑	↑↑	↓ (FN)
ACE inhibitors	↓	↑↑	↓ (FN)
ARBs	↓	↑↑	↓ (FN)
CCB (CHPs)	→↓	↑	↓ (FN)
Renin inhibitors*	↓	PRA ↓, DRC ↑	RPA ↑ (FP)
Potassium status			
Hypokalemia	↓	→↑	↓ (FN)
Potassium loading	↑	→↓	↑
Dietary sodium			
Sodium restriction	↑	↑↑	↓ (FN)
Sodium loading	↓	↓↓	↑ (FP)
Advancing age	↓	↓↓	↑ (FP)
Pre-menopausal women (vs. men)	→↑	↓	↑ (FP)
Other conditions			
Renal impairment	→	↓	↑ (FP)
PHA-2 ¶	↑	↑↑	↓ (FN)
Pregnancy	↑	↑↑	↓ (FN)
Reno-vascular HTN	↑	↑↑	↓ (FN)
Malignant HTN	↑	↑↑	↓ (FN)

* Renin inhibitors lower PRA, but raise DRC ⇒ false positive ARR for renin measured as PRA and false negative for renin measured as DRC.

¶ PHA-2 = pseudohypoaldosteronism type 2 (familial hypertension and hyperkalemia with normal GFR)

表格 2

對 plasma aldosterone levels 影響少的藥物，可用於 ARR and confirmatory tests for PA 測驗時血壓控制替代用藥

Drug	Class	Usual Dose
Verapamil SR	Non-DHP CCB	90 – 120 mg BID
Hydralazine	Vasodilator	10 – 12.5mg BID, increasing as required
Prazosin	α-adrenergic blocker	0.5 – 1 mg BID or TID, increasing as required
Doxazosin	α-adrenergic blocker	1 – 2 mg QD, increasing as required
Terazosin	α-adrenergic blocker	1 – 2 mg QD, increasing as required

Saline Infusion Test (SIT)

A. Objective:confirmatory test for primary aldosteronism

B. Principle

Normal saline infusion ⇒ volume expansion and saline load ⇒ suppress renin angiotensin system ⇒ suppression of PAC

C. Procedure

1. 停用會影響結果判讀的藥物
2. 開始測驗前需躺臥至少 1 小時，測驗過程中需保持躺臥姿勢
3. 早上 8:00 – 9:30 AM 開始測驗
4. **2000 mL 0.9% saline IV infusion over 4 hours** (with infusion pump)，
5. Monitor BP and HR throughout the test
6. 抽血：PRA, PAC before (0') and after (4-hr) saline infusion
7. (optional) 若有低血鉀疑慮，可在檢查前後驗血鉀濃度。

D. Modified procedure: Seated SIT – higher sensitivity

1. 開始測驗前需坐著至少 30 分鐘，測驗過程中需保持坐姿
2. 抽血：PRA, PAC, cortisol before (0') and after (4-hr) saline infusion

SIT	PRA	PAC	Cortisol	K
Before (0')	V	V	(if seated SIT)	(optional)
After (4 H)	V	V	(if seated SIT)	(optional)

* Cortisol ⇒ exclude a confounding ACTH effect

E. Interpretation:

- 若是採臥姿：(Sensitivity 83%, specificity 75%)
  - Post-infusion **PAC < 5 ng/dL** ⇒ A unlikely
  - Post-infusion **PAC 5 – 10 ng/dL** ⇒ indeterminate, eg. IHA (Bil. idiopathic hyperplasia)
  - Post-infusion **PAC > 10 ng/dL** ⇒ very probable PA
- 若是採坐姿：
  - Seated SIT: post – infusion PAC > 6 ng/dL ⇒ confirms PA
  - 但若 SIT 後 cortisol 上升，則無法排除 ACTH 的影響，SIT 的結果就算是 inconclusive。

F. Concern:

若病人有 severe uncontrolled hypertension, renal insufficiency, cardiac arrhythmia, or severe hypokalemia 則不建議做此測驗。

References:

1. Funder JW, et al. J Clin Endocrinol Metab, 2016, 101: 1889-1916

2. Young WF Jr, et al. Williams Textbook of Endocrinology, 13e, Chap. 16, p. 556-88

3. Ahmed AH, et al. J Clin Endocrinol Metab. 2014 Aug;99:2745-53.

Captopril Challenge Test

A. Objective: confirmatory test for primary aldosteronism

B. Principle: Captotpril (ACE inhibitor) ⇒ blocks (Angiotensin I → Angiotensin II) ⇒ suppression of PAC

C. Procedure:

1. 停用會影響結果的藥物，
2. 開始測驗前需直立 (坐或站) 至少 1 小時，測驗過程中需保持坐姿，
3. 給予口服 Captopril 25 – 50 mg，
4. 抽血：PRA, PAC, cortisol at 0', 1-h and 2-h after challenge

Captopril	PRA	PAC	Cortisol
Before (0')	V	V	V
1-Hour after	V	V	V
2-Hour after	V	V	V

D. Interpretation:

- PAC is normally suppressed > 30% by Captopril
- PA ⇒ **PAC remains elevated** and **PRA remains suppressed**
- May be some differences between aldosterone – producing adenoma (APA) and idiopathic adrenal hyperplasia (IAH): some decrease of PAC in IAH patients occasionally

E. Concern: 有相當數量的文獻報告此測驗偽陰性或是模擬兩可的結果。

References

1. *Funder JW, et al. The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab, 2016, 101: 1889-1916*

Postural Stimulation Test

Historical exam 參考用

A. Principle: 利用 aldosterone-producing adenoma (APA) 會受 ACTH regulate，卻不受 angiotensin II level 改變影響；而 idiopathic hyperaldosteronism (hyperplasia, IHA) 會受因站立而改變的 angiotensin II level 影響，來區分 APA 及 IHA。

B. Procedure:

1. 先停用會影響結果的藥物 (請見前面表格 1)，
2. 放寬鈉攝取限制 (因為低鈉飲食會刺激 aldosterone 分泌)，
3. 保持平躺至少 4 小時 (先不起床)，8AM 躺著先抽血 (基礎值)，
4. 保持站立或直立姿勢 4 小時後再抽一次血。

	8 AM (baseline)	12 PM (4-hour)
Plasma renin activity		
Aldosterone		
Cortisol		

C. Interpretation:

- 若 cortisol level 站立後升高，表示病人可能因某些因素感到壓力，連帶 ACTH level 也可能升高，會導致此檢查結果不準確 (無法判讀)。
- Normal or essential HTN: Aldosterone 上升 > 50% of recumbence。
- Aldosterone 不變 or 下降：Aldosterone-producing tumor, primary (unilateral) adrenal hyperplasia, or glucocorticoid-remediable aldosteronism。
- Aldosterone 上升 (>30%)：Idiopathic adrenal hyperplasia, or aldosterone producing renin-responsive tumor。

References:

1. Jameson JL, De Groot LJ, et al. Endocrinology: Adult and Pediatric, 7e, p1826-1827

2. Young WF Jr, et al. Williams Textbook of Endocrinology, 13e, Chap. 16, p. 575

3. Wu KD, et al. J Formos Med Assoc. 2001 Sep;100:598-603.

4. Gardner DG, et al. Greenspan’s Basic & Clinical Endocrinology, 8e, p. 401

5. Funder JW, et al. J Clin Endocrinol Metab, 2016, 101: 1889-1916

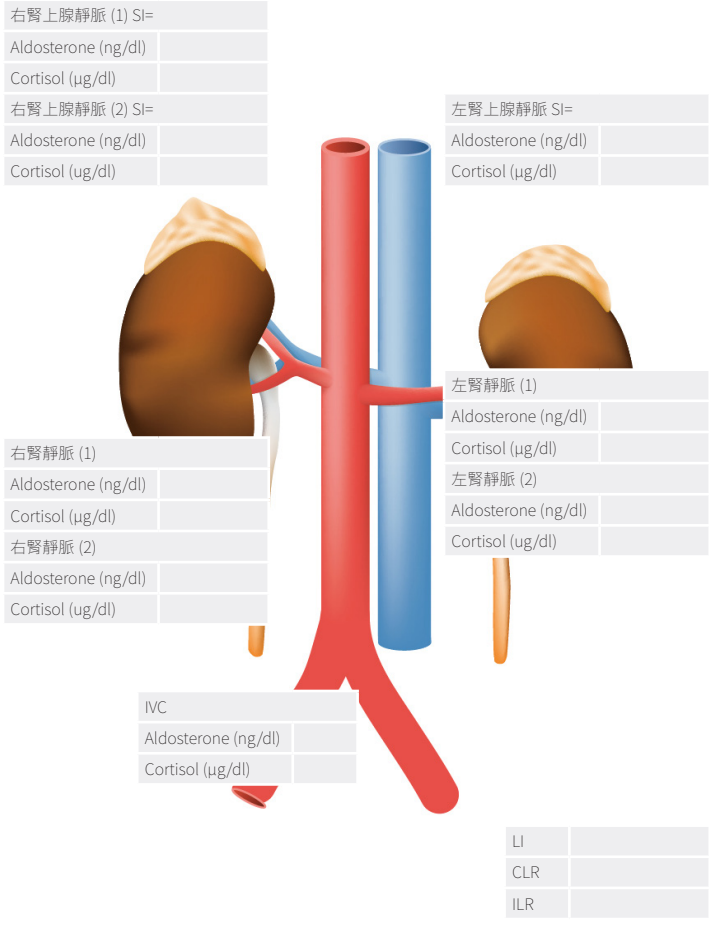
Adrenal venous sampling

A. Objective:

- Subtype classification for PA
- Distinguish bwteen unilateral and bilateral disease

B. Preparation:

- 需有專用、經驗豐富的 interventional radiologists，bilateral adrenal vein cannulation 成功率 > 90%，
- 停用會影響結果的藥物 (尤其是 diuretics and MR antagonists)，
- 不限制鈉的攝取
- Fast overnight



- Porcedure 前需躺臥至少 1 小時，最好能在早上進行此項檢查

C. Interpretation:

Clinical significance	Suggested cut-off
Selectivity index (SI) = Cortisol $_{AV}$ / Cortisol $_{PV}$	
Adequacy of cannulation of the adrenal veins	(Basal) SI > 2 (> 3 preferable) (ACTH infusion) SI > 3 (> 5 preferable)
Lateralization index (LI) = ACR AV / ACR contralateral AV	
Lateralization of aldosterone production. To distinguish between unilateral and bilateral PA	(Basal) LI > 2 → unilateral PA (ACTH infusion) LI > 4 → unilateral PA; (ACTH infusion) LI < 3 → bilateral PA (ACTH infusion) LI 3 – 4 → grey zone
Contralateral ratio (CLR) = ACR nondominant AV / ACR PV	
Inhibition of aldosterone secretion in the non-dominant adrenal galand	CLR < 1 indicative of unilateral PA A nondominant $_{AV}$ / A PV > 1.5 → bilateral
Ipsilateral ratio (ILR) = ACR dominant AV / ACR PV	
Gradient between the dominant adrenal and the peripheral vein	ILR > 2 with CLR < 1 → unilateral PA

* ACR, cortisol-corrected aldosterone ratio = Aldoterone/Cortisol

* AV, adrenal vein; PV, peripheral vein (= IVC)

References:

1. Funder JW, et al. J Clin Endocrinol Metab, 2016, 101: 1889-1916

2. Monticone S, et al. Lancet Diabetes Endocrinol 2015;3:296-303

3. Young WF Jr, et al. Williams Textbook of Endocrinology, 13e, Chap. 16, p. 556-88

4. Buffolo F, et al. Int J Mol Sci. 2017 Apr 17;18(4).

5. Ergin AB, et al. The Cleveland Clinic Manual of Dynamic Endocrine Testing, 2015, p. 51

TRH Test

A. Purpose:

- Detect hypopituitarism or subclinical hyperthyroidism/hypothyroidism;
- Assessment of prolactin (PRL) reserve and secretion

B. Procedure:

1. Contraindication: pregnancy
2. Caution: asthma, COPD, ischemic heart disease (TRH can cause smooth muscle spasm)
3. 不需要 NPO，但若可以 NPO 較佳 (因注射 TRH 時可能會有噁心感)
4. 建議檢查過程保持平躺姿勢 (因注射 TRH 後可能會有輕微血壓上升)
5. 第 0 分鐘抽血：baseline TSH and PRL
6. 給予 synthetic TRH (Protirelin) 400 μg (200-500 μg or 5-7 μg/kg/BW in children) iv over 15-30 sec
7. 第 30、60 分鐘抽血：TSH and PRL
8. Side effects: nausea, flushing, urge to micturate (occurs within 1-2 min of injection and last 5 min at most)

	0'	30'	60'
TSH			
PRL			

C. Interpretation:

1. TSH –

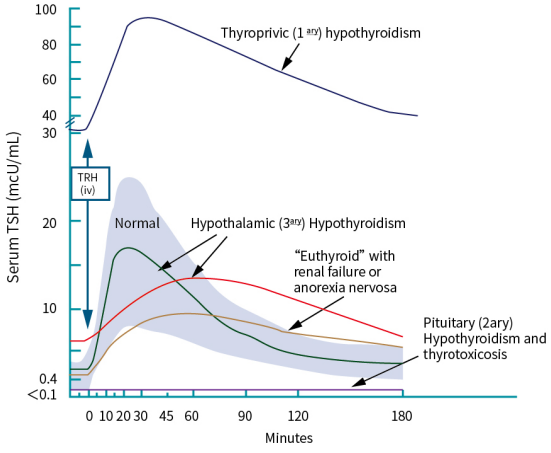
- Normal TSH response:
  - TSH rises to 7-30 mU/L (average 15-16 mU/L or 5-fold of baseline)
  - TSH rises by ≥ 5-6 mU/L (women and men < age 40),
  - TSH rises by ≥ 2-3 mU/L (men > age 40)
  - Peak TSH ≥ 2.5–fold
  - TSH peaks at 15 – 40 min (< 45 min), a subsequent decrease at 60 min (TSH higher at 20–min than 60–min)
- 以下狀況會有 blunted or decreased response: hypopituitarism, hyperthyroidism, euthyroid Graves' disease, suppressive thyroid therapy, isolated TSH deficiency, renal failure, depression, 服用以下藥物 : glucocorticoid, L-dopa, bromocriptine, oral contraceptive, acetylsalicylic acid.
- Primary hypothyroidism 可能會出現 Exaggerated TSH response:
- Women: Δ TSH >30 mU/L，Men: Δ TSH >15 mU/L
- TSH may typically remain low and unresponsive to TRH for several weeks following withdrawal of thyroid hormone replacement or after treatment of thyrotoxicosis

2. Prolactin –

- Normal PRL ≥ 2.5-fold; or PRL level > 2 μg/L and increase > 200% of baseline (varies with gender and age)
- A reduced or absent response with low baseline PRL level ⊠ deficient prolactin reserve and is typical of pituitary destruction, ablation, isolated gonadotropin deficiency, or idiopathic isolated prolactin deficiency

- 3) Not useful in the differential diagnosis of hyperprolactinemia

References:



1. Kaiser UB, et al. Williams Textbook of Endocrinology, 11e, Chap. 8, Table 8-35
2. Gardner DG, et al. Greenspan’s Basic and Clinical Endocrinology, 9e, Chap. 4, Table 4-9
3. Fauci AS, et al. Harrison’s Principle of Internal Medicine, 17e, Chap. 333, Table 333-3
4. Lavin N, et al. Manual of Endocrinology and Metabolism 4e, Appendix p.796
5. Doi SA, et al. Clin Med Res. 2007 Oct; 5: 145–148
6. Jameson JL, De Groot LJ, et al. Endocrinology: Adult and Pediatric, 7e, Chap. 78, p.1382-4; Chap. 154, p. 2685
7. Becker KL, et al. Principle and Practice of Endocrinology and Metabolism, 3e, Chap. 241, Table 241-1
8. Kageyama K, et al. Tohoku J Exp Med 2005;206:291-7
9. Chin SO, et al. Int J Endocrinol 2013; 2013: ID 159858, 7 pages

LHRH (GnRH) Test

A. Purpose:

- Assessment of pituitary gonadotropin secretion
- Differentiation of constitutional delayed puberty and hypogonadotropic hypogonadism

