

Newborn Screening for Congenital Hypothyroidism

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Overview of Presentation

- Screening Criteria
 - Overview of newborn screening
 - CHT - Incidence and Aetiology
 - CHT - Screening Strategies and Protocol
 - National Standards and Guidelines
 - Diagnosing the Cause of CHT
 - Audit of screening service in Manchester
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What is Screening?

- Screening is a process of identifying apparently healthy people who may be at increased risk of a disease or condition. They can then be offered information, further tests and/or treatment to reduce their risk and/or complications.
 - Screening is never 100% sensitive or specific. In any screening programme there is a minimum of false positive and false negative results.
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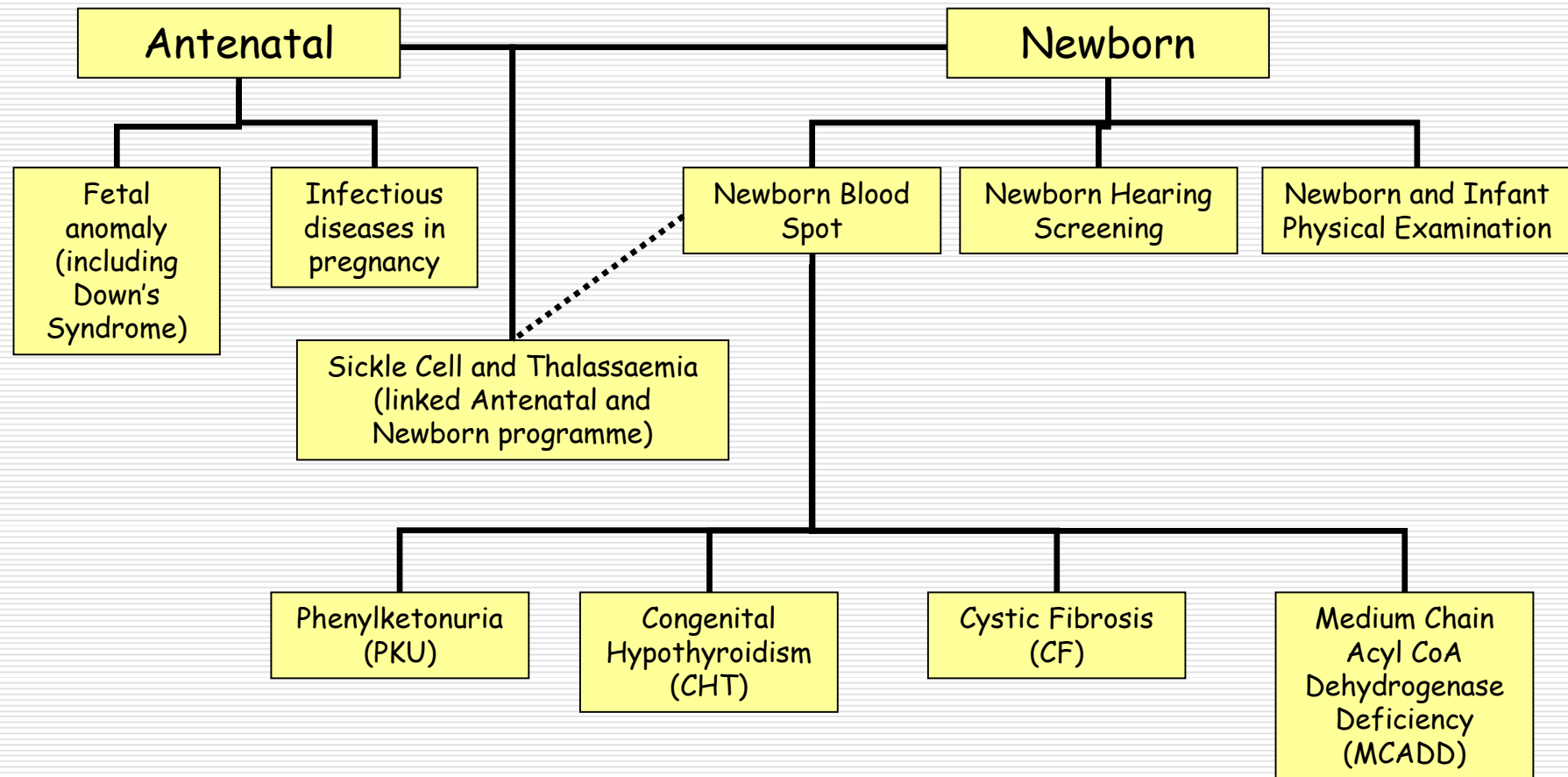
Wilson and Junger's Criteria for a Screenable Disease

1. The condition sought should be an important health problem.
 2. There must be an accepted and effective treatment for patients with the disease.
 3. Facilities for diagnosis and treatment should be available.
 4. There must be an appropriate, acceptable, and reasonably accurate screening test.
 5. The natural history of the condition, including development from latent to manifest disease, should be adequately understood.
 6. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
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The National Screening Committee

