Organisation of Biochemical Genetic Testing in Estonia

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ESTONIA

- 1,35 million inhabitants
- Approximately 300,000 children
- ~15,000 births per year

Genetic service in Estonia

- In 1990 medical genetic service was opened at Tartu Children's Hospital
  - For counselling children with rare inherited diseases (incl. metabolic diseases)
  - For prenatal testing
- In 1996 molecular diagnostic laboratory
  - For newborn screening (PKU, hypothyreosis)
  - For DNA testing of inherited diseases (over 30 different tests)
- Tallinn Children's Hospital
  - Genetic counselling
  - Official genetic centre in 2004

At the present moment

- Two genetic centres for counselling and investigating patients with metabolic diseases:
  - In Tartu University Hospital, Department of Genetics
  - In Tallinn Children's Hospital

Following analyses are available:

- **ammonia, lactate, uric acid**
- **simple urinary screening tests**:
  - Tests for mucopolysaccharidoses (MPS)
  - Teducing substances (Benedickt reaction)
  - Sulfites
  - Ketones (DNPH test)
- **phenylalanine** from dried blood (newborn screening since 1993)
- **homocysteine**
- total serum **sialotransferrine**

Following analyses are available:

- In cooperation with Central Laboratory of Chemistry of Health Protection Inspectorate in Tallinn:
  - **Amino acid** analysis (HPLC) since 1992
  - **Sugars** (HPLC) since 1992
  - **Organic acid** GC/MS since 2003
  - **Very long chain fatty acid** in serum since 2005
  - **Creatine** and **guanidinoacetate analysis** since 2007
  - **MPS analysis, SAICAR test** since 2007

No of quantitative biochemical analyses in 2007

	Total	Tartu	Tallinn
Amino acids	453	279	174
Sugars HPLC	64	26	38
Quantitative MPS	14	9	4
Organic acid GC/MS	439	246	193
GUAA/creatine	108	98	10
VLCFA	23	11	12

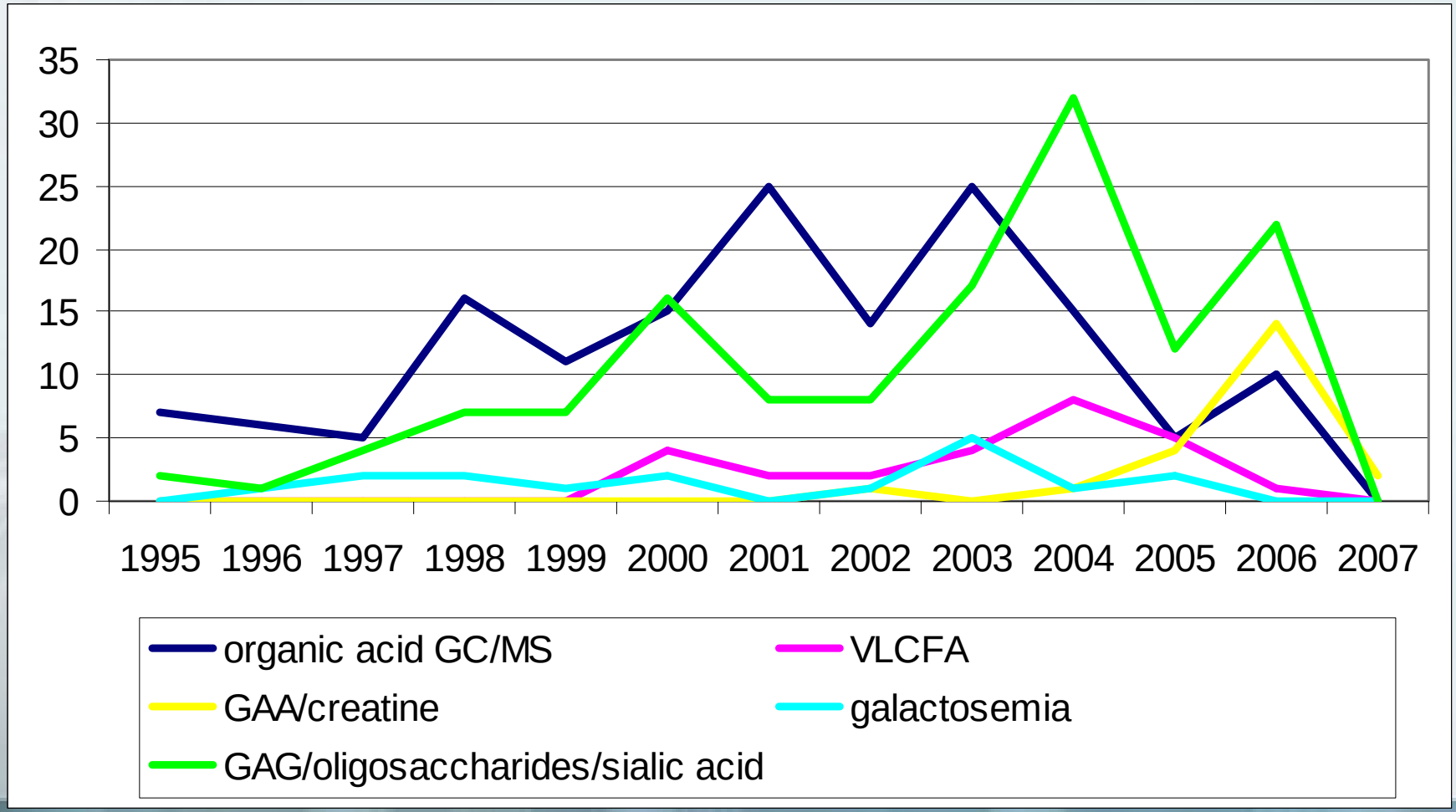
Following analyses are available:

- In Department of Genetics of Tartu University Hospital DNA tests for:
  - Phenylketonuria (PKU, 6 common mutations)
  - Classical galactosemia (Q188R, sequencing)
  - The main mutation of MCAD deficiency (985A>G)
  - The main mutation of LCHAD deficiency (G1528C)
  - CLN type III

Specific metabolic tests and investigations done elsewhere:

- Over 700 patients during 1990-2007:
  - **Urinary organic acid GC/MS** **154**
  - **Tandem MS screening (acylcarnitines)** **172**
  - **MPS, oligosaccharides, sialic acid in urine** **136**
  - **Specific enzymatic tests for LSD** **100**
  - Enzyme/DNA analysis for mitochondrial disease 34
  - The confirmation of classical galactosemia 17
  - VLCFA in serum 26
  - Isoelectric focusing of sialotransferrines 21
  - 7- dehydrocholesterol 26

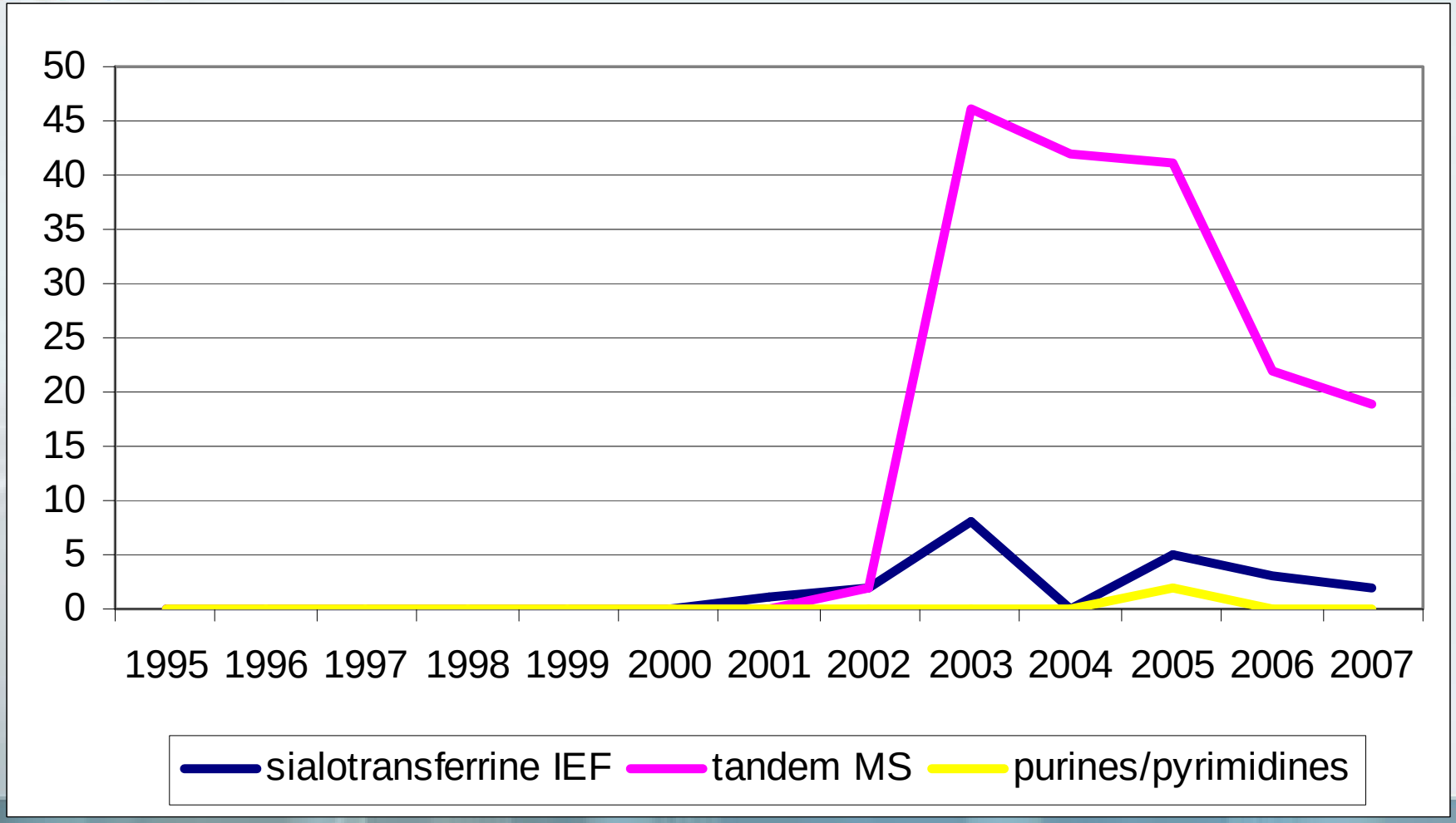
Tests developed out locally:



