

Risk Calculation Software Requirements for Down's Syndrome Screening



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1. Scope

This document presents definitions and requirements for risk calculation software used for Down's syndrome screening within the UK NHS. The definitions and requirements are intended to provide a minimal specification for T21 risk calculation software within the UK NHS.

2. General principles

This specification covers the following main elements

- i) the methods used to compute multiple of median (**MoM**) values and risks
- ii) the quality control and monitoring tools available for users of the software
- iii) data and audit requirements

The methods specified for **MoM** values and risks involve algorithms specified by a set of parameters. These parameters must be configurable and auditable.

Requirement: Configurability audit and validation

All parameters associated with the calculation of risk must be fully configurable under restricted access according to the requirements of the Fetal Anomaly Screening Programme (FASP). Parameters defining the distribution of **MoM** values will be specified by FASP. Configuration should be possible by electronic import of a file.

Requirement: Audit trail

All changes to the software parameters must be automatically recorded and auditable.

Requirement: Validation

For the purpose of validation, according to laboratory standard operating procedures, the software must be capable of running test cases to facilitate checks on **MoM** values and risks.

Requirement: CE marking

The software must comply with CE statutory regulations.

3. Gestational age from ultrasound measurements

Requirement: Calculation of gestational age from crown rump length (CRL)

For **CRL** in the range **a** to **b** inclusive, the software must be able to compute gestational age **g** in days as described below. If the **CRL** lies outside of the range **a** to **b**, the gestational age from this formula must not be used for risk calculation.

Singleton pregnancies

For singleton pregnancies, gestational age **g** in days at the time of the scan must be obtained from ultrasound measurements of **CRL** using the following formula.

$$g = A + \sqrt{(B \times CRL) + C}$$

Twin pregnancies

In twin pregnancies the gestational age must be obtained from the larger of the two **CRL** measurements using the above formula.

Requirement: Calculation of gestational age from head circumference (HC)

Singleton pregnancies

For **HC** in the range **a** to **b** inclusive, the software must be able to compute the gestational age **g** in days as described below. If the **HC** lies outside of the range **a** to **b** inclusive, the gestational age from this formula must not be used for risk calculation.

$$g = \exp(A + (B \times HC) + (C \times HC^2) + (D \times HC^3))$$

Twin pregnancies

In multiple pregnancies the gestation derived from the largest **HC** measurement must be used to determine gestational age.

Requirement: Calculation of gestational age in days at the time of serum sampling

The software must be able to calculate gestational age at the time of serum sampling using the formula.

$$g \text{ at time of blood sample} = g \text{ at scan} + \text{days}(\text{sample date} - \text{scan date})$$

In these expressions, **days(date 2 – date 1)** is the number of days from **date 1** to **date 2**. If **date 2** occurs before **date 1** this will be negative. **g** is the gestational age at the time of the scan.

4. Maternal age m (years)

Requirement: Calculation of maternal age

The software must be able to calculate maternal age at the expected date of delivery as described below.

Maternal age m (years) at the expected date of delivery (non IVF pregnancies)

$$m = (\text{days}(\text{date of scan} - \text{maternal DoB}) + 280 - g \text{ at time of scan})/365.25$$

Maternal age m (years) at the expected date of delivery (IVF pregnancies)

$$m = (\text{days}(\text{date of egg collection} - \text{donor DoB}) + 280 - 14)/365.25$$

For the calculation of prior risk, m , should be used with no rounding or truncation.

5. Standardisation: MoM values

The median marker value for pregnancies with gestational age ***g (days)***, maternal weight ***w (kg)***, smoking status (***s***) and ethnicity (***e***), is denoted by the function ***m(g,w,s,e, ...)***

For a marker value ***y***, in an individual pregnancy, the multiple of the median or ***MoM*** value is then given by:

$$MoM = \frac{y}{m(g,w,s,e, \dots)}$$

In current software systems ***m(g,w,s,e, ...)*** is specified by defining separate mathematical functions ***m_g(g)*** and ***m_w(w)*** for gestation and weight together with factor adjustments for smoking, ethnicity and other factors.

Requirement: Median regression equations

The software must be capable of incorporating log cubic regression relationships for both gestation and weight.

$$\log_{10}(m_g(g)) = A_g + B_g g + C_g g^2 + D_g g^3$$

$$\log_{10}(m_w(w)) = A_w + B_w w + C_w w^2 + D_w w^3$$

Requirement: Adjustments other factors

The software must be capable of incorporating gestational age (by day) factor adjustments for the following:

Ethnicity – at least eight configurable levels

Smoking – at least five configurable levels

Twins – monochorionic and dichorionic

Diabetes – at least five configurable levels

Method of conception – at least five configurable levels

Analysers – at least three configurable levels. (Analysers from the same manufacturer can give different results)

6. Localisation and updating

In some circumstances it is necessary to make changes to accommodate differences between populations, laboratories, equipment or reagent lots. Functional forms can be updated by changing parameter estimates in $m_g(g)$ and $m_w(w)$. This can be achieved through the incorporation of regression fitting functionality within the software or externally by export of data and analysis using standard statistical software. The inclusion of regression fitting software is not a requirement for the UK NHS.

