National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Quality control parameters of Dutch Down's syndrome screening laboratories 2010

RIVM report 230083003/2012

P.C.J.I. Schielen, on behalf of the Dutch Down's syndrome screening laboratories

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Colophon

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Abstract

Quality control parameters of Dutch Down's syndrome screening laboratories 2010

This is the second report on the performance of Dutch screening laboratories pertaining to Down's syndrome screening. Data were kindly provided by the seven screening laboratories, and the evaluation was performed at the RIVM (housing the reference laboratory). The main purpose of this evaluation was to provide the annual (2010) number of screening tests (50,494), the participation rate of the pregnant population (26.8%), the median age of the participating pregnant women (32-33.5 years) and to give an impression of the proportion of high risk results for several regions (AMC-laboratory; 7.6%, RIVM-laboratory; 4.7%, VUMC laboratory; 7.2% and Rijnstate and MUMC laboratory; 5.9%). As was the case in 2009, there was a notable difference in the gestational age at blood sampling (at about 10 weeks in some regions and 12 weeks in others). The analytic performance was analysed by evaluating the concentrations of the serum parameters (pregnancy-associated plasma protein A; PAPP-A), the free β subunit of human choriongonadotropin (fβ hCG) and the nuchal translucency (NT) measurement and secondary parameters, showing that mostly, these parameters were according to quality standards during 2010. As data of two other quality control programmes - that all laboratories participate in - were also according to standards, we conclude that no major problems occurred in 2010. Recommendations based on the conclusions of this report include a thorough evaluation of the settings of risk estimation software and an evaluation of the detection rates and false positive rates for Down syndrome, applying fixed targets for the evaluation. If possible, the evaluation will be performed using the national prenatal screening database, 'Peridos'.

Keywords:
Screening laboratories, quality assurance, Down's syndrome screening, first trimester combined test

Rapport in het kort

Kwaliteitsindicatoren van de Nederlandse downsyndroom screening laboratoria 2010

Het RIVM heeft voor de tweede keer de prestaties van de Nederlandse downsyndroom-screeninglaboratoria geanalyseerd, en wel over het jaar 2010. Hieruit blijkt dat de tests naar behoren zijn uitgevoerd. De screening bestaat formeel sinds 1 januari 2007 en omvat een test op twee parameters uit bloed en een nekplooimeting. Met de evaluatie wordt voldaan aan de opdracht aan het referentielaboratorium om de kwaliteit van de screening te bewaken.

Voor de analyse hebben de zeven screeningslaboratoria, verspreid over Nederland, die de bloedtests uitvoeren, hun data over 2010 beschikbaar gesteld. Eén daarvan is het referentielaboratorium, dat is ondergebracht bij het RIVM.

Algemene bevindingen
In 2010 zijn in totaal 50.494 screeningstests afgenomen; dit betekent dat 26,8 procent van de zwangeren een dergelijke test laat uitvoeren (iets meer dan in 2009). De leeftijd waarop de test het vaakst wordt afgenomen ligt tussen 32 en 33,5 jaar (mediane leeftijd). Het percentage zwangeren dat volgens de screeningtest een hoog risico loopt op een kind met het Downsyndroom ligt rond de 6%

De prestaties van de laboratoria voldeden in het algemeen aan de kwaliteitseisen, en vielen bovendien allemaal binnen de internationale kwaliteitsnormen (UK NEQAS).

Analyse bloedtests en nekpooimeting
Verder zijn de gemiddelde concentraties (van de eiwitten PAPP-A en hCG-beta) van de bloedtests geëvalueerd, evenals de uitslagen van de nekplooimeting. Uit die analyse blijkt dat ze voldoen aan de kwaliteitscriteria die voor de screentests zijn opgesteld. Aanbevolen wordt onder andere om de instellingen van de kansberekeningssoftware van de laboratoria te evalueren, en daarbij nadrukkelijk aan te geven hoeveel van de kinderen die met downsyndroom zijn geboren, met de test zijn gedetecteerd. Een andere aanbeveling is om de screening naar andere chromosomale afwijkingen, te weten trisomie 13 en 18 in de evaluatie mee te nemen.

Trefwoorden:
screening laboratorium, kwaliteitsborging, downsyndroom screening, eerste trimester combinatietest

Conclusies en Aanbevelingen (Nederlands)

De conclusie van dit rapport is dat er in het algemeen weinig reden tot zorg is met betrekking tot de prestaties van de downsyndroomscreening zoals uitgevoerd door de Nederlandse screeningslaboratoria. Punt van aandacht is een bijstelling van de formules in de risicoberekeningssoftware (die voor de NT) bij het VUMC. De grote verandering in de risico's in de regio van de SPSNN is zorgelijk, en illustreert dat acute veranderingen in de risicoberekening leiden tot acute veranderingen in het resultaat van het regionale programma. Deze verandering in de risicoberekening bemoeilijkt de kwaliteitsbewaking van de combinatietest in de SPSNN regio.
Vanaf 2011 worden alleen nog de concentraties uit het UMCG laboratorium geëvalueerd in de jaarrapportage van de screeningslaboratoria. MoM (gewichtsgecorrigeerd en ongecorrigeerd) en risico's zullen verschillen van die van andere laboratoria, maar of dit een gevolg is van een kwaliteitsprobleem of een gevolg van een alternatieve risicoberekeningsmethode kan niet worden vastgesteld. Daarom is inclusie van deze gegevens niet van toegevoegde waarde bevonden.

De aanbevelingen naar aanleiding van dit rapport zijn dat in de toekomst het functioneren van de screeningslaboratoria eenmaal per kwartaal aan de hand van een vaste set criteria wordt beoordeeld. Deze criteria zijn vastgelegd in 2011 en zullen worden meegenomen in het rapporten over de laboratoriumgegevens van 2011. Tevens dient er een volledige evaluatie van de geüpdate software plaats te vinden, waarin met name de correlatiecoëfficiënt tussen PAPP-A en fβ hCG onderzocht wordt. Op basis van deze evaluatie zullen de instellingsparameters van de software op de website van het referentielaboratorium geplaatst worden. Een compleet nieuw onderdeel van de evaluatie zal de screening op trisomie 13 en 18 zijn, met meer aandacht voor de detectiepercentages van de screeningstest.

Contents

Abbreviations/Afkortingen

CI	Confidence Interval (betrouwbaarheisinterval)
CRL	Crown-rump length (kruin-stuit lengte)
DR	Detection rate (detectie)
Fβ hCG	vrije β subunit van humaan choriongonadotropine (Free β subunit of Human Chorionic Gonadotropin)
FMF	Fetal Medicine Foundation
GA	Gestational age (zwangerschapsduur)
IVF	In Vitro Fertilization
MoM	Multiple-of-the-median (veelvoud van de mediaanwaarde)
NT	Nuchal translucency (nekplooimeting)
OAPR	Odds of being affected given a positive result
PAPP-A	Pregnancy-associated plasma protein-A
QA	quality assurance (kwaliteits bewaking)
SKML	Stichting Kwaliteitsbewaking Medische Laboratoriumdiagnostiek (Dutch Foundation for Quality Assessment in Medical Laboratories)
SPR	screen positive rate
UK NEQAS	United Kingdom National External Quality Assessment Service
VWS	Ministerie van Volksgezondheid, Welzijn en Sport (Ministry of Health, Welfare and Sports)
Wpb	Wet bescherming persoonsgegevens

1 Introduction

The Dutch national programme for Down syndrome screening started formally on January 1st, 2007.

