Pitfalls in the interpretation of thyroid function tests - how to avoid being caught out...

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Potential pitfalls in TFT interpretation

When to tread carefully…

1. TFTs discordant with the clinical picture

2. TFTs discordant with each other

‘Anomalous TFTs’
‘Discordant TFTs’
‘Funny TFTs’
‘Perplexing TFTs’
‘Puzzling TFTs’
‘Weird TFTs’
1. Physiology of the HPT axis and factors that govern thyroid hormone action at a tissue and cellular level

2. Principles underpinning laboratory measurement of T4, T3 and TSH; potential mechanisms of assay interference

3. Conditions associated with ‘discordant TFTs’
Thyroid hormone action and regulation
Thyroid hormone action and regulation

Deiodinase

T4 → T4

T3 → T3

MCT8

CoA

RXR

TR

T3

T4

DNA

+ve

+++
TFT pattern recognition

- subclinical hyperthyroidism
- recent Rx for hyperthyroidism
- drugs (e.g. steroids, dopamine)
- assay interference
- NTI

- Thyrotoxic
  - FT4/FT3 $\uparrow$
  - TSH $\downarrow$

- ‘Normal’
  - FT4/FT3 $\leftrightarrow$
  - TSH $\leftrightarrow$

- Hypothyroid
  - FT4/FT3 $\downarrow$
  - TSH $\uparrow$

- FT4/FT3 $\leftrightarrow$
- TSH $\leftrightarrow$

- FT4/FT3 $\leftrightarrow$
- TSH $\leftrightarrow$

- FT4/FT3 $\leftrightarrow$
- TSH $\leftrightarrow$

- FT4/FT3 $\leftrightarrow$
- TSH $\leftrightarrow$

- FT4/FT3 $\leftrightarrow$
- TSH $\leftrightarrow$

- FT4/FT3 $\leftrightarrow$
- TSH $\leftrightarrow$

• subclinical hypothyroidism
• recent Rx for hyperthyroidism
• drugs (e.g. amiodarone)
• assay interference
• NTI

• central hypothyroidism
• isolated TSH deficiency
• assay interference

• assay interference; FDH
• thyroxine replacement therapy (including poor compliance)
• drugs (e.g. amiodarone, heparin)
• NTI (incl acute $\varphi$ disorders); neonatal period
• TSH-secreting pituitary adenoma
• Resistance to thyroid hormone (RTH)
• Disorders of thyroid hormone transport or metabolism

Illustrative cases
Case 1 – clinical vignette

47-yr-old woman

**PC**  Increasing tiredness and fatigue

**HPC**  6 month history of:
- general deterioration
- marked tiredness and fatigue
- excessive sleepiness
Stable weight, no constipation

**PMH**  Radioactive iodine therapy for hyperthyroidism (1991)

**DH**  Thyroxine 275 mcg/day
Morphine sulphate, gabapentin, citalopram, diazepam
Case 1 – examination & initial investigations

O/E

- BMI 33.1 kg/m² (Wt 88 kg)
- normal secondary sexual features
- no palpable thyroid gland
- myxoedematous facies
- slow-relaxing reflexes

- ankle oedema
- bibasal lung crepitations

- visual fields full to confrontation

<table>
<thead>
<tr>
<th></th>
<th>TSH (0.4–4.0)</th>
<th>FT4 (9.0–20.0)</th>
<th>FT3 (3.0–7.5)</th>
<th>TPO TRAb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;100 mU/L</td>
<td>0.3 pmol/L</td>
<td>1.9 pmol/L</td>
<td>negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>
Case 1 – question

Which is the most likely explanation for this lady’s failure to respond to supraphysiologic thyroxine therapy?