- The UK National Screening Committee advises ministers and the NHS in all 4 countries about all aspects of screening policy.
 - It assesses the evidence for programmes against defined criteria. These are an extended version of the Wilson and Junger criteria (first defined in 1968) and can be viewed in full on the UK National Screening Committee website (www.screening.nhs.uk/criteria)
 - Screening programmes are grouped into 6 broad categories. The Antenatal and Newborn category includes Newborn Blood Spot screening.
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Antenatal and Newborn Screening Programmes



Newborn Bloodspot Screening Process

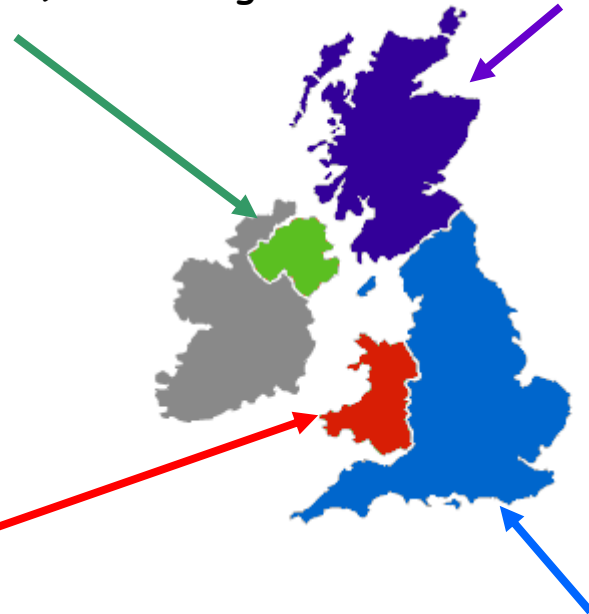
- ❑ Babies are screened by testing a capillary sample of blood obtained by a heel-prick stab - this is collected on to a card to form dried blood spots.
 - ❑ In the UK babies are tested at 5-8 days of age - in other countries the practice is to test earlier.
 - ❑ There are some differences across the UK in terms of the specific conditions screened for since each part of the UK can decide when and how to implement UK National Screening Committee policies.
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Northern Ireland

Universal screening offered for phenylketonuria (PKU), congenital hypothyroidism (CHT), cystic fibrosis (CF), homocystinuria and tyrosinaemia. Medium chain acyl co-A dehydrogenase deficiency (MCADD) screening commenced in 2009 and sickle cell disease (SCD) screening in 2010.

Scotland

Universal screening offered for phenylketonuria (PKU), congenital hypothyroidism (CHT) and cystic fibrosis (CF). Sickle cell disease (SCD) and medium-chain acyl-CoA dehydrogenase deficiency (MCADD) screening commenced in 2011.



Wales

Universal screening offered for phenylketonuria (PKU), congenital hypothyroidism (CHT) and cystic fibrosis (CF). In addition, Duchenne Muscular Dystrophy screening (boys only) is offered as part of routine care.

England

Universal screening offered for phenylketonuria (PKU), congenital hypothyroidism (CHT), sickle cell disease (SCD), cystic fibrosis (CF) and medium-chain acyl-CoA dehydrogenase deficiency (MCADD).

Newborn Screening Laboratories

- ❑ Screening laboratories test a population of 25,000 - >100,000.
 - ❑ Organisation of screening into a limited number of laboratories serving a defined minimum population is cost-effective, concentrates experience and information, facilitates audit and promotes development of expertise for these relatively rare disorders.
 - ❑ In addition to analysis and reporting, the screening lab provides an advisory service, conducts clinical audit and is involved in teaching and training of other health professionals involved in the service.
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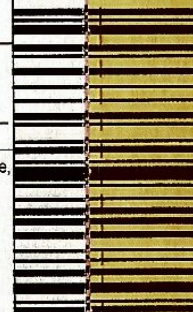
Newborn Bloodspot Screening Card

