Thyroid Disorder in CYP with Down syndrome: Surveillance and when to initiate treatment: April 2020
Information update: Down syndrome PCHR inserts 2020

Dr Shiela Puri
On Behalf of the DSMIG U.K & Ireland
22nd May 2020
Webinar Outline:

• Housekeeping & Introductions: Dr Vicky Ho
• Overview of the Guidelines on Thyroid Disorder in CYP with Down syndrome: Surveillance & Initiation of Treatment Dr Shiela Puri
• Q & A : Guideline Development Group Panellist
• What’s new in the 5th edition Down syndrome specific PCHR inserts: February 2020: Dr Shiela Puri
• Q & A : DSMIG Steering Group Members
Overview of Guidelines on Thyroid Disorder in CYP with Down syndrome: Surveillance & Initiation of Treatment

• Physiology of the thyroid gland
• Clinical need for the guidelines
• Process development of the guidelines
• Aims and objectives of the guidelines
• Methodology
• Evidence and recommendations
• Audit & Research
• Summary of the recommendations
• Q & A : Open to panel
## History of hypothyroidism

<table>
<thead>
<tr>
<th>Year</th>
<th>Person</th>
<th>Event</th>
</tr>
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<tbody>
<tr>
<td>1527</td>
<td>Paracelsus</td>
<td>Described association of goitrous hypothyroidism and mental retardation</td>
</tr>
<tr>
<td>1850</td>
<td>Curling</td>
<td>Described non-goitrous hypothyroidism</td>
</tr>
<tr>
<td>1891</td>
<td>Murray</td>
<td>Postulated treating hypothyroidism with thyroxine</td>
</tr>
<tr>
<td>1896</td>
<td>Smith</td>
<td>Advocated treating all with people DS with thyroxine to improve their physical and mental health</td>
</tr>
<tr>
<td>1970</td>
<td>Dussault</td>
<td>Developed dried blood spot screening for CH</td>
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<tr>
<td>1972</td>
<td>Quebec</td>
<td>First to initiate screening programme for congenital hypothyroidism T4 measured</td>
</tr>
<tr>
<td>1974</td>
<td>U.K.</td>
<td>Included Congenital Hypothyroidism in screening</td>
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<tr>
<td>2001</td>
<td>DSMIG</td>
<td><strong>Recommended screening for thyroid disorder in DS</strong></td>
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</tbody>
</table>
Pathophysiology of the Thyroid Disorders

- Congenital absence/dysgenesis
- Dyshormogenesis
- Autoimmune
- Iodine Deficiency
- Post Radiation
- Infiltration/Tumour
- Drugs e.g. Amiodarone
- Hypothalamic/Pituitary abnormality
- Genetic
Pathophysiology of the Thyroid Disorders: Hypothyroidism

Hypothamic Dysfunction
Central / Tertiary Hypothyroidism
- TSH low/Normal
- fT4 Low

Pituitary Dysfunction
Secondary Hypothyroidism
- TSH: Low, fT4: Low

Thyroid Gland Dysfunction
- Primary Hypothyroidism 90-95%
- Absence/Dysgenesis/Autoimmune/ Post radiation etc
- TSH: High, fT4 Low

Diagram:
- Hypothalamus
  - TRH
  - +
  - Pituitary gland
    - TSH
    - TSH
  - Thyroid gland
    - T4 & T3
    - T4 & T3
  - Peripheral tissues
    - T4 → T3
Clinical impact of thyroid disorders

- **Brain development**
  - Permanent impact if untreated in infancy
  - Reversible – Moya moya disease

- **Growth**
  - Permanent impact if untreated

- **Mood, Behaviour, Sleep, Energy**
  - Reversible

- **Constipation**
  - Reversible

- **Skin, hair, nails**
  - Reversible

- **Puberty, liver, cardiac, haematological**
  - Reversible
Clinical need for the guidelines

• **Prevalence**
  • Hypothyroidism
    • First year of life 15.1% to 17.5% (Erlichman et al 2016, Purdy et al 2014)
    • In childhood 5.5% (Noble et al, 2000; McGowan et al, 2011) vs 0.135% in the general child UK population
  • Hyperthyroidism
    • 1% (Goday-Arno et al, 2008)

