ROLE OF EXTERNAL QUALITY ASSESSMENT SCHEMES IN THE STANDARDIZATION AND POSTMARKET VIGILANCE

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Purpose of EQA schemes

To support the quality improvement of in vitro diagnostic services by

- Objective evaluation of the overall performance of clinical laboratories
- Education and training for the participants
- Assessment of the efficiency of their analytical procedures:
  – testing method,
  – reagents,
  – instrument and
  – calibration.
- Support the implementation of reference measurement systems (RMSs)
- Postmarket vigilance of the IVD MDs – EN 14136:2004

Support of RMSs in the laboratory medicine

Requirements:

- QCMs with reference values traceable to RMSs
- Identification of individual procedures / devices
- Statistically significant number of participant laboratories

Advantages:

- Detection of standardisation, specificity and interference problems
- Might be used for the evaluation of the commutability of RMs
- Conformity to the harmonised standard EN ISO 14136:2004
- Enable the postmarket vigilance of IVD MDs

Vigilance of *in vitro* diagnostic (IVD) medical devices (MDs)

IVD Directive (98/79/EC), Article 11: **Vigilance procedure**

1. Member States **shall take the necessary steps to ensure that any information brought to their knowledge**, in accordance with the provisions of this Directive, **regarding the incidents mentioned below involving devices bearing the CE marking is recorded and evaluated centrally**:

(a) any malfunction, failure or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labelling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient, or user or of other persons or to a serious deterioration in their state of health;

(b) any technical or medical reason in relation to the characteristics or performance of a device for the reasons referred to in subparagraph (a), leading to systematic recall of devices of the same type by the manufacturer.

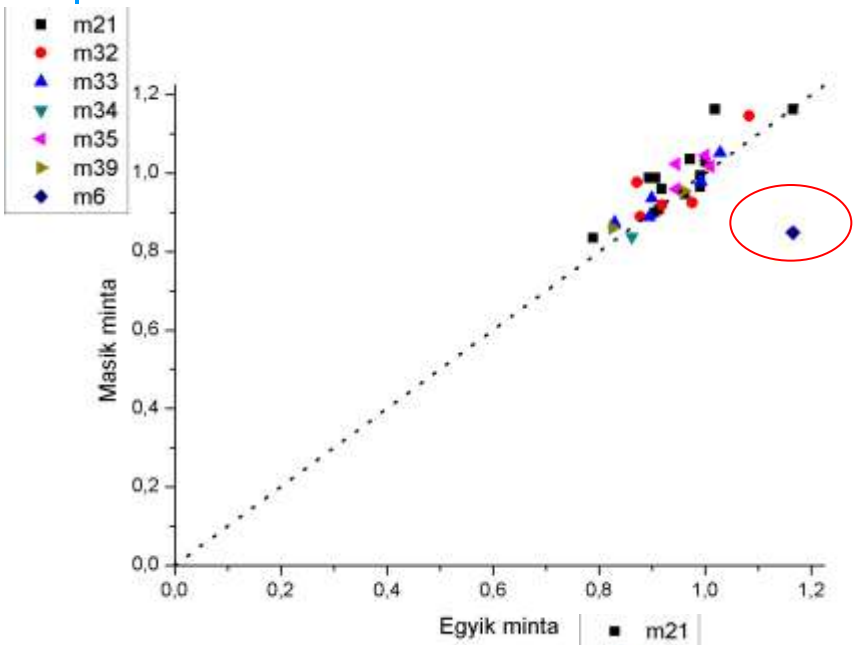
Is the postmarket vigilance a business of the EQA schemes?

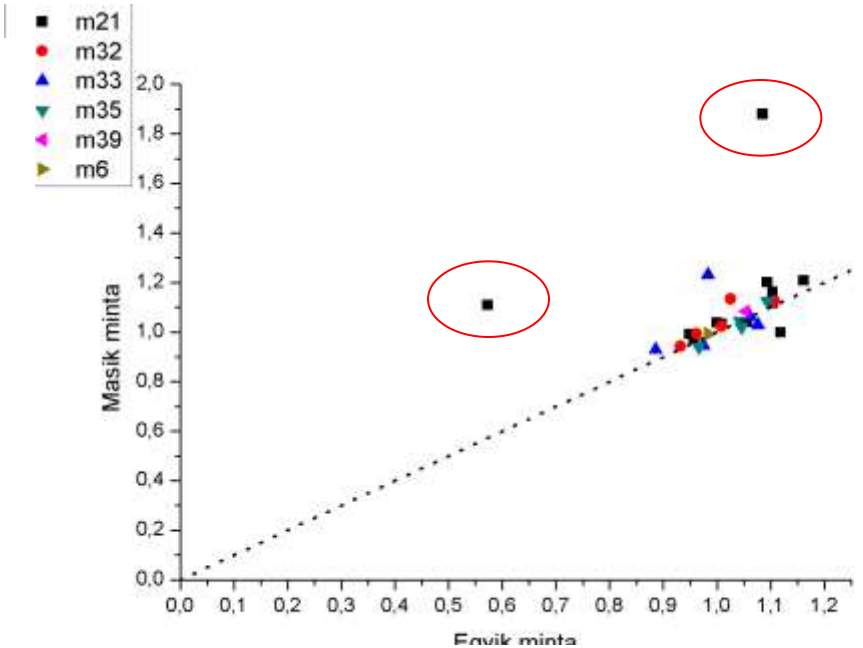
IVD Directive (98/79/EC), Article 11: **Vigilance procedure**

