American Thyroid Association, October 2013
Meet-the-Professor session

Congenital hypothyroidism (CH): management of mild cases

Guy Van Vliet, M.D.

Université de Montréal/Ste-Justine Hospital

PRESENTATION FROM THE 83rd ANNUAL MEETING OF THE AMERICAN THYROID ASSOCIATION, OCTOBER 16-20, 2013 (Guy Van Vliet)

Disclosure

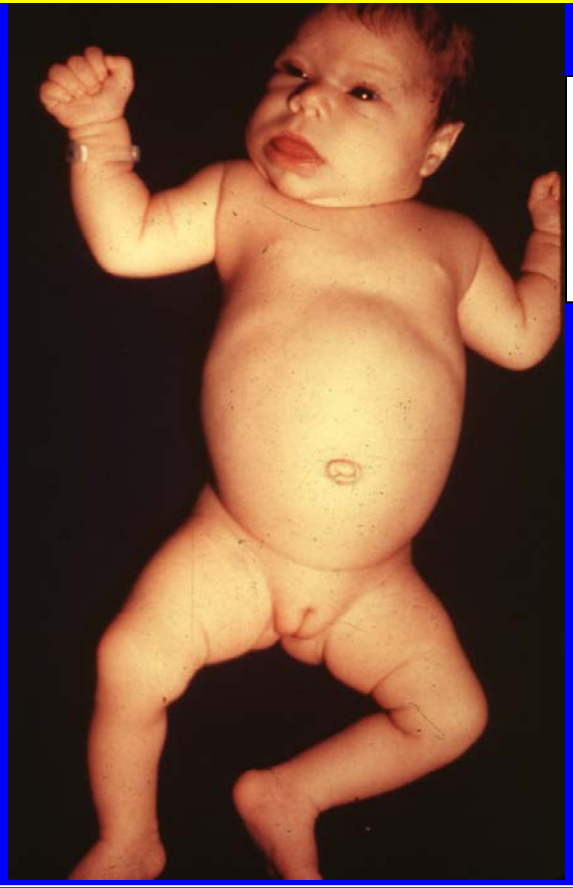
Guy Van Vliet has reported no commercial affiliation associated with this presentation

Learning objectives

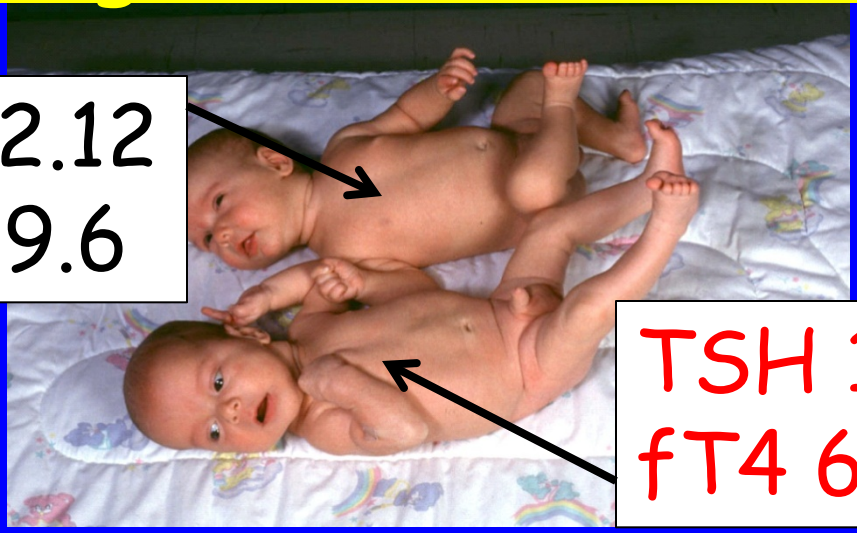
At the conclusion of this presentation, the participant should be able to:

1. Differentiate screening for and diagnosis of CH
2. Make a differential diagnosis of neonatal hyperthyrotropinemia
3. Counsel parents about the causes and consequences of overt and mild CH

