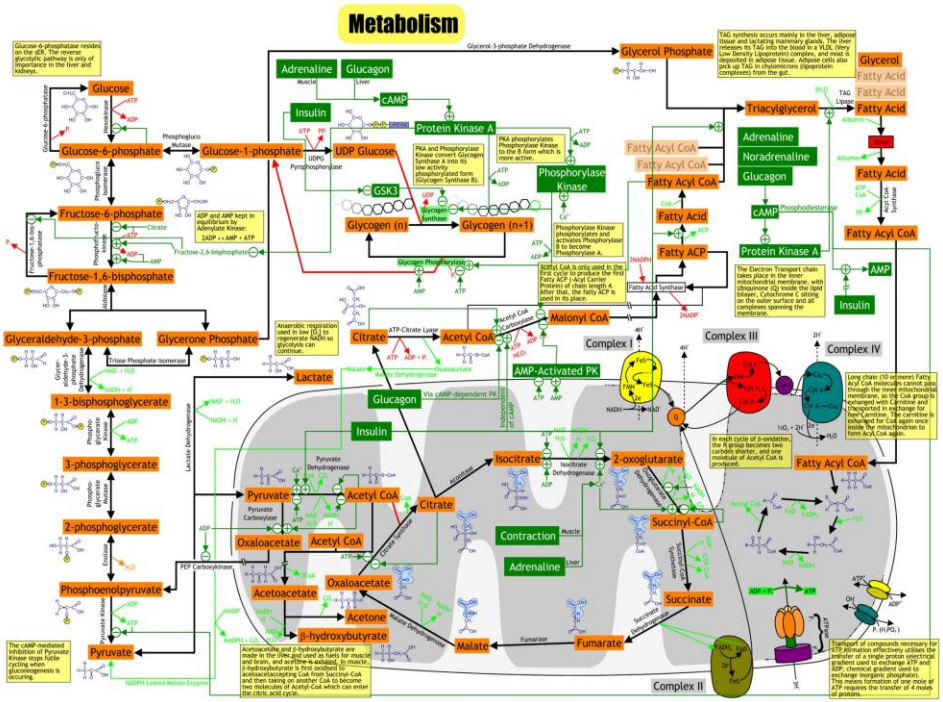
Diagnosis and treatment of inborn errors of metabolism

Viktor Kožich
Martin Hřebíček

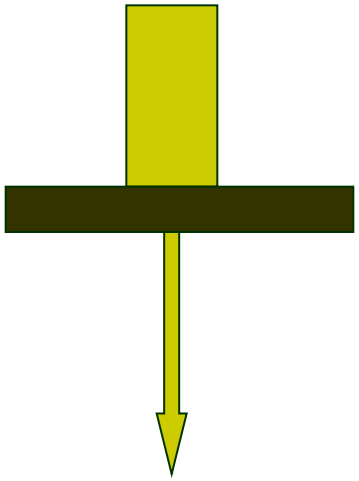
Ústav dědičných metabolických poruch
1.LF UK a VFN Praha


Metabolism
Glucose
Glucose-6-phosphate
Glucose-1-phosphate
UDP Glucose
Fructose-6-phosphate
Fructose-1,6-bisphosphate
Glyceraldehyde-3-phosphate
Glycerone Phosphate
1-3-bisphosphoglycerate
3-phosphoglycerate
2-phosphoglycerate
Phosphoenolpyruvate
Pyruvate
Lactate
Adrenaline
Glucagon
Insulin
cAMP
Protein Kinase A
GSK3
Glycogen (n)
Glycogen (n+1)
Phosphorylase Kinase
Glycerol Phosphate
Triacylglycerol
Glycerol
Fatty Acid
Fatty Acyl CoA
Fatty Acid
Fatty ACP
Noradrenaline
Fatty Acyl CoA
Malonyl CoA
AMP-Activated PK
Citrate
Acetyl CoA
Isocitrate
2-oxoglutarate
Succinyl-CoA
Succinate
Fumarate
Malate
Oxaloacetate
Acetoacetate
Acetone
β-hydroxybutyrate
Contraction
Complex I
Complex II
Complex III
Complex IV

n=800

Patophysiology IEM

substrate



product

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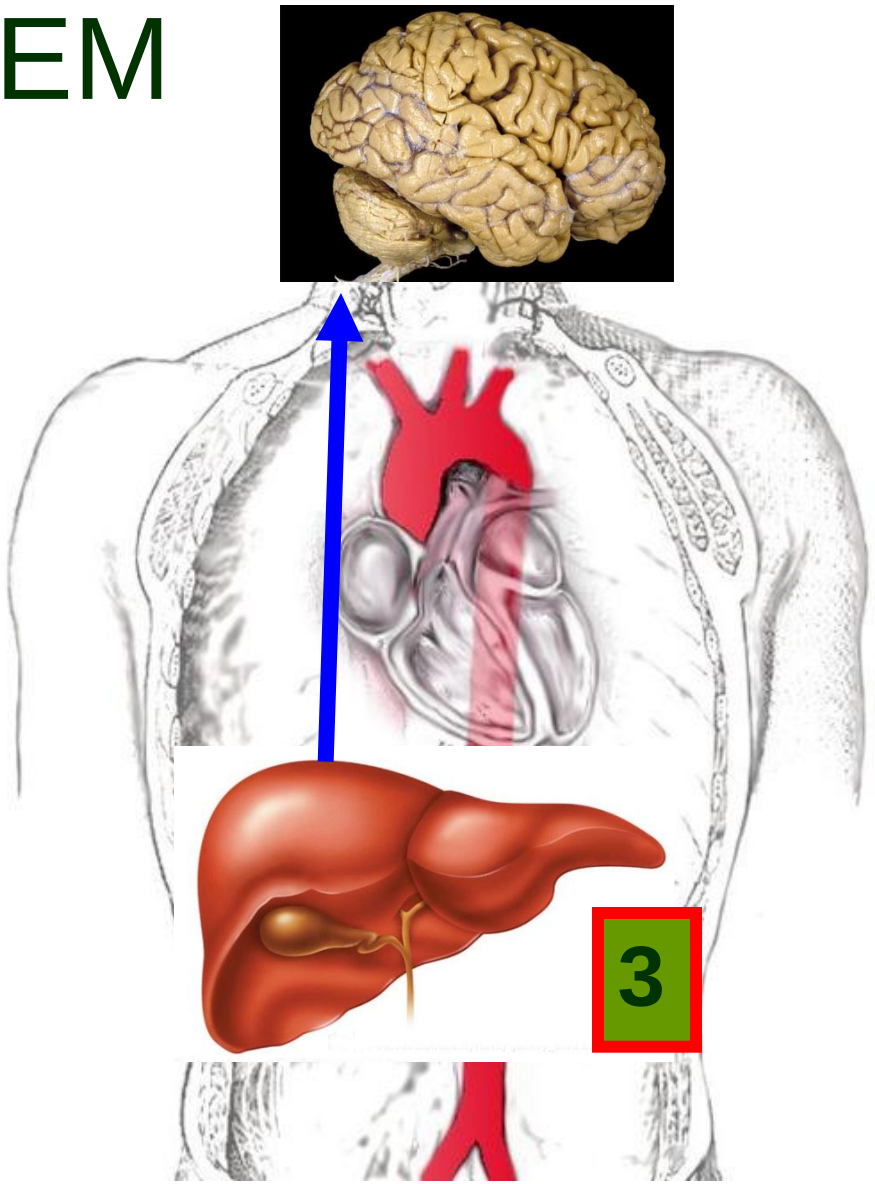

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2

3

Categories of IEMs-examples

	Small molecule	Complex molecule
Substrate accumulation	•*Aminoacidopathies Hyperammonemias* •*Org.acidurias*	•*Lysosomal storage diseases*
Product deficiency	•*Glycogenoses* •*FAO* •*Creatine synthesis defects*	•*CDG syndromes* •*Generalised peroxisomal diseases*

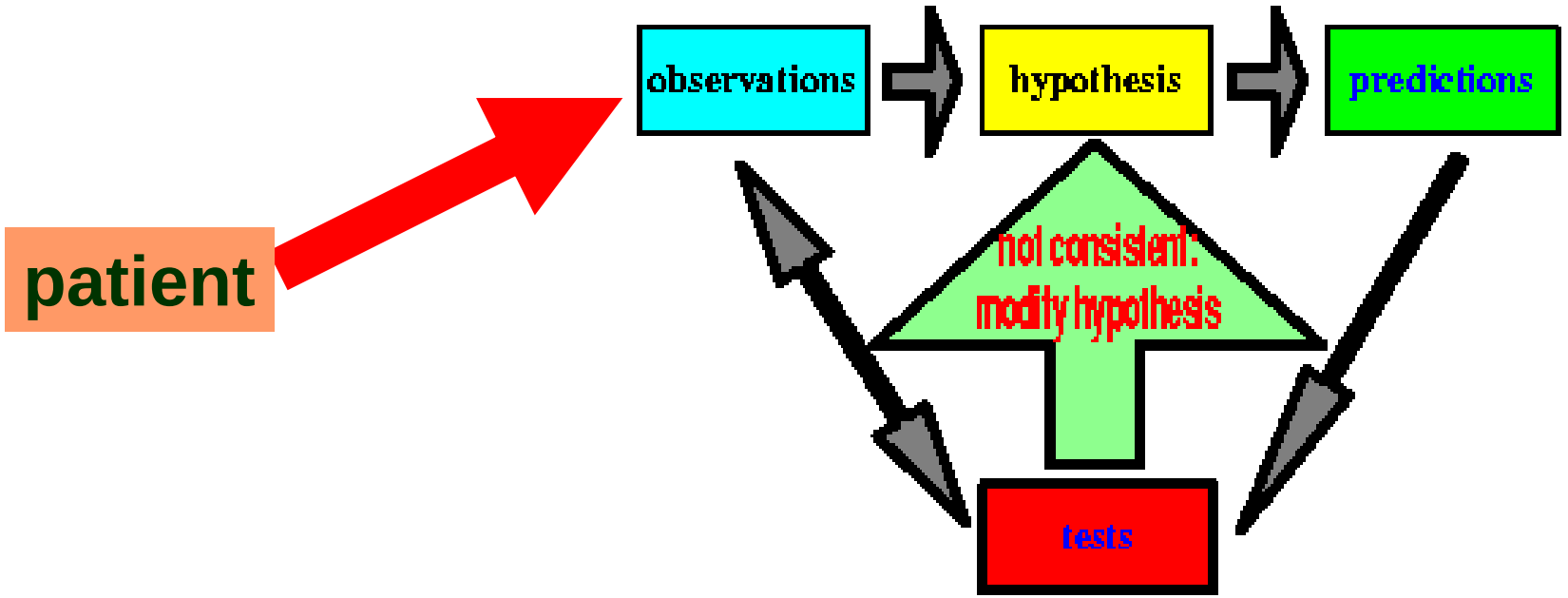
Structure

- **Diagnosis in general**
- **Neonatal screening**
- **Selective screening**
- **Treatment**

Why do we need diagnosis?

- To explain the clinical symptoms and signs
- To prevent unnecessary investigations
- To reduce anxiety and uncertainty
- To prevent further damage
- To start treatment
- To estimate the risk for relatives

Diagnosis ≈ hypothesis verification



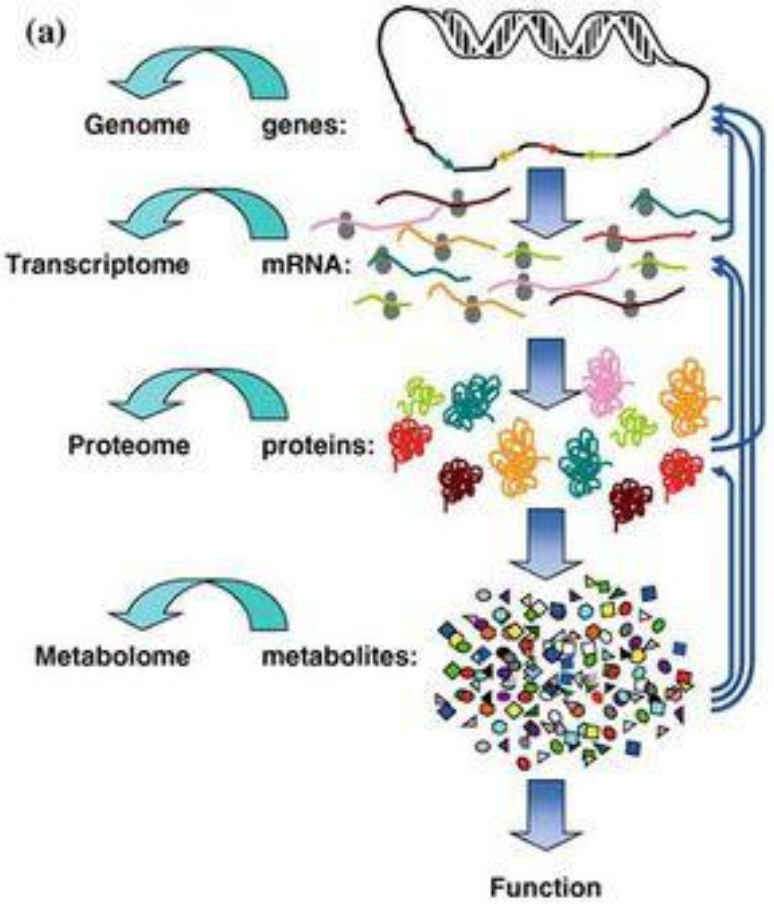
http://farm1.static.flickr.com/21/100467846_832c312de1_o.gif

Diagnosing IEMs

is

genetic testing

Levels of diagnosis

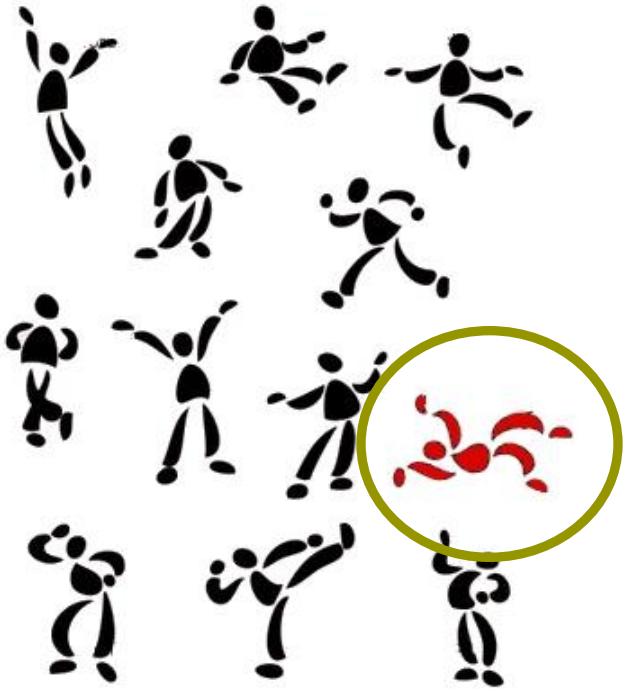


Structure

- **Diagnosis in general**
- **Neonatal screening**
- **Selective screening**
- **Treatment**

Genetic testing

Selective screening



Population screening

Screening

- Screening= identification of individuals with an increased risk of a particular disease
- Diagnosis is always confirmed by independent methods


healthy
false findings
patients

Successful diagnosis of IEM

knowledgeable physician

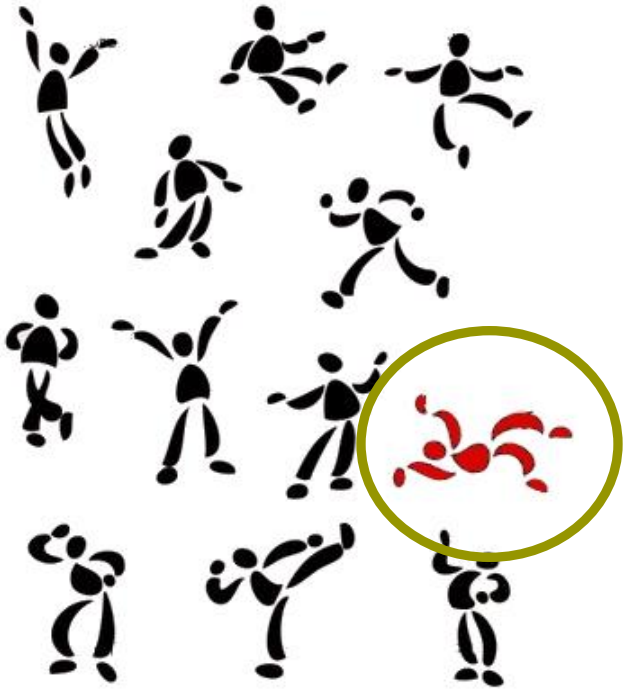
+

availability of appropriate test

3.bp.blogspot.com/.../s320/physicianatdesk.jpg

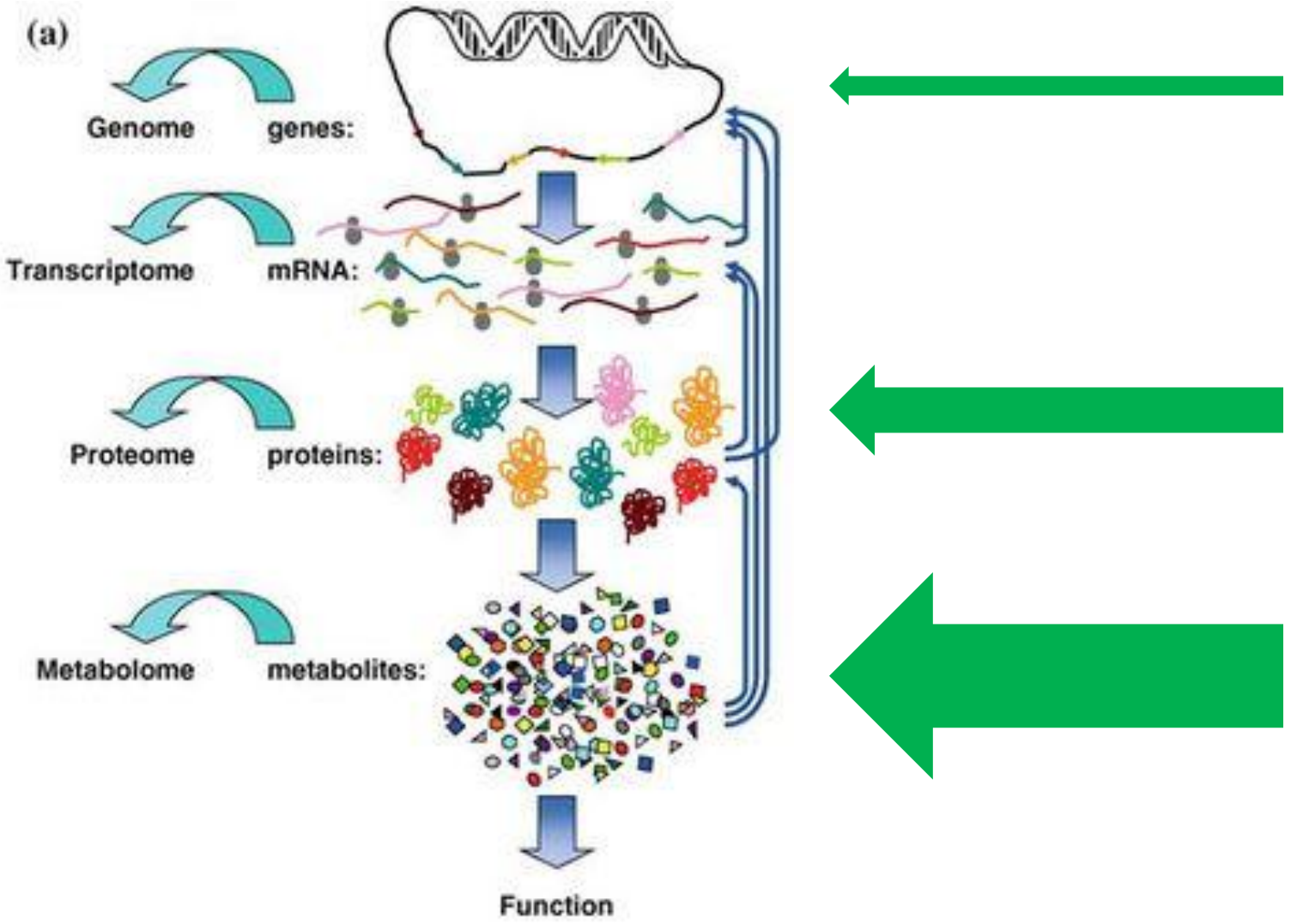
Genetic testing

Selective screening



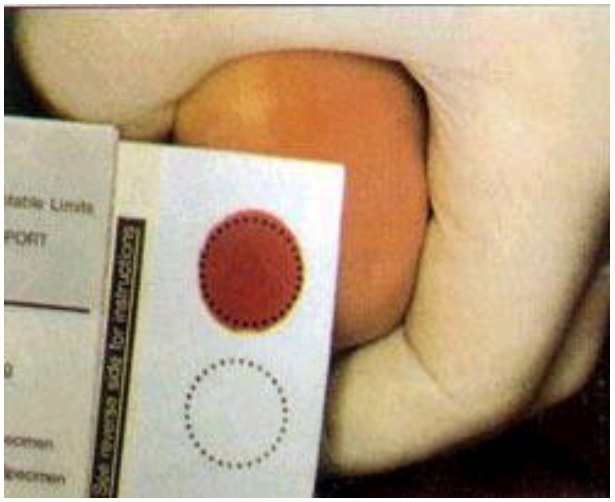
Population screening

Neonatal screening



Neonatal screening

- Active search for disease in the entire population, presymptomatic diagnosis
- Sensu stricto- laboratory analyses of diseases using dry blood spots
- Founder-Prof. Robert Guthrie 1916-1995

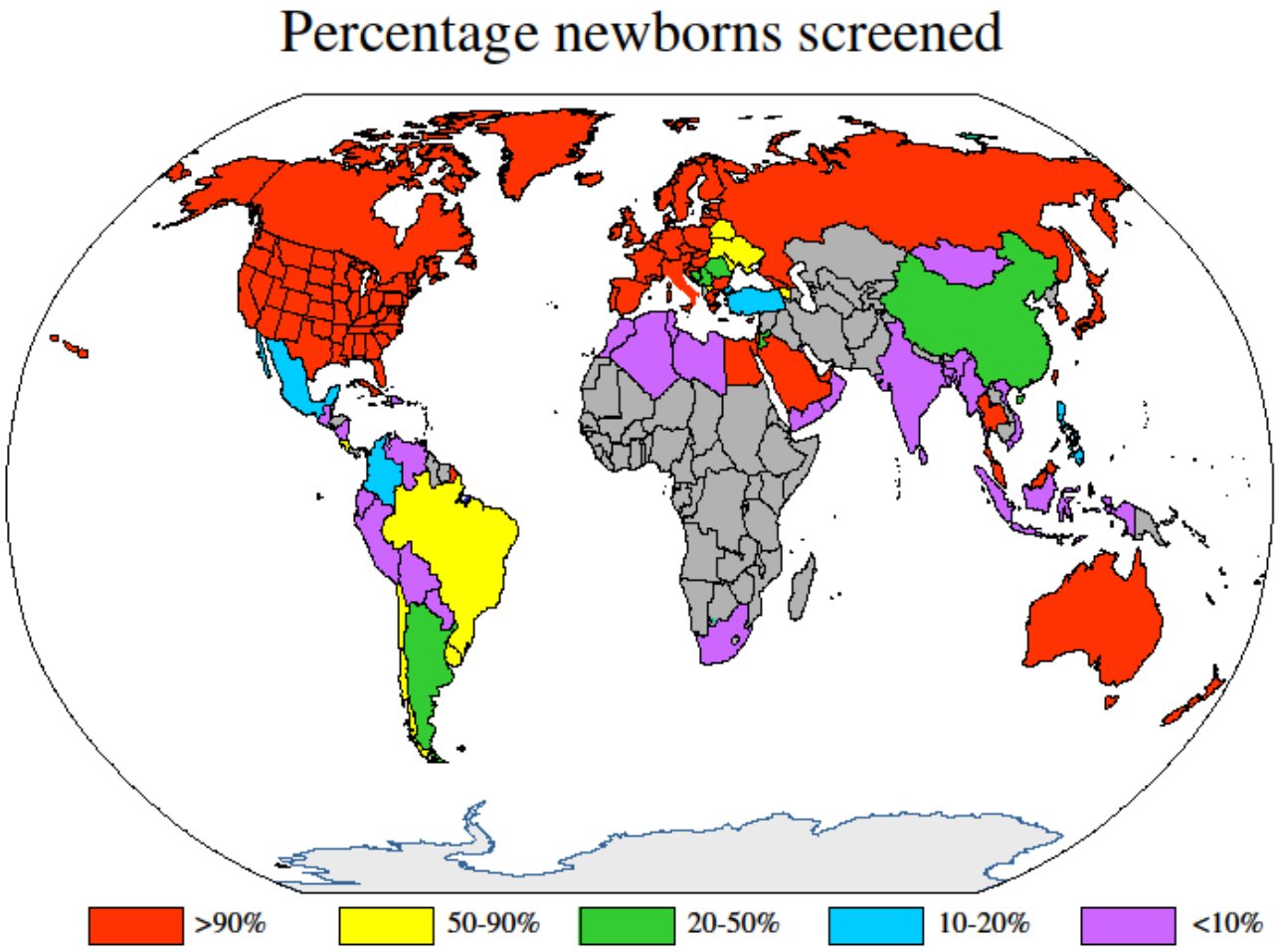


JMG Wilson and G Jungner: **Principles and Practice of Screening for Disease,** WHO 1968

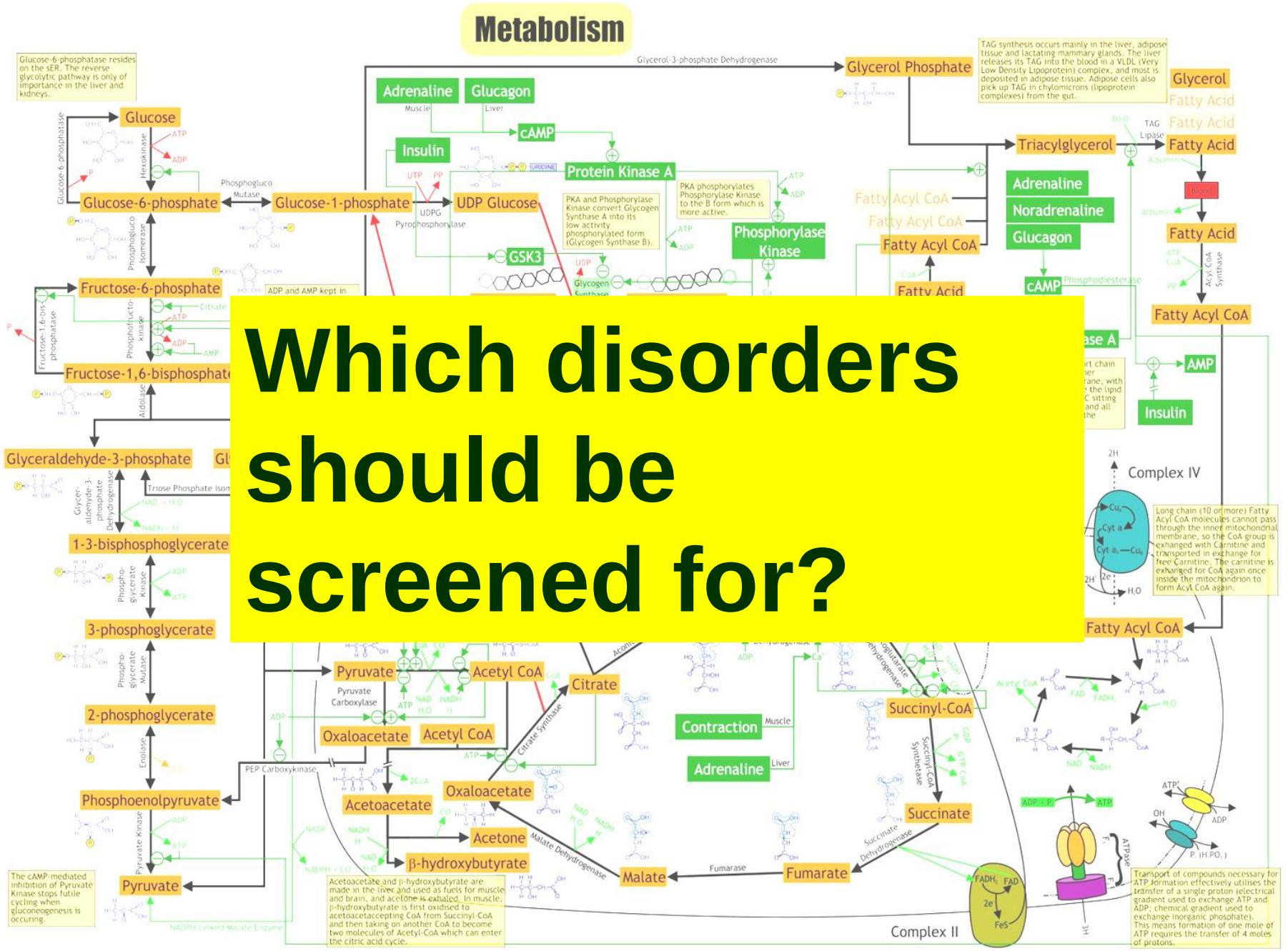
Classical criteria for NBS

- **Diseases freqeuncy and severity**
- **Asymptomatic latent phase**
- **Disease mechanisms are known**
- **Reliable test**
- **Test is acceptable by the population**
- **Program is a continuous process**
- **Acceptable treatmetn**
- **Conditions for dx and rx established**
- **Consensus on whom and how to treat**
- **Cost-benefit ratio acceptable by the system**

ISNS data 2007



www.isns.org



Which disorders should be screened for?