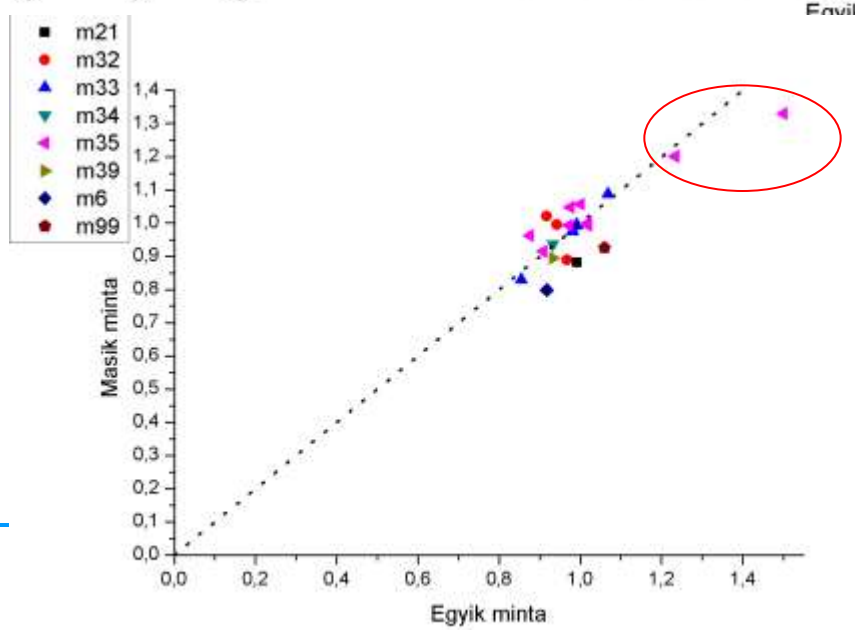
2. Where a Member State requires medical practitioners, the medical institutions or **the organisers of external quality assessment schemes** to inform the competent authorities of any incidents referred to in paragraph 1, it shall take the necessary steps to ensure that the manufacturer of the device concerned, or his authorised representative, is also informed of the incident.

- The requirements of the EQAS to fulfil their function in the postmarket vigilance procedure is further specified in a harmonised standard:
  EN 14136:2004 Use of external quality assessment schemes in the assessment of the performance of in vitro diagnostic examination procedures

Complement C3 (IgG, Transzferrin)







Successful standardization

[ERM/IFCC-DA470K]