B. Procedure:

1. For female, preferably in the early follicular phase (D1-7)
2. Check baseline LH and FSH at 0'
3. Synthetic GnRH (Gonadorelin) 100 μg (25~100 μg) iv over 15 sec
4. Blood sampling: at 30', 60', 120' obtain LH and FSH; (obtain GH in suspected acromegaly)
5. Side effect: rare

	0'	30'	60'	120'
LH				
FSH				

C. C. Interpretation:

- LH – normal response ≥ 2-3 folds or rise by 10 IU/L (12-23 IU/L) at 15-45'(正常 LH 上升幅度應該要大於 FSH)
- FSH – normal response 1.5-2 folds & rise by 2 IU/L (less markedly than LH) (some normal males fail to have an increase in FSH following GnRH)

- Primary testicular failure ⇒ respond exaggerated increases in LH and FSH Seminiferous tubular damage alone ⇒ abnormal FSH rise and normal LH response
- Can not adequately distinguish hypothalamic from pituitary lesion
- GH – "paradoxical response" in acromegaly (50%)

References:

1. Kaiser UB, et al. Williams Textbook of Endocrinology, 12e, Chap. 8, p. 209

2. Gardner DG, et al. Greenspan’s Basic and Clinical Endocrinology, 9e, Chap. 4, Table 4-9

3. Fauci AS, et al. Harrison’s Principle of Internal Medicine, 17e, Chap. 333, Table 333-3

Clomiphene Stimulation Test

A. Principle

- Clomiphene: 合成的 non-steroidal 化合物，是 weak estrogen，可以跟下視丘的 steroid receptors 結合而阻斷 gonadal steroids (testosterone and oestradiol) 的 negative feedback，而增加 pituitary LH/FSH 分泌
- 此 test 可用來檢測下視丘 - 腦下垂體的 gonadal axis 是否正常。

< 第一種作法 > (Reference: Greenspan's Basic and Clinical Endocrinology, 9th edition, Chaper 4, table 4-9)

B. Procedure

1. 執行檢查的時機 : Started on D5 after onset of menses in menstruating women.
2. Clomiphene citrate 50 mg bid po

- Women: D1-D5.
- Men: D1-D7

3. Check LH and FSH

- Women: 0', D6.
- Men: 0', D8

D. Interpretation

- Women: D6 的 LH 和 FSH 會比正常值高
- Men: D8 的 LH 會是 0' 的 2 倍。FSH 會上升，但不會上升那麼多

< 第二種作法 > (Reference: Endocrine and Metabolic Testing Manual. 3ed, p.7-19)

A. Procedure:

1. 執行檢查的時機 :

- At any time in men or amenorrheic women.
- Started on D5 after onset of menses in menstruating women.

2. Clomiphene citrate 50 mg bid po

- Women: D1-D5
- Men: D1-D7

3. Check LH and FSH

- Women: 0', D4, D7, D10, D21.
- Men: 0', D7, D10

B. Interpretation:

- 到 D10 時 , LH 應上升至少 30%，FSH 上升至少 20%。
- 大部分正常人在 D10，LH 和 FSH 是 baseline 的 2 倍。
- Blunted responses (peak LH <2 U/L or < 30% rise): prepubertal children, patients with inadequate gonadotrope cell reserves, chronic loss of GnRH pulses, anorexia nervosa, hyperprolactinemia.
- A serum progesterone > 10 ng/mL in a woman on D21 indicates ovulation and normal luteal function.

References:

1. Gardner DG, et al. Greenspan’s Basic and Clinical Endocrinology, 9e, Chap. 4, table 4-9

2. Endocrine and Metabolic Testing Manual, 3e, p. 7-19

OGTT (Oral Glucose Tolerance Test)

A. Purpose:

- Diagnosis of DM
- Diagnosis of acromegaly (GH suppression test)

B. Procedure:

1. Overnight fasting for 8 hours
2. Oral 75 g anhydrous glucose in 300 ml of water intake, consumed within 5 minutes
3. For diagnosis of acromegaly

   Blood sampling: GH at 0', 30', 60', 90', 120'

   (註：Glucose at 120' was for DM diagnosis in acromegaly p't)

	0'	30'	60'	90'	120'
GH					
Plasma Glucose		x	x	x	

4. For diagnosis of DM

   Blood sampling: plasma glucose 0', 120'

	0'	120'
Plasma Glucose		

C. Interpretation:

- For DM –
  - Normal OGTT:fasting glucose <100 mg/dl AND 120'glucose<140 mg/dl
  - Diagnosis of DM:fasting glucose ≥ 126 mg/dl OR 120'glucose ≥ 200 mg/dl
  - False-positive results: malnourished, bedridden, afflicted with an infection or severe emotional stress, or drugs (diuretics, oral contraceptives, glucocorticoids, excess thyroxine, phenytoin, nicotinic acid, some psychiatric drugs)
- For acromegaly –
  - Normal response: GH level suppressed(nadir) to < 1 ng/ml at 60 min
  - Acromegaly:
  - GH nadir > 1 ng/ml (lower cut-off in newer more sensitive assays); 1/3 increase, 1/3 remain unchanged, 1/3 fall modestly (but not < 1 ng/ml)]
  - False positive: starvation, protein-caloric malnutrition, anorexia nervosa

References

1. Melmed S, et al. Williams Textbook of Endocrinology, 13e, Chap. 9, p.235; Chap. 31, p. 1387

2. Gardner DG, et al. Greenspan’s Basic and Clinical Endocrinology, 9e, Chap. 4, table 4-9

3. Ergin AB, et al. The Cleveland Clinic Manual of Dynamic Endocrine Testing, 2015, p. 51

Bromocriptine Test

A. Purpose:

- Alternative test for diagnosis of acromegaly (some patients with acromegaly, GH falls by bromocriptine);
- Evaluation of GH level response to bromocriptine in acromegaly patients (for further treatment)
  -

B. Procedure:

1. Overnight fasting for 8 hours
2. Take Parlodel® (bromocriptine) 2.5 mg (1 tab) po stat
3. Blood sampling: serum GH and prolactin at 0, 1-, 3-, and 6-hour

	0'	1 hr	3 hr	6 hr
GH				
PRL				

C. Interpretation:

- If GH level decreased 50% below the baseline GH level → bromocripitine could be a potential medical treatment for patient who had high risk for surgical intervention and for recurrence of disease after operation
- Somatomammotroph adenoma 可能會同時分泌 GH 和 prolactin。其中一個如果無法被抑制，可能之後用 bromocriptine 治療效果也有限。

Reference:

1. Karashima T, et al, Endocrinol Jpn. 1986 Apr;33:163-7.

Water Deprivation Test

Protocol 1

A. Purpose: Differential diagnosis of polyuria

B. Procedure:

項目 / 時間	體重	血壓	抽血		尿量	尿液 (2 管)		
	kg	mmHg	Sodium	Osmol	ml	Urine Sp.Gr	Urine Osmol	
08:00 am	v	v	v	v	v	v	v	禁食 + 禁水
09:00 am					v	v	v	
10:00 am	v	v	v	v	v	v	v	
11:00 am					v	v	v	
一直測....								
到 n 時間 (0')	v	v	v	v	v	v	v	
n 時間 (0') 定義 : 連續兩次 urine osmolality 差異≦ 10%，且病人體重下降 2%。 或連續兩次 urine osmolality 差異 <30 mOsmol/kg。 或 Urine osmolality 達到 600-700 mOsmol/kg。 或 Pasma osmolality 達到 295-300 mOsmol/kg								
(0'): DDAVP (2 μg) 0.5 ml sc								
60 min					v		v	
120 min	v	v	v	v	v		v	

