

Sample/Result Flow

All cytogenetic samples (along with blood from parents) have to be sent to the study reference lab (Genzyme Genetics) for chromosome analysis. A portion will then be routed to one of the participating laboratories for microarray analysis (Baylor, Emory, Signature or Columbia.)

Chromosome analysis via karyotype will be reported to the referring physician/counselor as per usual. Microarray results will follow and will be reported by the Clinical Coordinating Center to the physician/counselor. In the event that an abnormality of unknown clinical significance is found, a Clinical Advisory Committee, composed of experts in clinical genetics, will review the case. Should they consider the finding to be of potential clinical significance, the information will be forwarded to the physician/counselor by the Chairperson of the Committee. All such cases will be followed until age 2.

Each site must undergo training by the study coordinator and the data coordinating center prior to recruiting patients. The certification requirement checklist must be completed prior to patient recruitment to ensure proper compliance with all study-related procedures.

NOTE:

As an ancillary activity, a tissue repository will be established, which will permit resource sharing, and eventual collaboration in the further development of an international web-based database. This database will allow sharing of cytogenetics and phenotypic information from prenatal cases evaluated by microarray technology.

PRENATAL CYTOGENETIC DIAGNOSIS BY ARRAY- BASED COPY NUMBER ANALYSIS



Please contact the Study Coordinator with any questions or concerns:

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Study Objectives

The main objective of the multi-centered collaborative study is to evaluate the accuracy, efficacy and clinical advantages of prenatal diagnosis using microarray analysis as compared with conventional karyotyping. Specifically, the aims are as follows:

1. Demonstrate the performance of CGH-microarray (aCGH) as a clinical method for prenatal cytogenetic diagnosis with regard to:
 - a. Accuracy in the detection of the common autosomal and sex chromosomal aneuploid (trisomies, 13,18,21, 45,X, 47,XXY, etc.)
 - b. Ability of aCGH to diagnose less common, but clinically significant, cytogenetic aneusomies (e.g. DiGeorge, Williams, Smith-Magenis, Prader-Willi syndrome, etc) currently not detected by conventional karyotype.
 - c. Evaluation of the utility of aCGH in specific clinical scenarios such as ultrasound detection of congenital anomalies and fetal growth disorders.
2. Evaluate the appropriate construction of prenatal diagnostic microarray devices to allow maximal detection of clinically relevant information with minimal detection of unexpected and difficult to interpret findings which have no clinical significance but might provoke patient anxiety.
3. Evaluate the feasibility and cost-effectiveness of using microarrays as a primary prenatal diagnostic tool.
4. Evaluate approaches to integrate microarray into clinical prenatal cytogenetic diagnostic practice.
5. Develop a prenatal diagnostic tissue repository (TDR) to facilitate the further development of microarray technology. This will be used to investigate the molecular etiologies of specific fetal anomalies and to test newer technologies, such as higher resolution microarrays.

Acceptable Ultrasound Anomalies

- Structural anomalies in 2 or more organ systems
- Unexplained fetal growth restriction defined as estimated fetal weight less than the 5th %ile and not accounted for by maternal disease
- CNS structural anomaly
 - Ventriculomegaly/hydrocephalic
 - Structural abnormality of posterior fossa
 - Dandy Walker syndrome or variant
 - Cerebellar hypoplasia
 - Agenesis of the corpus collosum
 - Holoprosencephaly
 - Abnormality of cortical gyri (e.g. lissencephaly)
- Myelomeningocele
- Structural cardiac abnormality
- Cleft lip and/or palate
- Congenital diaphragmatic hernia
- Absence of stomach/TE fistula
- Situs inversus or dextrocardia
- Omphalocele
- Ambiguous genitalia
- Hydronephrosis with renal pelvic ap diameter ≥ 7
- Polycystic or multicystic dysplastic kidneys
- Megacystis including posterior urethral valves
- Skeletal dysplasia
- Arthrogyriposis
- Clubbed feet
- NT ≥ 3.5 mm or Nuchal fold ≥ 6.0 mm
- Hydrops fetalis of unknown etiology

Exclusions:

- Fetal growth restriction as the only anomaly in a woman with any of the following disorders known to alter fetal growth: chronic hypertension on meds, class F-R diabetes, lupus, smokes > 1 pack of cigarettes/day, thrombophilia (not including MTHFR or Factor V Leiden heterozygote), moderate or severe preeclampsia
- Hydrops fetalis secondary to known hematologic or infectious etiology

Participants

Study participants will be designated into 2 groups. The first group will consist of 1,750 sequential consenting patients undergoing prenatal testing for standard indications (advanced maternal age, abnormal maternal serum screening results, etc.) The second group will consist of 2,250 pregnancies in which invasive testing is being performed for specific ultrasound findings. Acceptable abnormalities are included on the following page, and are subject to change at the investigator's discretion.

Inclusion criteria:

Sequential Unselected Group:

1. Singleton pregnancy having CVS or amniocentesis (after 16 weeks) performed for prenatal cytogenetic diagnosis
2. Karyotyping to be performed at Genzyme Genetics Cytogenetics Laboratory
3. Genetic counseling available by study-trained counselor
4. Presenting at pre-specified sites using Genzyme Genetics for routine prenatal diagnostic services

Selected Group:

1. 1 - 3 above AND ultrasound detection of at least one pre-specified fetal structural or growth anomaly (refer to list)

Exclusion criteria:

1. Non-availability of both biologic parents to provide blood sample (i.e. egg or sperm donor, non-paternity, one parent not present)
2. Patient refusal to allow follow-up through the neonatal period and up to age 2 if selected
3. Previous participation in the study
4. No sample obtained