A Elevated T4 & T3 binding capacity
B Enhanced metabolism of thyroxine
C Increased deiodination of T4 to rT3 (reverse T3)
D Malabsorption
E Non-concordance with thyroxine therapy
Case 1 – examination & initial investigations

O/E
- BMI 33.1 kg/m² (Wt 88 kg)
- normal secondary sexual features
- no palpable thyroid gland
- myxoedematous facies
- slow-relaxing reflexes
- ankle oedema
- bibasal lung crepitations
- visual fields full to confrontation

<table>
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<th>TSH</th>
<th>FT4</th>
<th>FT3</th>
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<tbody>
<tr>
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<td>(3.0–7.5)</td>
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<td></td>
<td>&gt;100 mU/L</td>
<td>0.3 pmol/L</td>
<td>1.9 pmol/L</td>
</tr>
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</table>

TPO and TRAb negative
Coeliac serology negative
Faecal elastase normal

Clinical Δ: Poor (non!) concordance
### Case 1 – review of historical TFTs

<table>
<thead>
<tr>
<th>Date</th>
<th>TSH (0.5–4.2 mU/L)</th>
<th>Free T4 (9.7–25.7 pmol/L)</th>
<th>Thyroxine (mcg/day)</th>
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<tr>
<td>05/06</td>
<td>&lt;0.1</td>
<td>22.4</td>
<td>300</td>
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<tr>
<td>07/06</td>
<td>0.94</td>
<td>-</td>
<td>250</td>
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<tr>
<td>03/07</td>
<td>8.8</td>
<td>6.1</td>
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</table>

‘Lost to follow up’

<table>
<thead>
<tr>
<th>Date</th>
<th>TSH</th>
<th>Free T4</th>
<th>Thyroxine</th>
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<tr>
<td>06/09</td>
<td>5.5</td>
<td>10.2</td>
<td>?250</td>
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<tr>
<td>07/09</td>
<td>0.12</td>
<td>23.3</td>
<td>?300</td>
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<tr>
<td>04/10</td>
<td>&gt;100</td>
<td>1.7</td>
<td>250</td>
</tr>
<tr>
<td>06/10</td>
<td>&gt;100</td>
<td>1.9</td>
<td>300</td>
</tr>
</tbody>
</table>
Consider Assay Interference

Dietary factors
- Fibre
- Espresso Coffee

GI Disorders
- Coeliac disease
- Lactose intolerance
- Achlorhydria

Binding capacity
- Oral E2 therapy
- SERMs
- Mitotane

Investigations
- Prescription history
- L-T4 absorption test
- Supervised dosing

Consider TH malabsorption

Drugs
- Cholestyramine
- FeSO₄
- Sucralfate
- Aluminium hydroxide
- Calcium carbonate
- Sevelamer HCl
- PPIs
- Orlistat

Consider increased metabolism/excretion/binding capacity

Metabolism
- Carbamazepine
- Phenytoin
- Phenobarbitone
- Rifampicin
- Imatinib

Weekly Dosing may be a treatment option

Consider Compliance

Anomalous TFTs in patients receiving L-T4 therapy
Case 1 – supervised thyroxine administration

→ Do not underestimate the ingenuity of your patients!
SUPERVISED THYROXINE ABSORPTION TEST

Pre-test:
• Exclude:
  – confounding dietary factors/medications
  – conditions associated with thyroxine malabsorption (e.g. coeliac disease, achlorhydria, lactose intolerance)
  – overt non-compliance (e.g. failure to collect regular thyroxine prescription)
  – assay interference
• Check no contraindications to high-dose thyroxine therapy (consider performing ECG)

On day of the test:
• Ensure patient:
  – has fasted from midnight
  – empties bladder immediately prior to dosing (to allow continuous observation for 60 min post-dosing)
• Under direct supervision, administer the equivalent of one week’s cumulative thyroxine dose [e.g. 1.6 × body weight (kg) × 7 mcg] in liquid (preferred option) or tablet form (with dose rounded to nearest 50 mcg)
• Follow immediately with 200mL water orally, and observe patient for 60 min (keep fasted during this time)
• Collect blood samples for measurement of FT4, FT3 and TSH at 0, 30, 45, 60, 90, 120, 240 and 360 min

