Thyreoglobuline assay: validatie van een nieuwe test

Paul Menheere

Maastricht Universitair Medisch Centrum

28-10-2009

Delfia TG assay uit productie

Kulderij, Bas [Bas.Kulderij@perkinelmer.com]

U hebt geantwoord op 02-11-2009 13:54.

Aan: Menheere, P
CC: Kempen, Maarten

Geachte heer Menheere,
Zoals telefonisch besproken heeft PerkinElmer besloten om de productie van de Delfia Thyreoglobuline kit (1244-038) stop te zetten.
De keuze hiervoor is gemaakt op basis van de problemen die wij ondervinden in het aankopen van het ruwe materiaal voor het produceren van de kit, alsmede de teruglopende vraag voor deze kit wereldwijd.

De laatste batch die geproduceerd zal worden, zal in September 2010 zijn. Deze batch zal een houdbaarheidsdatum hebben t/m Januari 2011.
Onze excuses voor het ongemak dat dit voor u zal geven, maar wij hopen dat door deze tijdige informering, het ongemak tot een minimum beperkt zal zijn.

Wij hopen u hierbij voldoende geinformeerd te hebben hierover, mocht u nog vragen hebben dan horen wij deze graag.

Met vriendelijke groet,

Bas Kulderij | Account Manager Genetic Screening
PerkinElmer | For the Better

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Belgium: Imperiastraat 8 | 1930 Zaventem
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direct fax: +31 (0)320 23 20 31

Answer: 3-11-2009

Dear Bas,

most awful idea

Thank you for informing me about the m[illegible]obulin assay.
The determination of thyroglobulin con[illegible] However, the concentration of thyroglobulin in human blood is of extreme importance in the follow-up of thyroid cancer patients.
Regardless of the type of cancer (papillary or follicular), thyroglobulin concentrations are among the most important pillars in the detection of recurrences. In the follow-up of patients with a low risk profile, nothing else is done but yearly thyroglobulin. Knowing this, we have a long experience (for more than 10 years already) in the use of Tg during follow-up. We have been able to check our experience versus the results of ^{131}J, and ^{124}J, completed in recent years with PET-CT and echo of the thyroid region. We are able to differentiate between stable disease, complete remission and recurrence. Based on the results of the Tg, patients with a low risk profile don't receive any more a yearly check-up with ^{124}J (for detection of positive lymph nodes), PET-CT (for detection of eventual tumour localizations) and a total body scan with ^{131}I (after stimulation by TRH or stopping thyroxin therapy for some weeks to detect tumour localizations out of the thyroid region). They just receive only an assay of the concentration of thyroglobulin in their blood. Recent developments show that even $T_2N_{1-0}M_0$ patients may be considered to be low risk patients.
This experience is undoubtedly linked to the actual thyroglobulin assay in use: the assay of PerkinElmer. We have a long experience with this assay and appreciate it for the low variation in the results, the stability of the reagents, the reproducibility, the low occurrence of bad recoveries and the relation of recovery and Tg-antibodies. All these items have been important in the clinical use of the results.
Some years ago, we wanted to start a comparison study with the assays of Nichols. In fact, the Nichols assay seemed attractive at that time since all assays (Tg, anti-Tg and Tg recovery) used the same reagents and secondarily, the Nichols assay was used in all other university hospitals). Effectively, we started with the study, but were unable to finish due to the disappearance of Nichols. Clearly, the Tg-assay of Perkin Elmer is accepted both in my clinics and in my laboratory as the best assay on the market.
If I'm forced to stop with this assay, undoubtedly, patients will suffer from it. We will need to re-consider the actual policy of low and medium risk in patients with thyroid carcinomas. Surely, we will need to study the sensitivity and the specificity of a new Tg-assay in recurrent disease. This will take a lot of time and it will cost a lot of money. The patient discomfort is undeniable. It's even impossible to adapt without additional work the threshold values that we use at the moment: due to matrix influences, quality control samples behave in the available assays in a different manner once they have been frozen or lyophilized.
I hope to have convinced you that stopping the production of the thyroglobulin assay is nothing else than a disaster.
Furthermore, I don't understand the reasons to do so. Surely, you can show around you villages and other place that are still in contact with more important locations by uneconomic bus-lines. The bus company decides to do so in order to have a complete distribution area and perhaps also from a social point of view to avoid isolating people. Perhaps you allow me to add, that Roche has produced for many years a CEA assay to be used only by Dr. E. van Kampen, famous clinical chemist in Groningen since the latter had a very, very large population of follow-up and the results of the CEA assay were essentially different from the new CEA assay (also by Roche). Perhaps less differences, but the similarity with my thyroglobulin assay is great.
Is it for economic reasons that you are going to stop? Think about the bus lines; eventually, you may raise the prices for the test.
Is it because I'm the only user? Perhaps I'm the only user, but I'm using a lot of other products of Perkin Elmer. You must realize also, that if I'm the only user (which is true for the Netherlands), I'm also the user that is always asked why I'm still using the PE kit for Tg. I have to explain my choice (especially, since I'm president of the quality control surveillance program) and I can explain it and I'm proud on my explanation. Next, I cannot believe I am the only user worldwide. And if so, shouldn't you show more respect for your only user?
Is it difficult to obtain the raw materials? Surely, it is difficult, but definitely not impossible.
I remember Perkin Elmer stopped some years ago the assay for NSE. But at that time, there was an ethical reason to do so: people had troubles in collecting raw human brains to prepare the reagents. Accepting that decision wasn't a problem for me, but, as far as I know, this isn't the case for thyroglobulin. However, the decision to stop the production of the thyroglobulin assay isn't far away from being non-ethical: a lot of patients are harmed.
I hope Perkin Elmer will r[illegible]

reconsider this decision

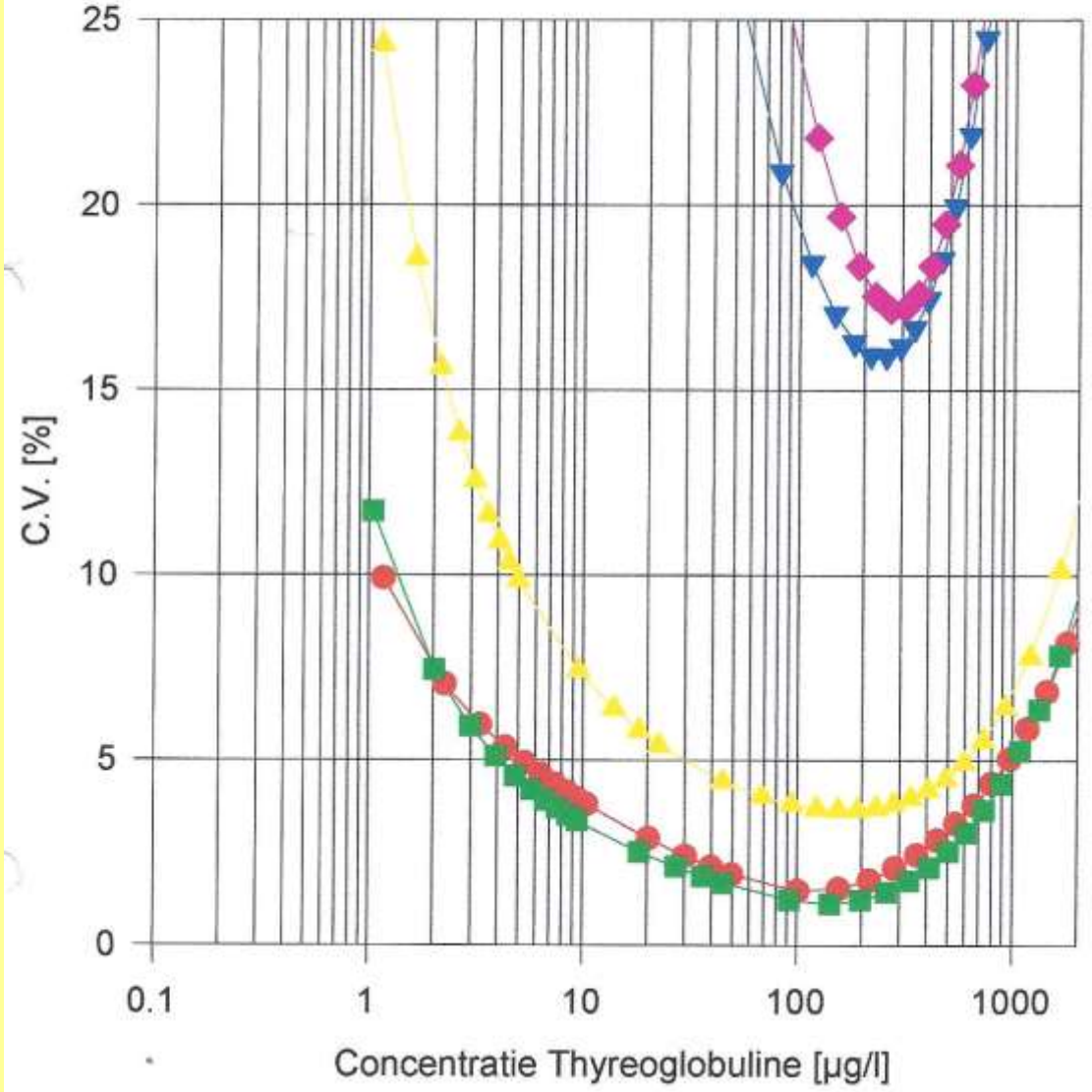
Yours sincerely,

Paul Menheere

Thyreoglobuline:

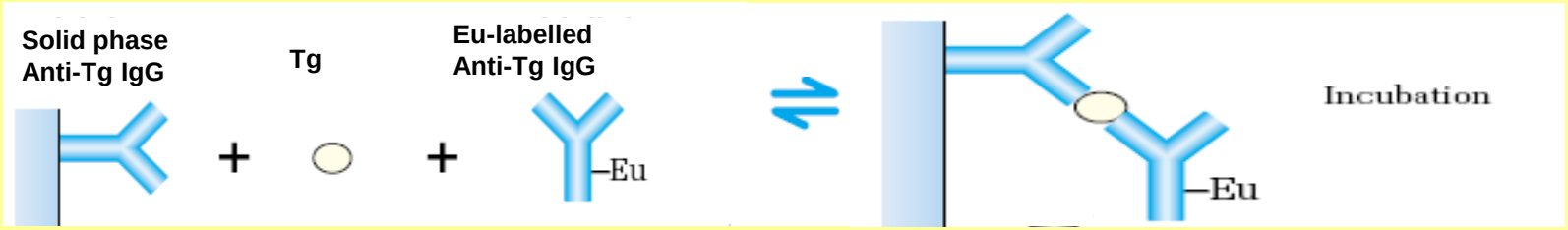
- Tot 1997 werd bepaling opgestuurd naar AMC, Prof Dr. J. de Vijlder
  - vaak gestoord door (auto-)antilichamen en dan helemaal geen uitslag
- In 1997 keuze uit:
  - Brahms (manueel; ^{125}J)
  - CIS (manueel; ^{125}J)
  - Perkin Elmer (Arcus; Eu)
- Verder diverse (manuele) technieken