Biochemical screening for CH: rationale



TSH 2.12
fT4 19.6



TSH 109
fT4 6.5

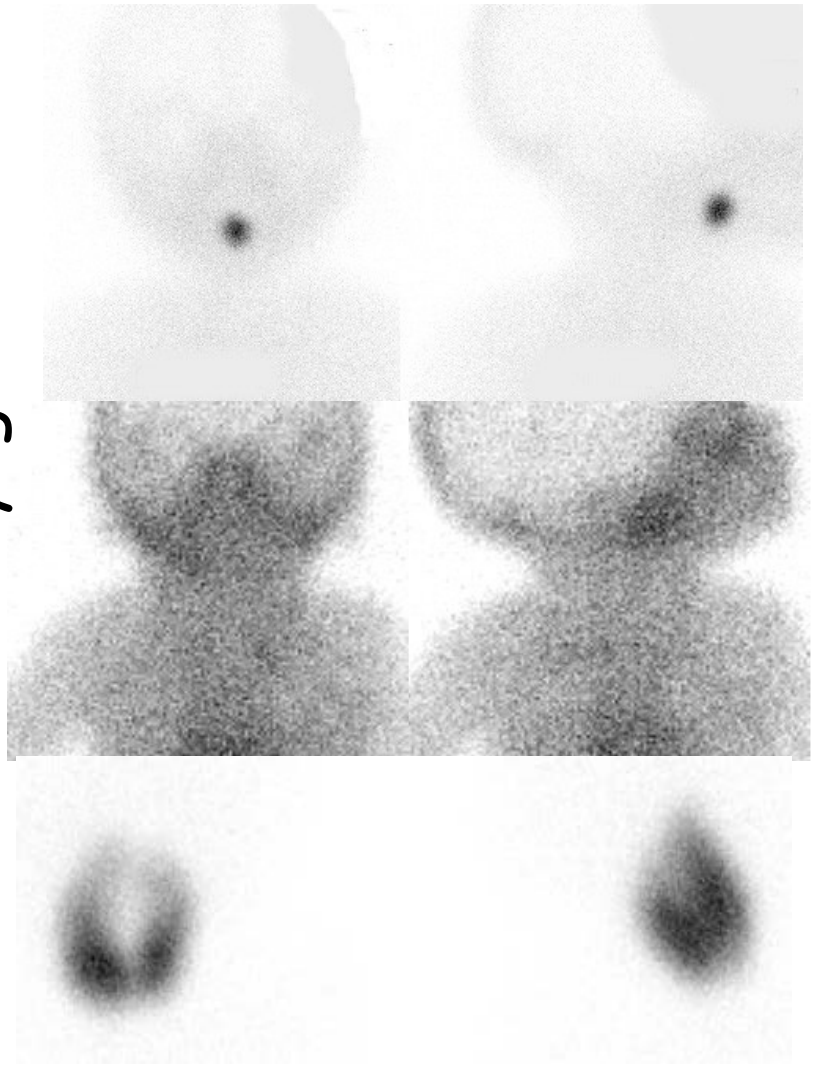
Which of these twins, aged 14 d, has severe CH?

Severe CH, 4 mo:
- easy diagnosis
- too late for brain

Of ~ 300 newborns sent by the screening lab, only 2 suspected clinically

^{99m}Tc scintigraphy establishes etiology of *overt* CH in 20 min., within 24 hours of screening result, before 2 weeks of age

Dysgenesis



Ectopy*: 70%
missed by ultrasound
(Jones *et al*, Pediatr Radiol 40: 725, 2010)

Athyreosis: 15%
-true (Tg undetectable)
-apparent (Tg measurable)*

Dyshormonogenesis*:10-15%
Goiter, ↑ uptake, N shape/site)
(missed clinically in ~ 90%)
(25% recurrence risk in sibs)

View: Frontal Lateral

* May have only mild ↑ in TSH

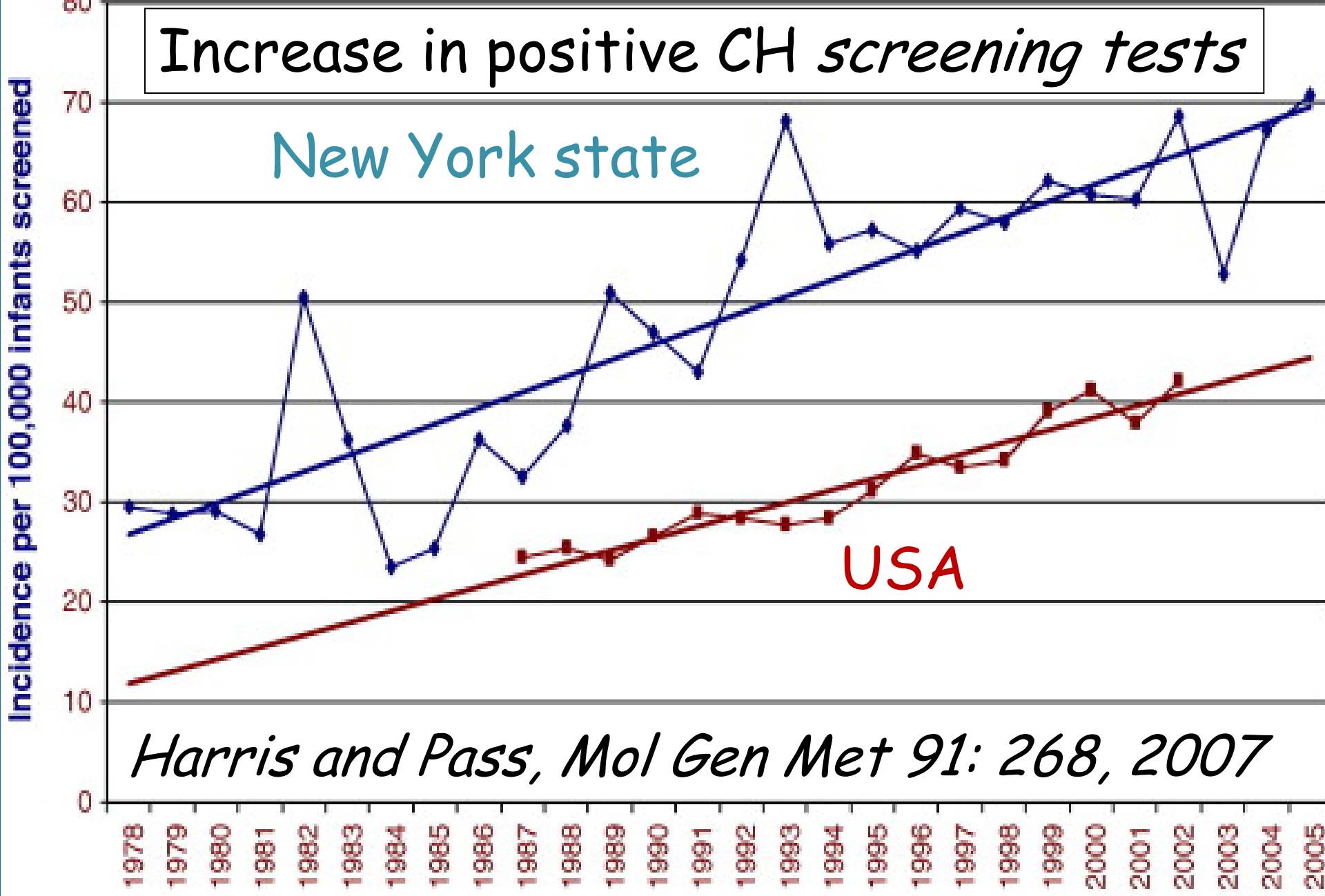
Screening for a disease generally increases prevalence estimates: CH is no exception