Balancing benefits and risks

USA: child health

Europa: false positives and uncertain prognosis

Newborn Screening: Toward a Uniform Screening Panel and System

Michael S. Watson, PhD, Marie Y. Mann, MD, MPH, Michele A. Lloyd-Puryear, MD, PhD, Piero Rinaldo, MD, PhD, and R. Rodney Howell, MD, editors

Genet Med 2006:8(5,Supplement):1S–11S

The Maternal and Child Health Bureau commissioned the American College of Medical Genetics to outline a process for the standardization of outcomes and guidelines for state newborn screening programs and to define responsibilities for collecting and evaluating outcome data, including a recommended uniform panel of conditions to include in state newborn screening programs. The expert panel identified 29 conditions for which screening should be mandated. An additional 25 conditions were identified because they are part of the differential diagnosis of a condition in the core panel, they are clinically significant and revealed with screening technology but lack an efficacious treatment, or they represent incidental findings for which there is potential clinical significance. The process of identification is described, and recommendations are provided.

Table 2

Combined criteria and distribution of scores in the data collection instrument(Highest possible score: 2100)
I. Condition/Disorder (subtotal score 700)

Criterion	Categories in criterion	Score
Incidence of condition	>1:5x000	100
	>1:25,000	75
	>1:50,000	50
	>1:75,000	25
	<1:100,000	0
Signs and symptoms clinically identifiable in the first 48 hours	Never	100
	<25% of cases	75
	<50% of cases	50
	<75% of cases	25
	Always	0
Burden of disease (natural history if untreated)	Profound	100
	Severe	75
	Moderate	50
	Mild	25
	Minimal	0
Individual benefits of early intervention	Clear scientific evidence that early intervention resulting from screening optimizes outcome	200
	Some scientific evidence that early intervention resulting from screening optimizes outcome	100
	No scientific evidence that early intervention resulting from screening optimizes outcome	0
Familial and societal benefits of early intervention	Early identification provides clear benefits to family and society (education, understanding prevalence and natural history, cost effectiveness)	100
	Early identification provides some benefits to family and society	50
	No evidence of benefits	0
Early diagnosis and treatment prevent mortality	Yes	100
	No	0

Frequency

Early clincial signs

Severity

Individual benefit

Familial and societal benefit

Mortality prevention

Up to 700 points ea
-disease
-test
-treatment

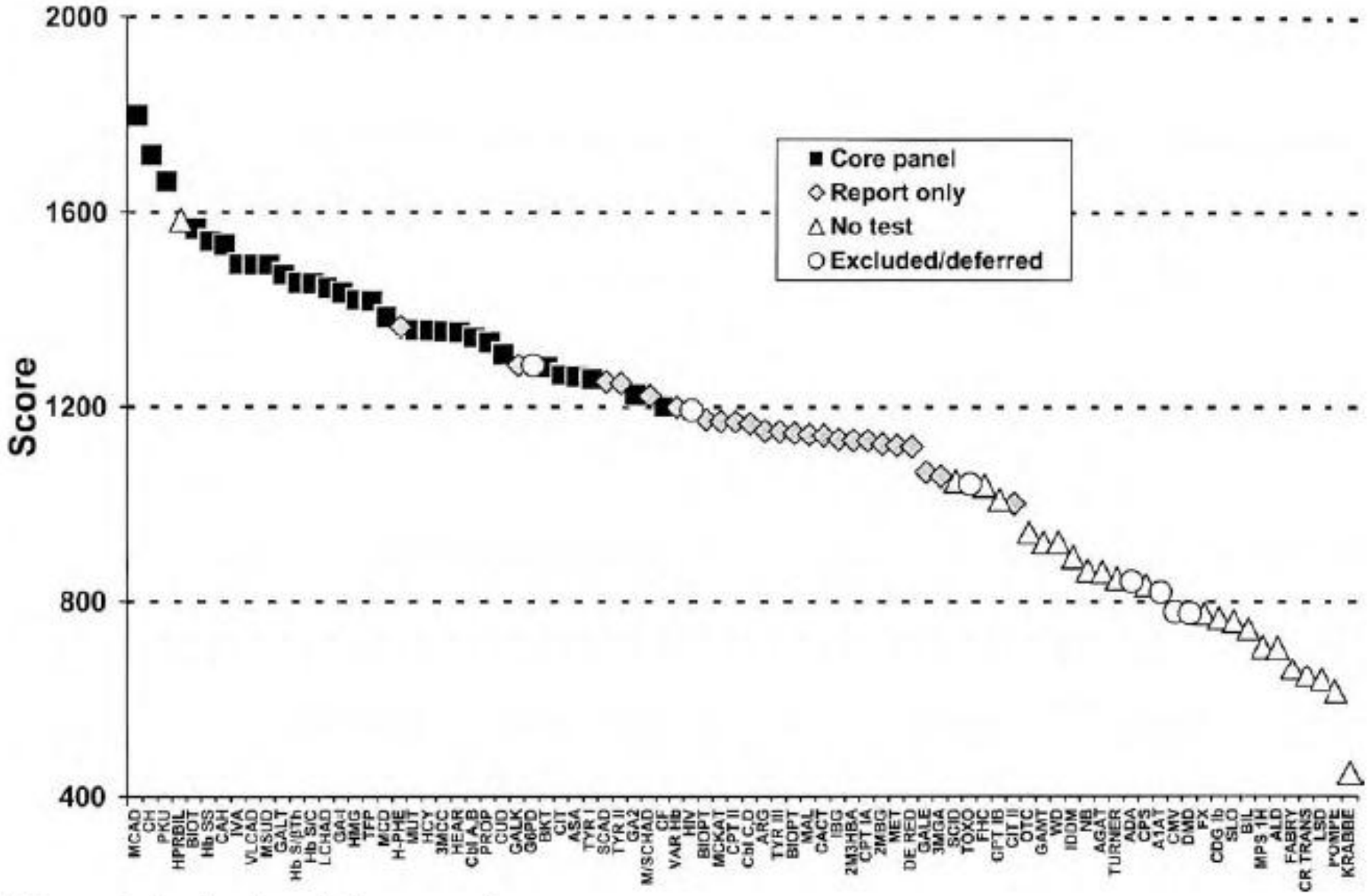
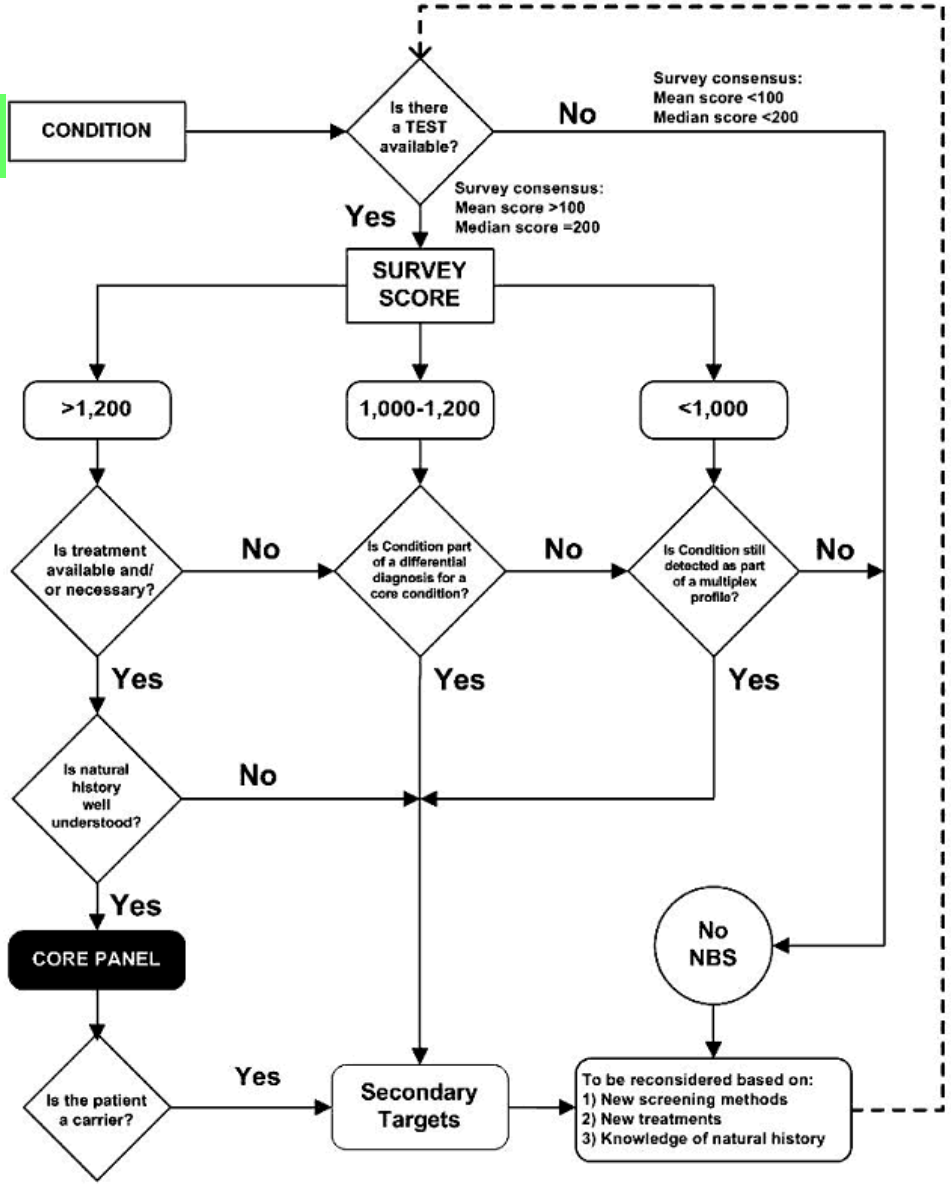


Fig. 7. Scores for all conditions distinguished by screening panel category

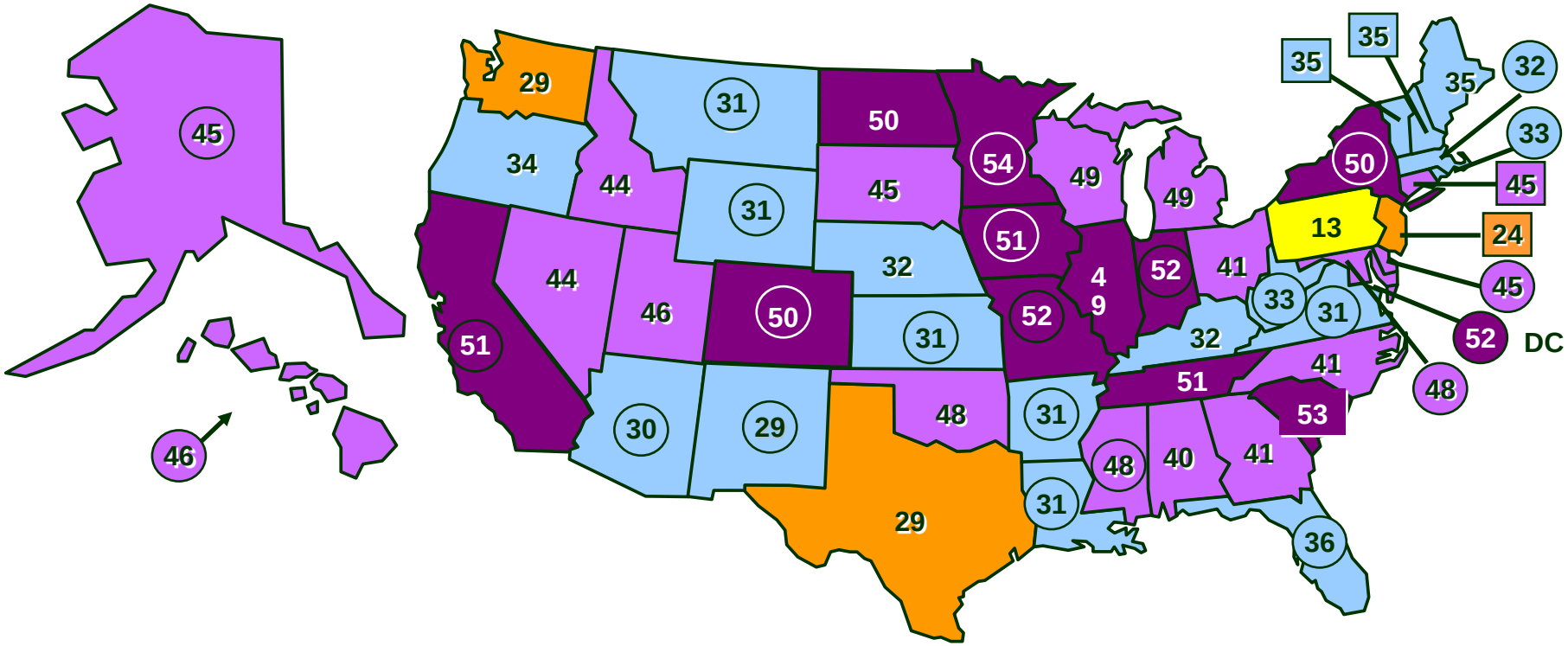
81 diseases



29 diseases

http://www.bioethics.gov/images/new_born_screening.gif

NBS USA-2009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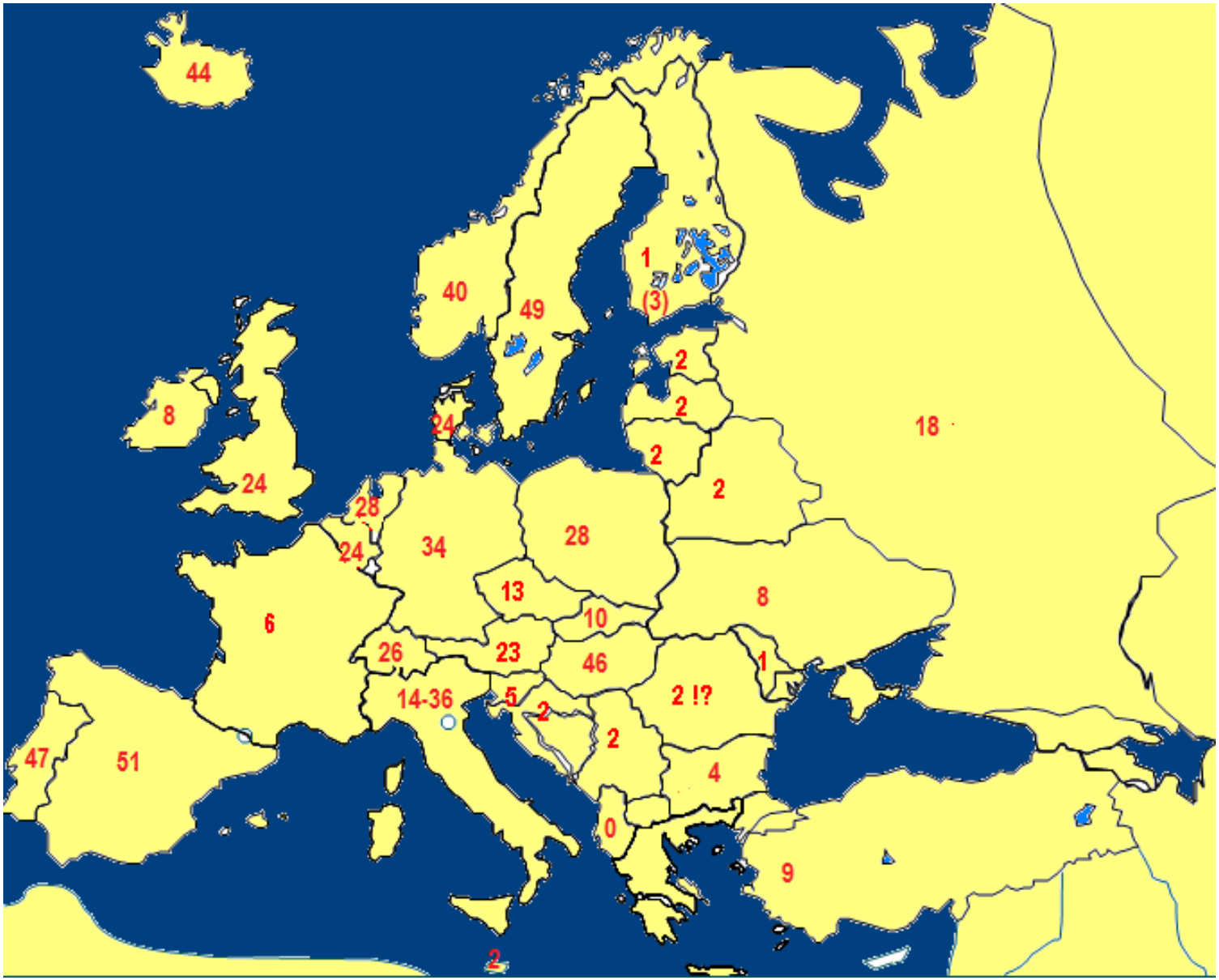
Jaké choroby screenovat ? Evropa - ISNS:

ISNS
International Society for Neonatal Screening

Základní skupina (metodika screeningu není složitá a zdravotní efekt je prokázán)		**Kandidátní skupina** (19 onemocnění, u kterých NS zatím představuje více výzev a nejasností ve vztahu ke kriteriím dle Wilsona a Jungnera)
7 onemocnění s relativně vysokou prevalencí	3 onemocnění s nižší prevalencí	
PKU/HPA, CH, CAH, CF, MCADD, Hb S/Th, Hb S/C	**MSUD, GA I**, GAL	BD, **CPTD II**, **CACTD**, GA II, HMGD, HCSD, HCY, **IVA**, BKT, **LCHADD**, LSD, 3MCC, TYR I TYR II a III, **VLCADD**, deficit vitaminu B12, SCID, CMV



Zdroj: Therell BL et all: Current status of newborns screening worldwide: 2015. Seminars in Perinatology 2015;39: 171-87

MINISTERSTVO ZDRAVOTNICTVÍ
ČESKÉ REPUBLIKY

Věstník

Ročník **2009**

MINISTERSTVA ZDRAVOTNICTVÍ

ČESKÉ REPUBLIKY

Částka 6 **Vydáno: 12. SRPNA 2009** **Cena: 294 Kč**

METODICKÝ NÁVOD K ZAJIŠTĚNÍ CELOPLOŠNÉHO NOVOROZENECKÉHO LABORATORNÍHO SCREENINGU A NÁSLEDNÉ PÉČE

Diseases screened in ČR 10/2009

(2) V rámci novorozeneckého laboratorního screeningu jsou ze suché kapky krve vyšetřovány níže uvedené onemocnění:

~1:2 900

Cummulative 1:1 200

Endokrinní onemocnění (EO):

a) kongenitální hypotyreóza (CH)

b) kongenitální adrenální hyperplazie (CAH)

~1:4 000

Dědičné poruchy metabolismu (DMP):

c) fenylketonurie (PKU) a hyperfenylalaninemie (HPA)

d) leucinóza (nemoc javorového sirupu, MSUD)

e) deficit acyl-CoA dehydrogenázy mastných kyselin se středně dlouhým řetězcem (MCAD)

f) deficit 3-hydroxyacyl-CoA dehydrogenázy mastných kyselin s dlouhým řetězcem (LCHAD)

g) deficit acyl-CoA dehydrogenázy mastných kyselin s velmi dlouhým řetězcem (VLCAD)

h) deficit karnitinpalmitoyltransferázy I (CPT I)

i) deficit karnitinpalmitoyltransferázy II (CPT II)

j) deficit karnitinacylkarnitintranslokázy (CACT)

k) glutarová acidurie typ I (GA I)

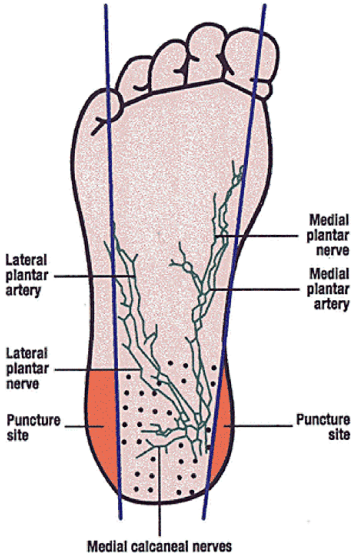
l) izovalerová acidurie (IVA)

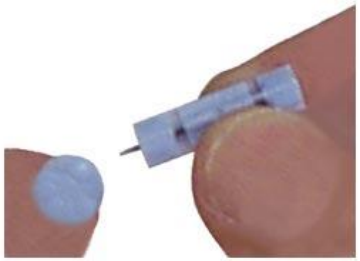
~1:4 000

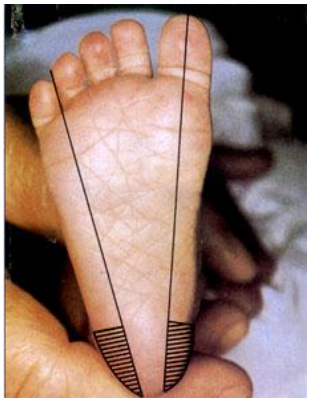
Jiná onemocnění:

m) cystická fibróza (CF)

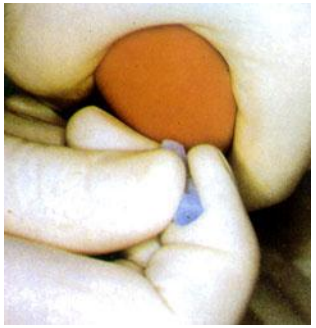
Good sampling practice

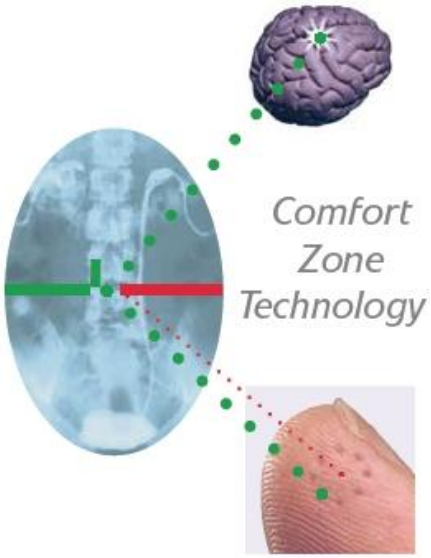






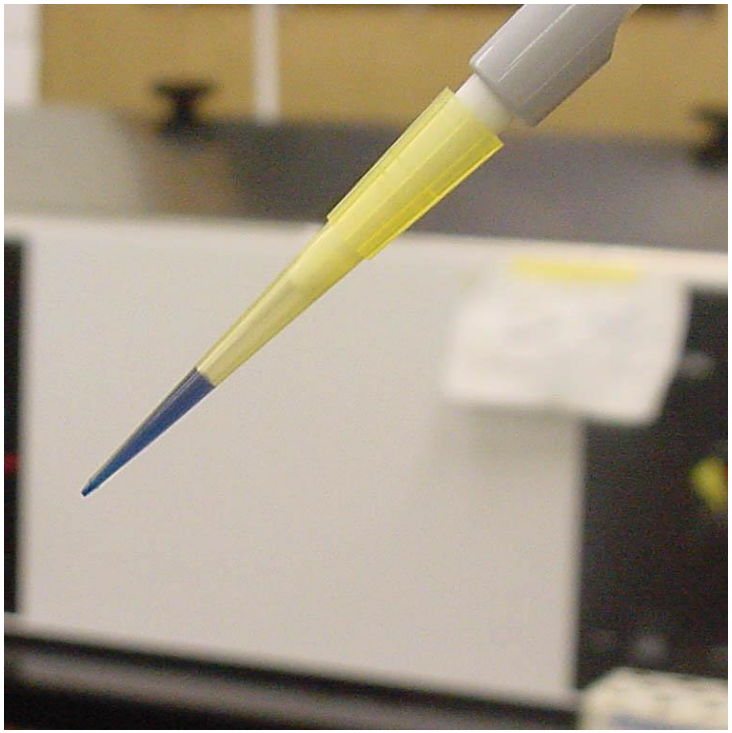
correct drying
3 hrs, no direct heat

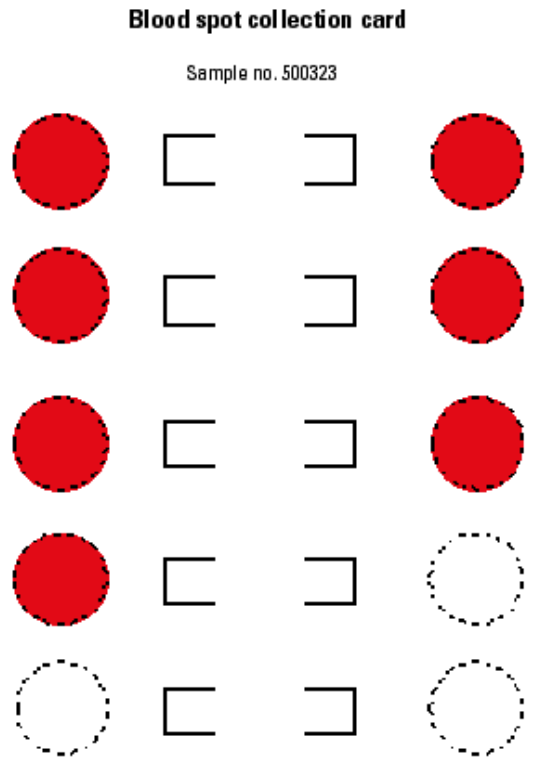




http://cms.ich.ucl.ac.uk/website/imagebank/images/Neonatal_appendix.gif

Why is correct sampling crucial?