Both the reports of the Dutch Health Council (1) and the letters to Parliament of State Secretary Ross van Dorp in 2004 and 2005 (2, 3), stressed the importance of the programmes quality assurance. Limiting the number of screening laboratories to seven was one of the measures to meet this aim, enabling the rigid control of the quality of the screening test, and, because of the high number of analyses per laboratory, allowing for timely corrective action in case of an incident (4). The quality assurance guidelines for the screening test and the laboratories were issued by the 'Centraal Orgaan' (Central Agency), the main advisory board of the Centre for Population Research (RIVM), which is responsible for the organization of the prenatal screening programme.

Already since 2004, the Dutch ('candidate') screening laboratories have met frequently with 3-4 months' intervals, to discuss operational matters and, especially, quality assurance and quality control issues. To minimize operational variations the laboratories agreed to all use the same equipment to measure serum concentrations of PAPP-A and fβ hCG and to all use the same risk estimation software. Subsequently, they decided to all participate in the UK NEQAS quality assurance programme for the first trimester combined test and to initiate a Dutch programme for quality assurance as well. They also agreed on mutual and regular evaluation of their UK NEQAS results. Moreover, they evaluate the settings of their risk estimation software annually.

In this -second- report, written on behalf of all screening laboratories and by assignment of the RIVM-Centre for Population Research, the performance indicators related to the quality of the analysis of PAPP-A and fβ hCG for all laboratories is presented, as is the evaluation of the settings and performance of the risk calculation software. This report aggregates data adapted from annual reports of the individual laboratories. Additional data concerning the performance of the Down screening laboratories was already published in three RIVM reports (5-8).

2 Materials and Methods

For the performance of the test, all laboratories complied with the guidelines issued by the director of the programme, the Centre for Population Research and assembled by the Central Agency.[1] In general, blood sampling was done between a gestational age (GA) of 8 and 14 weeks and the nuchal translucency (NT) measurement carried out at a crown-rump-length (CRL) of 45-84 mm.

All Dutch screening laboratories used Lifecycle 2.2 risk estimation software, in combination with Elipse Configuration Tool 2.1 (PerkinElmer Life sciences, Turku, Finland). The parameters in Elipse are virtually the same for all laboratories and are available online.[2]

The Dutch screening laboratories were asked to send relevant data to evaluate the performance of the combined test and to the reference laboratory (RIVM). These data were analysed to identify regional differences in the screened population and in the execution of the test. Moreover, data were used to review the performance indicators of the combined test. For part of that work, the software programme 'QA tools' was used (version 1.0; MediaInnovations, Leeds, UK).
All laboratories participated in the UK NEQAS first trimester combined test quality assurance scheme. The collective data of the seven laboratories were reported on a monthly basis and these reports are crafted into evaluation reports that are discussed in the regular meetings of the group of screening laboratories (available on http://www.rivm.nl/downlab/Rapportagedatabase/).
A summary of the 2010-UK NEQAS data is given in Annex 1.
Finally, in Annex 3, a summary is provided of the performance of the screening laboratories in the Dutch SKML quality assurance scheme, 2010 being the first full year to be covered by that scheme.

The seven screening laboratories are

- Reference laboratory Down's Syndrome screening, RIVM, Bilthoven (RIVM) Utrecht and Leiden region (SPSRU and RCPS-NZH)
- Clinical Chemical laboratory, Free University Medical Centre, Amsterdam (VUMC) Amsterdam region (RCPS)
- Clinical Chemical laboratory, Amsterdam University Medical Centre, Amsterdam (AMC) Amsterdam region (SPSAO)
- Clinical Chemical Laboratory, Groningen University Medical Centre, Groningen (UMCG) Northern region (SPSNN)
- Clinical Chemical laboratory, Alysis Zorggroep, Arnhem (Rijnstate) Nijmegen and Tilburg region (SPN)
- StAR, Medical Diagnostic Centre, Capelle a/d IJssel (StAR) Rotterdam region (SPSZN)
- Clinical Chemical Laboratory, Maastricht University Medical Centre, Maastricht (MUMC) Southern region (RSPSM)

[1] http://rivm.nl/Bibliotheek/Professioneel_Praktisch/Richtlijnen/Preventie_Ziekte_Zorg/Algemene_kwaliteitseisen_voor_laboratoria

[2] http://www.rivm.nl/downlab/Images/instellingen_LC_19052008_tcm30-38017.pdf

3 Results

3.1 Number of tests performed, gestational age, maternal age

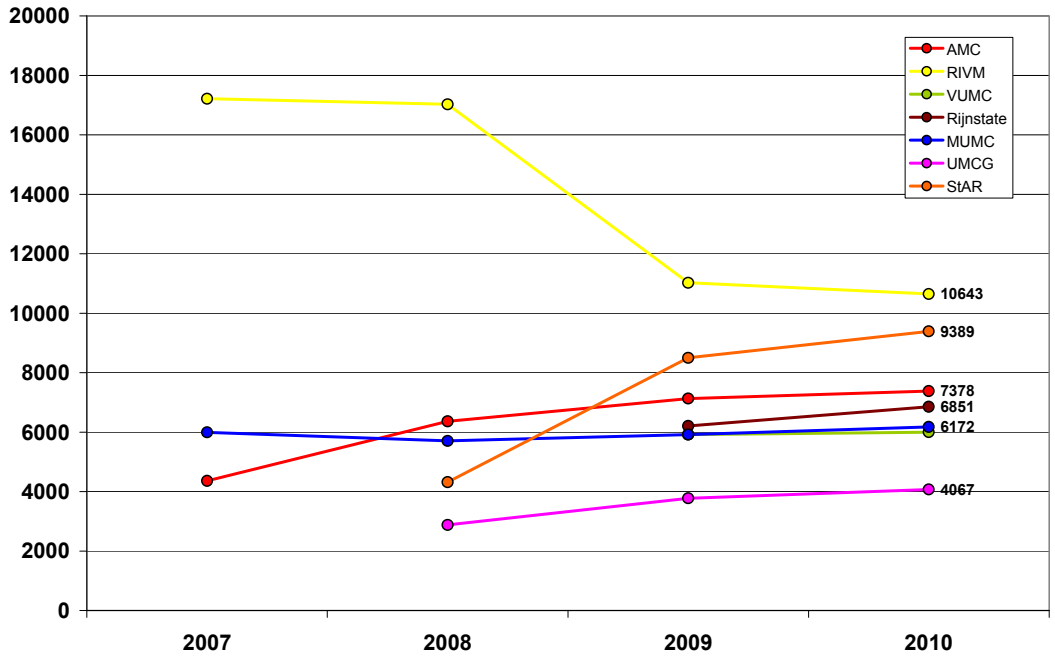

Figure 1 Number of samples analysed by the screening laboratories between 2007 and 2010
Note: not for all years data were provided or available.

In Figure 1 the total number of samples submitted to the first trimester combined tests of all the laboratories is given. This number for 2010 was 50,494 representing a 26.8% uptake, based on a birth rate of 184,397 live-births for 2010 (www.cbs.nl, 14 September 2011) and a 2% correction for lost pregnancies. Of these, 1.5% were obtained from women with a twin pregnancy (range for the laboratories: 0 – 3.0%). In addition 0.3% (0 – 0.5%) were samples from women with a previous DS pregnancy.