	Before	*After*
Prevalence	~ 1 in 6,500*	~ 1 in 2,500**

* Alm *et al*, BMJ 289:1171, 1984
**Deladoëy *et al*, JCEM 96: 2422, 2011

Even since screening, many laboratories report a steadily increasing incidence

Increase in positive CH *screening tests*



→2-day CDC conference (Pediatrics, 5/2010)

↓ TSH cut-offs in Lombardy

Cut-off (mU/L)	*Prevalence*	*On Rx (%)*	*in situ (%)*
20	1:2,654	85	33
10	1:1,154	43	68

(Corbetta *et al*, Clin Endo 71: 739, 2009)

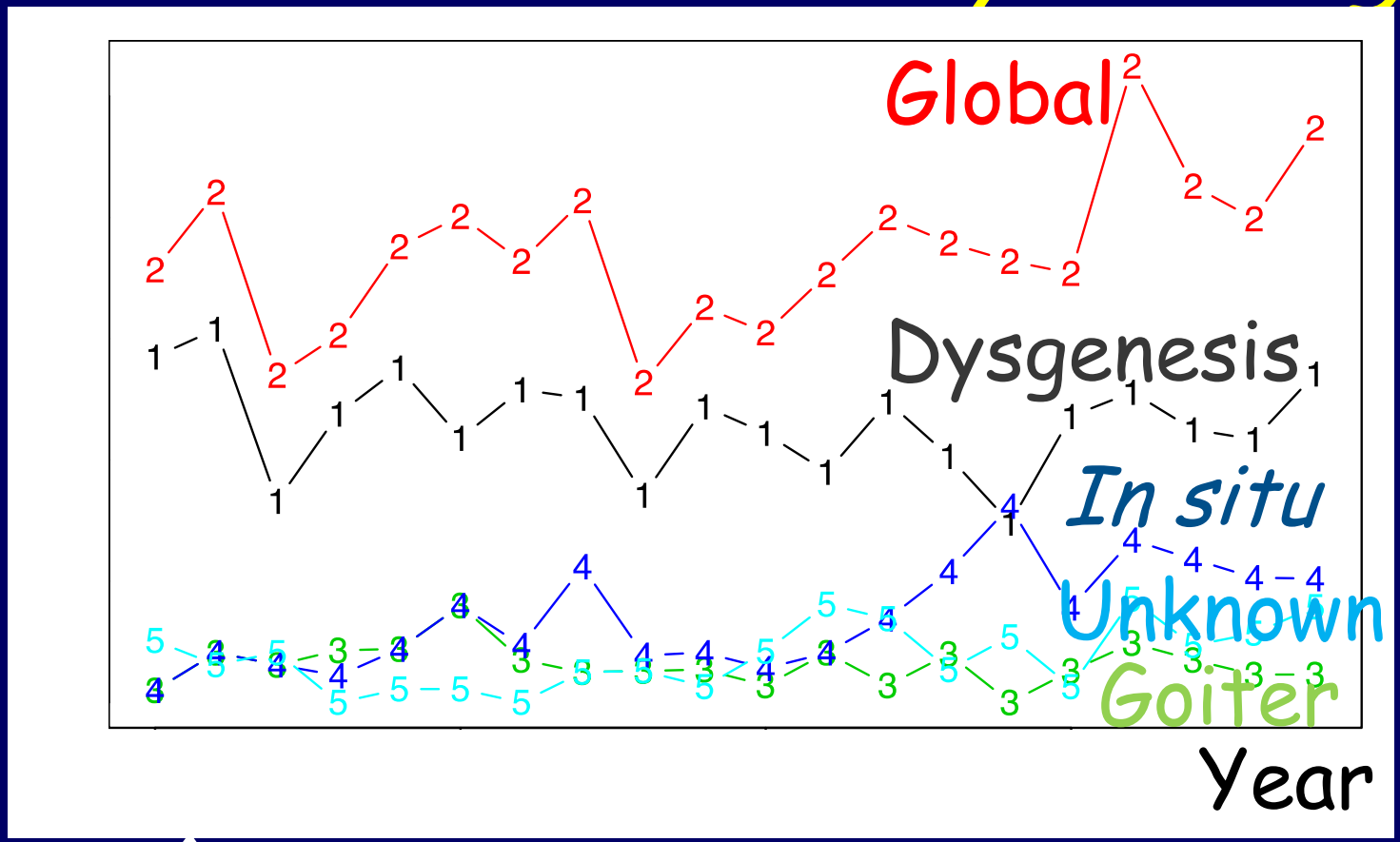
↓ TSH cut-offs in Greece

Cut-off (mU/L)	*Recall rate (%)*	*Confirmed permanent*
20	0.12	1:3,300
10	1.2	1:1,749

The 'price' of a two-fold increase in detection is a 10-fold increase in recall rate