Tandem mass spectrometry

- modern analytical method
- profile of analytes
- wide spectrum of compounds: amino acids, acylcarnitines, sugars.....enzyme activities
- used for NBS since mid 1990s

http://cache.boston.com/resize/bonzai-fba/Globe_Photo/2008/01/22/1201060537_1951/300h.jpg

Patients with IEM (NBS, ČR, 12 mo)

Disease	Selective screening (est/y/ČR)	Pilot phase ÚDMP (n=98 039)	Whole ČR 2009-2010 (n= 117 705)
PKU/HPA	(15-20)	15	18
MCAD def.	0-1	2	10
LCHAD def.	0-1	3	0
GA I	0-1	0	2
MSUD	0-1	0	1
Other (IVA, CPTI, CACT, CPTII, VLCAD)	0-1	0	0
total	**15-25**	**20**	**31**

Diagnostic efficacy

576,000 newborns (IX/2009-XII/2014)

IEM	Pt	Incidence
PKU/HPA	110	1:5 200
Deficit MCAD	29	1:19 900
Deficit LCHAD/MTP	10	1:57 800
Deficit VLCAD	4	1:144 400
Hydroxyprolinemie	3	1:192 600
MSUD	3	1:192 600
IVA	3	1:192 600
GA I	3	1:192 600
Total	165	1:3 500

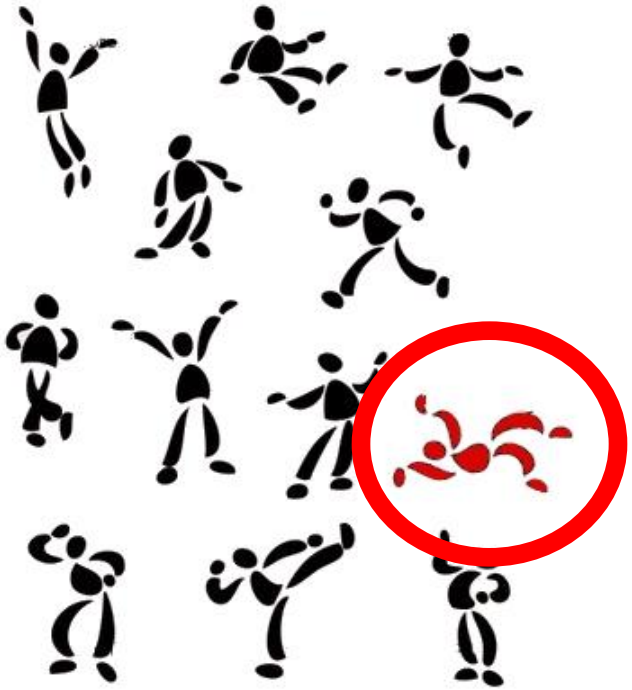
www.novorozeneckyscreening.cz

Structure

- **Diagnosis in general**
- **Neonatal screening**
- **Selective screening**
- **Treatment**

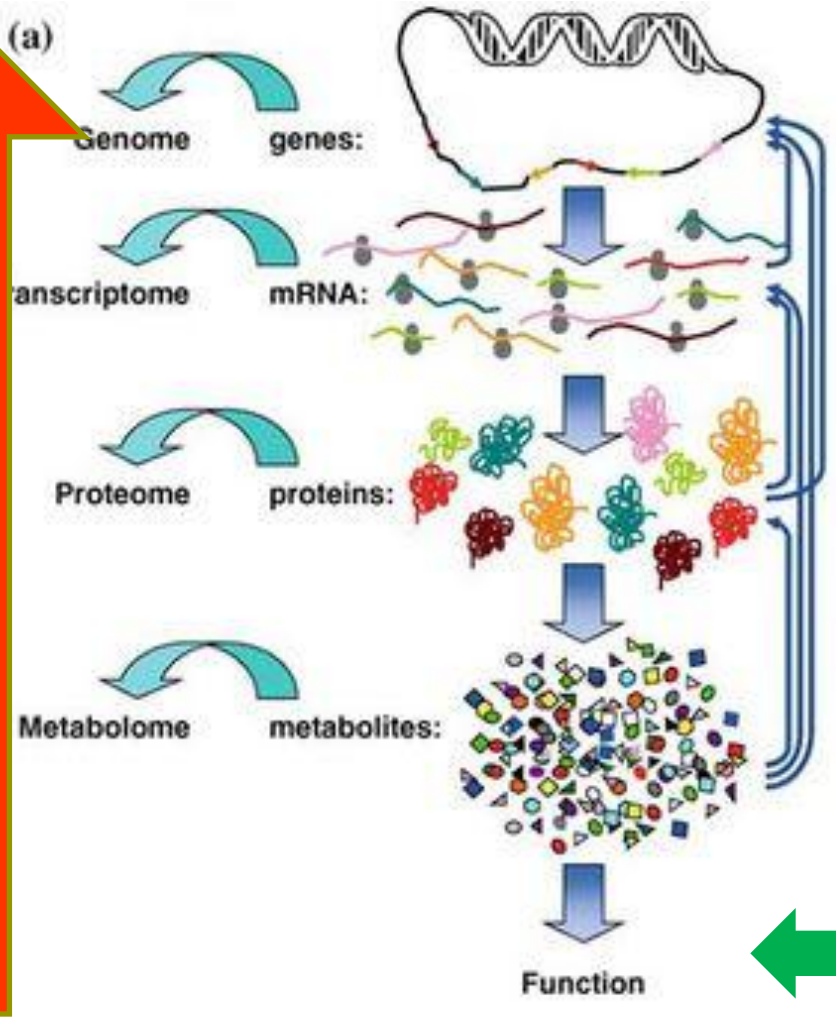
Genetic testing

Selective screening



Population screening

Selective screening



Clinical selection of patients is a key component of selective screening

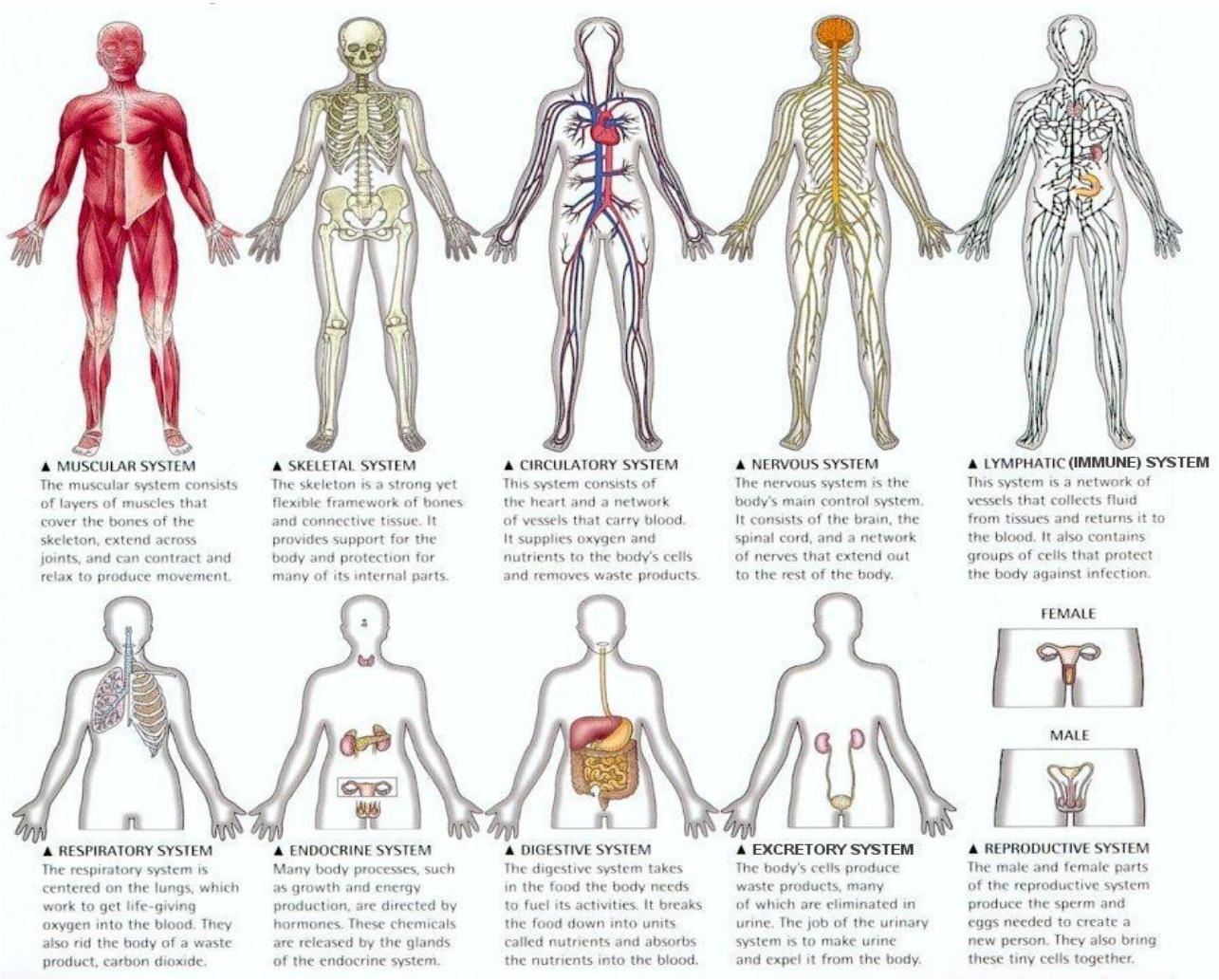
Clinical features of IEMs-age

http://www.hrr.co.uk/acatalog/crocodile_toddler.jpg

http://www.co.shasta.ca.us/html/DSS/images/FosterParentingAdopt/infant.jpg

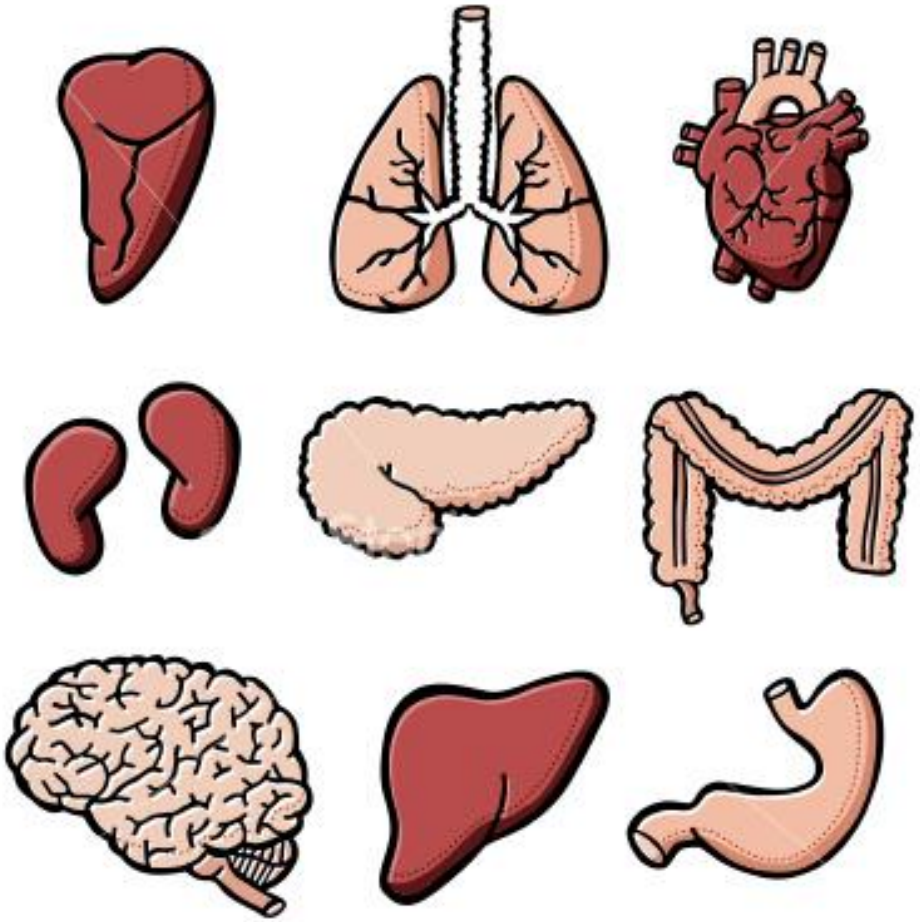
http://markandrich.googlepages.com/Old-woman.jpg/Old-woman-full.jpg

Clinical features of IEMs-organs



http://universe-review.ca/I10-82-organs.jpg

Clinical features-multisystemic involvement



http://www.istockphoto.com/file_thumbview_approve/5982111/2/istockphoto_5982111-human-internal-organs.jpg

Hints of the possibility of IEM

- Family history: consanguinity or typical family tree, similar diseases in relatives, unexplained death in relatives
- Ilness considered originally a common disease does not respond adequately to treatment
- Multisystemic involvement
- External factors/food influencing the course
  - catabolism
  - Fasting
  - Proteins or sugars (galactose, fructose) aggravate diseases
- Unexplained routine lab tests

Courtesy- Dr.D.Behulová

Selected common situations with high risk of IEM

- Small molecules
  - acutelly ill newborn
  - (repeated) atack of long-term uncosciousness
  - failure to thrive
- Complex molecules
  - progressive CNS and musculature involvement
  - facial dysmorphy
  - organomegaly (liver, spleen, heart)

Abnormal urinary smell and color

- smell (small volatile molecules):
  - sweaty feet-isovalerate
  - maple syrup-branched ketoacids
  - boiled cabbage-methionine oxid
  - fish-trimethylamine
  - blackcurrant- organic acids
  - mouse-phenylacetate
- color
  - orange-urate
  - black upon oxidation-homogentisate
  - blue-indoxyl derivaties
  - green-4-OH-butyrate

Common labs in IEMs

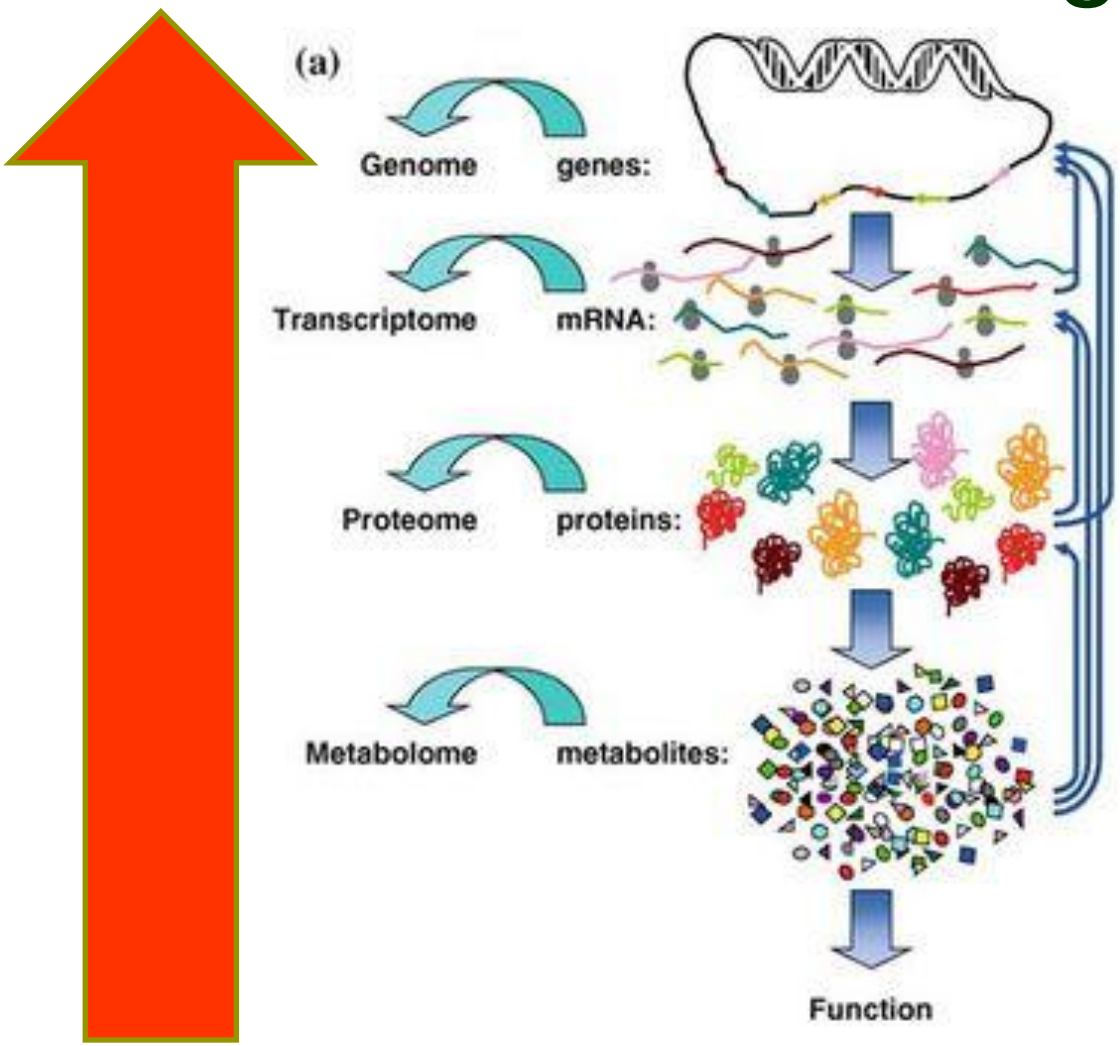
Blood

- glycemia
- cholesterol
- TG
- uric acid
- MAc
- hyperammonemia, RAlk
- ALT,AST
- CK
- anemia/pancytopenia

Urine

- ketone bodies
- uric acid
- crystaluria
- myoglobinuria

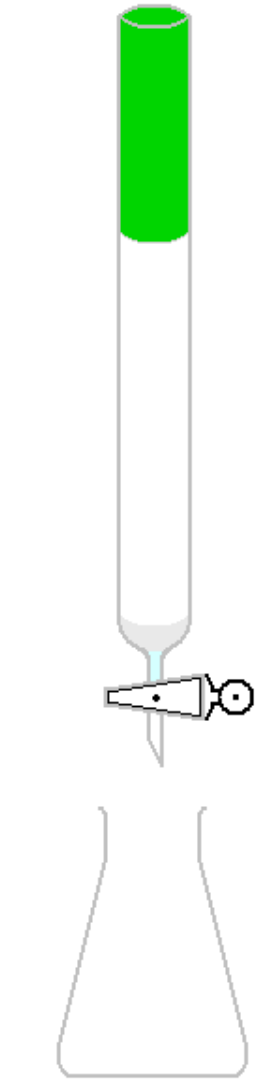
Selective screening

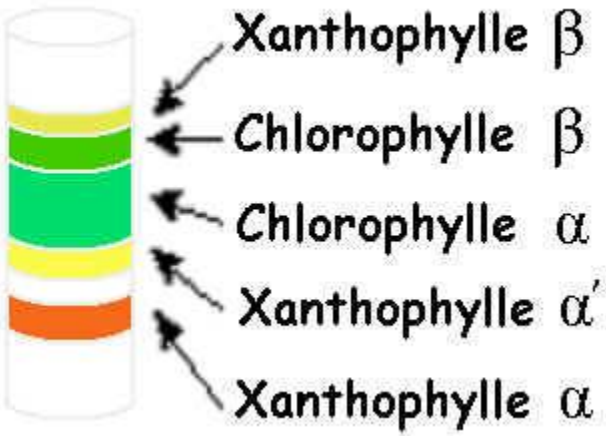


Single metabolite

Profile of metabolites= metabolomics

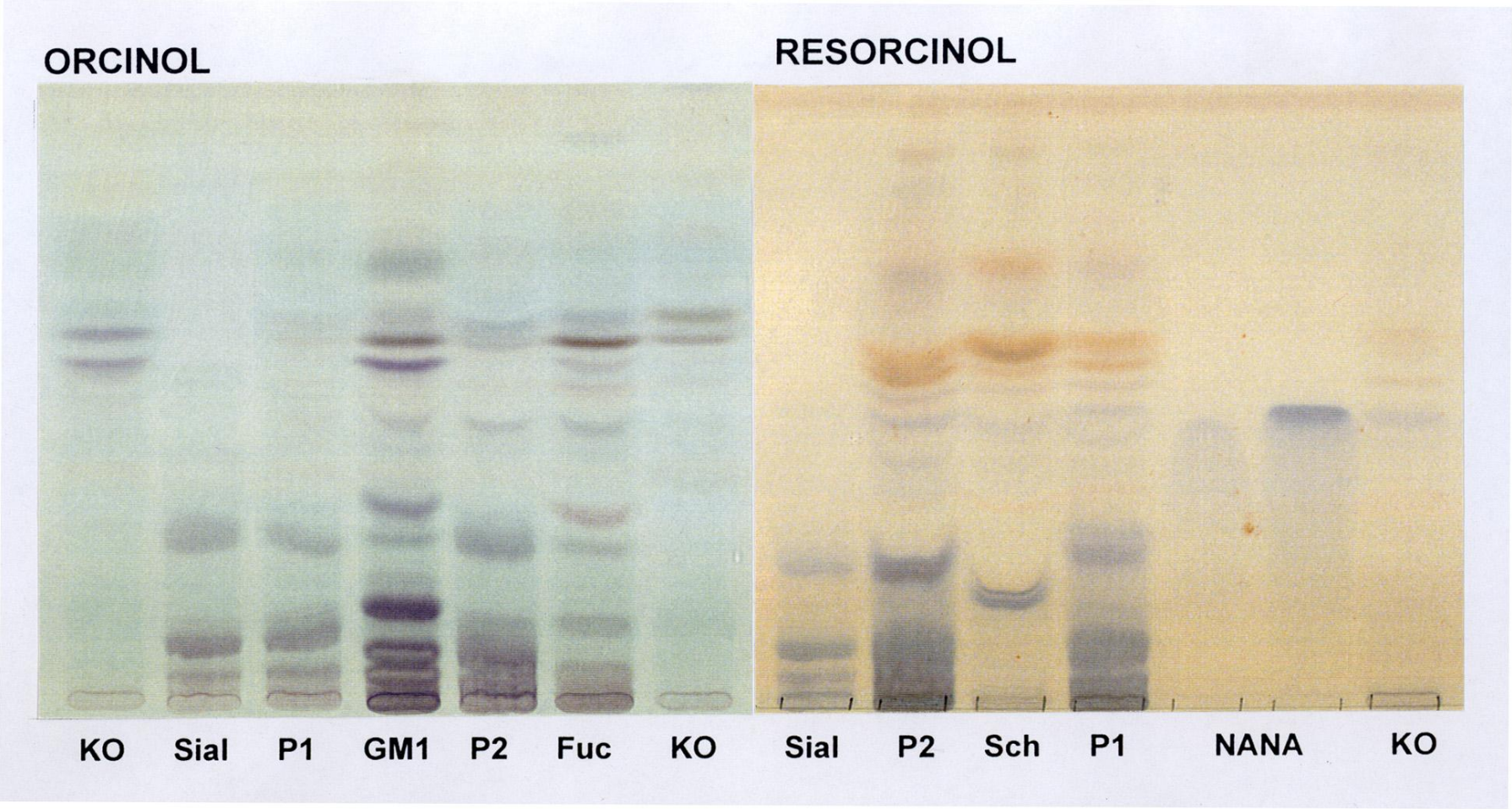
http://www.surlalunefairytales.com/illustrations/cinderella/images/hall_cinderella.jpg





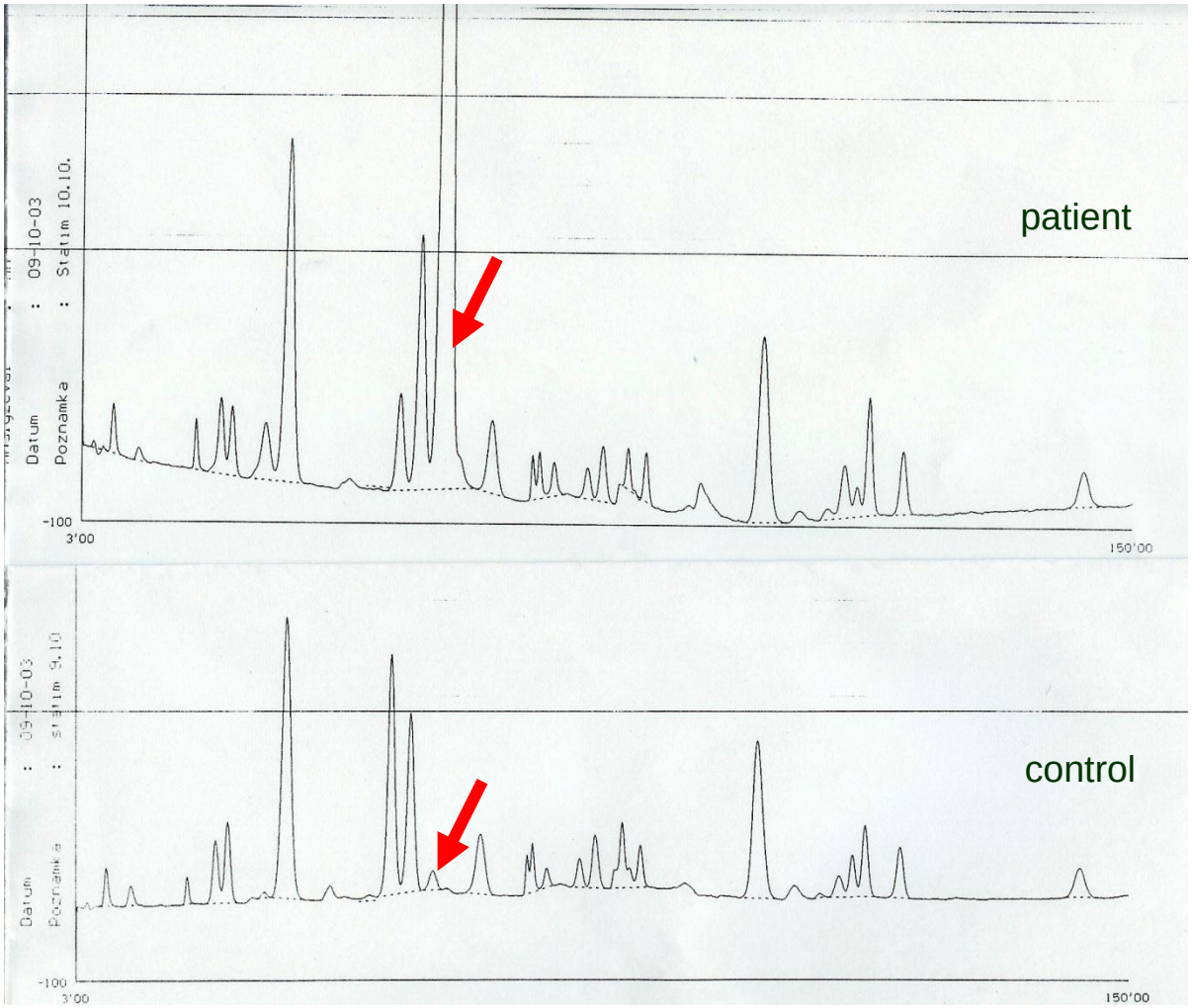
http://ustl1.univ-lille1.fr/chimie/html/Enseignement/ATE_web/chrom/Tswett_final.jpg

HPTLC- oligosaccharides in urine

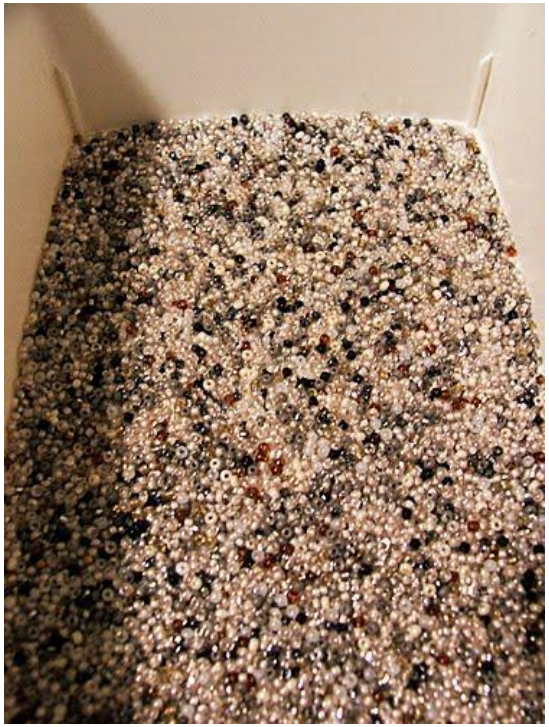


courtesy Dr.Ledvinová

AA- citrullinemia



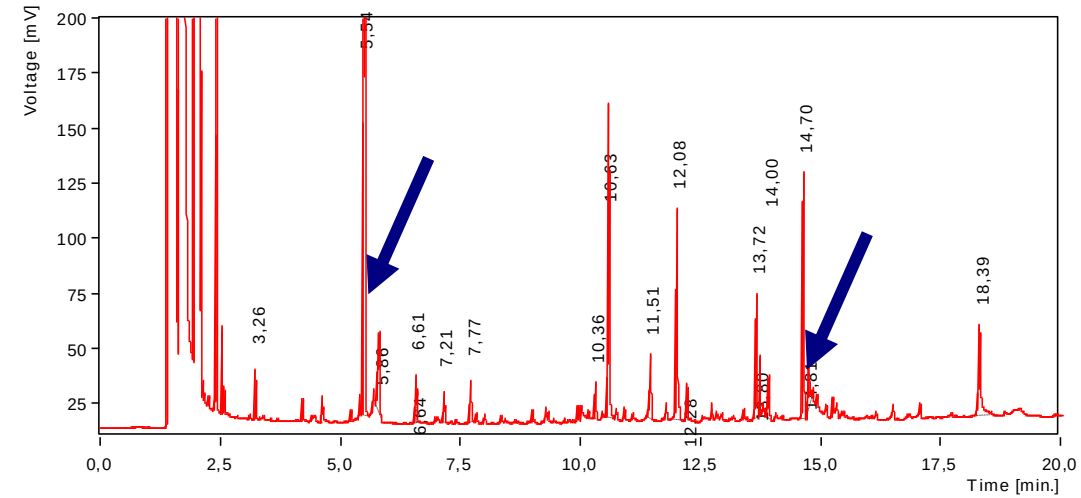
Complex mixtures-no easy detection

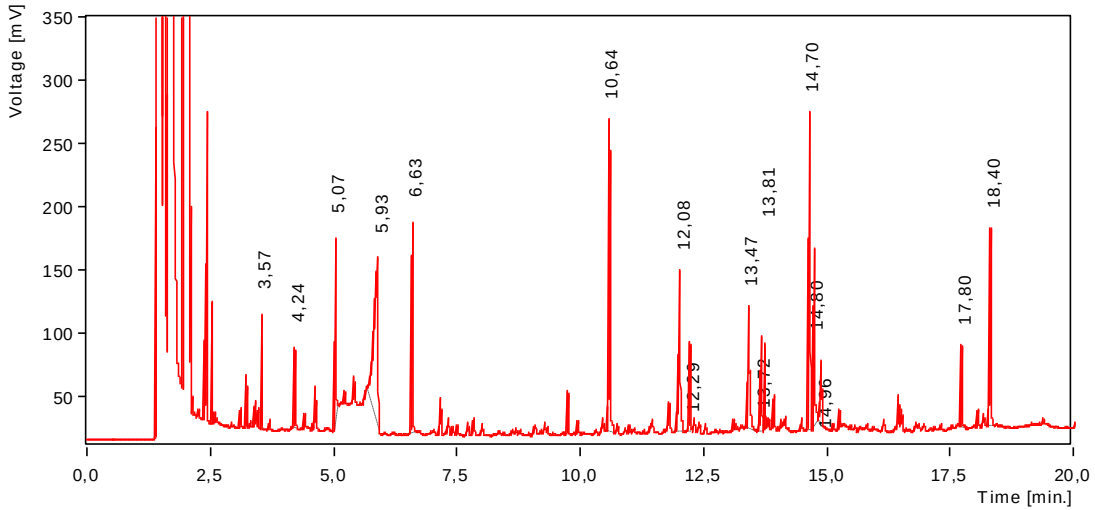


http://www.surlalunefairytales.com/illustrations/cinderella/images/hall_cinderella.jpg