| NEWBORN SCREENING BLOOD SPOT TEST | | | | | | | | | | | | | | | | | | | | | | | |
|-------------------------------------|--|--|--|----------------------------------|--|----------------------|--|--|--|--|--|--------------------------------------|--|--|--|--|--|----|--|--|--|--|--|
| Baby's NHS No. <input type="text"/> | | | | | | | | | | | | | | | | | | | | | | | |
| SURNAME | | | | | | DATE OF SPECIMEN | | | | | | | | | | | | | | | | | |
| FORENAMES | | | | | | D D M M Y Y | | | | | | | | | | | | | | | | | |
| HOME ADDRESS | | | | | | Is this a repeat (✓) | | | | | | | | | | | | | | | | | |
| Please Affix Label on Every Page | | | | | | YES | | | | | | NO | | | | | | | | | | | |
| | | | | | | BABY'S D.O.B. | | | | | | Has baby had a blood transfusion (✓) | | | | | | | | | | | |
| | | | | | | D D M M Y Y | | | | | | YES | | | | | | NO | | | | | |
| | | | | | | GEST | | | | | | If yes, date of last transfusion | | | | | | | | | | | |
| | | | | | | /40 | | | | | | D D M M Y Y | | | | | | | | | | | |
| | | | | | | RANK | | | | | | Is the baby in hospital (✓) | | | | | | | | | | | |
| | | | | | | / | | | | | | YES | | | | | | NO | | | | | |
| | | | | | | ETHNIC CODE | | | | | | If yes, current hospital and ward: | | | | | | | | | | | |
| POSTCODE | | | | | | SEX (✓) M F | | | | | | | | | | | | | | | | | |
| G.P. PRACTICE NAME | | | | MOTHER'S FULL NAME | | | | BIRTH WEIGHT (g) | | | | | | | | | | | | | | | |
| G.P. ADDRESS | | | | MOTHER'S DOB | | | | COMMENTS (Family history e.g. Mother's carrier status (Antenatal HBO code, HBO Outcome code); temporary address) | | | | | | | | | | | | | | | |
| G.P. PRACTICE CODE | | | | MOTHER'S NHS NUMBER | | | | | | | | | | | | | | | | | | | |
| PCT | | | | PARENT TELEPHONE NUMBER | | | | | | | | | | | | | | | | | | | |
| HOSPITAL OF BIRTH | | | | ALTERNATIVE SURNAME | | | | | | | | | | | | | | | | | | | |
| | | | | TEL. NO. OF PERSON TAKING SAMPLE | | | | NAME OF PERSON TAKING SAMPLE (PRINT) | | | | | | | | | | | | | | | |