(Mengreli *et al*, JCEM 95: 4283, 2010)

Québec: time trends *by etiology*



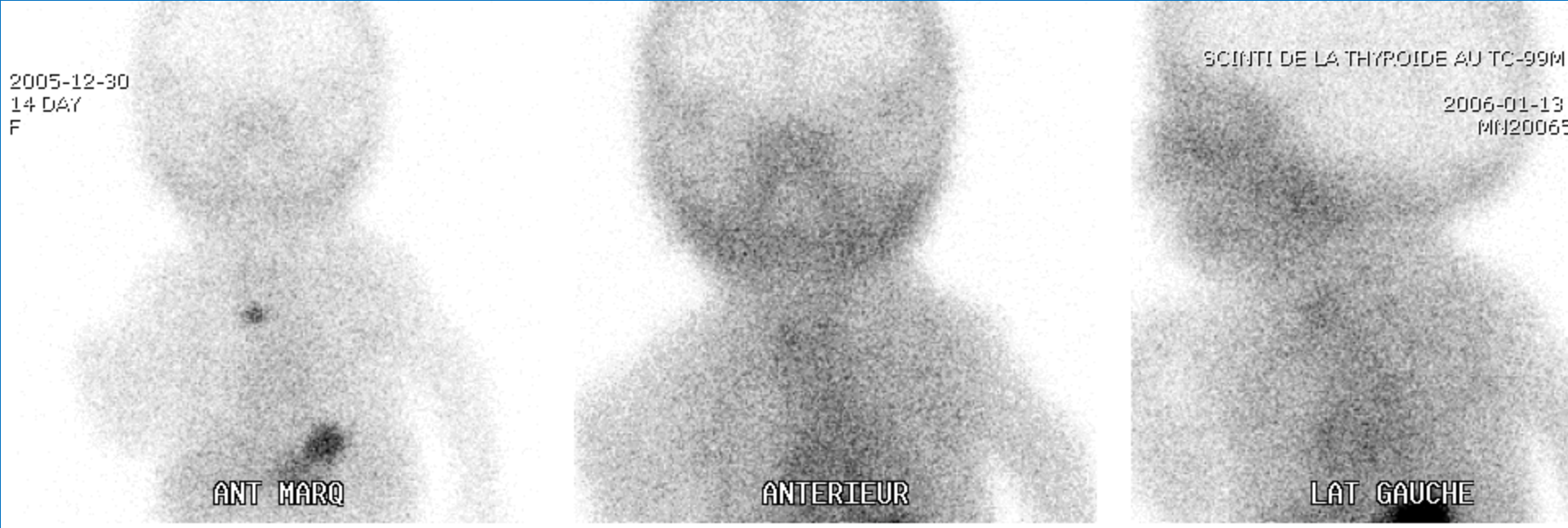
Global ↑ in prevalence accounted for by:

- ↓ in TSH cut-off (15→5) on 2nd sample
- CH w/thyroid *in situ* or unknown cause

(Deladoëy *et al*, JCEM 96: 2422, 2011)

Mild ↑ TSH at screening: Pt 1

- 2nd child (girl) of healthy, unrelated parents
- Brother, 2 y, neonatal TSH normal
- Pregnancy: IUGR noted, hence labor induced
- Born 38 w, C/S re: fetal distress, wt 1,670 g
- Transient hypoglycemia and RDS
- Screening day 2: TSH 28 total T_4 45
- Serum day 12: TSH 27 fT_4 10.4
- Mother: TSH 0.5, TPO antibodies negative



^{99m}Tc scintigraphy:

- Normal shape, size and location
- Very low uptake

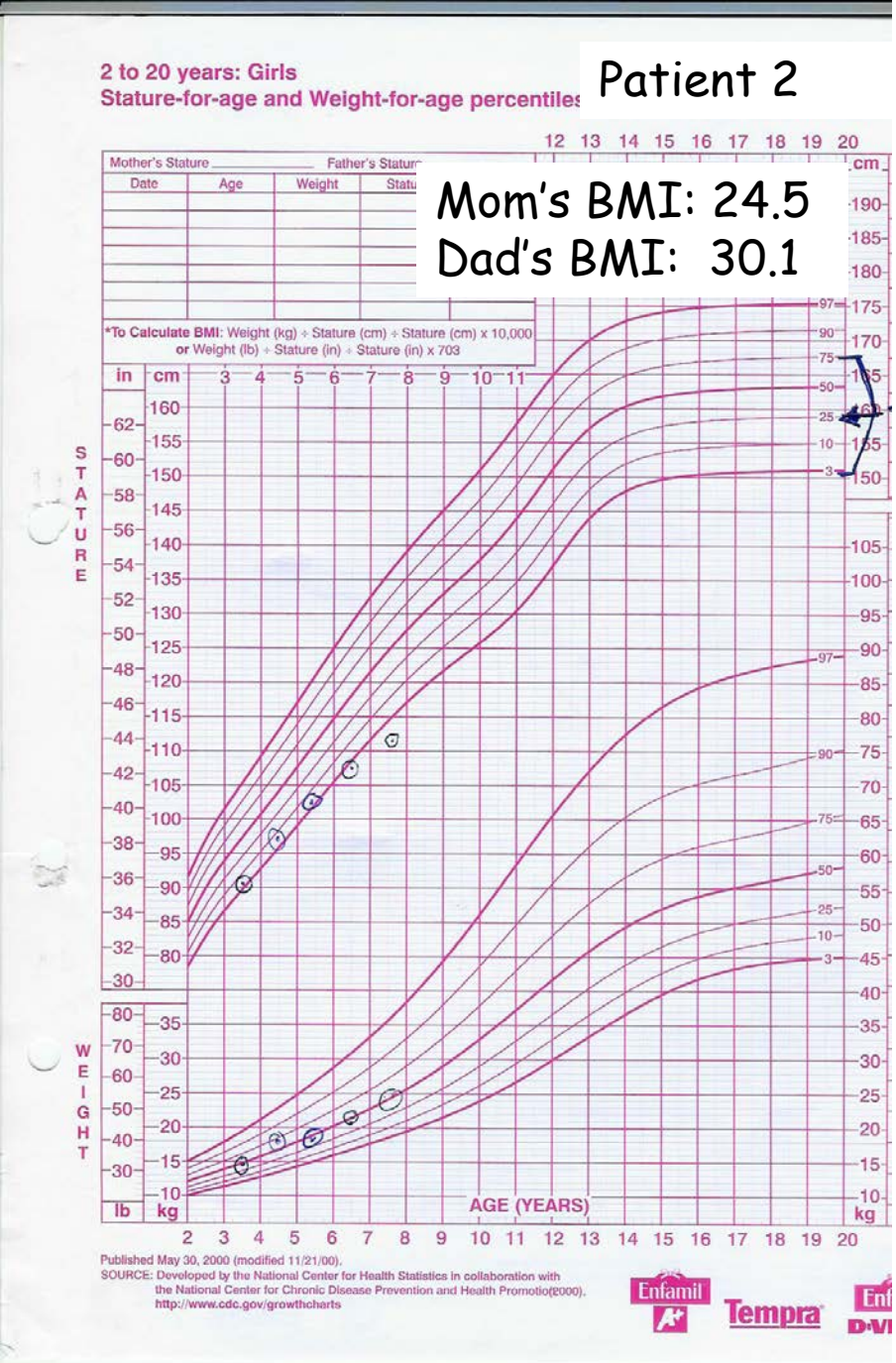
Patient 1 (continued)

- Rx: L-T_4 25 → 50 μg/d. because of ↑ in TSH
- Diagnosis of craniosynostosis (Crouzon-type)
- Unspecified dysmorphic syndrome
- Sitting at 11 months, mild speech delay

Clinical photographs at age 2 y 9 months

Patient 1 (continued)

- Age 3 y, Rx stopped: TSH 55, fT_4 5.5
- Age 7 y, stocky, small hands and feet:
  - Ca: 2.51
  - PTH: 29
  - *GNAS* analysis: c.344C>T (p.P115L)



PubMed search: 'PHP & craniosynostosis':

PHP Type 1a Caused by GNAS Mutation (deltaN377), Craniosynostosis, and Severe Trauma--Induced Bleeding. Graul-Neumann *& al*, Am J Med Gen Part A 149A: 1487-1493, 2009

Mild ↑ TSH at screening: Pt 2

(Lucas-Herald *et al*, JPEM 26: 583, 2013)

- Boy born at 41 w, forceps, BW 3,430 kg
- Two older sisters in good health
- Referred at 11 days re: spot TSH 11
- Day 5 (Mom's history): TSH 27, fT_4 26
- Day 11 (on referral): TSH 13, fT_4 20
- Decision to observe without treatment
- Strong family history noted (M, F, aunt)

Pt 2: ped. endo. evaluation

- Day 57:
  - Neither dysmorphism nor sign of hypo
  - Serum: TSH 21, fT_4 15, Tg 63 µg/L
  - Echo: heterogeneous, 'slightly small'
  - ^{99m}Tc: no uptake ('apparent athyreosis')
  - Abs to TPO & TSHR (mom+baby): negative
- Day 94:
  - Serum: TSH 13, fT_4 18, Tg 64 µg/L
  - Echo: homogeneous, volume low normal