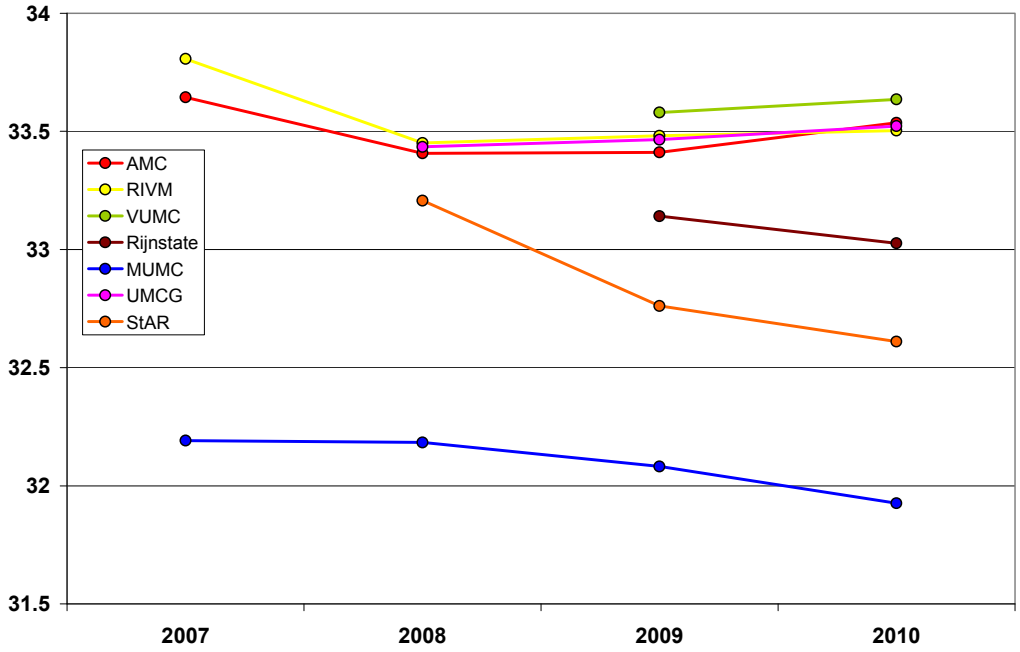

Figure 2 Median maternal age (at the moment of the test) of women requesting a combined test

In Figure 2 the maternal age for 2010 is represented.
While in general there is not much difference in median maternal age at testing between 2007-2009, there is some difference between the median ages of the populations of the various laboratories. Especially those of the MUMC and StAR are notably lower.

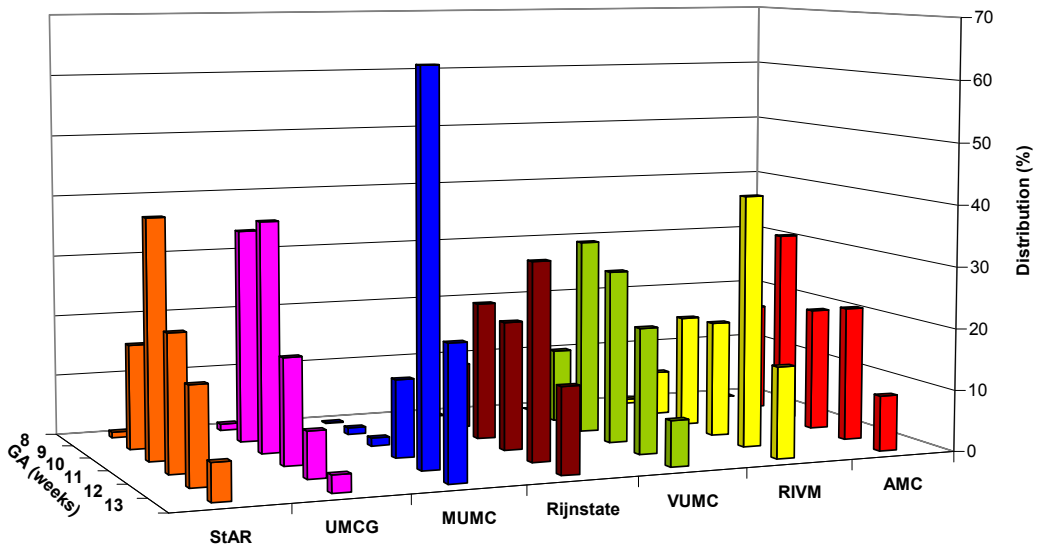

Figure 3 Distribution of GA at blood sampling (2010)

In Figure 3, the distribution of GA at blood sampling for the various laboratories is presented. Notable differences still appear between the practice of the regions. The laboratories of the StAR, UMCG and AMC process samples taken at quite early GA (around ten weeks), while the distribution is more even for the laboratories of VUMC, RIVM and Rijnstate. The samples analysed at the MUMC are collected rather late.

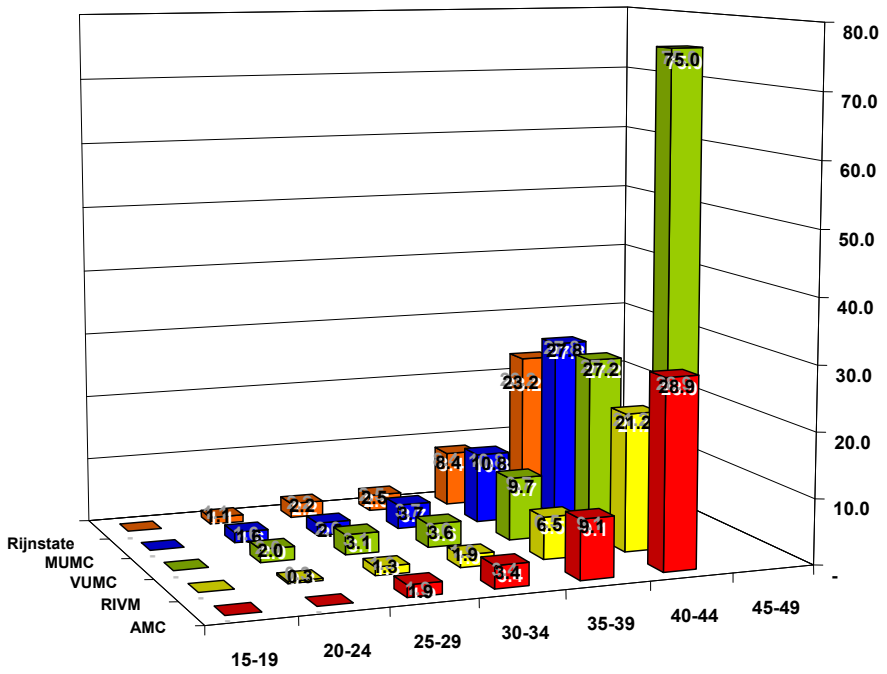

Figure 4 Percentage of high risk results for laboratories in which combined risks are calculated

In the Netherlands, the final, combined risk is either calculated by the screening laboratory based on LifeCycle-Elipse software, or, alternatively, in a peripheral hospital or centre for sonography, using the FMF/Astraia software. Thus, from the StAR, and UMCG laboratories, no combined risks are available. In the regions of the VUMC and MUMC, risks are calculated exclusively by the laboratories. Ultimately, 81% 42% and 17% of the risks of the RIVM, Rijnstate and AMC laboratories respectively, are calculated in the laboratory. Thus, only for the latter five laboratories, a relationship between maternal age and the percentage of high risk results can be given (Figure 4). Data of these laboratories are rather consistent concerning the percentage of high risk results per age class. Data of the VUMC in the 45-49 class were based on four analyses.

