Why not growing?

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Outline:

- Case presentation
- Highlights about the diagnosis
- Take home message

History:
Chief complaint

A 22 months old girl who has:

- Diarrhea
- Not gaining weight

For around a year

History:
HPI

- Diarrhea since around the age of 4 months
  - passing stool up to 5 times/day
  - oily, bulky, and foul smelling
- Diet: breastfeeding
  - her mother had tried formula supplementation --> persistent vomiting (resolved by the age of 6 months).
- By the age of 9 months, there was obvious failure to thrive and the family started seeking medical advice
- She was investigated and started on a high-calorie formula through nasogastric tube
  - weight and height remained <3rd centile

History:
Perinatal Hx, PMHx

- She was born in Egypt at full term by a C-section due to a previous C-section, and her birth weight was 2.5 kg.
- At 1 month, she faced the bleeding problem as a result of ear piercing:
  - admitted to the hospital and given FFP and Vit K
  - coagulation profile, factor assays, platelet function tests → normal limits
- The child also had features of rickets (frontal bossing, protrusion of the abdomen, and bowing of legs) and was started on Vit D
- The family also gave a history of recurrent infections; one of which required pediatric intensive care unit for 1 week along with this. She also had persistent oral thrush.

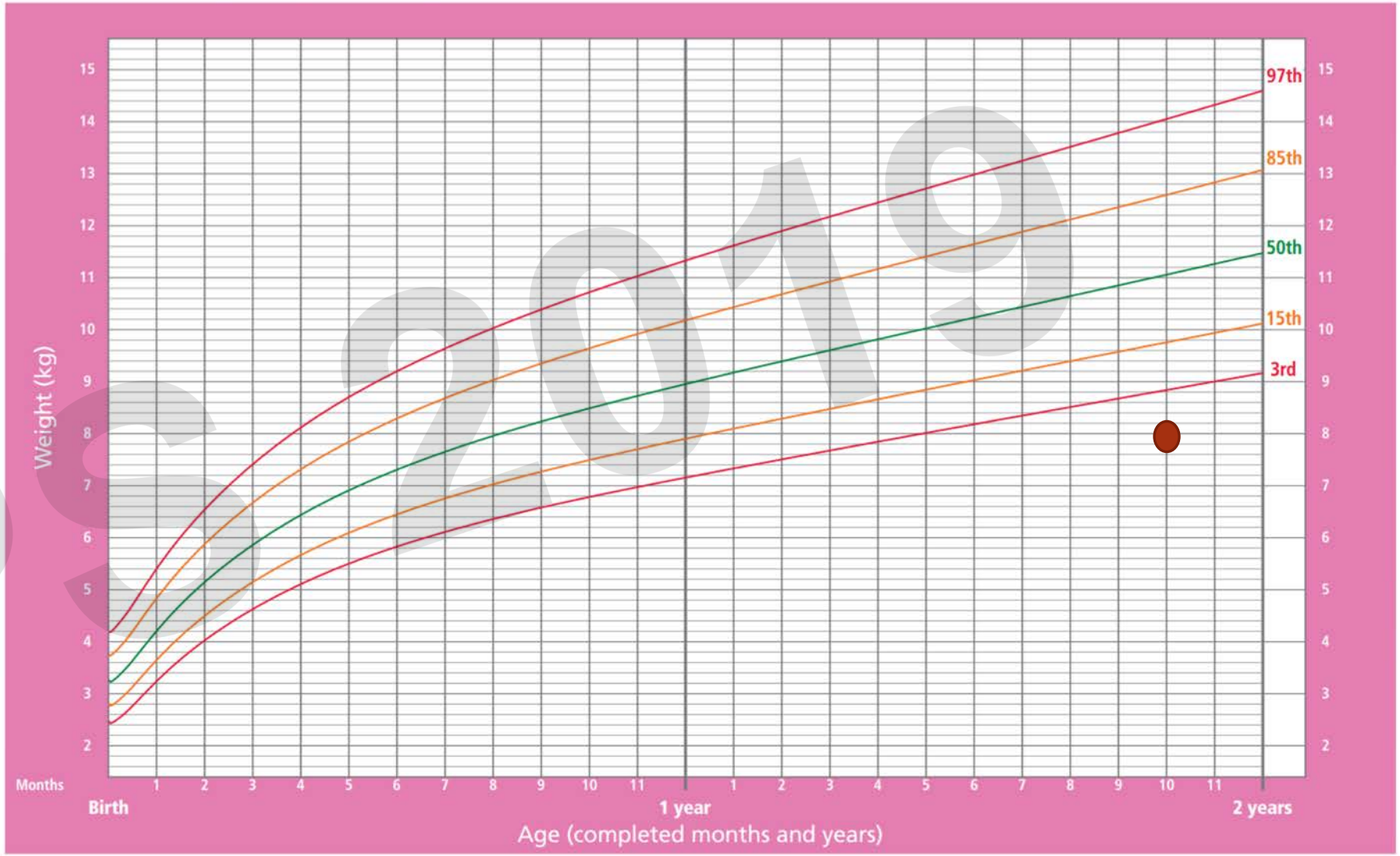
History:
FHx, Developmental Hx

- The patient's parents were 4th-degree cousins; she had an elder brother, who was healthy
- Her development was delayed for all her milestones;
  - she was able to sit independently at the age of 18 months
  - started walking independently at the age of 22 months
  - could hold a pen and scribble but could not take off her shoes
  - using single words only, (very limited vocabulary, of around 10 words)
  - knew only one body part

Weight-for-age GIRLS

Birth to 2 years (percentiles)

