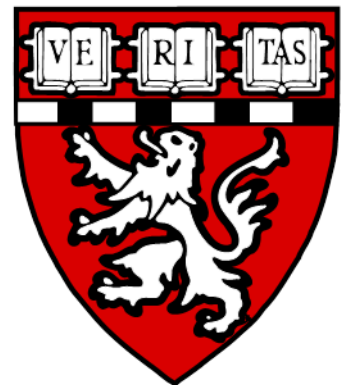


Generic & Brand-Name L-T4 Are Not Bioequivalent for Children With Severe CH

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Disclosure

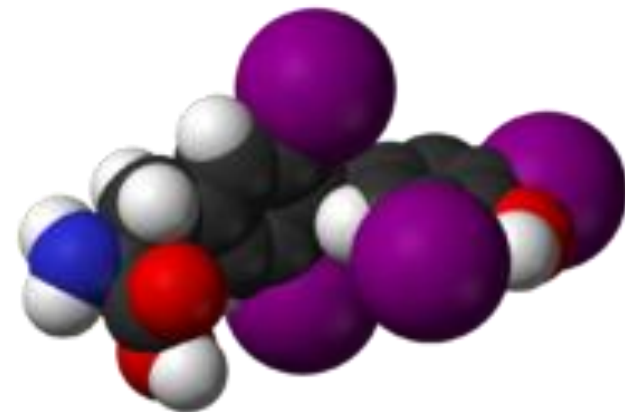
- No relevant conflicts to disclose

Learning Objectives

- Potential limitations of FDA methods to determine L-T4 bioequivalence.
- Significance of small changes in L-T4 dose on cognitive development in infants with congenital hypothyroidism (CH).
- Bioequivalence of brand name vs. generic L-T4 in children with severe hypothyroidism.
- Other clinical situations in which similar changes may be found.

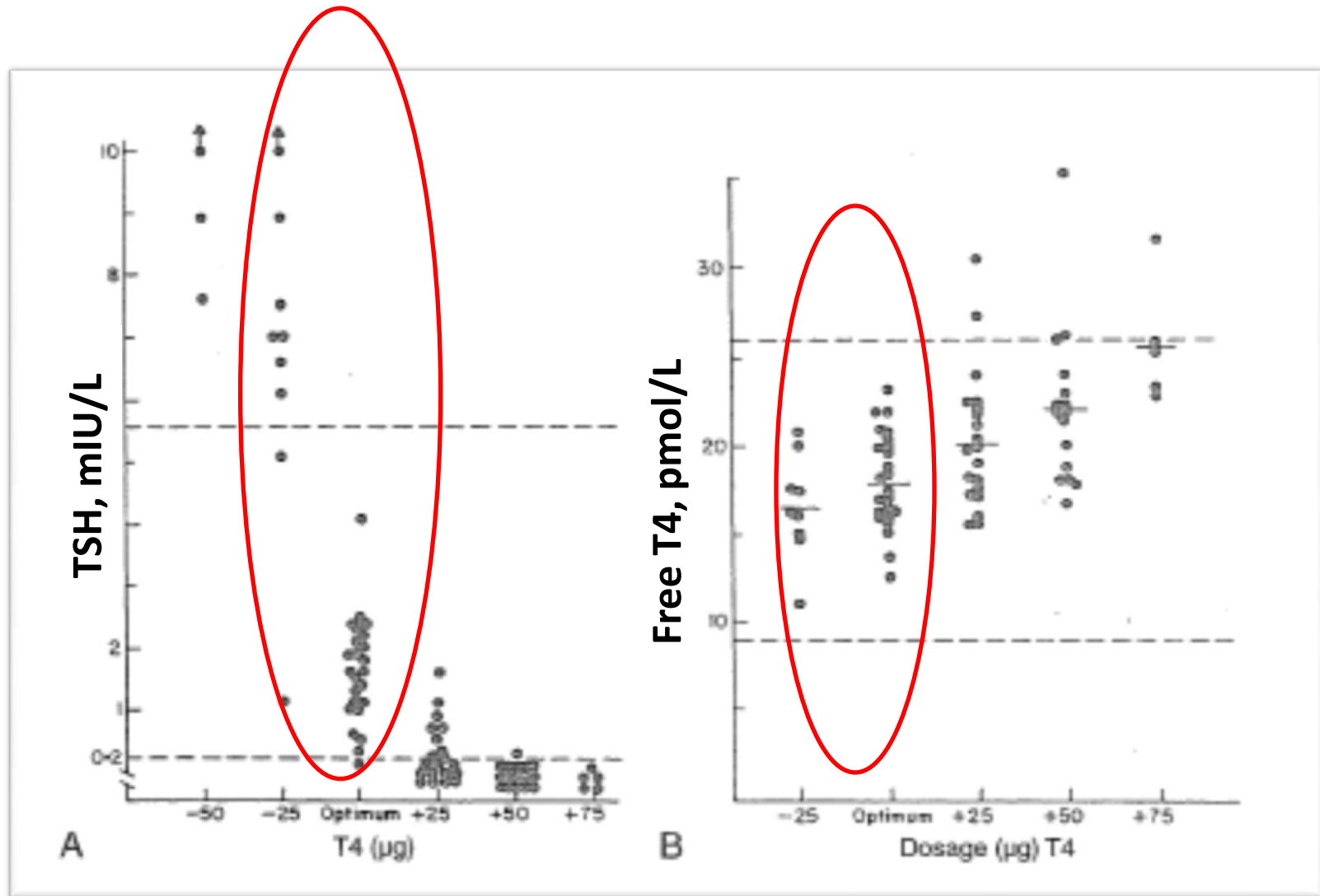
Determination of Bioequivalence (FDA)