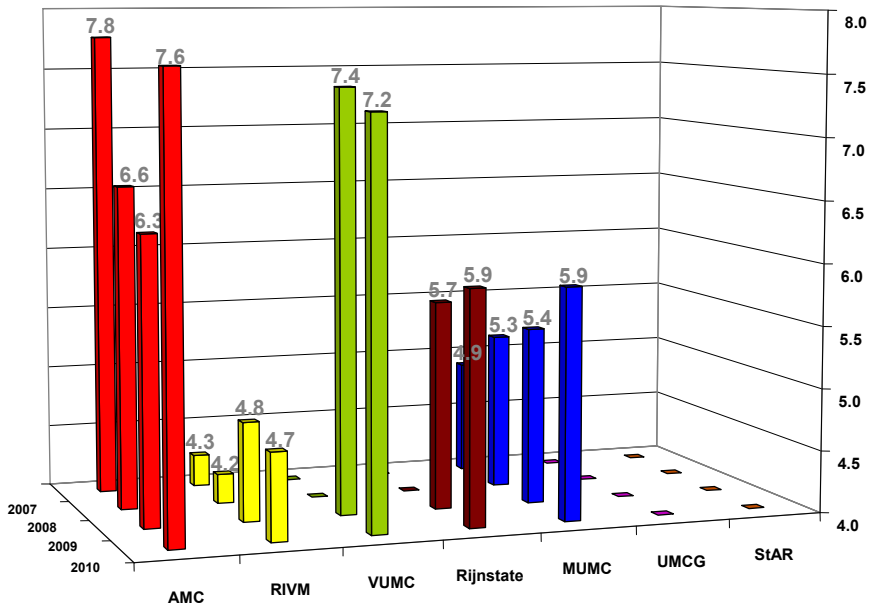

Figure 5 Overall Percentage of high risk results for laboratories in which combined risks are calculated (2007-2010)
Please note the scaling of the y-axis (adapted to illustrate the differences between the laboratories).

In Figure 5 the percentage of high risks for 2007-2010 is presented for those laboratories for which data is available. Apparently, the percentages of high risk results of the RIVM are rather low, while those of the AMC and UMCG are rather high.

3.2 Evaluation of laboratory parameters

For a properly functioning risk calculation process, a number of demands needs to be met. Thus, the concentrations of PAPP-A and fβ hCG need to increase and decrease respectively, with GA, and to the amount defined by the settings in the risk estimation software. Concentrations are converted to MoM values that relate to the maternal weight. Again, this relationship is closely defined in the software and the data of the laboratories should match this definition. Finally, monthly median MoMs of normal pregnancies should match 1.0 and the log MoM should be a Gaussian distribution. An evaluation of all these parameters is given below.

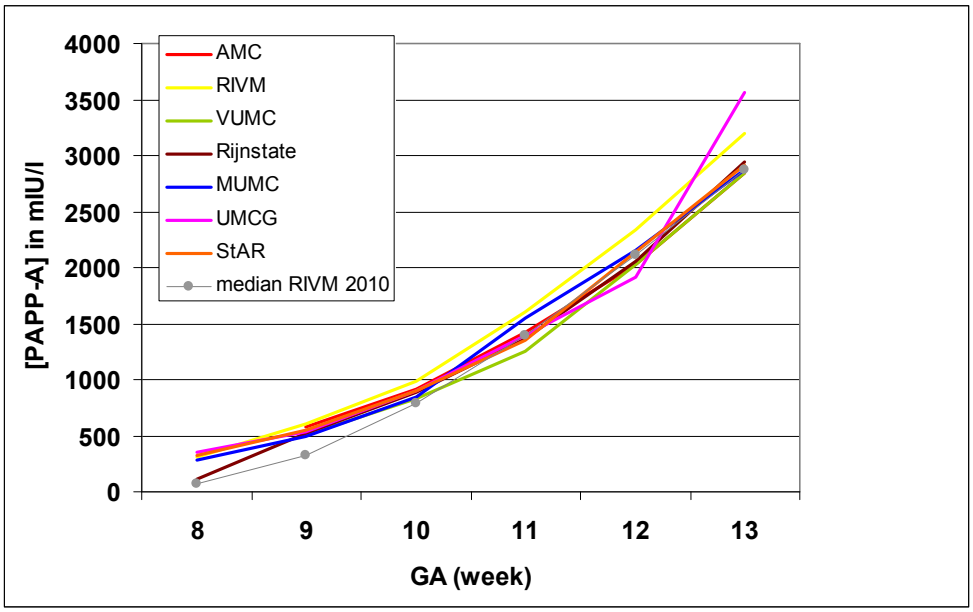

Figure 6 Median serum concentration PAPP-A for GA (weeks)
As a reference in grey, the median concentration as defined in the software of the RIVM (2010) is plotted.

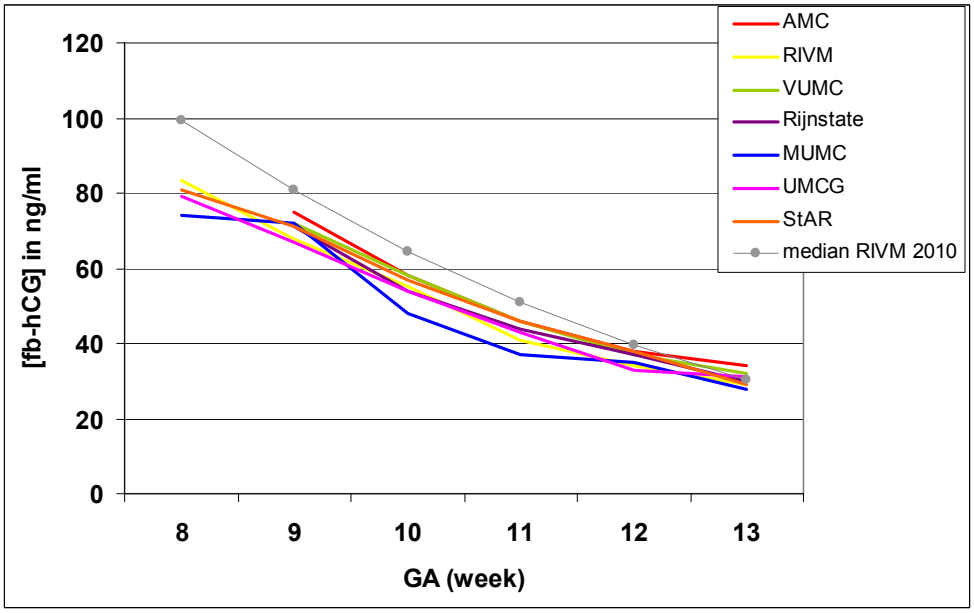

Figure 7 Median serum concentration fβ hCG for GA (weeks)
As a reference in grey, the median concentration as defined in the software of the RIVM (2010) is plotted.

PAPP-A and fβ hCG concentrations in relation to GA
In Figures 6 and 7 the median concentrations of PAPP-A and fβ hCG are depicted, as compared to the modelled median concentration set in the software of the RIVM (2010). For PAPP-A the median concentrations approximate these settings rather well, with the possible exception of week 9. For fβ hCG, the concentrations of all laboratories are slightly lower than the modelled median. The week 8 value of the Rijnstate laboratory was based on a single value.

