

History of Screening for CF and CH in New Zealand

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New Zealand

- Country is small 268680 km²
- Population 4.4M
 - Maori 15%
 - Pacific 7%
 - Asian 9%
 - Rest NZ European
- Annual number of newborns 65,000



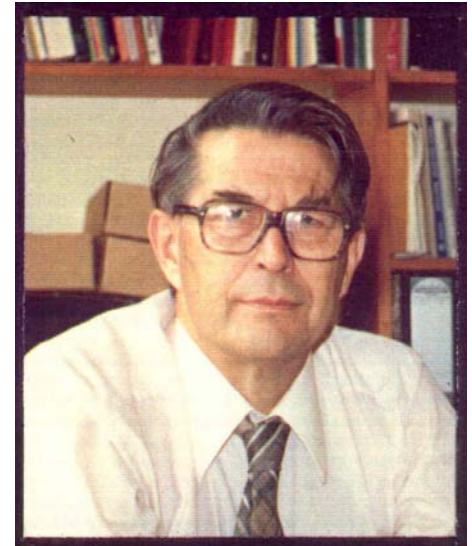
History of Newborn Screening



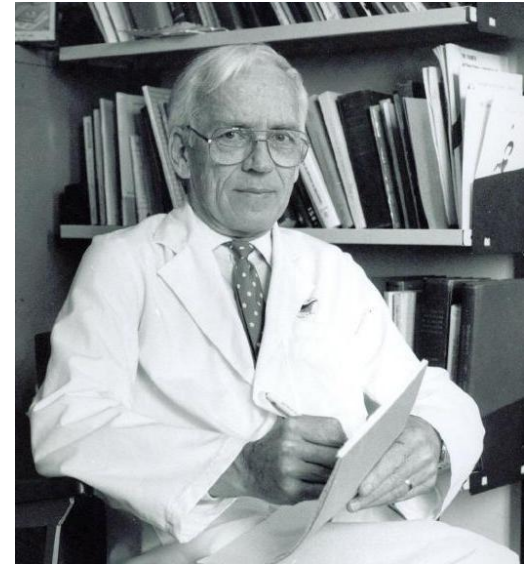
- Archibald Garrod – what is an inborn error of metabolism
- Asbjorn Folling – what is PKU
- Horst Bickel – treatment – why early detection is helpful
- Bob Guthrie – how to detect early

Screening in New Zealand

- Early 1960s screening for PKU *ad hoc*
- hospital laboratories
- – government healthcare funding
- Mid 1969 full coverage one laboratory national program for PKU – Medical Research Council of New Zealand funding



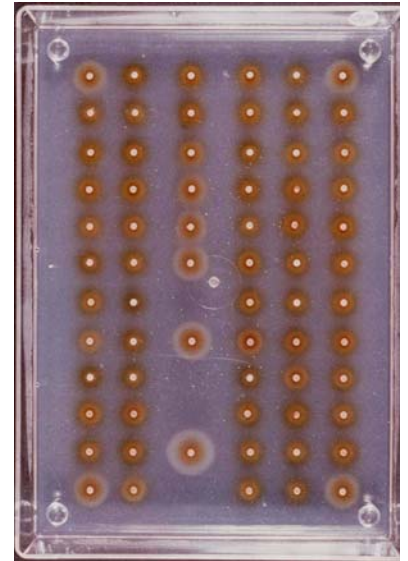
- 1980s transition to government healthcare funding
- Dr Ian Lyon foundation Director



- 2005 involvement of Ministry of Health National Screening Unit
- All screening, diagnosis and treatment fully government funded from start of screening

Screening in NZ

- 1969 newborn screening PKU, MSUD, histidinemia, homocystinuria for NZ and Pacific Islands
- 1978 Screening for congenital hypothyroidism
- 1979 Screening for CF
- 1983 CAH, biotinidase, stopped histidinemia
- 1986 Stopped homocystinuria
- 2006 Fatty acid oxidation disorders and aminoacid breakdown disorders



Screening for Congenital Hypothyroidism



Jean Dussault Guthrie Award 1998

To end 2010

- 1978-2010 1,736,183 infants tested
- T4-TSH to 1983, TSH primary TSH since then
- 441 CH
- 10 missed
- 69 transient

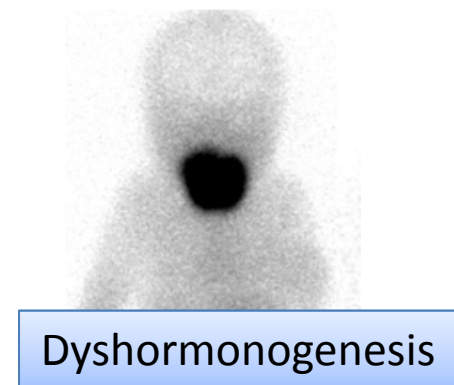
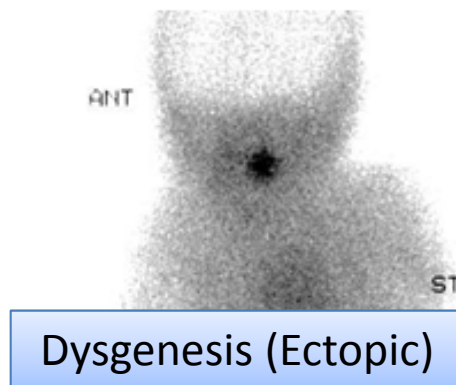
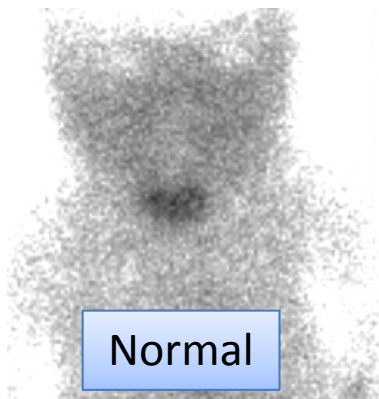
2010

- Referral directly 50 mIU/L blood
- 2nd dried blood spot 15-50 mIU/L blood
- Followup achieved 100%
- Sensitivity 100%
- Specificity 99.9%
- PPV 20%
- 10 missed in 18yrs



Increasing incidence of CH

- Case database kept since 1992 (from audit form)
- Paediatric endocrine review of scan data (scintiscan recommended for all new cases)
- Missing information obtained from notes
- Transients excluded