- Supraphysiologic dose (600 μg) of liquid L-thyroxine administered to adult volunteers
- AUC and C_{max} of serum T4 determined
- Results compared with 1 of 4 reference preparations (Unithyroid[®], Synthroid[®], Levoxyl[®], Levothyroid[®])
- Bioequivalent* if AUC and C_{max} 80-125% of reference (90% CI)



*AB rated

Potential Pitfall: Ignores effect on TSH






Carr D et al Clin Endocrinol 28:325, 1988

L-T4 Critical for Brain Development

- An \uparrow in recommended starting L-T4 dose from 6-8 to 10-15 mcg/kg/d \propto 'd with significant \uparrow IQ in NB babies with CH
- Even mild maternal HT \propto 'd with \downarrow intellectual/motor devt.
- In practice, dose adjusted by increments of 10%



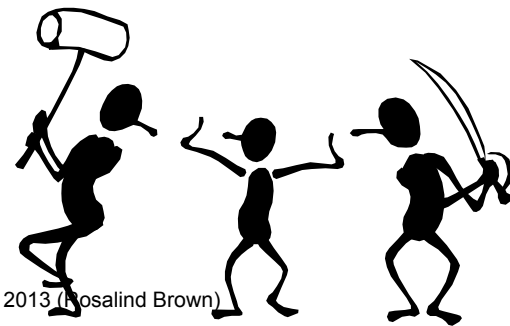
Bioequivalence Results Controversial

- One commonly cited study purported to show bioequivalence, but highly flawed¹ 
- In another controlled study of 31 adults, severity of hypothyroidism not described² 
- In recent pharmacovigilance study, 177 AEs attributable to changes in TSH reported³ 
- No prospective randomized controlled trials in patients with little endogenous hormone