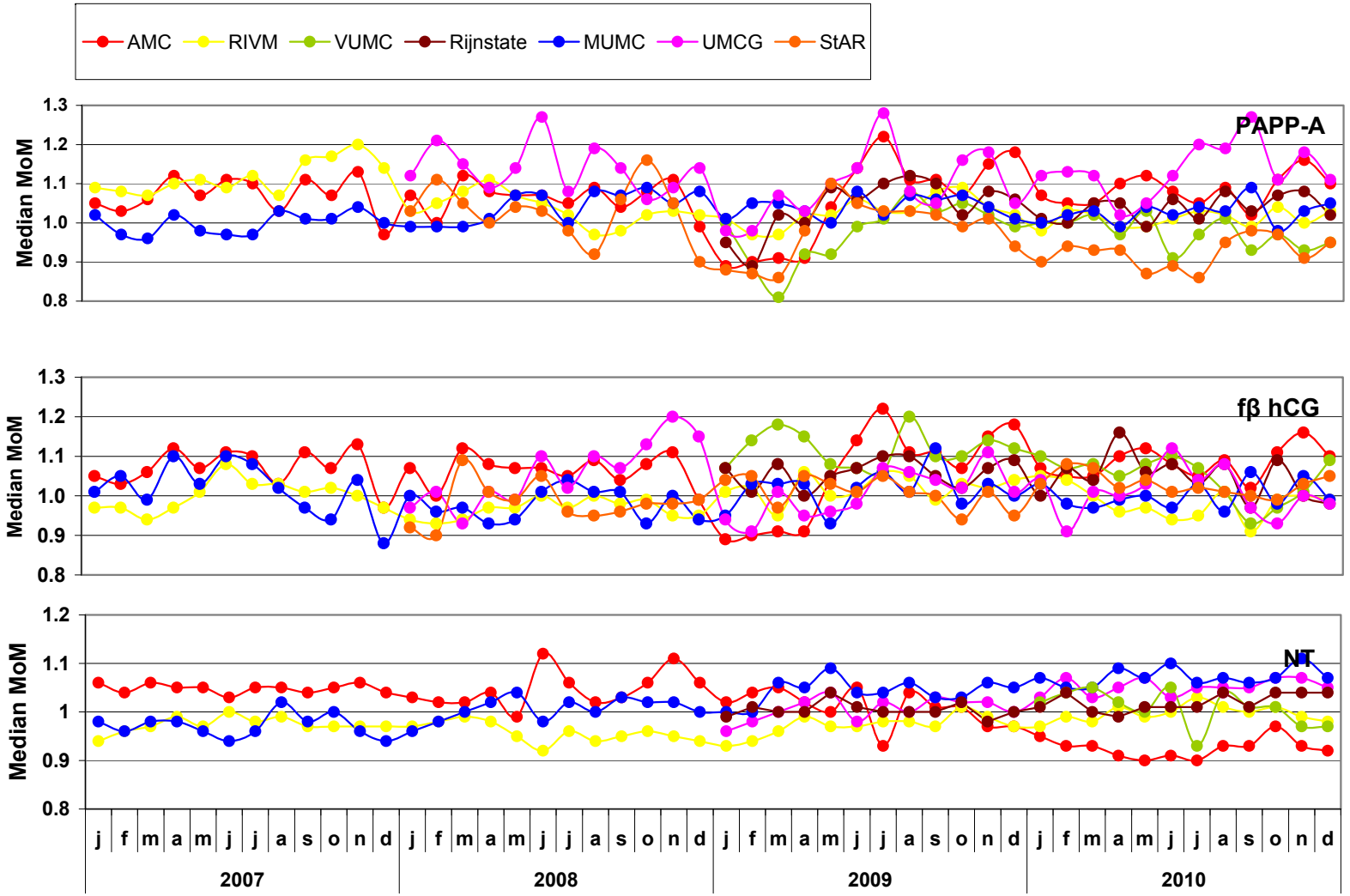

Figure 8 Monthly weight-corrected medians (PAPP-A, fβ hCG and NT) of the Down's screening laboratories 2007-2010.

PAPP-A and fβ hCG monthly median MoM

Data on the monthly medians are presented in Figure 8. The data show that for 2010 monthly medians in general are between 0.9 and 1.1 (an arbitrary but generally accepted range), with the exception of the PAPP-A monthly medians of the UMCG in the first half of 2010.

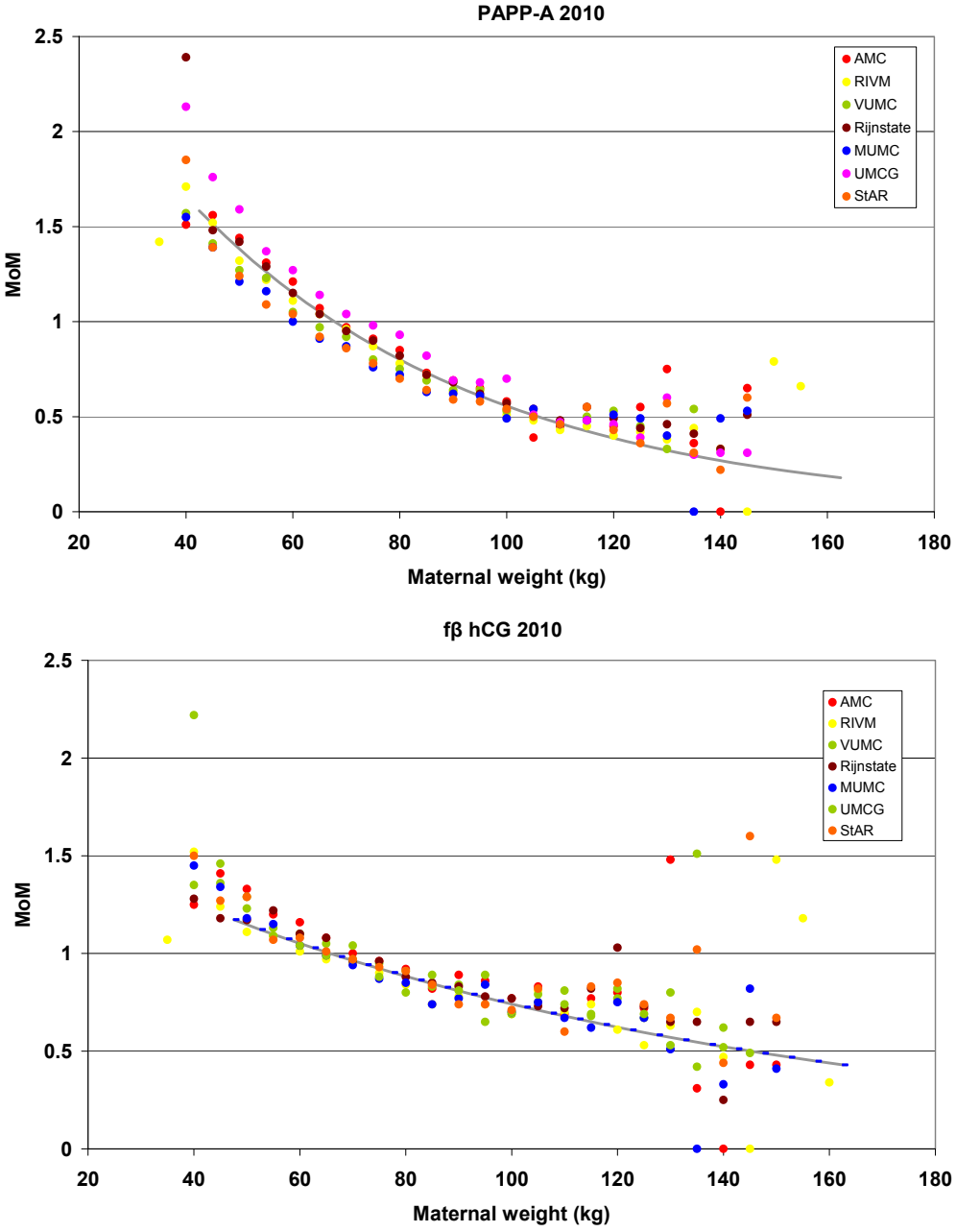

Figure 9 Median MoM (upper panel: PAPP-A and lower panel: fβ hCG) per weight class of the Down screening laboratories 2010
In grey the modelled weight correction as applied in the risk calculation software.