World Health Organization

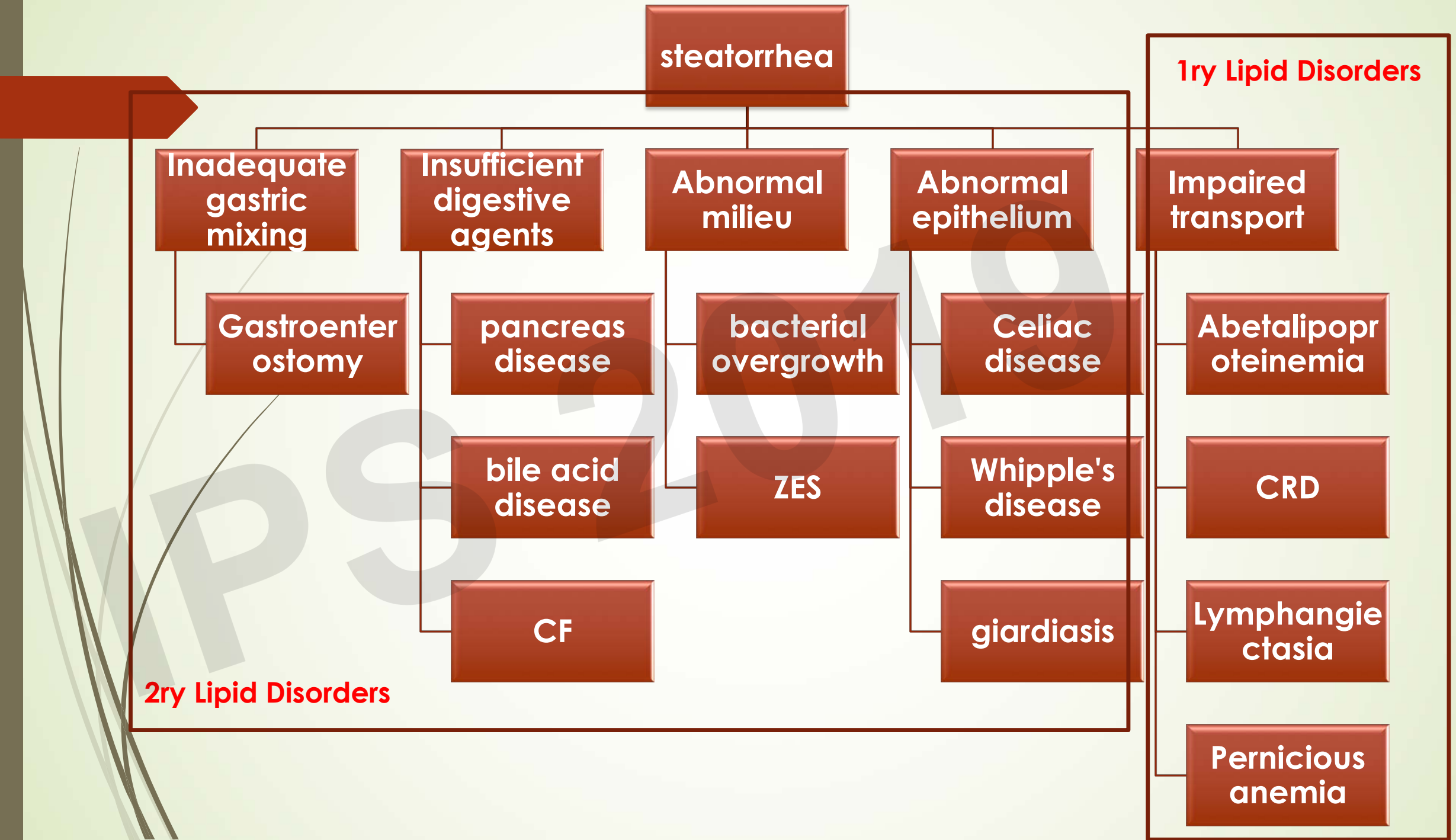


WHO Child Growth Standards

Examination:

- no distinctive features but she had frontal bossing
- her limbs were wasted and bowed, and her abdomen was distended
- her gait was clumsy, no truncal ataxia
- rest of the physical examination was unremarkable

What are your differentials?


steatorrhea
1ry Lipid Disorders
Inadequate gastric mixing