Individual errors

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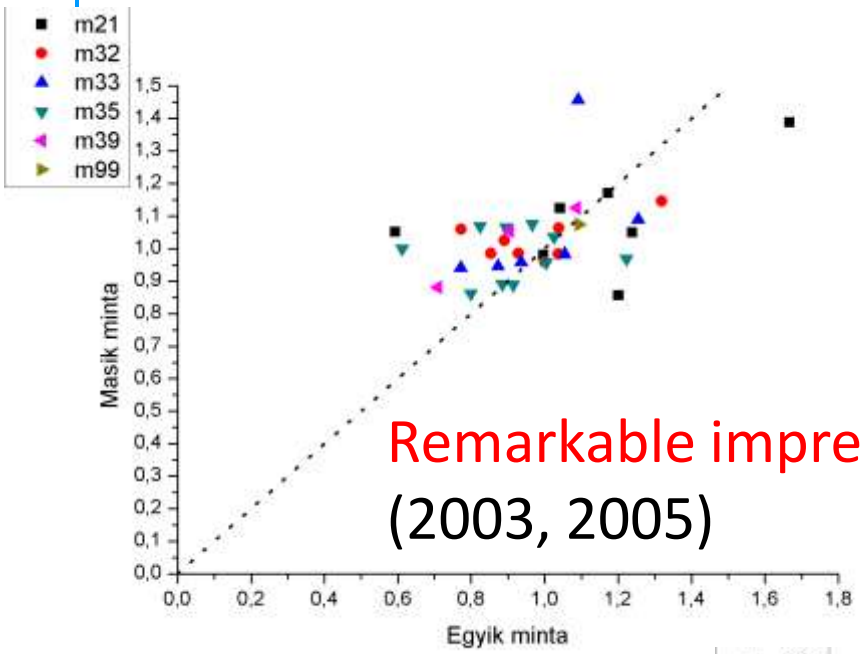
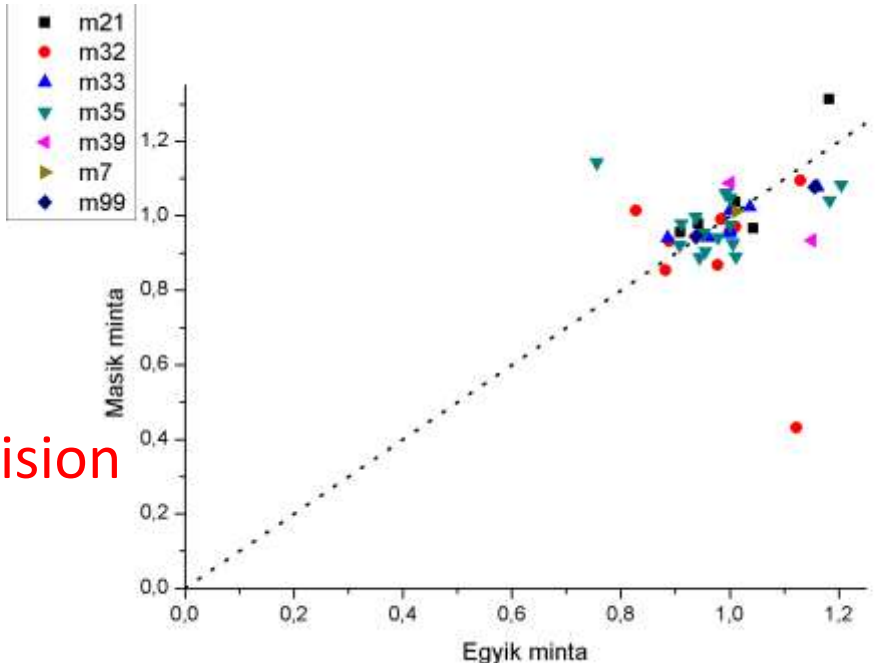
C-reactive protein (CRP)



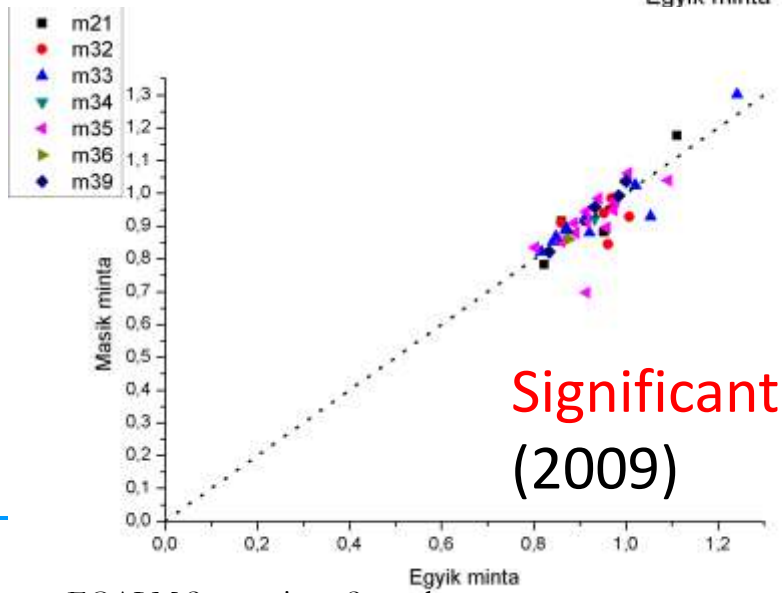
Remarkable imprecision

(2003, 2005)



Possible explanations:

- incorrect execution of the measurement procedure?
- lot-related differences?
- susceptibility to operator or instrument influences?
- *susceptibility to deterioration in shipment or in use?*