95% of initial body weight = _____

- 注意事項：
- 前一天聯絡檢驗醫學部，確認 30 分鐘以內可以發出 osmolality 報告。
- 若有使用 desmopression 要先停止 24 小時以上，另不能有喝酒、吃含咖啡食物或抽菸。
- 8am 開始檢查前，先將尿解乾淨。8am 前可以進食，整個 test 當中需要禁食 + 禁水。
- 8am 開始禁食禁水後，
  - 每 1 小時記錄尿量和 urine osmolality
  - 每 2 小時記錄體重、血壓、血鈉、plasma osmolality
- 當有以下任一情況時，紀錄體重、血鈉、血 osmolality，準備給予 DDAVP
  - 連續兩次 urine osmolality 差異≦ 10%，且病人體重下降 2%
  - 連續兩次 urine osmolality 差異 <30 mOsmol/kg
  - Urine osmolality 達到 600-700 mOsmol/kg
  - Pasma osmolality 達到 295-300 mOsmol/kg
  - 給予 DDAVP (2 μg) 0.5 ml sc，之後每小時測量一次 urine osmolality 和 volume，共測兩小時
- 當有以下任一情況應立刻停止試驗
  - Serum Na > 正常值
  - 體重下降 5%
  - 低血壓 (SBP < 100mmHg)
- 實驗後應立即補充足夠液體以防止脫水。

Reference

1. Robinson AG, et al. Williams Textbook of Endocrinology 13e, Chap. 10, p. 305-306

2. Ergin AB, et al. The Cleveland Clinic Manual of Dynamic Endocrine Testing, 2015, p. 71-75

3. Lavin N, et al. Manual of Endocrinology and Metabolism 4e, Appendix A, p799.

Protocol 2 (Reference: Prof. 張慶忠)

A. Purpose: Differential diagnosis of polyuria

B. Procedure: 請依照表格及注意事項進行

項目 / 時間	體重	尿量	血壓	抽血	留兩管小便		
	kg	ml	mmHg	Plasma Osmol	Urine Sp.Gr	Urine Osmol	
08:00 am							禁食 + 禁水
09:00 am							
10:00 am							
11:00 am							
12:00 N							DDAVP (2 mcg) 0.5 ml sc
01:00 pm							禁食 + 禁水
02:00 pm							
03:00 pm							
04:00 pm							

- 注意事項：
  - 8am 前可以進食，8 am~4 pm(整個 test 當中) 需要禁食 + 禁水
  - 若病人排尿有困難，可以使用單導或是尿管。
  - 12 noon 紀錄完了之後，再打 DDAVP (2 μg) 0.5 ml sc (0.5 vial)
  - 嚴重尿崩症患者可能因過度限水而導致脫水，甚至因血液中滲透壓過高而發生意識變化，尤其在體重下降達 3-5% 者，因此過程中需留意病人體重變化及臨床症狀之有無，若有明顯意識變化或是血壓降低，請立即停止 test 且給予點滴補充水分且通知總醫師。
  - 若限水前血液滲透壓已高達 300 mOsm/Kg 以上，則停止禁水，可直接給予 DDAVP 測其反應。
  - 若病人體重下降 3%，orthostatic hypotension，則停止禁水，可直接給予 DDVAP 測其反應
  - 實驗後應立即補充足夠液體以防止脫水。

C. Interpretation

	Urine osmolality (mOsm/kg)			
Reference	Williams Textbook 13th ed		Arch Dis Child 1998;79:84–89	
	After dehydration	After DDAVP	After dehydration	After DDAVP
Normal			>750	>750
Central DI	No elevation	至少上升 50%，常上升 200-400%	<300	>750
Nephrogenic DI	No elevation	Little or no increase	<300	<300
Partial CDI	Mild elevation, but no more than 800-1200mOsm/kg	At least > 10%	300-750	<750
Primary polydipsia		No increase		
Partial NDI				

References

1. Robinson AG, et al. Williams Textbook of Endocrinology 13e, Chap. 10, p. 305-306

2. Manktelow BN, et al. Arch Dis Child Fetal Neonatal Ed. 2010 Mar;95:F95-8

Glucagon Test

A. Principle: for determine beta cell reserve, for patients suspicious of type 1 DM

B. Procedure:

1. 準備病人：

- 確定病人做 test 前 3 天有攝入足夠碳水化合物 (不得 < 5 g/kg BW)，不得處在 ketotic 狀態
- Test 前 10 hrs 或 test 中不得劇烈運動、抽煙、使用會干擾的藥物或營養食品
- 平躺
- RI/NPH injection 最好暫 test 前 12hrs 停用，會影響 insulin 分泌的 OHA 需停 1 天以上
- 可 midnight NPO，於次日早上 9~10 AM 進行 test

2. 溶解 glucagon in its diluting solution: 1 mg in 1 ml diluent (30 μg/kg) IV infusion 4 mins，速度需緩慢一致
3. Check plasma C-peptide at 0 minutes and 6 minutes

	0 min	6 min
C-peptide		

C. Interpretation:

If C-peptide peak < 1.8 ng/ml (0.5 nmol/L) 或
baseline C-peptide < 0.5 ng/ml (0.33 nmol/L)
或△小於 0.7 ng/ml → type 1 DM is likely

References:

1. Maldonado M, et al. J Clin Endocrinol Metab. 2003 Nov;88:5090-8.

2. Tung YC, et al. Eur J Pediatr. 2008 Jul;167:801-5.

3. Madsbad S, et al. Acta medica Scandinavica 1981;210:153-156.

4. Juang JH, et al. Taiwan Yi Xue Hui Za Zhi. 1989 Jun;88:579-83.

72-Hour Fasting Test & Mixed Meal Test

A. Principle: Hypoglycemia will suppress insulin secretion. If C-peptide & insulin level are still high under hypoglycemic status, endogenous hyperinsulinemia is likely

B. Procedure (72-hour fasting test):

1. 開始 fasting 時抽 baseline serum glucose, insulin, C-peptide 及 on IV line
2. 只能喝 calorie-free 及 caffeine-free fluids; 鼓勵 supervised activity (如 : 走路) (需有人陪伴)
3. 測量 urine ketones → 在 " 開始 fasting 時 "，之後 "Q12H"，與 " 結束時 "
4. Check one touch sugar Q4H 直到 < 60 mg/dl ⇒之後 check one touch sugar Q1H 直到 < 55 mg/dl ⇒此時抽血測 serum glucose, insulin, C-peptide，同時 monitor 是否有 neuroglycopenic symptoms (weakness, lethargy, confusion,incoordination, blurred vision…)

	0' (hypoglycemia)	30'
One touch		
Plasma Glucose (請 key 急單 (STAT)		
Insulin		
C-peptide		
Cortisol (如果病人也懷疑有 adrenal insufficiency 時才需要抽)		

5. Check one touch sugar Q4H 直到 < 60 mg/dl。若 one touch 接近或

<60 mg/dl，可一起抽 plasma glucose+C-peptide+insulin+cortisol，但是 C-peptide+insulin +cortisol 的試管先不要送去檢驗室，等到 plasma glucose data 確認為 < 55 mg/dl，再把 hypoglycemia 時，準備的 C-peptide+insulin +cortisol 送出至檢驗單位。

(ex. one touch 58 mg/dl ⇒一起抽 plasma glucose+C-peptide+cortisol

⇒後來 plasma glucose 出來是 58 mg/dl=>C-peptide,insulin,cortisol 那 3 管不送出。

one touch 56 mg/dl ⇒一起抽 plasma glucose+C-peptide+cortisol →後來 plasma glucose 出來是 52 mg/dl ⇒ C-peptide,insulin,cortisol 那 3 管送出。)

不可依據 one touch sugar 結束 test；需等到 central lab serum glucose result

6. 當有 adequate hypoglycemia 時，即可給熱量補充，依嚴重度給 D50W or 食物，繼續監控血糖，Hypoglycemia 後雖然有吃東西或給 D50W，但是在 30 mins 後要抽 C-peptide+insulin +cortisol。
7. 有下列任一情況即可抽血結束檢查：

- 出現嚴重 hypoglycemia symptoms，例如 neuroglycopenic symptoms: imparered cognitibe function, disorientation, unusual behavior, loss of conscious
- 有低血糖症狀，並且 serum glucose (central lab) < 55 mg/dl
- 無低血糖症狀，serum glucose (central lab) < 45 mg/dl
- 已經過 72 hours

⇒抽血 check serum glucose, insulin, C-peptide

⇒測驗結束之後可開始進食；如無法進食時給予 50 ml D50W

⇒ 結束時抽血後的 30 min 再抽一次血 (glucose, insulin, C-peptide)

C. Procedure (Mixed meal test for suspected post-prandial hypoglycemia)

1. 先抽病人空腹血糖、insulin、C-peptide
2. 食用 Mixed meal：疑似造成病人餐後產生低血糖之食物，或可使用 nutritional supplement formula mixed meal，不可使用 75 gram glucose。