Insufficient digestive agents
Abnormal milieu
Abnormal epithelium
Impaired transport
Gastroenterostomy
pancreas disease
bile acid disease
CF
bacterial overgrowth
ZES
Celiac disease
Whipple's disease
giardiasis
Abetalipoproteinemia
CRD
Lymphangiectasia
Pernicious anemia
2ry Lipid Disorders

Investigations:

LFTs were normal
Amylase and Lipase were normal

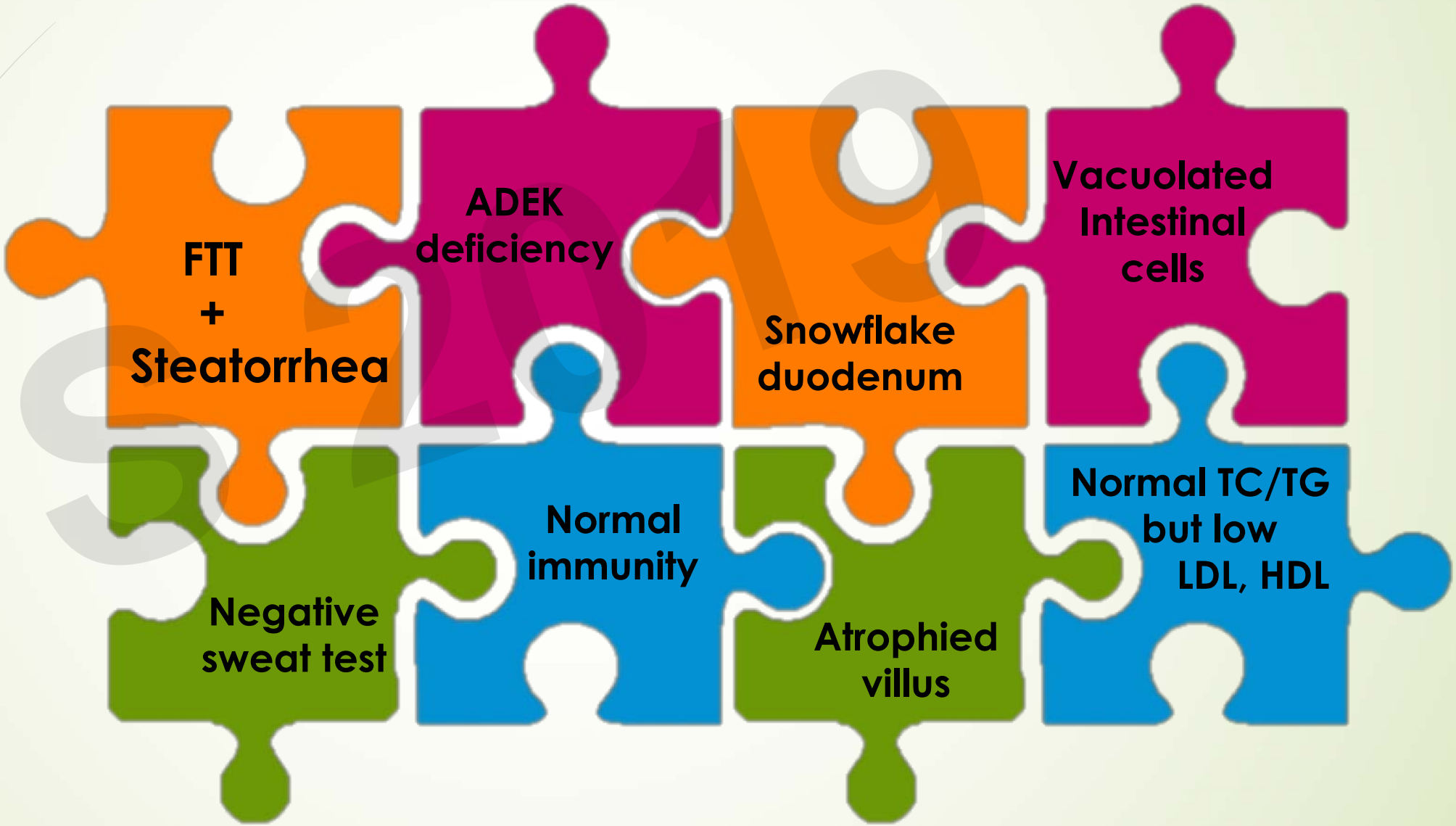
Detailed ophthalmic examination was normal

