

# The Controversy on Mild (Compensated) Congenital Hypothyroidism – The Path We Took to Resolve the Dilemma in Washington Newborn Screening

**Caroline T. Nucup-Villaruz, MD**

**Primary Author**

**Washington State DOH**

**Newborn Screening Program**

**Patricia Y. Fechner, MD**

**Co-Author & Presenter**

**Washington NBS Endocrinology Consultant**

**Seattle Children's Hospital, Division of Endocrinology**

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# OBJECTIVES

1. To present the issues and dilemma of either confirming or ruling out the diagnosis of CH based on the serum thyroid results.
2. To define compensated or subclinical hypothyroidism.
3. To determine the appropriate TSH threshold at a certain age that merits further monitoring and follow-up.
4. To share the consensus from endocrinologists regarding appropriate follow-up of mild (compensated) hypothyroidism.

# Congenital Hypothyroidism

## Estimated Prevalence

USA 1:2,300

Washington State 1:3,600 (T4 used from 1977-2004)

Washington State 1:1,200 (TSH used since 2004)

# Compensated (subclinical) Hypothyroidism

- ❖ Serum TSH is above upper limit of normal range
- ❖ Thyroxine (total or free T4) level is normal
- ❖ TSH is a sensitive indicator of decreased thyroid function
- ❖ Does lack of treatment result in mental retardation?
- ❖ Developing brain requires thyroid hormone
- ❖ Does early treatment result in normal neurocognitive outcome?

# Compensated (subclinical) Hypothyroidism

## ❖ **Permanent Hypothyroidism**

- abnormalities of thyroid morphology
- partial thyroid hormone dyshormonogenesis

## ❖ **Transient Hypothyroidism**

- significant exposure to iodine in-utero or via breast milk
- transplacental passage of thyroid-blocking antibodies

# Normal Thyroid Physiology

- ❖ At birth, there is high TSH surge with peak of 70 mIU/L at 30 min
- ❖ Increase in FT4 is TSH dependent and lasts 1 – 2 months

# “Normal” TSH (mIU/L) Ranges

Laboratories (reference labs in WA)	0 -7 days	7 days - 1 month	1- 3 months	3 - 11 months
Esoterix (ICMA)	1.3-16		0.9-7.7	0.9-7.7
P A M L (ICMA)	0.52-16.0 M 0.72-13.1 F	0.52-16.0 M 0.72-13.1 F	0.55-7.1M 0.46-8.1F	0.55-7.1 M 0.46-8.1 F
Quest	0.7-15.4	1.7-9.1	0.8-8.2	0.8-8.2
O H S U	0.7-18.1	0.7-18.1	1.2-8.21	1.2-8.21
S C H (chemilucnet)	1-20 (0-3 d)	0.5-6.5 (10 is critical value)	0.5-6.0	0.5-6.0 ≤ 5m 0.5-4.5 ≥ 5m

# TSH Percentiles

Age	TSH mIU/L 25 <sup>th</sup> %	TSH mIU/L 50 <sup>th</sup> %	TSH mIU/L 97.5 <sup>th</sup> %
1week-3months	0.92	2.3	4.38
>3m-6months	0.79	2.24	4.23
>6m-12months	0.84	2.37	4.31

\*Chaler EA et al. Clin Chem Lab Med 2012;50(5):885-890 (Buenos Aires)



# TSH Reference Range

Age	-2 SDS	-1 SDS	0	1 SDS	2 SDS
Birth	2.43	3.84	6.44	11.75	24.03
1 day	1.90	3.21	5.44	9.76	17.58
2 days	1.40	3.21	5.44	9.76	17.58
3 days	0.94	2.03	3.75	6.24	9.65
4 days	0.60	1.48	2.85	4.64	6.82
1 week	0.58	1.18	2.14	3.57	5.58
1 month	0.58	1.18	2.14	3.57	5.57
3 months	0.58	1.18	2.14	3.57	5.57
6 months	0.58	1.18	2.14	3.56	5.56
1 year	0.57	1.17	2.13	3.55	5.54

