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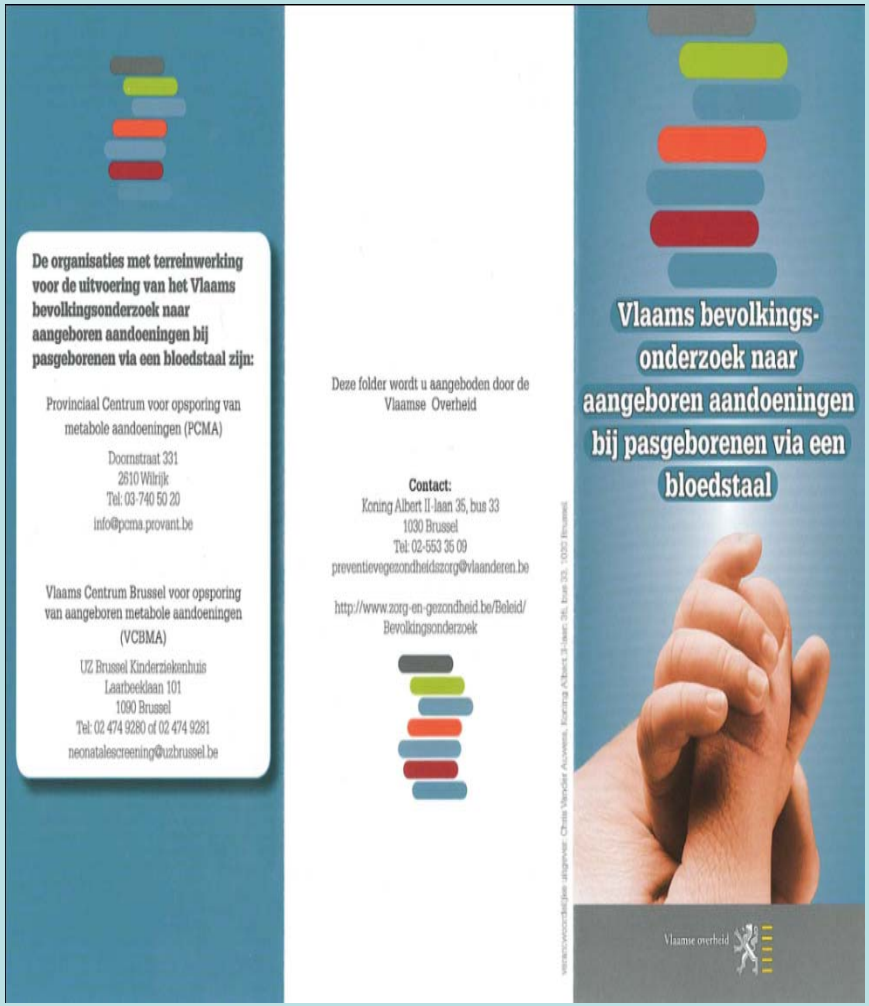
Confirmation the diagnosis by Reduced Very-long –chain Acyl-coA Dehydrogenase Activity in Newborns Identified by Newborn Screening.

FJM Eyskens, EVA PCMA vzw, Antwerp, Belgium.