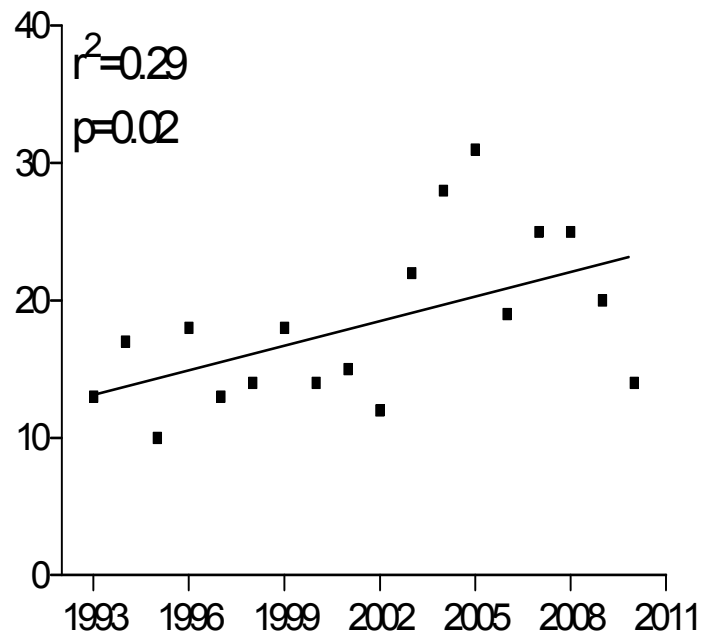


1993-2010 – 18 yrs

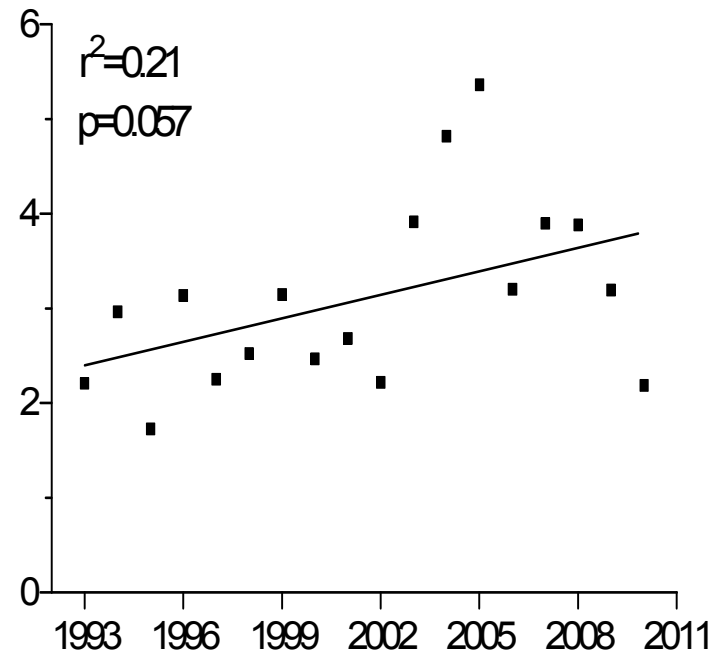
- 1 053 457 babies screened
- 328 cases
- 3.1 / 10 000 live births or 1:3212 live births
- 86% of cases had thyroid scintiscan
- Of patients who had a scintiscan
 - 26% Athyreosis
 - 41% Ectopic or Eutopic Hypoplastic thyroid
 - 33% Dyshormonogenesis

Incidence of CH in New Zealand

New cases / year

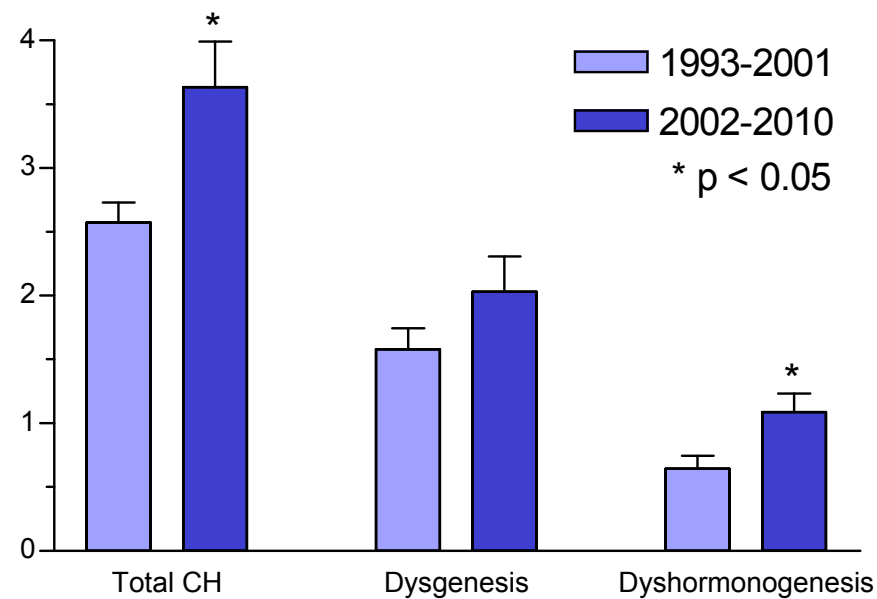


Incidence / 10 000 live births



Overall rise is due to Dyshormonogenesis

Congenital Hypothyroidism Incidence over 9 year epochs
(rate / 10 000 live-births)



	1993-2001	2002-2010	p
Thyroid Dysgenesis	1.6	2.0	0.18
Dyshormonogenesis	0.6	1.1	0.02
Total CH	2.6	3.6	0.01

(1:3890)

(1:2760)

*2 tailed unpaired t test

- No rural bias (some suggestion that increased incidence due to environment possibly pollutants)

Incidence by Ethnicity

	NZ European	Maori	Pacific Island	Asian
Incidence / 10000 live births	2.4	2.0	3.4	3.9*
Odds Ratio	1	0.84	1.39	1.51
95% CI	(reference)	(0.61-1.15)	(0.99-1.04)	(0.98-2.33)

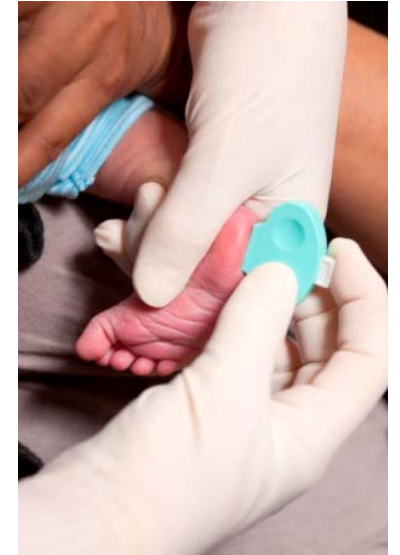


- Congenital Hypothyroidism rate is higher in Asians
- Fast increasing number of Asian live births
- Contributes to rising NZ rate of congenital hypothyroidism

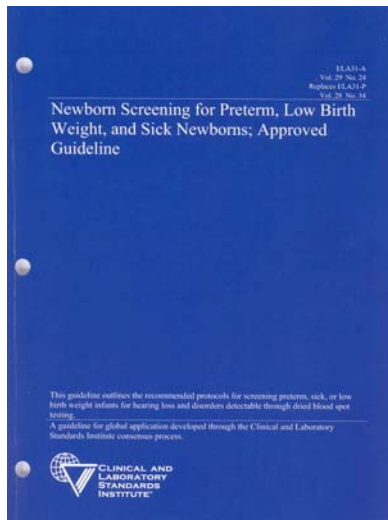
*Incidence and odds ratios calculated over 15 years, except Asian (10 years) as data was skewed by low birth rate

Lessons from Not-Detected cases

- Presented clinically 3/12
 - No sample received by lab
 - ??
-
- Lesson – ways to ensure all babies are screened (all results are reported)



