Dr Lal PathLabs

INNOVATIVE MedicoForum

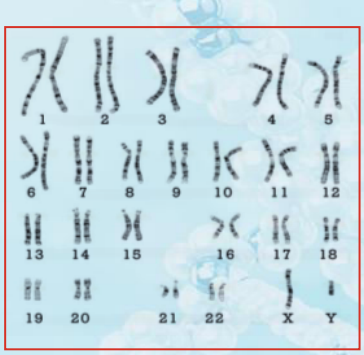
Advanced Cytogenetic Technique: Microarray Testing

Prenatal diagnosis for fetal anomalies

- 20% of stillborn babies have a major malformation
- 3% of live-births have congenital anomalies
- Diagnosis of a malformation requires:
  - A number of "broad spectrum" analysis
  - Followed by more sophisticated, accurate and targeted tests
- Detailed ultrasound and invasive fetal testing
  - Etiology
  - Prognosis
  - Recurrence risk
  - Prevention / options in future pregnancies

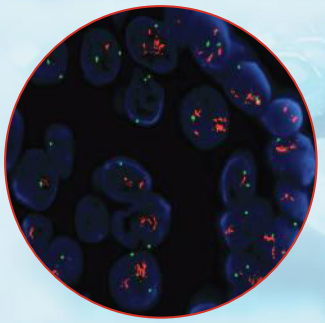
Classical Cytogenetics

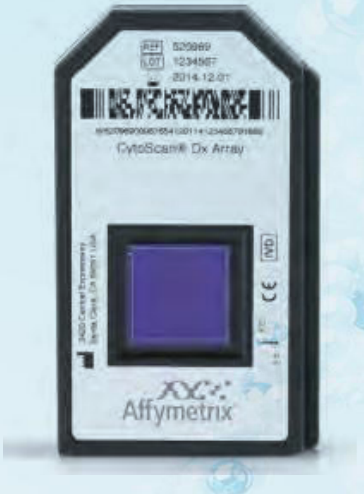
Whole genome - low resolution



In comparison, G-banding and FISH have a combined yield of about 7%

Targeted High resolution





Genomic microarray technology

Each microarray contains 2.6 million markers for copy number & 750,000 SNPs markers

Yield is 15-20%

Whole genome- High resolution

Microarray revolutionizing Cytogenetics

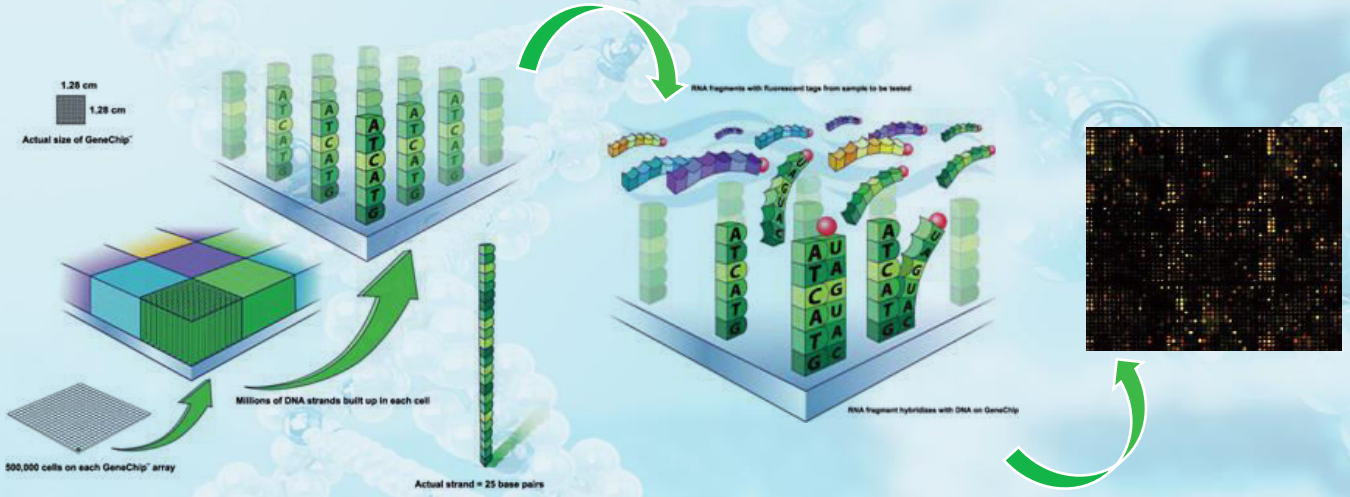
ACMG Recommends Replacing Karyotyping with Chromosomal Microarrays as 'First-Line' Postnatal Test

"Increased resolution of microarray technology over conventional cytogenetic analysis allows for identification of chromosomal imbalances with greater precision, accuracy and technical sensitivity."

How Chromosomal Microarrays Analysis works?