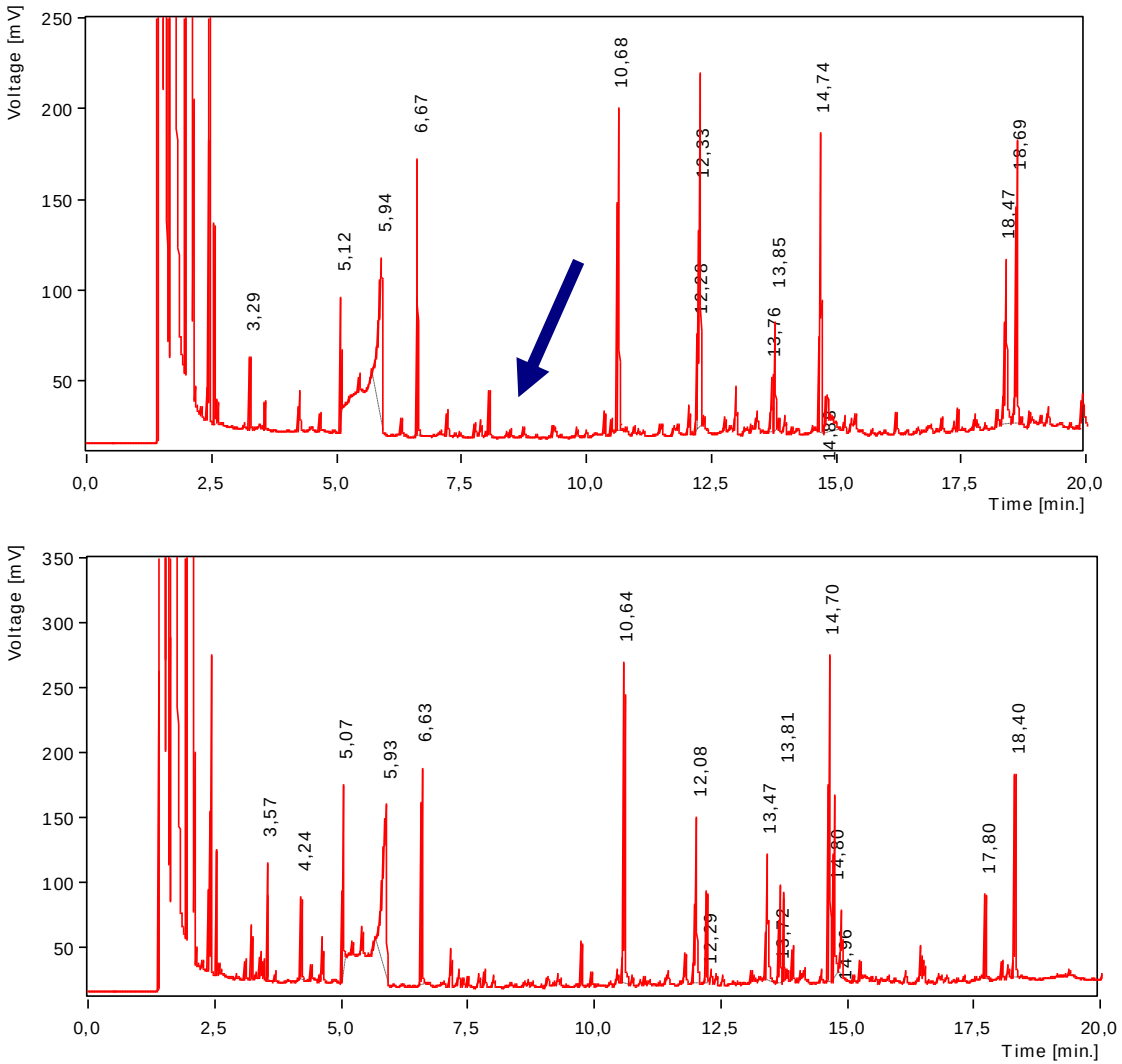
http://2.bp.blogspot.com/_ndSioEQ29iM/THGz8dhNaKI/AAAAAAAACwI/mbO0743ibKQ/s1600/Kym+Hepworth,+mixed+beads.jpg

GC-MS: methylmalonic aciduria

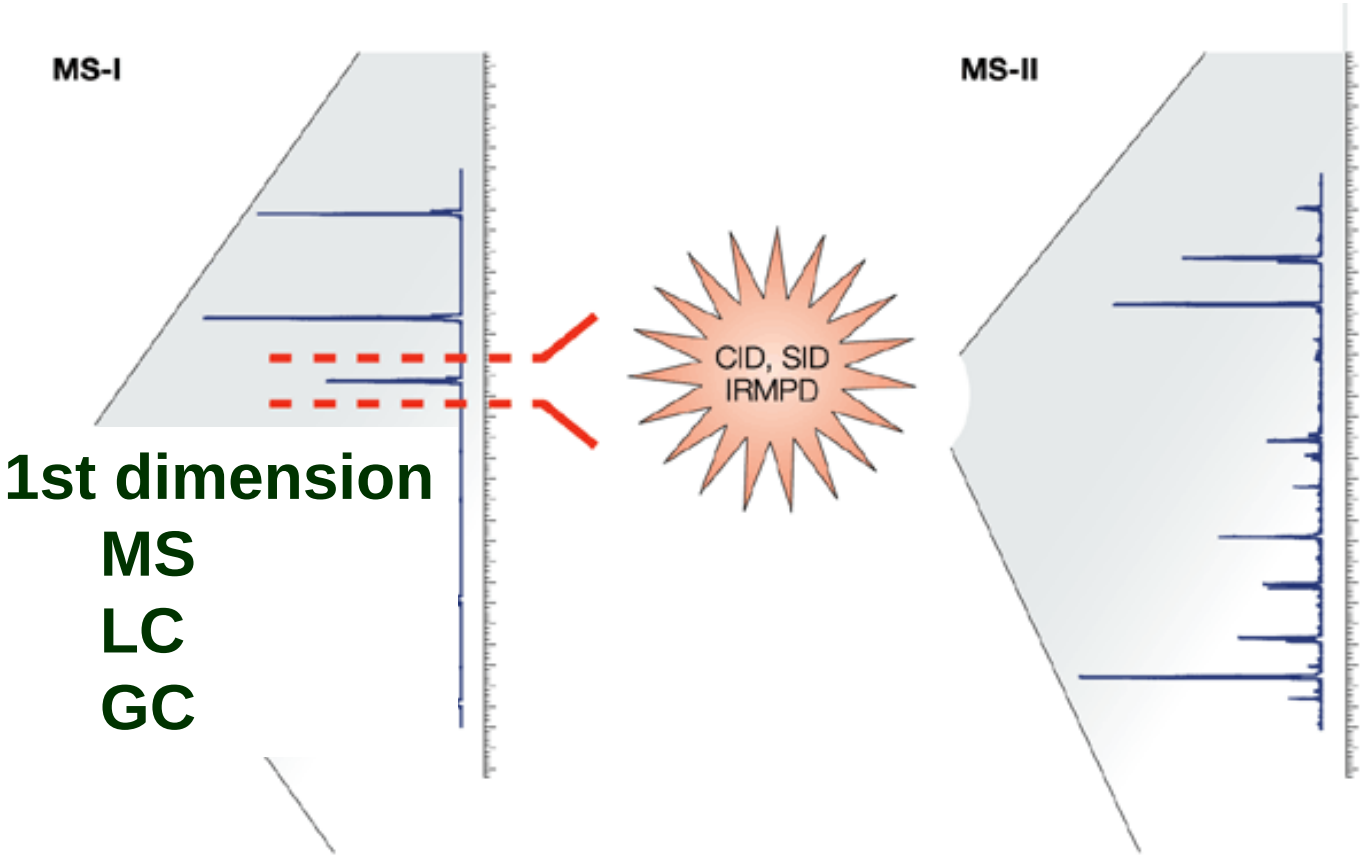




GC-MS: MCAD deficiency



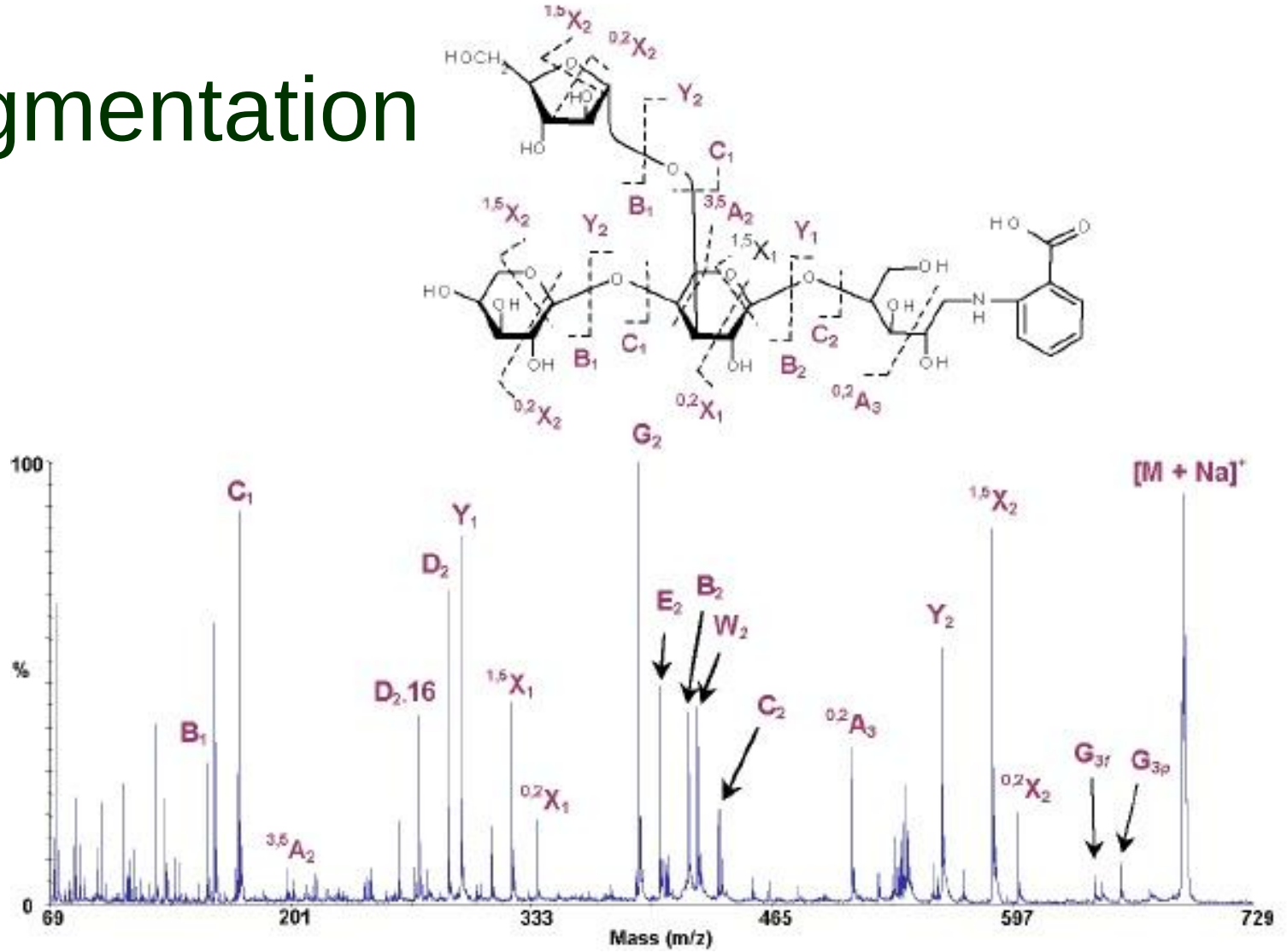
Mass spectrometry



www.nature.com/.../v2/n2/fig_tab/nrd1011_F5.html

Nature Reviews | Drug Discovery

Fragmentation



http://www.ch.cam.ac.uk/staff/pics/es1.jpg

Sensitivity

- Alkaptonuria: 1-5 g homogentisate /d
- Cystinuria: 1-5 g cystine /d

urine- liters

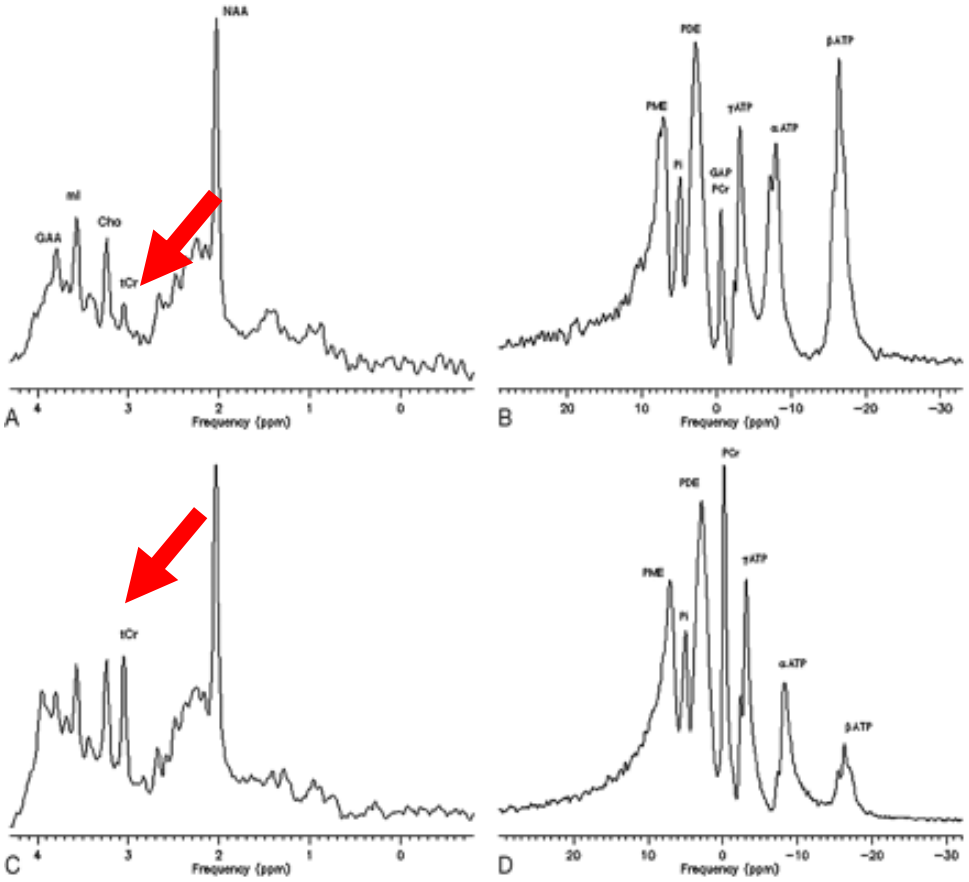
- PKU: 0.1 g Phe /l blood

0.2 – 1 ml serum

- MCAD: C8 acylcarnitin 0.0001 g / l blood

DBS punch 0.003 ml blood

In vivo metabolite measurement



before treatment

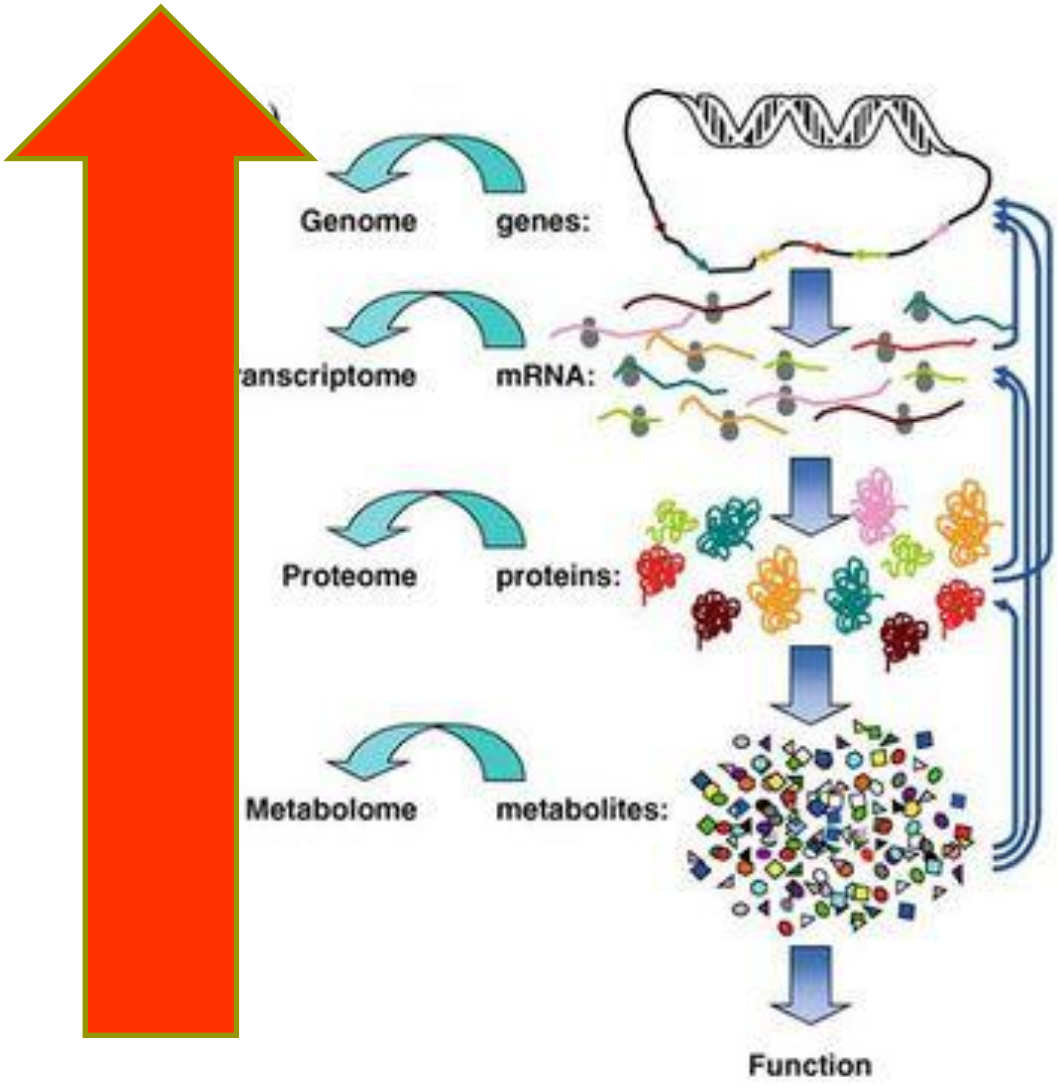
brain creatine deficiency (MRS)

after treatment

Metabolite analysis- IEMs

- specialized tests
- usually not available in routinely labs
- mostly profile analyses
- mostly chromatographic techniques, expensive equipment needed
- laborious methods, lack of kits and control material
- complex interpretation (e.g. organic acids) by specialist

Selective screening

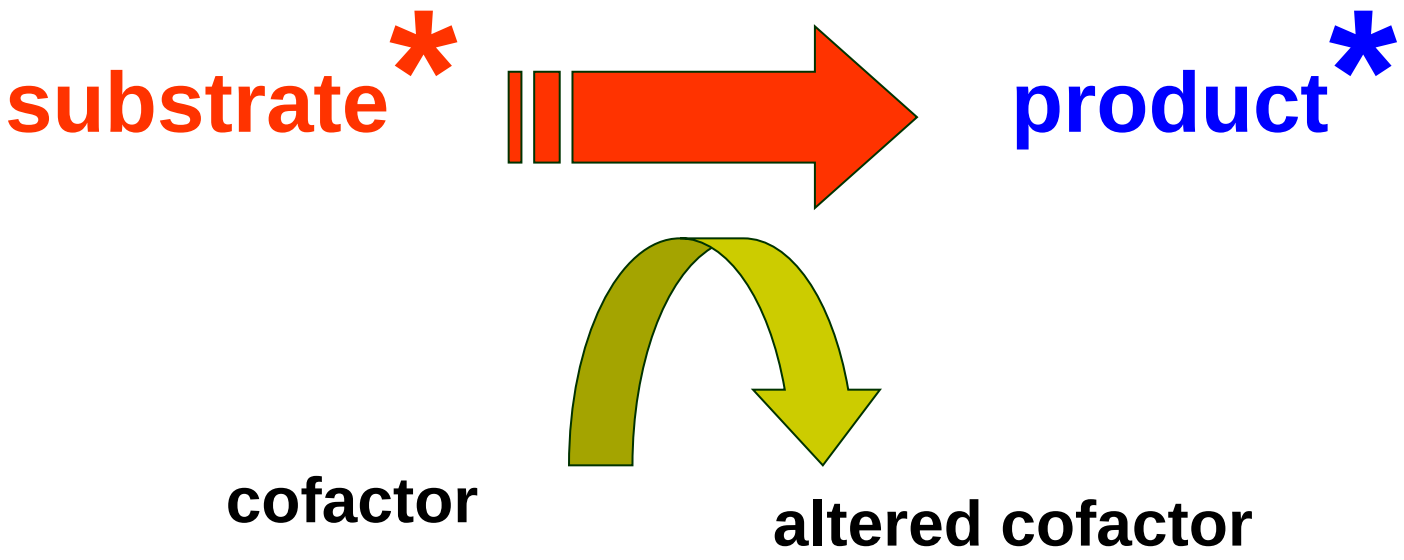


Enzyme activity
Transporter efficacy

Amount of enzyme ?
Use of ELISA?

Principles of enzyme assays

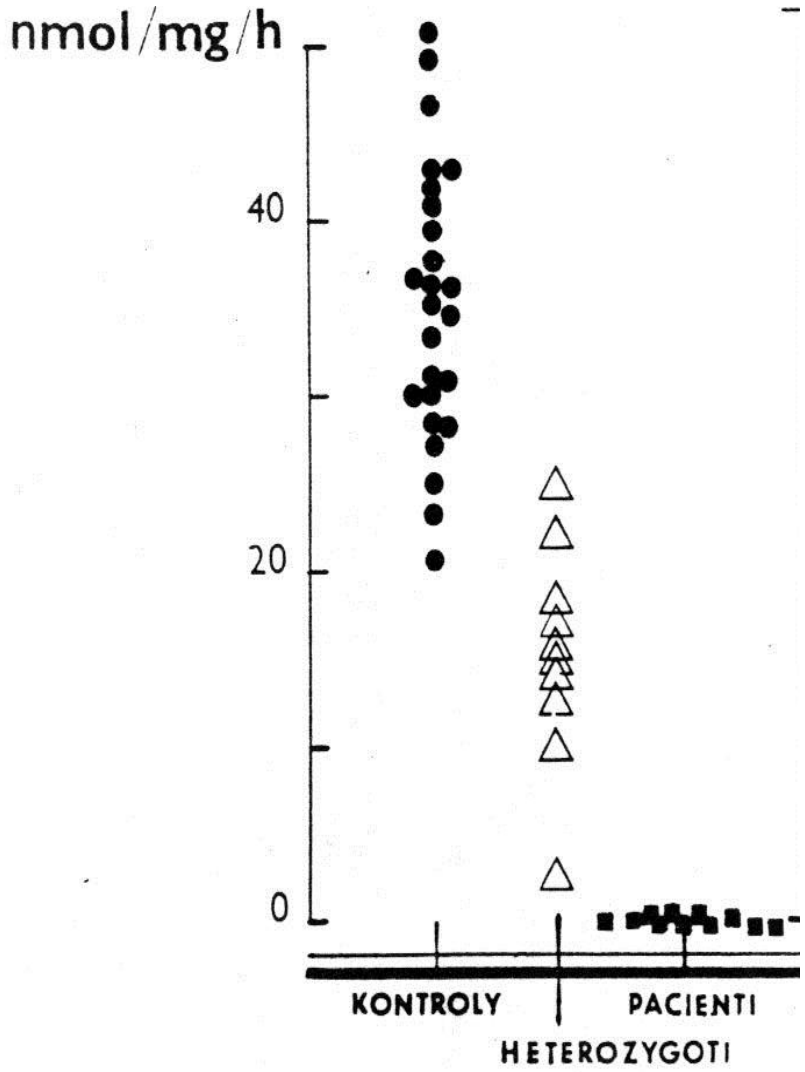
- **separation of substrate from product**
- **quantitation of change**



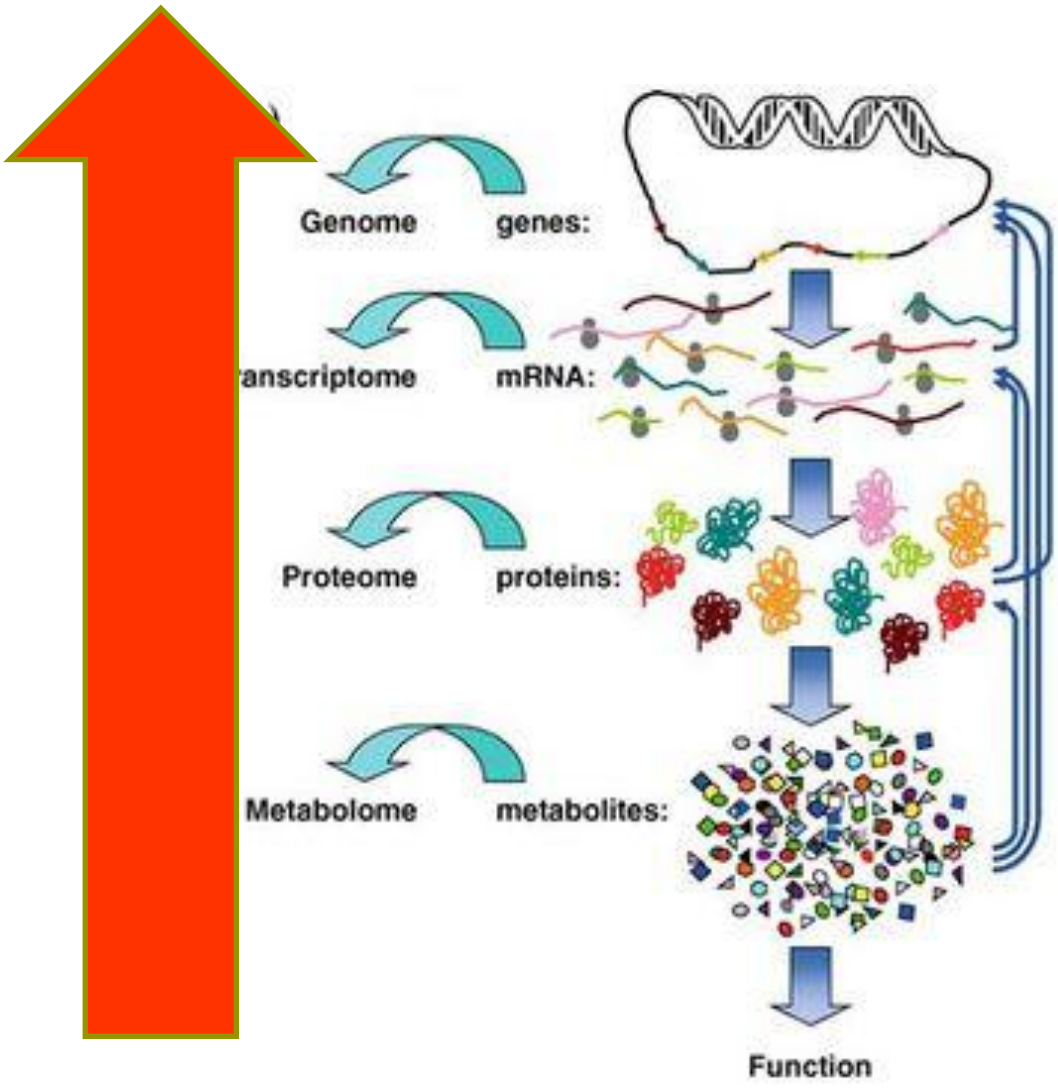
Enzyme assays in IEM diagnosis

- **Cells are usually needed**
  - **leukocytes, fibroblasts**
  - **chorion, amniocytes**
- **Fluorimetry and radiometry (photometry)**
- **LC-MS/MS methodology on rise**
- **Measured variables:**
  - **substrate/product concentration change**
  - **cofactor concentration change**