- 715 g baby TSH 2d 2 mIU/L; 14d 10 mIU/L athyroid
- 760 g baby TSH 5d 3 mIU/L athyroid
- Very low birthweight – development of hypothalamic – pituitary axis
- NICU protocol



NTC USE ONLY BABY NAME _____
NHI # _____

NTC USE ONLY

BABY INFORMATION - FILL OUT OR USE LABEL
NHI Number _____
Surname _____
First Name _____
Sex _____ Ethnicity: _____
Birth Time: _____ Date: _____

MOTHER'S INFORMATION - If not on label
Surname _____ First Name _____

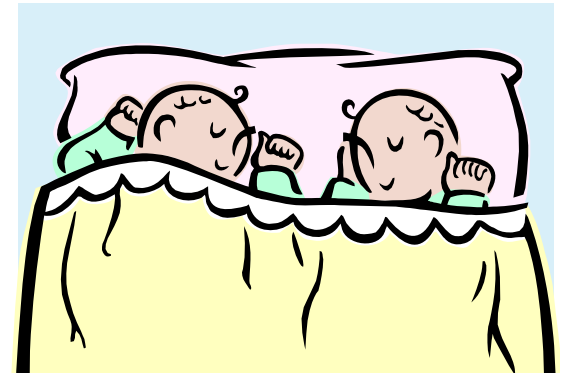
REPORT TO
Name or role _____

COPY TO (LMC OR WELL CHILD PROVIDER)
Name _____ Address _____

Hospital _____ Ethnicity: _____
Birth Time: _____ Birth Date: _____
Birth Wt. (g) _____ Gestation age _____ wk
Collection _____ Collection _____
Time _____ Date _____

Baby 48 hours old Y N 1st sample Y N
(minimum) (circle correct answer)

- Monozygous twin 2980 g
- TSH 3d 1 mIU/L
- Athyroid
- Twin-twin transfusion
- Known for monozygous and dizygous twins
- Systematic twin resample?
 - 1000 for one case (regular screening 5 for 1 case)
 - Other programs aware but don't monitor
- Advisory committee – costs too high, paediatric advice re differential development in twins



- 3630 g baby, TSH 3d <1 mIU/L
panhypopituitarism
- All Australasian programs use TSH
- Other programs use TSH-T₄ or T₄-TSH
- Netherlands TSH-T₄-TBG CH 1:1800 (Kempers 2006) PPV 25% (TBG deficiency)
- Cost of an additional case \$US11,000 (Lanting 2005)
- ? Count as missed case as not primary congenital hypothyroidism

- 2740 g baby TSH at 4d 8 mIU/L blood – ectopic gland
- 3760 g baby TSH at 2d 4 mIU/L dyshormonogenesis
- 2320 g baby TSH at 2d 8 mIU/L dyshormonogenesis
- 2590 g baby, TSH 3d 8 mIU/L athyroid
- So reviewed cutoffs

Considerations in cutoff review

- CDC data
- 44 US labs and 165 international labs
- Range 8.8 – 27.7 ; 3.4 – 22.7 (Nb big variation in levels between assays)
- High cost of lowering cutoff in test specificity
eg 15 -> 10 mIU/L blood 215 more recalls, no more cases

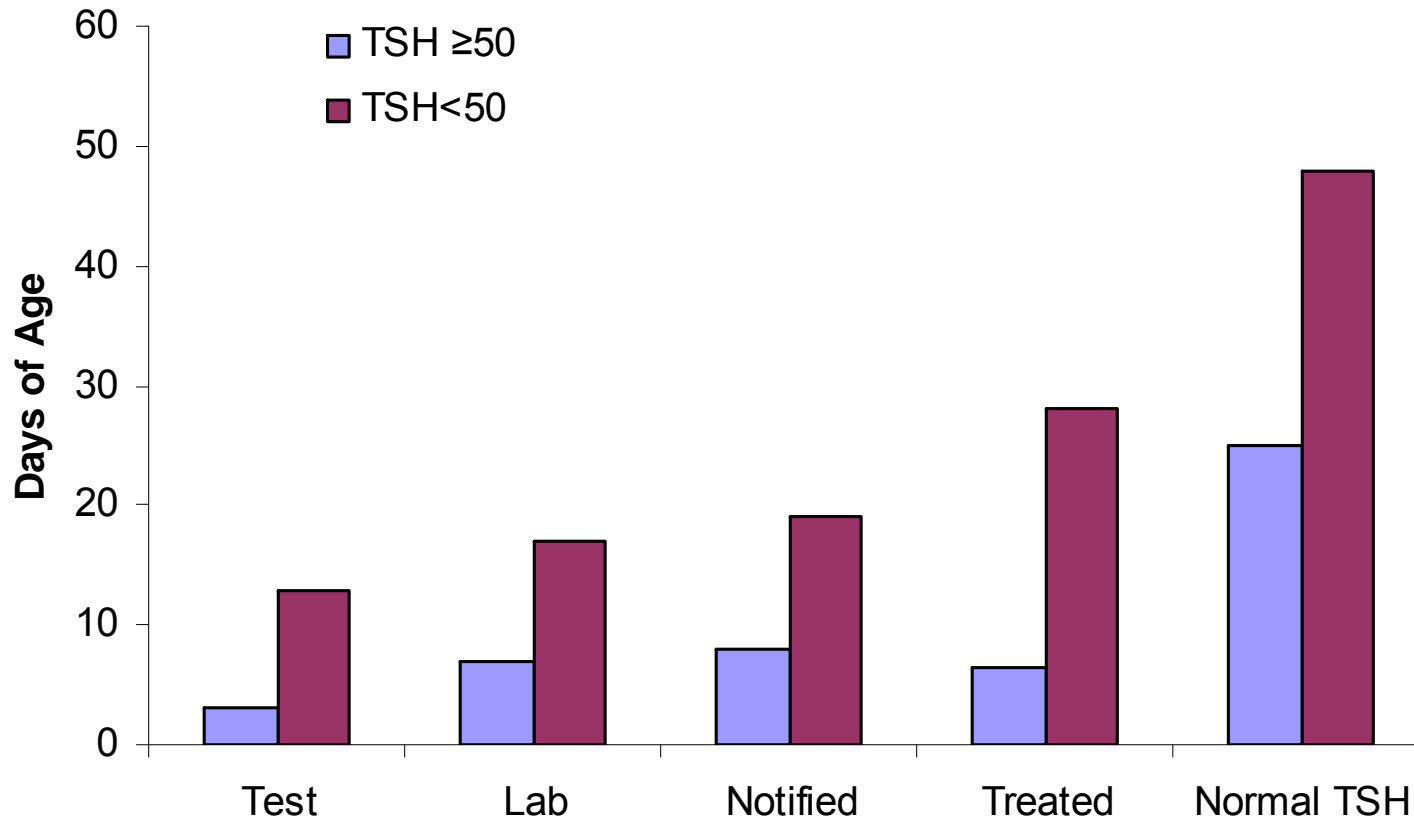
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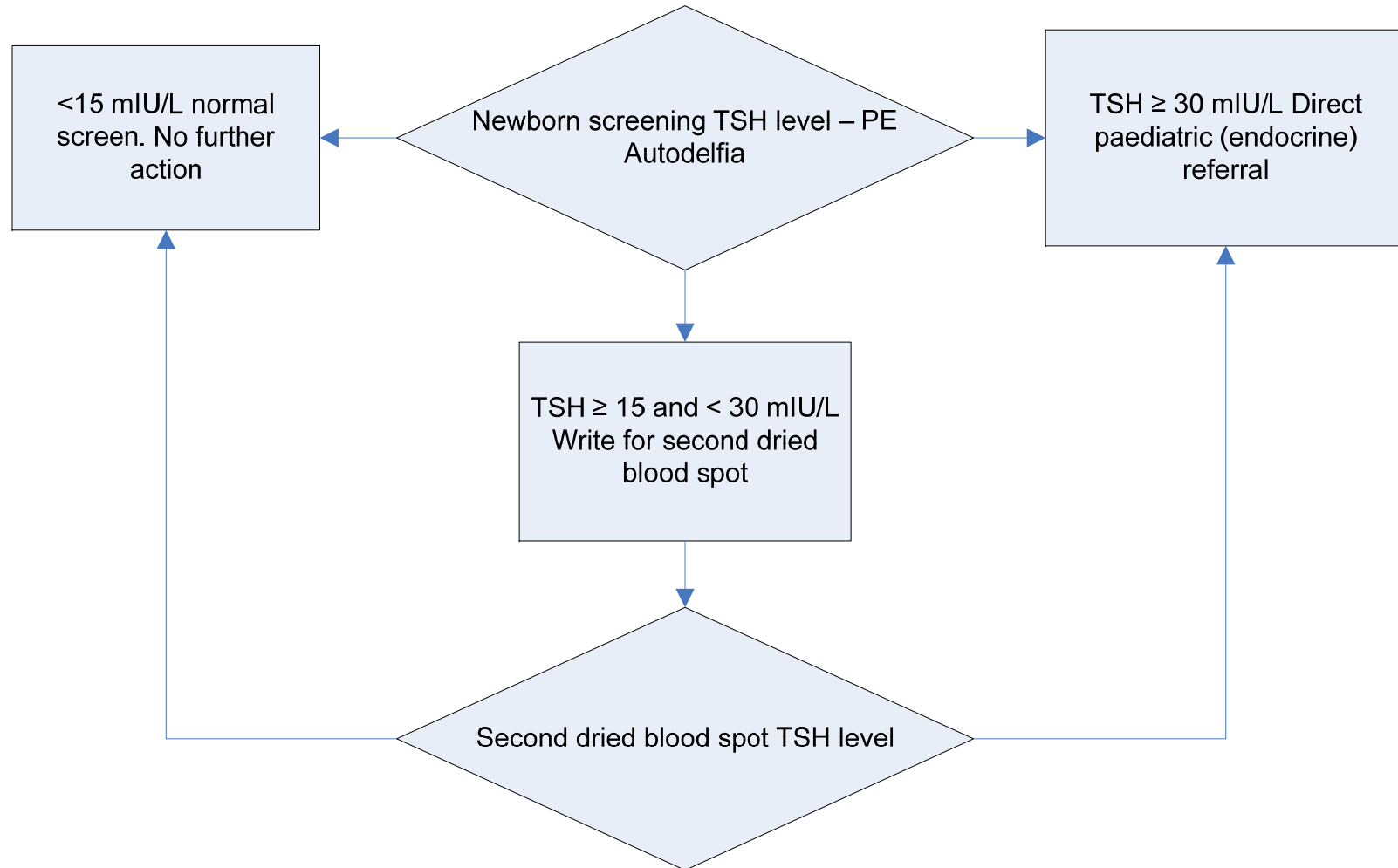
- Mission Creep
- Start screening for a severe condition then find more and more mild
- ?benefit of detection of very mild cases no evidence treating subclinical hypothyroidism is of clinical utility eg Ulm 1998
- Decided to leave cutoff unchanged, 8mIU/L for older babies