NHS

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Expiry Date: 10-2013

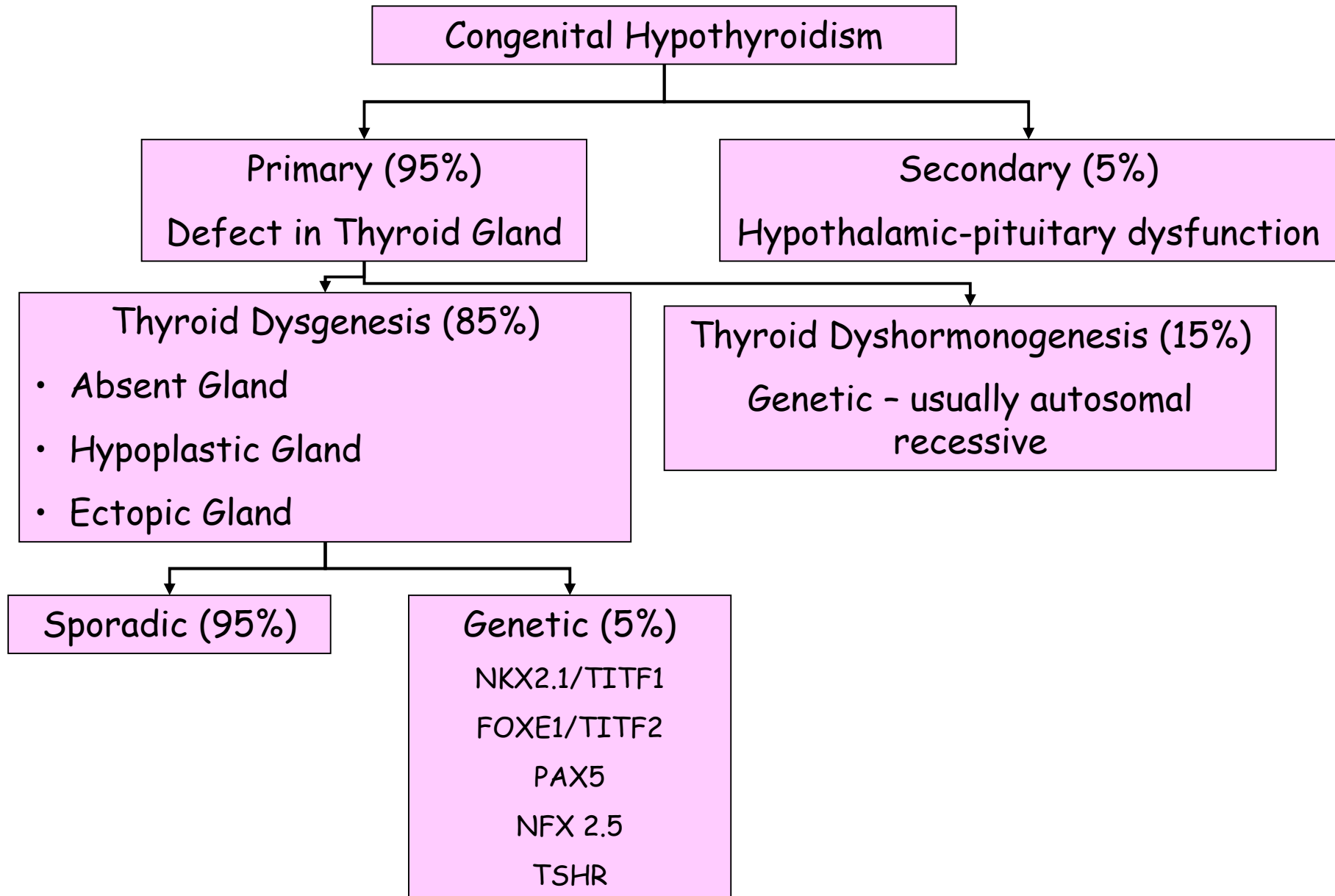


Surname _____

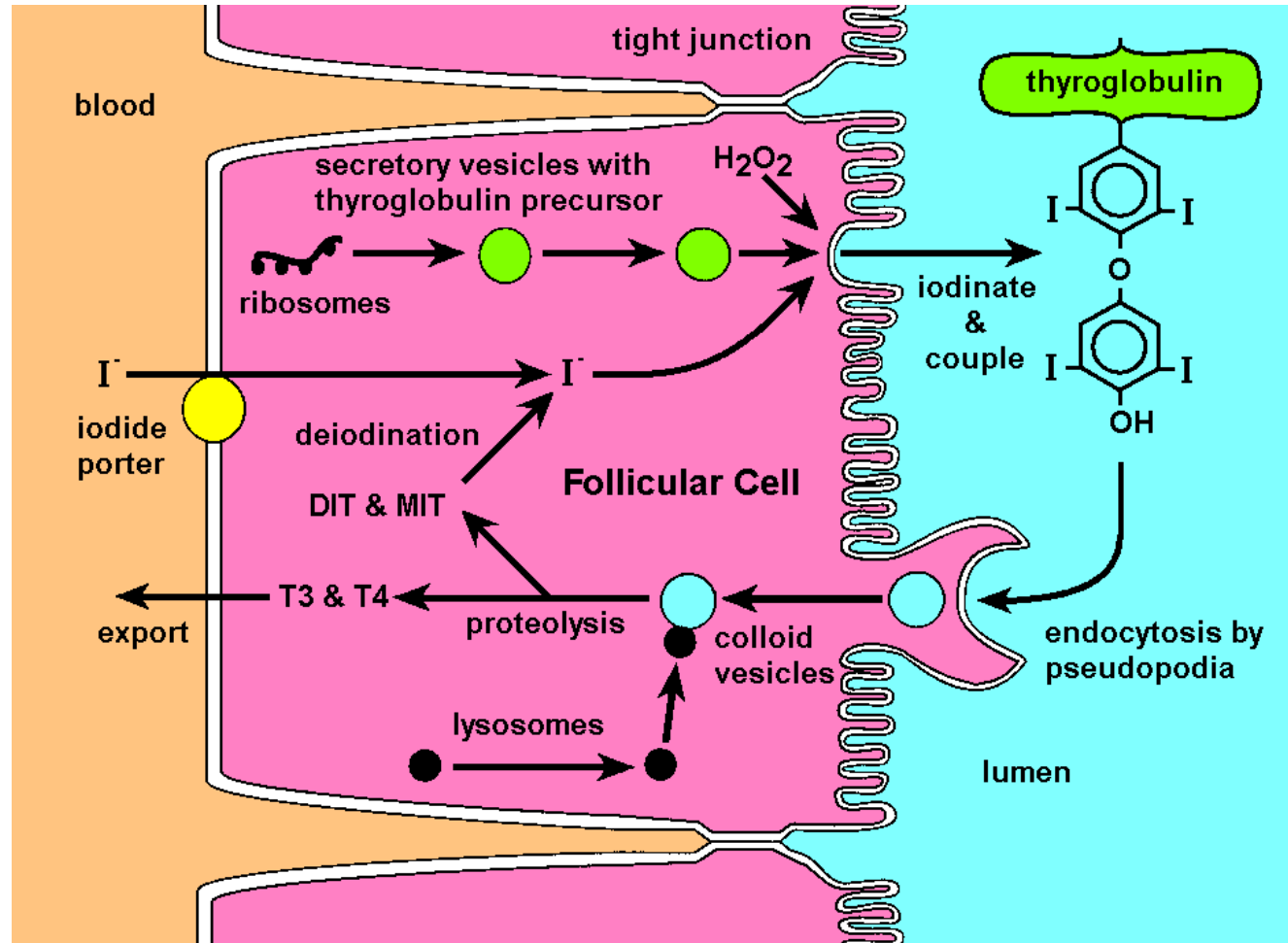
Congenital Hypothyroidism (CHT)

- ❑ CHT is defined as defective function of the thyroid gland from birth.
 - ❑ CHT is the most common treatable cause of mental retardation.
 - ❑ In initial studies incidence of 1 in 3000 to 1 in 4000 obtained - current estimate 1 in 2500.
 - ❑ ?Increased incidence may be due to greater sensitivity of current screening methods or inclusion of infants with transient disease.
 - ❑ Female to male ratio 2:1
 - ❑ Usually sporadic
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Congenital Hypothyroidism - Aetiology