	0'	30'	60'	90'	120'	150'	180'
One touch							
Plasma Glucose							
Insulin							
C-peptide							

3. Check one touch sugar every 30 mins 直到 < 55 mg/dl，此時抽血測 serum glucose 確定真正小於 55 mg/dL 之後才送出 insulin, C-peptide，若檢查當中出現嚴重低血糖症狀則直接抽 blood glucose, insulin, C-peptide 並中止檢查，給予病人補充糖分。
4. 須做到至少 3 小時 (視情況延長至 5 小時)

D. Interpretation:

當 plasma glucose < 55 mg/dl or severe hypoglycemic symptoms/signs

(+) 時，C-peptide level > 0.6 ng/ml (0.2 nmol/L)

+ insulin > 3.0 μU/ml (18 pmol/L)

(pro-insulin > 5.0 pmol/L) ⇒ endogenous hyperinsulinemia

Reference

1. Gardner DG, et al. Greenspan’s Basic & Clinical Endocrinology, 8e, p.759.

2. Endocrine and Metabolic Testing Manual 3e, p. 5-14.

3. Ergin AB, et al. The Cleveland Clinic Manual of Dynamic Endocrine Testing, 2015 2, p. 97.

4. Manual of Endocrine and Metabolism 4e, p. 801.

5. Cryer PE, et al. Williams Textbook of Endocrinology, 13e, Chap. 34. p. 1599

6. Cryer PE et al, J Clin Endocrinol Metab 2009 Mar; 94 2, 709-28.

Octreotide Test

A. Principle: Neuroendocrine tumor 上常會有 somatostatin receptor，在 insulinoma 的病人身上可以藉由此測試來得知 somatostatin analogue 對於病人是否有療效。

B. Procedure:

1. 6 AM 測病人 basal plasma glucose, serum insulin & C-peptide (0 min).
2. 給予皮下注射 100 μg octreotide，並在 7 AM (60 min), 8 AM (120 min), 10AM (240 min), 12 AM (360 min) 及 2 PM (480 min) 抽血驗 basal plasma glucose, serum insulin

Venous sampling (h)	Plasma glucose(mg/dL)	Serum insulin(μIU/mL)
0		
1		
2		
4		
6		
8		

C. Interpretation:

If the suppression of insulin secretion is insufficient (plasma glucose concentration <55 mg/dL (3 mmol/L) despite plasma insulin concentration ≥ 3 μIU/mL) after injection of octreotide, the patient is classified as a negative response in the octreotide test.

Reference

1. Nakamura A 2, et al, Endocrine Journal 63:135-42, 2016

Selective Arterial Calcium Stimulation Test (SACST)

A. Principle: 確診 endogeneous hyperinsulinemia 的病人，若用一般影像學無法找到 insulinoma，可以此檢查做 insulinoma 的 localization，或與 nesidioblastosis 做進一步的鑑別診斷。放射科醫師將導管放入供應 pancreas 不同區段的動脈，給予 calcium injection，刺激該區域的 β cell 分泌 insulin，觀察是否有區域性之差異。

B. Procedure:

1. To sample hepatic venous blood, a five French catheter is inserted transfemorally into the right hepatic vein.
2. The contralateral femoral artery is then punctured, and a five French catheter is introduced into the coeliac trunk and the mesenteric artery.
3. Pancreatic and hepatic angiography consists of the selective catheterization of
   - The splenic artery (SA) supplying the body and tail and
   - The gastroduodenal artery (GDA) and the superior mesenteric artery (SMA) supplying the head of the pancreas.
4. After each angiographic catheterization, calcium chloride is injected intra-arterially at a dose of **0.025 mEq/kg body weight (i.e. 5 ml calcium chloride 0.27 mEq/mL in a 53-kg adult)** to evoke insulin secretion by the β cell tumour.
5. **Before (T0) and 20, 40 and 60** s after each arterial injection, 5 ml of hepatic vein blood was sampled.
6. A **glucose intravenous infusion (5 % glucose)** was maintained during the SACST procedure in order to avoid hypoglycaemic episodes.

Right hepatic vein sampling (seconds)	Splenic artery (SA)	Gastroduodenal artery (GDA)	Superior mesenteric artery (SMA)
0	insulin-SA-0"	insulin-GDA-0"	insulin-SMA-0"
20	insulin-SA-20"	insulin-GDA-20"	insulin-SMA-20"
40	insulin-SA-40"	insulin-GDA-40"	insulin-SMA-40"
60	insulin-SA-60"	insulin-GDA-60"	insulin-SMA-60"

C. Interpretation: the doubling of insulin concentration from baseline with an insulin peak >100 μIU/ml (this criteria was established in order to exclude false-positive patients with very low basal and stimulated insulin level).

Reference:

1. Thompson SM, et al. J Clin Endocrinol Metab. 2015 Nov;100:4189-97.

Clinical Criteria for the Diagnosis of Diabetes Mellitus

A. 糖尿病的診斷標準

1. 糖化血色素 (hemoglobin A1c) ≧ 6.5%	或
2. 空腹血漿葡萄糖≧ 126 mg/dL(7.0 mmol/L) 空腹的定義：至少 8 小時未攝取熱量	或
3. 口服葡萄糖耐受試驗 第 2 小時血漿葡萄糖≧ 200 mg/dL	或
4. 高血糖症狀 (包括多尿、頻渴和體重減輕) 且隨機血漿葡萄糖≧ 200 mg/dL(11.1 mmol/L)	

- 口服葡萄糖耐受試驗需要依照世界衛生組織的規定，口服溶於 300 ml 水的 75 g 無水葡萄糖。
- Hemoglobin A1c 的檢測方法宜有 National Glycohemoglobin Standarization Program(NGSP) 的認證或符合 Diabetes Control and Complications Trial (DCCT) assay。
- 貧血和血色素疾病的病人建議以血漿葡萄糖值來診斷糖尿病。

B. 糖尿病高風險群 (Categories of increased risk for diabetes，以前稱為糖尿病前期，prediabetes) 的分類

1. 葡萄糖失耐 (impaired glucose tolerace)： 口服葡萄糖耐受試驗 第 2 小時血漿葡萄糖為 140-199 mg/dL(7.8-11.0 mmol/L)
2. 空腹血糖偏高 (impaired fasting glucose)：空腹血漿葡萄糖值為 100-125 mg/dL(5.6-6.9 mmol/L)
3. 糖化血色素 : 5.7-6.4%

C. C. 第 1 型和第 2 型糖尿病的鑑別診斷

	第 1 型糖尿病	第 2 型糖尿病
發病年齡	通常小於 30 歲	通常大於 40 歲
發病症狀	急性－有明顯症狀	慢性－通常無症狀
臨床表現	體型瘦 體重減輕 多尿 頻渴	肥胖 有明顯的第 2 型糖尿病家族史 種族－高盛行率的族群 黑色棘皮症 (acanthosis nigricans) 多發性囊泡卵巢症候群 (polycystic ovary syndrome)
酮酸血症	常常出現	通常沒有
空腹血清 C- 胜肽濃度	低或無法偵測	低、正常或高
升糖素刺激後 血清 C- 胜肽濃度	低或無法偵測	低、正常或高
自體抗體 (ICA, Anti-GAD65, ICA 512)	常常出現	通常沒有
治療	依賴胰島素	改變生活型態、口服抗糖尿病藥或胰島素
自體免疫疾病的關聯性	多數有	無

- ICA: islet cell antibody， GAD: glutamic acid decarboxylase

D. 成年人糖尿病的治療目標

血糖	糖化血色素 (HbA1c)	< 7.0 % (需個別化考量)
	空腹 (餐前) 血糖	80 ~ 130 mg/dl
	餐後 1-2 小時血糖	< 160 mg/dl
血壓	一般建議	< 140/90 mmHg
	腎病變患者	< 130/80 mmHg
	65 歲以上長者	< 150/90 mmHg
血脂肪 (首要目標)	低密度脂蛋白膽固醇 (LDL-C)	< 100 mg/dl (首要目標)
血脂肪 (次要目標)	總膽固醇 (TCH)	< 160 mg/dl
	血脂肪	< 130 mg/dl (次要目標)
	高密度脂蛋白膽固醇 (HDL-C)	> 40 mg/dl (男) ，> 50 mg/dl (女)
	三酸甘油酯 (Triglyceride)	< 150 mg/dl
生活型態改變	戒菸	強烈建議
	運動	中等強度有氧運動，建議每週 > 150 分鐘 ; 較中等強度稍強的體能活動，建議每週至少 3 日，每日至少 20 分鐘。
	身體質量指數 (BMI)	18.5 ~ 24 kg/m2
	腰圍	< 90 cm (男) ，< 80 cm (女)