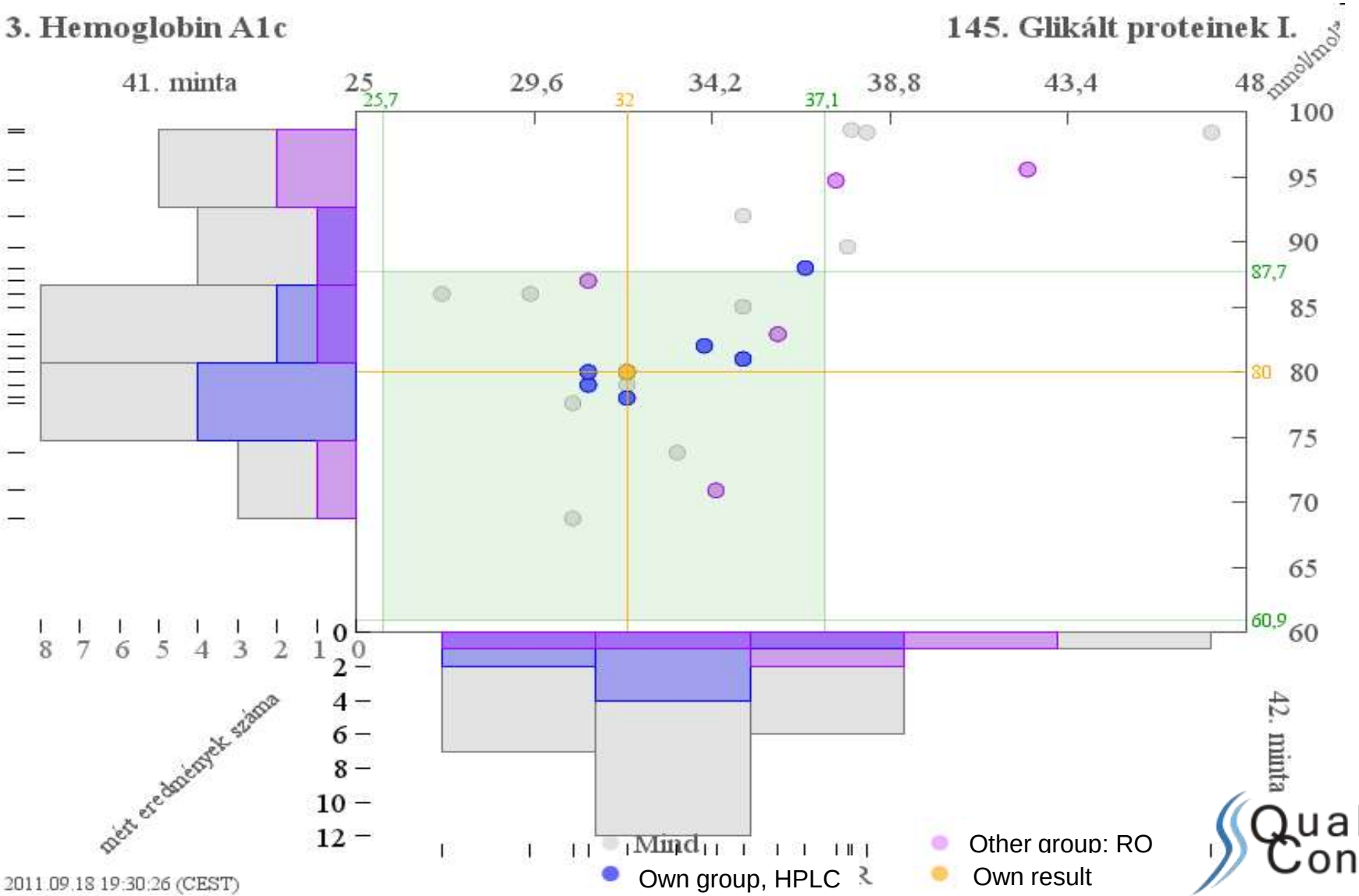
Significant improvement

(2009)