Factor updates

Often the changes required are simple factor updates. This means that all median levels for the particular marker are multiplied by the same constant factor which can be achieved by defining a local factor a

$$MoM = \frac{y}{m(g,w,s,e, \dots)a}$$

In the reference configuration $a = 1$ and during an update $a \leftarrow af$ where f is an update factor. For example, if the overall median MoM value were 1.1, a would be multiplied by 1.1.

Requirement: Factor updates

Software must be capable of making factor updates using a median MoM value entered manually by the laboratory. The acceptable range of median MoM values should be from a to b inclusive.

7. Prior risk models

Requirement: Prior term risk of trisomy 21 at maternal age m at expected date of delivery in decimal year.

The software must be capable of calculating the prior risk of Down's syndrome using any of the following

$$\Pr[T21 \text{ at term given } m \text{ and no previous trisomy}] = A + \exp(B+C \times (m-D))$$

$$\Pr[T21 \text{ at term given } m \text{ and no previous trisomy}] = A + B / (1 + \exp(C+D \times (m-E)))$$

$$\Pr[T21 \text{ at term given } m \text{ and no previous trisomy}] = 1 / (1 + \exp(A+B / (1 + \exp(C \times (m-D))))))$$

$$\Pr[T21 \text{ at term given } m \text{ and previous trisomy}] = \Pr[T21 \text{ at term given } m \text{ and no previous trisomy}] + Q_{\text{Trisomy}}$$

8. Likelihoods and risk calculation

Risks are obtained by combining the prior risk of Down's syndrome with a multivariate Gaussian likelihood for the \log_{10} *MoM* values. These multivariate Gaussian distributions are specified in terms of a set of marker means, a correlation matrix and a set of marker standard deviations for each condition (e.g. normal or trisomy 21).

Requirement: Truncation limits

The software must be capable of applying condition-specific lower truncation limits *a* and upper truncation limits *b* to each marker *MoM* value to produce a truncated *MoM* value for use in risk calculation. Values below the lower truncation limit must be replaced by the lower truncation limit. Values above the upper truncation limit must be replaced by the upper truncation limit. In cases where *MoM* values are truncated, the original *MoM* value and the truncated value must be stored and it must be possible to display the original *MoM* value and truncated *MoM* value on the risk report.

Requirement: Mean \log_{10} *MoM* values

It must be possible to specify mean \log_{10} *MoM* values in Down's syndrome pregnancies by gestational day for singleton pregnancies, for monochorionic twin pregnancies and for dichorionic twin pregnancies.

Requirement: Fetus specific risks in twins

In situations where one or more markers (e.g. NT) are measured on each twin and the twins can be assumed to be dizygotic, the software must be able to produce fetus specific risks.

9. Recalculation of risks

Requirement: Recalculation of risk

In cases where information is updated and the risk recalculated by the user, the most recent information and risk information should be displayed. All previous information should be kept in the database for the purposes of auditing.

10. Reporting risk information

Requirement: Minimum and maximum risks

The software must be capable of imposing truncation limits on the reported risk so that the minimum reported risk is *less than 1 in a* and the maximum reported risk is *greater than 1 in b*.

For example, less than 1 in 5,000; greater than 1 in 5.

The database should contain both the reported risk and the risk to full precision as calculated.

11. Diagnostics

Requirement: MoM diagnostics

It must be possible for the user to select a subset of data based on any combination of date range, ethnic group, smoking status, singleton or twin pregnancy, analyser, reagent lot or sonographer.

The software must then be able to produce the following diagnostic plots.

CUSUM plots of \log_{10} MoM values

Plots of the standardised screen positive rate, with 95% confidence intervals, by calendar month.

Estimated median MoMs with 95% confidence intervals by gestational week

Estimated median MoMs with 95% confidence intervals by maternal weight group

Estimated median MoMs with 95% confidence intervals by smoking status

Estimated median MoM with 95% confidence intervals by ethnicity

Estimated median MoM with 95% confidence intervals by diabetes status

Estimated median MoM values by analyser

Requirement: Event log

The software must be able to maintain an event log to record events such as lot change, analyser service, recalibration and median updates. The software must be capable of indicating these events to the CUSUM chart.

12. Export facility

Requirement: Export

It should be possible for the user to specify a list of database fields and a date range to obtain a Microsoft Excel copy of the records over the date range containing the data in the specified fields. The fields must include all data used in the calculations of **MoM** values and risks including all ultrasound measurements. Identification codes for sonographers should also be included.

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