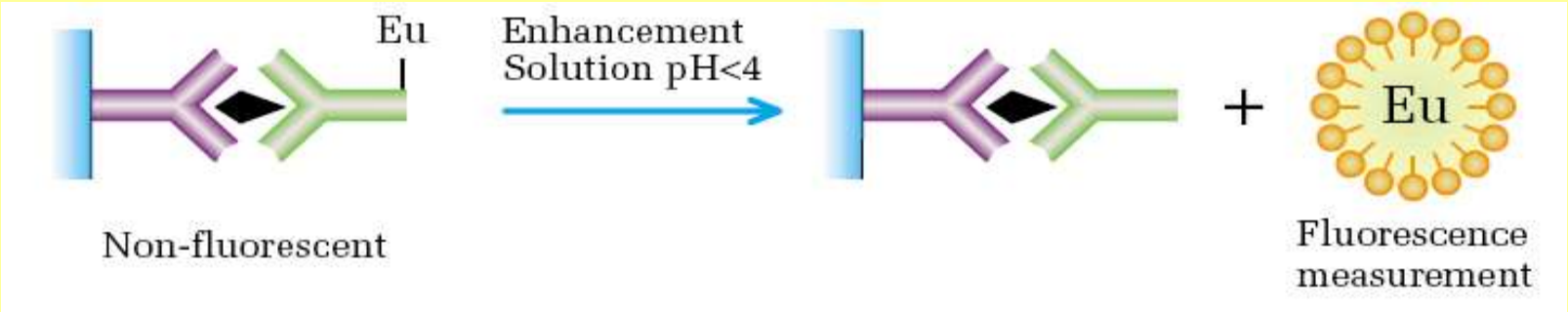
Precision Profiles
Thyreoglobuline bepalingen
mei 1997

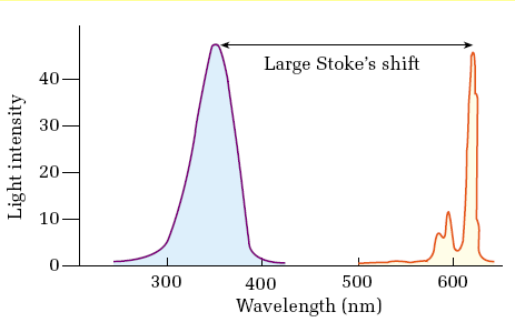


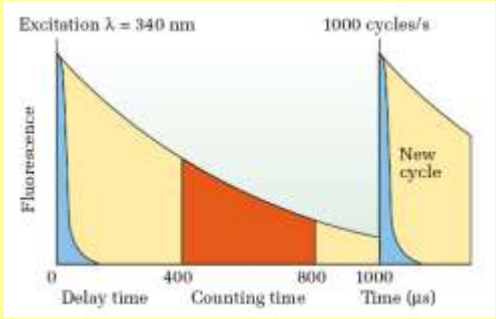
Karakteristieken Delfia Tg

- opbouw









Karakteristieken Delfia Tg

- MDC

Statistieken van: MDC

Uit | Per kitlot | Per controlelot

Totalen

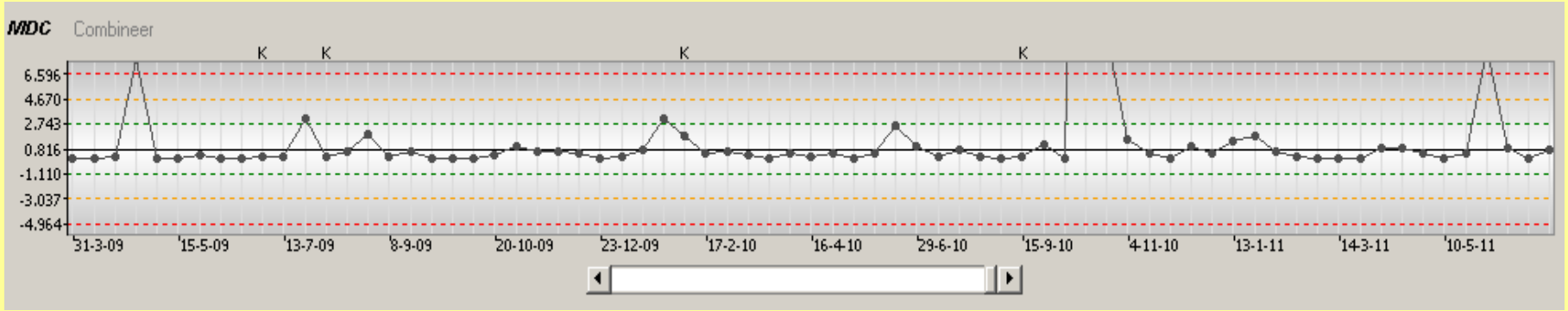
Gem.: 0.816

SD: 1.927

VC: 236.029%

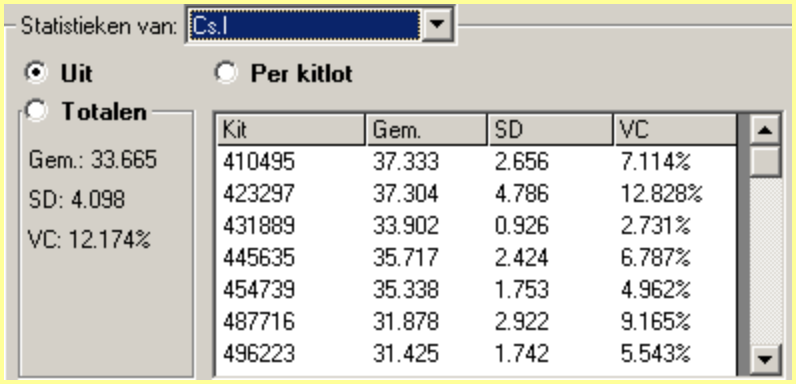
Kit	Gem.	SD	VC
410495	0.224	0.257	114.905%
423297	0.507	0.347	68.506%
431889	0.197	0.123	62.338%
445635	0.277	0.377	136.097%
454739	0.922	1.358	147.298%
487716	4.14	8.008	193.463%
496223	0.698	2.103	301.134%

Controle lot	Gem.	SD	VC
010102	0.816	1.927	236.029%

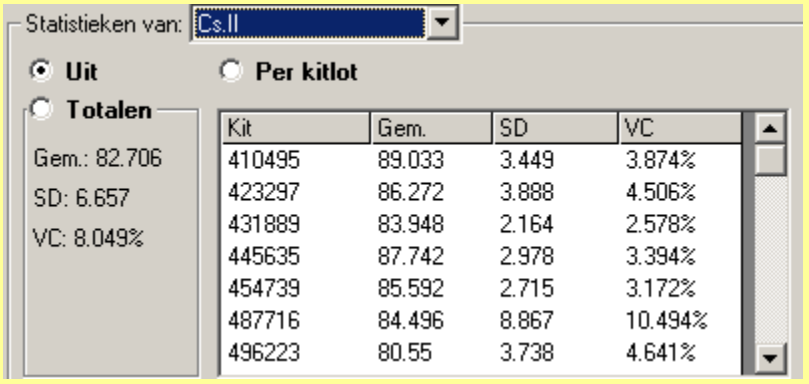


Karakteristieken Delfia Tg

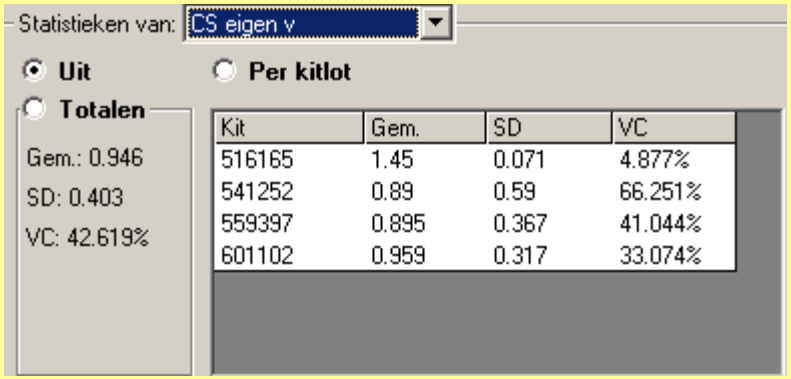
- VC



Kit	Gem.	SD	VC
410495	37.333	2.656	7.114%
423297	37.304	4.786	12.828%
431889	33.902	0.926	2.731%
445635	35.717	2.424	6.787%
454739	35.338	1.753	4.962%
487716	31.878	2.922	9.165%
496223	31.425	1.742	5.543%