Post-test:
• Continue weekly supervised (observed for 60 min) administration of the same dose of thyroxine for a further 5 weeks
• Collect blood samples for measurement of FT4, FT3 and TSH at 0 and 120 min at weeks 2, 3, 4, 5 and 6

Interpretation and follow-up:
• TSH normalization → non-compliance; explore patient perspective; consider continued weekly dosing
• Inadequate FT4 rise post-thyroxine administration → institute further investigations for malabsorption
• Consistent rises in FT4 post-thyroxine, but no change in TSH levels → consider dose adjustment and/or further investigations into disorders of TH metabolism/excretion

SUPERVISED THYROXINE ABSORPTION TEST

Case 2 – a near miss…!

Pituitary MRI:

Presentation + 5 months + 5 years

**Δ:** Correction of poor-compliance with L-T4 therapy
→ reversible thyrotrroph hyperplasia
### Case 3 – clinical vignette & investigations

#### Patient Information

- **Age**: 77-yr-old female
- **Presentation (PC)**: Fall → left fractured neck of femur
- **Past Medical History (PMH)**: Hypertension (amlodipine 10mg/day)
- **Post-operatively**: developed AF

#### Examination (O/E)

- Euthyroid; no goitre
- AF 110 bpm; no cardiac failure
- Nil else of note

#### Laboratory Results

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal Range</th>
<th>Result</th>
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<tbody>
<tr>
<td>TSH</td>
<td>(0.4–4.0)</td>
<td>3.2</td>
</tr>
<tr>
<td>FT4</td>
<td>(9.0–20.0)</td>
<td>35.0</td>
</tr>
<tr>
<td>TPO</td>
<td>negative</td>
<td></td>
</tr>
<tr>
<td>TSH</td>
<td>(0.4–4.0)</td>
<td>3.1</td>
</tr>
<tr>
<td>TT4</td>
<td>(53–135)</td>
<td>118</td>
</tr>
</tbody>
</table>
Case 3 – question

Which is the most likely explanation for this pattern of TFTs?

A  Drug effect
B  Non-thyroidal illness (sick euthyroid syndrome)
C  Radiographic contrast agent-induced thyrotoxicosis
D  Subclinical hyperthyroidism
E  TSH-secreting pituitary adenoma (TSHoma)
Heparin-induced elevation in free thyroid hormone levels

Heparin-induced elevation in free thyroid hormone levels

Non-thyroidal illness (NTI; ‘sick euthyroid syndrome’)

Definition:

Any condition, not directly affecting the HPT axis, that is accompanied by abnormal thyroid function tests

Patterns of thyroid function tests in NTI:

• Thyrotropin (TSH) – depressed or normal

• Thyroxine:
  total T4 (TT4) – normal / reduced / (elevated)
  free T4 (FT4) – normal / reduced / (elevated)

• Triiodothyronine (T3)
  total T3 (TT3) – reduced / (normal)
  free T3 (FT3) – reduced / (normal)
Non-thyroidal illness (NTI; ‘sick euthyroid syndrome’)

Aetiology/Pathogenesis:

Contentious but may include:
- alterations in serum thyroid hormone binding capacity
- reduced cellular uptake of T4
- decreased peripheral conversion of T4 to T3
- reduced hypothalamic (TRH) – pituitary (TSH) secretion (role of IL-1, IL-6, leptin, glucose and $O_2$ availability)

Other factors:
- cortisol / exogenous glucocorticoids / dopamine

Adaptive vs Maladaptive?