Thyroid Hormone Synthesis

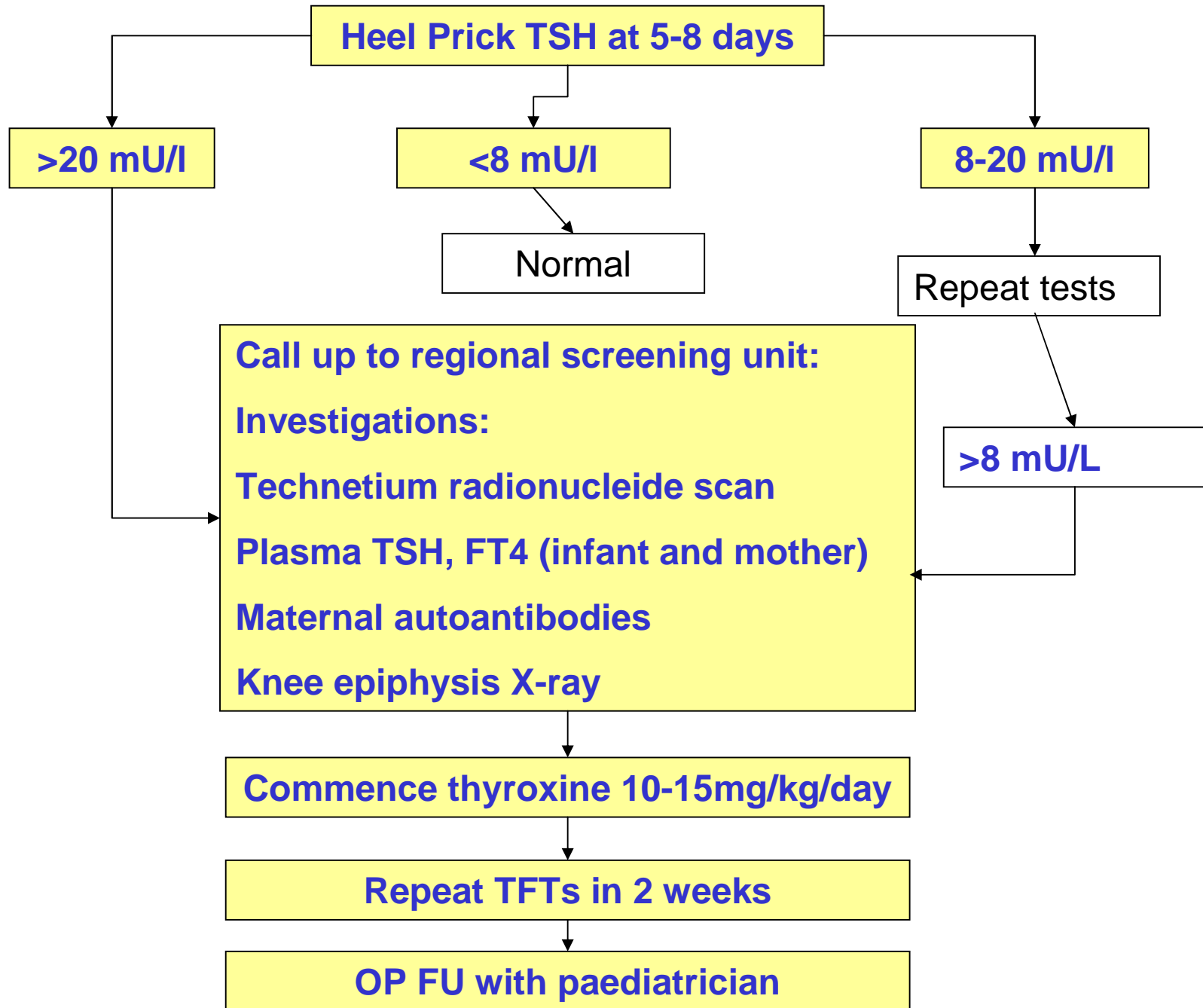


Genes Causing Defects In Thyroid Hormone Synthesis

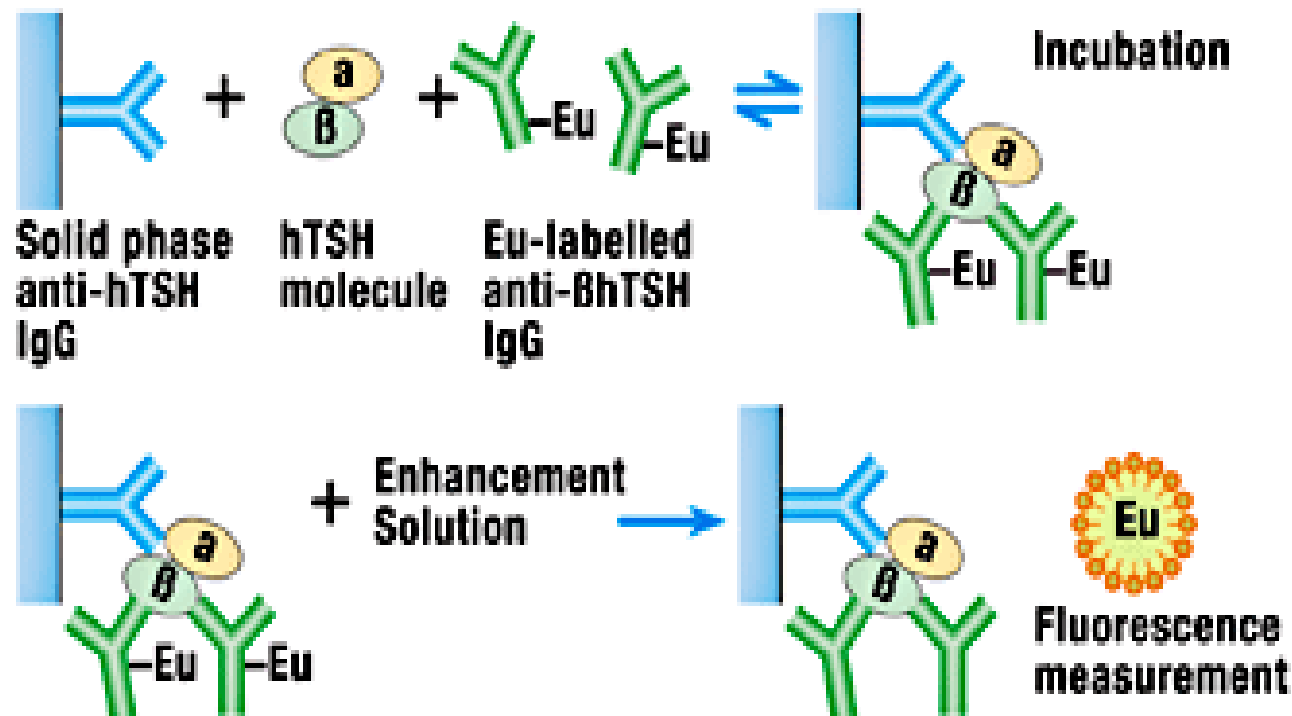
| Gene | Protein Function | Inheritance |
|---|---|-------------|
| Sodium-iodide symporter (NIS) | Transports iodine across basal membrane | AR |
| Thyroperoxidase (TPO) | Catalyses the oxidation, organification, and coupling reactions | AR |
| Dual oxidases (DUOX1 and DUOX2) | H ₂ O ₂ generation in the follicle | AR and AD |
| Dual oxidase maturation factor 2 (DUOXA2) | Required to express DUOX2 enzymatic activity | AR |
| Pendrin (PDS) | Transport iodine across apical membrane | AR |
| Thyroglobulin (TG) | Support for thyroid hormone synthesis | AD and AR |