F. Eyskens, MD, PhD [1,2]

[1] UZA, [2] PCMA vzw, Antwerp, Belgium

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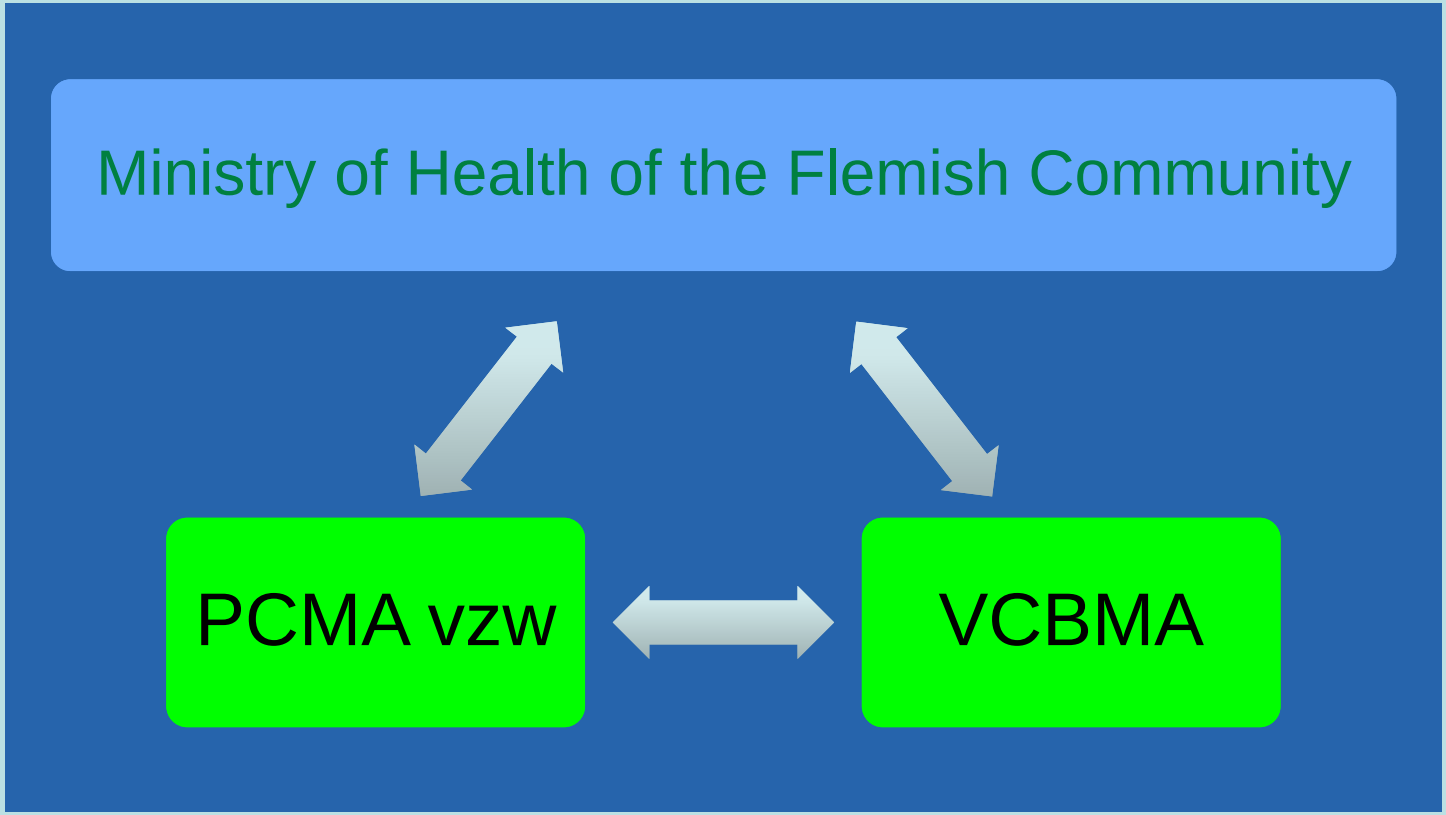
Neonatal Mass Screening in Flanders from 01/01/2012