Time of Diagnosis

- Notified median 11d (5-47)
- Normal T₄ 14d (5-54)



CH Screening



Nb units mIU/L blood

Congenital hypothyroidism and your baby



You have just learned that your baby has congenital hypothyroidism. The information in this leaflet will help you understand more about this condition and answer some of your questions.

Congenital hypothyroidism

Congenital hypothyroidism is a condition where a baby is born with a thyroid gland that does not work properly. The thyroid gland is a butterfly-shaped organ at the base of the neck. Its job is to make thyroxine hormone that helps the cells of the body function correctly. A normally working thyroid gland is critical for normal growth and brain development.

A small, under-developed (not fully grown) thyroid gland or one that is missing altogether are the commonest causes of congenital hypothyroidism. The reasons why the thyroid gland does not develop properly in the fetus are not known.

Sometimes congenital hypothyroidism is caused by the absence of an enzyme in the thyroid gland, preventing it from making thyroxine.

One case of congenital hypothyroidism occurs in about every 2,300 babies born in New Zealand so there are about 30 babies born with this condition each year.

Treatment

As soon as you know your baby has congenital hypothyroidism, baby will be given thyroxine suspension. Enough thyroxine is given to your baby to increase levels to those of unaffected babies.



During the first two years of your baby's life your paediatrician (doctor for children) will arrange frequent blood tests (usually weekly for six weeks then monthly until one year of age) to make sure that the thyroxine levels are normal. The thyroxine suspension will be given in different amounts for the first few months of life depending on the thyroid blood results.

The thyroxine suspension has to be made up by a pharmacist each week as it won't work reliably for longer than this. As it is a suspension it needs to be shaken well before using. The suspension should always be kept in the fridge.

Your baby will also have regular checkups to make sure they are growing and developing normally. As your child becomes older, blood tests and hospital checkups are needed less often.

Some Answers



What does the thyroid gland do?

The thyroid gland is responsible for making thyroxine which has 3 main functions:

- Thyroxine helps develop your baby's brain in the first two years of life. A lack of thyroid hormone during this time will lead to intellectual disability.
- Thyroxine is needed for normal growth, so not having enough can lead to poor growth and short height as an adult.
- Thyroxine is the 'get-up-and-go' hormone – a child without it may feel cold, tired, and be constipated (not able to move their bowels).

Will my child be normal when they grow up?

There can never be a guarantee. With careful monitoring and treatment with thyroxine every day your baby has the best chance of achieving their full potential in growth and development.

Where does congenital hypothyroidism come from? Is it inherited?

The more common forms of congenital hypothyroidism such as an under-developed or absent thyroid gland are not inherited. Only conditions where the thyroid gland enzyme is absent are inherited. Your paediatrician can talk to you about this.

Could congenital hypothyroidism have been prevented during pregnancy?

No. The reasons for underdevelopment of the thyroid gland are not known, so we do not know if there is any way of preventing it.



What are the symptoms of congenital hypothyroidism?

In the first weeks after birth, a baby with congenital hypothyroidism may have no obvious symptoms and be difficult to distinguish from an unaffected baby. However, babies born with congenital hypothyroidism may be very sleepy and feed slowly. They may have a tendency to be constipated and suffer from yellowing of the skin that lasts a long time.

Congenital hypothyroidism can be diagnosed by a blood test before the baby develops any symptoms and signs of the condition. The blood test (heel prick test) is done as part of the Newborn Metabolic Screening Programme.