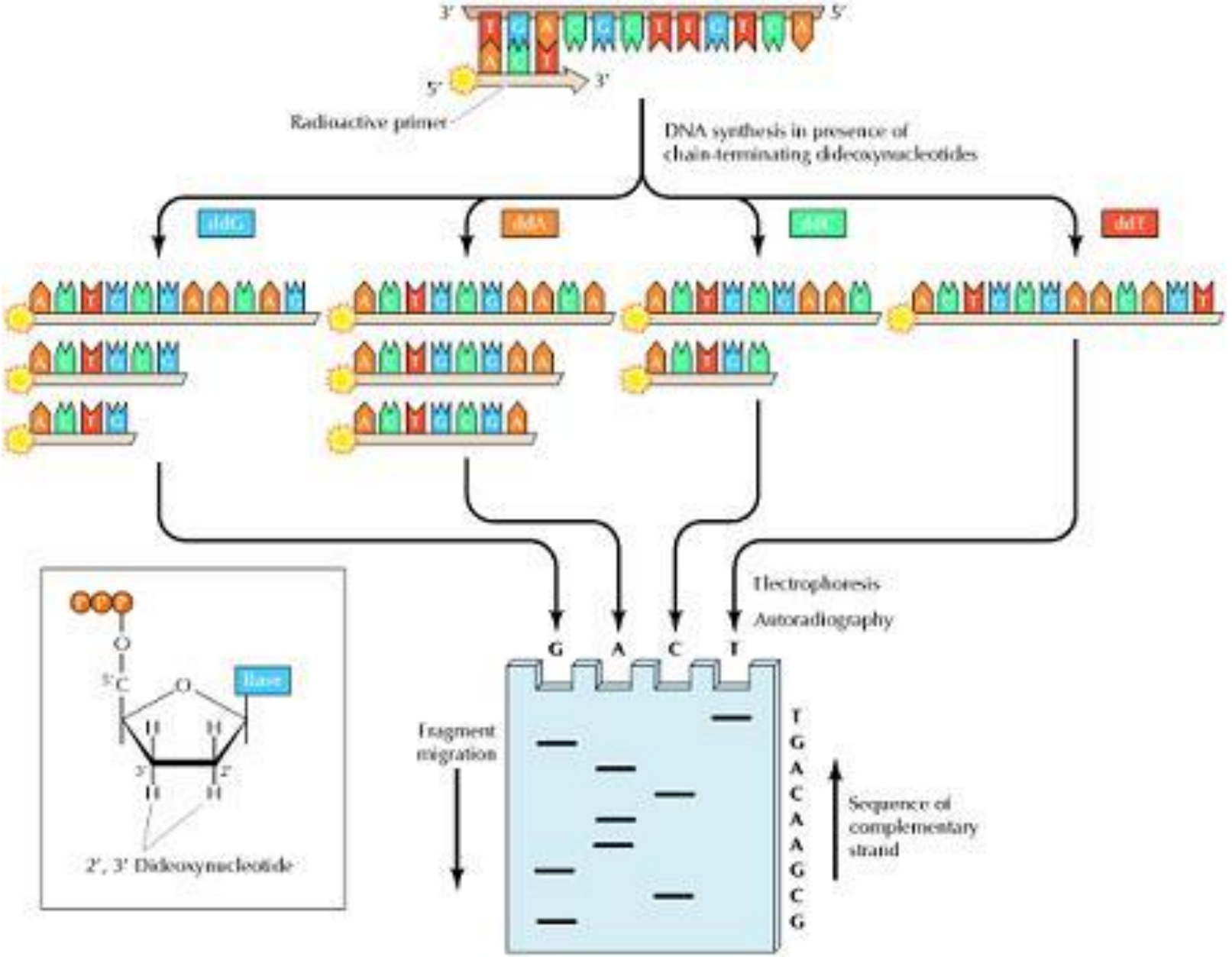
Typical results



Selective screening

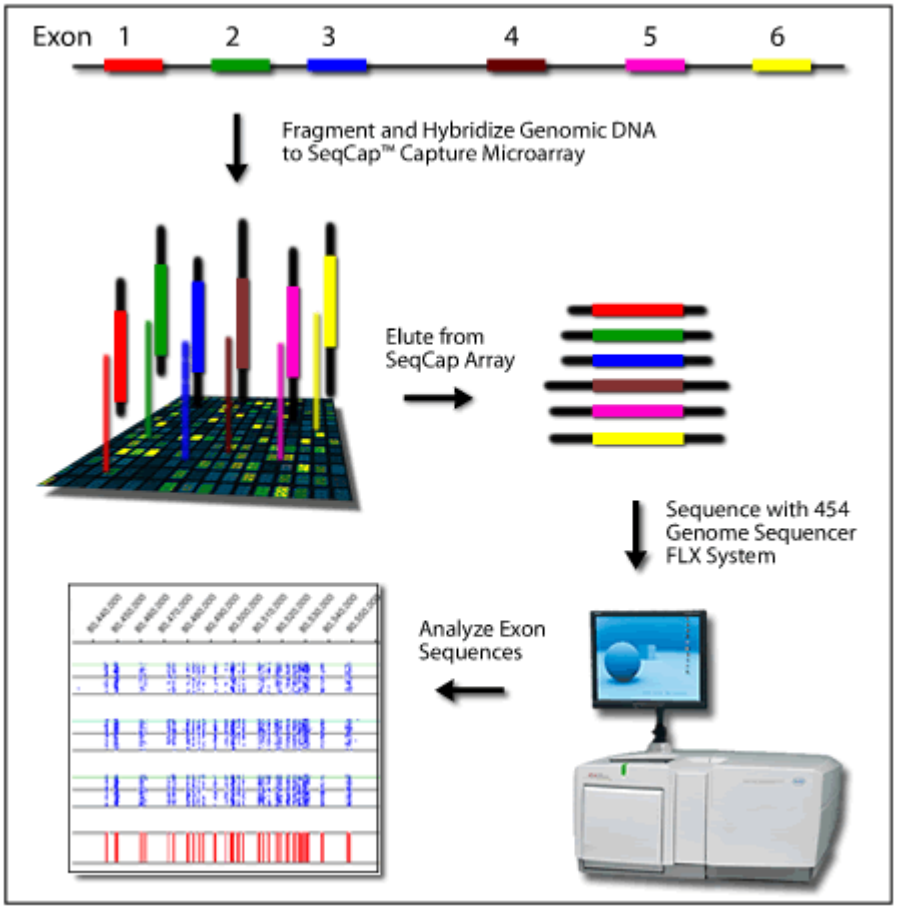


DNA/RNA analysis



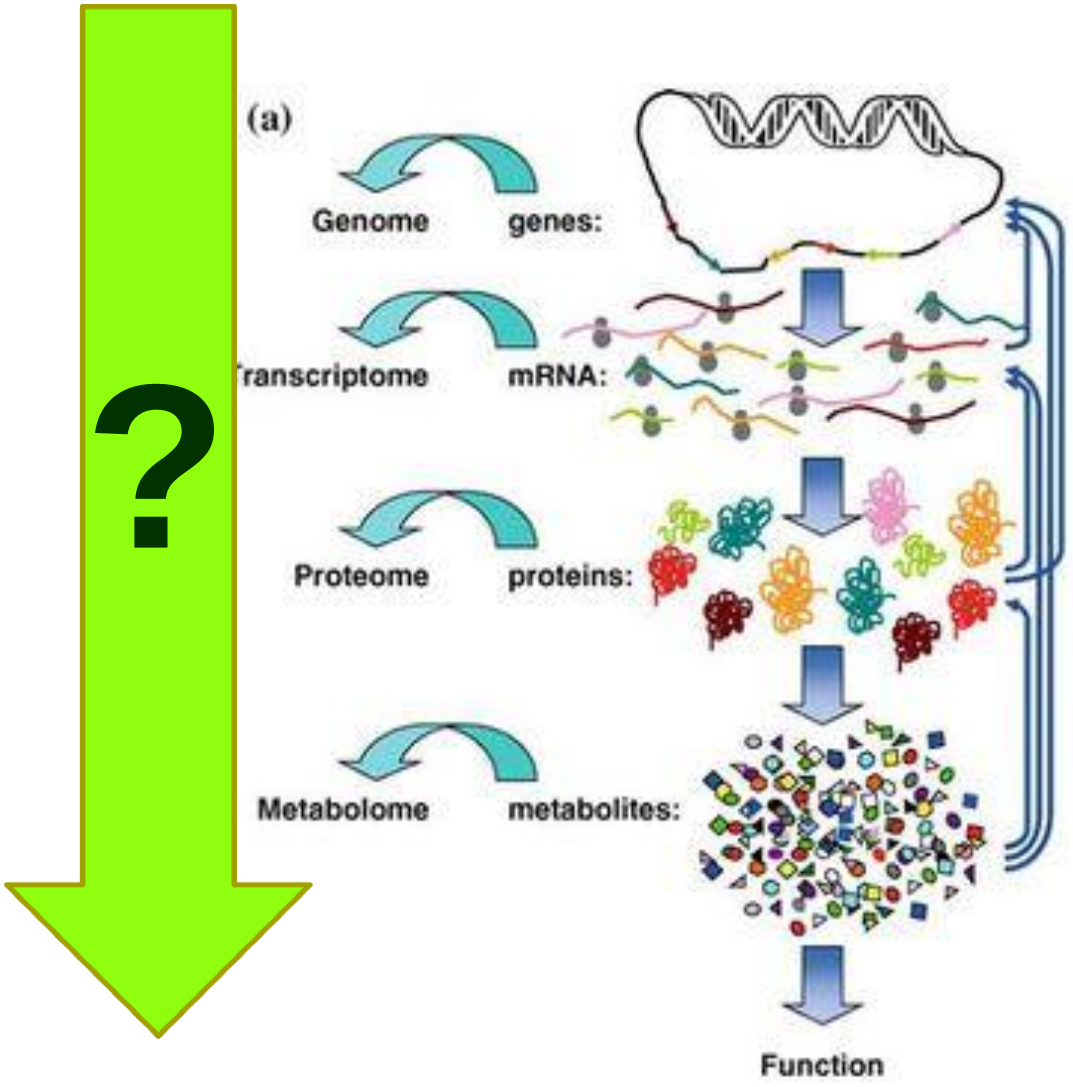
http://openwetware.org/images/6/61/DNA_sequencing.JPG

Next generation sequencing



- Exome sequencing is reality
- Price is sinking (target 1,000 USD/genome)
- Data analysis is the bottleneck!!!

Next generation sequencing?



Uncertainty about functional consequences of observed genetic variants

Filtering

- Data analysis based on variants filtering
- dbSNP, EVS, 1000genomes and in-house databases

Individual exome vs reference sequence

Aprox. 20k coding variants

9.5k nonsynonymous variants
10k synonymous variants
500 small InDels

150 loss of function variants
100 variants associated with genetic diseases
100-150 private variants
0-2 de novo germline mutation

Courtesy: Viktor Stránecký

Successful diagnosis of IEM

knowledgeable physician

+

availability of appropriate test

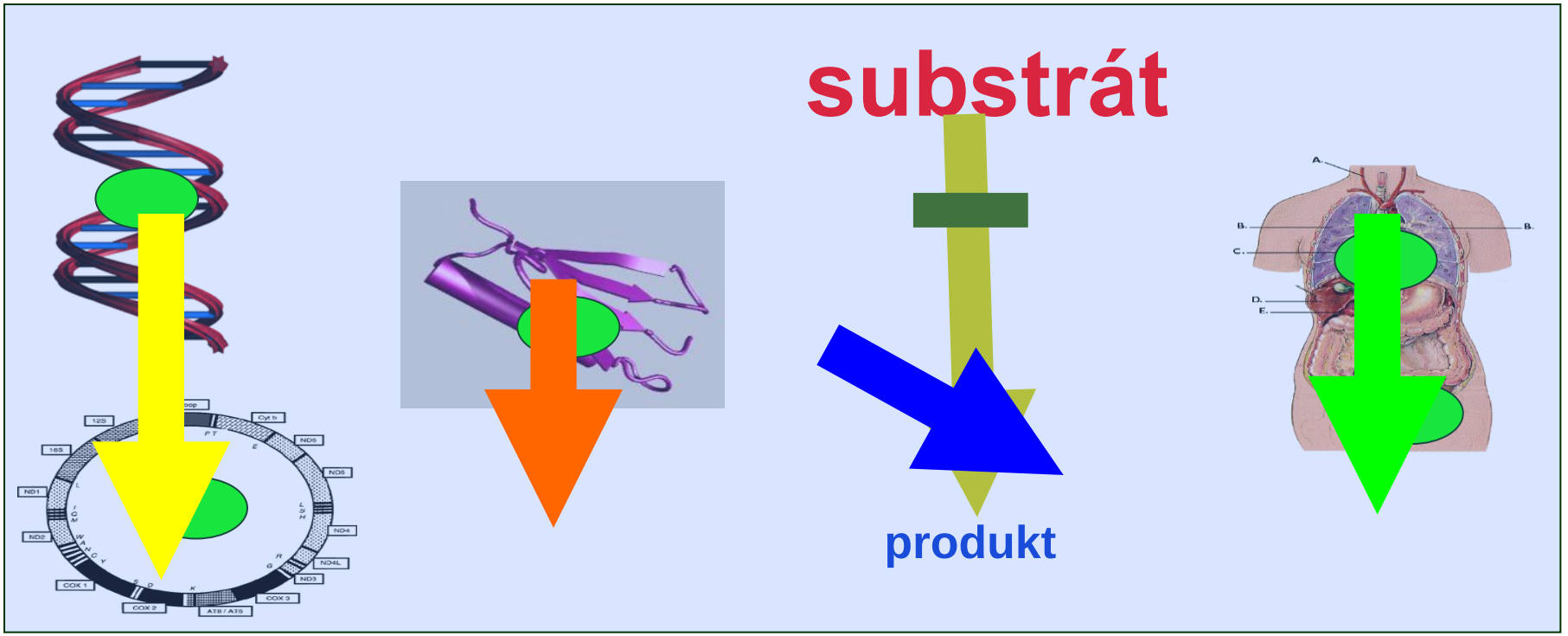
3.bp.blogspot.com/.../s320/physicianatdesk.jpg

http://unitedcaremedical.com/pharmacy_tech.gif

Structure

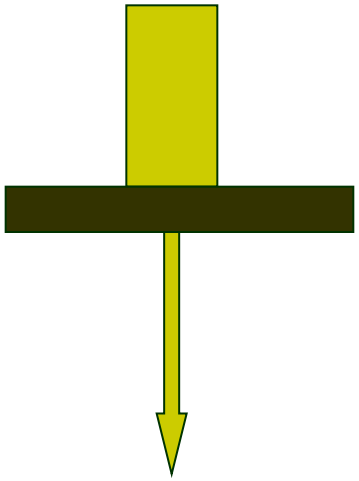
- **Diagnosis in general**
- **Neonatal screening**
- **Selective screening**
- **Treatment**

Treatment of IEMs



Patophysiology IEM

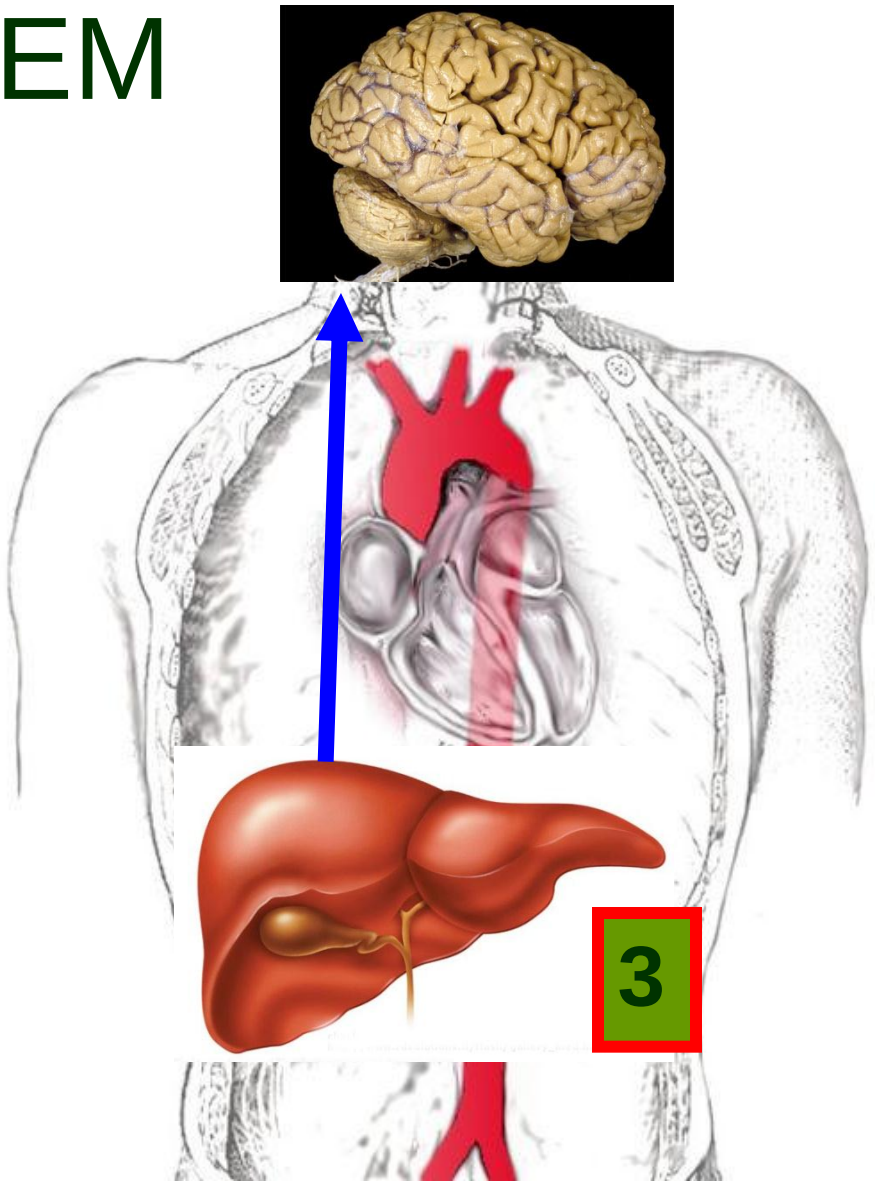
substrate



product

<1500 Da

>1500 Da

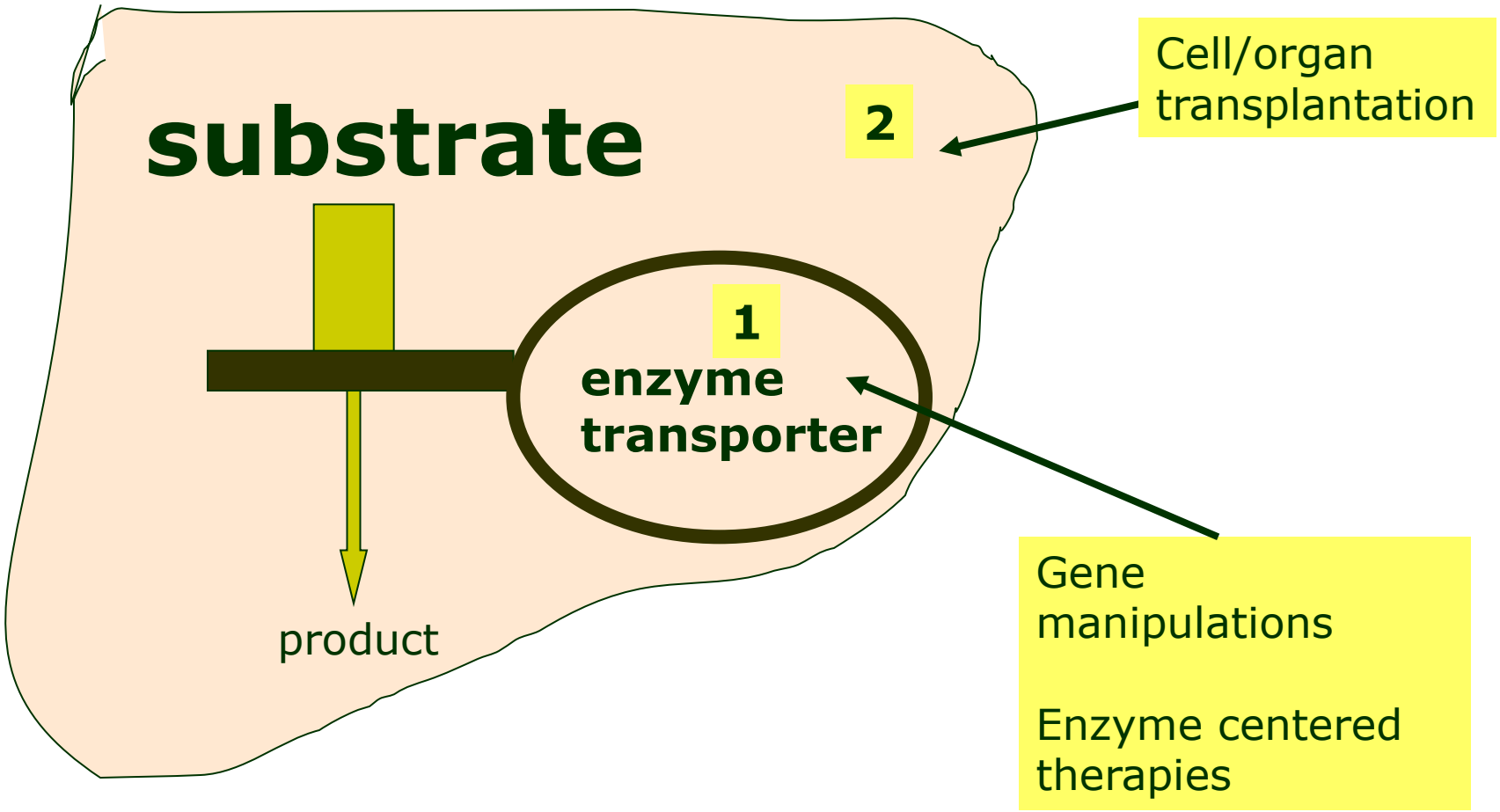


1

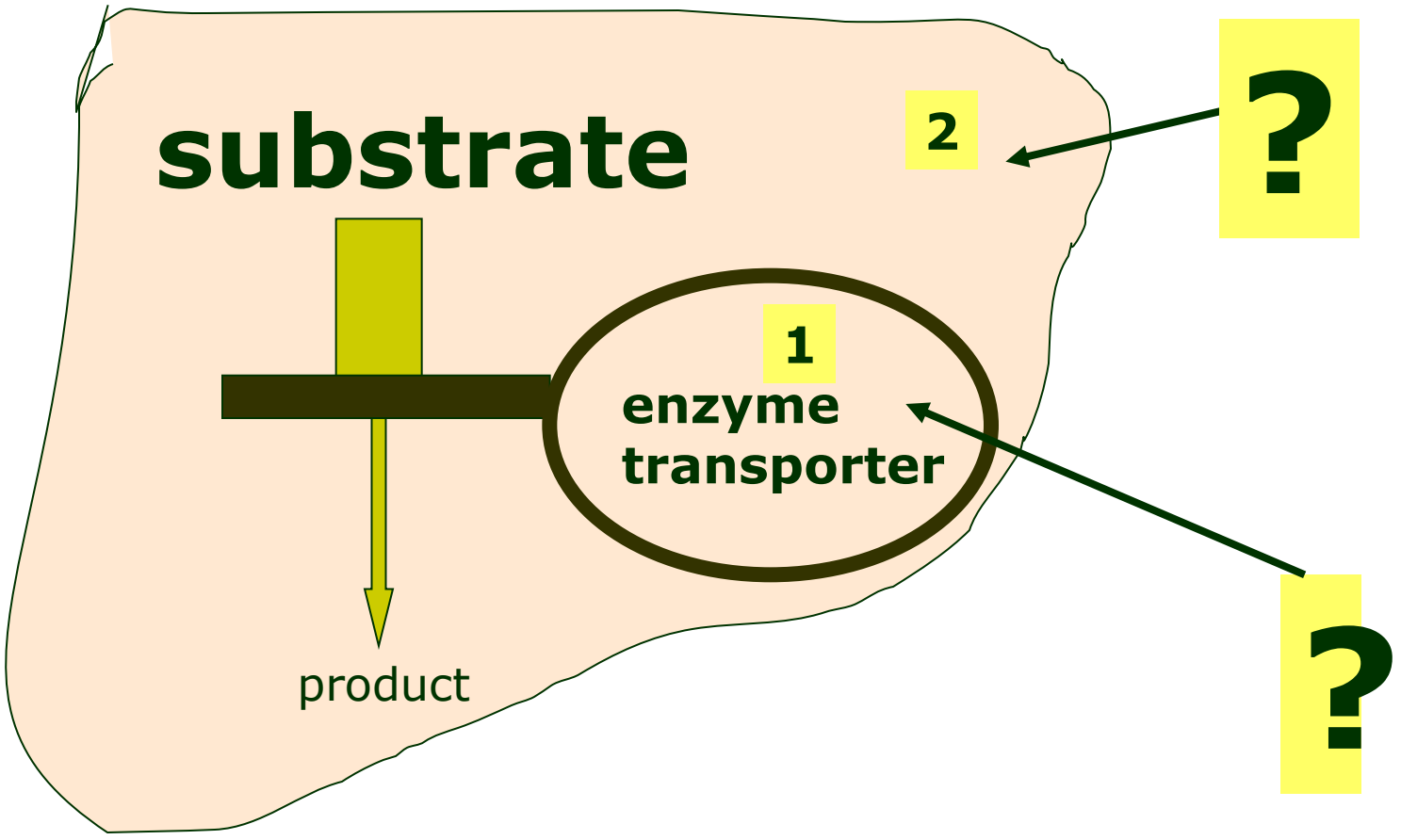
2

3

Treatment of primary defect



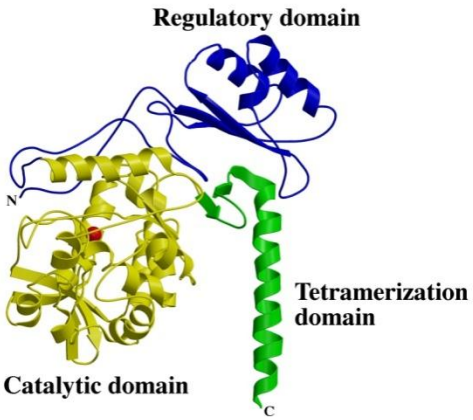
Treatment of primary defect



Manipulation of genes

- Gene replacement therapy
  - ADA deaminase- trial in 90th
  - Insertional mutagenesis with leukemia in some patients
  - Search for safe viral vectors
- Gene expression manipulation
  - Small molecules (PBA, VPA…)
  - Glucose in porphyrias-HO 1
- Correction of mutation
  - Premature stop codon readthrough
  - Antisense oligos for splicing defects

Enzyme centered therapies



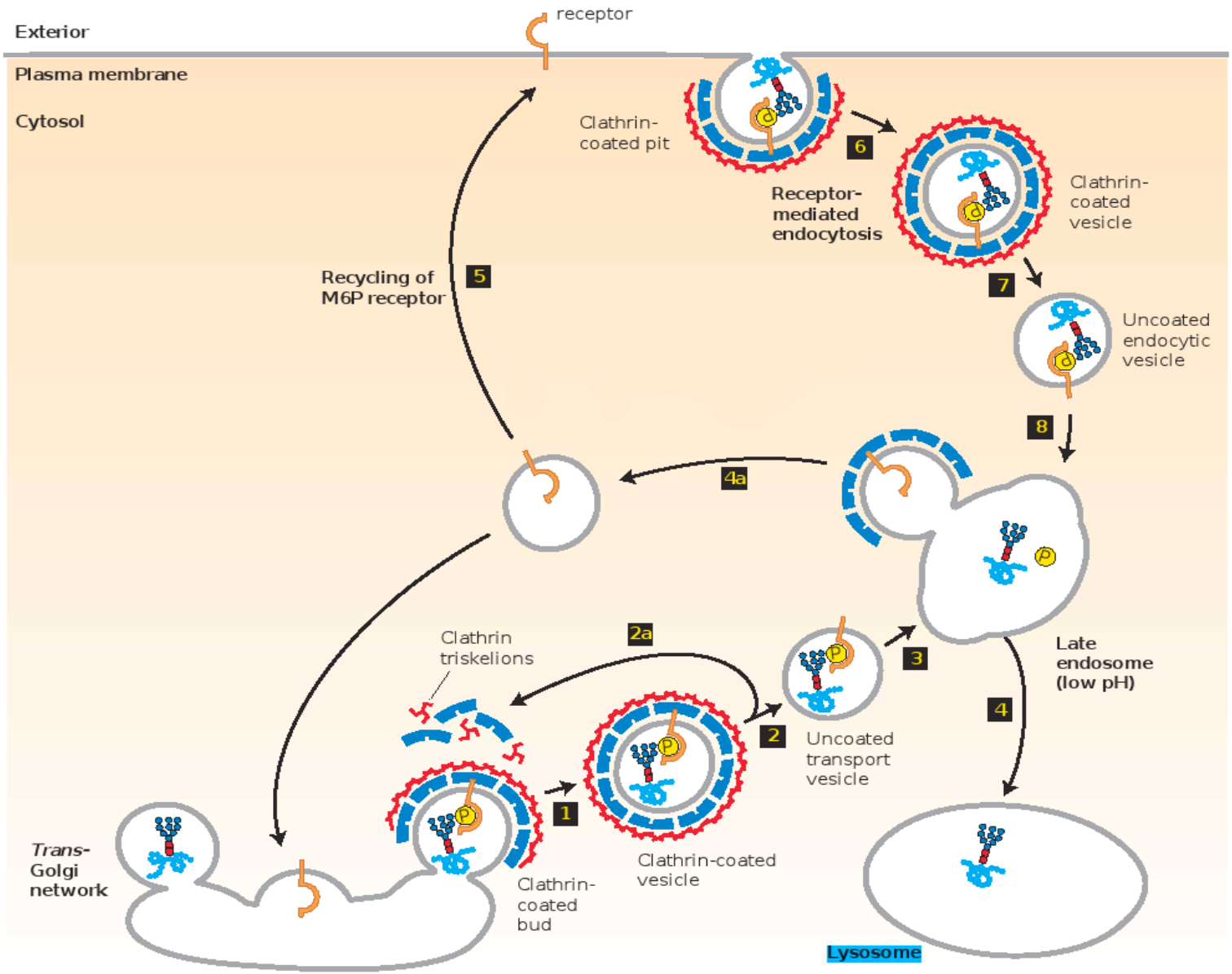
- Wild type enzyme replacement
  - Parenteral administration
  - Delivery to target organ/efficacy
  - Immune response
  - Cost and production
- Mutant enzyme stabilization
  - Natural ligands- cofactors
  - Artificial ligands-small molecules (pharmacological chaperones)
  - Promissing approach

Erlandsen H and Stevens RC, The Structural Basis of Phenylketonuria. *Mol Genet Metab.* 1999 Oct; 68(2):103-125.