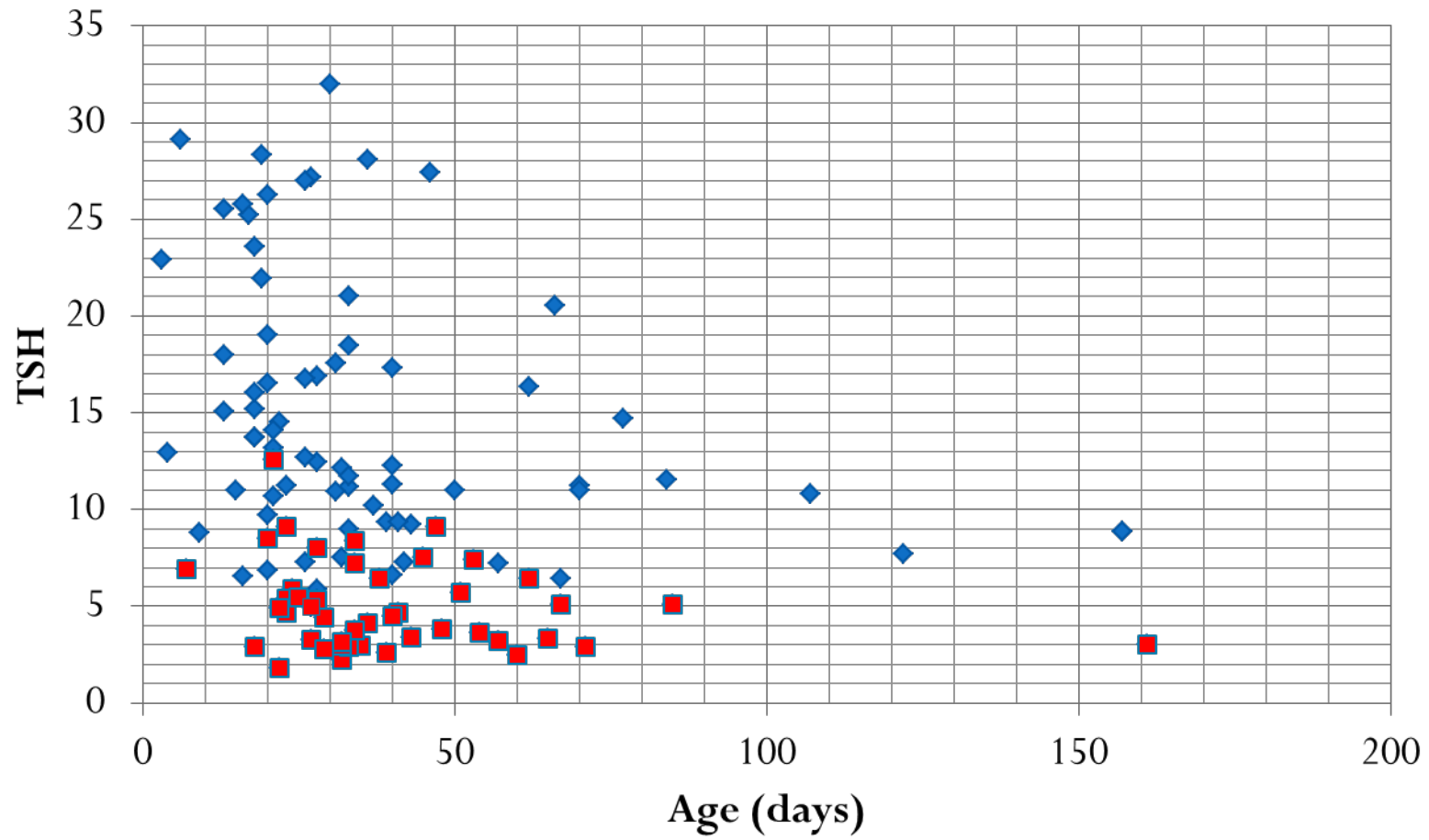
\*Lem et al. JCEM 2012, 97:3170-3178



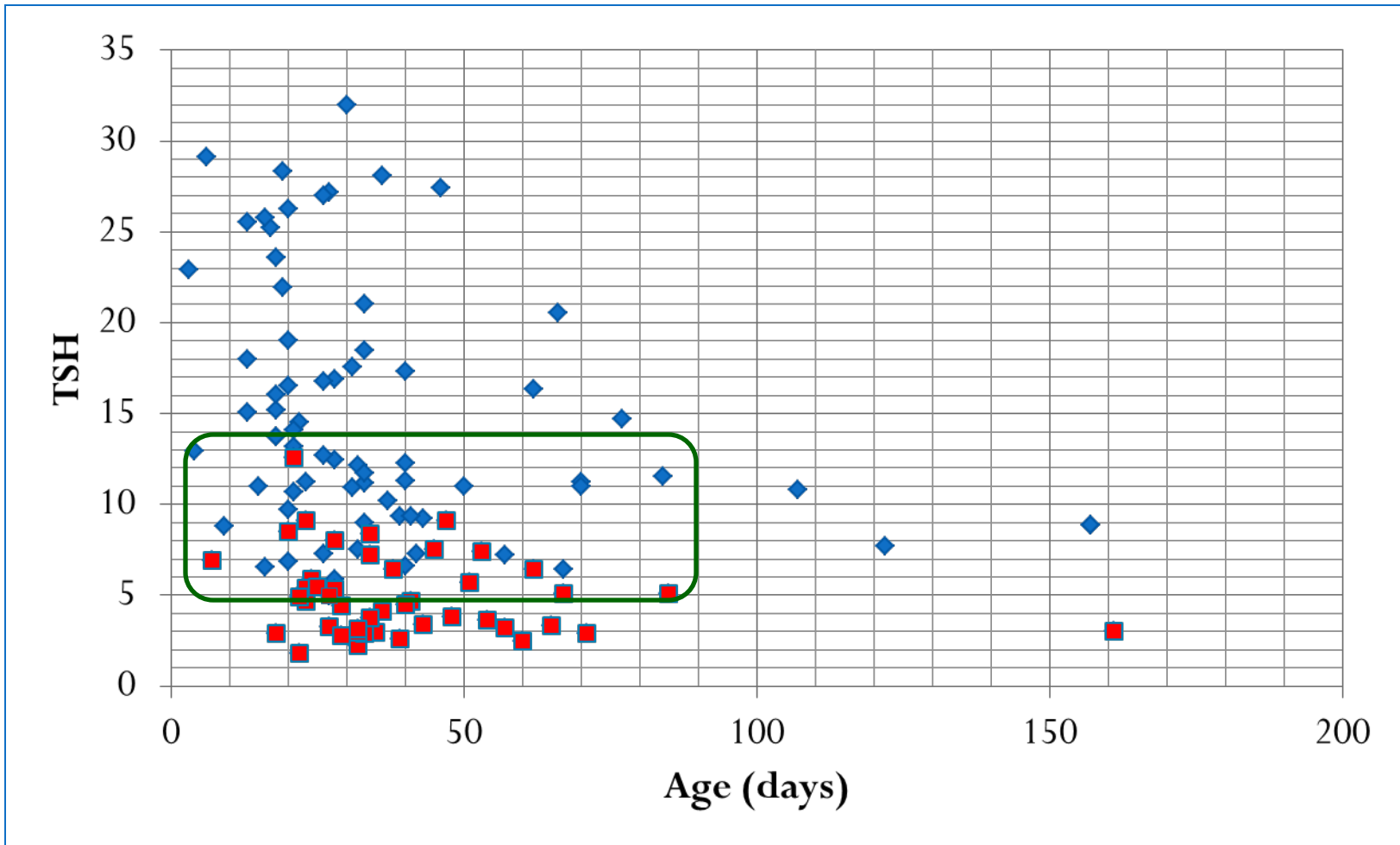
# 2012 Mild CH Data

Screen + (n=95)	Serum TSH		Highest TSH value at diagnosis/ resolution	Lowest TSH value at diagnosis/ resolution	Age at Diagnosis (days)		Age at Treatment	
	median	mean			median	mean	median	mean
True + (n=58)	15.4	12.2	29.1@11d	4.8@23d	28	36	31	44
False + (n=37)	5.1	5.8	9.13@23d	1.83@22d	33	38	N/A	