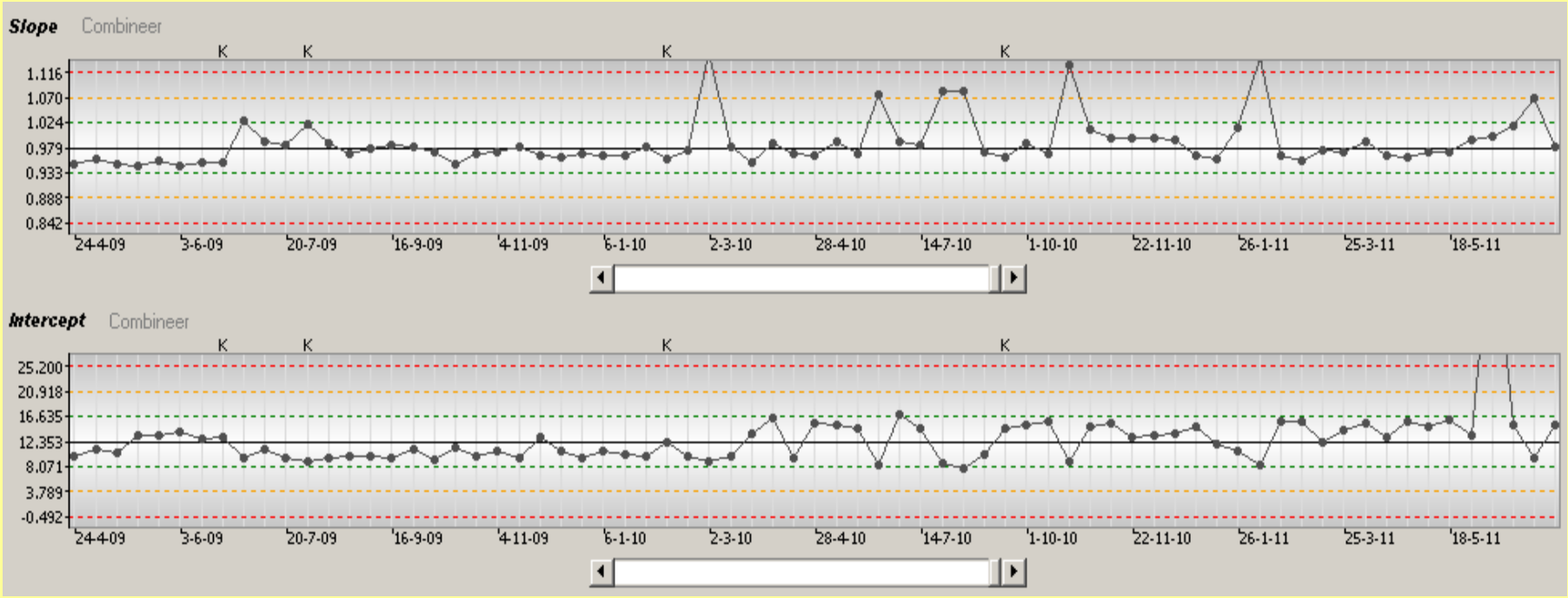
Kit	Gem.	SD	VC
410495	89.033	3.449	3.874%
423297	86.272	3.888	4.506%
431889	83.948	2.164	2.578%
445635	87.742	2.978	3.394%
454739	85.592	2.715	3.172%
487716	84.496	8.867	10.494%
496223	80.55	3.738	4.641%



Kit	Gem.	SD	VC
516165	1.45	0.071	4.877%
541252	0.89	0.59	66.251%
559397	0.895	0.367	41.044%
601102	0.959	0.317	33.074%

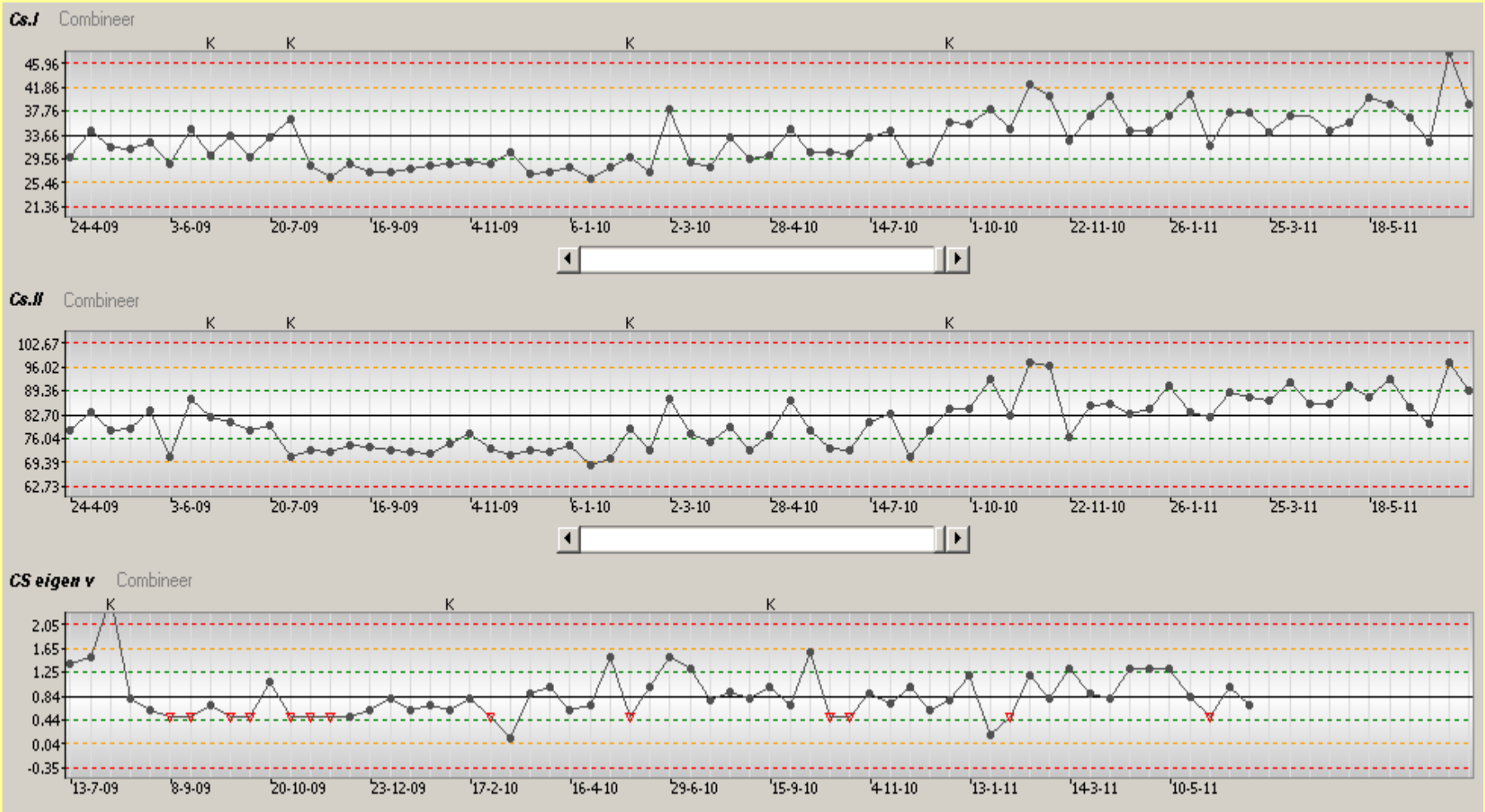
Karakteristieken Delfia Tg

- VC curveparameters



Karakteristieken Delfia Tg

- VC controle sera



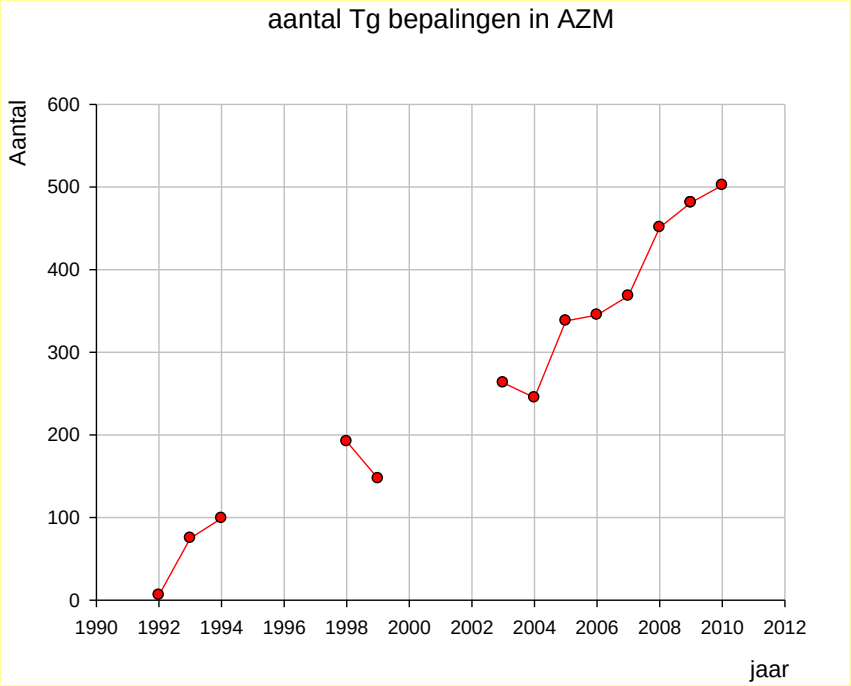
Karakteristieken Delfia Tg

- opbouw
- MDC
- VC
- overtuiging dat recidieven opgespoord zouden worden
  - Vergelijking van uitslagen met die van AMC
- gemakkelijke recovery
- gezamenlijk besluit
- geïntroduceerd in 1997

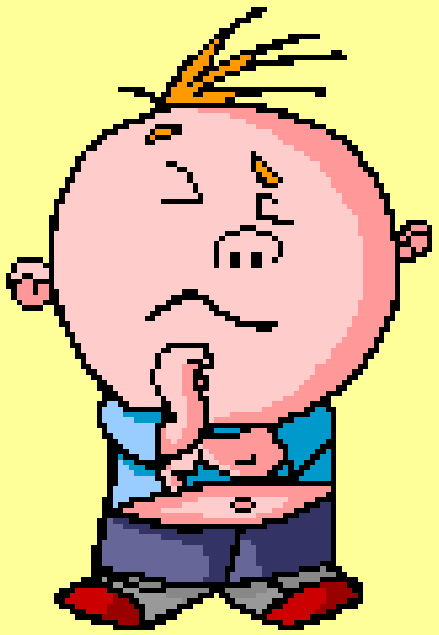
Tg Delfia later Autodelfia

tot 1-11-2010:

3993 bepalingen



En nu, hoe verder?