27,000-40,000 newborns screened/lab/year

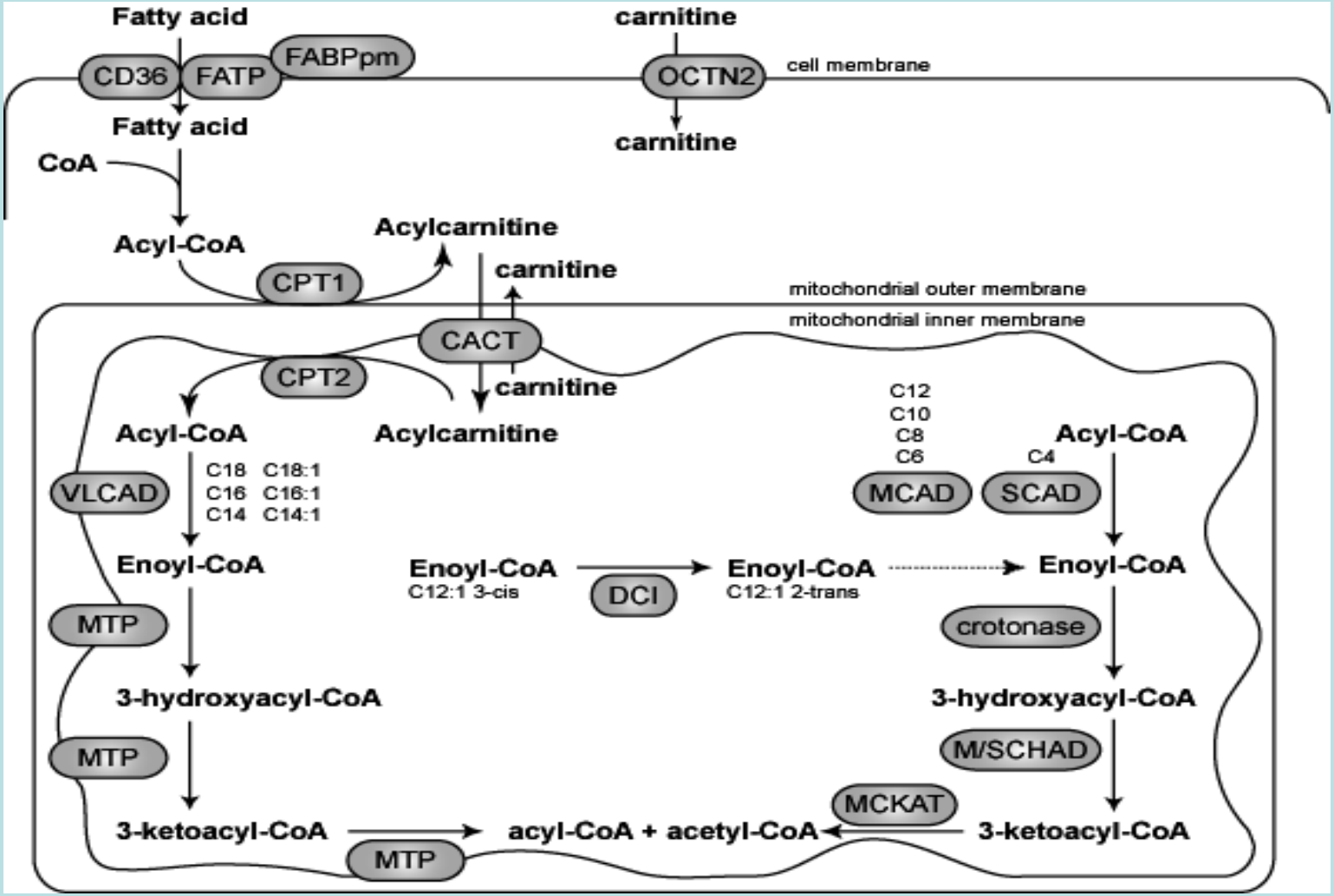
Comparison: Core panel USA-Flanders

OA	FAO	AA	Hb	other
IVA	MCAD	PKU	HbSS	CH
GA1	VLCAD	MSUD	HbS/bTh	CAH
HMG	LCHAD	HCY	HbS/C	BIOT
MCD	TFP	CIT1		GALT
MMA	CUD	ASA		HEAR
PA		TYR1		CF
BKT	MADD			

OA	FAO	AA	Hb	other
IVA	MCAD	PKU	HbSS	CH
GA1	VLCAD	MSUD	HbS/bTh	CAH
HMG	LCHAD	HCY	HbS/C	BIOT
MCD	TFP			GALT
MMA	CUD?			HEAR
PA		TYR1		CF
BKT	MADD			