• **Diagnostic Overshadowing** Challenges in making clinical diagnosis

• **Meets the criteria for screening and surveillance**
  • Treatable, Common, Clinical diagnosis unreliable, Cost effective

• **Variation in clinical practice**
  • Frequency of testing
  • Tests offered
Clinical variation
Caoimhe McKenna
Personnel communication
Thesis to be published 2020

<table>
<thead>
<tr>
<th>Primary outcomes from paediatric DS health surveillance protocols</th>
<th>Protocol recommendations on assessment N=64*</th>
</tr>
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<tbody>
<tr>
<td>TFTs &amp; thyroid antibodies</td>
<td>TFTs (N=52)</td>
</tr>
<tr>
<td>1st check at 1yr (N=45)</td>
<td>35 (77.8%)</td>
</tr>
<tr>
<td>&gt;1 year</td>
<td>Annual 11 (21.1%)</td>
</tr>
<tr>
<td></td>
<td>Biennial 36 (69.2%)</td>
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The challenge of making a clinical diagnosis

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The Process: Timeline

- **June 2001/7**: DSMIG Thyroid Disorder Best Practice Guidelines
- **June 2014**: DSMIG Steering group explore NICE/RCPCH accreditation
- **November 2018**: DSMIG AGM Agreement to obtain formal support
- **January 2019**: Agreement with RaU LLP to provide technical support
- **February 2019**: Initial scope submitted to RCPCH
- **March 2019**: RCPCH Approved Scope of guidelines
- **April 2019**: Scope of Guidelines circulated to RCPCH & DSMIG
- **May 2019**: formation of GDG, Meetings in May, July, Sep, Oct, Nov 2019
- **September 2019**: Draft Guidelines submitted to Stakeholders
- **November 2019**: Review and responded to stakeholder queries
- **December 2019**: Re Submit to College(s) for approval
- **April 2020**: Endorsement received from RCPCH, RCGP, RCN, DSA, DSS, DSi
Guideline development group

• **Chair**
  • Shiela Puri Consultant Paediatrician in Community Child Health, Leeds

• **Clinical Leads**
  • Gita Croft Consultant Paediatrician in Community Child Health, London
  • Mary Small Consultant Paediatrician, Surrey

• **Clinical Expert Representatives**
  • Edna Roche Professor in Paediatrics, Paediatric Endocrinologist, Dublin
  • Catherine Peters Consultant Paediatric Endocrinologist, GOSH, London
  • Kath Leyland Consultant Paediatrician in Community Child Health, Glasgow (Rtd)

• **General Practice Representative**
  • Jill GC Rasmussen Clinical Representative Dementia and General Practitioner, RCGP, Surrey

• **Parent Representative**
  • Ruth Harris London

• **Voluntary Sector Representative**
  • Andrew Boys Executive Director, Dsi & Brother of

• **Royal College of Paediatrics and Child Health Representative**
  • Liz Marder Consultant Paediatrician in Paediatric Neurodisability, Nottingham

• **Technical Support Team**: RaU LLP
  • Roz Ullman Partner, Wendy Riches Partner, Elizabeth King Researcher for RaU LLP

• **DSMIG Information office** Lyn Nixon & Clare Sadie
Young people’s feedback

• None of them knew why they were having the test.
• 2 thought the doctor had explained to them but they couldn’t remember.
• Confusion between in having an injection and taking a blood sample.
• 2/5 described being frightened when younger.
• A young woman, aged 28, with Down syndrome from Scotland stated: She had experienced finger prick tests and had blood samples taken. She said she had regular finger prick tests for thyroid because she was overweight. She thought the test was every 6 months. She said she would prefer not to have blood tests at all, but would prefer a finger prick test to having blood taken. She understood that having the test was a good thing because it meant that she could have treatment if she needed it.
Consultation and endorsement process:

Consultation period 23rd September – 23rd October 2019

• Circulated to stakeholders:
  • RCPCH & Speciality groups
  • Royal College of GP’s
  • Royal College of Nursing, Learning disability subgroup
  • British Association Of Paediatric Endocrinologists, British Thyroid Foundation
  • DSMIG U.K & Ireland
  • District General Hospitals
  • Parent support organisations DSi, DSA, DSS, DSI, DS Centre, Bradford, Leeds
  • Expert Peers: Dr Guftar Shaikh & Dr Tim Cheetham Paediatric Endocrinologists
    Dr Louise Bryant Professor of Psychological and Social Medicine, Leeds
    Dr Kevin Stuart, Consultant Chemical Biologist/Metabolic Medicine, Leeds