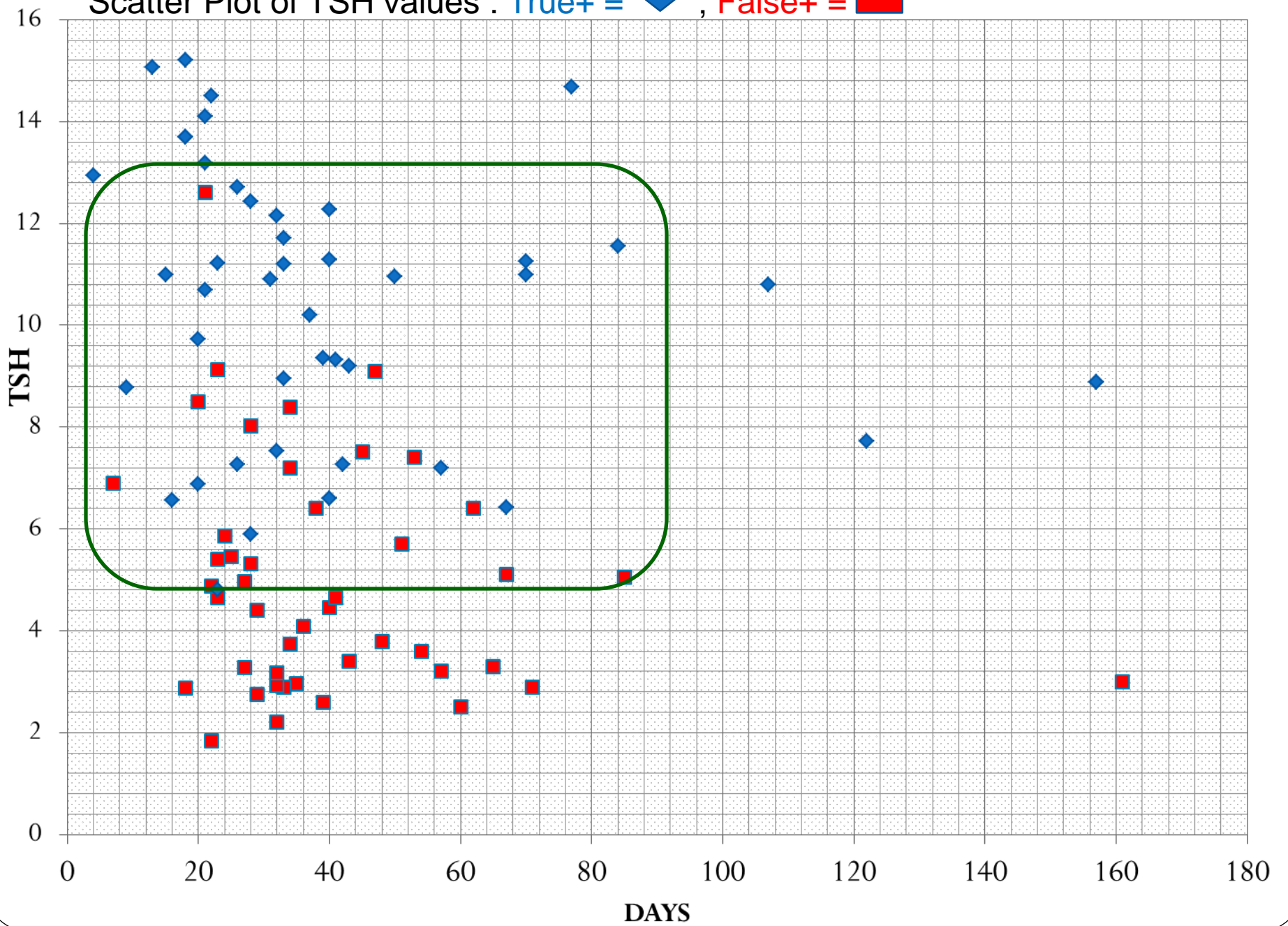
Scatter Plot of TSH values  
(2012 Mild CH: True+ vs False+)