Affymetrix microarrays

Affymetrix-25 mers are *in-situ* synthesized on a glass wafer nucleotide by nucleotide using photolithography



Indications and Recommendations on Microarray

Indications for prenatal diagnosis

- Advanced maternal age
- Previous child with *de novo* chromosome aneuploidy
  - Woman 30 years, child with T21: Increased Recurrence risk for any chromosome abnormality (1/100) versus age-related risk (1/390)
- Parental structural chromosome abnormality
- Family history of genetic disorder
- Elevated risk based on maternal screening
- Foetuses with abnormal ultrasound findings

Recommendations

Based on the increased detection of clinically relevant abnormalities in both structurally normal and abnormal pregnancies, Chromosomal Microarray Analysis (CMA) should be transitioned to become the First Tier Test for invasive prenatal diagnosis.

Source: New England Journal of medicine,Vol 367,No 23,Dec.2012

Conclusion

- CMA detects chromosome abnormalities and new genetic syndromes which would be missed by conventional cytogenetics
- Most Copy Number Variations can be interpreted based on gene content, size, inheritance, databases
- Counseling issues are not unique to prenatal CMA
- As CMA transitions into clinical practice counseling by professional with knowledge and expertise in CMA will be required
- Need large databases of array findings and associated phenotype from "unbiased populations"

ACOG Recommendation

- If a fetal structural anomaly is identified on ultrasound examination, invasive prenatal diagnosis should be offered
- A negative cell free fetal DNA test result does not ensure an unaffected pregnancy
- A patient with a positive test result should be referred for genetic counseling and offered invasive prenatal diagnosis for confirmation of test results
- Cell free fetal DNA does not replace the accuracy and diagnostic precision of prenatal diagnosis with CVS or amniocentesis, which remain an option for women

Pre-natal Array testing is likely to be used as confirmation of NIPT as once an invasive procedure is offered, the best option should be chosen

1. In patients with a fetus with one or more major structural abnormalities identified by ultrasound who are undergoing invasive prenatal diagnosis, Chromosomal Microarray Analysis is recommended. This replaces traditional fetal karyotype – which may be viewed as a low-resolution whole genome analysis.
2. In patients with a structurally normal fetus undergoing invasive prenatal diagnostic testing, either traditional chromosome analysis or chromosome microarray analysis may be performed.
3. As most copy number mutations identified by Chromosomal Microarray Analysis are not associated with increasing maternal age, the use of CMA for prenatal diagnosis should not be restricted to women aged 35 and older.
4. In case of intrauterine fetal demise or stillbirth, when further cytogenetic analysis is desired, Chromosomal Microarray Analysis on fetal tissue is recommended. This increases the likelihood of obtaining results and improves the detection of causative abnormalities.

Chromosomal Microarrays Analysis for POC analysis

- Approximately 60-70% of first trimester miscarriages are being caused by chromosomal abnormalities
- Traditional cytogenetic analysis of these samples is challenging due to high rates of culture failure and maternal contamination
- Chromosomal microarray analysis overcomes these limitations and has proven to be an excellent tool for detection of chromosomal aberrations in these samples

Ref. : Wang et al.Molecular cytogenetics 2014 7:33

Tests available with us

Code	Name	Specimen	Room	Refrigerated	Frozen	Method	Report
Q023	**CHROMO FIC**, CHROMOSOME SNP MICROARRAY 750K, HIGH RESOLUTION	4mL (2 mL min.) whole blood in 1 lavender top (EDTA) tube. Ship refrigerated. DO NOT FREEZE. Give clinical history on Genomic Microarray Requisition form.	NA	24 hrs.	NA	Affymetrix CytoScan™ microarray	Sample Daily by 4 pm; Report in 10 days
Q024	**CHROMO TOUCH**, CHROMOSOME SNP MICROARRAY OPTIMA, PRENATAL	**Amniotic fluid:** 15 mL (5 mL min.) amniotic fluid in a sterile screw-capped container. Chorionic villus: 30 mg (20 mg min.) chorionic villus biopsy collected asceptically in 10 mL transport medium available from LPL. **Umblical Cord blood:** 4 mL (2 mL min.) cord blood in 1 Lavender top tube. Avoid clot formation during sampling. Ship refrigerated immediately. DO NOT FREEZE. Give clinical history on microarray test request form. Consent form for Prenatal genetic testing is mandatory.	NA	24 hrs.	NA	Chromosome microarray using Affymetrix Optima Suite™	Sample Daily by 4 pm; Report in 10 days
Q025	**CHROMO TOUCH**, CHROMOSOME SNP MICROARRAY OPTIMA, PRODUCTS OF CONCEPTION	Submit 5 mg (2 mg min.) curetted tissue in normal saline.Give clinical history on chromosomal microarray test request form.	NA	24 hrs.	NA	Chromosome microarray using Affymetrix Optima Suite™	Sample Daily by 4 pm; Report in 10 days

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