Lab test	Result	Normal value
CBC: - Hb - Hct - MCV - MCH - Blood film	 105 g/L (low) 0.32 L/L (low) 75.5 fL 24.5 pg no abnormal cells	 11.5 –15.5 34 - 40 75 - 87 24 - 30
Prothrombin time	21.1 (high)	12.1 - 14.5
INR	1.8 (high)	0.86 – 1.22
Vitamin A	135 µg/L (low)	194 – 421
Vitamin E	<1.40 mg/L (low)	3.02 – 9.05
Vitamin D	35.9 nmol/L (low)	52 – 250
Total cholesterol	1.99 mmol/L	1.15 – 4.70
HDL	0.42 mmol/L (low)	0.91 – 2.12
LDL	1.05 mmol/L (low)	1.63 – 3.63
Triglycerides	1.14 mmol/L	0.31 – 1.41

Investigations:

- Negative sweat chloride test
- Normal celiac profile
- Normal absolute neutrophil count (ANC) & lymphocytes count, normal lymphocytes subset counts, CH50, and immunoglobulin levels
- Normal abdomen MRI and US
- Colonoscopy: snowflake appearance of the duodenum
- Histopathology: mild villous atrophy and vacuolated intestinal cells

Putting it all together



Primary lipid absorption disorders:

- Tangier disease
- Abetalipoproteinemia
- Familial hypobetalipoproteinemia (FHL)
- Chylomicron retention disease (CRD)

Lipid malabsorption

ApoA1 level	0.7 g/L	1.08 – 2.25
ApoB level	0.84 g/L	0.6 – 1.17

- No change in Apo A&B level after meals
- High protein low-fat diet for 1 week → 1.3 kg, 16.3% of her presentation weight
  - Her diarrhea improved to twice daily

Chylomicron retention disease (CRD)