E. 住院病人的血糖控制目標

	目標
重症住院 (加護病房)	140 ~ 180 mg/dl
非重症住院	空腹 < 140 mg/dl 隨機 < 180 mg/dl

F. 妊娠糖尿病 (Gestational diabetes mellitus, GDM) 診斷標準 :

有兩種方法，one-step 與 two-step strategies

靜脈血漿葡萄糖值標準 mg/dl(mmol/L)	75 g OGTT*" one-step"	100 g OGTT † "two-step"
空腹	≥ 92(5.1)	≥ 95 (5.3)
OGTT 第 1 小時	≥ 180(10.0)	≥ 180 (10.0)
OGTT 第 2 小時	≥ 153(8.5)	≥ 155 (8.6)
OGTT 第 3 小時		≥ 140 (7.8)

* 為 IADPSG 的建議，孕婦於懷孕後第一次產檢，檢查空腹血糖或糖化血色素，以診斷潛在之糖尿病 (空腹血糖≥ 126 mg/dl、或糖化血色素≥ 6.5%)。若此次空腹血糖 ≥ 92mg/dl、但 <126 mg/dl，則診斷為妊娠糖尿病。此次空腹血糖 <92 mg/dl 的孕婦，建議於 24-28 周時進行 OGTT，若任一數值超過標準，就診斷為妊娠性糖尿病。此方式美國糖尿病學會稱為 "one-step" 方法。

† 建議於 24-28 周時進行。常先以 50g glucose challenge test 篩檢 (非空腹)，若 1 小時血糖 ≥ 130mg/dl (敏感性 90%) 或 ≥ 140mg/dl (敏感性 80%) 時，再進行 100g OGTT。若 100g OGTT 檢查結果中，任兩數值超過標準，就診斷為妊娠性糖尿病。100g OGTT 檢查的結果最早由 National Diabetes Data Group Data Group 提出，後來由 Carpenter 與 Coustan 做出修正，即為表中所示之切點 (3)。美國糖尿病學會稱此方式為 "two-step" 方法。

Reference:

1. *American Diabetes Association. Standards of Medical Care in Diabetes- 2016. Diabetes Care 2016; 39(suppl 1): S1-S109*
2. *中華民國糖尿病學會，2015 糖尿病臨床照護指引*

α-glucosidase inhibitor 主要效果 : for 飯後高血糖者 with meal 吃 , ↓ PC sugar ↓ 0.5~1 % HbA1c 藥效馬上 onset Mechanism: 抑制小腸上皮細胞 α-glucosidase →抑制澱粉及雙糖水解 →延緩碳水化合物吸收 →減緩飯後血糖上升	Acarbose (Glucobay 50 mg/tab) Max: 100 mg tid	Side effect : ∗ GI disturbance (diarrhea, flatulence) ∗不易低血糖，但若合併其他藥物造成低血糖時，需要服用單糖 (葡萄糖或是牛奶) ∗ GFR<25ml/min 時，不建議使用 ---------- Benefit : ∗ ↓ BW
Biguanides 主要效果 : 糖尿病人的首選藥物 PC 吃 => ↓ AC sugar ↓ 1% HbA1c 約 1wk 達 peak effect Mechanism: - 抑制 GI 吸收葡萄糖 - 抑制 hepatic glucose output - 促進週邊組織對葡萄糖利用 , 減少 insulin resistance	Metformin (Glibudon 500 mg/tab) (Glucophage 850 mg/tab) Dose: ½# qd ~ 2# tid Max: 3000 mg/day	Side effect : ∗ GI disturbance (diarrhea, abdominal cramping) ∗ eGFR<30 ml/min/1.73m2 者禁用，eGFR 30-45 ml/min/1.73 m2 者應減量使用 (衛生福利部部授食字第 1031412405A 號公告) ∗ 80 歲以上老年病人，若以前未曾使用過 metformin，也不建議開始使用 (衛生福利部衛署藥字第 0980325034 號公告) ∗病人合併肝、腎、心臟功能不全，低血氧時，不建議使用。 ∗ Vitamin B12 deficiency (due to ↓ absorption but seldom cause anemia) ---------- Benefit ∗ ↓ CV event and mortality in obese subjects ∗ ↓ BW ∗單獨使用時不會發生低血糖 ∗ Low cost

Sulphonylurea 主要效果 : ↓ 1~2% HbA1c 4 個 half-life 達 effect (3~4 days) Mechanism: 作用於胰臟 B cell 細胞膜的 ATP- dependent K channel blocker ➡↑胞內 Ca ➡↑釋出 insulin Meglitinides 與 sulfonylurea 作用在同一個 receptor 不同部位， 不建議與 sulfonylurea 併用。	Glimepiride (Amaryl 2 mg/tab) Max:8 mg/day Gliquidone (Glurenorm 30 mg/tab) Max: 120 mg/day Gliclazide (Diamicron MR 30 mg/tab) Max:120 mg/day Gliburide (Gliben 5 mg/tab) Max:20 mg/day	∗ QD 的藥物，較會按時吃藥 ∗大多由肝臟代謝，腎臟 / 膽道排出 ∗老人或腎功能不好，不建議使用 gliburide (代謝物有 50% 藥效) ∗大部分藥物，使用到 1# bid 就幾乎達到最大效果。進一步增加劑量，增加的效果有限 ∗如果使用長效藥物發生低血糖，常常需要住院觀察 ---------- Side effect : ∗ Weight gain ∗ Hypoglycemia ---------- Benefit: ∗ Low cost
Meglitinides 主要效果 : ↓ PC sugar ↓ 1% HbA1c Mechanism: 作用於胰臟 B cell 細胞膜的 ATP- dependent K channel blocker ➡↑胞內 Ca ➡↑釋出 insulin Meglitinides 與 sulfonylurea 作用在同一個 receptor 不同部位， 不建議與 sulfonylurea 併用。	Repaglinide (Novonorm 1 mg/tab) Dose : ½~1# tid, Max:16 mg/day ●肝臟代謝，膽汁排出，因此腎功能不佳的人可用 ●有些人會有腸胃不適等副作用	Side effect : ∗ Weight gain ∗ Hypoglycemia ---------- Benefit: ∗ Onset 快 , Duration 短，適合作息不正常的人，沒進食時不用吃藥。

Thiazolidinediones (TZD) 主要效果 : ↓ 1 %HbA1c 藥效 1 month onset, 3 months peak Mechanism: Insulin sensitizer, Activate PPAR-γ ➡↑ insulin 敏感性	Pioglitazone (Actos 30 mg/tab) Max: 45 mg/day	Side effect : ∗ Weight gain ∗ Edema ∗ Heart failure, NYHA III or IV 禁用 ∗ Abnormal liver function ∗ Bone fracture, esp. in post-menopausal female ---------- Benefit: ∗單獨使用時不會發生低血糖
DPP-4 inhibitor 主要效果 : ↓ 0.6~0.8 %HbA1c Mechanism: Inhibit DPP-4 activity ➡ prolong incretin circulating half life ➡↑ insulin secretion ➡↓ glucagon secretion	Sitagliptin (Januvia 100 mg/tab) 1/4#-1# qd Saxagliptin (Onglyza 5 mg/tab) 1/2#-1# qd Linagliptin (Trajenta 5 mg/tab) 1# qd ●腎功能不好時仍可使用 Alogliptin (Nesina 25 mg/tab) 1/4#-1# qd	Side effect : ∗有鼻咽炎和泌尿道感染等副作用，並注意可能發生急性胰臟炎。 ∗ Saxagliptin 在 SAVOR-TIMI53 trial 顯示心衰竭住院率顯著增加 ---------- Benefit : ∗單獨使用時不會發生低血糖 ∗ Weight neutral