- Induced hypothyroidism – a ‘beneficial’ response or
- Central hypothyroidism – a potentially ‘disadvantageous’ response?
Algorithm for discordant TFTs

Step 1: re-evaluate clinical history

Age

Consider:
- Neonatal period
- Elderly

Pregnancy changes

Consider:
- ↓ TSH (first trimester; secondary to ↑ hCG)
- ↑ TT4 and ↑ TT3 (from first trimester; secondary to ↑ TBG)
- Changes in FT4 and FT3
- Pregnancy RR

Thyroxine therapy

Consider:
- Confounding dietary factors or medications
- Malabsorption syndromes
- Altered TH metabolism
- Non-compliance
- Other factors

Confounding medications

Consider:
- Amiodarone
- Furosemide
- Heparin
- Corticosteroids
- Dopamine
- Others

Non-thyroidal illness

hCG, human chorionic gonadotropin; RR, reference range; TBG, thyroxine-binding globulin; TFT, thyroid function test; TH, thyroid hormone; TT3, total triiodothyronine; TT4, total thyroxine
Case 4 – clinical vignette

78-yr-old male

PC  Tiredness

HPC 6 month history of:
  • tiredness
  • cold intolerance
  • dry skin

PMH  Prostate carcinoma

DH  Bicalutamide

O/E  P=60 bpm SR
     No goitre

Clinical impression: Hypothyroidism
### Case 4 – initial investigations

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>FT4</td>
<td>51.0 pmol/L</td>
<td>(11.0–22.0)</td>
</tr>
<tr>
<td>TSH</td>
<td>16.3 mU/L</td>
<td>(0.35–5.5)</td>
</tr>
<tr>
<td>TPO</td>
<td>2551 U/L</td>
<td>(0–100)</td>
</tr>
</tbody>
</table>
Case 4 – question

Which is the most likely underlying diagnosis?

A  Factitious hyperthyroidism (covert thyroxine administration)
B  Hashitoxicosis (thyrotoxic phase of Hashimoto’s disease)
C  Primary autoimmune hypothyroidism
D  Resistance to thyroid hormone (THRB)
E  TSH-secreting pituitary adenoma (TSHoma)
Case 4 – further investigations

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FT4</td>
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<tr>
<td>TSH</td>
<td>16.3 mU/L</td>
</tr>
<tr>
<td>TPO</td>
<td>2551 U/L</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time</th>
<th>TSH (mU/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>16.3</td>
</tr>
<tr>
<td>20’</td>
<td>32.0</td>
</tr>
<tr>
<td>60’</td>
<td>58.0</td>
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</table>

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FT3</td>
<td>2.9 pmol/L</td>
</tr>
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## Case 4 – further investigations

<table>
<thead>
<tr>
<th></th>
<th>Beckman Access</th>
<th>Abbott AxSYM</th>
<th>Perkin-Elmer (Wallac) DELFIA</th>
<th>Roche E170</th>
<th>Immulite 2500</th>
<th>Bayer Centaur</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FT4</strong></td>
<td>2.0 (7.5–21.1)</td>
<td>5.0 (8.0–21.0)</td>
<td>3.3 (9.0–20.0)</td>
<td>19.5 (12.0–22.0)</td>
<td>21.6 (10.0–24.0)</td>
<td>44.7 (11.0–22.0)</td>
</tr>
</tbody>
</table>
FT4/FT3: ‘1-step’ competition assays

\[ T3/T4 = \text{endogenous } T3/T4 \]
\[ T3/T4 = \text{competing labelled } T3/T4 \]

Enhancement Solution

variant albumin

T3/T4 binding Ab

Fluorescence Measurement
FT4/FT3: ‘2-step’ assays

Wash

T3/T4

Enhancement Solution

Fluorescence Measurement
Case 4 – further investigations

<table>
<thead>
<tr>
<th></th>
<th>Beckman Access</th>
<th>Abbott AxSYM</th>
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<th>Immulite 2500</th>
<th>Bayer Centaur</th>
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<tbody>
<tr>
<td><strong>FT4</strong> (pmol/L)</td>
<td>2.0 (7.5–21.1)</td>
<td>5.0 (8.0–21.0)</td>
<td>3.3 (9.0–20.0)</td>
<td>19.5 (12.0–22.0)</td>
<td>21.6 (10.0–24.0)</td>
<td>44.7 (11.0–22.0)</td>
</tr>
<tr>
<td><strong>TSH</strong> (mU/L)</td>
<td>25.0 (0.3–5.6)</td>
<td>22.0 (0.2–4.5)</td>
<td>25.0 (0.4–4.0)</td>
<td>30.0 (0.3–4.5)</td>
<td>24.5 (0.35–5.5)</td>
<td></td>
</tr>
</tbody>
</table>