| Iodotyrosine deiodinase (DHEAL1) | Nitroreductase-related enzyme capable of deiodinating iodotyrosines | AR |

Screening Strategies for Congenital Hypothyroidism

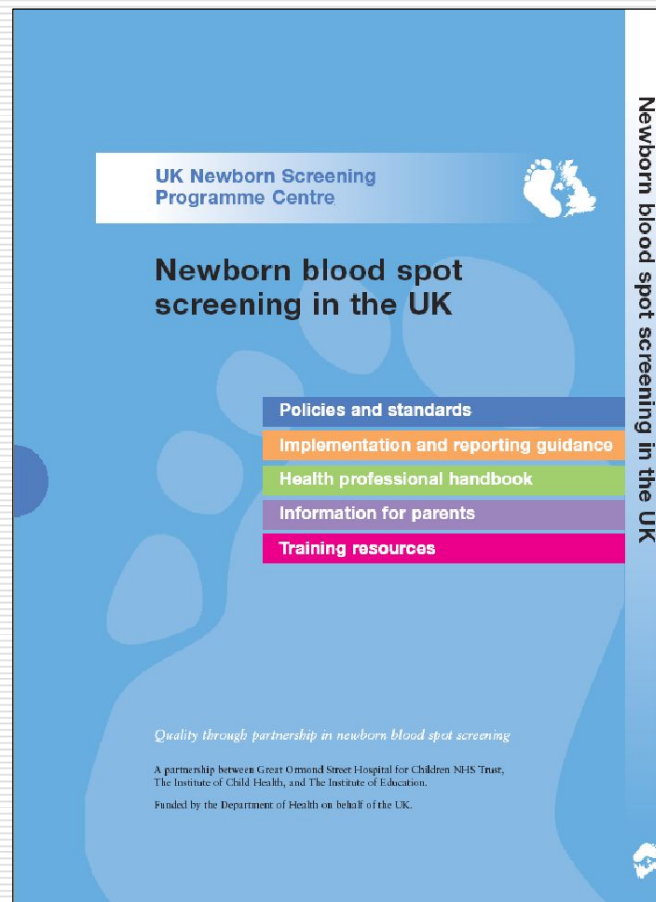
- Two strategies
 - primary T4/back-up TSH (N America and Netherlands)
 - primary TSH (most of Europe including UK and Japan)
 - Primary TSH strategy is more sensitive in detecting primary hypothyroidism and more specific
 - TSH will not detect babies with secondary hypothyroidism due to pituitary failure
 - TSH may detect some newborn babies with temporary (transient) hypothyroidism who subsequently develop normal thyroid function without treatment
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Measurement of Bloodspot TSH using DELFIA