PAPP-A and fβ hCG and correction for maternal weight

Figure 9 presents the relationship between MoM and maternal weight for 2010. There is some scatter of the data at low and high maternal weights due to the low number of samples but basically, the relationship is the same for all laboratories for both PAPP-A and fβ hCG, and closely matches the curve indicating the weight correction equation as set in the LifeCycle Elipse software of the RIVM.

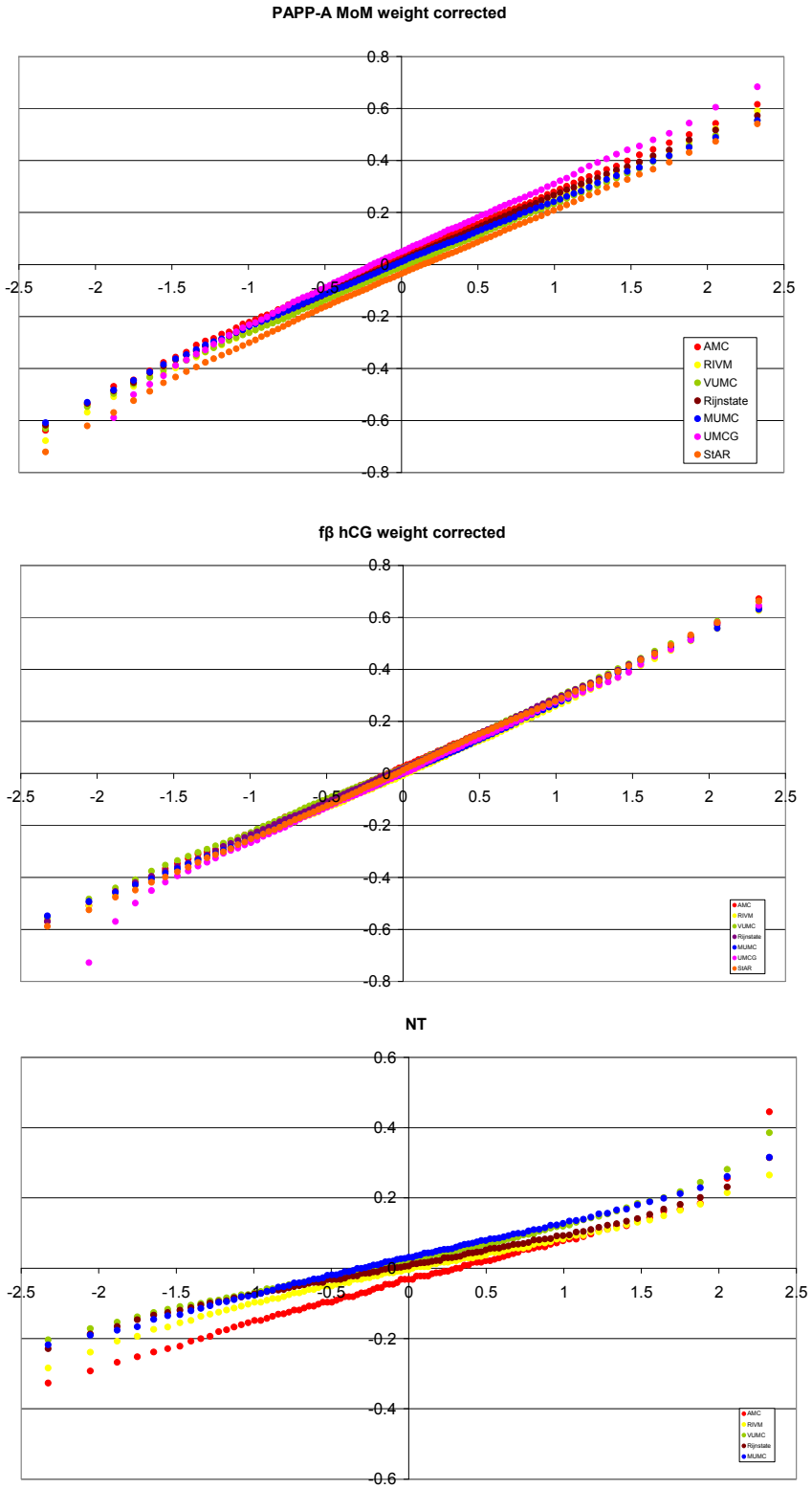

Figure 10 Normal distribution of the PAPP-A, fβ hCG and NT MoM (weight corrected) for the Dutch screening laboratories (2010)

To investigate whether the distributions of the log MoM PAPP-A and log MoM fβ hCG were Gaussian (a prerequisite when applying the risk estimation software), the percentiles of the log MoM on a Z-scale should produce a straight line through the origin. For all parameters this appeared to be the case in 2010 (data

Figure 10). Data show that the distributions for PAPP-A, fβ hCG and NT, for all laboratories were quite comparable. The NT values of the AMC are a little different from the other laboratories.

	2010	
	Log-not weight_corr	Log_weight corrected
AMC	0.202	0.234
RIVM	0.263	0.215
VUMC	0.249	0.234
Rijnstate	0.288	0.223
MUMC	0.279	0.225
UMCG	0.283	0.226
StAR	0.283	0.234

Table 1 Coefficients of correlation between PAPP-A and fβ hCG in singleton pregnancies for 2010

In Table 1 the correlation coefficients between PAPP-A and fβ hCG are given. These should match those set in the risk calculation software. Results in table 1 show that there is some difference between the coefficients but in general they are similar (the UK-National screening committee, as a reference, suggested this correlation coefficient to be between 0.05 and 0.25 [3]).

[3] National Down's syndrome screening programme for England-National Specification for Risk Calculation Software and Guidance on implication. October 2004.

4 Discussion

This report is the second in an annual series on the performance of the Dutch Down's screening laboratories. It is an aggregation of relevant data reported by the laboratories themselves and data reported by the UK NEQAS organisation for quality assurance (Edinburgh, UK). The aim of these reports is to account for the quality of the first trimester combined test and adaptation of the test as a consequence of the ongoing process of quality assurance.

Data on the total number of screening samples show that there is a slight rise in 2010, as compared to 2009 (Figure 1). Figure 2 shows that there is some variation in maternal age at sampling, but between 2007 and 2010 there are no significant changes.
As can be seen from Figure 3, the GA at blood sampling in the first trimester varies, sampling in some regions taking place early (AMC, UMCG) and in others at the end of the spectrum (MUMC). As mentioned previously (8), there is evidence that early blood sampling is beneficial for the performance of the combined test. Accordingly, an advice was issued on the website of the SPSRU to sample between 9-11 weeks. Whether this will influence the GA at blood sampling remains to be seen.