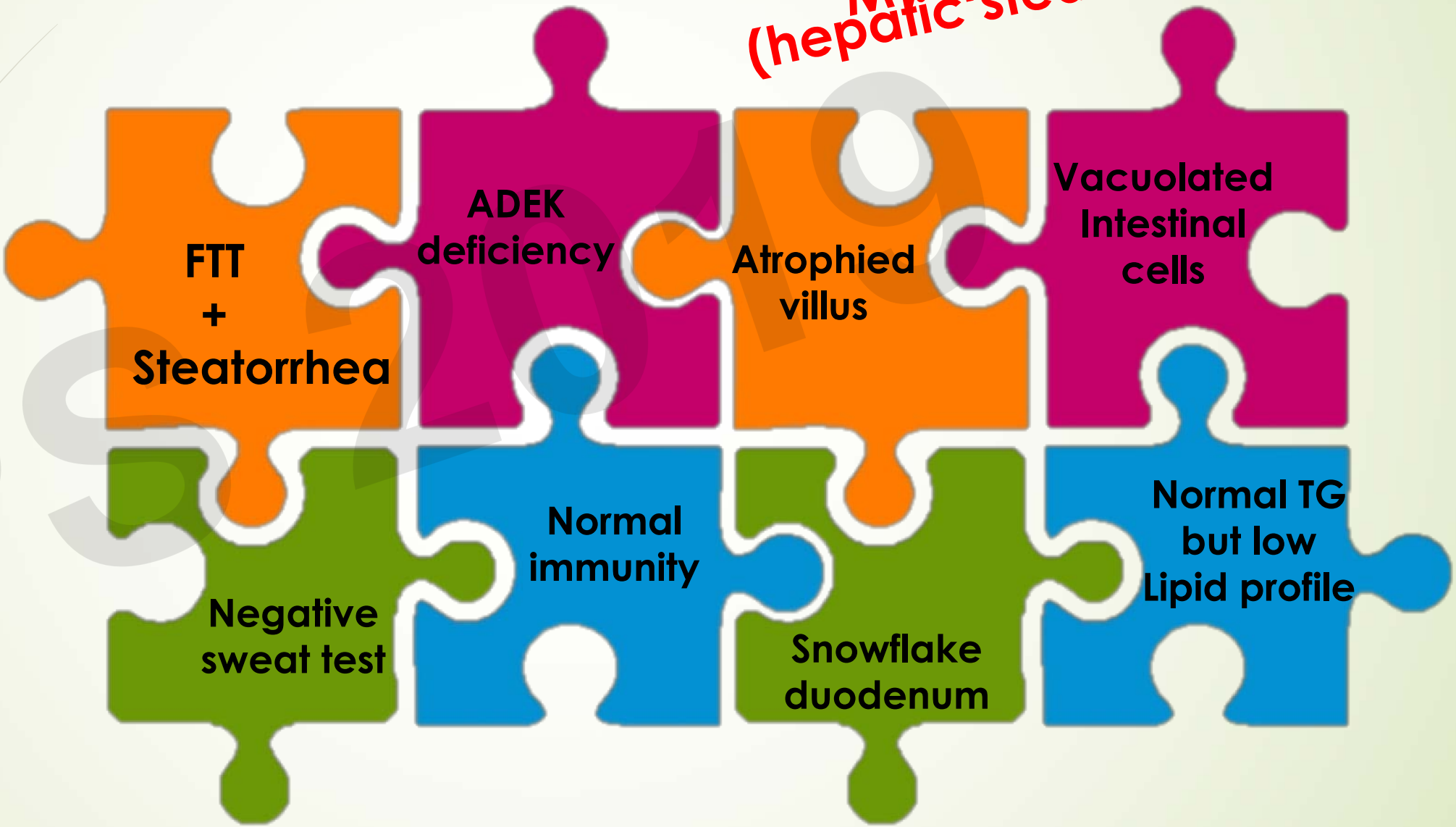
Confirming it took time:

- Normal sequence analysis of the *SAR1B*
  - But; could not amplify exon 3
  - A deletion/duplication analysis revealed a homozygous deletion encompassing exon 3 (never reported before)