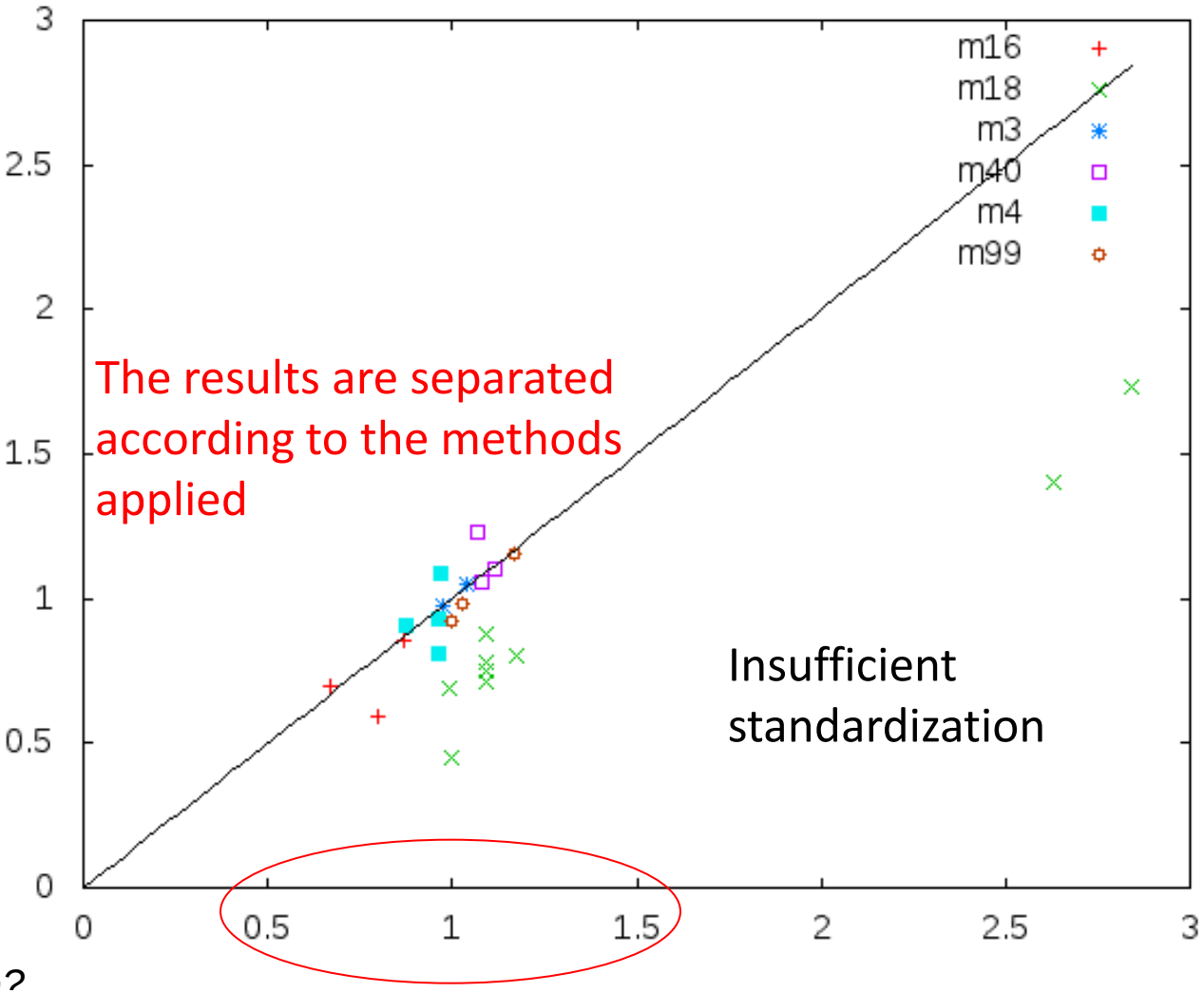
HgbA1C, 2011/IV. survey

results in mmol/mol

target: RMV, mmol/mol, green zone: acceptable range, lab's result with yellow



Troponin I (cTnI)



Possible explanations:

- *incorrect calibration?*
- *different specificities (between procedures)?*
- *susceptibility to interference?*
- lack of commutability of survey sample?

Proficiency testing study on rare SNPs

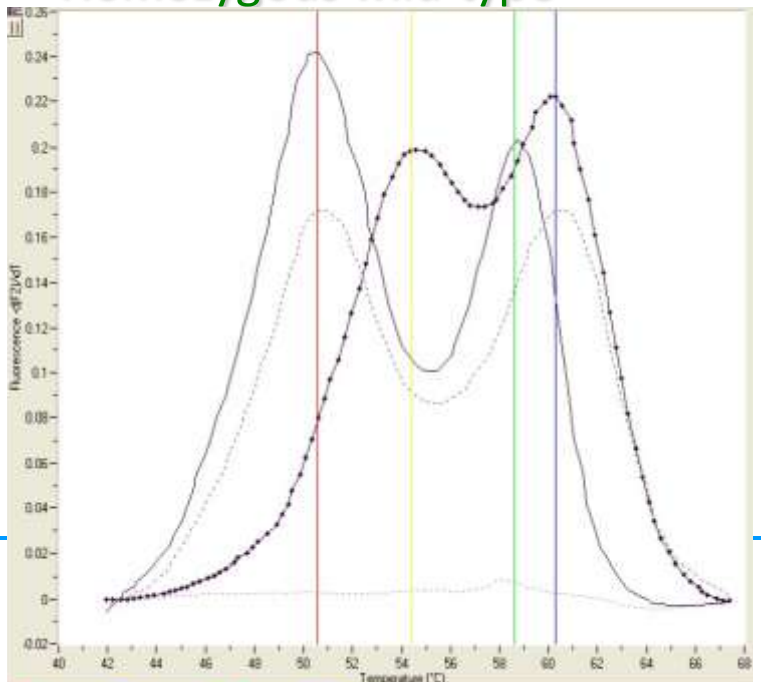
- Institute for Reference Materials and Measurements (IRMM) and three EQA organisers (DGKC, Instand eV, QualiCont Kht.)
- On the coagulation Factor II (FII, prothrombin) gene G20210A variant and adjacent rare mutations resulting in unusual genotyping results using some techniques (e.g. LightCycler).