Training possibilities

- Biochemist K. Kall studied in Amsterdam MC in 2005 January (3w)
  → organic acid GC/MS, GUAA/creatine, VLCFA
- Biochemist K. Krabbi studied in Rotterdam Erasmus MC in 2006 (5m)
  → urinary MPS, oligosaccharides

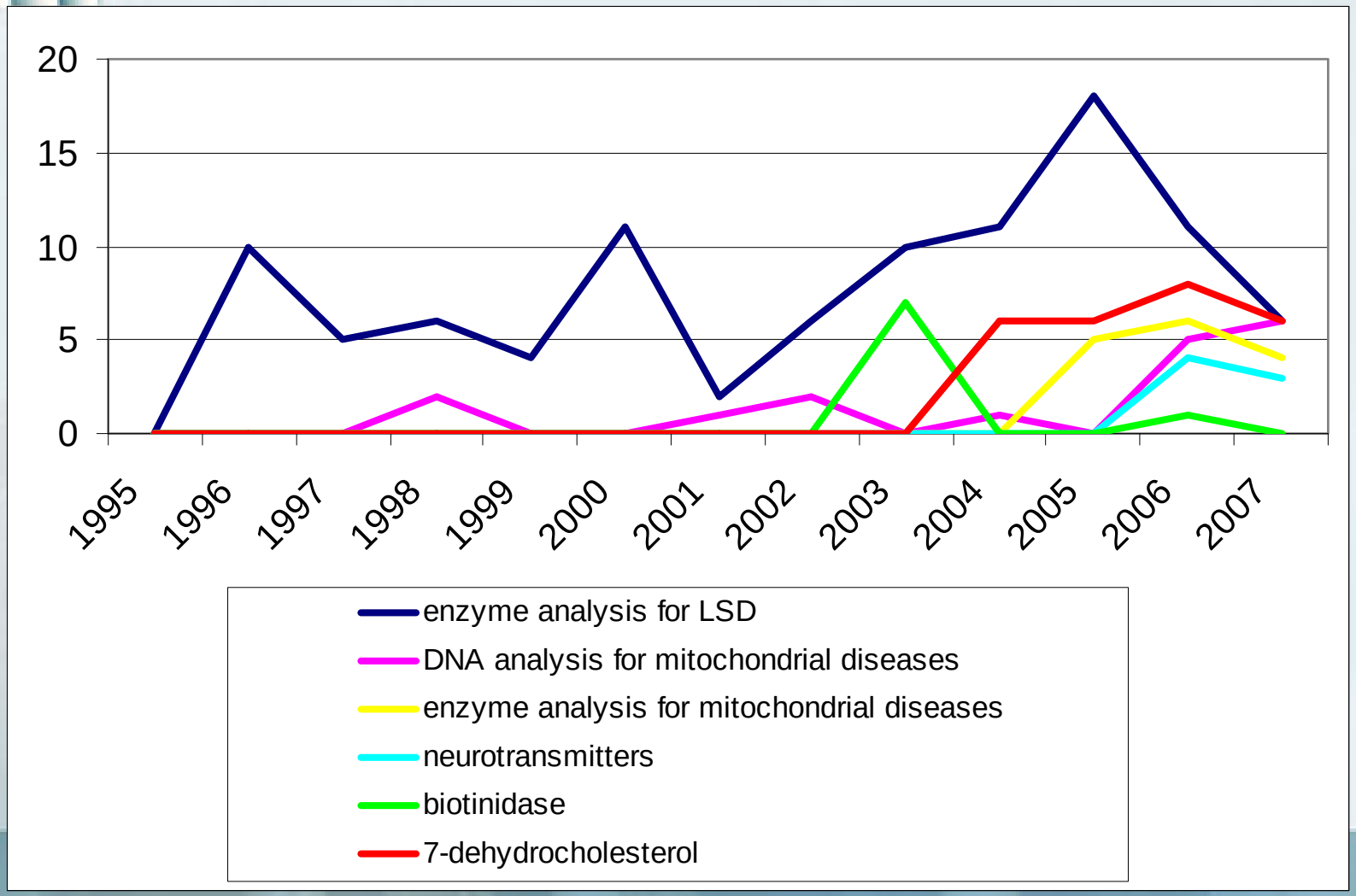
Tests to work out in the near future:



Tandem MS analysis

- 3200 Q-TRAP LC MS/MS mass spectrometer (Applied Biosystems, USA)
- In Department of Biochemistry of Tartu University
- Dr. K. Joost (ERNDIM scholarship) and biochemist K. Kilk will study in Amsterdam MS in May 2008

To continue ordering from abroad



Problems in ordering from abroad

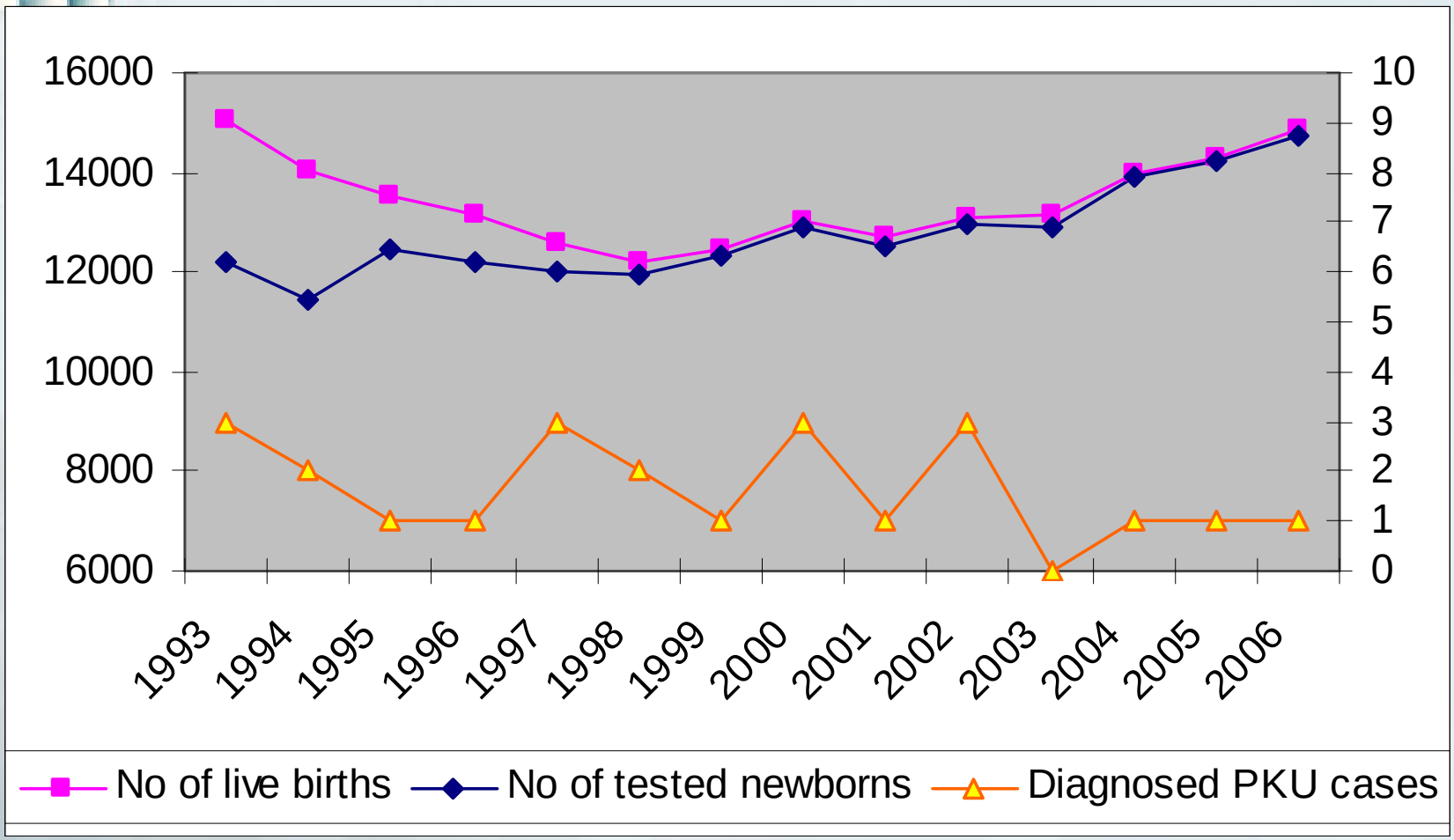