Enzyme replacement therapy

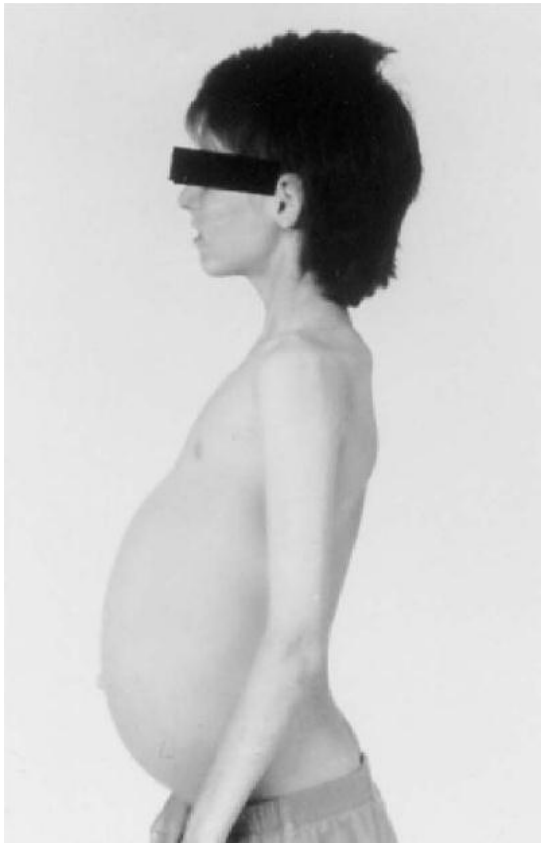
- Diseases treated (LSDs)
  - Gaucher disease (glucocerebrosidase)
  - Fabry disease (alpha galactosidase A)
  - Pompe disease (acid alpha glucosidase)
  - MPS I (alpha iduronidase)
  - MPS II (alpha iduronate sulfatase)
  - MPS VI (arylsulfatase B)
  - Niemann-Pick disease B (acid sphingomyelinase)
  - MPS IVA
  - Wollman disease (acid lipase)
- Production of recombinant enzymes

  Genzyme, TKT, Biomarin, Shire, Inotech


Exterior
receptor
Plasma membrane
Cytosol
Clathrin-coated pit
6
Receptor-mediated endocytosis
Clathrin-coated vesicle
7
Uncoated endocytic vesicle
8
Recycling of M6P receptor
5
4a
Late endosome (low pH)
3
2a
Clathrin triskelions
2
Uncoated transport vesicle
4
1
Clathrin-coated vesicle
Clathrin-coated bud
Trans-Golgi network
Lysosome

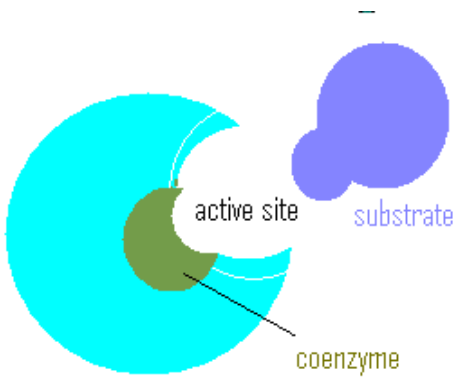
ERT in Gaucher disease

- Accumulation of glucosylceramide preferentially in cells of macrophage origin (Gaucher cells)
- Treatment: receptor-mediated endocytosis
  - mannose receptor (macrophages, endothelia, liver)
  - No transport into brain
  - macrophage targeted glucocerebrosidase (treatment with exoglycosidases)
- Enzyme isolated from human placentas X recombinant enzyme CHO cells X recombinant enzyme in carrots



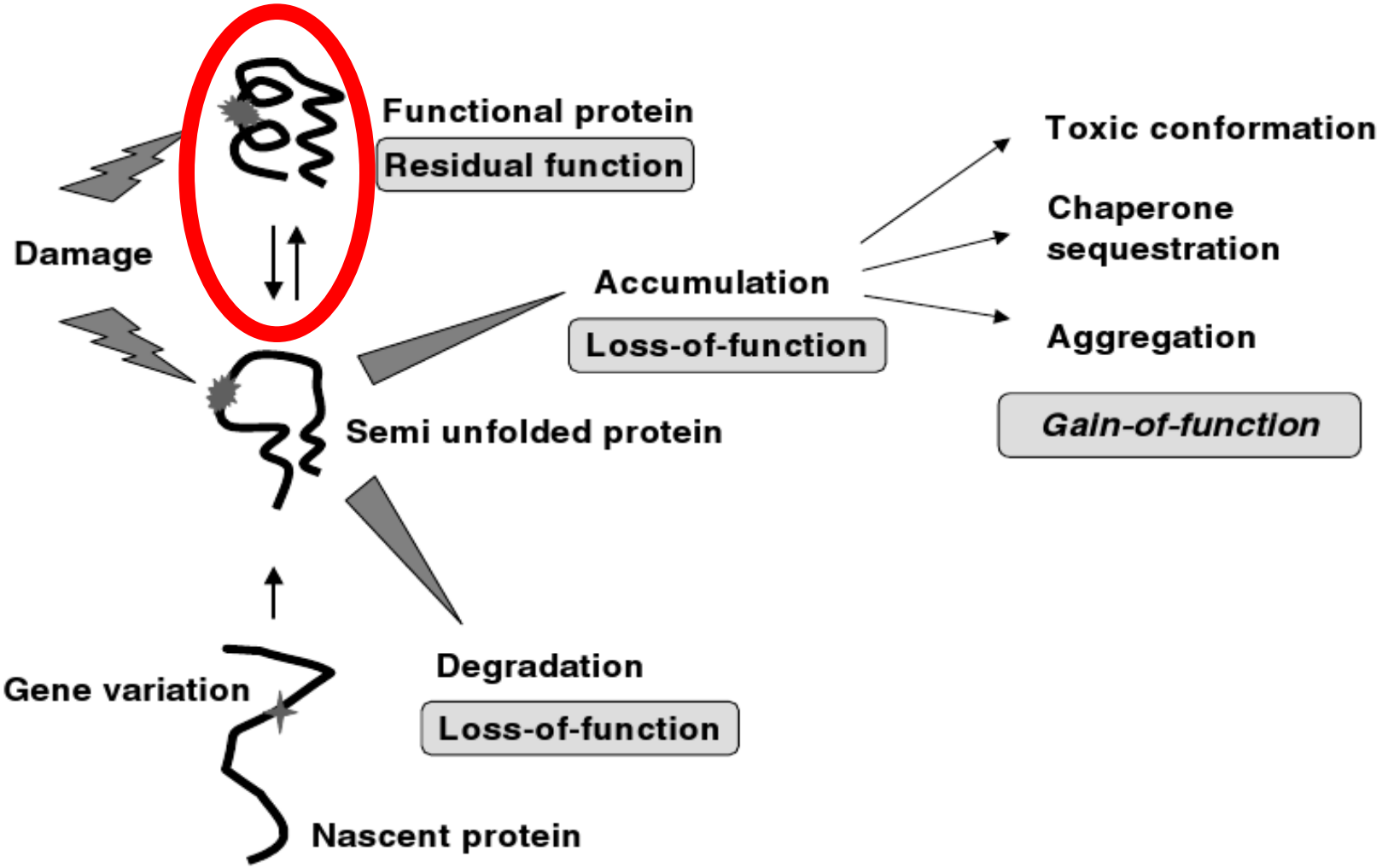
Natural cofactors

- Many vitamins=cofactor precursors
- Examples of use
  - BH4 in PKU
  - Pyridoxine in CBS deficiency, OAT deficiency
  - Riboflavine in ETF-DH deficiency
  - Vit.B12 in cblA and cblB
  - Ubiquinone in respiratory chain disorders
  - Mo-cofactor in combined XO/SO deficiency



http://upload.wikimedia.org/wikibooks/en/8/89/Coenzyme.GIF

Pharmacological chaperones



Gregersen N J Inherit Metab Dis (2006) 29:456–470

Pharmacological chaperones

- Promissing area of research
- Often competitive inhibitors of enzymes
- Efficacy to be improved
- M.Fabry, Gaucher - clinical testing

Table 3. PCT in LSDs

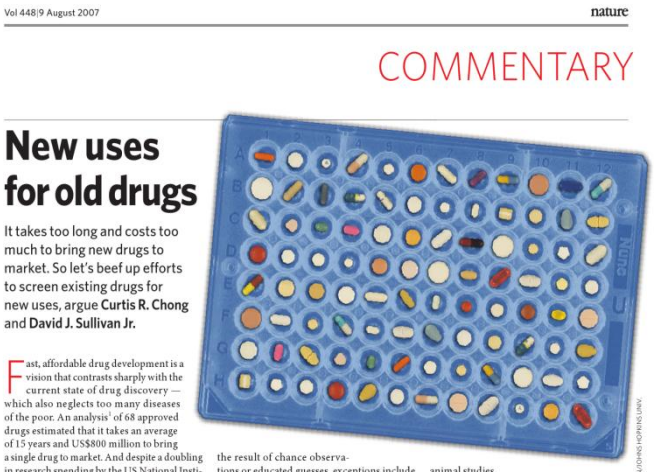
Disease	Enzyme deficiency	Chaperone(s)
Fabry disease	GLA	DGJ, galactose, 1-DGJ-lysine, galactostatin bisulphite
Gaucher disease	GBA	IFG, NB-DNJ, DNJ, NOV, 2,5-anhydro-2,5-imino-D-glucitol
G_{M1} gangliosidosis	GLB1	NOEV
G_{M2} gangliosidosis	HEXA	Pyrimethamine
Pompe disease	GAA	DNJ, NB-DNJ

NOV: *N*-octyl-beta-valienamine.

High-throughput screening (HTS) of small molecules

- Libraries – hundreds of thousands of compounds
- Libraries of approved drugs – e.g. NINDS etc.

- Assays
  - Interaction with protein: fluorescence, absorbance, melting curves
  - Functional consequences: enzyme activity, biological assay
- Automation, microtiter plates



Vol 448|9 August 2007 nature

COMMENTARY

New uses for old drugs

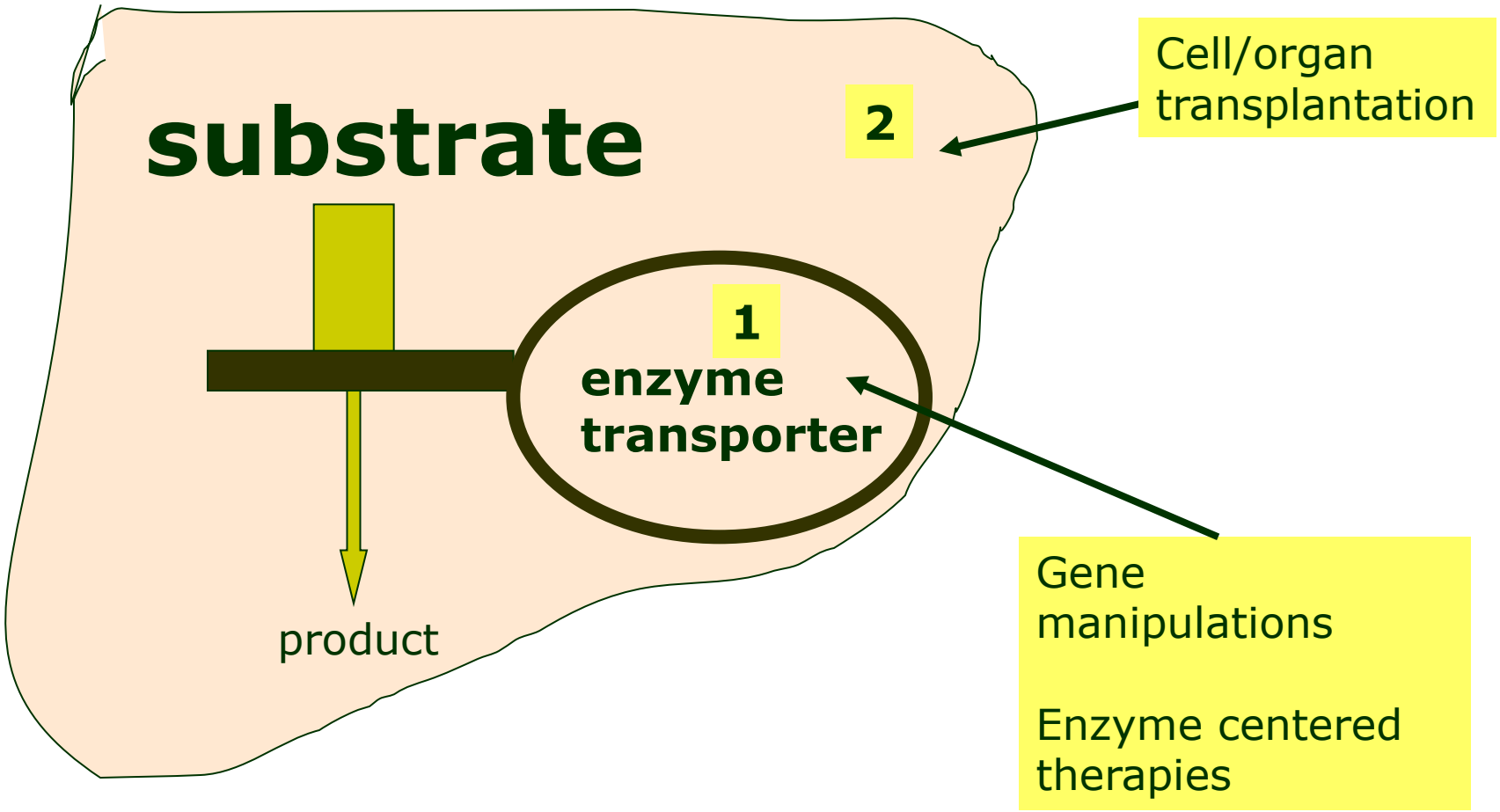
It takes too long and costs too much to bring new drugs to market. So let's beef up efforts to screen existing drugs for new uses, argue **Curtis R. Chong** and **David J. Sullivan Jr.**

Fast, affordable drug development is a vision that contrasts sharply with the current state of drug discovery — which also neglects too many diseases of the poor. An analysis[1] of 68 approved drugs estimated that it takes an average of 15 years and US$800 million to bring a single drug to market. And despite a doubling

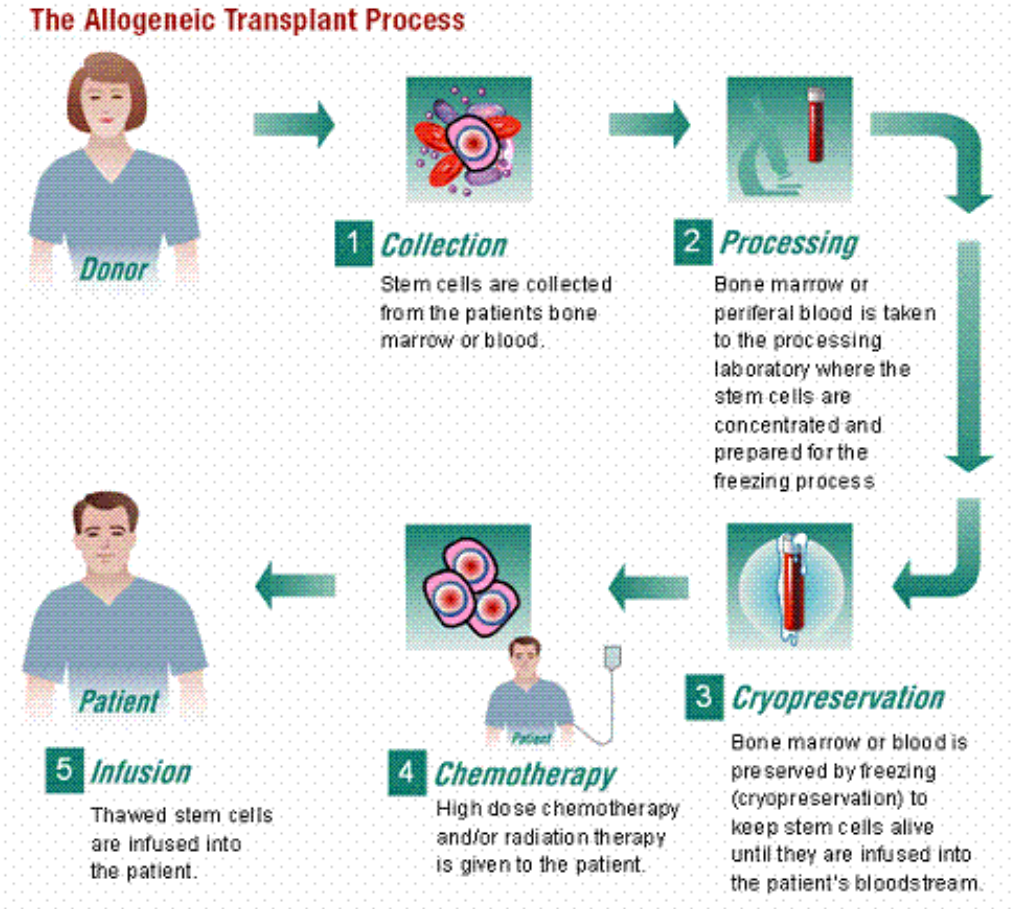
the result of chance observa-

http://bccg.burnham.org/HTS/HTSInstrumentation.aspx

Treatment of primary defect



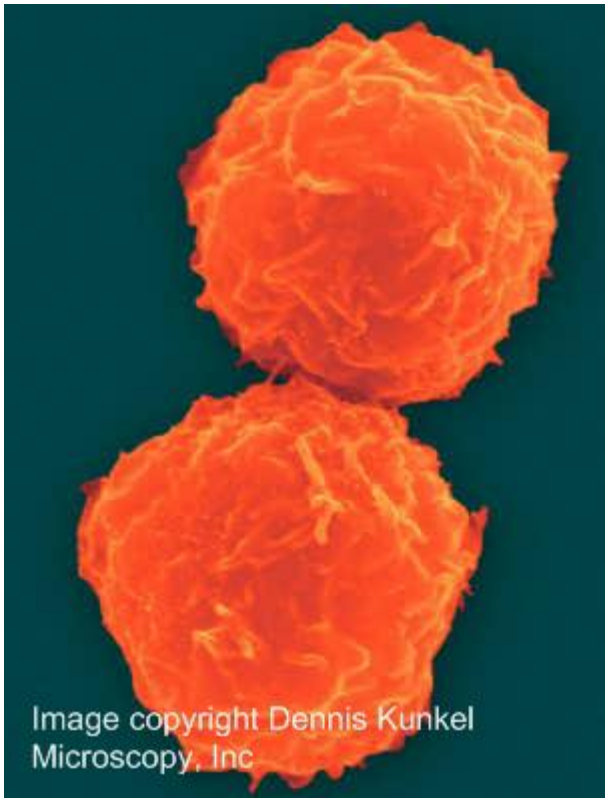
Transplant procedure



http://2.bp.blogspot.com/_uqBx13aymCE/TA9EBoLq_bI/AAAAAAAAB3w/aJ7yl-gU43o/s1600/Allogenic.gif

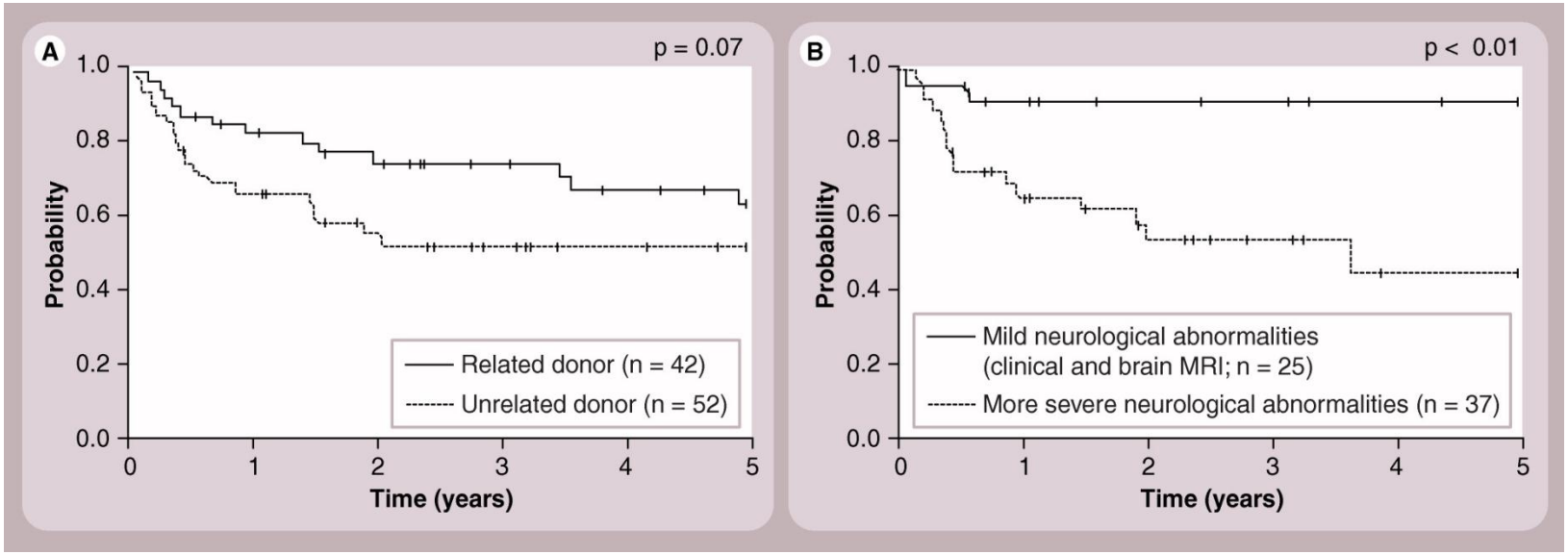
Haematopoietic stem cell transfer

- Source: bone marrow, cord blood
- Advantage: cells cross BBB
- Disadvantage: high mortality
- Lysosomal disorders
  - Mucopolysacharidosis I-good response
  - MPS III – no improvement of neurological progression
  - Other lysosomal disorders-promissing results in early treated patients with Krabbe disease
- Peroxisomal disorders
  - X-ALD



http://www.sflorg.com/sciencenews/images/imscn060807_01_01.jpg

Survival for cerebral X-linked adrenoleukodystrophy following hematopoietic cell transplantation



Expert Review of Neurotherapeutics 2008, Vol. 8, No. 9, Pages 1367-1379

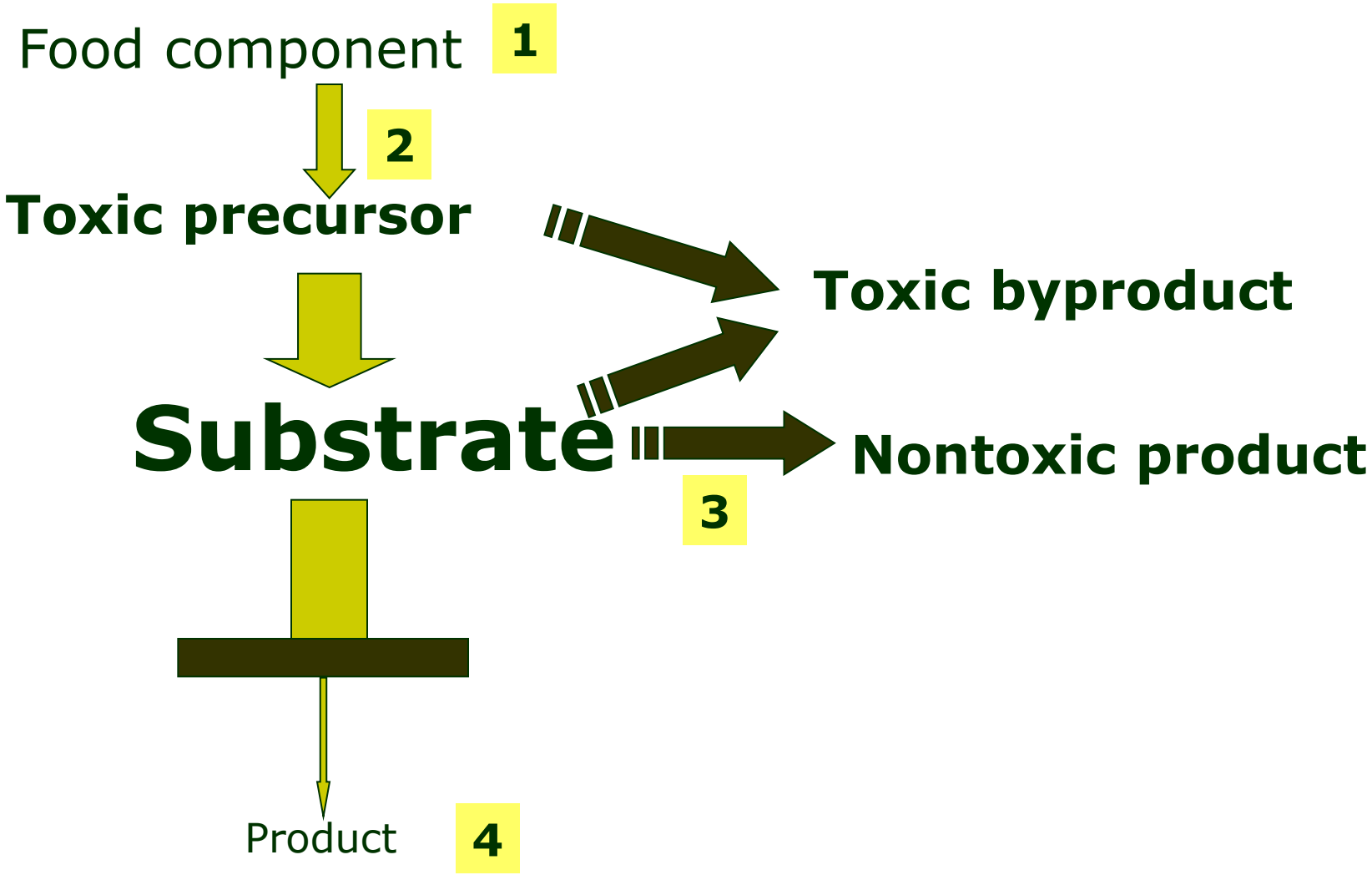
Expert Review of Neurotherapeutics 2008, Vol. 8, No. 9, Pages 1367-1379