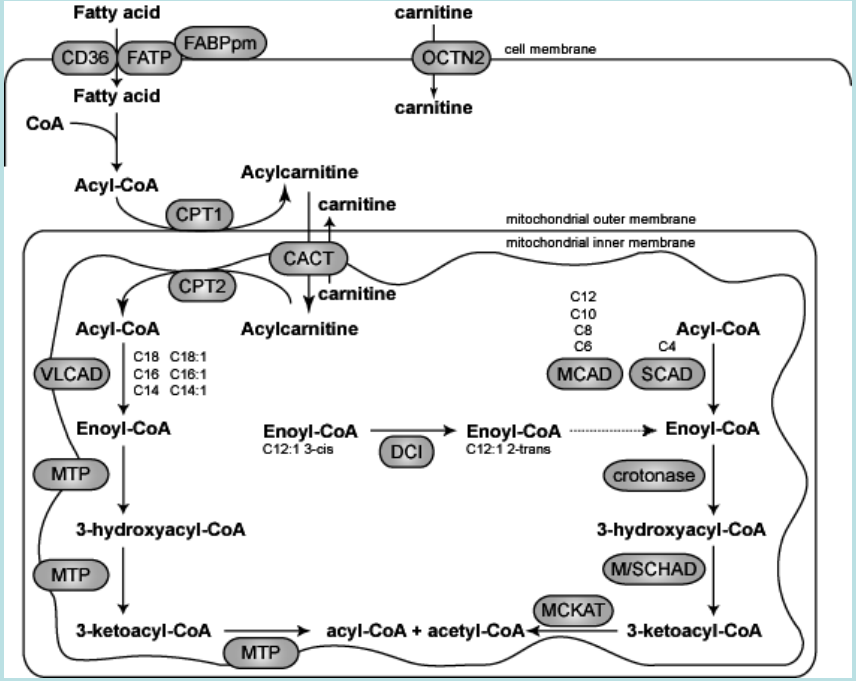
Mandatory screening panel

Mitochondrial fatty acid β-oxidation



S. Houten, R. Wanders. J Inherit Metab Dis (2010): 33: 469-477

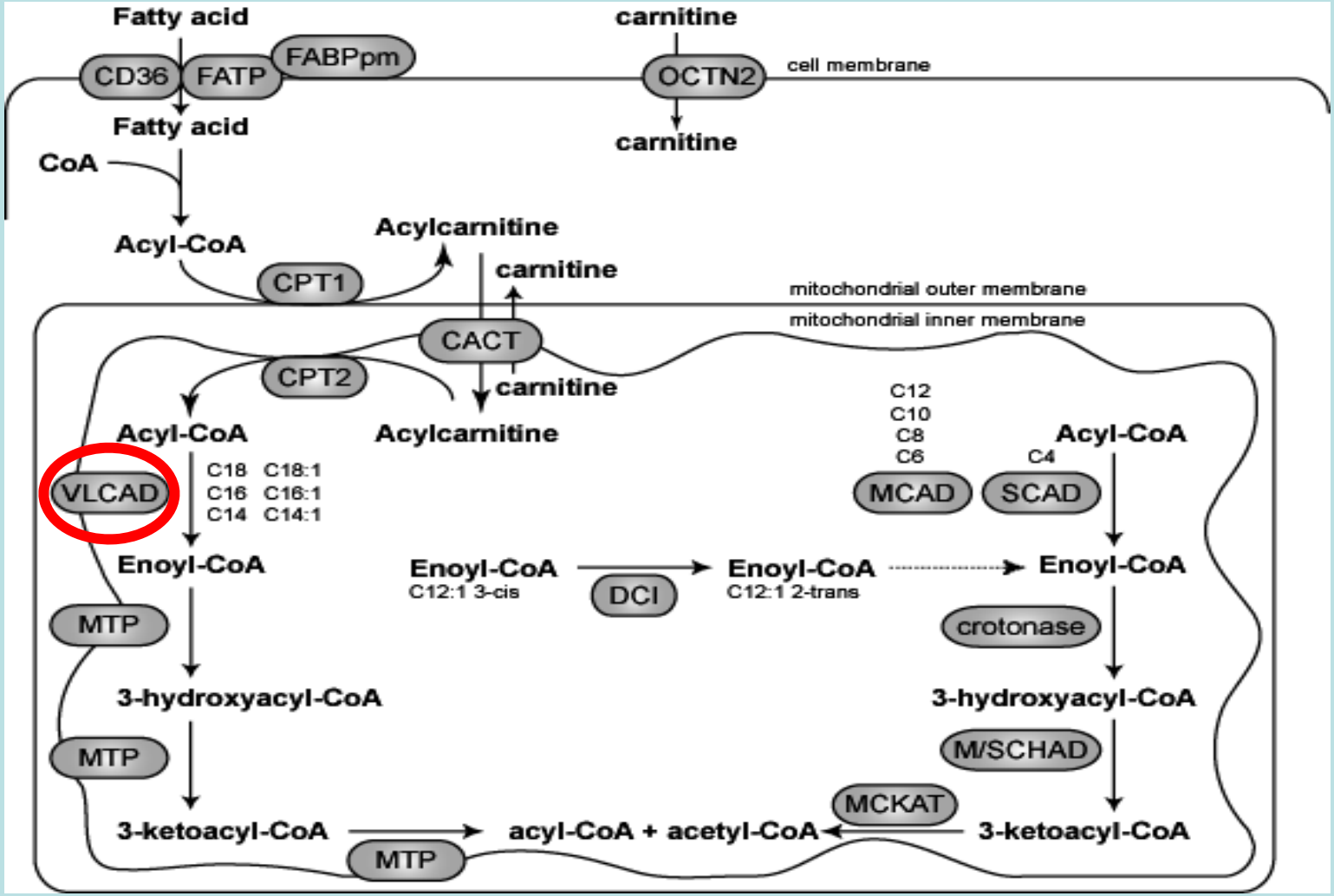