Patient 2: follow-up

- Treatment from day 94 (25 → 50 μg/d)
- 6 TFTs/3 y: median TSH 5.3, fT_4 18
- Novel missense heteteroz. mut. in TSHR (c.1196G>T;p.C390F) in child & mother
- Also in euthyroid mat. GM (TSH 1.8)
- Not in father (TPO Abs+), nor in sister
- *GNAS* sequence normal in proband

Patient 2: further follow-up

- Rx stopped in proband and mother
- Proband:
  - 6 weeks after stopping: TSH 14.6, fT_4 13
  - 6 months after stopping: TSH 8.5, fT_4 16.7
- Mother:
  - Off treatment, TSH 6.4 and fT_4 13
  - Fatigue → Rx re-started by G.P. after 6 w

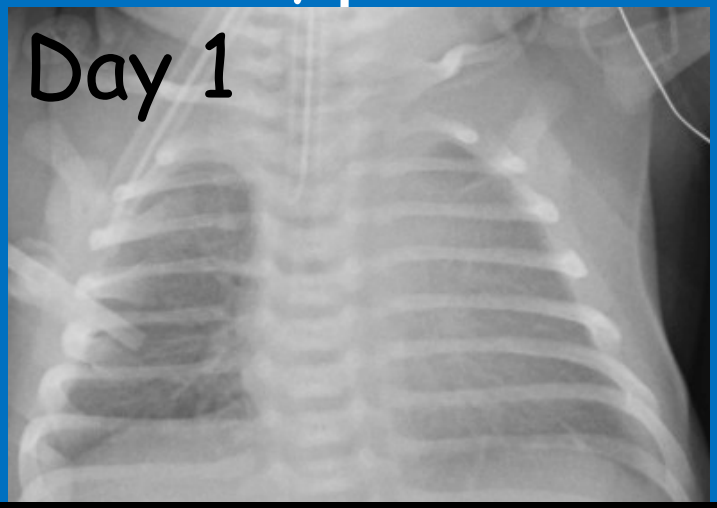
Mild ↑ TSH at screening: Pt 3

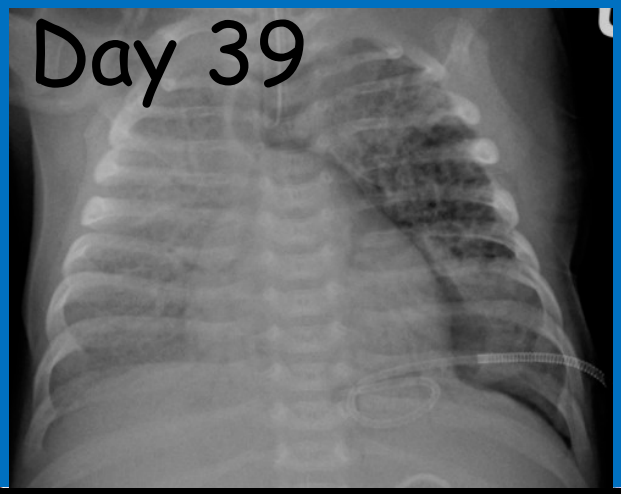
- Girl, 1st child, healthy, unrelated parents
- Born at 41 w after induced labor
- BW 3,460 g, APGAR 9^1, 10^5
- Day 1: RDS, pulmonary hypertension
- Day 2: screening TSH 31, total T_4 245
- Day 12: serum TSH 17, fT_4 12
- *De novo,* novel, het. NKX2.1 mut. (I207F)

(↓ DNA binding & transactivation of Tg & SP-B, Maquet *et al*, JCEM 94:197, 2009)

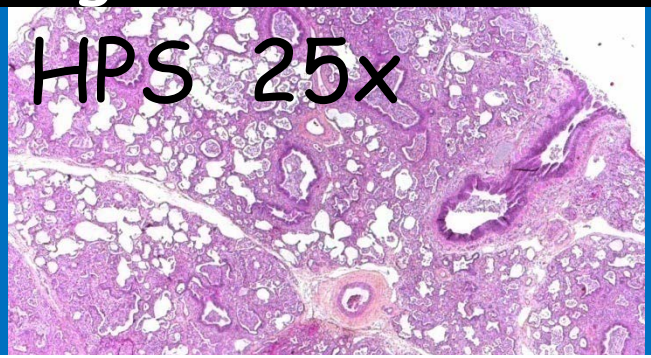
Pt 3:Brain-Lung-Thyroid syndrome

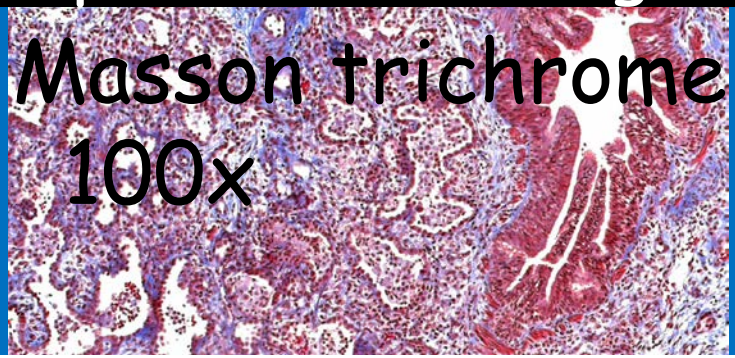
In spite of mechanical ventilation, L-T_4, surfactant, pulm. vasodilators, death Day 40