• 110 comments received and reviewed and considered by GDG
• Report updated and to submitted to RCPCH, RCN, RCGP
• Endorsement received from RCPCH, RCN, RCGP, DSi, DSA, DSS
The Process: Resources

Financial: Approximately 23,000£
- **Technical Support Team**: RaU LLP 21,000£
  Roz Ullman Partner, Wendy Riches Partner, Elizabeth King
- **Travel, Subsistence other**: approximately £ 2,000

Time Resource (exclusive of technical support team)
- 4 Face to Face meetings in London with GDG
  - 3 at Fraser Jones Recruitment Company (Social Pay Back), 1 RCPCH
- 8 Teleconferences: Core team: Technical team, Chair & Clinical leads
- 10 days of additional dedicated time to review papers and liaison
- Time from GDG members, DSMIG Information Officers
- Stakeholders
Aims & Objective

Aim:
To improve surveillance and timely initiation of treatment of thyroid disorder in CYP who have Down syndrome.

Objectives:
• To increase the proportion of CYP with Down syndrome who have thyroid disorder who are correctly identified.
• To lower the mean age at which CYP with Down syndrome who have thyroid disorder are identified.
• To increase the proportion of CYP with Down syndrome who have thyroid disorder for whom treatment is initiated at the optimum time for treatment to have the maximum benefit.

Treatment of thyroid disorders was excluded as this is no different to the general population: NICE guidelines: Thyroid Disease Assessment and treatment
Clinical questions:

• **What blood tests** should be undertaken **as part of routine surveillance** to identify thyroid disorders in children and young people with Down syndrome?

• **When should routine surveillance blood tests commence** in children and young people with Down syndrome and **how often should they be repeated**?

• **At what thresholds should treatment be initiated** when **hypothyroidism** has been detected, including clinical symptoms and biochemical thresholds?

• **At what thresholds should treatment be initiated** when **hyperthyroidism** has been detected?
Literature search

• Population
  • CYP who have Down syndrome up to their 19th birthday
  • Majority of sample >50% have DS, or results reported separately

• Intervention
  • Blood tests to determine TFT as surveillance for thyroid dysfunction
  • Include any tests undertaken for surveillance for thyroid dysfunction
  • EXCLUDE treatment/management of thyroid dysfunction

• Comparator
  • Surveillance findings in general population of CYP

• Outcomes
  • Diagnosed thyroid dysfunction hypothyroidism, hyperthyroidism, transient conditions, sub-clinical conditions
Literature search

- **Study Design**
  - **Include:** All comparative experimental studies, comparative observational studies, longitudinal observational studies, studies of diagnostic accuracy/predictive ability and systematic reviews
  - **Exclude:** Non-systematic literature reviews, cross-sectional non-comparative observational studies, case reports, studies with small sample size (n<12)

- **Other criteria**
  - English language, 1989 – 2019, all countries
  - Exclude: Abstracts of conference proceedings

**Databases: Searched**

Medline; Science Citation Index Expanded; Arts and Humanities Citation Index; Conference Proceedings Citation Index – Science edition; Conference Proceedings Citation Index – Social Science + Humanities edition; Emerging Sources Citation Index (2015–); Book Citation Index (2005–); BIOSIS Citation Index; BIOSIS Previews; Cochrane Central Database of Controlled Trials (CENTRAL) [Cochrane Library]; SciELO Citation Index.
### Aversa 2015 - Prevalence of euthyroidism at time of diagnosis in CYP with Hashimoto's thyroiditis: CYP with Down syndrome vs controls (timing of exposure: median 5.1 years; assessed with: Serum fT4 and TSH)

<table>
<thead>
<tr>
<th>No of studies</th>
<th>Certainty assessment</th>
<th>Effect</th>
<th>Certainty</th>
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<tbody>
<tr>
<td></td>
<td>Study design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
</tr>
<tr>
<td>1</td>
<td>observational studies</td>
<td>serious (^{a,b})</td>
<td>not serious</td>
</tr>
</tbody>
</table>