Mitochondrial fatty acid β-oxidation



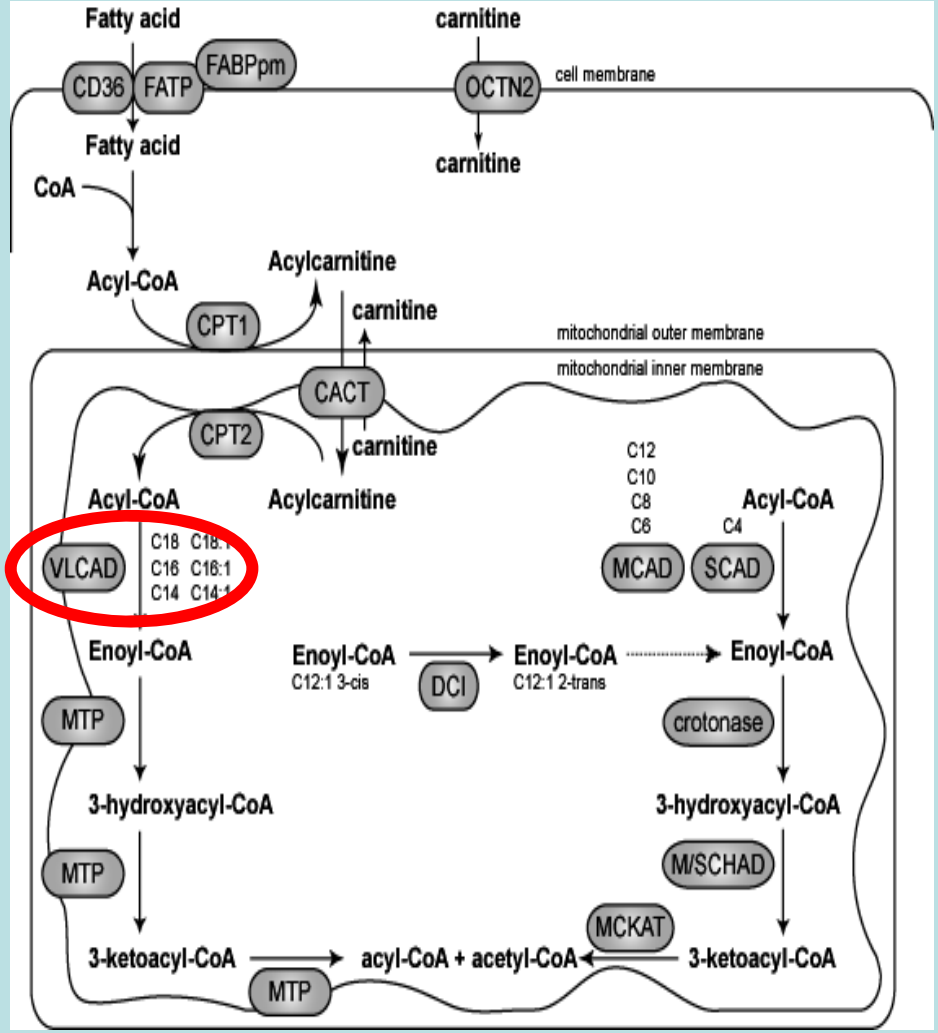
- Provides energy in the postabsorptive and fasted state
- Important energy source for the heart
- Important during exercise in skeletal muscle