Aims of the study:

- Commutability study on the FII reference plasmids
- Identify the weaknesses in molecular genetic testing
- To assess the competence of clinical laboratories to recognize interfering rare sequence variants and report them correctly.

Samples prepared for the ring trial

- Sample A (—): 20210A / T20175G+20179_80delAC
  Melting peaks on the LC: 50 °C **and** 58 °C*
  Other methods: Heterozygous mutant
- Sample B (—•—): G20210 / C20209T
  Melting peaks on the LC: 54 °C **and** 60 °C
  Other methods: Homozygous wild-type
- Sample C: Homozygous mutant
- Sample D: Homozygous wild-type



The ring trial

- 189 laboratories
  (21 countries)
- 50 different genotyping procedures

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Laboratory performance I: Overall results

	Sample A[a]	*Sample B*	*Sample C*	*Sample D*	*Total*
Usual results	112	104	189	189	596
Correct	102	100	177	180	559
False	7	3	12	8	30
Not reported	3	1	–	1	5
Error rate	6.4 %	2.9 %	6.3 %	4.3 %	5.1 %
Unusual results	67	85	n. a.	n. a.	152
Not reported (false)	50 (74.6 %)	33 (38.8 %)	n. a.	n. a.	83 (54.6 %)
Technical issue[b]	10 (14.9 %)	22 (25.9 %)	n. a.	n. a.	32 (21.1 %)
Recognised variant	7 (10.5 %)	30 (35.3 %)	n. a.	n. a.	37 (24.3 %)

[a] Without Allelic Discrimination assays affected by an impaired amplification of the "wild-type" sequence due to the [20175T>G; 20179_20180delAC] mutation

[b] Refers to laboratories not reporting genotypes but describing observations such as unusual results of presumed technical origin

- Typical figures in the field of molecular genetic testing
- Only a fraction of laboratories recognised and adequately reported unexpected SNPs.

Laboratory performance II: Error sources

- 2 labs used **inadequate nomenclature!**
- **21/30 (70 %) of the false results concentrate 9 laboratories only!**
- Majority of the false results arose from the inadvertence of laboratory personnel
  - Mixing up of the results post-analytically
  - Genotypes assigned incorrectly although the raw data showed the expected patterns.
- Allele-specific PCR assays proved to be less robust than other techniques
- The elevated error rate of certain LDTs indicates that they, as a group, have to be more carefully validated
  - Insufficiently robust laboratory developed LightCycler assay
- Alertness for the presence of additional mutations