Lungs: low alveolar counts, impaired branching





Couple has had a healthy child since then

Screening: begins a process…

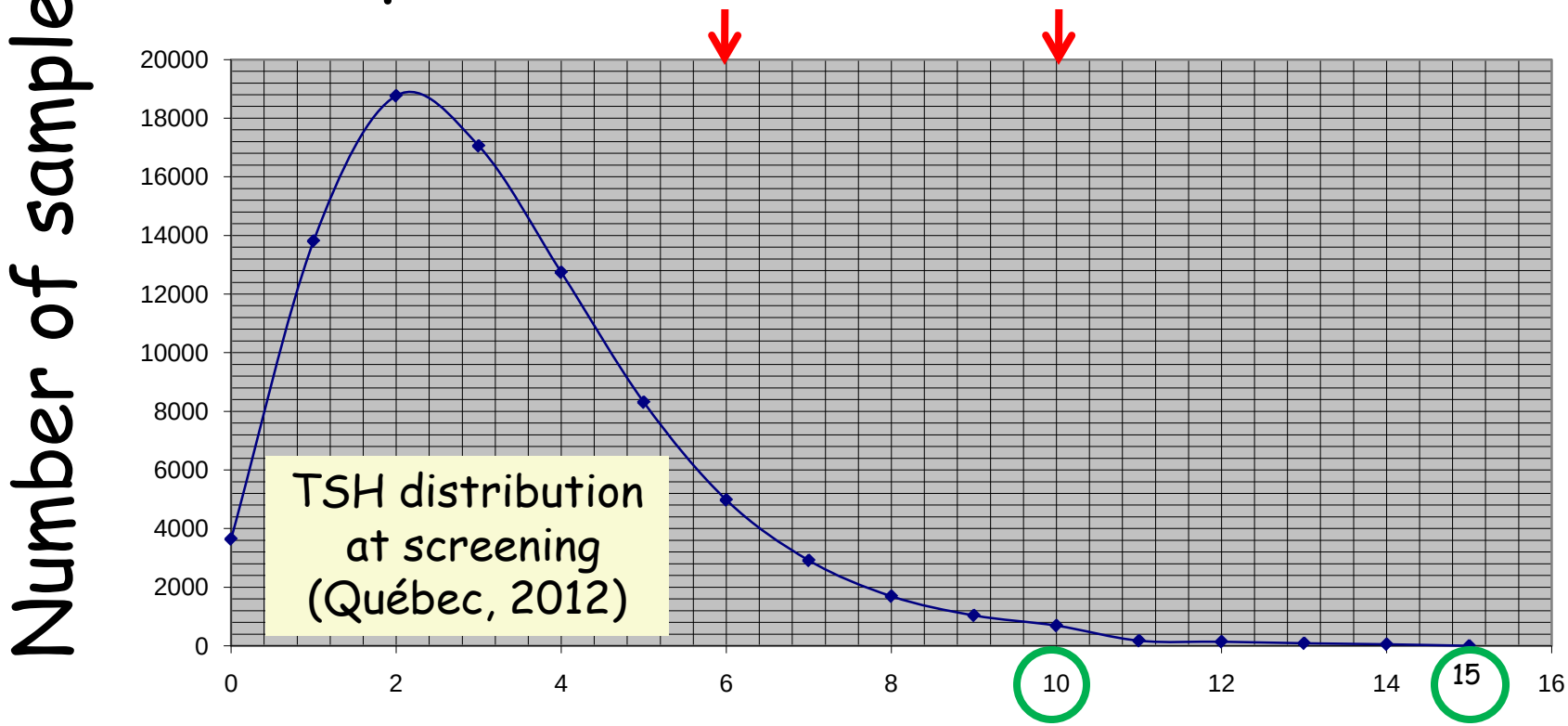
- That leads to Dx of a range of conditions:
  - Overt CH (dysgenesis/dyshormonogenesis)
  - Hyperthyrotropinemia: isolated/syndromic
- It is therefore essential to:
  - Establish etiology (^{99m}Tc scan: r/o ectopy)
  - Document outcome/re-assess need for Rx