S. Houten, R. Wanders. J Inherit Metab Dis (2010): 33: 469-477

Mitochondrial fatty acid β-oxidation



Mitochondrial fatty acid β-oxidation



Provides energy in the postabsorptive and fasted state

- Hypoketotic hypoglycemia

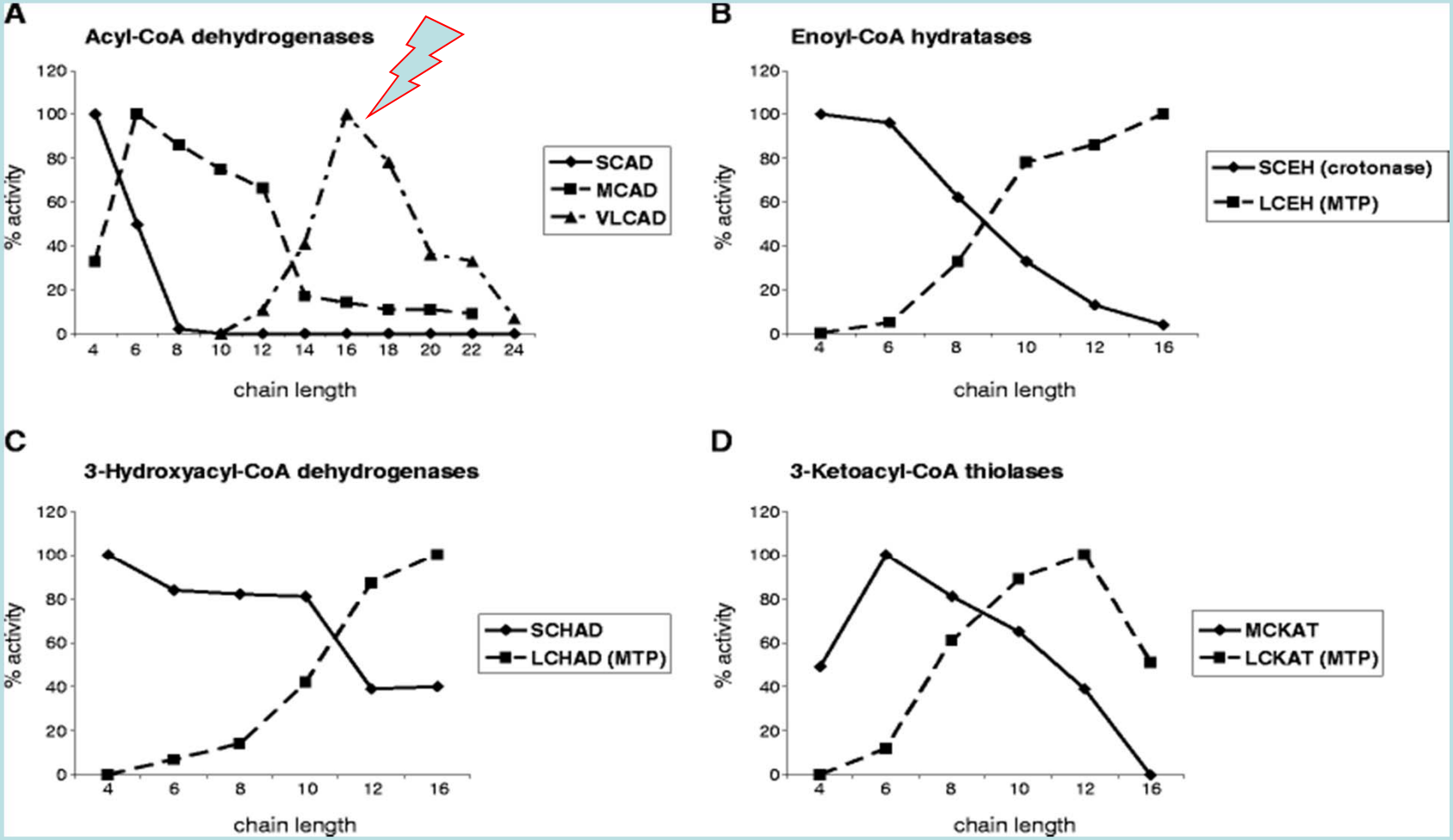
Important energy source for the heart

- Cardiac disease

Important during exercise in skeletal muscle

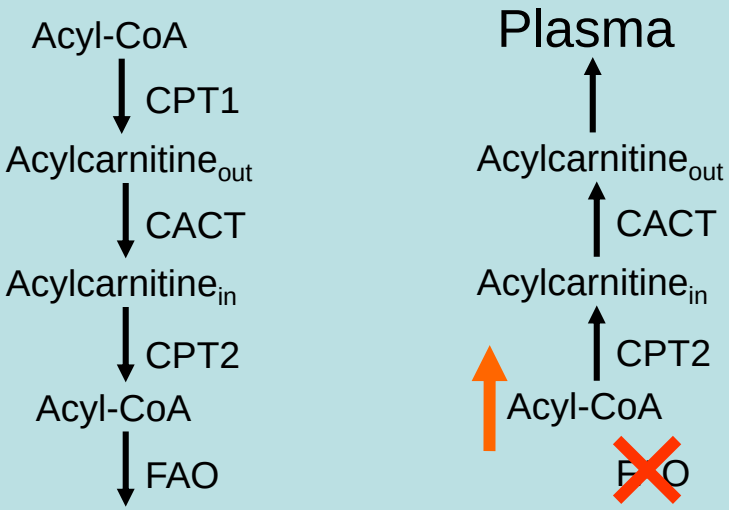
- Hypotonia;
- Myopathy and Rhabdomyolysis

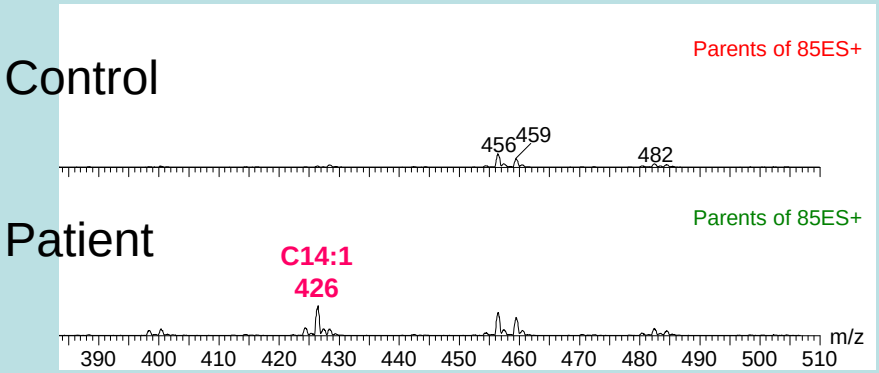
Substrate specificity of the different beta-oxidation enzymes



R. Wanders et al. J Inherit Metab Dis (2010); 33: 479-494

Acylcarnitines in fatty acid oxidation disorders





- VLCAD deficiciency
  - C14:2, C14:1, C14 (C14:1/C16)
- MCAD deficiciency
  - C6, C8, C10:1, C10
- LCHAD / MTP deficiciency
  - C16:1OH, C16OH, C18:1OH, C18OH