Why are babies screened for congenital hypothyroidism?

The aim of screening is to identify as soon as possible which babies are more likely to have congenital hypothyroidism so that treatment can be started. Most babies with congenital hypothyroidism are not obviously different from unaffected babies. Without a screening test your child may be months or years old before you find out. This delay in diagnosis and treatment will lead to intellectual disability.

Where can I go for further information?

- Talk to your paediatrician
- View www.newbornscreening.info/Parents/otherdisorders/CH.html
- View www.nsu.govt.nz for information on the Newborn Metabolic Screening Programme



New Zealand Government

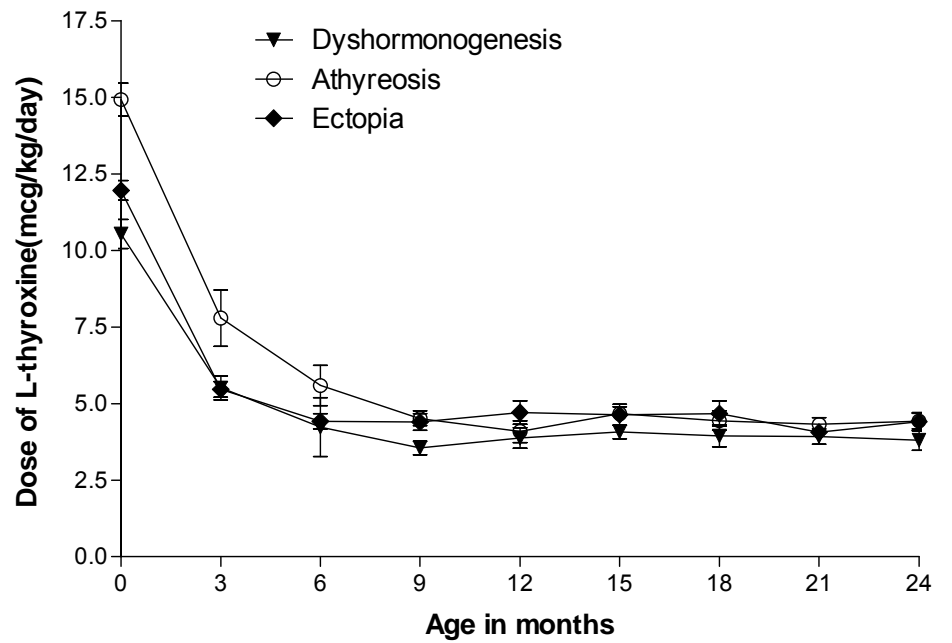
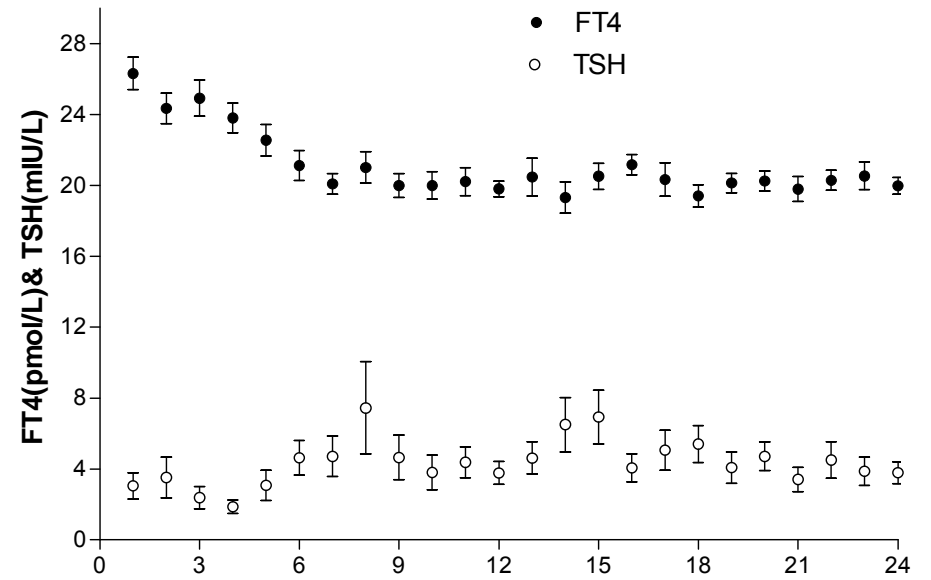
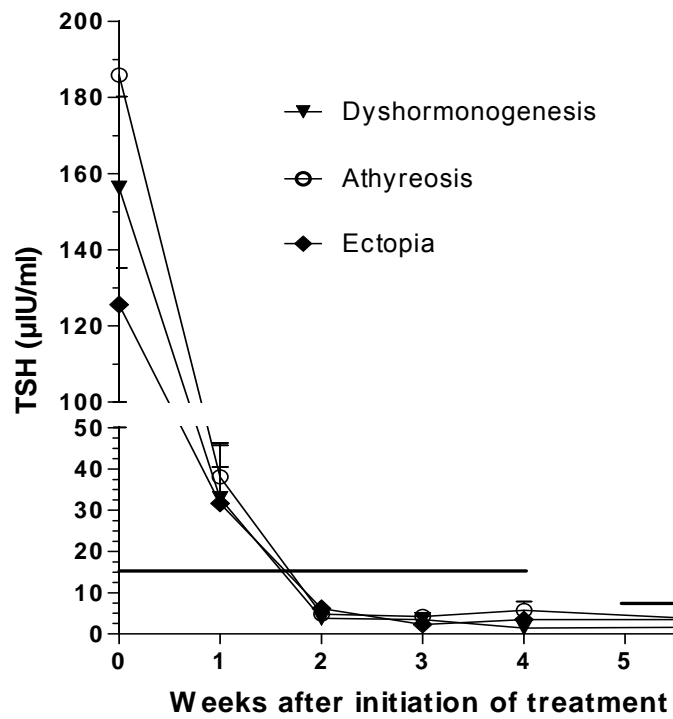
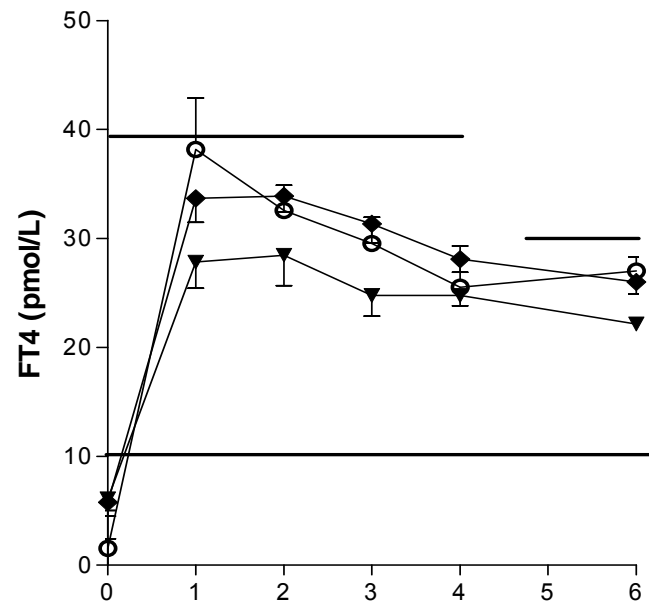


www.nsu.govt.nz

Auckland treatment regime

- 17 dyshormonogenesis thyroxine 10 $\mu\text{g}/\text{kg}/\text{day}$
- 35 ectopia thyroxine 12 $\mu\text{g}/\text{kg}/\text{day}$
- 17 athyreosis thyroxine 15 $\mu\text{g}/\text{kg}/\text{day}$
- Thyroid functions for 2years (weekly for one month then monthly)





