TABLE 83e-2 INDICATIONS FOR CYTOGENETIC AND CYTOGENOMIC ANALYSIS ACROSS THE LIFESPAN

Timing of Testing	Indications for Testing
Prenatal	Advanced maternal age
	Abnormalities on ultrasound
	Increased risk for genetic disorder on maternal serum screen
Neonatal and Childhood	Multiple congenital anomalies
	Intellectual disability
	Autism
	Developmental delay
	Failure to thrive
	Short stature
	Disorders of sexual development
	History of familial chromosomal alteration
	Cancer
Adult	Infertility
	Recurrent miscarriage
	Cancer

10 weeks has resulted in reduced use of this test in some centers. Fetal blood sampling (percutaneous umbilical blood sampling [PUBS]) is a riskier procedure that is carried out in the second or third trimester of pregnancy, usually to follow up on an unclear finding from an amniocentesis (such as mosaicism) or an ultrasound abnormality that was detected later in pregnancy. One of the far-reaching recent advances in prenatal diagnosis of chromosome and other genetic disorders is the utilization of cell free fetal DNA that can be identified in maternal serum. The obvious advantages of using fetal DNA obtained from maternal serum is that the DNA can be obtained at minimal risk to the pregnancy, because it requires a maternal blood sample, rather than amniotic fluid which is obtained by puncturing the uterine membranes and carries a risk of miscarriage or infection. Although cell free fetal DNA screening, also called noninvasive prenatal screening, has started to be offered clinically, it requires further confirmation of fetal tissues when an abnormal result is identified. Furthermore, ethical concerns have been raised, because it is feared that the ease of doing this test may encourage testing for individuals who are not truly prepared to deal with the choices that accompany diagnosis of a genetic disease and this testing may change the ethical implications of prenatal testing. Nevertheless, this is an active of area of research, both in terms of the technology and the utilization and implications.

Common Indications Common indications for prenatal diagnosis by cytogenetic or cytogenomic analysis are (1) advanced maternal age, (2) presence of an abnormality of the fetus on ultrasound examination, and (3) abnormalities in maternal serum screening that reveal an increased risk for chromosome abnormality.

Maternal age is well known to be an important risk factor for having a fetus with trisomy. At a maternal age less than 25 years, 2% of all clinically recognized pregnancies are trisomic, but by a maternal age of 36 years, this figure increases to 10%, and by the maternal age of 42 years, the figure increases to >33%. Based on the risk of having a chromosomally abnormal fetus in comparison to the risk for an adverse event from amniocentesis or CVS, the recommendation is that women over the age of 35 consider prenatal testing if they want to know the chromosomal status of their fetus. The precise mechanism for the maternal age effect is not known, but it is believed that it involves a breakdown in the process of chromosome segregation. A similar effect is not seen for trisomy and paternal age. This difference may reflect the fact that oocytes are generated early in ovary development in the female, whereas spermatogonia are generated continuously after puberty in the male.

Abnormalities on prenatal ultrasound are the second most frequent indication for prenatal genetic screening. Ultrasound screening can reveal structural or functional anomalies in the fetus, which might be associated with chromosome or genomic disorders. Follow-up chromosome studies may therefore be recommended.

Maternal serum screening results are the third most frequent indication for prenatal chromosome analysis. There have been several versions of maternal serum screening offered over the past few decades. Currently, the "quad" screen analyzes levels of α fetoprotein (AFP), human chorionic gonadotropin (hCG), estriol, and inhibin-A. The values of these analytes are used to adjust the maternal age–predicted risk of a trisomy 21 or trisomy 18 fetus.

POSTNATAL INDICATIONS

Postnatal indications for cytogenetic or cytogenomic analysis in neonates or children are varied, and the list has been growing with the increasing ability to diagnose smaller genomic alterations via array-based techniques. Common indications include multiple congenital anomalies, suspicion of a known cytogenetic or cytogenomic syndrome, intellectual disability or developmental delay both with and without accompanying dysmorphic features, autism, failure to thrive in infancy or short stature during childhood, and disorders of sexual development. The ability to detect smaller genomic alterations with involvement of fewer genes, sometimes as few as a single gene, suggests that a wider range of phenotypes could be investigated by cytogenomic analysis. Reasons for chromosome testing in adults include recurrent miscarriages or infertility, where balanced chromosome rearrangements such as reciprocal translocations may occur. Additionally, some adults with anomalies who were not diagnosed when they were children are referred for cytogenetic analysis, often when other members of their family want to understand any potential genetic implications, as they plan their own families.

TYPES OF CHROMOSOME ABNORMALITIES

NUMERICAL CHROMOSOME ABNORMALITIES

Aneuploidy (extra or missing chromosomes) is the most common type of abnormality, occurring in 3/1000 newborns and at much higher frequency (about 35%) in spontaneously aborted fetuses. The only autosomal trisomies that are compatible with being live born in humans are trisomies 13, 18, and 21, although there are several chromosomes that can be trisomic in mosaic form. Trisomy 21 is associated with the relatively common disorder Down syndrome. Down syndrome has characteristic features including recognizable facial features, along with intellectual disability and abnormalities of multiple other organ systems including the heart. Both trisomy 13 and trisomy 18 are much more severe disorders than Down syndrome, with low frequency of patients surviving past 1 year of age. Trisomy 13 is characterized by low birth weight, postaxial polydactyly, microcephaly, ocular malformations such as anophthalmia or microphthalmia, cleft lip and palate, cardiac defects, and renal malformations. Trisomy 18 neonates have distinct facial characteristics at birth accompanied by an abnormal neurologic exam, underdeveloped genitalia, general lack of responsiveness, and structural birth defects such as congenital heart disease, esophageal atresia, and omphalocele.

Mosaicism refers to the presence of two or more populations of cells with distinct chromosome constitutions: for example, an individual with a normal female karyotype in some cells (46,XX) and trisomy 21 in other cells (47,XX,+21). In general, individuals who are mosaic for a chromosomal abnormality have less severe phenotypes than individuals with that same finding in every cell. The severity and presentation of phenotypes are related to the mosaic levels and the tissue distribution of the abnormal cells. There are a number of trisomies that have been reported in mosaic form including mosaic trisomies for chromosomes 8, 9, 14, 17, and 22. A number of trisomies have also been reported in spontaneous abortions (SABs) that have not been seen in live-born individuals, including trisomy 16, which is the most common trisomy in SABs. Monosomy for human chromosomes is very rare, with the single exception being monosomy for the X chromosome, associated with Turner syndrome (45,X). Monosomy for the X chromosome occurs in 1% of all conceptions, yet 98% of these conceptions do not go to term and result in SABs. Trisomies for