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<tr>
<td></td>
<td></td>
<td>300</td>
<td>553 controls</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>54.3%</td>
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</tbody>
</table>
Outcome of search strategy

• **1,210** citations
• All abstracts screened **34** considered for inclusion
• **12** excluded based on PICO criteria
• **22** studies included and reviewed
• Overlap across all 4 questions – reviewed together
• Narrative summary of evidence provided to GDG to consider
  • What tests should be undertaken and timing of tests
  • Thresholds for referral

**Recommendations made based on evidence & opinion of the Guideline Development Group**
Clinical questions:

- **What blood tests** should be undertaken as part of routine surveillance to identify thyroid disorders in children and young people with Down syndrome?

- **When should routine surveillance blood tests commence** in children and young people with Down syndrome and **how often should they be repeated?**

- **At what thresholds should treatment be initiated** when hypothyroidism has been detected, including clinical symptoms and biochemical thresholds?

- **At what thresholds should treatment be initiated** when hyperthyroidism has been detected?
Evidence for what blood tests should be undertaken: TSH blood spot

  - 1 year prospective study 305/395 tested, Of those not tested 12 were diagnosed with a thyroid disorder 73 already tested 4 declined (1%)

  - 2 year prospective study 200/214 successfully screened 93.4%

  - 5742 capillary TSH tests were performed on 1329 children. 132 elevated capillary TSH, 76/132 confirmed thyroid dysfunction


- Young people & Parent representatives views
  - DSA, DSS and Murphy J et al 2008
Evidence for what blood tests should be undertaken: TSH blood spot

- TSH
  - Most common cause of thyroid dysfunction is due to thyroid gland dysfunction

- Pitfalls of TSH dried blood spot test
  - Laboratory variation
  - False negative: High haematocrit or due to milking effect with finger prick
  - False positive: Low haematocrit
  - Transient hyperthyroaenia
  - Hypothalamic or Pituitary causes will not be detected as TSH normal or low
  - Hyperthyroidism will not be detected

- Ideal screening
  - Combination of TSH & fT4
Evidence for what blood tests should be undertaken: TSH, Ft4, TPO

- Autoimmune thyroid disorders is more common in Down syndrome
- Presence of antibodies associated with ↑↑TSH & severe dysfunction
  - Ivarsson 1997; McGowan 2011; Claret et al, 2013; Iughetti et al, 2014; Pierce et al, 2017
- Absence of antibodies is associated with an increased likelihood of remission
  - Claret et al, 2013; Selikowitz et al, 1993
- Presence of thyroid antibodies increases with age, more common after age 8 rare in children under two years
  - Ivarsson 1997; Karlsson 1998; Van Trotsenburg, 2006; McGowan 2011; Iughetti 2014

GDG advised a baseline TPO antibody level would be useful, even in younger children as the natural history of thyroid disorders in DS is still unknown.
Recommendation Summary:
What blood tests should be undertaken as part of routine surveillance?

- **If clinical suspicion of thyroid dysfunction**
  - Offer venous TSH, fT4 and TPO antibodies

- **If routine surveillance**
  - Offer dried blood spot test: TSH or Venous: TSH, fT4 and TPO antibodies
    - In accordance with the local arrangements and taking into account the preferences of the CYP and their parents/carers
  - Time blood tests for routine surveillance to coincide with other blood tests or appointments wherever possible, to minimize any disruption
  - *Remember an illness can affect the concentration of TSH, fT4 & fT3*
Clinical questions:

• **What blood tests** should be undertaken as part of routine surveillance to identify thyroid disorders in children and young people with Down syndrome?

• **When should routine surveillance blood tests commence** in children and young people with Down syndrome and **how often should they be repeated?**

• **At what thresholds should treatment be initiated** when hypothyroidism has been detected, including clinical symptoms and biochemical thresholds?

• **At what thresholds should treatment be initiated** when hyperthyroidism has been detected?
When should routine surveillance commence?

Neonatal screening

• Follow the national newborn screening blood spot programme for screening for congenital hypothyroidism. Do NOT undertake any additional tests, unless clinically undertaken or stipulated in screening programme.


