The FMF Germany Approach to Calculating the Risk of Chromosomal Abnormalities in the 1st Trimester of Pregnancy

Comments on DoE

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DoE = Degree of Extremeness

- DoE values are considered instead of MoM values for the evaluation of the „conspicuousness" of a single measurement
- DoE indicates the deviation from the regression line as a multiple of the margin at the respective location
- advantage of not only taking into account the distance to the median of the distribution but also the ideal value as well as to the upper (95. percentile) or lower limit (5. percentile) of the norm
- in contrast to the MoM system, the DoE always indicates exactly whether the measured value is within the reference range or not

MoM Formula

MoM = Measured value / median value of unaffected pregnancies at the same gestational age

DoE Formula

Measuring the outlyingness of individual observations

In order to assess the outlyingness of any individual subject with regard to his value obtained for the respective marker, a new index termed "degree of extremeness" (DoE) was defined replacing the traditional MoM measure by reasons explained in the discussion. In order to make this concept precise, let us define:

t_i = CRL of the ith subject ($i = 1, \ldots, N$);

y_i = corresponding value of the dependent variable;

$y_{pred}(t_i)$ = measurement value predicted according to the regression model defining the central line of the reference band;

$y_*(t_i)$ = lower reference limit;

$y^*(t_i)$ = upper reference limit.

Then, the DoE of the point (t_i, y_i) has to be computed by means of the formula

$$\mathrm{DoE}(y_i) = \begin{cases} \dfrac{y_i - y_{pred}(t_i)}{y^*(t_i) - y_{pred}(t_i)} & y_i \geq y_{pred}(t_i) \\ \text{for} & \\ -\dfrac{y_{pred}(t_i) - y_i}{y_{pred}(t_i) - y_*(t_i)} & y_i \leq y_{pred}(t_i) \end{cases}$$

In particular, $\mathrm{DoE}(t_i, y_i) = +1$ and $\mathrm{DoE}(t_i, y_i) = -1$ holds if and only if the data point (t_i, y_i) lies exactly on the upper and lower reference bound, respectively.

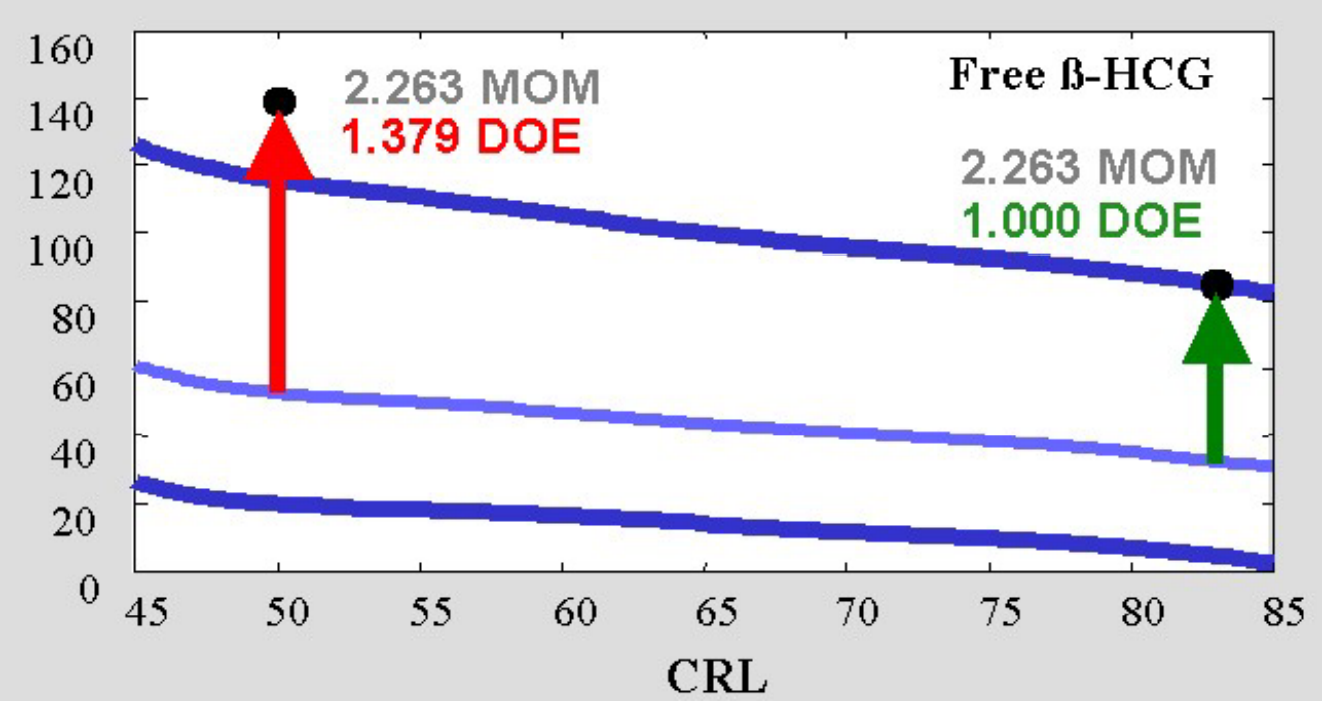
MoM results in contrast to DoE

Examples:

1.0 MoM	value on median of unaffected population (50. percentile)
0.5 MoM	value half of median but no information if the value is outside reference range!
2.0 MoM	value twice of median but no information if the value is outside reference range!
0.00 DoE	value is on median of unaffected population (50. percentile)
-1.00 DoE	value is on the 5. percentile (lower limit)
1.00 DoE	value is on the 95. percentile (upper limit)
0.75 DoE	value above median, but within reference range (–1.00 to 1.00)
1.25 DoE	value 25% above the upper limit (95. percentile)
-1.25 DoE	value 25% below the lower limit (5. percentile)

MoM in contrast to DoE

Merz, E., C. Thode, et al. (2008). "A new approach to calculating the risk of chromosomal abnormalities with first-trimester screening data." Ultraschall Med 29(6): 639-45. B·R·A·H·M·S Lit. # Med PNS SW0029



Two examples of Free ßhCG results (IU/L) are shown. In contrast to the MoM system, the DoE always indicates exactly whether the measured value is within the reference range or not.

Biochemical marker levels in T21 pregnancies

Marker	Trend	MoM	DoE
PAPP-A	↓	< 1.0	< 0.0
Free ßhCG	↑	> 1.0	> 0.0

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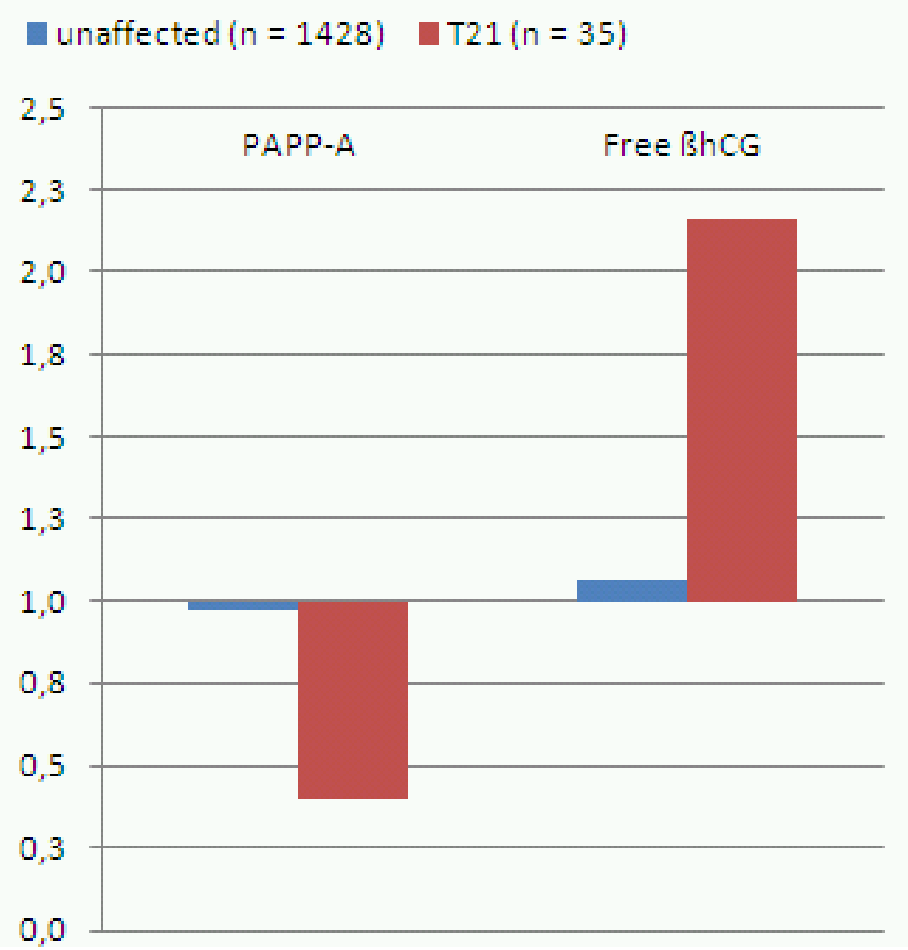
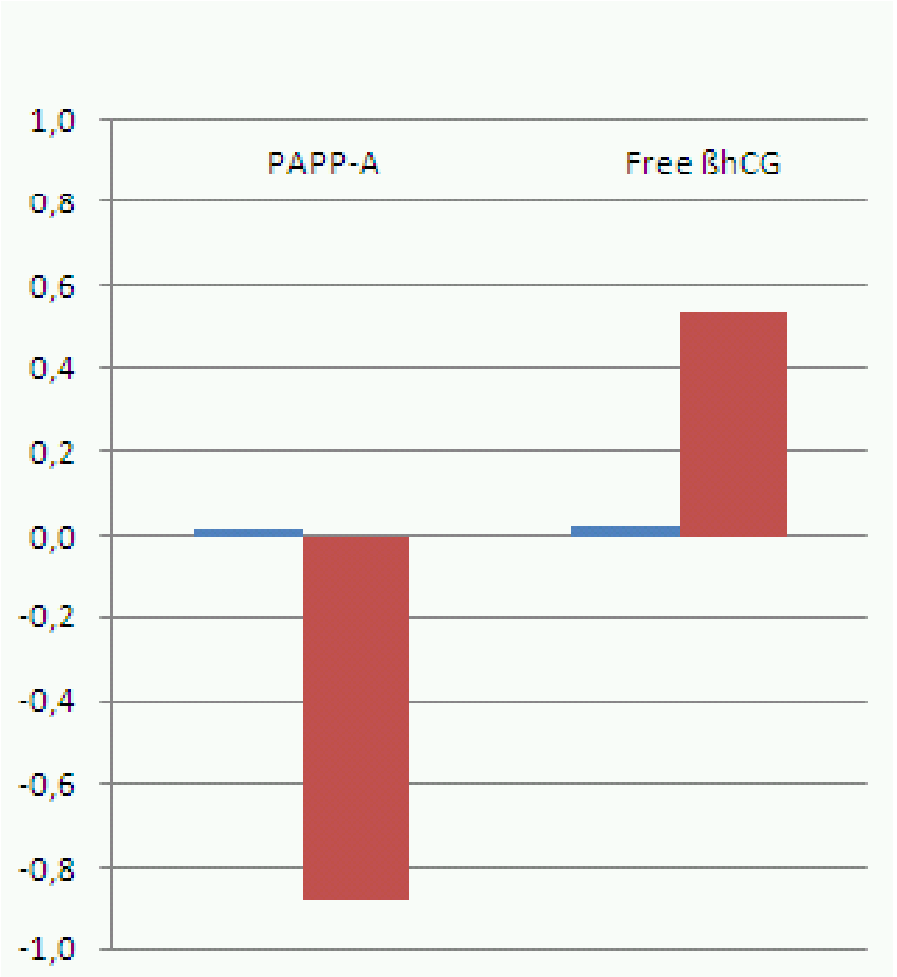
Median MoM



Median DoE



Biochemical marker levels in T13/18 pregnancies

Marker	Trend	MoM	DoE
PAPP-A	↓	< 1.0	< 0.0
Free ßhCG	↓	< 1.0	< 0.0

FMF Germany vs FMF UK Algorithm - Differences

- The database was established for a different population with another distribution of basic characteristics like maternal age at delivery and ethnicity.