# Scatter Plot of TSH values (2012 Mild CH: True+ vs False+)



Scatter Plot of TSH values : True+ =  ; False+ = 



# Issues and Dilemma

- Different State NBS: T4 vs TSH, 1 screen vs 2 screens
- Different physicians/endocrinologists use different labs
- Different laboratories use different reference ranges
- NBS dilemma regarding when to resolve, treat or continue monitoring serum thyroid levels ???
- Is there a universal or regional consensus regarding appropriate management of compensated hypothyroidism?
- *Presented above issues along with 2012 TSH data to the PEARL (Pediatric Endocrinology Association for Research and Learning) conference on March 8, 2014 in Portland, OR*



# Literature Review

1. LaFranchi SH, Connelly KJ. Detection of **neonates** with mild congenital hypothyroidism (primary) or isolated hyperthyrotropinemia: an increasingly common management dilemma. *Expert Rev. Endocrinol. Metab.* May 2014, Vol. 9, No. 3, pages 263-271.
2. Leger J, et al. European Society for **Paediatric** Endocrinology Consensus Guidelines on Screening, Diagnosis & Management of Congenital Hypothyroidism. *The Journal of Clinical Endocrinology & Metabolism.* Feb 2014;99(2):363-84.
3. Tenenbaum-Rakover Y. Approach to Subclinical Hypothyroidism in **Children**. Intech 2013..
4. Aijaz NJ, et al. Neurocognitive Function in **Children** with Compensated Hypothyroidism: Lack of Short Term Effects on or off Thyroxin. *BMC Endocrine Disorders* 2006, 6:2.
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6. Kaplowitz PB. Review Article - Subclinical Hypothyroidism in **Children**: Normal Variation or Sign of a Failing Thyroid Gland? *International Journal of Pediatric Endocrinology*, April 2010, Volume 2010, Article ID 281453, 8 pages.
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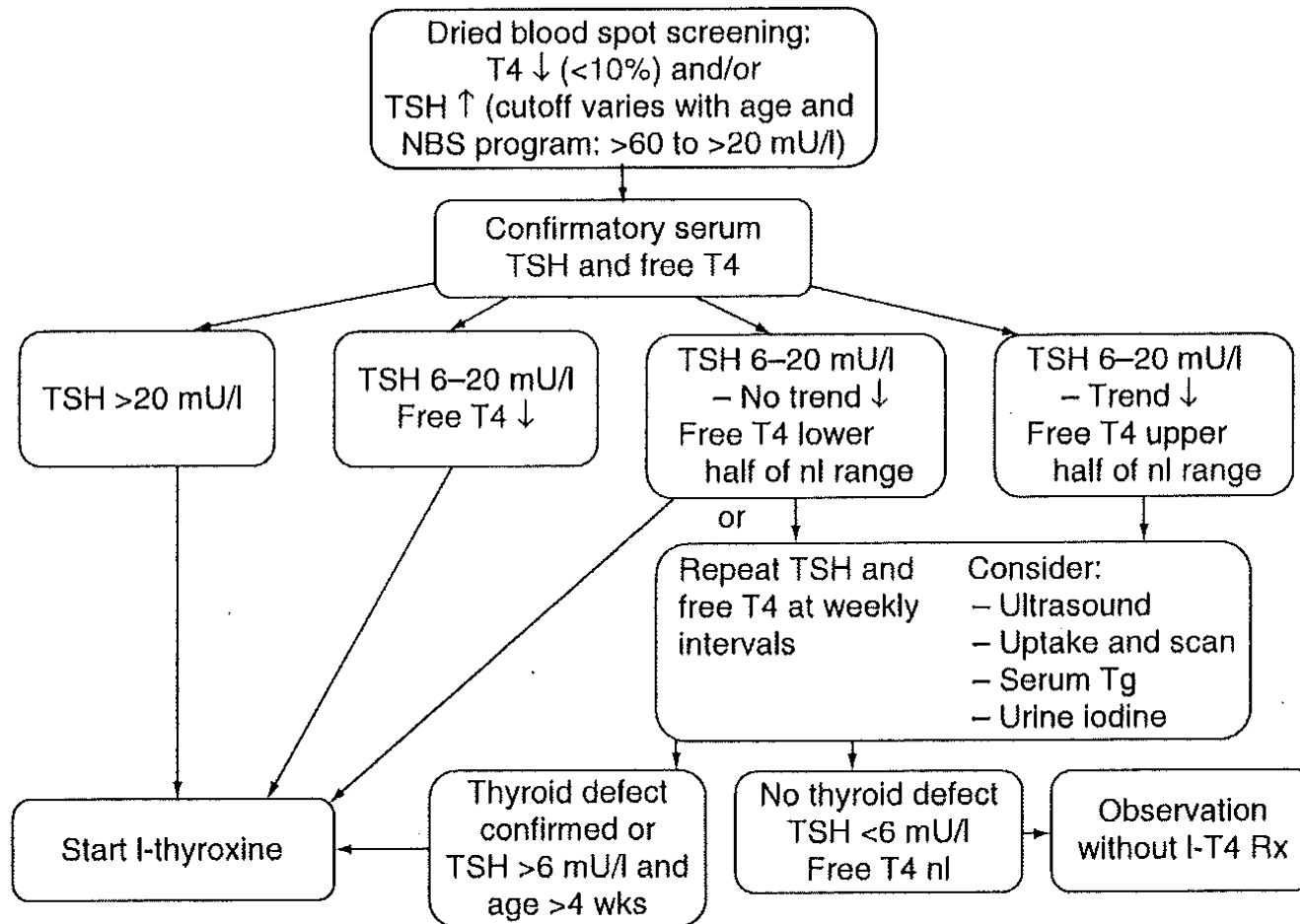
**\*\*\*6 favor TX & FU, 2 will treat depending on other factors, 2 favor no TX**

