CHM.31800 Median Values **Phase II**

There is a record that the laboratory has established its own median values or verified that the medians from another source are appropriate for the population being screened.

NOTE: Systematic biases in maternal serum assay values of up to 30% can occur when kits from different manufacturers are used. In addition, between laboratory differences in equipment, reagents, and technique may introduce bias in assay results even when the same kit lot is used. These differences can be minimized by reporting results in multiples of the normal median (assuming that the medians are calculated using values measured on the population to be tested using the kit designated for screening). Ideally, day-specific medians would be established by testing approximately 100 patients per week of gestation. A second approach is to perform a split specimen study with another laboratory and transfer the other laboratory's medians using the comparison regression equation from the split specimen study. However, in practice the most practical method is to measure values on 300 consecutively collected specimens spread over the appropriate gestational age range, and perform weighted regression analysis using published models. It is not necessary to document that all specimens are collected from unaffected pregnancies because specimens from pregnancies affected with neural tube defects, Down syndrome etc., are infrequent. Smoothing data by weighted regression analysis allows median values to be calculated for weeks with limited data. Package insert medians may be outdated or inappropriate and should not be used even for a short time. Incorrect reference data may lead to inappropriate recommendations in the laboratory report.

Evidence of Compliance:

✓ Records establishing/verifying median values using in-house data

REFERENCES

1) Erickson JA, Ashwood ER, Gin CA. Evaluation of a dimeric inhibin-A assay for assessing fetal Down syndrome; establishment: comparison, and motoring of median concentrations for normal pregnancies. *Arch Pathol Lab Med.* 2004; 128(4):415-20.
2) Clinical and Laboratory Standards Institute (CLSI). *Maternal Serum Screening; Approved Standard - Second Edition.* CLSI document I/LA25-A2. Clinical and Laboratory Standards Institute, Wayne, PA; 2011.
3) Knight GJ. Quality assessment of a prenatal screening program. *Early Human Development.* 1996;47(Supp):S49-S53

CHM.31900 Median Value Review **Phase II**

Medians are reviewed at specified intervals or test volumes and when new reagent lots are introduced, and the medians are recalculated if necessary.

NOTE: Systematic shifts in analyte values observed with new reagent lots can cause significant deterioration in screening performance if not taken into account. One method for assessing a new lot is performing a split specimen comparison study between the new and old lot typically using 25 to 50 specimens. Bias between an existing and a new lot, if important (eg,>5%) can then be taken into account by adjusting the existing set of median values (or median equation).

In addition, review of medians at specified intervals is a valuable quality control mechanism to ensure validity of reported MoMs. Epidemiological monitoring of Down syndrome screening can be accomplished by determining the median MoM value at frequent intervals (eg, every 500-1000 patients, or weekly or monthly). If a persistent shift is noted (median MoM less than 0.90 or greater than 1.10), new medians should be determined. Records of the median MoMs must be retained.

Evidence of Compliance:

✓ Records of median value calculation or review at defined frequency or test volume

REFERENCES

1) Report of a workshop sponsored by the National Institute of Child Health and Human Development (NICHD), Bethesda, Maryland. The quality control of alpha-fetoprotein reagents and assay for the antenatal screening and diagnosis of open neural tube defects. *Clin Chim Acta.* 1980;105:9-24
2) Erickson JA, Ashwood ER, Gin CA. Evaluation of a dimeric inhibin-A assay for assessing fetal Down syndrome: establishment, comparison, and monitoring of median concentrations for normal pregnancies. *Arch Pathol Lab Med,* 2004 Apr;128(4):415-20.
3) Ashwood ER, Grenache DG, Lambert-Messerlian G. Pregnancy and its Disorders. *In: Textbook of Clinical Chemistry and Molecular Diagnostics. 5th ed.* Burtis CA, Ashwood ER, Bruns DE (eds), Elsevier Saunders: Philadelphia, PA, 2011.

***REVISED** 12/26/2024*

CHM.31950 Nuchal Translucency (NT) Measurement Quality **Phase I**

If screening panels are offered using nuchal translucency (NT) values, the laboratory has a process to ensure the quality of those measurements.

NOTE: The NT value is an important component of the test and may impact the results. Risk assessment can be used to determine if laboratories report the NT results.

Evidence of Compliance:

✓ Documentation of a quality assurance process

REFERENCES

1) American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No 77: Screening for fetal chromosomal abnormalities. *Obstet Gynecol.* 2007;109:217-27.
2) Ashwood ER, Grenache DG, Lambert-Messerlian G. Pregnancy and its Disorders. *In: Textbook of Clinical Chemistry and Molecular Diagnostics. 5th ed.* Burtis CA, Ashwood ER, Bruns DE (eds), Elsevier Saunders: Philadelphia, PA, 2011.
3) Schuchter K, et al. The first trimester 'combined test' for the detection of Down syndrome pregnancies in 4939 unselected pregnancies. *Prenat Diagn.* 2002; 22(3):211-5.
4) Malone FD, et al. Use of overall population, center-specific, and sonographer-specific nuchal translucency medians in Down Syndrome screening: which is best? (results from the faster trial). *Am J Obstet Gynecol.* 2003; 189(6):S232.
5) Palomaki GE, et al. Quality assessment of routine nuchal translucency measurements: A North American laboratory perspective. *Genet Med*, 2008;10(2):131-8.
6) Malone FD, D'Alton ME. First trimester sonographic screening for Down syndrome. *Obstet Gynecol.* 2003; 102(5):1066-79.

CHM.31960 Monitoring of Nuchal Translucency (NT) Measurements **Phase I**

If screening panels are offered using nuchal translucency (NT) values, the laboratory routinely performs epidemiological monitoring of these measurements.