GLP-1 receptor agonist 主要效果 : ↓ 0.5~1 %HbA1c Mechanism: Activate GLP-1 receptor ➡↑ insulin secretion ➡↓ glucagon secretion ➡ slow gastric emptying ➡ enhance satiety & reduce appetite	Liraglutide (Victoza 6 mg/ml,3 ml/pen) dose: 0.6~1.8 mg qd sc Max: 1.8 mg qd sc Dulaglutide (Trulicity) 0.75~1.5 mg qwk	Side effect : ∗ GI disturbance (nausea, vomiting, diarrhea) ∗ Pancreatitis ∗ C-cell hyperplasia/ Medullar thyroid tumors in animal ---------- Benefit : ∗單獨使用時不會發生低血糖 ∗ Weight reduction ∗ Potential CV benefit (Liraglutide in LEADER trial)
GLT-2 inhibitor 主要效果 : ↓ 0.5~1 %HbA1c Mechanism: ➡↓ urinary glucose reabsorption	Dapagliflozin (Forxiga 10 mg/tab) 1# qd, CCR 需 >60 Empagliflozin (Jardiance 25 mg/tab) 1# qd, CCR 需 > 45	Side effect : ∗增加泌尿道及生殖器感染風險 ∗ case reports of ketoacidosis ∗ volume depletion and hypotension ---------- Benefit : ∗單獨使用時不會發生低血糖 ∗ Weight reduction ∗ blood pressure reduction ∗ Potential CV benefit (Empagliflozin in EMPA-REG trial)

Insulin regimen

胰島素種類	起始作用時間	最大作用時間	持續作用時間
速效胰島素類似物			
Insulin lispro (Humalog) [B] Insulin aspart (Novorapid) [B] Insulin glulisine (Apidra) [C]	5-15 分 5-15 分 5-15 分	30-90 分 30-90 分 30-90 分	3-5 小時 3-5 小時 3-5 小時
短效胰島素			
Regular insulin (Humulin R) [B]	30-60 分	2-3 小時	5-8 小時
中效胰島素			
Isophane insulin, NPH (Humulin N) [B]	2-4 小時	4-10 小時	10-16 小時
長效 (基礎) 胰島素類似物			
Insulin glargine U-100 (Lantus) [C] Insulin glargine U-300 (Toujeo) [C] Insulin detemir (Levemir) [B]	2-4 小時 6 小時 1-3 小時	無 無 6-8 小時	20-24 小時 36 小時 20-24 小時
預混型胰島素			
70/30 human insulin (Mixtard, Humulin 70/30) [C] 70/30 aspart insulin (NovoMix) [B] 50/50 lispro insulin (Humalog Mix50) [B]	30-60 分 5-15 分 5-15 分	2-8 小時 1-4 小時 1-4 小時	10-16 小時 10-16 小時 10-16 小時

Insulin regimens:

1. Intermediate and long-acting preparations act as a basal supplement to suppress hepatic glucose production and maintain near normoglycemia in the fasting state
2. Short-acting insulin is given before meals to cover the additional glucose load.

常見胰島素使用方法

Regimen 1: Basal insulin + oral anti-diabetic agents

- 當使用 oral anti-diabetic agents 仍未到達治療目標時使用。
- Basal insulin 選用中效或長效胰島素，於睡前使用。
- 起始劑量 : 0.1~0.2 U/kg/day。
- 依據空腹血糖調整 basal insulin 劑量，直到達到目標。

Regimen 2 : Basal-bolus regimen

- 一天打 4 次，三餐前使用速效或短效胰島素，睡前使用中效或長效胰島素。
- 起始劑量：先計算每天劑量 0.6 U/kg/day (actual body weight)，再除以 4 得到每次劑量。例如 60 kg 的人，36 U/day，36/4 = 9, RI 9 U tid ac + NPH 9 U hs。
- 利用餐後血糖來調整速效或短效胰島素，早上空腹血糖來調整中效或長效胰島素，直到達到目標。

Regimen 3 : Pre-mixed insulin bid

- 一天打 2 次，早餐前一次，晚餐前一次。
- 起始劑量：每日劑量的 2/3 於早餐前施打，1/3 於晚餐前施打。例如：原

本使用 RI 12-15-16 U tid + NPH 14 U hs，每日劑量 =12+15+16+14=57 U，可改變成 Novomix 38 U -19 U bid。

- 之後依據午餐前與晚餐前血糖，調整早餐前胰島素劑量；依據睡前與早上空腹血糖調整晚餐前胰島素劑量，直到達到目標。
- 如果晚餐吃得多，或是半夜容易低血糖的人，可將晚上的 pre-mixed insulin 改為 50/50 劑型，即早上打 Novomix，晚上打 Humalog Mix50。

Regimen 4 : Humalog Mix50 tid for patients with NG feeding

- 一天打三次，於 NG feeding 第 1, 3, 5 餐前使用。
- 起始劑量 : 如果一天 NG feeding 6 次，則將每日劑量除以 3 使用。
- 血糖測量時間要配合 NG feeding 的時間。
- 之後依據第 3, 5 餐前血糖來調整第 1, 3 餐前胰島素劑量，依據第 1 餐前血糖調整第 5 餐胰島素劑量，直到達到目標。

Reference:

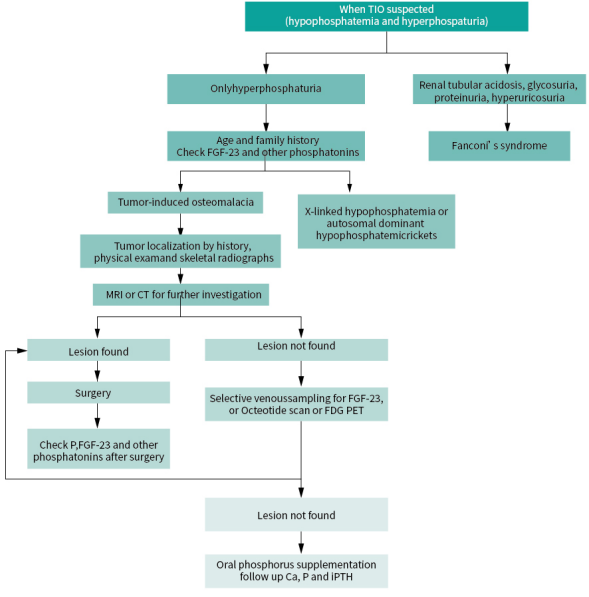
1. Morello CM, Int J Gen Med. 2011;4:827-35.

2. 中華民國糖尿病學會，2015 糖尿病臨床照護指引

3. 台大醫院處方集，2013

4. Gardner DG, et al. Greenspan’s basic & clinical endocrinology 9e, Chap. 17

Suspicious hypophosphatemic osteomalasia



A. Lab:

- Plasma phosphate, calcium, albumin, iPTH, vitamine D, ALP, albumin, CBC/DC. FGF23 (分機 61613)
- Check TRP (TRP = [1-(P (urine) x Cre (plasma))/ (Cre (urine) x P (plasma)]) (Normally TRP >85%). 24 hr urine phosphate loss.
- Working for foci of tumors: urine and serum electrophoresis, LDH, PSA
- Genetic study (PHEX gene) if available

B. Image:

- CXR
- Whole body skeletal X-ray
- Prostate or breast echo
- CT/MRI as indicated
- FDG PET

C. Treatment:

- Phosphate supplement
  - Joulie solution: 10 c.c. tid to 40 c.c. tid (1-4 g/day)
  - K-phos No.2 (1 tab K-phos No.2 = 250 mg P = around 8 mL Joulie solution) (Max: 8#/day)
- Vitamine D
  - Calcitriol (0.25 μg) 1# qid - 3# qid (1-3 μg/day)
  - Onealfa (1 μg) 1-4# qd

D. Monitor:

- q3month: calcium, phosphate, creatinin, ALP
- q6month: iPTH, urine calcium
- renal echo: q1year

E. Adjustment:

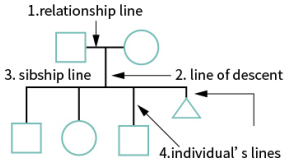
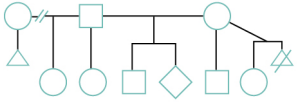
- iPTH ↑ => ↑ calciriol and/or ↓ phosphate
- urine calcium > 4 mg/kg/day => ↓ calcitriol
- urine calcium/cre > 0.7 in first year, or > 0.3 after first year => ↓ calcitriol

Reference:

1. Carpenter TO. N Engl J Med. 2003 Apr 24;348:1705-8.

2. de Menezes Filho H, et al. Arq Bras Endocrinol Metabol. 2006 Aug;50:802-13.