Outcome

- 44 CH and 53 sibling controls
- IQ similar
- Treated with Auckland protocol
- Motor function and body composition similar
- CH severity does not influence outcome
- Time to normalise thyroxine does
- No additional benefit from earlier diagnosis in this timeframe

Screening for Cystic Fibrosis





Lancet 1977;310 (8048):1093-5



CYSTIC-FIBROSIS SCREENING IN THE NEWBORN

JEANETTE R. CROSSLEY

COLLEEN C. BERRYMAN

ROBERT B. ELLIOTT

*Department of Paediatrics, School of Medicine, University of
Auckland, New Zealand,*

Summary In a new method of testing stool samples from newborn babies for cystic fibrosis (C.F.), a colourless substrate, benzoyl-arginine-*p*-nitroanilide (B.A.P.N.A.), releases yellow *p*-nitroaniline when hydrolysed by trypsin. Samples from infants with C.F., who lack trypsin, give negligible colour. 2 infants with C.F. were detected among 2500 consecutive newborn babies tested. The incidence of false-positive results was 1.2% after the first specimen and 0.05% after the second specimen. A further refinement has reduced the positive rate to 0.1% after the first specimen (2000 samples). Tests on samples from 5 other older patients with untreated C.F. have yielded no evidence for false-negative results.



Lancet 1979;313 (8114): 472-4



**DRIED-BLOOD SPOT SCREENING FOR
CYSTIC FIBROSIS IN THE NEWBORN**

JEANETTE R. CROSSLEY

R. B. ELLIOTT

PATRICIA A. SMITH

*Department of Pædiatrics, School of Medicine University of
Auckland, New Zealand*

Summary Serum-immunoreactive-trypsin (I.R.T.) was measured in children with cystic fibrosis (C.F.) and a variety of controls. In the first few months of life all C.F. children had a raised serum-I.R.T. A dried blood-spot assay for I.R.T. was established and has potential as a screening test for C.F. in the newborn.

Jeanette recognised -

- IRT is not a single molecule
- No correlation between batches of trypsin between immunogenicity, protein and tryptic activity
- Units in early publications AU/L
- Screening kits supplied to NSW for the start of their screening

- 1986 MRC Funding stopped.
- NTC applied to DOH for continued funding.
- Rejected.
- CF Association involvement
- DOH funding as part of NTC contract since October 1986
- Contract now with MOH National Screening Unit

1986 Screening

- Measure IRT in 3-d sample
- If elevated, request 2nd sample and fecal sample for chymotrypsin
- Refer based on low chymotrypsin or elevated IRT

- 1988 reviewed use of chymotrypsin, only one extra case in 8 years, stopped June 1988

1995

- Replaced 2x IRT with genes $\Delta F508$, G551D, G542X and R117H on top 1% of IRT
- Reviewed 1999, stopped R117H – 97% of CF patients have at least one of the measured mutations.

May 2010 Replaced specific gene testing with High Resolution Melt methodology – detects the same mutations and maybe a few more rare ones

A Comparison of High-Resolution Melting Analysis With Denaturing High-Performance Liquid Chromatography for Mutation Scanning

Cystic Fibrosis Transmembrane Conductance Regulator Gene as a Model

Lan-Szu Chou, PhD,¹ Elaine Lyon, PhD,^{1,2} and Carl T. Wittwer, MD, PhD^{1,2}*

Key Words: *CFTR*; High-resolution melting analysis; Mutation scanning; Denaturing high-performance liquid chromatography; dHPLC

DOI: 10.1309/BF3MLJN8J527MWQY

Am J Clin Pathol 2005;124:330-6.