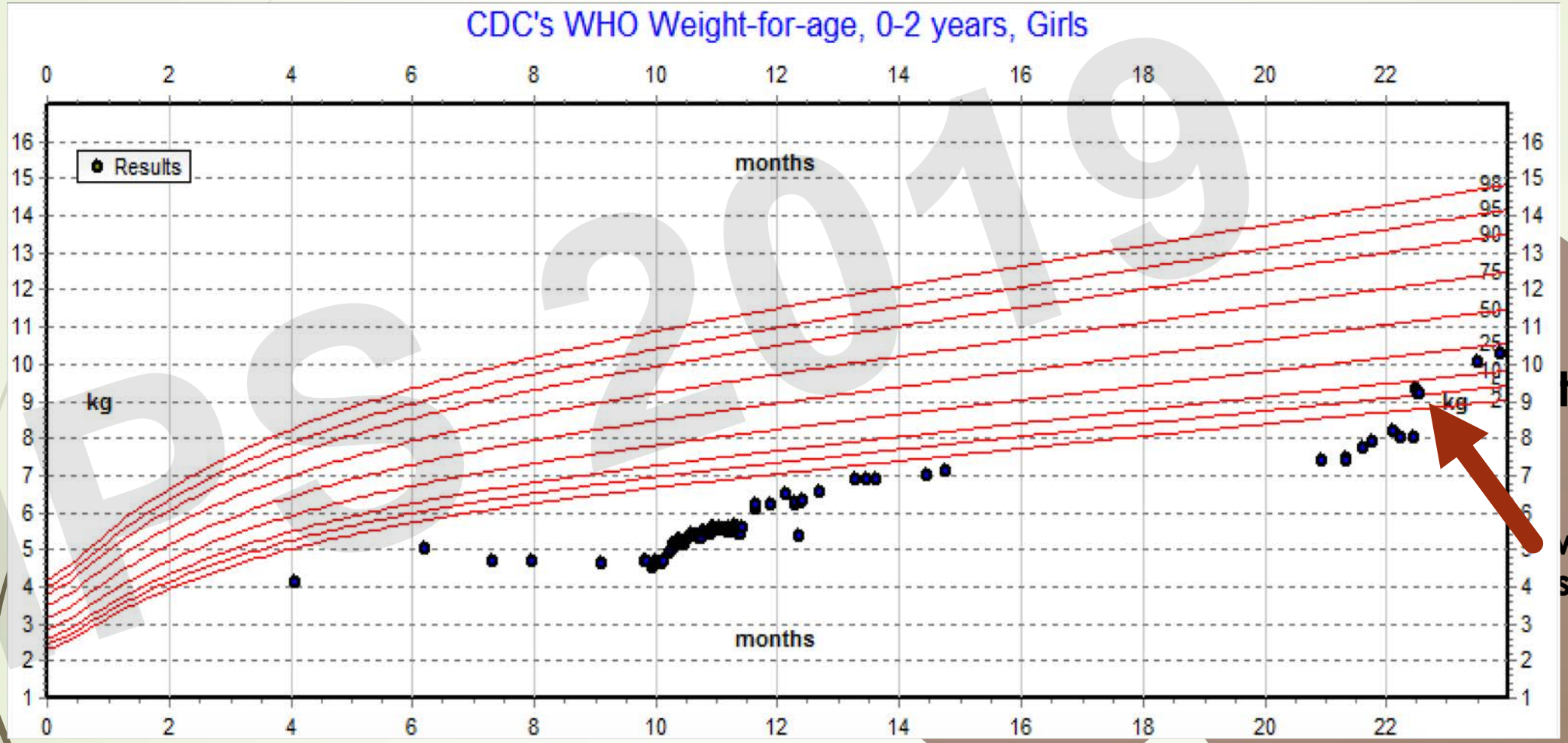
Chylomicron Retention disease

CRD manifestations:

+/- Hepatomegaly
+/- Myopathy
(hepatic steatosis)