With respect to the percentage of high-risk results (SPR) of the screening laboratories (Figures 4 and 5) it appears that there are small differences between the laboratories. As data of consecutive years become available it shows that through the years, these rates are rather constant, with the possible exception of the AMC. Explanations for these differences could be a selected population (AMC calculating a combined risk for only 17% of their population, originating from the hospital), age (the AMC and VUMC have the oldest population), as well as small differences in the screening parameters. Previously, the NT median as applied by the VUMC was suggested to be significant in this. The data of the UK NEQAS of 2010 are in line with this, showing the highest risks at the VUMC as compared to the other Dutch laboratories (Annex 1, panel H).

In Figures 6 and 7 the relationship between concentrations and GA is given, as compared to the relationship defined in the risk estimation software. The fβ hCG concentration of all laboratories are generally lower than the modelled median. As the monthly median MoM is not exceptionally low, and normal as compared to UK NEQAS data of laboratories that use the Delfia method, the low fβ hCG MoM is not of great concern but is under constant evaluation.
There is good agreement between the UK NEQAS (panels A and B of Annex 1) and SKML programmes (Annex 3) concerning measured concentrations, the laboratory of the VUMC producing low concentrations in both programmes, and of the UMCG producing high concentrations. Especially in the SKML programme, it appears that the recoveries of all laboratories are in close proximity, indicating that the analytical variation among the laboratories is limited.

The monthly median (weight-corrected) MoM (Figure 8) shows that in 2010 monthly medians were generally between 0.9 and 1.1 with the exception of the PAPP-A MoM of the UMCG mid-2010. At the end of 2010 the PAPP-A MoM appeared to be within range again.

The relationship between the maternal weights and the MoM (Figure 9) were generally in accordance with the equations as implemented in the software. With respect to the distributions of the various parameters, it can be concluded that the log MoM were distributed normally and that the mean log MoM approached 0.0 (equal to a median MoM of 1.0) (Figure 10). The coefficients of the correlation between the MoM PAPP-A and MoM fβ hCG (Table 1) varied to some extent among the laboratories. Again, as correlation coefficients of consecutive years become available, it appears that these coefficients are rather constant for a given laboratory. While the correlations are in line with UK standards (range; 0.05 -0.25) they are higher than the ones currently in the software. The significance of this will be reviewed in the annual report concerning 2011.

As is evidenced in Annex 2, the settings of the risk estimation software of all the laboratories, were reviewed in 2010. No shortcomings were found. For the 2011 report, a full review is planned, after an update of the risk estimation software. As of July 1st, 2010, risks in the SPSNN region are calculated using the concentrations generated by the UMCG laboratory and Astraia/FMF risk calculation software. Consequently, the risk estimation software of the laboratory is no longer maintained and updated. Therefore, a sharp decrease was seen in the risks as reported for the UK NEQAS programme (Annex 2, panel G). The consequences of the SPSNN to calculate risks with a different risk calculation software is subject of discussion within the Central Organ.

Follow up of recommendations of the 2009 report
Concerning the conclusions and recommendations of the report on the data of 2009, the aim to incorporate the SKML quality assurance cycle in the quality assurance was met.
The identification of the small but significant differences in risk calculations among the laboratories was subject of the three-monthly meetings of the laboratories. They have led to an initiative to try to persuade the manufacturer of the experimental kits to produce larger lots with smaller lot-to-lot differences. Moreover, with the introduction of an update of the LC-risk estimation software, new efforts were done to unify the remaining differences in the risk calculation parameters.
The collection of data on the pregnancy outcome, whether in the 'Peridos' database or elsewhere, is still not in place and is not foreseen for the next two years. The ambition to make the actual performance of the screening programme a subject of this report is maintained. As an illustration of the actual performance, two publications on the performance of the first trimester combined test may be considered, indicating that the performance of the RIVM and VUMC laboratories, in terms of OAPR (roughly 1 in 10) met expectations (9, 10).

5 Conclusions and Recommendations

The conclusion of this report is that in 2010 the performance of the screening laboratories in general showed little indications for concern. The median equation for the NT of the VUMC-laboratory is still planned to be updated. The sharp change in the risks produced by the SPSNN is discussed within the working group laboratory activities and risk estimation. It shows that acute changes in risk calculation lead to acute changes in the results of the regional programme. The change to another method of risk calculation makes the quality assurance of the combined test in the SPSNN region difficult. As of 2011, only the concentrations of the UMCG laboratory will be included in the annual report of the screening laboratories. MoM (weight-corrected as well as non-corrected), and risks will differ from those of the other laboratories but whether this is as a result of quality assurance issues or merely a consequence of an alternative risk calculation software cannot be established. Including those data is therefore meaningless.

The recommendations of this report are that in the future, the evaluations of the performance of the screening laboratories should be judged according to fixed targets. These targets were established in 2011 (working group laboratory activities and risk estimation-to be annexed in the next annual report) and will be applied in the 2011-report. Moreover, a full evaluation of the updated software should be performed, with special reference to the correlation coefficients between PAPP-A and fβ hCG. Based on that evaluation, the settings of the software of the laboratories and their origin should be published on the website of the reference laboratory. A completely novel aspect of the evaluation will be the screening for trisomy 13 and 18.

6 References

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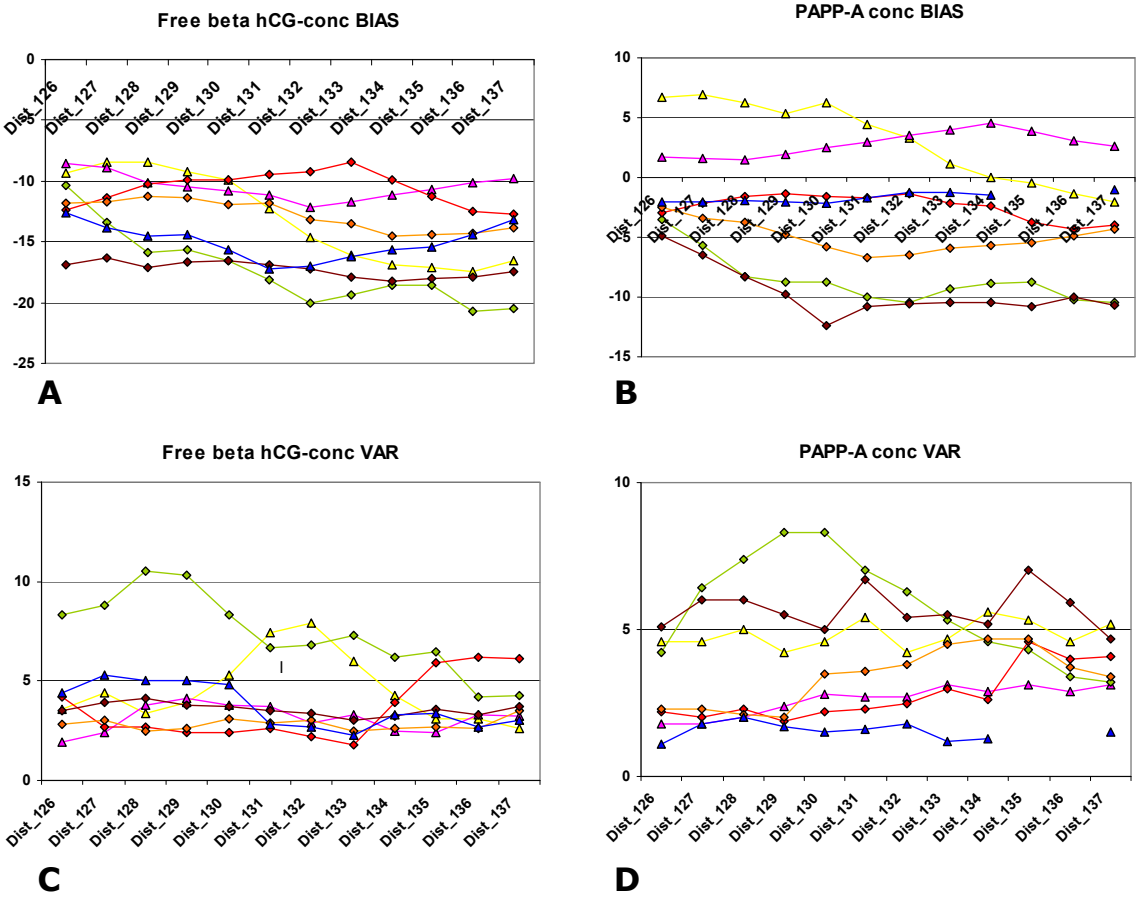
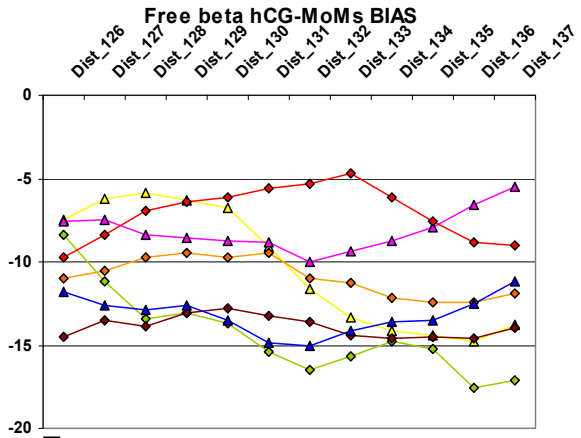
Annex 1 UK NEQAS report on Down's syndrome screening laboratories, 2010