- It takes time !
- The price list of our Health Insurance Fund (HIF) for BGT is ~3-4x lower than in developed EU countries
- Our HIF does not give us E112 form, but the give the guarantee letter, if we send
  - The application from MD
  - The application from parents
  - Answer within 2-4 weeks

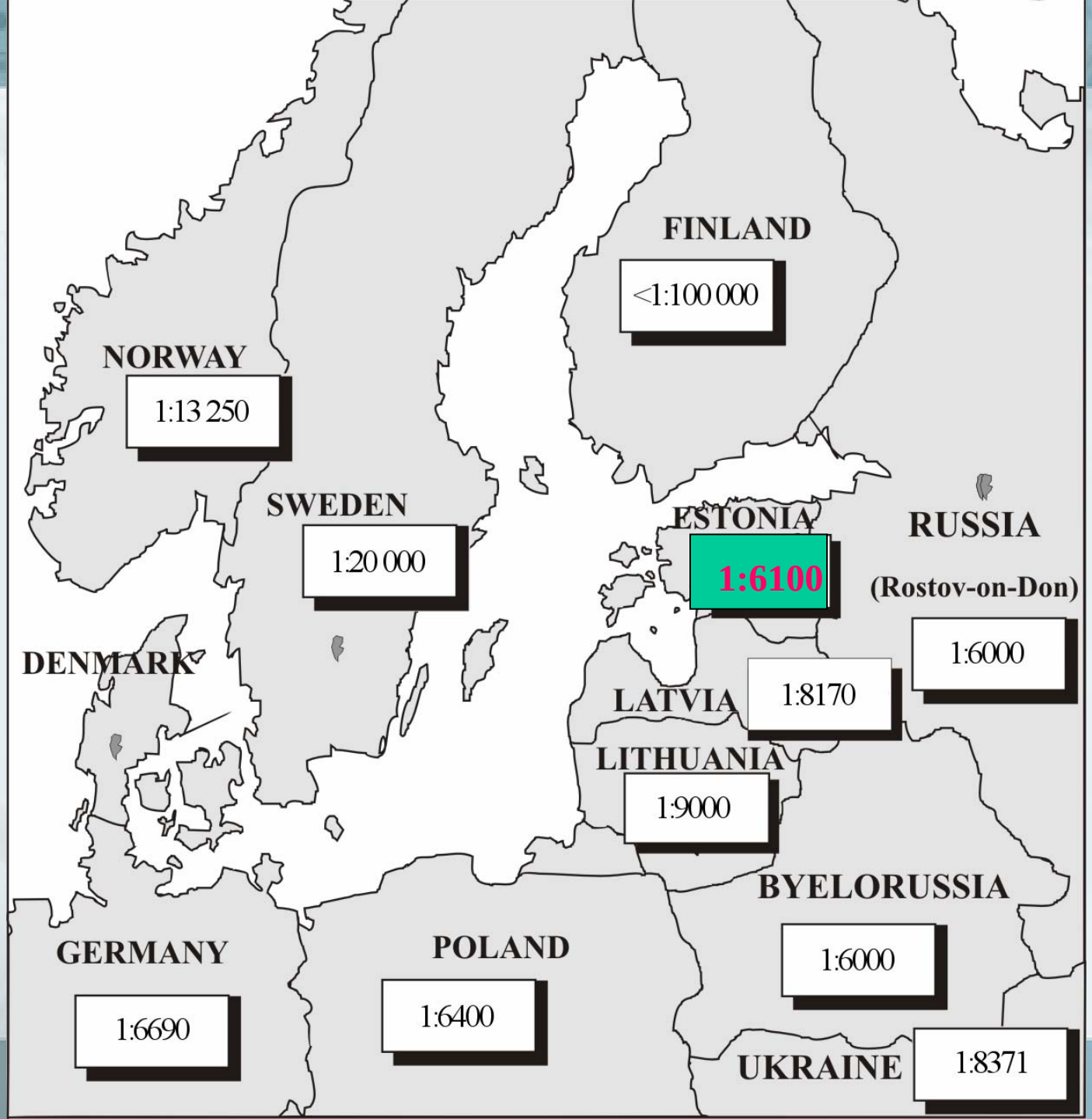
Results during 1990-2007:

- In 123 patients the diagnosis of inherited metabolic disease was confirmed:
  - **PKU 38 cases (31%)***
    - 24 during newborn screening program since 1993
    - 13 late diagnosed PKU cases
    - 1 prenatally diagnosed PKU case

* There are altogether 77 PKU cases in the register (1979-2007)

PKU screening programme

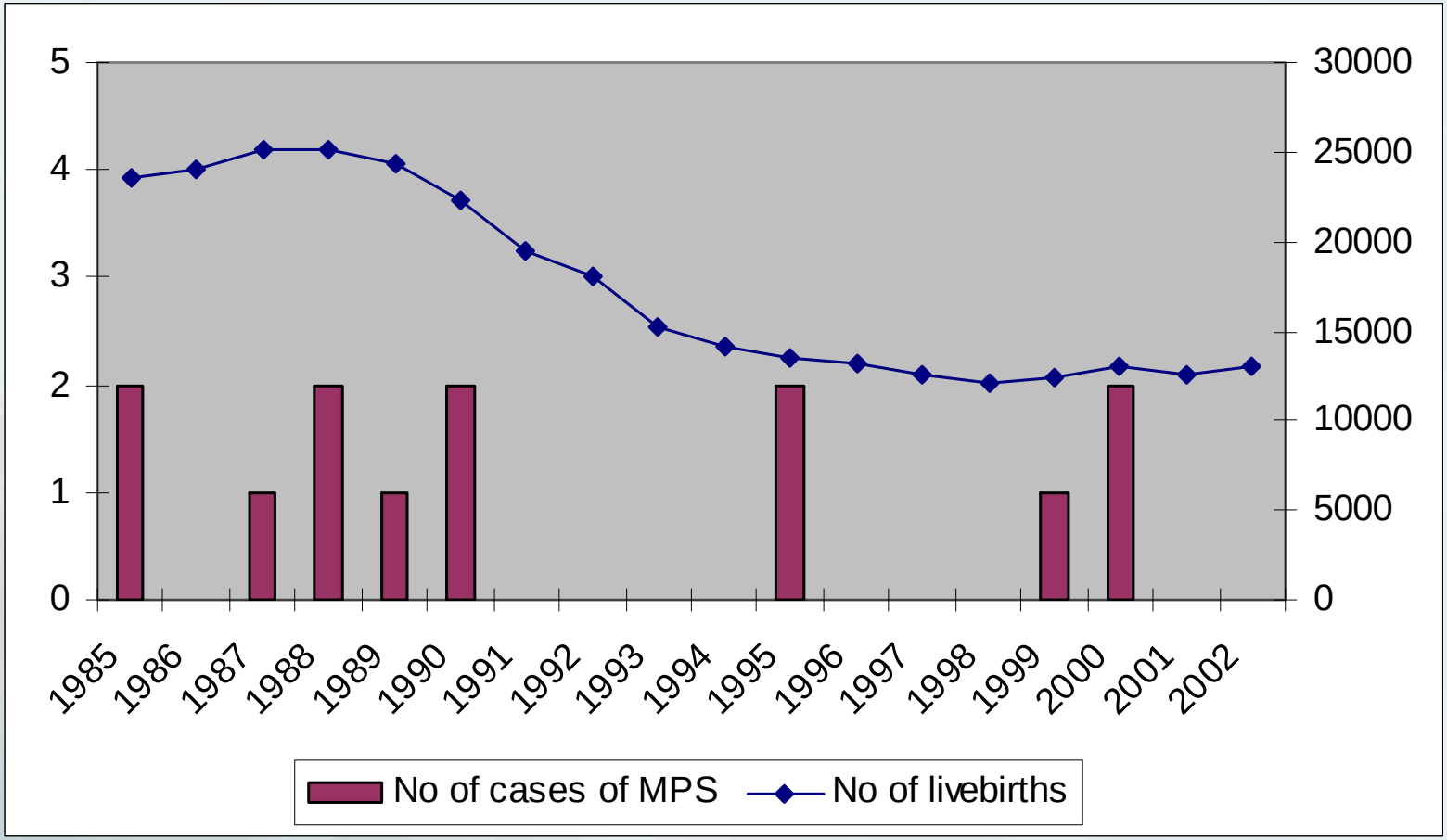



FINLAND
<1:100 000
NORWAY
1:13 250
SWEDEN
1:20 000
ESTONIA
1:6100
RUSSIA
(Rostov-on-Don)
1:6000
DENMARK
LATVIA
1:8170
LITHUANIA
1:9000
BYELORUSSIA
1:6000
GERMANY
1:6690
POLAND
1:6400
UKRAINE
1:8371

Lysosomal storage disorders:

- **35 patients (28%) during 1990-2007**
- **Mucopolysaccharidoses (MPS) 14 cases**
  - 8 patients with MPS II (Hunter syndrome)
  - 4 patients with MPS IIIA (Sanfilippo syndrome)
  - 2 patients with MPS VI (Maroteaux-Lamy s.)
- **Others 21 cases**