Treating patients, not numbers

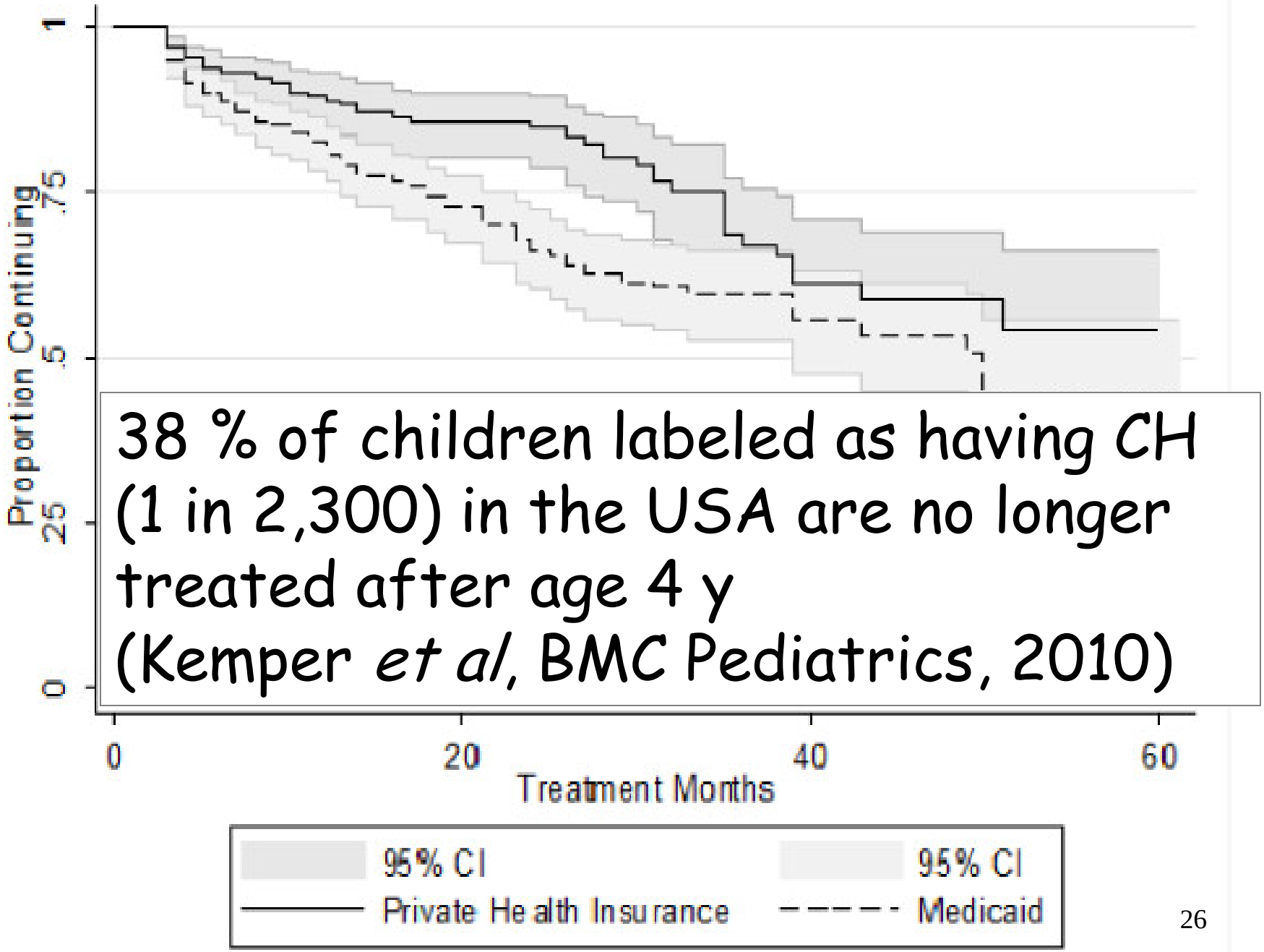
- Once ectopy has been ruled out:
  - Cause of ↑ TSH? Transient or permanent?
  - How many have mutations in GNAS, TSHR, NKX2.1 or 2.5, PAX8, THR, TSHB?
  - Most cost-effective approach: targeted exome sequencing + MLPA?
- Risk of intellectual disability?
- Impact of L-T_4 treatment on outcome?

Strategies to assess risk of ↑ TSH for ↓ IQ

Compare areas with cut-off of 6 & 10



Randomize newborns w/TSH 10-15 mU/L to L-T_4 or placebo



38 % of children labeled as having CH (1 in 2,300) in the USA are no longer treated after age 4 y
(Kemper *et al*, BMC Pediatrics, 2010)

Should we worry about *transient* neonatal hyperthyrotropinemia?

Patient	Neonatal TSH	IQ at 5 y
1	>100	112
2	>100	103
3	62	109
4	56	106
5	46	114
6	42	98
Patients	Mean±SD	107±6
Controls	Mean±SD	103±11

Transient neonatal hyperthyrotropinemia (even when severe) does not seem harmful (Alm *et al*, BMJ 289:1171-5, 1984)

Newborn screening: gaps in the evidence

The harms likely from newborn screening largely relate to the worry caused by false positive results or, worse, results of uncertain significance—which leave parents in limbo, uncertain whether or not their child is affected—and to overmedicalization in cases where treatment is not needed, with attendant anxiety and costs of unnecessary clinical care. These are not trivial issues and are sure to increase if, in the near future, newborns are screened by whole-genome, exome, or more targeted genetic sequencing

(Wilcken, Science 342:197, 2013)

Don't get me wrong: screening for CH *is* a public health triumph!

	Before	*After*
Prevalence	1 in 6,500	1 in 2,500
Mean IQ	~ 86	~ 105
% with IQ < 70	8 to 27 %	None

…but there is no need to make it too sensitive!

…and it is essential to document outcome

(Grosse & Van Vliet, Arch Dis Child 96:374, 2011)

Thanks to…

- Ste-Justine:
  - Endocrinology: staff, fellows & lab
  - Genetics: J. Maassen *et al*
  - Clin. mol. biol. lab: I. Thiffault *et al*
- Screening lab: Y. Giguère *et al*
- M.D.s 'feeding' the Québec database
- …you for your attention
- … and visit http:www.thyroid4kids.org