Genetic Test for Endocrine Disorders

Definitions		Comments
		If possible, male partner should be to left of female partner on relationship line Siblings should be listed from left to right in birth order (oldest to youngest) For pregnancies not carried to term (SABs and TOPs), the individual' s line is shortened.
1. Relationship line (horizaotal)		
a. Relationship		A break in a relationship line indicates the relationship no longer exists. Multiple previous partners do not need to be shown if they do not affect genetic assessment.
b. Consanguinity		If degree of relationship not bovious from pedigree, it should be stated(e.g., third cousins) above relationship line.

Am. J. Hum. Genet. 56:745-752,1995

A. Purpose

There are several possible reasons for genetic testing, including

- Confirmation of the diagnosis,
- Counseling for family members (including prenatal genetic testing),
- Guidance of treatment choices, and/or
- Academic interest

B. Available items (as of Oct, 2017; will keep increasing)(for details, see appendix)

- MEN1, MEN2, familial medullary thyroid cancer, PHP1a, PHP1b (NTD 3,500-7,500, please see the website for the exact cost)
- Pheochromocytoma/paraganglioma, Mitochondrial DM (NTD 25,000-30,000, please see the website for the exact cost)
- Upcoming items: CAH, HLA-B*38:02, HLA-DRB1*08:03, familial papillary/follicular thyroid cancer, MODY (through whole exome sequencing, WES)
- There might be some additional items provided for "research" purpose only. Please contact with Dr. Pei-Lung Chen(陳沛隆)(paylong@ntu.edu.tw; 0972651926)for details.

C. Procedure:

- If you cannot find the test you want (or if you do not exact know which test to order), please call 71917 or 71910 for help.
- If you order the test for inpatients, please make sure the sampling "tubes" and amount of blood are correct.
- No need of fasting

- At this moment, we only accept ‘blood’ as the testing sample
- At this moment, the orders are available only at the “main” NTUH
- None of the tests is covered by the National Health Insurance.
- Usually the patient needs to sign a informed consent form.

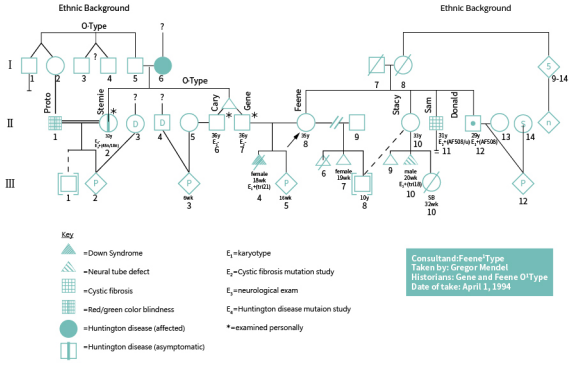
D. Reports:

- It takes 8-12 weeks to get the report on NTUH Portal system (or call 02-23123456 ext 71917/71910 for detailed information)

E. Appendix: (the available genetic testing items) (as of Oct, 2017)

醫令代碼	醫令中文名稱	醫令英文名稱	價格	特別說明
000X0221	甲狀腺髓質癌基因檢測 (有家族史)	Medullary Thyroid Cancer (MTC) Genetic Test(family history)	3500	對比 000X0235。
000X0222	多發性內分泌腫瘤第二型基因檢測	Multiple Endocrine Neoplasia, Type2(MEN2) Genetic Test	3500	
000X0223	偽副甲狀腺功能低下症基因檢測	Pseudohypo-parathyroidism (PTH) Genetic Test	7000	For PHP1a, PHP1b, and PPHP
000X0224	單一已知基因變異位點檢測	Genetic test of single known genetic variant	1500	對比 000X0238。（此欲檢驗之單一變異點原來『是』在台大檢驗出來的）
000X0227	次世代定序疾病基因突變檢測	Next Genera-tion Sequenc-ing for Disease associated Gene Mutation Test	30000	Pheochromo-cytoma and paraganglioma 先以此醫令勾選，未來可能會有單獨醫令
000X0228	多發性內分泌腫瘤第一型基因檢測	Multiple Endocrine Neoplasia,-Type1(MEN1) Genetic Test	7000	
000X0235	甲狀腺髓質癌基因檢測 (無家族史)	Medullary Thyroid Cancer (MTC) Genetic Test (no family history)	6000	對比 000X0221。
000X0238	全新設計已知基因變異單一位點檢測	Brand New Designed Genetic Testing for An Untested Variant	2840	對比 000X0224。(此欲檢驗之單一變異點原來不是在台大檢驗出來的)
000X0239	次世代定序粒線體 DNA 基因變異檢測	Next Generation Sequencing for Mitochondrial DNA Variation Test	25000	For mitochon-drial DM

* 備註：關於送檢流程，對於『非』台大醫院本院檢體 (或是台大檢體但是送件流程有不確定的事項)，請透過實驗室網頁 (http://www.genet-ics-core-ntuh.tw/) 或是台大醫院分機 02-23123456 ext 71917 or ext 71910 得到最完整及最及時的資訊。



List of Abbreviation

ACTH	Adrenocorticotropic hormone
Anti-GAD-Ab	Anti-glutamic acid decarboxylase autoantibody
Anti-IA2	Anti-tyrosine phosphatase autoantibody
ARB	Angiotensin II receptor blocker
ARR	Aldosterone rRenin rRatio
APA	Aldosterone- – producing adenoma
ATA	Anti-thyroglobulin antibody
AVS	Adrenal venous sampling
BIPSS	Bilateral inferior petrosal sinus sampling
BMI	Body mMass Index
CLR	Contralateral ratio = ACR nondominant AV / ACR PV
DDAVP	Desmopressin acetate
DM	Diabetes mellitus
DPP-4	Dipeptidyl peptidase 4
DRC	Direct renin concentration
FGF-23	Fibroblast growth factor
FSH	Follicle stimulating hormone
GDM	Gestational diabetes mellitus
GFR	Glomerular filtration rate
GH	Growth hormone
GLP-1	Glucagon-like peptide-1
HDDST	High dose dexamethasone suppression test
IAH	Idiopathic adrenal hyperplasia
IADPSG	International Association of Diabetes and Pregnancy Study Groups
IBW	Ideal body weight
IGF	Insulin-like growth factors
ILR	Ipsilateral ratio = ACR dominant AV / ACR PV
IPSS	Inferior petrosal sinus sampling
iPTH	Intact -parathyroid hormone

ITT	Insulin tTolerance tTest
LDDST	Low dose dexamethasone suppression test
LH	Luteinizing Hormone
LHRH	Luteinizing hormone-releasing hormone
LI	Lateralization index = ACR AV / ACR contralateral AV
MEN	Multiple eEndocrine nNeoplasia
MODY	Maturity onset diabetes of the young
NCV	Nerve conduction velocity test
Non-DHP CCB	Non-dihydropyridine calcium channel blockers
OGTT	Oral glucose toleraence test
PAC	Plasma aldosterone concentration
PA	Primary aldosteronism
PHA-2	Pseudo-hypoaldosteronism type 2
PRA	Plasma renin activity
PRL	Prolactin
SACST	Selective Arterial arterial Calcium calcium Stimulation stimulation Testtest
SGLT-2	Sodium-glucose co-transporter-2
SIT	Saline iInfusion tTest
SI	Selectivity index = Cortisol AV / Cortisol PV
SU	Sulphonylurea
TBII	Thyrotropin binding inhibitory immunoglobulin
TPO antibody	Thyroid peroxidase antibody
TSH	Thyroid-stimulating hormone
TRH	Thyrotropin releasing hormone
TRP	The tubular reabsorption of phosphate
TZD	Thiazolidinediones
UACR	USpot urine microalbumin to /creatinine ratio
UPCR	USpot urine total protein to /creatinine ratio
VMA	Vanillylmandelic acid

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Graves' disease

Genetic test
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