

## Update on MSAFP Policy Statement from The American Society of Human Genetics

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*This publication is a supplement to The American Society of Human Genetics (ASHG) Policy Statement for Maternal Serum Alpha-Fetoprotein Screening Programs and Quality Control for Laboratories Performing Maternal Serum and Amniotic Fluid Alpha Fetoprotein Assays, published in February 1987 by ASHG in the American Journal of Human Genetics (40:75-82, 1987). The following statement is an integral part of the above-referenced Policy Statement, and neither should be relied on separately.*

*This updated policy statement is designed to provide accurate and authoritative information in regard to the subject matter covered as of April 20, 1989. It is published with the understanding that the ASHG is not rendering medical or other professional services. The contents are intended as suggestions only and should not be relied on for conclusive diagnosis. Users should rely on their own professional judgment or on consultation with other authorities and should ascertain whether more recent information has been disseminated by the ASHG or other authorities.*

### PREAMBLE

Maternal serum alpha fetoprotein (MSAFP) screening was originally developed to delineate a subgroup of pregnant women whose elevated MSAFP levels indicated an increased risk of having a fetus with an open neural tube defect (ONTD). As more data accumulated, it was found that elevated levels of MSAFP were also predictive of gastroschisis, omphalocele, cystic hygroma, congenital nephrosis, poor pregnancy outcome, and other maternal and fetal complications.

In 1984, Merkatz et al. reported on 41 cases of fetal autosomal trisomy diagnosed in utero for which corresponding MSAFP and amniotic fluid AFP (AFAFP) data could be reviewed. The authors found that the MSAFP levels expressed as multiples of the median (MOM) were significantly lower for these 41 women than for those in a group of normal matched control subjects. Subsequently, Cuckle and Wald (1984) presented their data

on 61 pregnancies associated with Down syndrome and found the average MSAFP level to be 0.72 MOM, which was a statistically significant reduction. The authors stated that the difference was great enough to form the basis for a screening test. Since the publication of the above articles, there have been other retrospective studies which have essentially supported the initial findings.

In 1987, DiMaio et al. presented their findings for prospective screening for Down syndrome by measuring MSAFP during the second trimester in women under age 35 years. Over a 2-year period 34,354 women in this age group were screened. From their available data and their population, the authors concluded that, using a cutoff risk of 1/270 (a risk at which 5% of women under age 35 years are offered amniocentesis), they would detect one-fourth to one-third of pregnancies in which the fetus has Down syndrome.

Results of prospective collaborative study (1988), designed to assess the feasibility of widespread application of AFP screening for Down syndrome, conducted by the New England Regional Genetics Group (1989) and provide further support for the feasibility of such screening. Data were collected on 77,273 women from eight centers located in New England by performing MSAFP screening for Down syndrome. A common protocol (with minor variations) was used by all centers

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and included screening only women under age 35 years, combining maternal age and MSAFP levels to assign risk, adjusting for maternal weight when calculating the MOM, analysis of only one serum for assigning risk, and classifying women as being at increased risk if their individual odds equaled or exceeded the second-trimester risk of 35-year-old women (i.e., 1/270). One Down syndrome fetus was detected for every 89 amniocenteses. The study concluded that one-fourth of fetuses with Down syndrome are potentially identifiable by routine MSAFP screening in women under the age of 35 years by performing amniocentesis in 2.7% of the younger population.

The committee did not reach a consensus concerning the investigational status of low MSAFP screening for Down syndrome. Some concern was expressed about using MSAFP screening before more data are available. High false-negative and false-positive rates, insufficient understanding of the limitations of the screening process in both the professional and lay sectors, and the consequent risk of undue reliance on Down syndrome screening were cited.

Most committee members felt that, taken together, the two large prospective studies (DiMaio et al. 1987; eight center prospective collaborative study 1988) indicated that a combination of maternal age and MSAFP can be used to identify a subgroup of pregnant women under the age of 35 years who have an increased risk of having a fetus with Down syndrome. In such a subgroup, counseling should be provided prior to the MSAFP screen, should be informational and nondirective, and should explain to the parents the possibility of false-positive and false-negative results.

#### SUPPLEMENTARY ASHG POLICY STATEMENT FOR MSAFP SCREENING

The Committee would supplement the original MSAFP policy statement with the following general statements:

1. Although quality control was emphasized in the original policy statement from The American Society of Human Genetics, this committee wishes to stress that quality control should continue to be an important part of every MSAFP program.
2. There is now sufficient data on the black population in the United States to support using data that are specific to that population.
3. It is the committee's recommendation that an MSAFP screening should be obtained from all women who are having a second-trimester amniocentesis due to a high-risk pregnancy.
4. Amniocentesis should remain a serious consideration, even

after a normal ultrasound, when there is an MSAFP result that indicates increased risk.

5. The committee did not reach a consensus concerning weight adjustment for either high or low MSAFP values. Some concerns were expressed that a reduction in detection efficiency results from this adjustment. Others believe that weight adjustment allows a better estimate of risk to be assigned and that it should be included as part of each reporting laboratory's protocol.

The Committee would supplement the original MSAFP policy statement with the following statement regarding elevated MSAFP:

It should be understood by physicians and other health professionals that women who have increased concentrations of MSAFP and whose fetus does not have a demonstrable abnormality by either level II ultrasound or karyotyping from amniotic fluid, continue to have an increased risk for having a fetus with major congenital malformation and poor pregnancy outcomes, such as perinatal death and low birthweight.

The committee would supplement the original MSAFP policy statement with the following statements regarding low MSAFP screening:

1. By using both MSAFP concentration and maternal age, a more precise statement can be made of the risk for the fetus having Down syndrome.
2. An improved risk estimate for Down syndrome may be possible for women at 35 or over. However, these women also have an increased risk for other autosomal chromosome aneuploidies and for sex-chromosome aneuploidies, for which adjustments by MSAFP are currently not available. In addition, current medical practice requires that women age 35 years or over be told of the availability of amniocentesis.
3. The committee has an abiding concern about the accuracy and precision of some test kits in assessing low values for serum AFP.
4. At present, there are no commercial test kits licensed for MSAFP Down syndrome screening and risk reporting by the FDA, and none are in the process of being reviewed for approval.

#### Acknowledgment

This document was drafted by an ad hoc ASHG committee under the aegis of the Social Issues Committee and the Genetic Services Committee. The ad hoc committee included Kenneth L. Garver, M.D., Ph.D., Chairman; Anita M. Buerkle, M.T., M.B.A.; George J. Knight, Ph.D.; Maurice J. Mahoney, M.D.; and Aubrey Milunsky, M.D.

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