¹Dong BJ et al, JAMA 1997; 277: 1205-1213

²Escalante DA et al Am J Med. 1995; 98:374-378

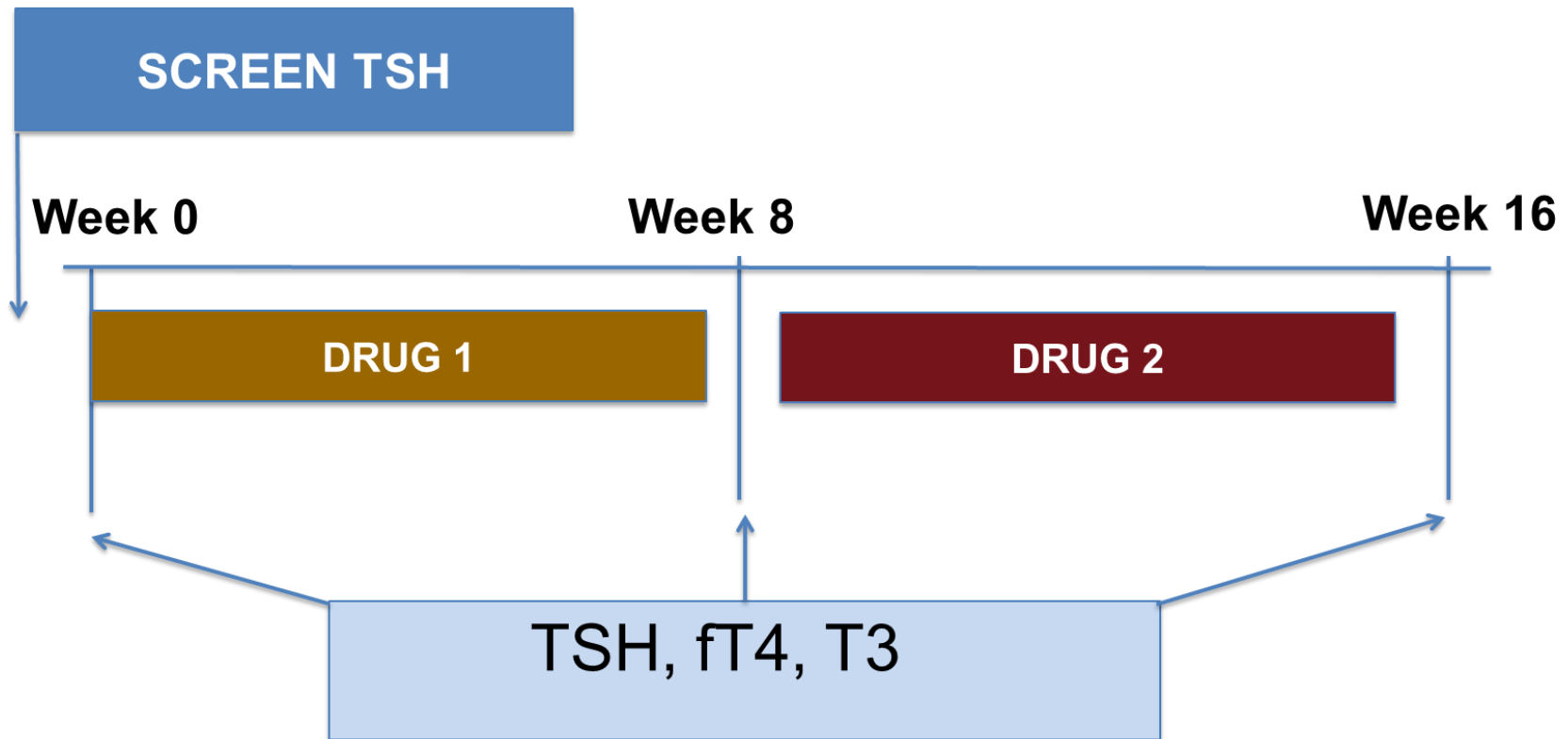
³Hennessey JV et al Endocr Pract. 2010; 16: 357-370



Are Brand Name and Generic T4 Bioequivalent in Children with Severe Hypothyroidism?