On going surveillance

• **4-6 months of age:** Surveillance for thyroid dysfunction to commence

• **12 months:** Surveillance repeated and **to continue annually life-long**

• **If a clinical suspicion of thyroid dysfunction** **at any stage** offer **venous blood tests**  
  TSH, free T4 and TPO antibodies

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The Down Syndrome Medical Interest Group

UK & IRELAND

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[Image]
Evidence for surveillance to commence at 4 - 6 months

  • Investigated incidence of hypothyroidism in neonates who were found to be euthyroid at birth and were then tested again before 4 months of age (n=79). Tests: venous TSH and total (t)T4. At second testing: 15% found to have compensated hypothyroidism and 17.5% were diagnosed with primary hypothyroidism and treated with thyroxine.

  • A retrospective longitudinal study (USA) 565 medical records of all CYP with Down syndrome attending one of 2 clinics at the research university between November 2007 and January 2015. Among those diagnosed with hypothyroidism outside of newborn screening, n=11 (7.5% of all acquired hypothyroidism) were diagnosed before 6 months of age.
Evidence for: How often should TFT blood tests be undertaken

Noble et al 2000 A prospective observational study over 2 years

• To establish the feasibility of a school-based annual screening programme
• Two hundred of 214 CYP were screened (93.5%).
• 15 CYP referred for further testing, aged 5 - 18 years (median 13).
• 7/15 were started on thyroxine treatment. None had sought medical attention
• 8/15 had mildly raised venous TSH levels with normal fT4. None of these children had clinical features of hypothyroidism and none were treated initially. On venous retesting one year later 4 of these CYP were started on thyroxine therapy.

• Evidence statement: Annual screening in pre-school and school settings is feasible using a dried blood spot test and detected hypothyroidism requiring treatment in 5.5% CYP tested. (UK study)
Evidence levels: feasibility moderate; accuracy low]
Clinical questions:

• **What blood tests** should be undertaken as **part of routine surveillance** to identify thyroid disorders in children and young people with Down syndrome?

• **When should routine surveillance blood tests commence** in children and young people with Down syndrome and **how often should they be repeated**?

• **At what thresholds should treatment be initiated** when **hypothyroidism** has been detected, including clinical symptoms and biochemical thresholds?

• **At what thresholds should treatment be initiated** when **hyperthyroidism** has been detected?
At what threshold should treatment be commenced Newborn period

Follow the recommendations for the National Newborn blood spot screening for congenital hypothyroidism

• ≥20 mU/L WB - Positive screening result for CHT
  • Refer to the paediatric endocrine team (regional specialist team) or to a clearly identified lead paediatrician with special interest in CHT and repeat venous sample TSH, fT4

• ≥10 mU/L and <20 mU/L WB  reported as CHT borderline
  • A repeat dried blood spot sample taken 7-10 days after the initial
At what threshold should treatment be commenced: 4 - 6 months onwards

TSH concentration above local laboratory-defined normal reference range

<table>
<thead>
<tr>
<th>Platform</th>
<th>Abbott</th>
<th>Beckman</th>
<th>Siemens</th>
<th>Roche</th>
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</thead>
<tbody>
<tr>
<td>Upper limit of normal (ULN) TSH</td>
<td>3.60</td>
<td>3.67</td>
<td>4.29</td>
<td>4.31</td>
</tr>
<tr>
<td>1.5X ULN</td>
<td>5.40</td>
<td>5.51</td>
<td>6.44</td>
<td>6.47</td>
</tr>
<tr>
<td>2 X ULN</td>
<td>7.20</td>
<td>7.34</td>
<td>8.58</td>
<td>8.62</td>
</tr>
<tr>
<td>2.5 x ULN</td>
<td>9.00</td>
<td>9.18</td>
<td>10.75</td>
<td>10.78</td>
</tr>
<tr>
<td>3 X ULN</td>
<td>10.80</td>
<td>11.01</td>
<td>12.87</td>
<td>12.93</td>
</tr>
</tbody>
</table>
At what threshold should treatment be commenced

• **Dried blood spot test TSH concentration above local laboratory-defined normal reference range on surveillance sample:**
  - Offer a venous blood test for TSH, fT4 and TPO antibodies within 5 working days of the initial blood test.
  - Consider initiating treatment whilst awaiting blood test results if TSH is very high and clinical suspicion of hypothyroidism.