# Conclusions

- Endocrinologists differ in regards to management and opinion on mild CH based on 2012 TSH data
- More endocrinologists favor monitoring, follow-up and treating mild CH based on literature review
- A consensus was reached during the 2014 PEARL conference on March 8, 2014 led by Dr. LaFranchi and Dr. Fechner that a serum TSH  $\geq 6.0$  at age  $\geq 14$  days will need repeat serum thyroid studies or a referral to a pediatric endocrinologist
- Washington TSH protocol and memo were modified based on the above consensus/recommendation







**Figure 1. Recommendations for management of neonates with borderline thyroid dysfunction.**

NBS: Newborn screening; TSH: Thyroid-stimulating hormone.

Expert Review of Endocrinology & Metabolism, May 2014, Vol. 9, No. 3 : Pages 263-271

Detection of neonates with mild congenital hypothyroidism (primary) or isolated hyperthyrotropinemia: an increasingly common management dilemma

Kara J Connelly, Stephen H LaFranchi  
(doi: 10.1586/17446651.2014.897607)



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# Future Directions

- More studies on pediatric Mild CH are needed to compare outcome of:
  - a) short-term vs. long-term follow-up
  - b) early vs. late treatment
  - c) with or without treatment
  - d) benefits and adverse effects
- Consensus on clinical practice guidelines, reference ranges and definitions (Mild CH, Compensated Hypothyroidism, Transient Hypothyroidism)

# THANK YOU!

## Acknowledgments



# Washington State Newborn Screening

[www.doh.wa.gov/nbs](http://www.doh.wa.gov/nbs)

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