National Standards and Guidelines



Newborn Screening Programme Centre

- ❑ Established in 2002.
 - ❑ Funded by DoH for England and is a collaboration between Great Ormond Street Hospital , Institute of Child Health and Institute of Education.
 - ❑ Remit to co-ordinate a UK-wide quality assurance programme for newborn bloodspot screening services.
 - ❑ First published standards in 2005.
 - ❑ Process standards cover general aspects of screening including timeliness of collection, dispatch, completeness of coverage, tracking etc. - revised in 2008
 - ❑ Condition specific clinical referral standards - CHTclinical referral standards currently under review
 - ❑ Website www.newbornscreening-bloodspot.org.uk
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Timely processing of CHT positive screening samples

Core Standard

100% of positive screening results available and clinical referral initiated within 4 working days of receipt by the screening laboratory.

Development standard

100% of positive screening results available and clinical referral initiated within 3 working days of receipt by the screening laboratory.

Recommendations

- Screening labs to report on a daily basis (working days)
- Babies to be referred to a consultant paediatric endocrinologist
- 98% of babies to have clinical referral by 14 days of age

Repeat Testing of Premature Babies

- ❑ Current TSH-based screening may not detect some pre-term infants with CHT.
 - ❑ Particularly babies born between 23 and 27 weeks gestation.
 - ❑ Premature babies may show a delayed rise in TSH levels after birth, mainly due to immaturity of the hypothalamic-pituitary axis.
 - ❑ Original policy specified repeat testing of all preterm babies when they reach the equivalent of 36 weeks gestational age.
 - ❑ Recently reviewed by expert sub-group.
 - ❑ New policy recommends only repeat testing babies born at <32 weeks gestation.
 - ❑ Repeat testing to occur at 28 days postnatal age or discharge home, whichever is sooner.
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Clinical Referral Standards

1. Communication of a Positive Result

- ❑ Labs to inform designated clinician and midwife/HV by telephone and in writing (fax/e-mail) of positive result.
 - ❑ Midwife/HV to be provided with:
 - standardised information,
 - contact numbers for responsible clinicians,
 - details of parent support groups
 - details of appointment with the designated clinician.
 - ❑ Parents should be offered an appointment on the next working day after being given the positive result.
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Clinical Referral Standards

1. Clinical History and Examination

- ❑ To be performed by designated clinician at referral.
 - ❑ Many of the classical features of CHT (large tongue, hoarse cry, facial puffiness, umbilical hernia, hypotonia, mottling, cold hands and feet and lethargy) when present are subtle and develop only with the passage of time.
 - ❑ Non-specific symptoms which suggest CHT include - unconjugated hyperbilirubinaemia, gestation >42 weeks, feeding difficulties, delayed passage of stools, hypothermia or respiratory distress in a baby >2.5kg.*
 - ❑ Congenital sensorineural hearing loss occurs in babies with Pendred syndrome.
 - ❑ The most common feature in babies with CHT is the absence of specific signs.
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Clinical Referral Standards

2. Diagnostic Tests

| Confirmatory Diagnostic Tests | Desirable Additional Diagnostic Tests |
|---|--|
| <p data-bbox="297 608 987 743">Free T4 (plasma or serum)* TSH (plasma or serum)*</p> <p data-bbox="297 839 893 1023">* Interpreted using the appropriate age-related reference ranges</p> | <p data-bbox="1137 608 1794 810">Imaging techniques to assess whether thyroid gland is present/normally situated/of a normal size</p> <p data-bbox="1137 839 1536 884">Thyroid antibodies</p> <p data-bbox="1137 903 1839 1007">Thyroglobulin (if no thyroid gland found on imaging)</p> <p data-bbox="1137 1026 1872 1118">Maternal Thyroid Antibodies, TSH and free T4</p> |

Diagnosing the Cause of CHT

- Considered important by expert working group
 - Determines prognosis.
 - Increases awareness and recognition of potentially related problems (e.g. deafness)
 - Provides useful information for the family about recurrence risk for subsequent children
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Tests Used to Complete the Diagnosis of CHT

Suspected Thyroid Dyshormonogenesis

Salivary iodide concentration (NIS)

Perchlorate discharge test (Thyroperoxidase or DUOX1/2) -
partial discharge + hearing loss suggests mutation in Pendrin gene

Thyroglobulin (Tg synthesis defect)

Urinary MIT and DIT (Deiodinase defect/DEHAL1)