Organ transplant

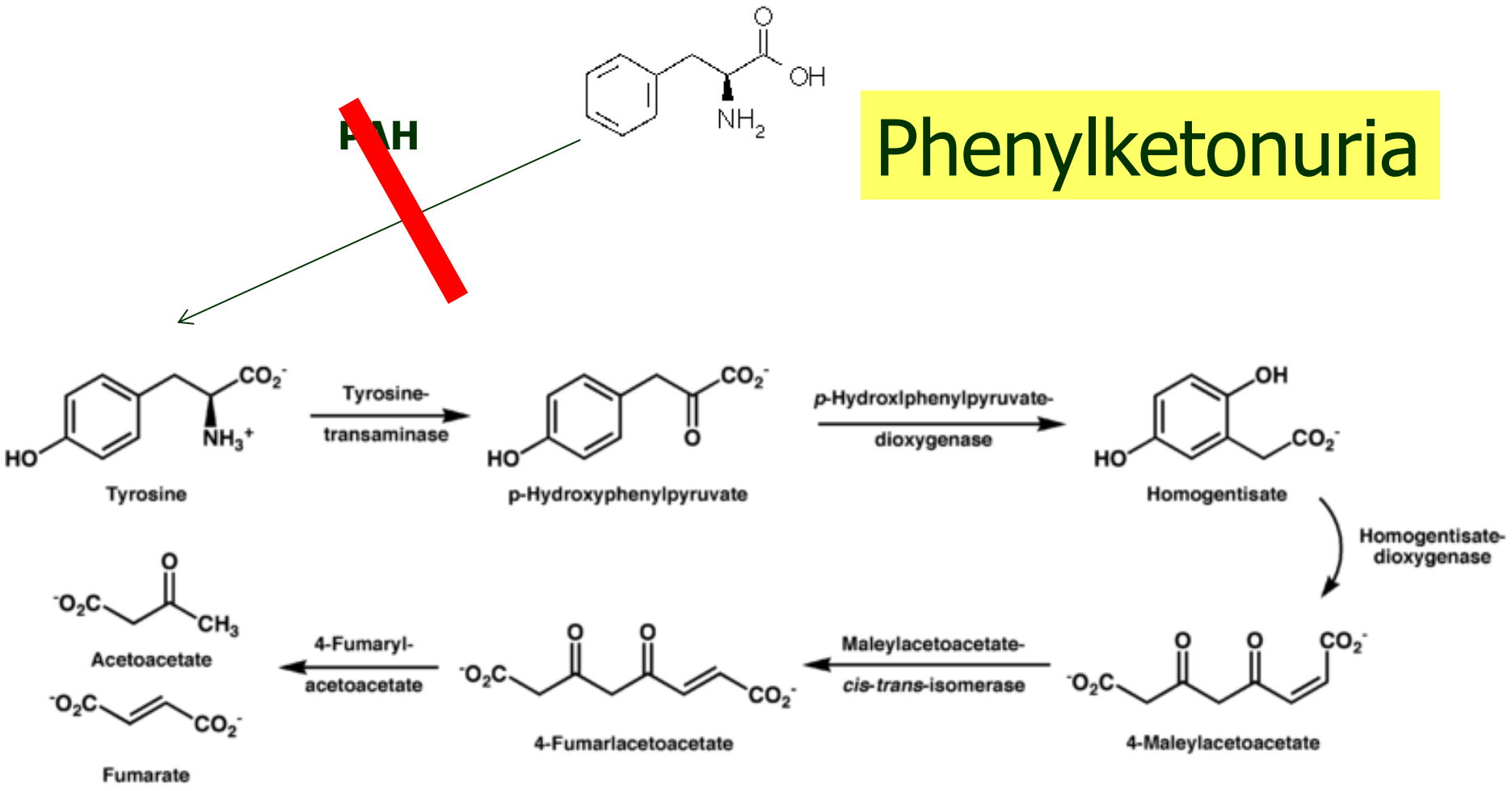
- **Liver transplant**
  - Glycogen storage disorders
  - Urea cycle disorders
  - Organic acidurias
- **Kidney transplant**
  - Cystinosis
  - Hyperoxaluria type I
  - Fabry disease
- **Combined liver and kidney transplant**
  - Organic acidurias (esp.MMA)
  - Hyperoxaluria type I
- **Heart transplantation**
  - Fabry disease

http://www.coldtruth.com/wp-content/uploads/2009/10/human-organ2.jpg

Treatment- pathway manipulation



Phenylketonuria



http://www.chemie.fu-berlin.de/chemistry/bio/aminoacid/gif/phe.gif

Jídla s vysokým obsahem Phe

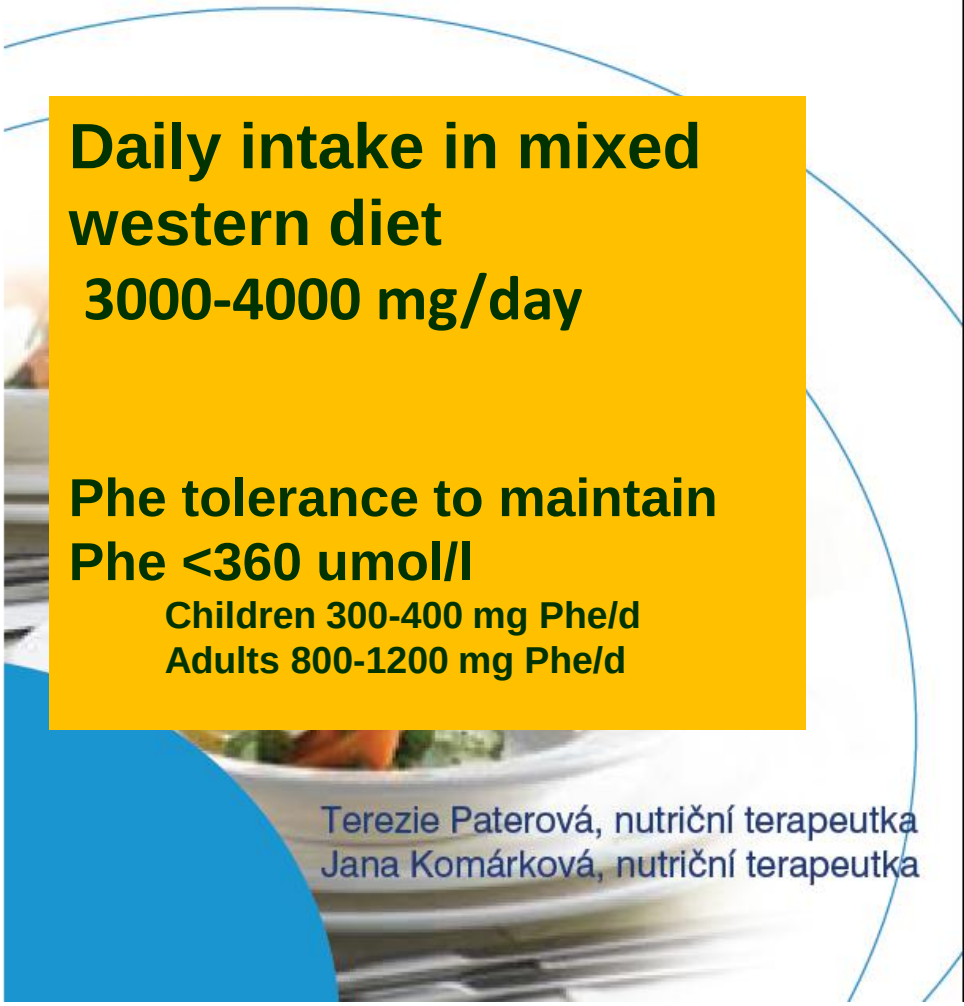
	množství	obsah Phe/mg
pstruh na grilu	200 g	1110
hranolky	100 g	
pečené kuřecí stehno	150 g	1300
vařené brambory	250 g	
smažený sýr Eidam	140 g	1900
hranolky	100 g	
tatarská omáčka	25 g	
smažený vepřový řízek	110 g	1170
vařené brambory	250 g	
špagety milánské/boloňské (se sýrem)	1 porce 330 g	1320

Hodnoty jsou orientační (průměrné), nikdy nelze určit přesnou hodnotu jídel z důvodu rozdílných receptur v jednotlivých restauračních zařízeních.

Vydáno za podpory firmy SHS, Na Pankráci 30, 140 21 Praha 4, www.shs-pku.cz

Národní sdružení PKU a jiných DMP vydává

Miniprůvodce jídelním lístkem s hodnotami Phe

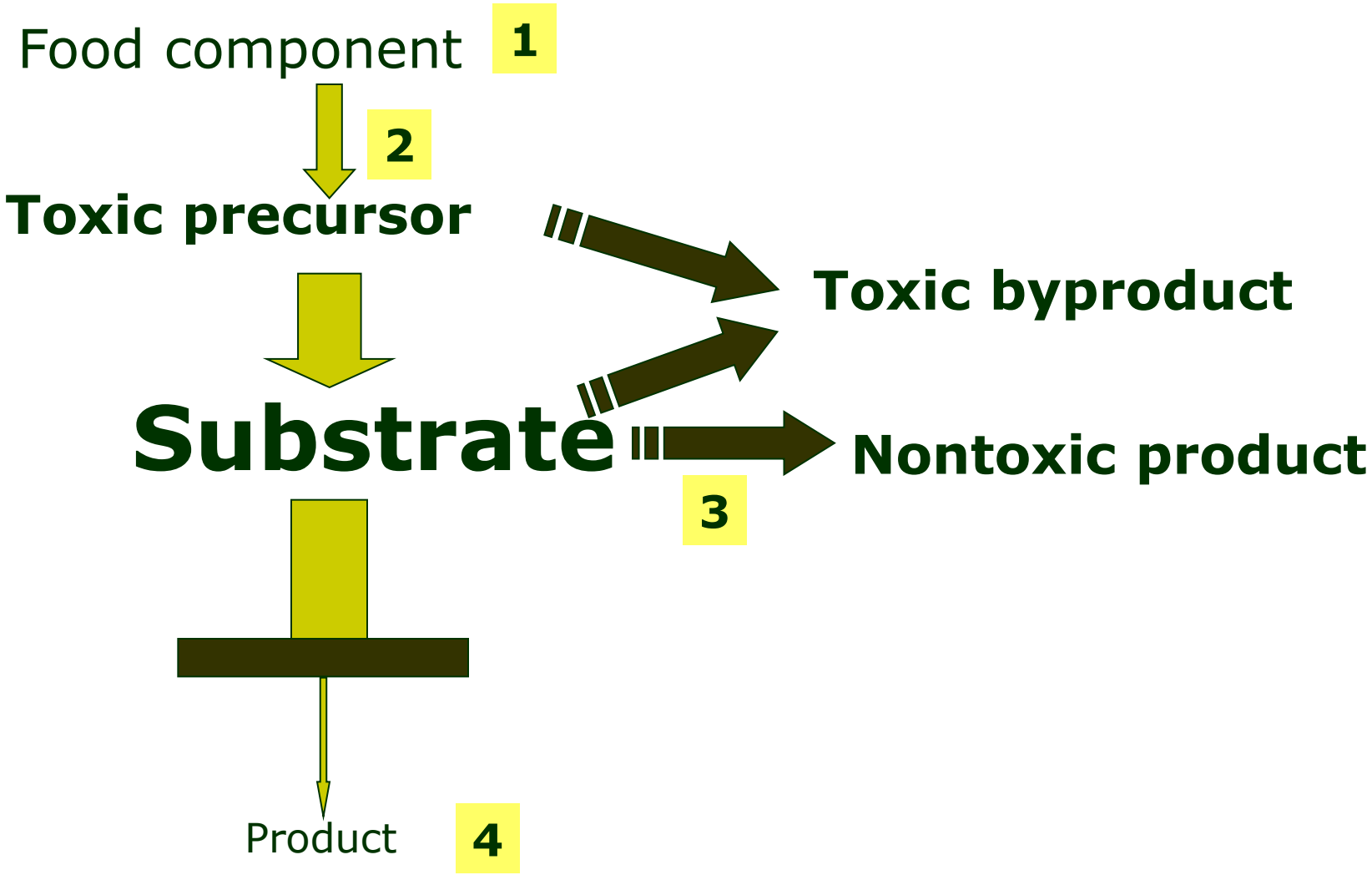


Daily intake in mixed western diet
3000-4000 mg/day

Phe tolerance to maintain Phe <360 umol/l
Children 300-400 mg Phe/d
Adults 800-1200 mg Phe/d

Terezie Paterová, nutriční terapeutka
Jana Komárková, nutriční terapeutka

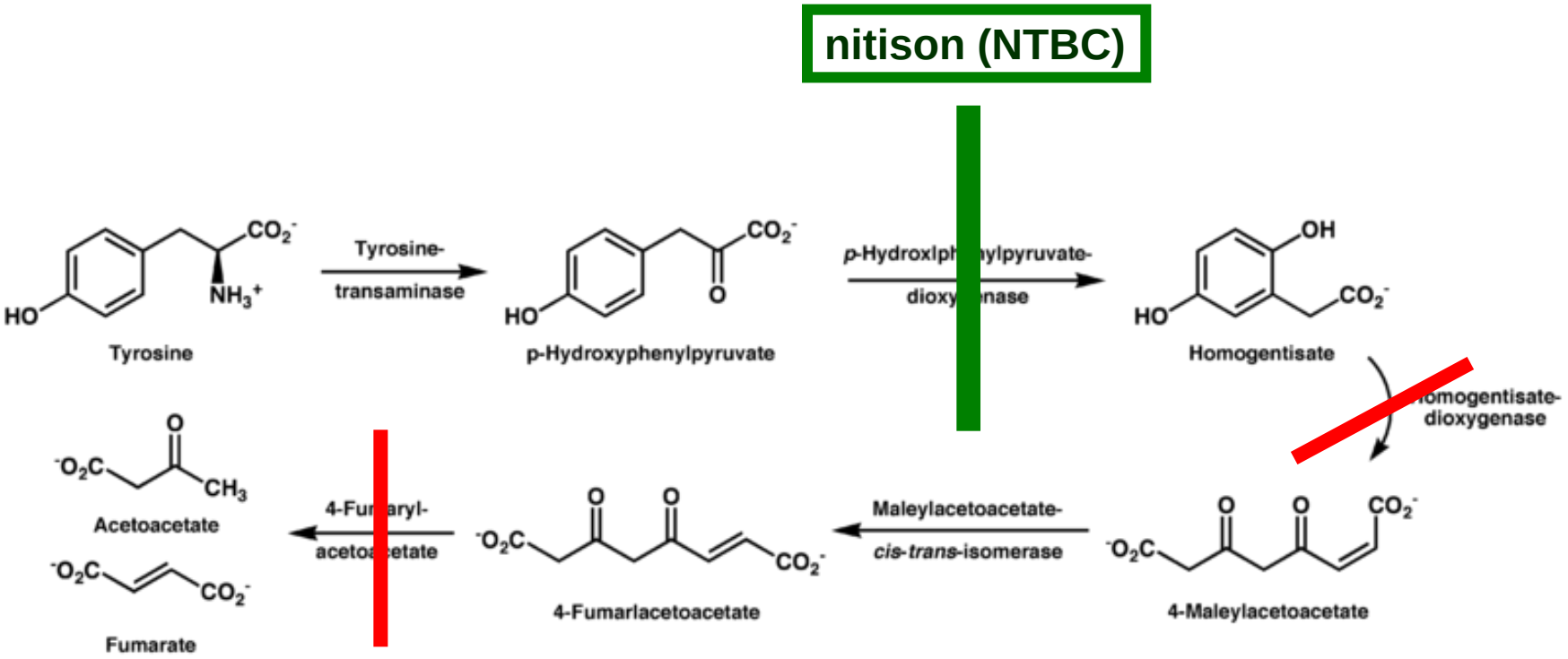
Treatment- pathway manipulation



Substrate reduction therapy

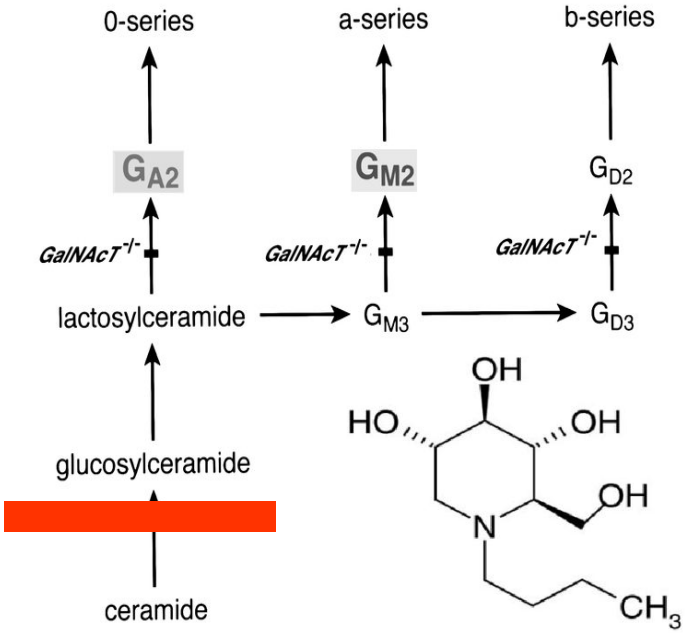
- Pharmacological modulation of reactions above the enzymatic block
- Examples
  - Nitisone in tyrosinemia I and alkaptonuria
  - Miglustat in lysosomal diseases
  - Metronidazole in propionic acidemia
  - LNAA in PKU-competition for transporter

Alkaptonuria and tyrosinemia 1 treatment



http://www.natuurlijkerwijs.com/english/b4f4ca00.gif

Substrate reduction for Gaucher disease



- Miglustat (OGT 918, SC-48334, N-butyldeoxynojirimycin)
- Orally active iminosugar
- Inhibits glucosylceramide synthase and synthesis of glycosphingolipids

- Mean leucocyte GM1 values fell by 38.5% over 12 months in these patients ($p < 0.05$)

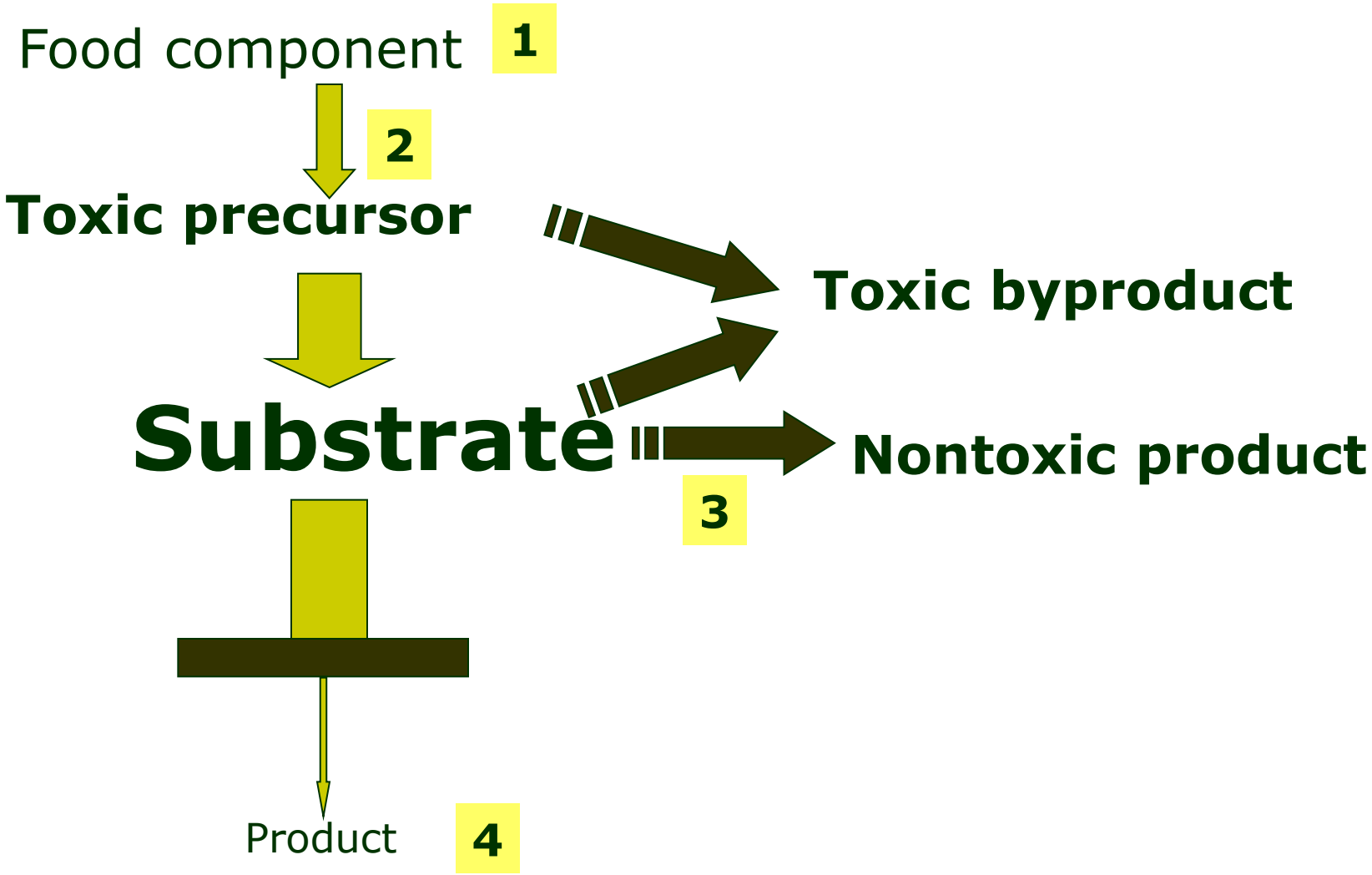
J. Clin. Invest. 103(4): 497-505 (1999)
THE LANCET • Vol 355 • April 29, 2000
.

Articles

Novel oral treatment of Gaucher's disease with *N*-butyldeoxynojirimycin (OGT 918) to decrease substrate biosynthesis

Timothy Cox, Robin Lachmann, Carla Hollak, Johannes Aerts, Sonja van Weely, Martin Hrebícek, Frances Platt, Terry Butters, Raymond Dwek, Chris Moyses, Irene Gow, Deborah Elstein, Ari Zimran

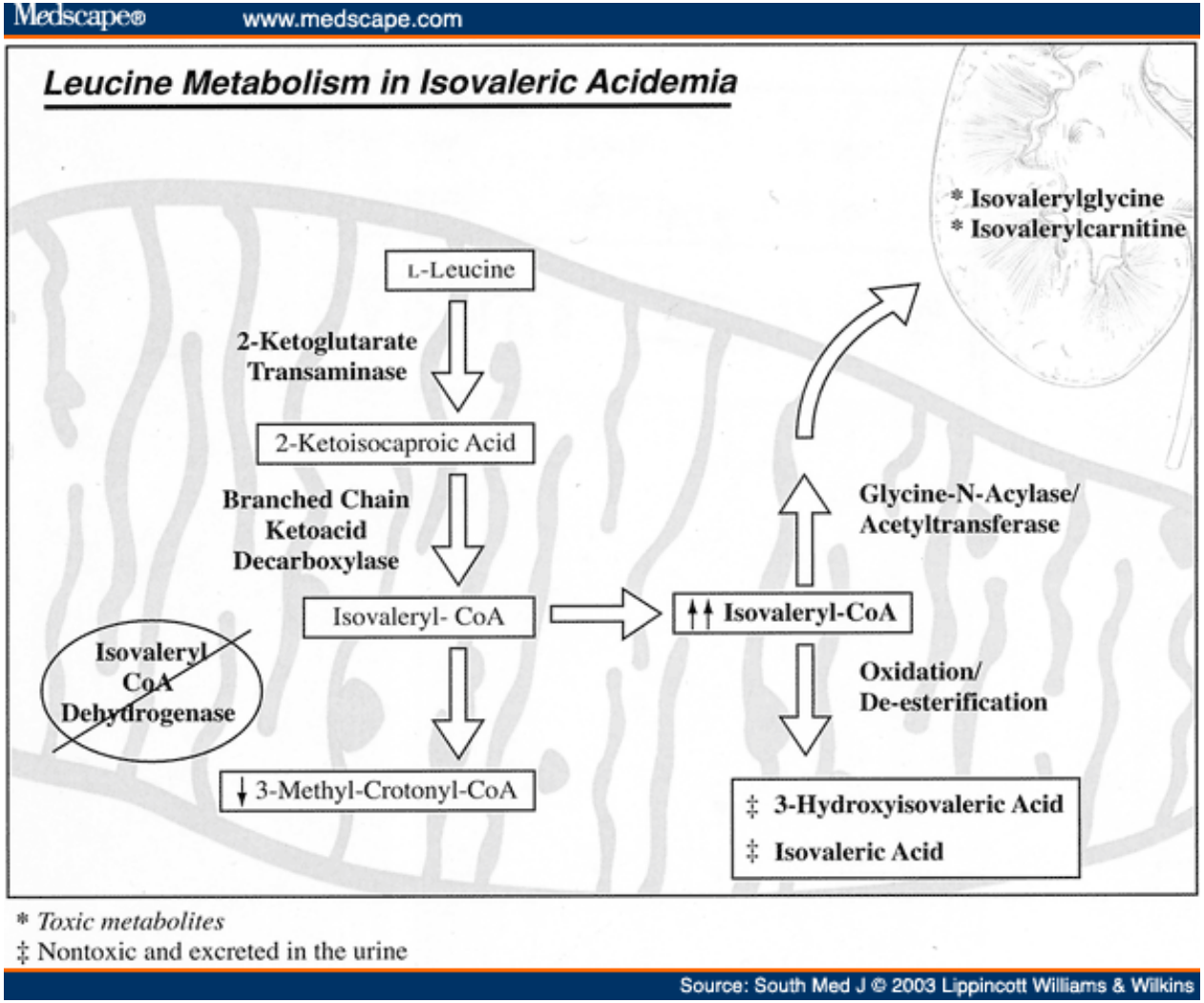
Treatment- pathway manipulation



Limiting toxicity of accumulated substrates

- Less toxic conjugates
  - Isovaleric acidemia-glycine
- More soluble complexes
  - Cysteamine
- Physical-chemical manipulations (urine)
  - Alkalinization
  - Increased fluid intake