→ Choose your ‘friends’ carefully (laboratory!)
Case 4 – further investigations

**Final Δ:** FT4 assay interference by anti-iodothyronine antibodies
Case 5 – clinical vignette

72-year-old male

**PC**  GP referral with ‘progressively rising TSH’ on long-term L-T4 therapy

**HPC**  - Primary hypothyroidism (1992)
          - Euthyroid on L-T4 125-150 mcg/day thereafter
          - Annual TSH monitoring

**PMH**  - Hypertension
          - Aortic valve replacement
          - Antiphospholipid syndrome - PE
          - Prostate carcinoma (‘active surveillance’)
Case 5 – clinical vignette

**DH**  
- Thyroxine 125 mcg/day  
- Lisinopril 10 mg/day  
- Bisoprolol 2.5 mg/day  
- Furosemide 40 mg/day  
- Simvastatin 20 mg/day  
- Warfarin

**AH**  
Nil known

**F/SH**  
Nil of note

**SE**  
Right hallux pain for several months
Case 5 - Examination / Initial investigations

O/E
BMI 28.9 kg/m² (Wt 95 kg)
‘euthyroid’
no palpable thyroid enlargement

P = 68 bpm SR
BP 125/60 mmHg

nil else of note

<table>
<thead>
<tr>
<th>TSH</th>
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<tbody>
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<td>(0.35–5.5)</td>
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<td>FT4</td>
<td>19.8</td>
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<tr>
<td>(11.5–22.7)</td>
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<tr>
<td>TSH</td>
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<td>(0.35–5.5)</td>
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<tr>
<td>FT4</td>
<td>16.8</td>
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<tr>
<td>(11.5–22.7)</td>
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Diagnosis:  
? compliance  
? malabsorption
<table>
<thead>
<tr>
<th>Date</th>
<th>TSH 0.35–5.5</th>
<th>FT4 11.5–22.7</th>
<th>L-T4 mcg/day</th>
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<tr>
<td>09/2003</td>
<td>0.04</td>
<td>17.9</td>
<td>150</td>
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<tr>
<td>01/2004</td>
<td>0.54</td>
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<td>10/2004</td>
<td>1.6</td>
<td>-</td>
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<tr>
<td>05/2009</td>
<td>50.2</td>
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<td>175</td>
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**BUT:** History of right hallux pain!

**Urinary Uric Acid**

<table>
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<tr>
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<tr>
<td>Uric acid</td>
<td>0.43</td>
<td>(0.20–0.45)</td>
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**Rheumatoid Factor Tests**

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<th>Reference Range</th>
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<tr>
<td>Rheumatoid factor assay A</td>
<td>183</td>
<td>(0–30)</td>
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<tr>
<td>Rheumatoid factor assay B</td>
<td>&lt;10</td>
<td>(0–30)</td>
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**Thyroid Stimulating Hormone (TSH) Assays**

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<th>Reference Range</th>
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<tr>
<td>TSH Assay platform 1</td>
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<tr>
<td>FT4</td>
<td>23.8</td>
<td>(11.5–22.7)</td>
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<tr>
<td>TSH Assay platform 2</td>
<td>0.06</td>
<td>(0.4–4.0)</td>
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<tr>
<td>FT4</td>
<td>26.0</td>
<td>(9.0–20.0)</td>
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TSH assay interference

TSH assay interference

### TSH dilution studies

**Control subject**

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<th>dilution</th>
<th>TSH</th>
<th>TSH x dilution</th>
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<tbody>
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<td>1:1</td>
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<tr>
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<td>14.00</td>
<td>28.00</td>
</tr>
<tr>
<td>1:4</td>
<td>6.88</td>
<td>27.52</td>
</tr>
<tr>
<td>1:8</td>
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<td>26.80</td>
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<td>1.64</td>
<td>26.24</td>
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**Patient**