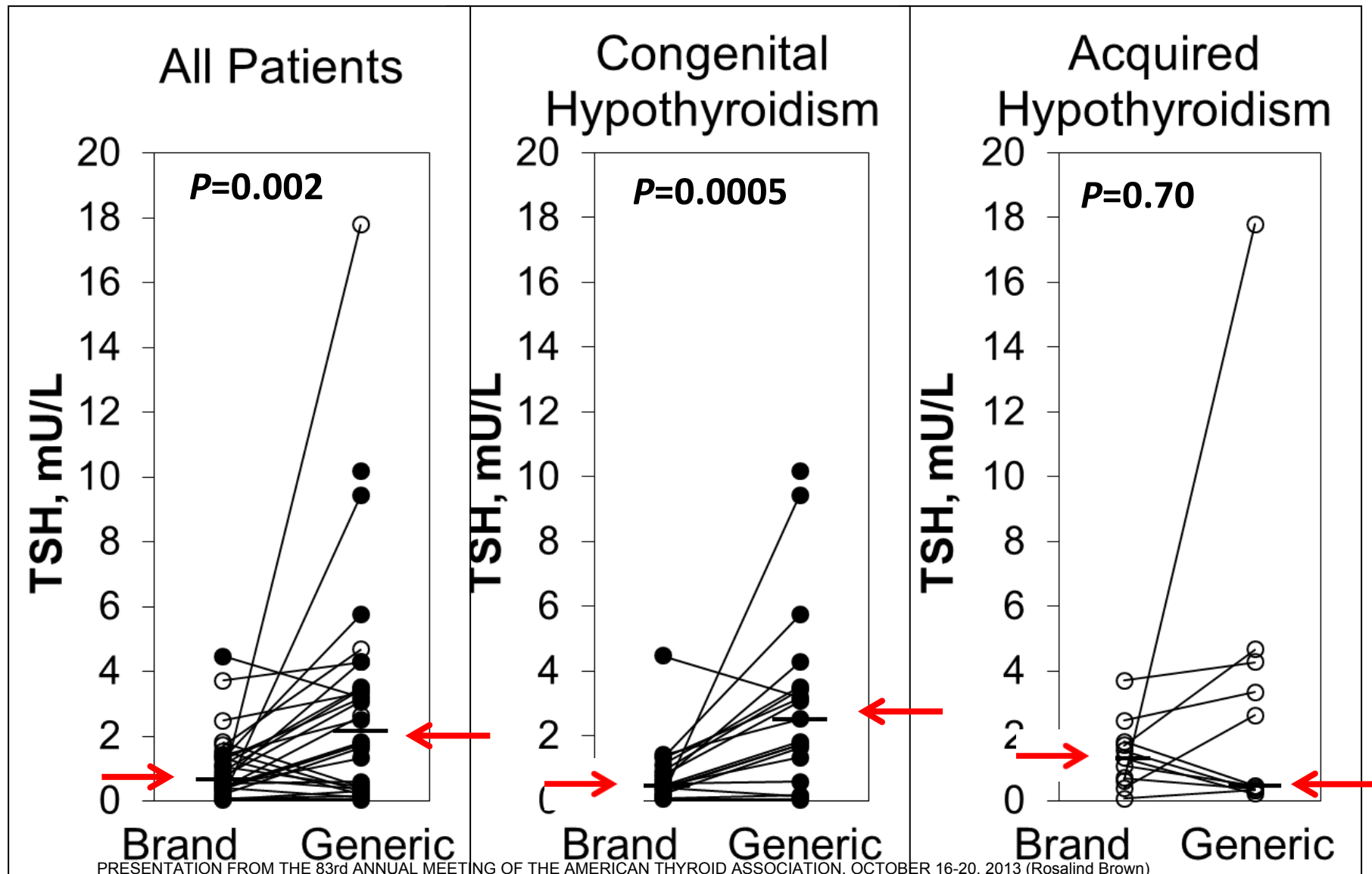
- **Objective:**
 - To evaluate BE of brand name Synthroid® vs. AB-rated generic (Sandoz)
- **Inclusion criteria:**
 - age 3 to 18 y
 - TSH concentration >100 mU/L at diagnosis
 - Normal TFTs within 4 wk of study entry
- **Exclusion criteria:**
 - GI disease
 - On medication that might affect results