Used by Permission by S. Houten, Metabolics.be 2012

Diagnosis of MCADD

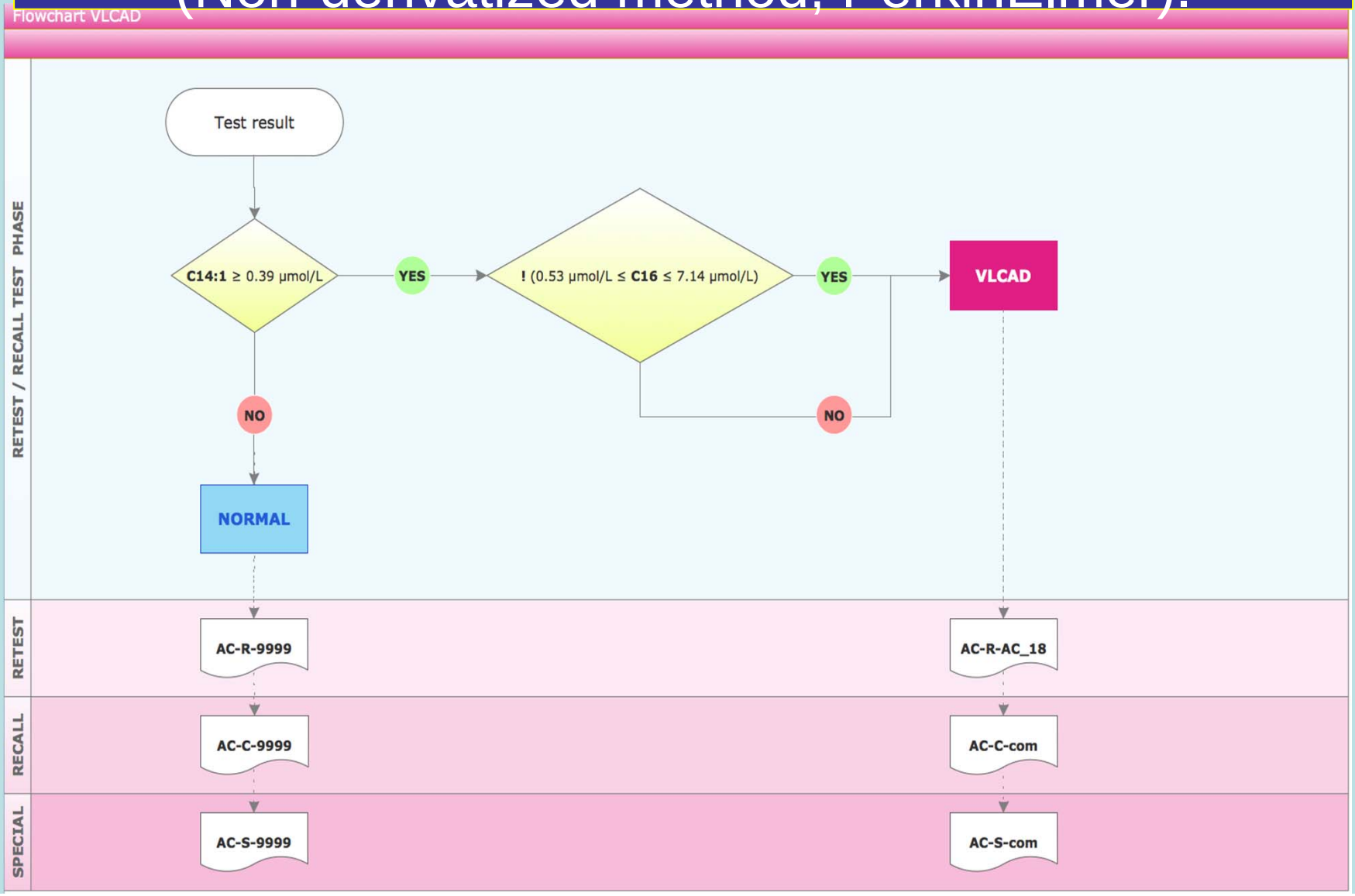
Incidence of MCADD 1:14,000 ~PKU

High incidence of unexpected mutation frequencies found by neonatal screening:

- Pennsylvania,USA
- Sydney, Australia
  - B. Wilcken: "*It is not yet clear which patients (MCADD "variants") with disorders diagnosed by such screening would have become symptomatic if screening had not been performed*".

Screening Algorithm VLCADD

Methods: MS/MS Xevo (Waters); Neobase kits (Non-derivatized method; PerkinElmer).



Results: 2008-2012
N= 181,246

- Screening parameter C14:1 acylcarnitine (cutoff: <0.39 µmol/L).
- Results:
  - The bloodsampling takes place between 3-4 days postpartum.
  - The recall rate is 0.07%. The false positives have a C14:1 median concentration of 0.52 µmol/L (range 0.43-0.87).
  - Specificity: 99.93%.
  - In 2012 the two first patients affected by VLCADD were found in our population. Two newborn girls were found with a C14:1 acylcarnitine concentration of 1.33 and 3.59 µmol/L, resp. The C14:1/C2 ratio was elevated in both patients (normal range <0.023).

Screening Results The Netherlands 2007-2012

VLCAD-patiënts 2007 - 06-2012 (EHP: 1.012.408)

	C14:1			C14:1/C2
	Referred	Confirmed	Missed	Extra det.
2007	1	1	0	1
2008	3+1[1] =4	3+1[1]=4	0	3 -1 = 2 [1]
2009	2	0	0	0
2010	3	2	0	1
2011	3	1	0	onbekend
06-2012	3	1	0	onbekend
totaal	**16**	**9**	**0**	**4** [1]

[1] één kind met C14:1=0.70; zou met huidige afkapgrens ook gevonden zijn

13 VLCAD

25.04.2013|Newborn Screening Benelux Meeting-Liège

Used by Permission of P. Schiele, RIVM; BeNeLux 2013

Revision of Screening Strategy

VLCAD deficiciency

- C14:1, C14:2, C14, C16
- C14:1/C16 Ratio

VLCAD deficiciency

- **C14:1**
- **C14:1/C2 Ratio**
- C14:2, C14, C16
- (C12, C12:1)
- ~~C14:1/C16 Ratio~~