The livebirth incidence of MPS in Estonia 1:24,154

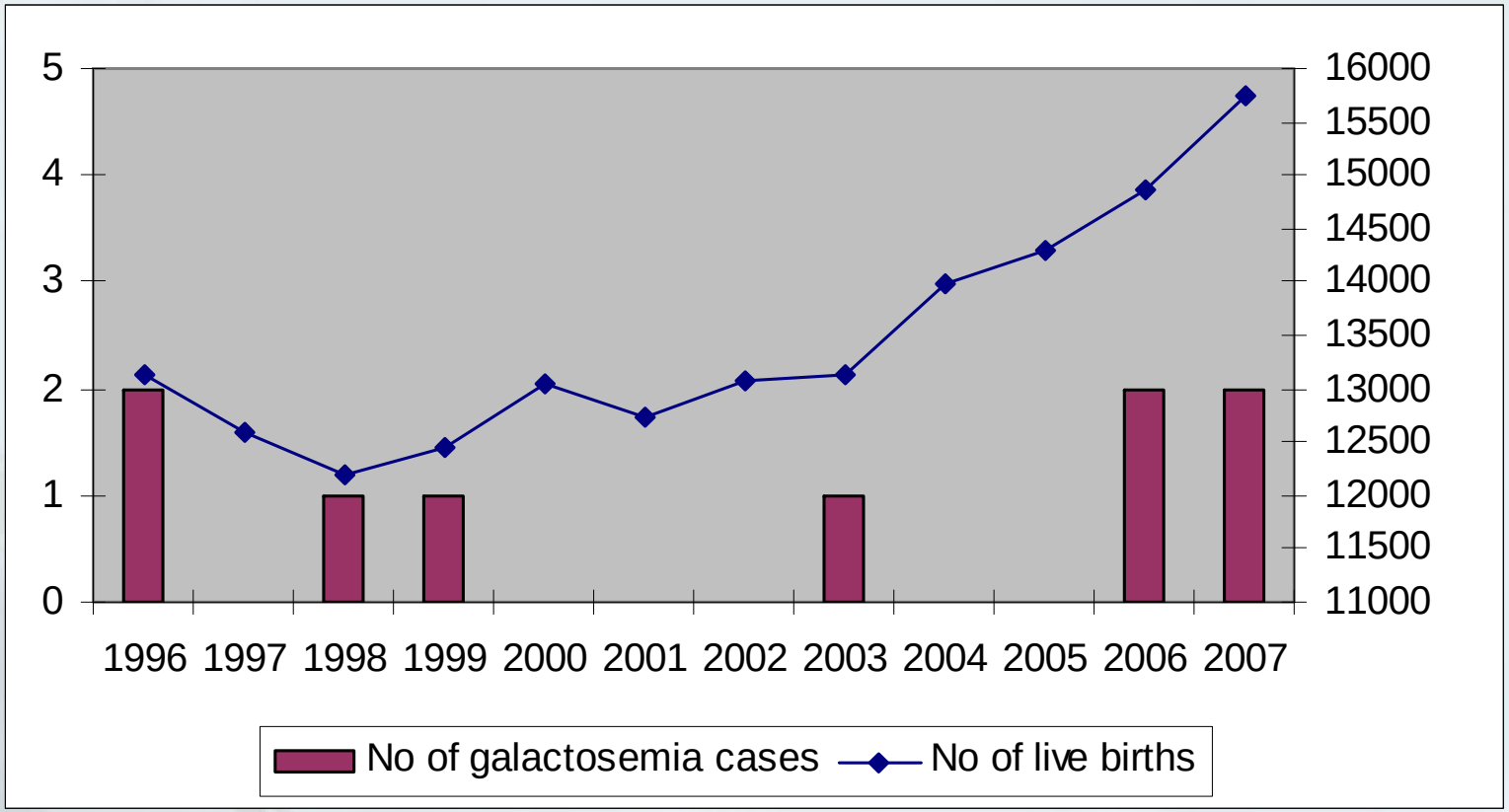


We excluded last 5 years (possible diagnostic time)

Other LSD

- Fabry disease 5 (2 families)
- GM1 gangliosidosis 3 (2 families)
- Gaucher disease 3 (2 families)
- CLN type 2 2
- CLN type 1 1
- CLN type 3 2 (1 family)
- Tay-Sachs disease 1
- Metachromatic leukodystrophy 1
- Wolman disease 1
- Niemann-Pick disease 1

Classical galactosemia :



- **10 patients (8%),** Birth prevalence is ~1:20,000

Mitochondrial disorders:

10 patients (8%) with mitochondrial disease:

- **Leigh syndrome (2 patients)**
  - Respiratory chain complex I deficiency (mtDNA mutation T10191C in *ND3* gene)
  - Respiratory chain complex I and IV deficiency (mutations in *SCO2 gene*)
- **Mitochondrial myopathy in a girl and her mother** – respiratory chain complex I and IV deficiency
- **PDH deficiency** (2 patients)
- **MELAS syndrome**
- **Kearns-Sayre syndrome** (2 patients)
- **LHON**

Urea cycle disorders:

- **7 patients (6%) with urea cycle disorders:**
  - 1 boy with hemizygous ornitine transcarbamylase (OTC) deficiency
  - 5 females with heterozygous OTC deficiency
  - 1 patient with argininemia

Fatty acid oxidation defects:

- LCHAD
  - One family with 2 children – genotype 1528G>C/IVS16-2A>G/A (Olsen *et al*.)
  - One family with 2 children – genotype 1528G>C/ 1528G>C
- MCAD:
  - We have not found any MCAD deficiency cases !
  - The frequency of possibly affected homozygotes 1 out of 193 000 (Lilleväli *et al*. 2000)

Other metabolic diseases:

- Alkaptonuria 2
- Tyrosinemia type I 1
- Lysinuric protein intolerance 2
- Maple syrup urine disease 1
- Hyperornithinemia/gyrate atrophy (HOGA) 2
- Dihydropteridine reductase (DHPR) deficiency 1
- Aromatic L-amino acid decarboxylase (AADC) deficiency 2
- Hereditary fructose intolerance 1
- CDG Ia 1

Many thanks!

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Thank you for your attention!