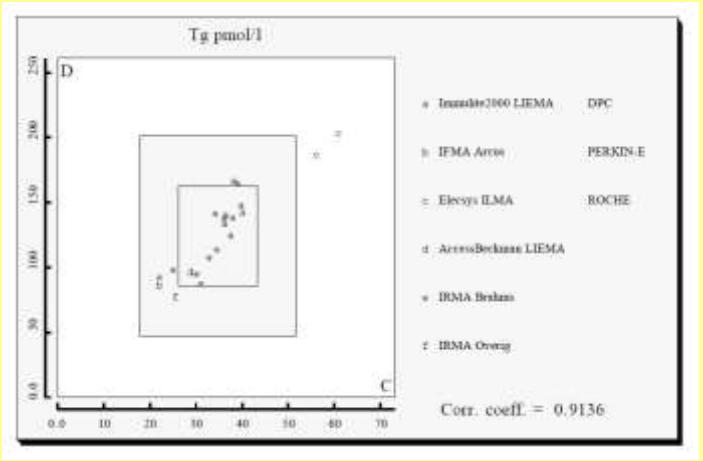


Plan van aanpak:

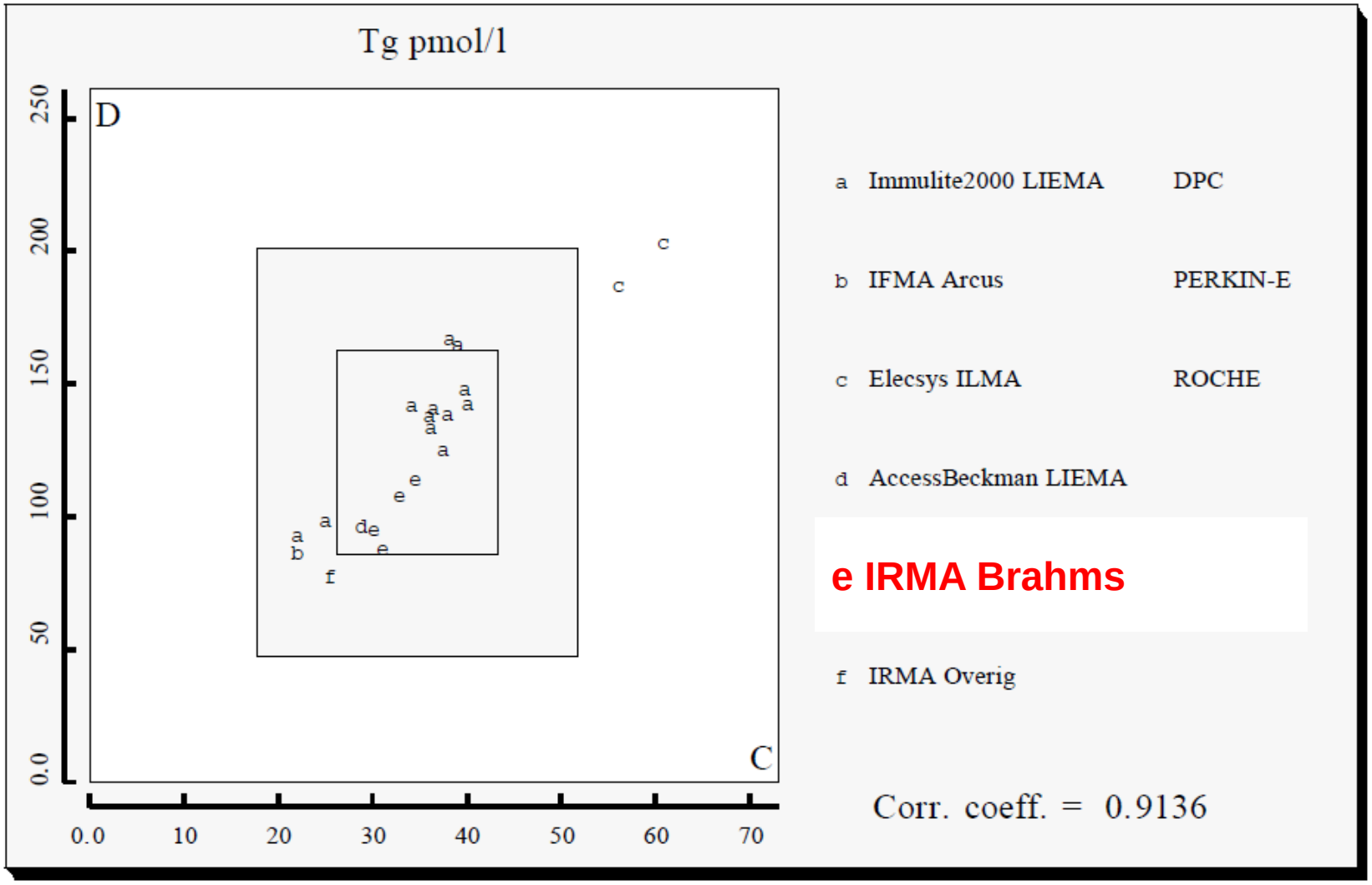
- zoektocht naar nieuwe bepaling
- vergelijking absolute waarden
- vergelijking reproduceerbaarheid
- lineariteit/verdunningen
- batch to batch
- LWBA/SKML
- recovery
- vergelijking op patiëntniveau
- Planning: 1 jaar
  - verzamelen monsters
  - uitvoering analyses

zoektocht naar nieuwe bepaling

- SKML: 22 labs
  - Autodelfia, Perkin Elmer 1
  - Immulite, Siemens 12
  - manueel, Brahms 5
  - Access, Beckman 1
  - Elecsys, Roche 2
  - IRMA,eigen 1
- Academische Ziekenhuizen
  - manueel, Brahms 5
  - IRMA, eigen 1
  - Autodelfia, Perkin Elmer 1



zoektocht naar nieuwe bepaling

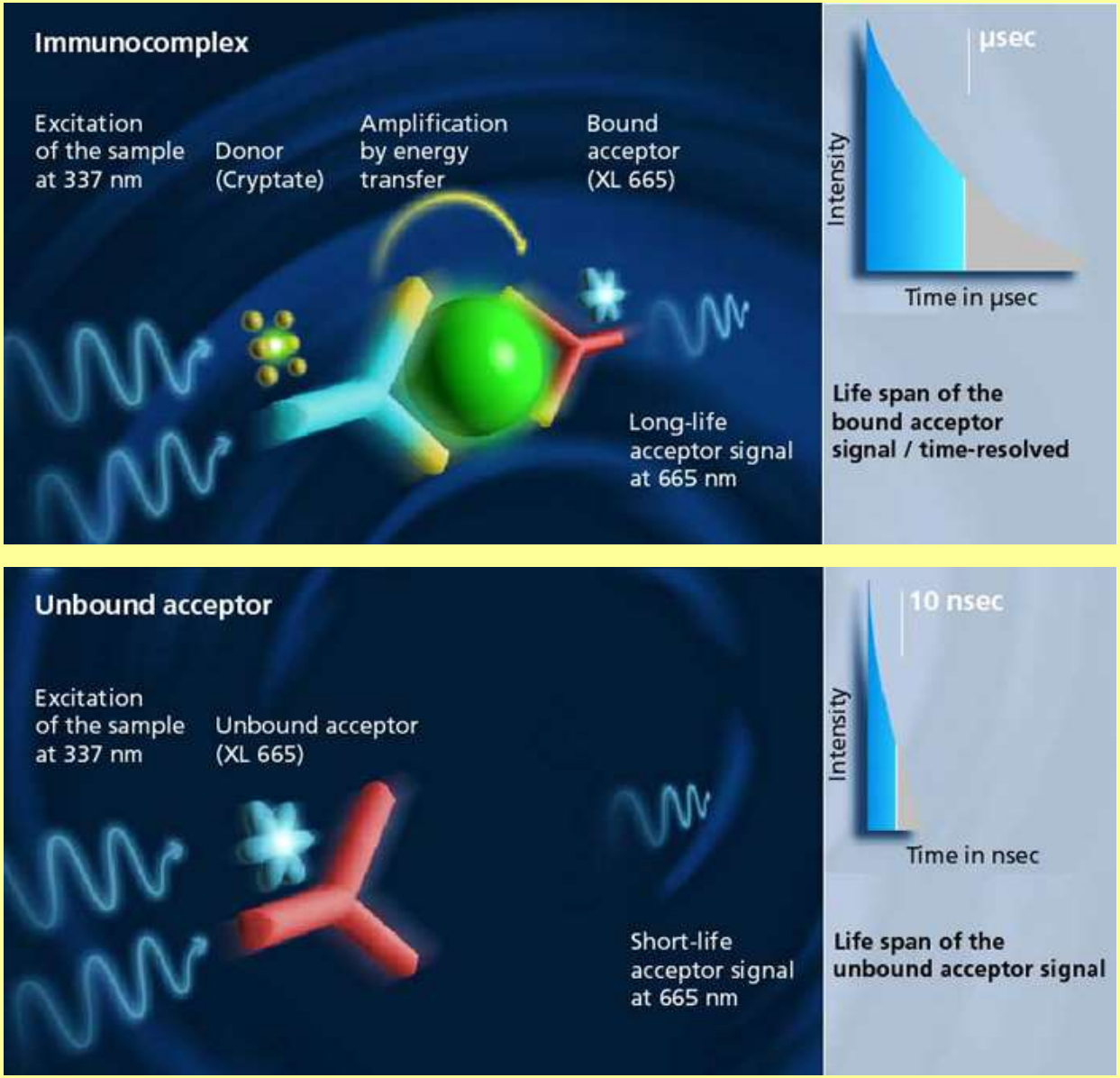


Gecharmeerd van Brahms:

- andere AC gebruiken deze ook
- goede ervaring met fabrikant
- persoonlijk contact met diverse sleutelfiguren
- 2 uitvoeringen:
  - Manueel
  - Kryptor
    - instrument in huis
    - verhoging van frequentie


1
2
3
4
5

Principe van de Kryptor:



Géén scheidingsmethode

Onderscheid tussen vrij en gebonden op basis van de afstand (=binding) van de moleculen

Plan van aanpak:

- zoektocht naar nieuwe bepaling
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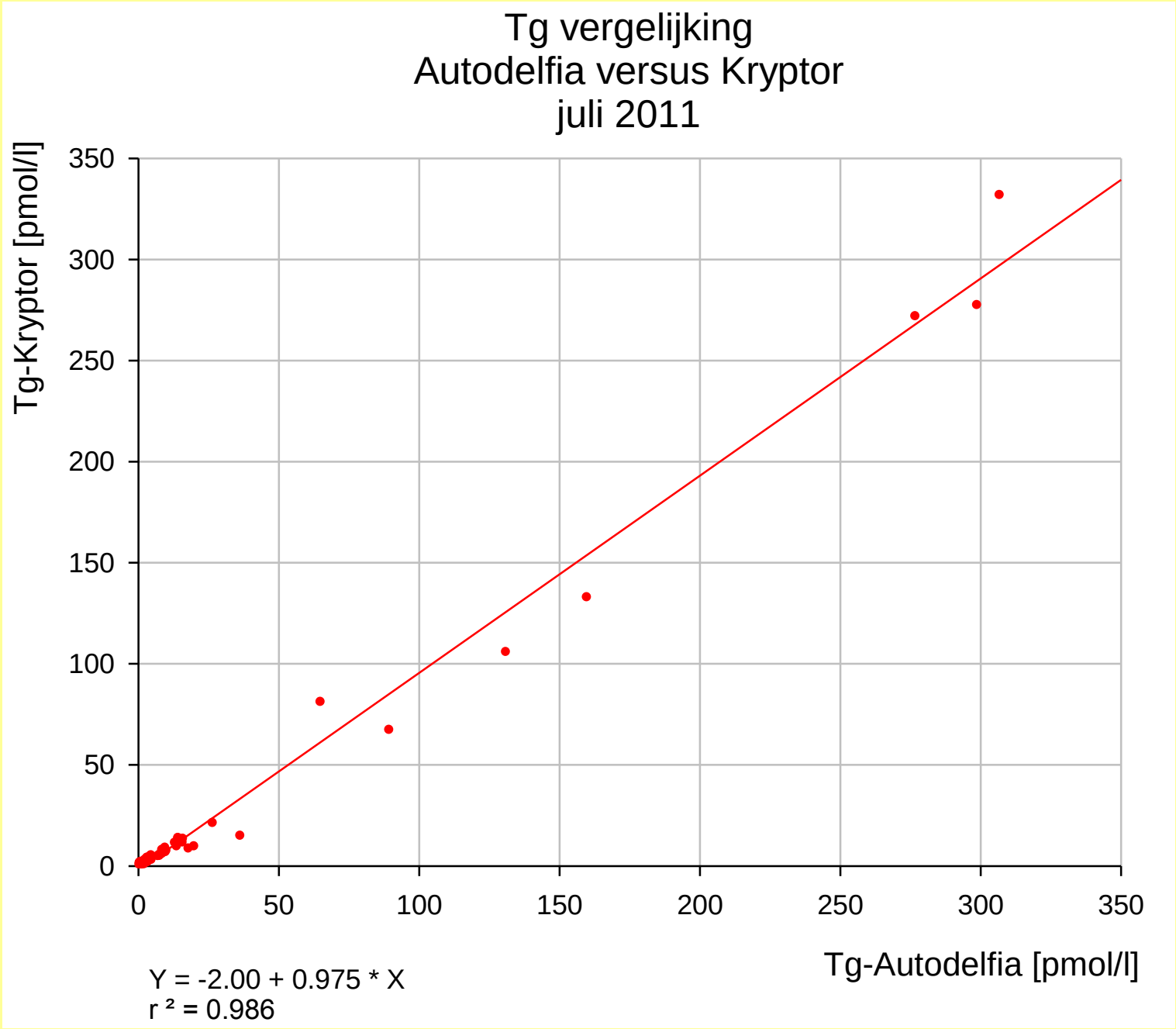
- LWBA/SKML
- recovery
- vergelijking op patiëntniveau
- Planning: 1 jaar
  - verzamelen monsters
  - uitvoering analyses

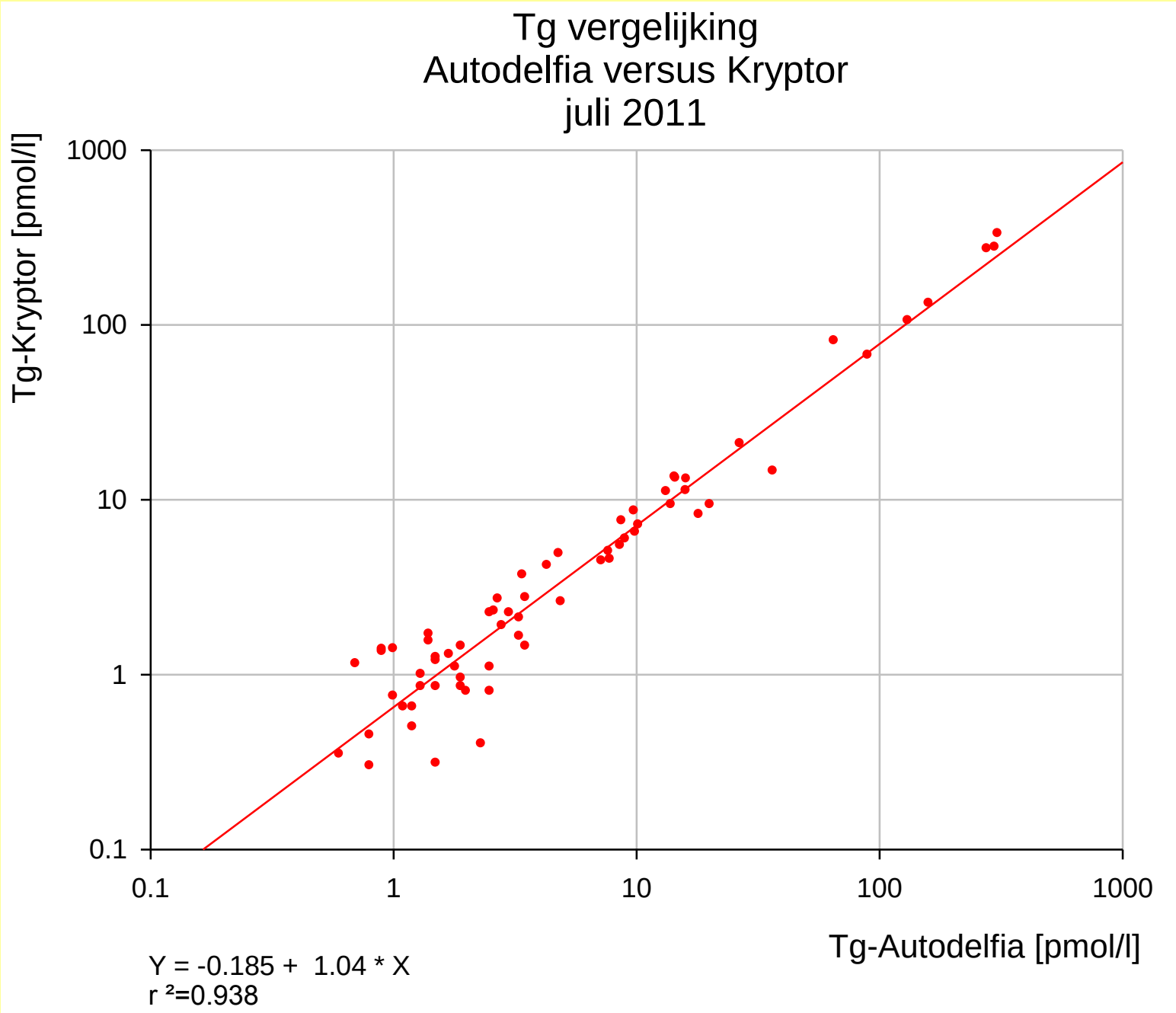
PvA: vergelijking absolute waarden

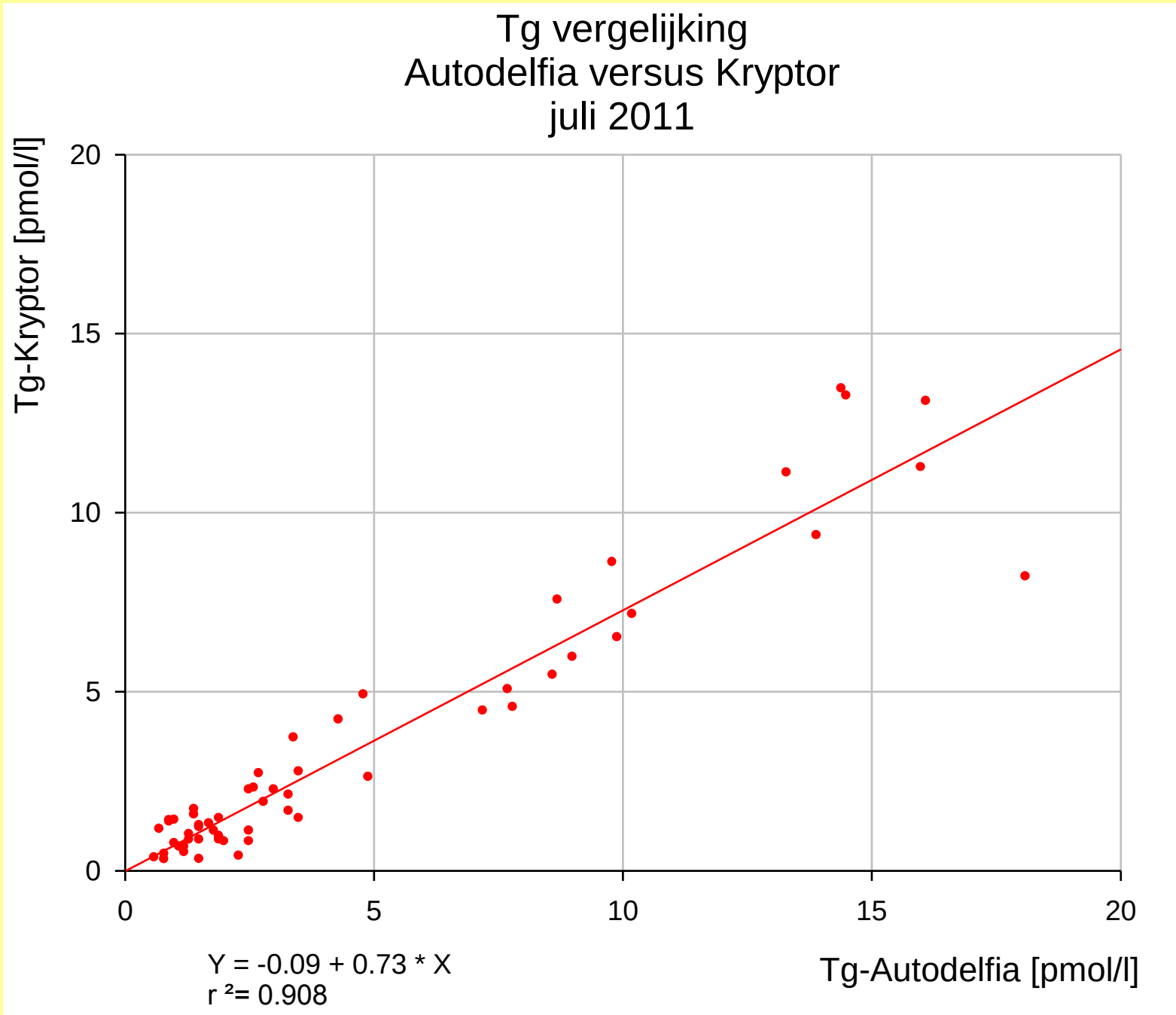
- N= 203 monsters
  - 111 met meetbare resultaten
  - 7 met <0.5 $[pmol/l]_{AD}$ en onvolledige recovery
  - 75 met <0.5 $[pmol/l]_{AD}$
  - 10 onvolledige recovery, meetbaar resultaat

