Genomics-2014
OMICS Group Conferences
Accelerating Scientific Discovery
2nd International Conference on
Genomics & Pharmacogenomics
September 08-10, 2014 Raleigh, North Carolina, USA

Contemporary Prenatal Diagnosis – The Clinician's Perspective

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Noninvasive Prenatal Testing (Screening)

- Introduced commercially October 2011
- High sensitivity and specificity in the high risk population
- Two types
  - Massive Parallel Shotgun Sequencing
  - Targeted Fetal DNA Sequencing

Criteria

- Currently: High risk population
  - 35 and above
  - Ultrasound findings
  - Increased risk via other screening
  - Family history

  - Prevalence = 1/8 vs. 1/600 (low risk population)
  - PPV 90% vs. 11%

Which is Best?

- Tough question
- MPSS (Sequenom, Vernata)
- Targeted Fetal DNA Sequencing
  - Ariosa DANSR/FORTE: hybridize, amplify, sequence
  - Natera: Massive multiplex isolation with SNP analysis

Sensitivities & Specificities

- All have high sensitivities
  - >99% DS and T18
  - More variable for T13
  - Less data for sex chromosomal abnormalities
- All have low false positive rates

False Negatives

- Gestational age (<10 wks)
- Fetal fraction
  - Maternal Weight
- Genetic Variants
- Failure to extract adequate material
- Individual variation in cfDNA amount
- GC rich regions

False Positives

- Contamination
- Vanishing twin
- Placental mosaicism (more in T13,18, 21)
- Low level mosaicism (esp. sex chromo)
  - Maternal mosaicism (loss of X in older women)
- Maternal Cancers
  (only a few cases, no specific pattern)

Failure Rates

Trial	Failure Rate	DS Detection	FP rate
Chiu et al. 2011	11/764 (1.4%)	86/86	3/146
Ehrich et al. (2011)	18/467 (3.8%)	39/39	1/410
Palomaki et al. (2011)	13/1696 (0.8%)	209/212	3/1471
Bianchi et al. (2012)	148/532 (3.0%)	89/89	0/404
Norton et al. (2012)	148/3228 (4.6%)	81/81	1/2888
Zimmerman et al. (2012)	21/166 (12.6%)	11/11	0/145
ALL	**424/6687 (3.2%)**	424/427 (99.3%)	8/5319 (0.15%)

Note: Not all study designs the same, different techniques, variety of FP rates, thresholds to call DS risk have different methodologies

Remember

- There is no free lunch
  - Nothing in biology is 100%
  - Are we going backwards in PNDx?
  - Does not detect many things… yet

ACOG,ACMG, ISPD, NSGC: Common Themes

- Great sensitivities and specificities for T21 & T18
- Not diagnostic
- Needs Genetic Counseling (pre- and post)
- Should only be used in validated groups
- More studies needed for the general population

Shifting Paradigms

- Does NIPT replace other screening tests available today?
  - Better sensitivity but… look what we are missing….
  - First & second trimester ultrasound benefits
    - Increased NT, early defects, cardiac esp.
    - Other anomalies seen in embryological progression (cranial, skeletal, cardiac)
  - Serum screening benefits
    - Unexplained increased MSAFP
    - Low uE3 (SLO, X linked ichthyosis, sulfatase deficiency, congenital adrenal hypOplasia, Zellweger, Antley Bixler, POMC deficiency, other cholesterol metabolism, IUGR, SAB)
    - Low PAPP-A
    - Combination of abnormal biochemical markers

Future

- Twin and population data
- Aneuploidy in all chromosomes
- Targeted microdeletion and microduplication syndromes
- “Low density” microarray (>10mB)
- Single gene defects (CF, β-thal, many others)
- Whole genome sequencing (ultimate goal)

Chromosomal Microarray (CMA)

- Introduced in the prenatal arena circa 2005
- Results and counseling still from postnatal databases
- Unknowns (VOUS)
- Comparative array hybridization vs. SNP oligo-array

CMA has changed Prenatal Diagnosis

- Increased detection of chromosomal variation
- Ability to detect absence of heterozygosity (SNP Oligo-array)
  - Consanguinity
  - UPD (heterodisomy is harder to detect)
  - Inherited disorders (AR, AD, X-linked)
  - Triploidy
- Both miss true balanced translocations (0.08-0.09%) and other balanced rearrangements

CMA Increases Detection

DOI: 10.1002/pd.3945

PRENATAL **DIAGNOSIS**

ORIGINAL ARTICLE

Experience with microarray-based comparative genomic hybridization for prenatal diagnosis in over 5000 pregnancies

Lisa G. Shaffer[1]*, Mindy P. Dabell[1], Allan J. Fisher[2], Justine Coppinger[1], Anne M. Bandholz[1], Jay W. Ellison[1], J. Britt Ravnan[1], Beth S. Torchia[1], Blake C. Ballif[1] and Jill A. Rosenfeld[1]

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Increases Detection

- Shaffer et al. Prenatal Diagnosis 2012
- 2004-2011
- N = 5003 prenatal cases, various reasons
- All known aneuploidy excluded from karyotype
- No fetal demises
- Detection of an additional 5.3% abnormals (6.5% & 8.2% for abnormal US and demise, respectively)
- 0.39% *de novo* copy number variations noted

- **71%** found below the resolution of karyotype (<10Mb). Thus ***29%*** should have been detected via karyotype!

Specific Ultrasound Anomalies

Detection rates of clinically significant genomic alterations by microarray analysis for specific anomalies detected by ultrasound n=2858 cases

- Clinically significant genomic alterations were identified in cases with a *single* ultrasound anomaly (n= 99/1773, 5.6%)

- Anomalies in *two or more* organ systems (n= 77/808, 9.5%), isolated growth abnormalities (n= 2/76,2.6%), and soft markers (n= 2/77, 2.6%).

- High detection rates: holoprosencephaly (n= 9/85, 10.6%), posterior fossa defects (n= 21/144, 14.6%), skeletal anomalies (n= 15/140, 10.7%), ventricular septal defect (n= 14/132, 10.6%), hypoplastic left heart (n= 11/68,16.2%), and cleft lip/palate (n= 14/136, 10.3%)

Shaffer et al, Prenatal Diagnosis 2012, 32: 986–995 (free)

“GENERAL” POPULATION?

- Issues:
  - Wapner et al. (NEJM 2012) showed 1.7% (1:60) of patients with abnormal CMA (aCGH) for AMA alone (no ultrasound findings) or abnormal serum screening
  - Positive Predictive Values decreases significantly
  - “Unknowns” – more so with Whole Genome/Exome Sequencing

The Unknowns – this is truly not unique to us

Copy number loss and gain

- Parentally inherited?
- Incompletely penetrant/variable phenotype?
- What genes are involved? Significance of these genes? Inherited disorders (AR, AD) involved? Does it agree with the phenotype?
- How large? Does this make a difference?
- What about future findings at this site? Are we obligated to follow up in the future? Who will take this responsibility?

How Do We Navigate Now?

- Talk with the patient : “nothing”, “everything” or “don’t know”
- Are patients truly informed?
- Find out the patient’s perception of risk and their comfort level
- The information (and decision) can be overwhelming for patients
- Time constraints for patient education (not everyone is at the same level)
- When to educate? Prenatal is ideal.

Paradox vs. Paradigm

- Noninvasive vs. Diagnostic (none vs. slight risk)
- Less vs. detailed information
- Missing clinically significant disorders vs. VOUS
- Explaining FP and FN with all tests
- Pleotropic phenotypes with all genetic disorders (or findings)
- Education for professionals and lay public

Thank you.

Questions?