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<th>TSH x dilution</th>
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<td>13.30</td>
<td>13.30</td>
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<td>1:2</td>
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<td>1.04</td>
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## Case 5 – further management

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<th>Date</th>
<th>TSH (0.35–5.5)</th>
<th>FT4 (11.5–22.7)</th>
<th>L-T4 (mcg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>09/2008</td>
<td>25.5</td>
<td>19.8</td>
<td>125</td>
</tr>
<tr>
<td>11/2008</td>
<td>28.5</td>
<td>16.8</td>
<td>125</td>
</tr>
<tr>
<td>12/2008</td>
<td>39.4</td>
<td>17.2</td>
<td>150</td>
</tr>
<tr>
<td>01/2009</td>
<td>37.9</td>
<td>20.3</td>
<td>175</td>
</tr>
<tr>
<td>05/2009</td>
<td>50.2</td>
<td>23.8</td>
<td>175</td>
</tr>
<tr>
<td>07/2009</td>
<td>0.59</td>
<td>17.3</td>
<td>125</td>
</tr>
</tbody>
</table>

- reduce L-T4 dose to 125 mcg/day;
- use DELFIA® platform for future TSH measurements

**Final diagnosis:** Stable primary hypothyroidism

TSH & RhF assay interference
Algorithm for discordant TFTs


Step 1: Re-evaluate clinical history

Age

Pregnancy changes

Thyroxine therapy

Confounding medications

Non-thyroidal illness (NTI)

Consider:
- neonatal period
- elderly

Consider:
- ↓TSH (1st trimester; 2° to ↑hCG)
- ↑TT4 & ↑TT3 (from 1st trimester; 2° to ↑TBG)
- changes in FT4 & FT3
- pregnancy RR

Consider:
- confounding dietary factors or medications
- malabsorption syndromes
- altered TH metabolism
- non-compliance
- other factors (see Table 2)

Consider:
- amiodarone
- furosemide
- heparin
- corticosteroids
- dopamine
- others (see Table 3)

Step 2: Re-assess thyroid status

? hypothyroid

? euthyroid

? hyperthyroid

Step 3: Decide which TFT is most likely to be discordant

Step 4: Exclude TH &/or TSH assay interference

Step 5: Investigate for rare genetic/acquired disorders of HPT function
# TFT Pitfalls – traps for the unwary!

<table>
<thead>
<tr>
<th>Pre-laboratory</th>
<th>Laboratory</th>
<th>Post-laboratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paying insufficient attention to the clinical context…</td>
<td>Failing to recognise limitations of commonly used T4/T3/TSH assays</td>
<td>Limited experience of dealing with rarer genetic or acquired HPT disorders</td>
</tr>
</tbody>
</table>

- **Age**
- **Pregnancy changes**
- **Thyroxine therapy**
- **Confounding medications**
- **Non-thyroidal illness (NTI)**
- **Assay interference:**
  - Heterophile Ab
  - Anti-animal Igs
  - Anti-iodothyronine Ab
  - FDH
- **Resistance to thyroid hormone**
- **Disorders of TH transport**
- **Disorders of TH metabolism**
- **TSHomas**
Acknowledgements

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Sue Oddy
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Krish Chatterjee

Referring Clinicians/Laboratories

Cambridge National TFTs Referral Service

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http://www.sas-centre.org/centres/hormones/cambridge.html
Further reading

What should be done when thyroid function tests do not make sense?
*Gurnell, Halsall & Chatterjee*  
Clinical Endocrinology (2011) 74: 673–678

How to interpret thyroid function tests
*Koulouri & Gurnell*  

Pitfalls in the measurement and interpretation of thyroid function tests
*Koulouri, Moran, Halsall, Chatterjee & Gurnell*  

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