Glycine in isovaleric acidemia



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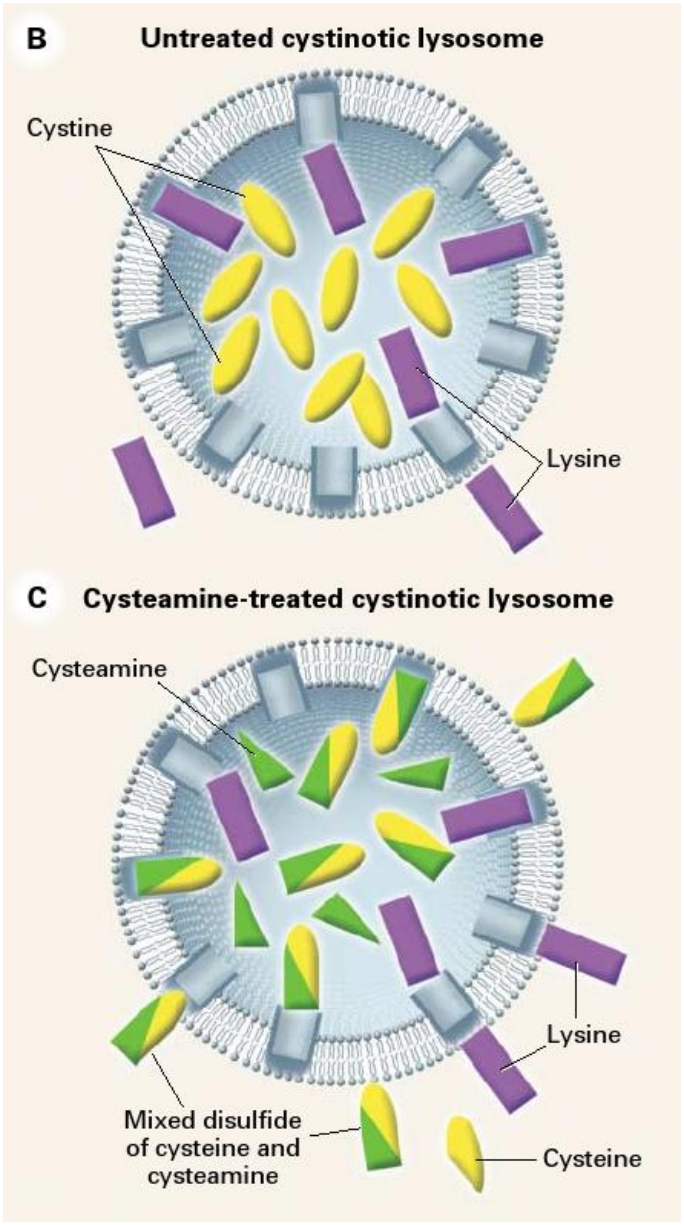
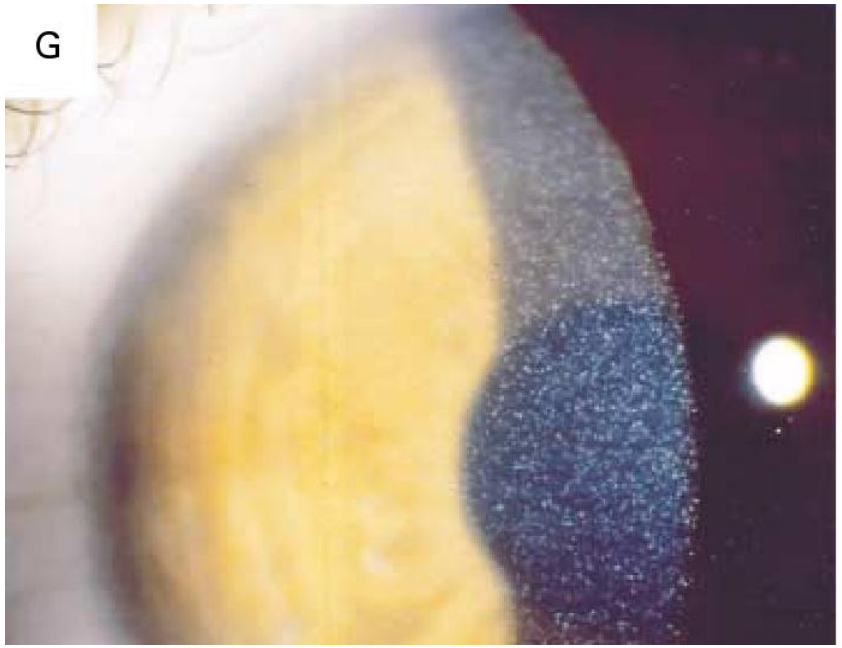
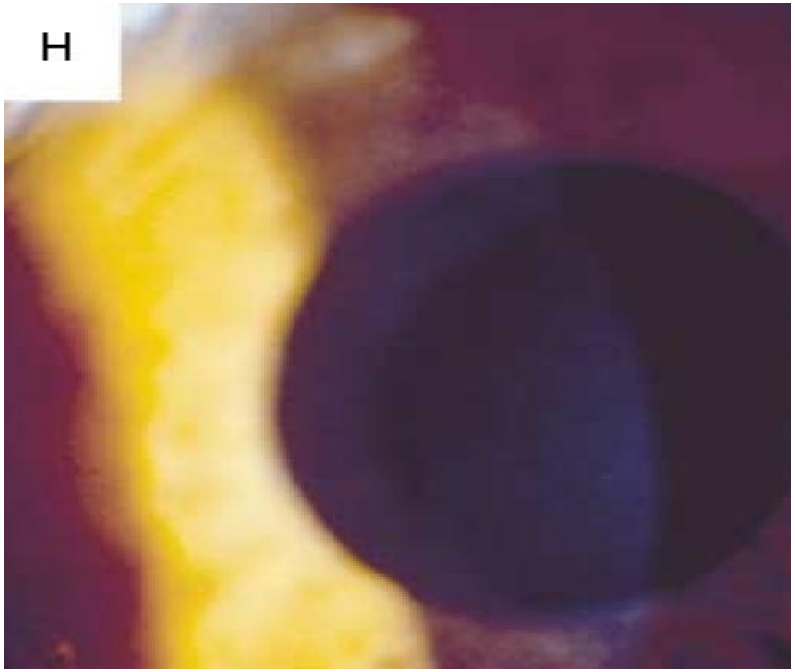
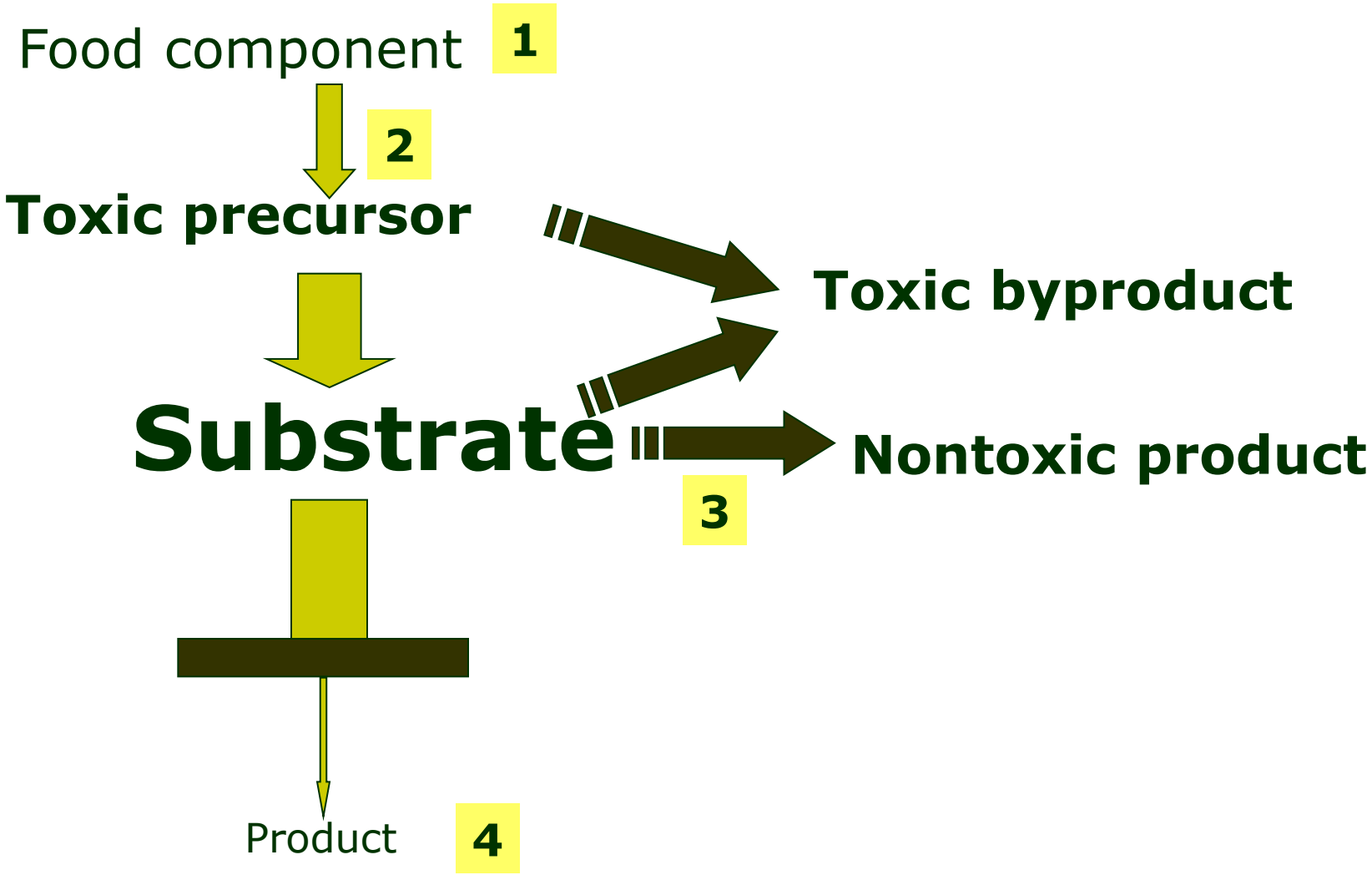

B
Untreated cystinotic lysosome
Cystine
Lysine
C
Cysteamine-treated cystinotic lysosome
Cysteamine
Lysine
Mixed disulfide of cysteine and cysteamine
Cysteine


G

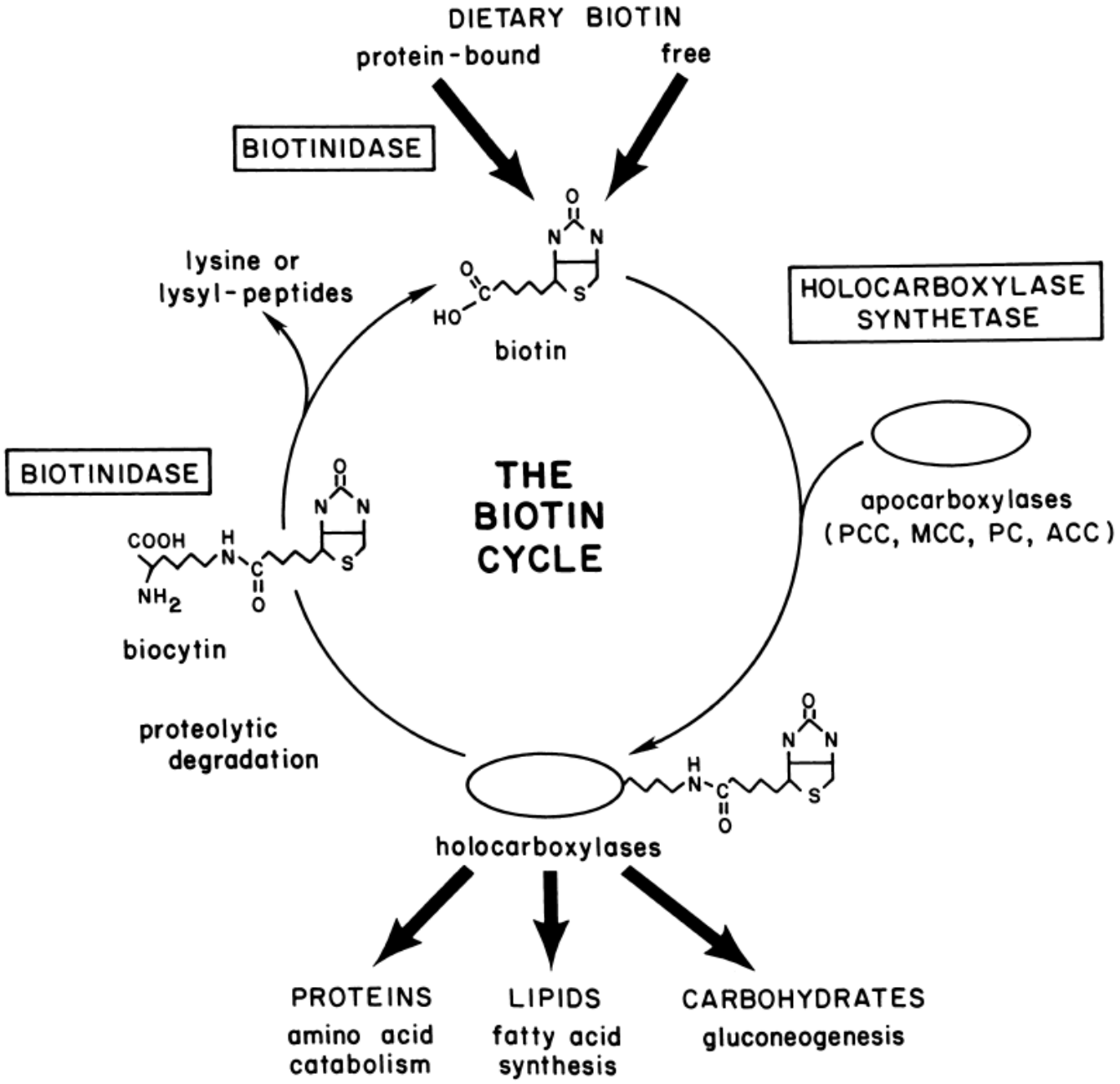

H

Treatment- pathway manipulation



Provision of reaction product

- Direct product of blocked reaction
  - Enrichment of AA mixtures with AAs below block
  - Glucose in GSD
  - Biotin in biotinidase deficiency
  - BH4 in defects of BH4 recycling/synthesis
- Bypassing block
  - Glucose in FAO defects
  - MCT in long chain FAO defects
  - Uridine in orotic aciduria
  - Cysteine enrichement in AA mixture for CBS deficiency
  - Heme arginate in AIP


DIETARY BIOTIN
protein-bound
free
BIOTINIDASE
lysine or
lysyl-peptides
biotin
HOLOCARBOXYLASE
SYNTHETASE
BIOTINIDASE
THE
BIOTIN
CYCLE
apocarboxylases
(PCC, MCC, PC, ACC)
biocytin
proteolytic
degradation
holocarboxylases
PROTEINS
amino acid
catabolism
LIPIDS
fatty acid
synthesis
CARBOHYDRATES
gluconeogenesis

Biotin supplementation

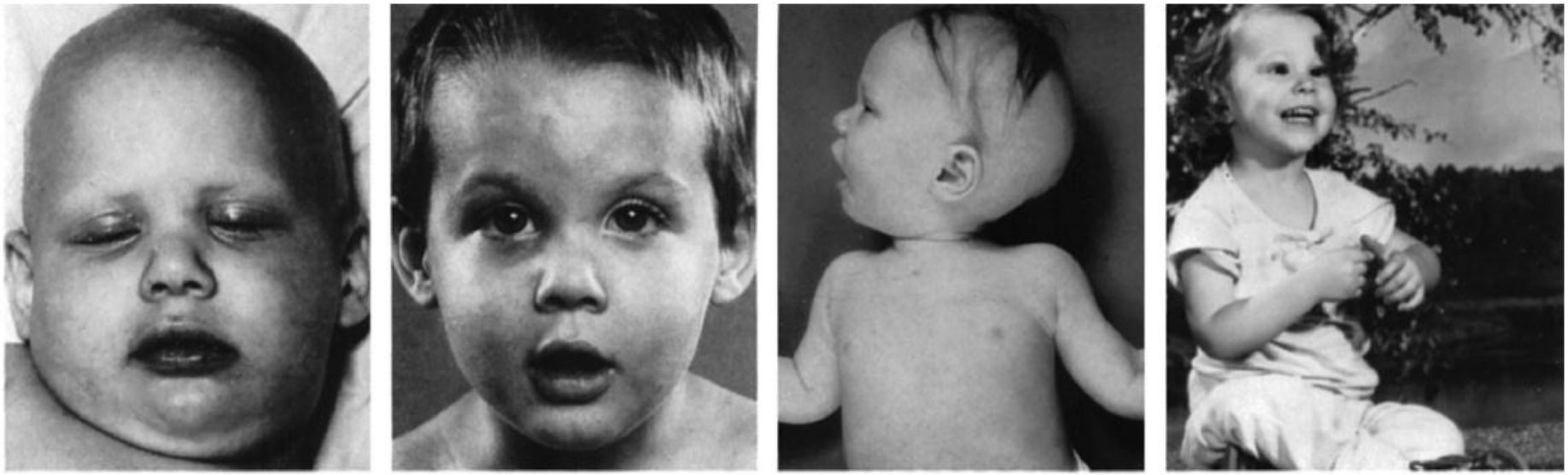
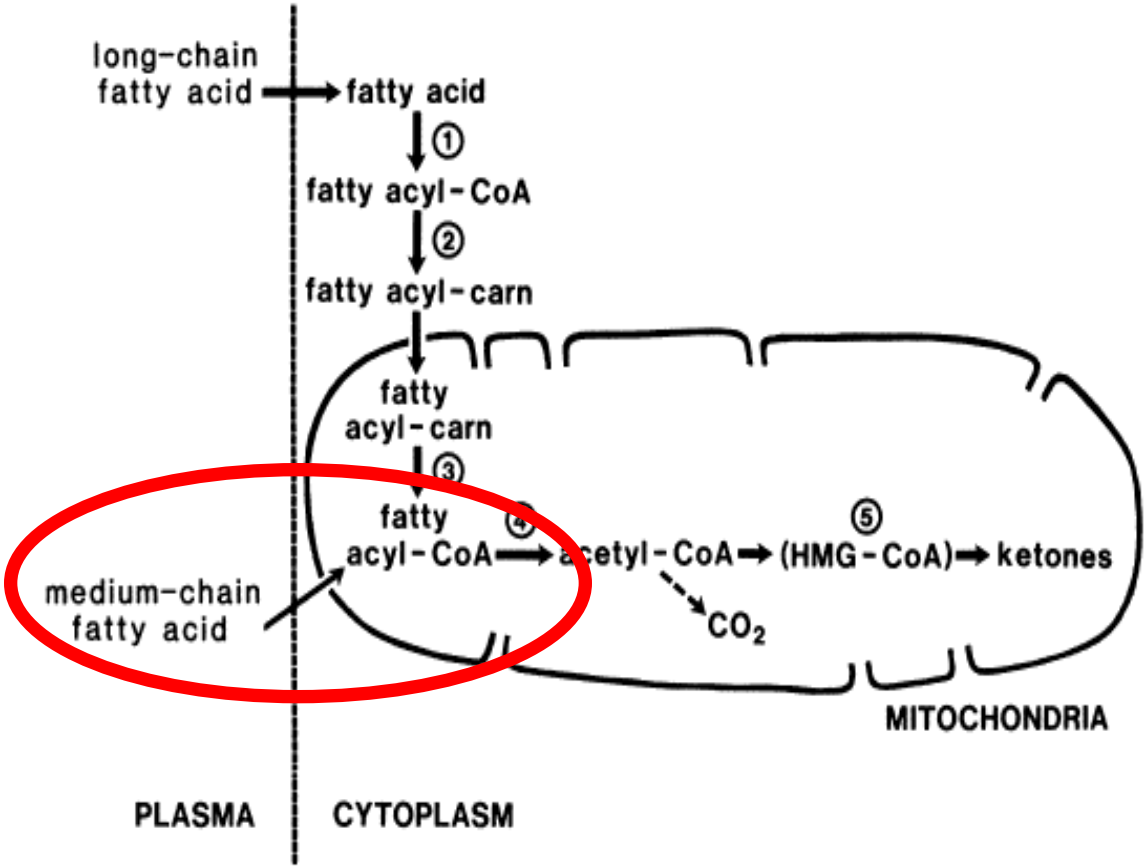


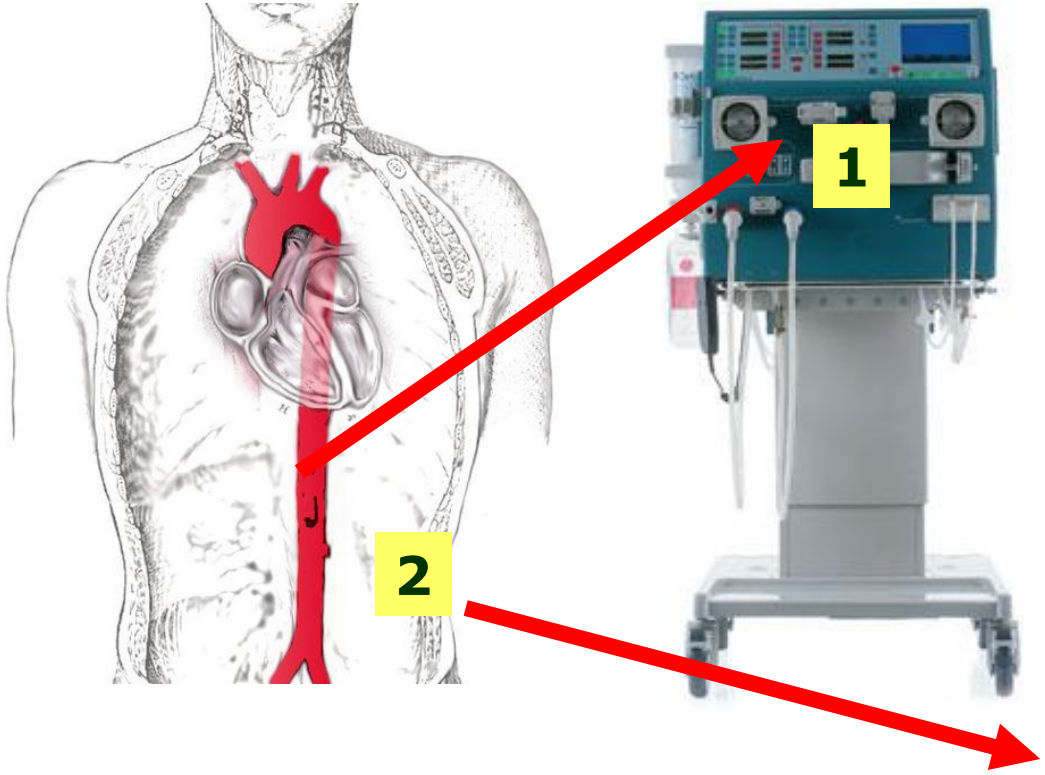
Fig. 156-6 Two children with biotinidase deficiency shown before and after biotin treatment. *A.* Child with biotinidase deficiency at 2 years and 9 months of age with alopecia and periorbital and perioral rash, before biotin therapy. *B.* Same child after 4 months of biotin therapy. *(From Thoene et al.*[251] *Used by permission of New England Journal of Medicine.) C.* Child with biotinidase deficiency at 10 months of age, before biotin therapy. *D.* Same child at 30 months of age, after 20 months of biotin therapy.

MCT and mitochondria



- MCT oils
- No need for carnitine transporters
- Use in CARN defects and VLCAD

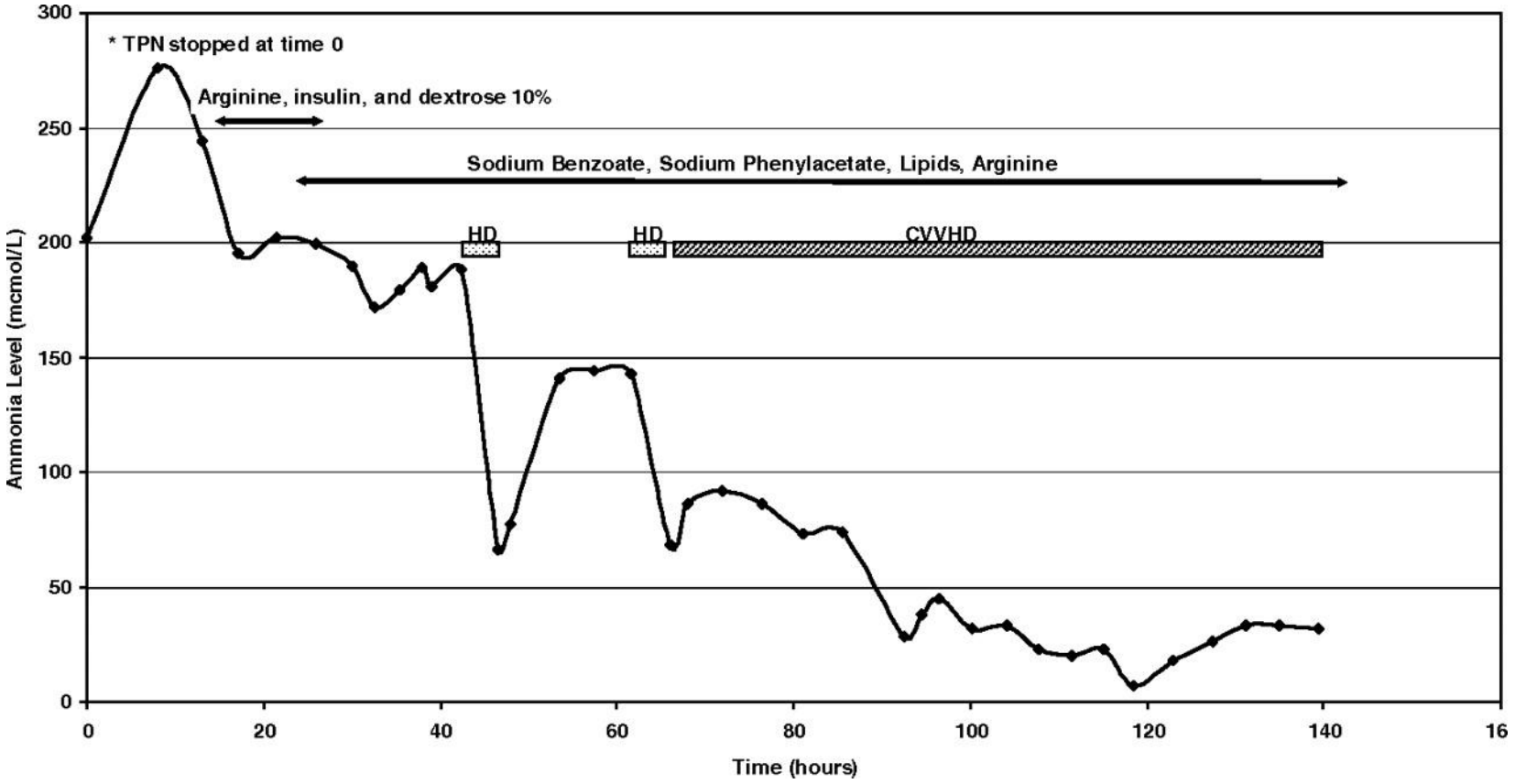
Treatment- nonspecific systemic



Toxin elimination
Hemodialysis
Hemadsorption
(exchange transfusion)
(peritoneal dialysis)

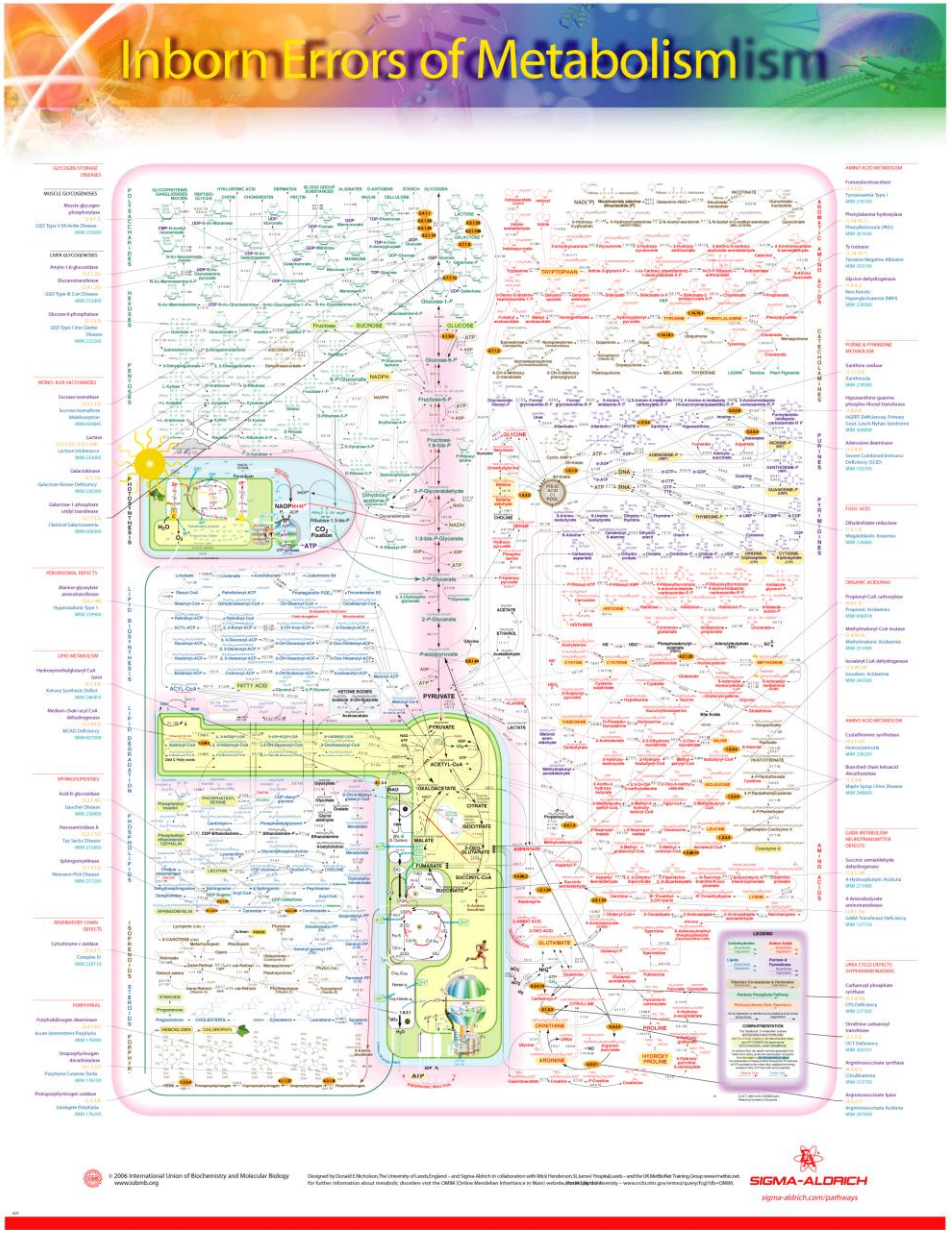
General treatment
Energy
Hydration
Control of infection
Etc.

Treatment of UCD



CVVHD = continuous venovenous hemodiafiltration; HD = hemodiafiltration.

Clay A S , Hainline B E Chest 2007;132:1368-1378



http://www.iubmb-nicholson.org/gif/images/InbornErrors.gif


I
Exams