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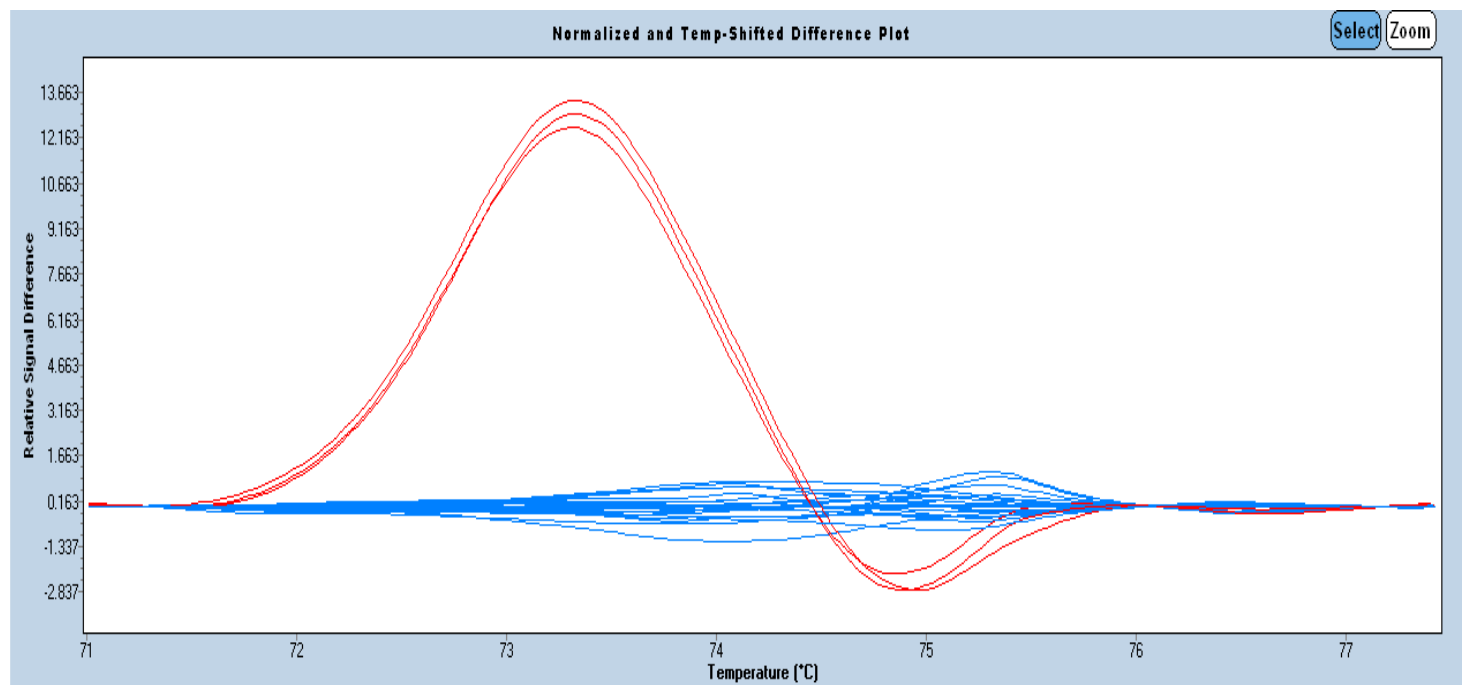
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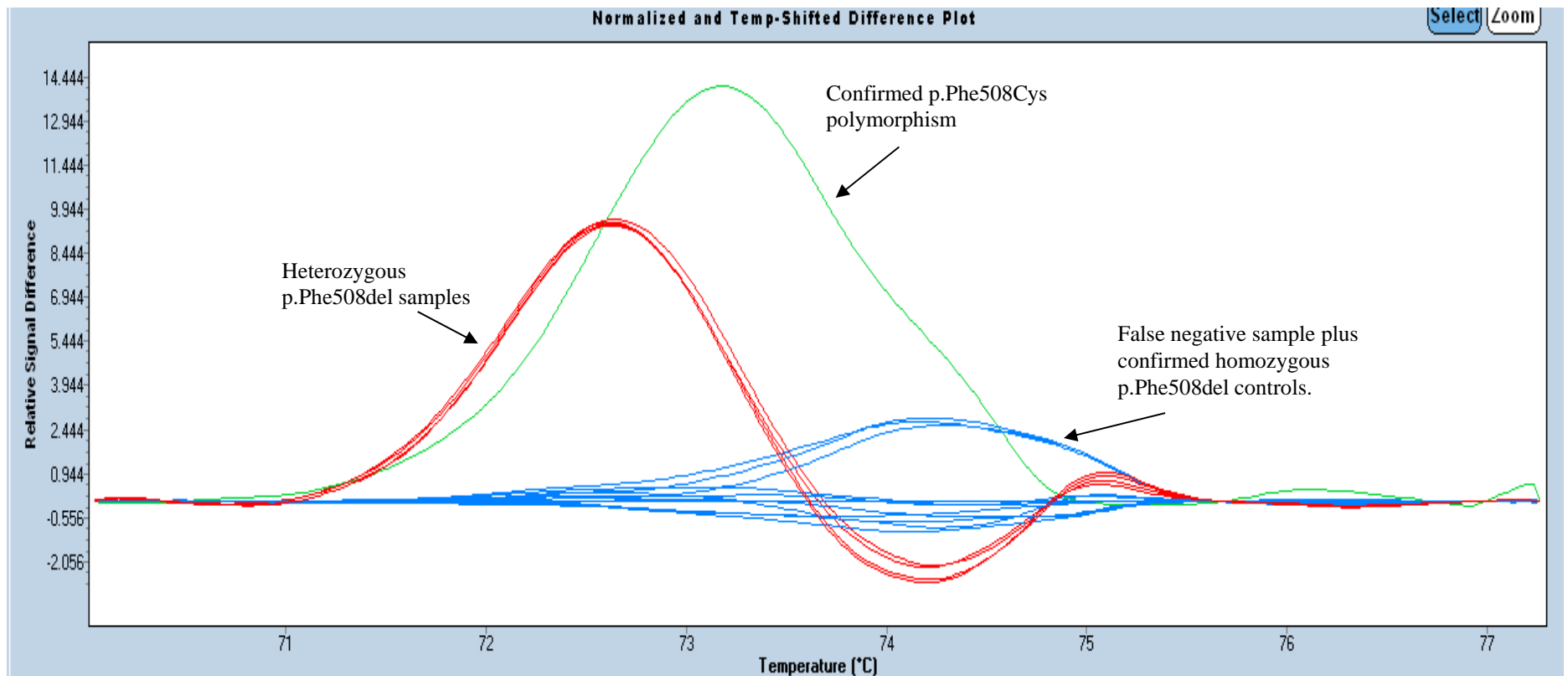
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Temperature [°C]



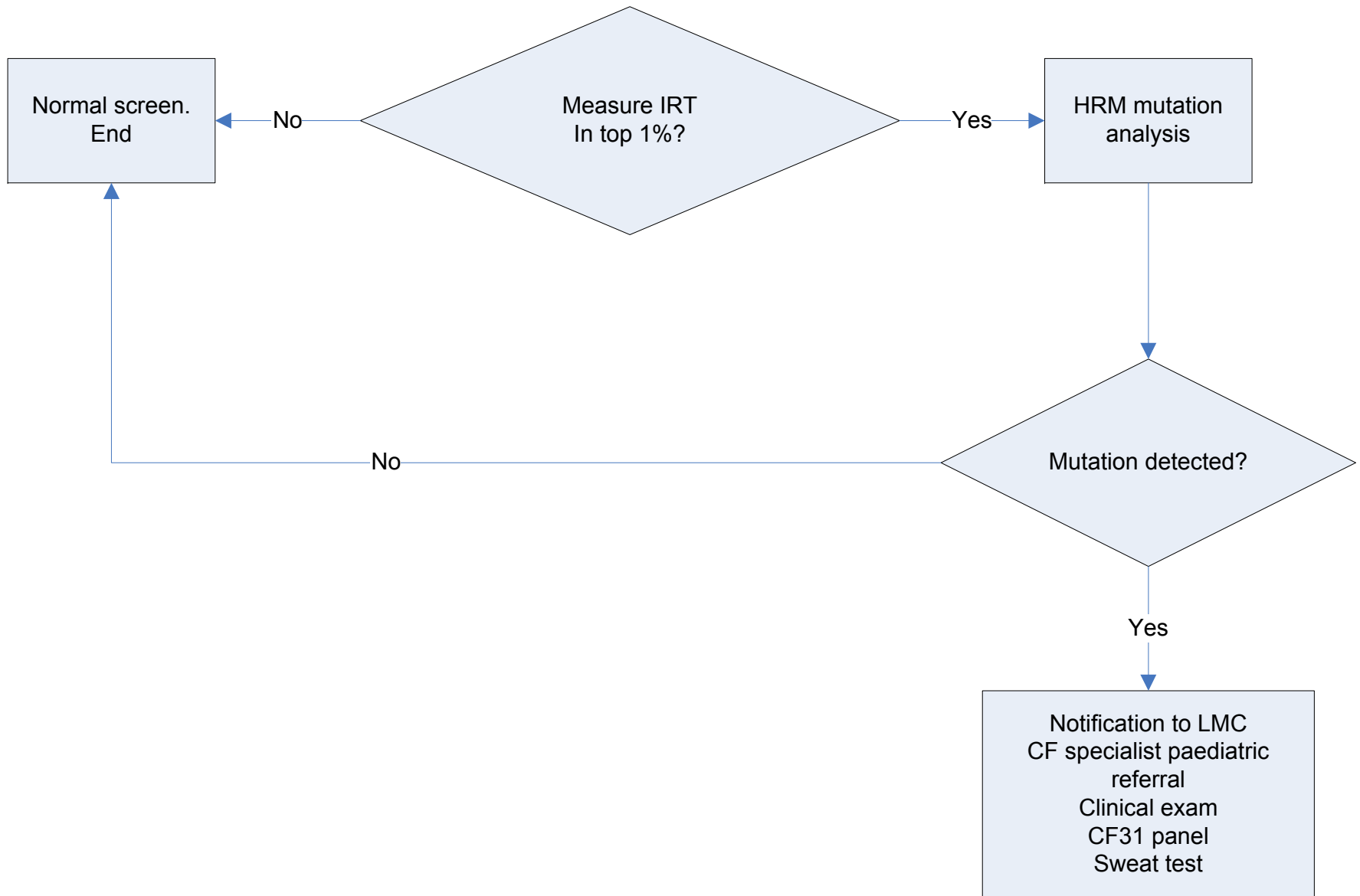
One false negative



Mutations 2010

Mutations	Number of Cases
• p.F508del/p.F508del	6
• p.F508del/p.G542X	2
• p.F508del/p.G85E	1
• p.F508del/R117H-5T	1
• p.F508del/p.N1303K	1
• p.F508del/p.W1282X	1
• p.G542X/p.L671X	1
• D579G/p.A455G*	1