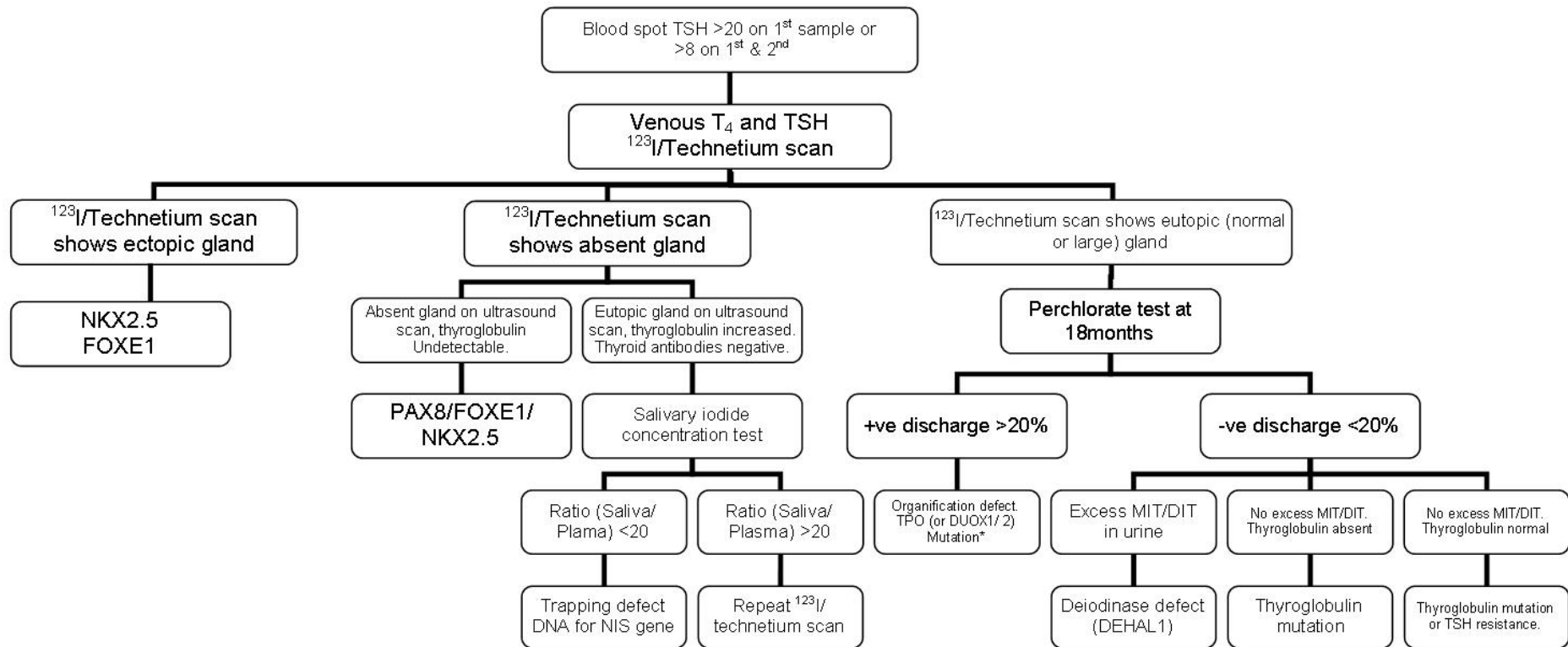
Suspected Autoimmune Thyroid Disease

Maternal and neonatal antibodies

Suspected iodine Deficiency

Urinary iodine

Algorithm for Diagnosing Cause of CHT



MIT = Mono-iodotyrosine
DIT = Di-iodothyrosine

* If there is a hearing impairment the defect may be in the Pendrin gene.

Clinical Referral Standards

2. Treatment and Follow-Up

- ❑ Thyroxine treatment should commence as soon as possible (by 14 days in 98% babies).*
 - ❑ Oral T4 is treatment of choice - recommended starting dose 10 μ g/kg/day (usually equates to 37.5 μ g/day).
 - ❑ Aim to restore serum T4 concentration as rapidly as possible to the normal range followed by continued biochemical euthyroidism.
 - ❑ Once treatment started, recommended that baby is reviewed (as a minimum) at 2 weeks, 6 weeks, 3 months, 6 months and 12 months with blood test at each visit.**
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Audit of Manchester Service 2005 - 2008

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|--------------------------------------|--|
| Number of CHT screen positive babies | 74 |
| Number followed up | 67 |
| Referrals within 4 working days | 94% (mean 3d, max 5d) |
| fT4 /TSH at referral visit | 100% |
| Imaging at referral visit | 98% |
| Starting dose of thyroxine | Data obtained in 41/67 cases 67% started on dose greater than or equal to 10 μ g/kg/day |
| Follow-up visits | 50/67 followed up locally Details available for 12/17 seen at RMCH/St Mary's Of these, 42% - 83% attended a follow-up visit at each of the recommended times |