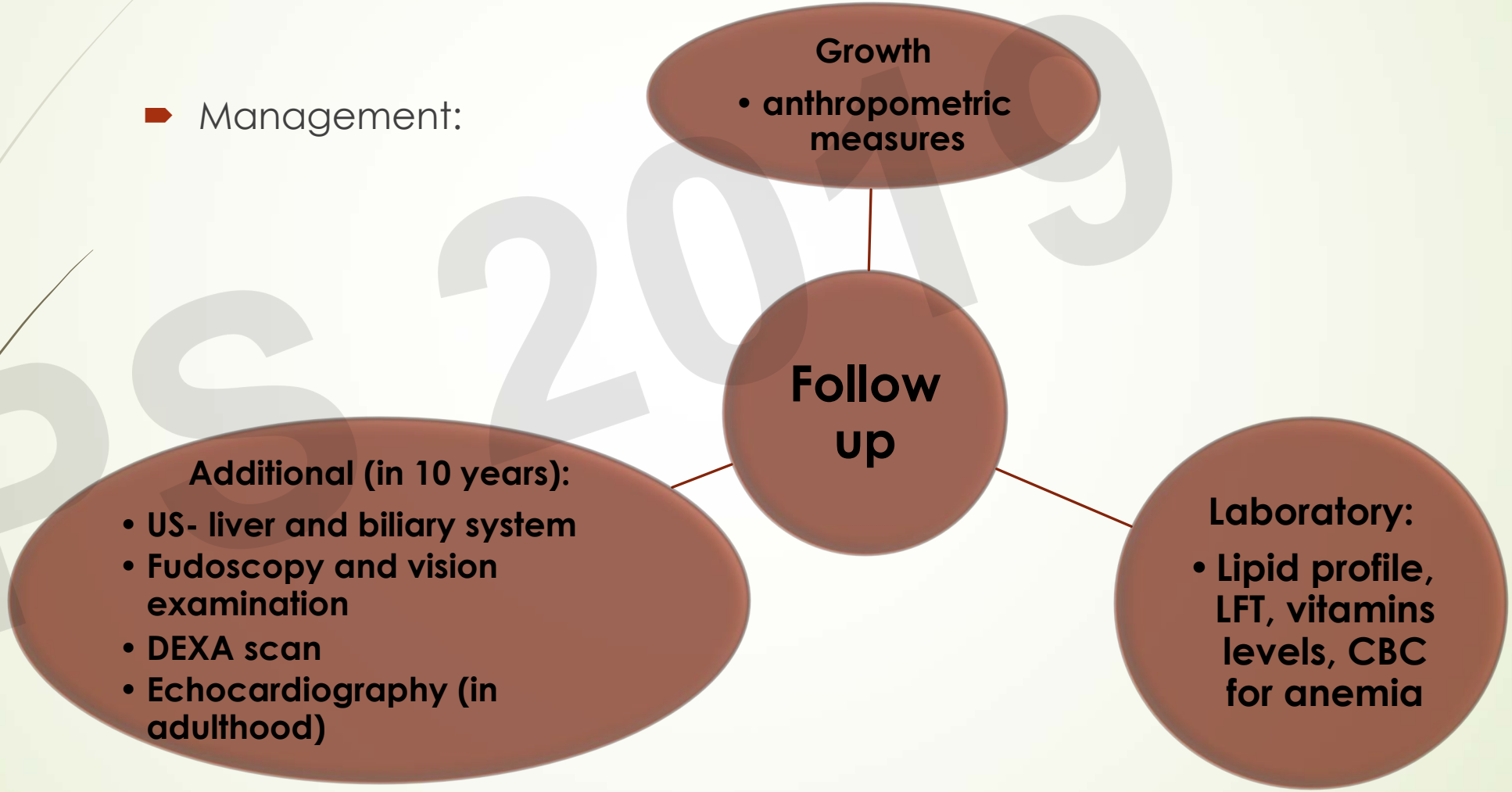


Highlights about CRD



Highlights about CRD

- Management:



Take home message

- **While further investigating steatorrhea; keep in mind lipid malabsorption as a differential**
- **CRD is a disease of hypolipidemia with no acanthosis on blood smear**
- **When the diagnosis is suspected a therapeutic trial with diet supports the diagnosis and helps to prevent its devastating complications**

Supervisor and mentor

Dr Jozef Hertecant

Consultant in pediatrics genetics/ metabolic diseases

References:

- Arthur C Jaffe. Failure to Thrive: Current Clinical Concepts. *Pediatrics in Review*. 2011; 32; 100.
- Valérie Marchand. The toddler who is falling off the growth chart. *Paediatr Child Health*. 2012; 17 (8): 447.
- Peretti N. Lessons from chylomicron retention disease: A potential new approach for the treatment of hypercholesterolemia? *Expert Opin Orphan Drugs*. 2018;6:163-5
- Sané AT, Seidman E, Peretti N, Kleme ML, Delvin E, Deslandres C, et al. Understanding chylomicron retention disease through sar1b gtpase gene disruption: Insight from cell culture. *Arterioscler Thromb Vasc Biol* 2017;37:2243-51
- Levic DS, Minkel JR, Wang WD, Rybski WM, Melville DB, Knapik EW, et al. Animal model of sar1b deficiency presents lipid absorption deficits similar to Anderson disease. *J Mol Med* (Berl) 2015;93:165-76.

Thank you!