* would not have been detected using old technology



Report CF screen positive

- To sample submitter (95% midwives) would they understand 6p.F508del/p.G542X?
- Not experienced in giving bad news to families
- Could be a mistake in lab or which baby blood on card – don't want baby in CF clinic for years if not CF
- Diagnostic process good for coming to terms with condition
- Early contact with specialist CF paediatrician so all information is current

1983-2010

- 2,451,235 infants screened
- 353 CF detected
- 27 (includes MI with low IRT) not detected – 93%
- 1:7,000 Corrected for non-European births
1:2,800.
- From 01.01.2000 152 cases / 788 notifications
(20% ppv)

CF audit form

- ID and information about baby
- DIAGNOSTIC LABORATORY TEST RESULTS (Sweat tests, pancreatic function tests), mutation analysis
- FOLLOWUP – genetic counselling (all notified are CF or carriers)
- For CF cases who is caring physician, clinical features at time of notification, family history, diagnosis suspected before screen (was screening helpful)
- Date treatment commenced (timely followup)

Genetic Counselling

- 788 carriers and affected from 01.01.2000
- 423 CF specialist paediatrician
- 232 genetic services
- 106 not known
- 21 GP
- 4 declined
- 2 already done (prenatal or FH)



GENETIC HEALTH SERVICE
NEW ZEALAND
RATONGA HAUORA IRANGA
AOTEAROA

Did screening help?

- 152 CF born this millenium
- Family history in 36 (24% - some quite distant)
- Other suspicions (antenatal scan, salty baby) in 14
- 43 (28%) symptomatic (failure to thrive, meconium ileus, vomiting, cough) at time of first paediatric assesment (median age 40 days)

18 CF late diagnosis in Starship Hospital

- **100** patients born 1985-2012
- 8 of 18 born overseas (3 UK, 2 Singapore, 1 Japan, 1 Australia, 1 South Africa)
- **10** born in NZ (**9** had a newborn screening)
- **9** missed (out of 91) = **9.9%**
- 1 homozygote missed – lab problem with HRM, 2 homozygotes and 3 heterozygotes normal IRT
- 3 uncommon genes raised IRT

9 Late Diagnosis

- 1 severe liver disease 11yrs
- 4 bronchiectasis 11, 9, 8.5 and 7.5 yrs
- 1 failure to thrive at age of 2yrs
- 1 recurrent pneumonias 2yrs
- 1 "chesty baby" 2months
- 1 respiratory distress 6 weeks
- 5 pancreatic insufficient, 4 pancreatic sufficient
- 4/5 pancreatic insufficient are homozygous for delta F 508

Cystic fibrosis and your baby



You have just learned that your baby may have cystic fibrosis or be a carrier of the disorder. The information in this leaflet will help you understand more about this condition and answer some of your questions.

Cystic fibrosis screening test

When your baby was a few days old, some blood was collected from your baby's heel. The blood was used to test for some rare disorders, including cystic fibrosis (CF).

The screening test result suggests that your baby may have CF or be a carrier of the disorder, though further tests are needed to confirm this. It is important to note that most babies with a positive screening result for CF are found to be carriers and will not have CF.

Children who are carriers of CF will not be affected by the disorder and will not need any special treatment. Further testing is needed to find out whether your child is a carrier or has CF. Each year in NZ about 30 - 50 babies are diagnosed as carriers of the CF gene and about 10 babies are diagnosed with CF.

Differences between being a carrier and having cystic fibrosis

We all have two copies of each gene in our body, one we inherit from our mother and one from our father.

If a baby inherits only one copy of the altered CF causing gene, they will be a carrier of the gene and will not have CF. They may pass this altered gene to the next generation, just like the parent they inherited the altered gene from.

If a baby inherits two copies of the altered gene (one from each parent) they will have CF.



Cystic fibrosis

CF is a genetic disorder inherited from both parents. CF is a lifelong illness that can affect all of the organs of the body. It often causes problems with digestion and breathing. It does not affect a person's looks or intellectual development.

The condition is caused by an altered gene that controls the movement of chloride in and out of the cells in the body.

Normally, the mucus secretions in our body, such as in our lungs, are thin and lubricating. In CF, the mucus turns thick which clogs up the body's tubes, ducts and passageways in many organs particularly the lungs and digestive system.

Testing

Your midwife will talk with you about referring you and your baby to the regional CF paediatrician. You will be seen at the hospital for further testing to find out if your baby is a carrier of the altered gene or has CF. This will occur within a few days of the newborn screening results.

The doctor will

- talk to you about your baby and family
- examine your baby
- organise further tests:
 - a blood test
 - a sweat test
 - sometimes a sample of baby's faeces.

Blood test: a small sample of blood is taken by a heel prick from your baby. This is sent to the laboratory to find out whether your baby carries one or two copies of the altered gene. This result may take a couple of weeks.

Sweat test: a sweat test is a safe procedure but can cause slight irritation to the baby's skin. The sweat test measures the amount of salt in their sweat. In CF these levels are high. For more information on a sweat test see www.kidshhealth.org.nz



Faeces test: sometimes a small sample of your baby's faeces is sent to a laboratory to look for a pancreatic enzyme. Babies with CF have a low level of this enzyme.

If the sweat test and other results support a diagnosis of CF, the doctor will discuss treatments available for your baby. You and your baby will be referred to a team of health professionals who take care of children with CF in your area. The team often includes a specialist doctor, a specialist nurse, a dietitian and a physiotherapist. The CF team will be able to give you support and detailed information about your baby's diagnosis. They will carefully discuss what treatments your baby will need and what you can do to help keep your child well.

Treatment

Babies with CF are treated as soon as they are diagnosed. The care of CF aims to:

- prevent lung problems with daily chest physiotherapy, daily exercise and frequent antibiotic therapy.
- promote normal growth and good health with high calorie foods.

The CF team will explain treatments to you more specifically as they are prescribed.

Further Information

- Talk to the nurse specialist and the CF paediatrician
- View www.newbornscreening.info/parents/otherdisorders/CF.html



New Zealand Government



www.nsu.govt.nz

Screening performance

- What are we screening for?
- Patient with one or more characteristic phenotypic features (including meconium ileus); *or* a history of CF in a sibling; *or* a positive newborn screening result AND 2 CFTR disease-causing mutations or a sweat chloride concentration greater than 35 mmol/L.
- Is presence of MI part of screening?

Thank-you