• **Initial venous TSH concentration above 10mU/l, and low free T4:**
  - Offer immediate repeat venous blood test to measure TSH, fT4 and TPO antibodies.
  - Consider initiating treatment whilst awaiting blood test results if TSH is very high and there is clinical suspicion of hypothyroidism.
At what threshold should treatment be commenced

Blood test shows a normal TSH and normal free T4 but raised thyroid peroxidase (TPO) antibodies:

• Offer a venous blood test to measure TSH, fT4 and TPO antibodies.

• The timing of these repeat tests should be:
  • in 6 months for children and young people aged 3 years and over
  • in 1 – 3 months in children aged under 3 years.

• Offer a repeat blood test sooner if there are clinical concerns.
At what threshold should treatment be commenced

Venous TSH normal or below local laboratory-defined reference range and low free T4

- Consider secondary/tertiary hypothyroidism due to hypothalamic pituitary dysfunction
- Seek advice from a paediatric endocrinologist
- Offer immediate repeat venous blood test to measure TSH, fT4 and TPO antibodies
At what threshold should treatment be commenced: Hyperthyroidism & goitre

Venous TSH below local laboratory-defined reference range and high free T4, or clinical symptoms of hyperthyroidism:

- Seek advice from a paediatric endocrinologist
- Offer a venous blood test for TSH, fT4, fT3, TPO antibodies and TRAB levels seek advice from a paediatric endocrinologist if clinical indicators of hyperthyroidism.

Presence of a goitre

- Offer venous blood testing for TSH, fT4 and TPO antibodies.
- Offer an ultrasound scan.
- Monitor closely for cervical lymphadenopathy.
- Seek advice from an endocrinologist if any abnormal findings / clinical concerns.
Summary

Flow charts included in the guidelines

- Neonatal screening
- Ongoing surveillance
- Marginally abnormal blood tests
- Abnormal blood tests
- Presence of a goitre
Summary of general recommendations

- **Offer information** to CYP and parents/carers at each contact
  - Offer information on thyroid disorders at each contact to parents/carers and children and young people with Down syndrome to explain the offer and importance of ongoing surveillance, for example using the following resources
  - Inform parents/carers that blood test results will show what the child’s or young person’s thyroid function is at the time of testing and that thyroid function can change over time so further tests will be offered throughout life or if the child or young person develops signs or symptoms.

- General recommendations **on performing blood tests**
  - Take measures to minimize any potential associated distress when performing blood tests
Summary of general recommendations

What blood tests and frequency of tests:

Neonatal screening
- Follow the national newborn screening blood spot programme

On going surveillance
Dried blood spot test TSH or Venous TSH, fT4, TPO antibodies dependent on local arrangements
- **4-6 months of age:** Surveillance for thyroid dysfunction to commence
- **12 months:** Surveillance repeated and to continue annually life-long
- **If a clinical suspicion of thyroid dysfunction at any stage offer venous blood tests:** TSH, fT4, TPO antibodies

Threshold for treatment
- **Confirm abnormal blood tests with repeat blood tests as soon as possible within five days**
- **TSH above 10miu/L and low fT4 treat – Hypothyroidism**
- **TSH normal or low and low fT4 – seek opinion for rare forms of hypothyroidism**
- **TSH low and high fT4 – seek opinion for hyperthyroidism**
- Goitre: Investigate
Audit & Research recommendations

• What is the incidence of thyroid dysfunction in children and young people who have Down syndrome and is thyroid dysfunction more common in the first year of life?

• What is the natural history of thyroid dysfunction in children and young people who have Down syndrome?

• What is the natural history of thyroid autoimmunity in children and young people with Down syndrome? How often should thyroid antibodies be evaluated?

• Audit tool developed and to be published on DSMIG website
Thank you & Acknowledgements

• Guideline development group
  Roz Ullman & Wendy Riches

• DSMIG U.K.& Ireland: Lyn Nixon & Clare Sadie, Steering Group & Members

• Stakeholders: DSA, DSS : Young people’s forums, DSi, DHG

• Families

• Expert peer reviewers

• Frazer Recruitment Company