- The time-interval was changed from 11+0 – 13+6 to 11+1 – 14+0 weeks of gestation since the latter corresponds more precisely to a range of 45-84 mm for the crown-rump-length (CRL).
- The CRL-dependent reference ranges for the basic measurements (NT, Free ßhCG and PAPP-A) were computed by special procedures allowing in particular for possible asymmetry of the conditional distributions and changes in variability over time.
- Bayes' formula for calculating posterior risk is applied to values transformed by taking relative deviations from the regression line making up the center of the reference band (DoEs) rather than MoMs.
- As recently admitted by the authors of the algorithm used by the FMF-UK, MoM values still depend on the CRL. In contrast, DoEs are perfectly uncorrelated from CRL.
- Maternal weight is not used for risk calculation, neither for T21 nor for T18/13.
  Reason behind this decision: The influence of maternal weight on the non-transformed concentrations of Free ßhCG and PAPP-A turned out to be negligible, with less than 10% of the variance explained by the corresponding linear regression.
- The final result is visualized in a very intuitive way easy to understand even for patients with low educational level [→"traffic-light plot"].

In both approaches, the cutoff is determined in such a way that the rate of false positive decisions equals 5% (⇔specificity = 95%). But in view of the differences between the populations underlying the databases for both algorithms, cutoffs cannot be the same!

Literature

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... further articles can be expected