PvA: vergelijking absolute waarden

- N= 203 monsters
  - 67 met meetbare resultaten
  - 60 toch te weinig restmateriaal voor Kryptor
  - 45 met <0.25 $[pmol/l]_B$ en <0.5 $[pmol/l]_{AD}$
  - 11 met <0.25 $[pmol/l]_B$ en 0.5 <AD<5.5
  - 7 met meetbare resultaten maar AD onv. rec.
  - 7 met AD < 0.5 [pmol/l] bij meetbare Brahms
  - 6 met <0.25 $[pmol/l]_B$ en onvolledige recovery


Tg vergelijking
Autodelfia versus Kryptor
juli 2011
Tg-Kryptor [pmol/l]
Tg-Autodelfia [pmol/l]
0
50
100
150
200
250
300
350
Y = -2.00 + 0.975 * X
r ² = 0.986


Tg vergelijking
Autodelfia versus Kryptor
juli 2011
Tg-Kryptor [pmol/l]
1000
100
10
1
0.1
0.1
1
10
100
1000
Tg-Autodelfia [pmol/l]
Y = -0.185 + 1.04 * X
r ²=0.938


Tg vergelijking
Autodelfia versus Kryptor
juli 2011
Tg-Kryptor [pmol/l]
20
15
10
5
0
0
5
10
15
20
Y = -0.09 + 0.73 * X
r ²= 0.908
Tg-Autodelfia [pmol/l]

PvA: vergelijking absolute waarden

- N= 203 monsters
  - 7 met AD < 0.5 [pmol/l] bij meetbare Brahms

Autodelfia	Brahms
<0.5	0.25
<0.5	0.25
<0.5	0.25
<0.5	0.27
<0.5	0.3
<0.5	0.75
<0.5	1.05

PvA: vergelijking absolute waarden

- N= 203 monsters
  - 7 met meetbare resultaten maar AD onvolledige recovery

Autodelfia onvolledige recovery	Brahms
58.0	43.8
5.3	2.0
38.3	31.1
21.7	20.2
1.9	2.6
1.8	0.8
0.9	1.2

PvA: vergelijking absolute waarden

- N= 203 monsters
  - 6 met <0.25 $[pmol/l]_B$ en onvolledige recovery

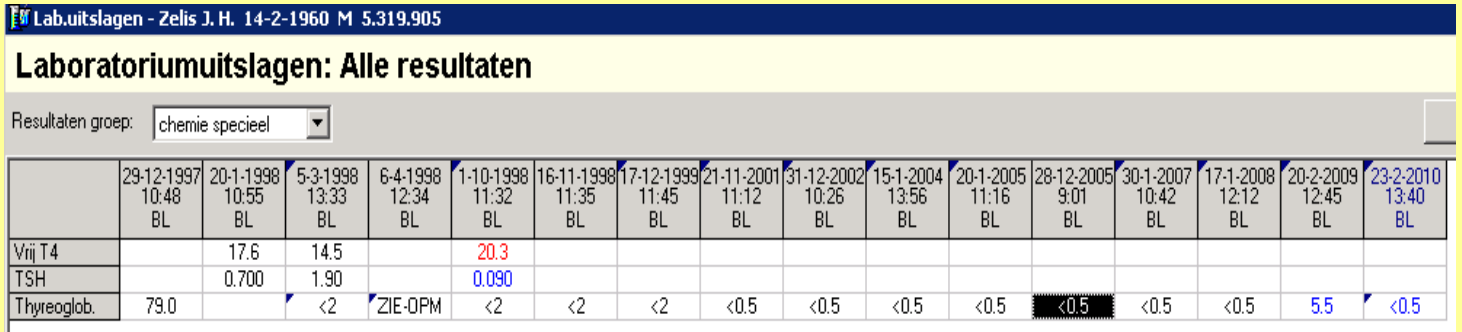
Autodelfia onvolledige recovery	Brahms
< 0.5	< 0.25
< 0.5	< 0.25
< 0.5	< 0.25
< 0.5	< 0.25
1.02	< 0.25
1.2	< 0.25

PvA: vergelijking absolute waarden

- N= 203 monsters
  - 11 met <0.25 $[pmol/l]_B$ en 0.5 <AD<5.5

Autodelfia	Brahms
0.5	< 0.25
0.5	< 0.25
0.5	< 0.25
0.5	< 0.25
0.6	< 0.25
0.6	< 0.25
0.7	< 0.25
0.7	< 0.25
0.7	< 0.25
1.3	< 0.25
5.5**	< 0.25

**waarschijnlijk is dit een Tg tijdens scan uit ander ziekenhuis



Lab.uitslagen - Zelis J. H. 14-2-1960 M 5.319.905

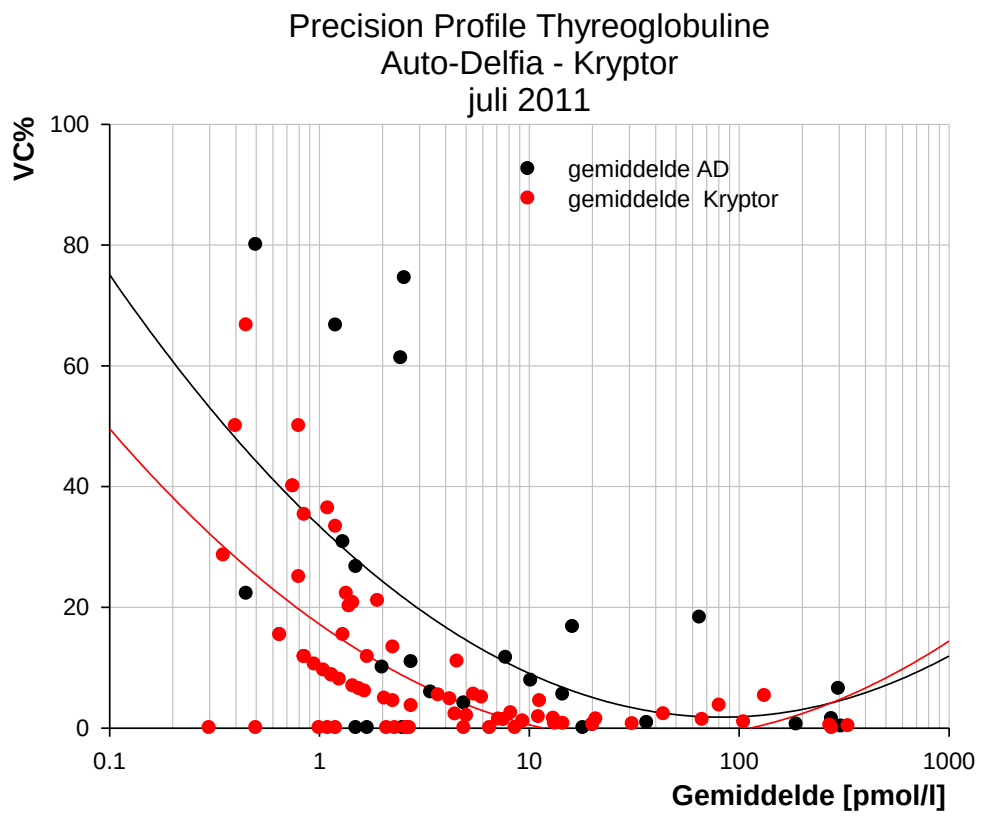
Laboratoriumuitslagen: Alle resultaten

Resultaten groep: chemie specieel

	29-12-1997 10:48 BL	20-1-1998 10:55 BL	5-3-1998 13:33 BL	6-4-1998 12:34 BL	1-10-1998 11:32 BL	16-11-1998 11:35 BL	17-12-1999 11:45 BL	21-11-2001 11:12 BL	31-12-2002 10:26 BL	15-1-2004 13:56 BL	20-1-2005 11:16 BL	28-12-2005 9:01 BL	30-1-2007 10:42 BL	17-1-2008 12:12 BL	20-2-2009 12:45 BL	23-2-2010 13:40 BL
Vrij T4		17.6	14.5		20.3											
TSH		0.700	1.90		0.090											
Thyreoglob.	79.0		<2	ZIE-OPM	<2	<2	<2	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	5.5	<0.5

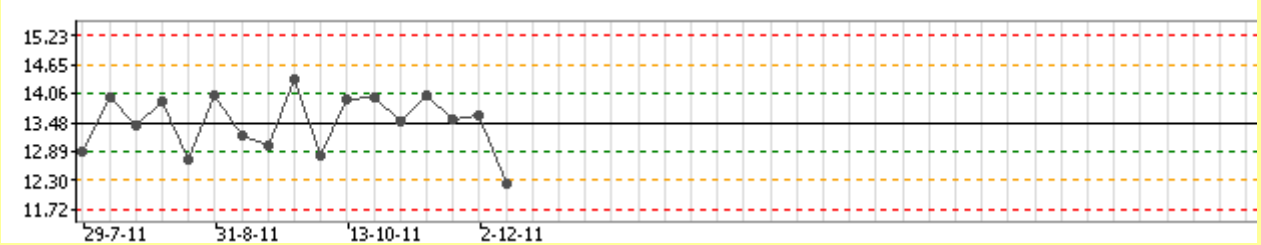
vergelijking reproduceerbaarheid

- precisie profiel

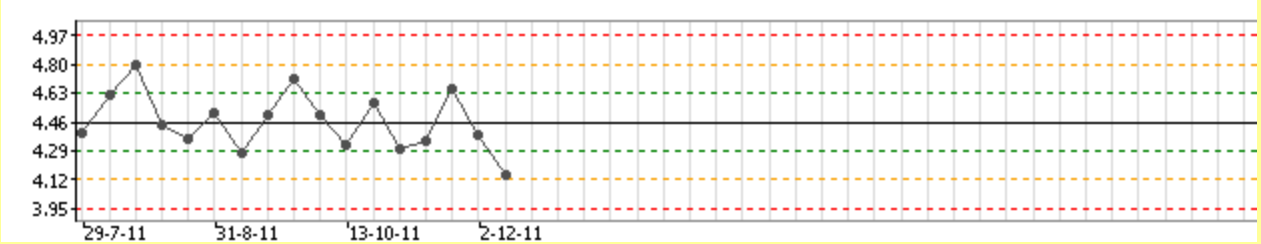


Resultaten dupliceerbaarheid/reproduceerbaarheid:

- Shewhartplots:
- Slechts één batch
- CS-eigen:

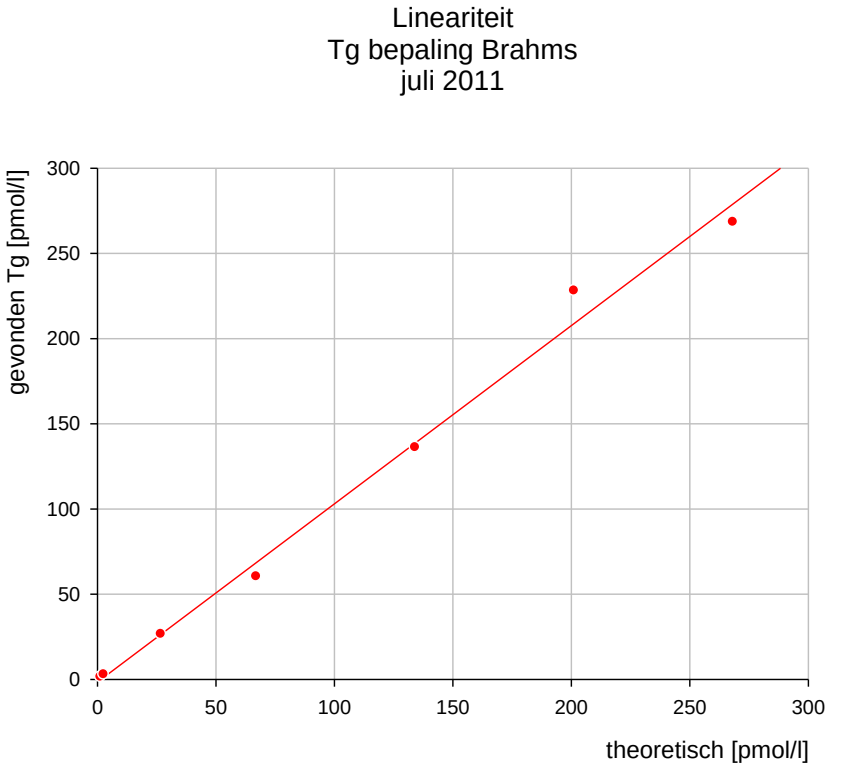


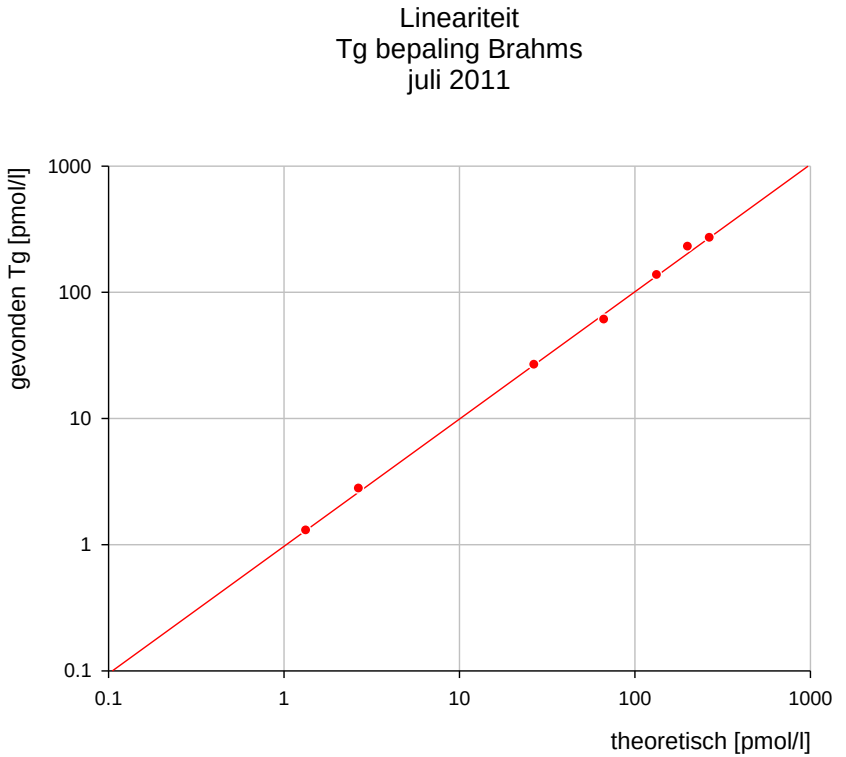
- Kit-1



- Kit-2

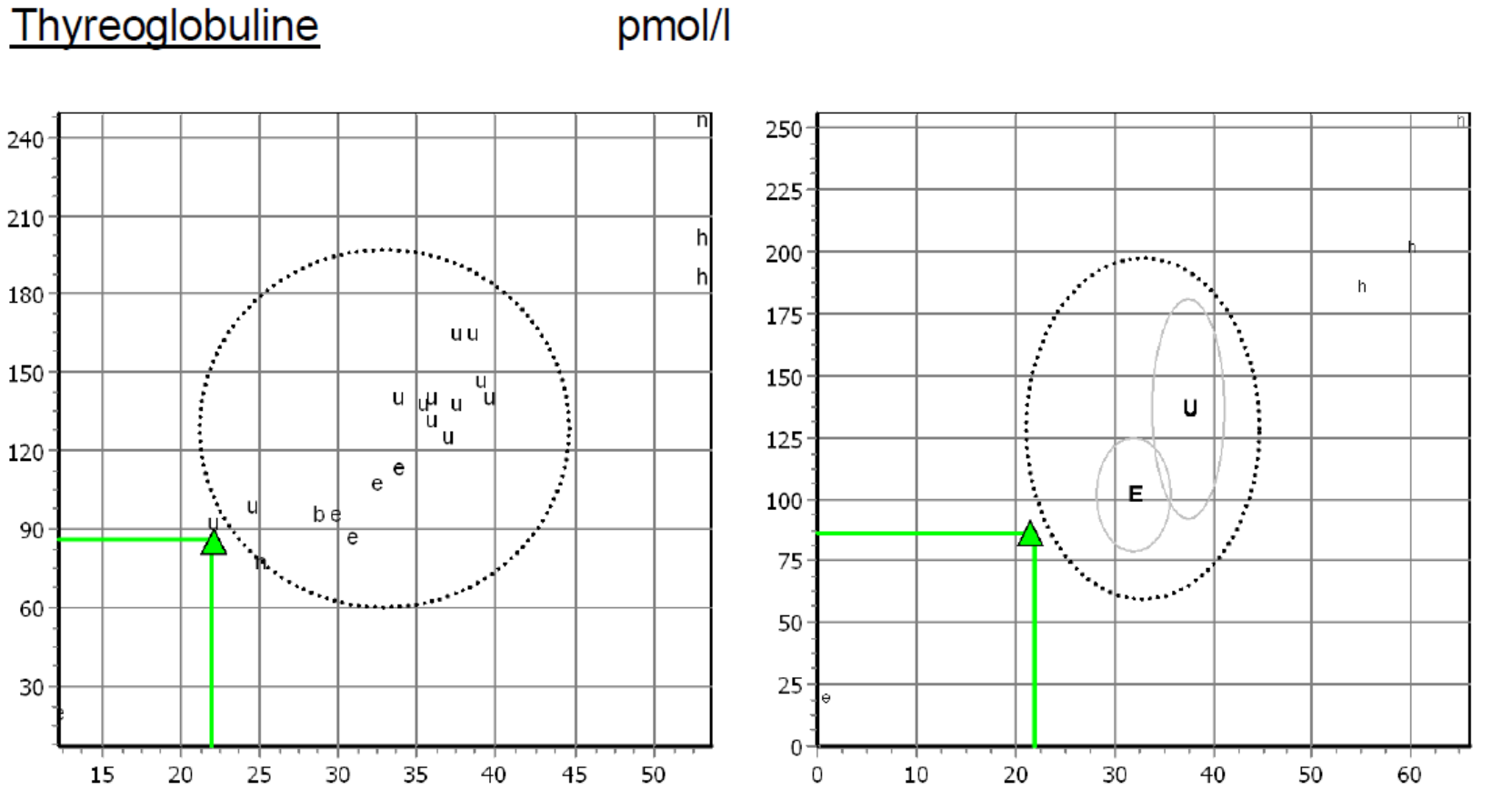
lineariteit/verdunningen





LWBA/SKML

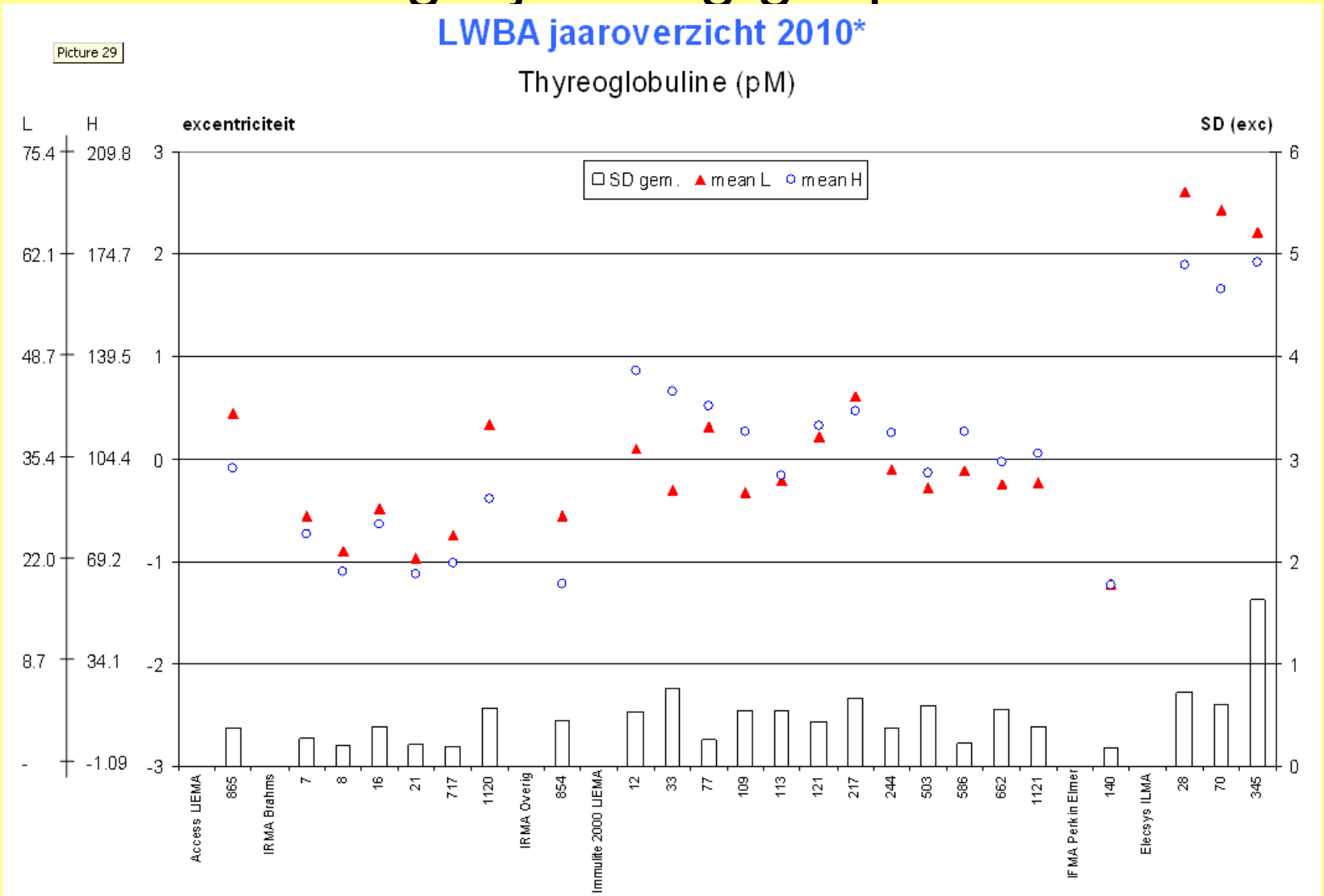
de verwachting zijn hoog gespannen:



e/E: Brahms; u/U: Immulite

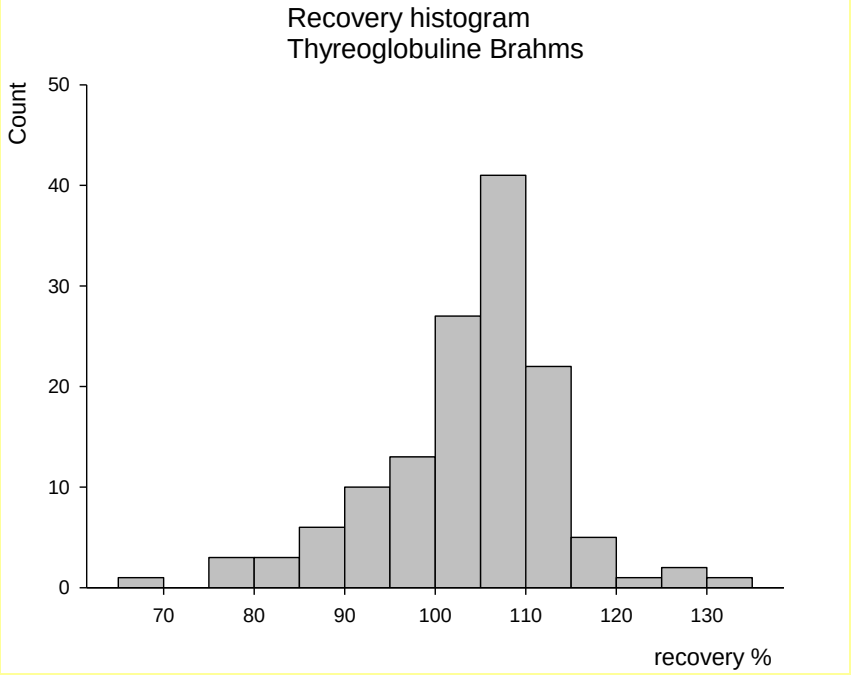
LWBA/SKML

de verwachting zijn hoog gespannen:



recovery

- N=203:
  - 68 te weinig materiaal
  - 135 numerieke uitslag voor recovery
    - (>70 % wordt beschouwd als normaal)
    - 1 keer < 70%
    - 3 keer tussen 70 en 80 %
    - 9 keer tussen 80 en 100%
  - Gemiddelde recovery 103 %
  - Mediaan recovery 105 %
  - Range: 68 - 130



vergelijking op patiëntniveau

- lopend project; resultaten bij elkaar te rapen

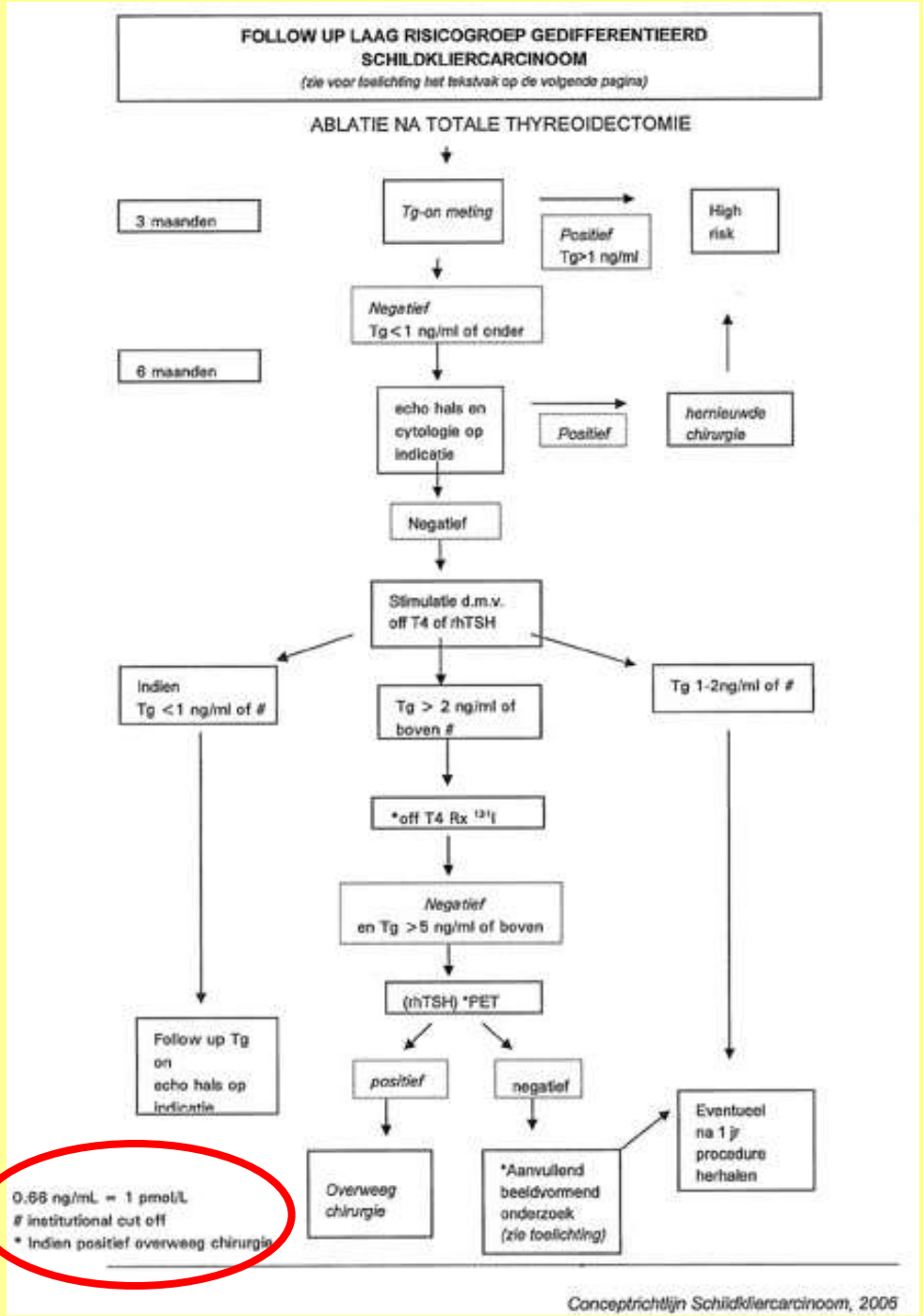
Conclusie analytische prestaties:

- vergelijking absolute waarden in lage gebied – 25 %
- in hoge gebied iets minder
- reproduceerbaarheid goed
- lineariteit/verdunningen goed
- batch to batch ervaring Brahms goed
- LWBA/SKML hoopvol gestemd
- recovery recovery nog wel meten?
- vergelijking op patiëntniveau lijkt goed, maar volgt nog
- bruikbaarheid in follow-up te bewijzen

9 Reference Range

The main indication for the hTg determination is in the context of differentiated thyroid cancer: After total surgical ablation of the thyroid gland and radioiodine therapy, the serum hTg level is less than 2 ng hTg/mL in 97 % of all metastasis- and recurrence-free patients (in complete remission) if TSH is completely suppressed. However, more than 90 % of all patients with distant metastases or tumor recurrence have serum hTg levels higher than the above mentioned hTg value. Higher serum levels are normally considered a direct indication for extensive diagnostic measures. Should residual thyroid tissue still exist, hTg secretion by that tissue must be taken into account.

A study with 208 presumably healthy test persons indicated that the samples were between 0.3 ng/mL and 58 ng/mL, with a median of 5.5 ng/mL.



$\therefore 1\ [ng/ml] = 1.5\ [pmol/l]$

Assay verandering:

leerzaam

ontzettend veel werk

veel klinisch begrip nodig

veel tijd nodig

∴

moet voor een langere periode zijn