Study Design



	Congenital Hypo (CH)	Acquired Hypo (AH)	<i>P</i> value
n	20	11	
M:F	6:14	1:10	0.413
Age at dx	4.3 \pm 0.6 da	10.0 \pm 0.6 y	N/A
T4, mcg/dL	6.2 \pm 0.9*	1.4 \pm 0.3	N/A
TSH, mIU/L	>200 (100-563)**	254 (100-1,000)	N/A
Age at study entry, y	8.4 \pm 0.8	12.9 \pm 1.1	0.003
Free T4, ng/dL	1.5 \pm 0.1	1.4 \pm 0.1	0.113
TSH, mIU/L	2.4 (0.2-4.6)	1.6 (0.3-5.3)	0.549
L-T4 dose, mcg/kg	3.0 \pm 0.2	2.0 \pm 0.2	<0.0005

Significant Difference in TSH



No Difference in Free T4 or Total T3

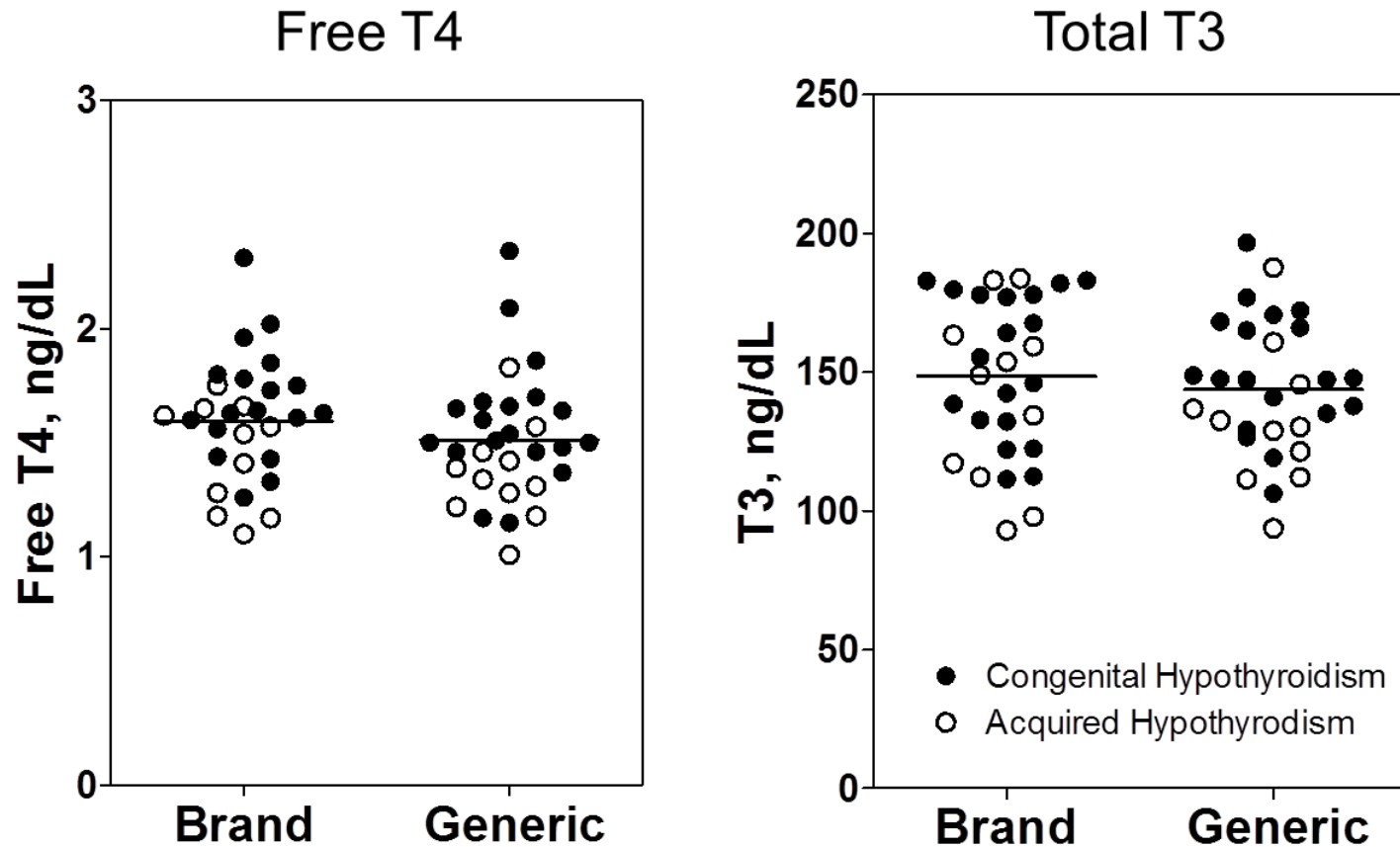
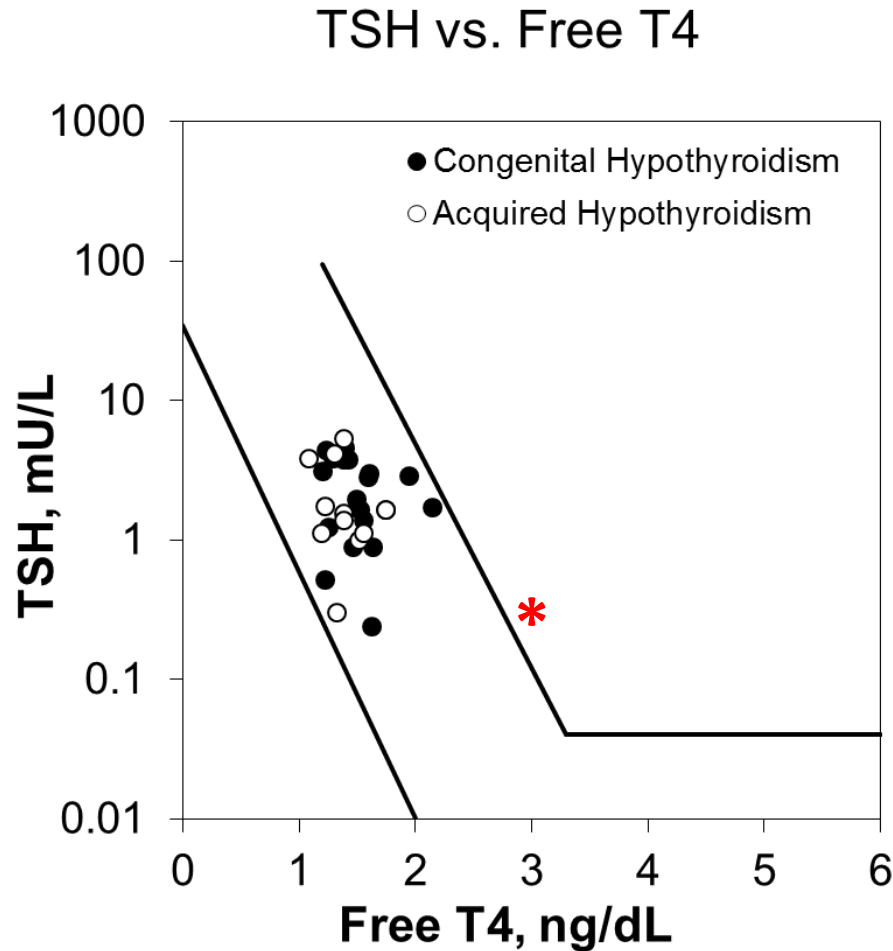


Figure 3.

No Evidence of TH Resistance



*Fisher DA et al. JCEM 2000;85: 2722-2717

Summary & Conclusions

- A brand name L-T4 (Synthroid) and an AB-rated generic formulation not bioequivalent in patients with severe CH*
- No difference in patients with severe AH
- Most likely explanation is diminished thyroid reserve
- Would seem prudent not to substitute L-T4 formulations in babies with severe CH
- Our findings may have implications for other populations with little thyroid reserve, e.g., pts S/P thyroid ablation for CA or GD and the elderly

*Carswell JM et al. JCEM 98: 610-617, 2013