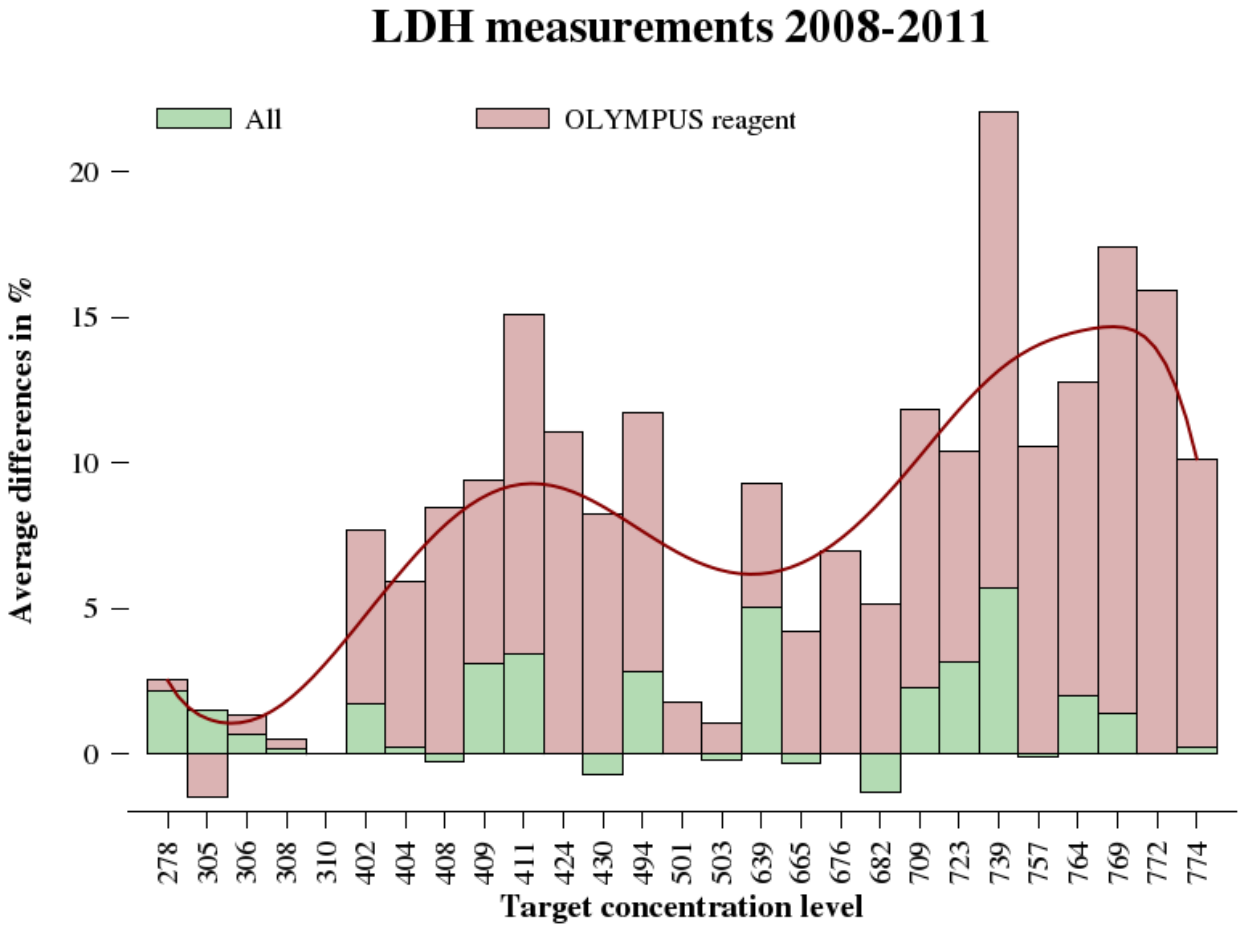
Laboratory performance III: conclusions

- The plasmidic FII QC Materials (QCMs) are commutable
- Raw data and description of methodology is indispensable for the identification of error sources!
- Weak points, which could be eliminated:
  - Allele Specific Amplification
  - Labs with poor performance
  - Training!!!

<u>Vigilance procedure</u>:

- Roche Diagnostics recalled and modified the Factor II (Prothrombin) G20210A Kit for the LC 2.0 instruments, because its macro component erroneously identified the C20209T mutation as wild-type genotype instead of an unknown variant.

Further examples for vigilance I: LDH (2008)



- Ca. 10% bias at the upper reference limit
- Difficult to detect by the individual laboratories

Further examples for vigilance II: Kell antigen (2005)

KörNév: 2005. III. Program: 231 Paraméter:

Reagens: BT

Módszer: 1

Labor	Eredm	

Laborszám: 001 Átl.: 1 1

VK%:

Célértékek: 1 2

Módszer: 3

Labor	Eredm	
351	1	1
437	1	1
837	1	2
844	1	2
856	1	1

Laborszám: 005 Átl.: 1 1,4

VK%: 0 39,12

KörNév: 2005. III. Program: 231 Paraméter: 7, Kell - antigén

Reagens: DM

Módszer: 1

Labor	Eredmények		

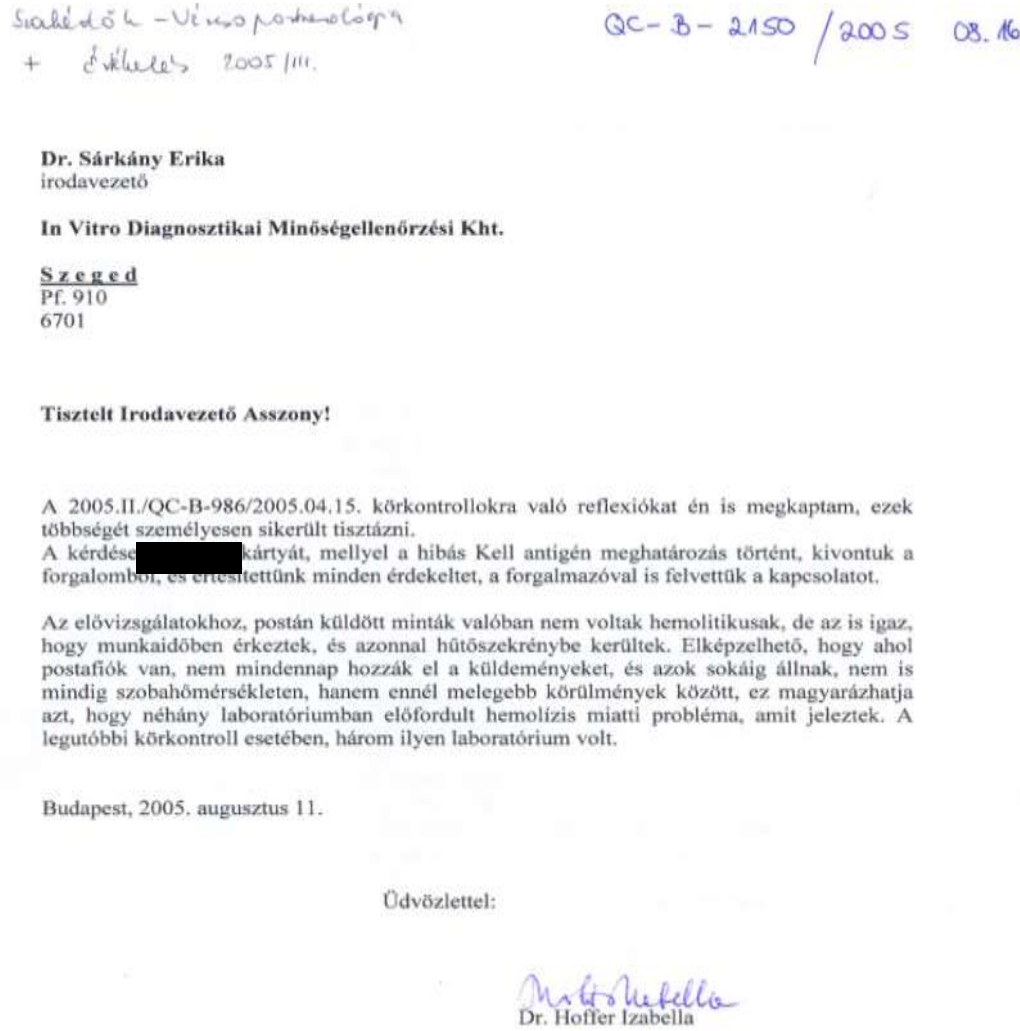
Módszer: 4

Labor	Eredmények		
148	1	2	
343	1	2	
347	1	2	
349	1	1	
350	1	2	
354	1	99	
433	1	2	
436	1	2	
438	1	2	
441	1	2	

Determination of blood group antigens such as the Kell antigen system belongs to the so called „high risk" measurements, the error in this measurements can lead serious deterioration in the patient state of health or may lead to death.

Further examples for vigilance II: Kell antigen (2005) /2

- The reagent kit was marketed under two different brand names.
- Only one batch was deteriorated
- The kit had been withdrawn from the market and
- All of the parties affected had been informed:
  - Laboratories,
  - Distributor/Manufacturer,
  - Authority



Szakértők – Vérsorpathológia
+ Értekezlet 2005/III.

QC-B-2150 / 2005 08.16

Dr. Sárkány Erika
irodavezető

In Vitro Diagnosztikai Minőségellenőrzési Kht.

Szeged
Pf. 910
6701

Tisztelt Irodavezető Asszony!

A 2005.II./QC-B-986/2005.04.15. körkontrollokra való reflexiókat én is megkaptam, ezek többségét személyesen sikerült tisztázni.
A kérdése[redacted]kártyát, mellyel a hibás Kell antigén meghatározás történt, kivontuk a forgalomból, és értesítettünk minden érdekeltet, a forgalmazóval is felvettük a kapcsolatot.

Az elővizsgálatokhoz, postán küldött minták valóban nem voltak hemolitikusak, de az is igaz, hogy munkaidőben érkeztek, és azonnal hűtőszekrénybe kerültek. Elképzelhető, hogy ahol postafiók van, nem mindennap hozzák el a küldeményeket, és azok sokáig állnak, nem is mindig szobahőmérsékleten, hanem ennél melegebb körülmények között, ez magyarázhatja azt, hogy néhány laboratóriumban előfordult hemolízis miatti probléma, amit jeleztek. A legutóbbi körkontroll esetében, három ilyen laboratórium volt.

Budapest, 2005. augusztus 11.

Üdvözlettel:

Dr. Hoffer Izabella

Conclusions

- As primary sources of inter-method performance data, EQAS distributing QCMs with target values traceable to a RMS are able to detect standardisation, specificity and interference problems, and efficient tools in the vigilance of IVD MDs
- In the EU, the contribution of the EQAS to the postmarket monitoring of IVD MDs is a legal obligation
- In order to utilize the full power of EQAS in the vigilance
  – a more exact identification of measurement procedures is needed, including also the cat# and lot# of reagents and calibrators, instruments
  – Gathering such additional data could be facilitated by harmonisation of EQA schemes and applying a standardised coding system and probably also a centralized database.

Thank you for your attention!