Revision of Screening Strategy

VLCAD deficiciency

- C14:1, C14:2, C14, C16
- C14:1/C16 Ratio

VLCAD deficiciency

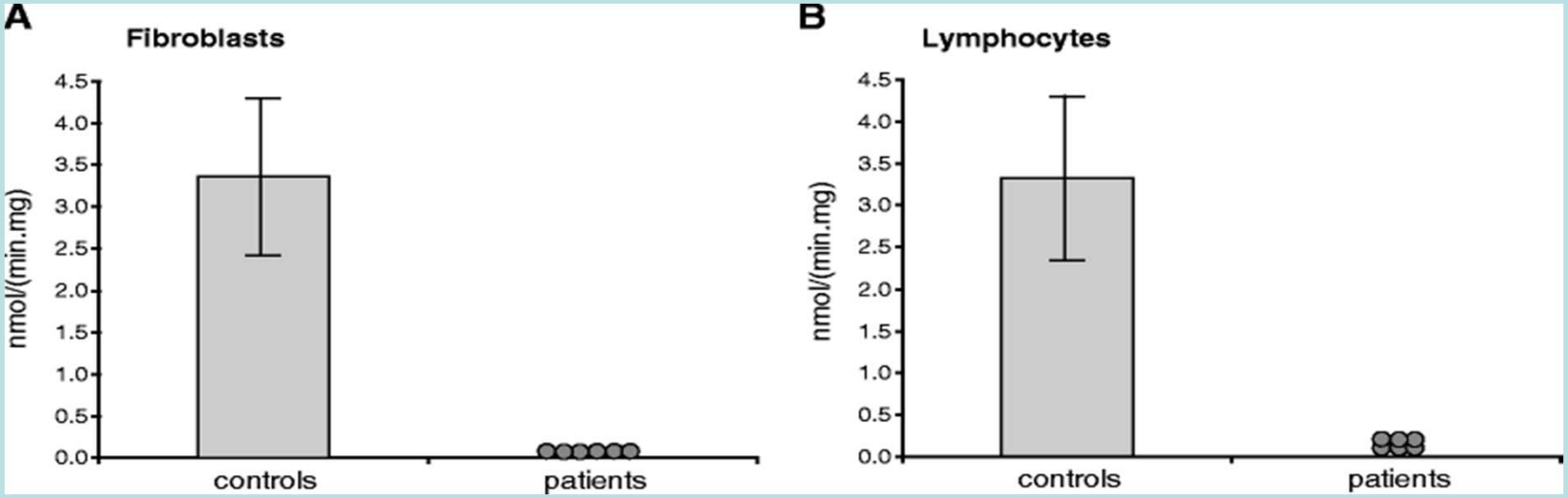
- **C14:1**
- **C14:1/C2 Ratio**

No prediction of being at risk to develop clinical disease

Enzymatic assay VLCAD Fibroblasts/Lymphocytes

A functional enzyme activity assay is the only reliable method to predict the clinical course in patients with VLCADD detected by newborn screening: patients showing a <10% residual enzyme activity are at risk to develop clinical disease (*)

R. Wanders et al. J Inherit Metab Dis (2010): 33; 479-494

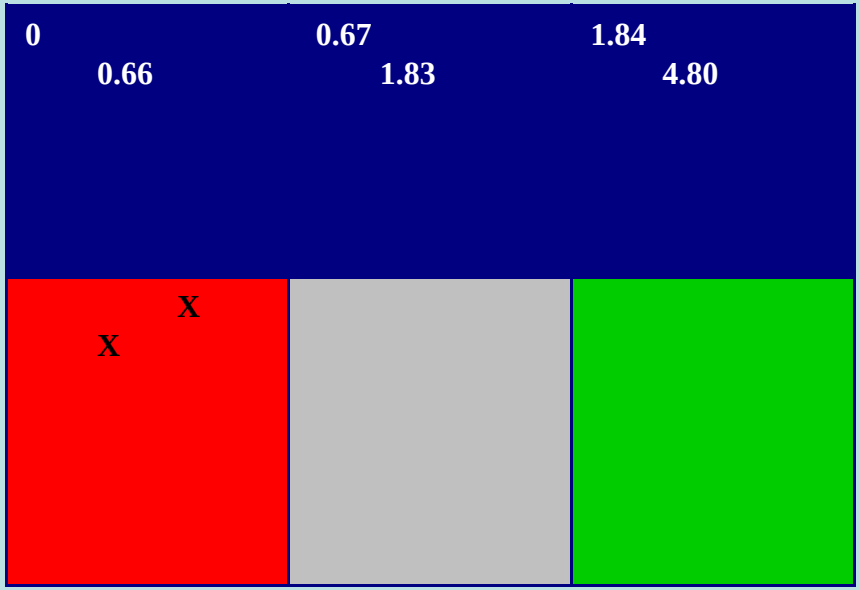


(* U. Spiekerkoetter, Duesseldorf, Germany, 2009)

Confirmation of diagnosis

- The diagnosis was confirmed by enzyme activity measurement in lymphocytes (AMC, Amsterdam, The Netherlands).
- The residual enzyme activity of VLCADD was 0.61 and 0.24 nmol/min/mg protein, resp (controls: 1.84-4.80 nmol/min/mg protein;

10% enzyme activity = 0.66).



Treatment; Follow-up
Clinical outcome

- Both patients are asymptomatic, including normal cardiac findings,at the age of diagnosis (4-6 weeks) and follow-up during 12 months;
- The patient with the lowest enzyme activity was put on a strict diet:
  - Normal muscle tone;
  - Normal motor development;
  - 1 hospitalisation during an episode of vomiting
    - **AVOID CATABOLISM**
- The other patient is carefully followed up in time under no dietary restriction of long-chain fatty acids
- No free L-carnitine deficiency

Spiekerkoetter U et al. EMG Workshop; J Inherit Metab Dis (2009): 3:488-497

Conclusions

- VLCADD has a wide clinical spectrum ranging from cardiomyopathy in infants to episodic rhabdomyolysis and exercise intolerance in adeloscents;
- Neonatal screening has shown that VLCAD deficiency is the second commonest fatty acid oxidation disorder in Europe and the USA, with a prevalence between 1:50,000 and 1:100,000. This is much higher than was detected clinically;
- Newborn screening of VLCADD is performed by MS/MS: parameters C14/1 **and/or** C14:1/C2 ratio;

Conclusions Ctd

- Confirmation of disease: enzymatic assay of VLCADD in lymphocytes (DNA analysis);
- The severely affected infants are treated with a formula enriched with Medium Chain fatty acids (MCT) and breast feeding is avoided. The mildly affected patients do not need a special diet;
- Early dietary intervention improves the outcome of severely affected patients.

Acknowledgements

- *PCMA vzw team*
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THANK YOU

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