NOTE: An example of such a monitoring procedure (with action limits) is provided below. For each sonographer with sufficient data (typically at least 30 to 50 measurements over six months), monitor and provide limits for three quality parameters.

- *Percent increase in NT measurements (in mm) by gestational age (eg, 15% to 35%)*
- *The NT median MoM (eg, 0.90 to 1.10) or the delta NT (eg, ±0.05 mm)*
- *The distribution of NT MoMs after a logarithmic transformation (log standard deviation), (eg, 0.08 to 0.13)*

Evidence of Compliance:

✓ Records of NT median data study(ies) **AND**

✓ Records of review at defined frequency

REFERENCES

1) Palomaki GE, Neveux LM, Donnenfeld A, Lee JE, McDowell G, Canick JA, Summers A, Lambert-Messerlian G, Kellner LH, Zebelman A, Haddow JE. Quality assessment of routine nuchal translucency measurements: A North American laboratory perspective. *Genet Med*, 2008 Feb;10(2):131-8
2) Ashwood ER, Grenache DG, Lambert-Messerlian G. Pregnancy and its Disorders. *In: Textbook of Clinical Chemistry and Molecular Diagnostics. 5th ed.* Burtis CA, Ashwood ER, Bruns DE (eds), Elsevier Saunders: Philadelphia, PA, 2011.
3) Palomaki GE, *et al*. Technical standards and guidelines: Prenatal screening for Down syndrome that includes first-trimester biochemistry and/or ultrasound measurements. *Genet Med,* 2009;11(9):669-681
4) Malone FD, et al. Use of overall population, center-specific, and sonographer-specific nuchal translucency medians in Down Syndrome screening: which is best? (results from the faster trial). *Am J Obstet Gynecol.* 2003; 189(6):S232.

CHM.32000 Screening Performance Monitoring **Phase II**

The percentages of women with screen-positive test results for neural tube defects (NTD), Down syndrome, and Trisomy 18 are calculated and reviewed at least biannually.

NOTE: Data from large studies provide guidelines for the percentage of pregnancies that will fall above specified AFP MoM levels (NTD screening) or with risks greater than specified risk cutoff levels (Down syndrome screening). Regular comparison of a laboratory's screen-positive rates with expected rates serves as a continuing measure of assay quality, appropriateness of medians, accuracy of gestational dating, and the distribution of maternal age. The frequency of

monitoring screen positive results will be dependent on the number of specimens analyzed per unit time, but it is recommended at least biannually, or optimally, quarterly.

Evidence of Compliance:

- ✓ Records of statistical analysis and evaluation of screen-positive test results at least biannually

REFERENCES

1) Report of a workshop sponsored by the National Institute of Child Health and Human Development (NICHD), Bethesda Maryland. The quality control of alpha-fetoprotein reagents and assay for the antenatal screening and diagnosis of open neural tube defects. *Clin Chim Acta.* 1980;105:9-24
2) Ashwood ER, Grenache DG, Lambert-Messerlian G. Pregnancy and its Disorders. *In: Textbook of Clinical Chemistry and Molecular Diagnostics. 5th ed.* Burtis CA, Ashwood ER, Bruns DE (eds), Elsevier Saunders: Philadelphia, PA, 2011.
3) Palomaki GJ, *et al*. Risk based screening for trisomy 18 using alpha-fetoprotein, unconjugated estriol, and human chorionic. *Prenat Diagn* 1995;15:713-723
4) Knight GJ, *et al*. Epidemiologic monitoring of prenatal screening for neural tube defects and Down syndrome. *Clin Lab Med* 2003;22:531-551
5) Wald NJ, Hackshaw AK, George LM. Assay precision of serum alpha fetoprotein in antenatal screening for neural tube defects and Down's Syndrome. *J Med Screen*. 2000;7(2):74-7
6) Wald NJ, Rodeck C, Hackshaw AK, Walters J, Chitty L, Mackinson AM. First and second trimester antenatal screening for Down's syndrome: the results of the Serum, Urine and Ultrasound Screening Study (SURUSS). *Health Technol Asses* 2003;7(11)

CHM.32200 Computer Calculations — Phase II

Gestational age, maternal age, neural tube defect and Down syndrome risk calculations are initially verified for accuracy and are reverified with any software updates or changes.

NOTE: Verification can be accomplished by interlaboratory comparisons, by comparison with results calculated or reported by proficiency testing programs, or by use of risk tables available on the CAP website (located in the CAP/ACMG Biochemical and Molecular Genetics Resource Committee Genetics Topic Center section). At a minimum, the accuracy of calculated gestational age, maternal age, and patient-specific risks must be verified.

Evidence of Compliance:

- ✓ Records of initial and subsequent calculation checks

*****REVISED** 12/26/2024***

CHM.32300 Prenatal Screen Requisition and Report — Phase II

The prenatal screen requisition and report contain all information collected from the provider that is relevant to the clinical interpretation of the results.

NOTE: Prenatal screen risk calculation requisitions must include the information required by the laboratory to perform the risk assessment.

Evidence of Compliance:

- ✓ Requisitions with required elements **AND**
- ✓ Reports with required elements

CHM.32400 Multiple of Population Median — Phase II

Test results are reported as multiples of the population median (MoM).

NOTE: Reporting of results in terms of multiple of the population median (MoM) simplifies interpretation at various gestational ages, reduces possible systematic between-laboratory and between-kit bias in assay results, and facilitates comparison among laboratories. Laboratories can also compare their experiences with large-scale published studies more readily by using MoM as the reportable interpretive unit. The initial MoM is calculated as the measured analyte value divided by the median value for the appropriate gestational age. The MoM should also be adjusted for the other clinical variables known to influence the concentration of each analyte, generally by dividing by a factor specific for each variable.