As mentioned in the Introduction, the Dutch screening laboratories all participate in the UK NEQAS quality assurance programme for the first trimester Down's syndrome screening. Of the combined results, a monthly summary report is assembled and published on the web site of the reference laboratory, for the reference of the participating laboratories. In this annex a summary of the 2010 results is presented. Please note that demonstrating high or low values in this overview is by no means related to the performance of the laboratory –only after ranges of correctness are given (to be established) do the data become meaningful. Possibly, all the laboratories are within these limits.





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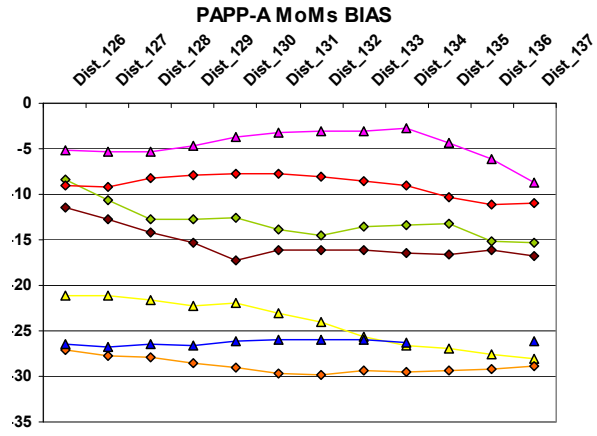

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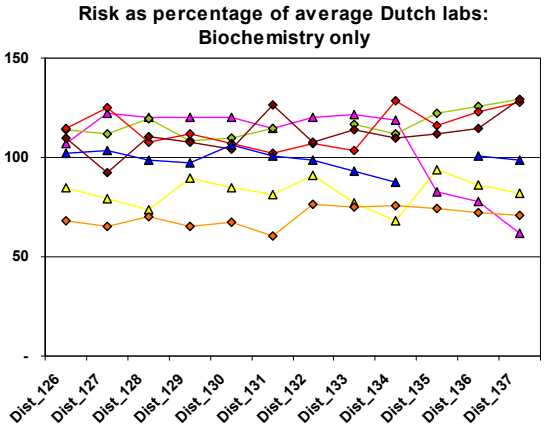

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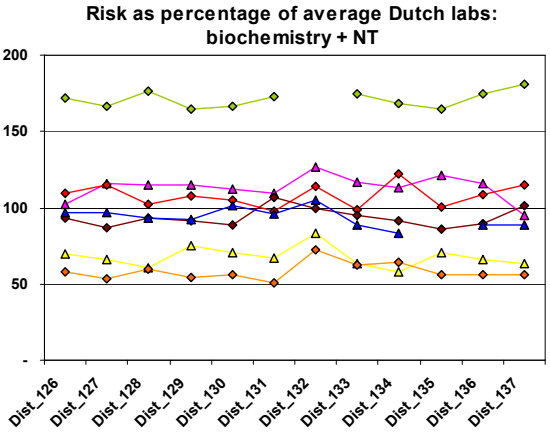

H

In panel A and B the difference of concentrations in percentages is given of the Dutch laboratories as compared to the mean of all laboratories participating in the UK NEQAS scheme (several hundreds). In general concentrations were within 15% difference for all laboratories.

In panel C and D the variance (a measure for the difference between repeat measures of the same sample) is given. Typically, this value should be below 5% for all laboratories. No major and prolonged deviations were found for the laboratories.

In panel E and F the difference of MoM in percentages is given of the Dutch laboratories as compared to the mean of all laboratories participating. In general, this difference was stable during 2010 for all laboratories and within a 20% range.

In panel G and G the difference of risks as a percentages of the mean risk of the Dutch laboratories is given. The high risks in panel H are of note, as well as the decrease of the risks of the UMCG.

Annex 2 Evaluation of the settings of the risk calculation software of the Dutch screening laboratories

Within the policy of the Dutch screening programme we aim to harmonise the risk calculations as closely as possible. Therefore, the screening laboratories work with the same software and use the same settings. Nevertheless, based on discussions during meetings of the screening laboratories, adjustments were allowed to cover for various problems, e.g. the use of two different types of analysers (AutoDelfia and Delfia Xpress). Thus, in the laboratory of the UMCG different equations for PAPP-A and fβ hCG medians and for the PAPP-A weight correction are applied and at the VUMC, a different equation for the NT median MoM is used.

Late in 2009, a survey was sent from the reference laboratory giving details of five imaginary pregnancies, with the request to report the MoMs (both uncorrected and weight-corrected), age risk, combined risk and the risk of an Edwards syndrome (trisomy 18) pregnancy using these data. If the risk calculation software was installed equally in all laboratories, the calculated MoM and risks should exactly match.

In 2010, a different approach was taken. All laboratories were asked to produce an overview of all the settings of their risk estimation software, for review in the reference laboratory.

Settings were received from the AMC, VUMC, Rijnstate and UMCG laboratories. No differences were found, except for the ones already known (see above).

Annex 3 Preliminary results of the SKML-QA programme

In 2009, a Dutch QA programme was started, organised by the SKML (Stichting Kwaliteitsbewaking Medische Laboratoriumdiagnostiek). Summarised results of 2010 are presented in table 2, below.

	PAPP-A			***Fβ hCG***		
	N	average recovery	average %CV	N	average recovery	average %CV
AMC	65	85.8	3.0	62	100.3	3.3
AZM	62	93.6	2.7	62	96.6	2.6
StAR	72	86.3	3.2	72	98.4	2.5
Rijnstate	72	89.7	3.1	72	100.7	3.3
RIVM	68	96.9	2.7	68	96.4	2.8
VUMC	72	83.8	3.3	60	96.3	4.1
UMCG	66	99.8	2.4	66	100.6	2.2

Table 2 Results of the Dutch QA programme (SKML)

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