ALBERTA PRECISION LABORATORIES
Leaders in Laboratory Medicine

Genetic Investigation of Stillbirth or Fetal Loss: Information for Ordering Providers

Genetic testing may include:

- Rapid Aneuploidy Detection (RAD)
- Chromosomal Microarray (CMA)
- Maternal Cell Contamination (MCC)

RAD provides molecular results for aneuploidy involving chromosomes 13, 18, 21, X and Y.

CMA allows for the detection of chromosome imbalances (gains or losses) that are smaller than can be detected by a standard karyotype.

Indications

- Ultrasound anomaly or pathology suggestive of a chromosomal or contiguous gene disorder
- Clinically significant *unexplained* growth abnormality
- Unexplained stillbirth or neonatal death (≥ 20 weeks' gestation)
- A third and/or subsequent miscarriage(s)
- Family history of a cytogenetic anomaly

RAD is the first line test on all eligible fetal tissue specimens.

If RAD is normal

CMA testing will be initiated if ordered on eligible specimens.

Sample Requirements

- Preferred tissue types include umbilical cord or direct fetal tissue (e.g. muscle or thymus).
- Tissue must be fresh or fresh/frozen. Tissue CANNOT be fixed or paraffin embedded.
- A maternal blood sample is REQUIRED to assess for MCC if placenta or products of conception are the only available sample type (see box to right).

Maternal Cell Contamination (MCC)
Samples may be contaminated with maternal cells which prevents the interpretation of the results (nil result).
A maternal sample may permit test interpretation in some contaminated samples.
A maternal blood sample must be collected (2 EDTA tubes each containing 3.0 mL of blood).

Please note that culturing/karyotyping of perinatal tissue samples is no longer performed. Do NOT send placenta unless fetal tissue is unavailable.

CMA Testing on Stillbirth or Fetal Loss Samples

Potential Benefits

- May help to understand the cause of the loss or stillbirth
- May help guide management and care of future pregnancies
- May provide recurrence risks for the family

Considerations

- May find an imbalance unrelated to the pregnancy loss, which indicates risk for other unanticipated health problems for the parents and family members (e.g. cancer, late onset neurological disease)
- Identification of a copy number variant (CNV) that cannot be interpreted (variant of uncertain significance)
- Parental testing may be required to assist in interpretation, establish the pattern of inheritance and clarify clinical implications
- Detects absence of heterozygosity (AOH) which may be suggestive of uniparental disomy (UPD) or a recessive disorder
    - If AOH results are consistent with a second degree or closer relationship between parents, the laboratory will inform the referring physician as it raises concern of maternal safety; it is the physician's responsibility to assess whether the mother may be at risk

Limitations

- A normal CMA result does not exclude all genetic causes of disease
- Low levels of mosaicism, polyploidy or balanced chromosome rearrangements cannot reliably be detected

It is the ordering physician's responsibility to obtain the appropriate consent and discuss the limitations and unanticipated outcomes of CMA with their patients where feasible.

Types of CMA Results

Result	Interpretation
Normal	No abnormality identified. The cause of the loss/stillbirth remains unexplained (can still be a genetic condition due to a gene variant).
Pathogenic Copy Number Variant (CNV)	A CNV that is associated with a specific pattern of health and/or developmental problem is identified. An additional blood sample from the parents may be required to investigate the origin of the CNV.
Variant of Uncertain Significance (VUS)	A CNV of uncertain significance is identified. This variant may or may not be related to the reason for testing. Testing of the parents may be recommended to assist with the interpretation.
Incidental Finding	A CNV is identified that is unrelated to the reason for testing but may have implications for family members.
Absence of heterozygosity (AOH)	AOH suggestive of UPD will require follow-up testing. AOH of multiple chromosome regions will be reported for clinical interpretation by the referring physician.

Reporting Results
RAD results will be available within 3 weeks.
CMA results will be available within 6 weeks of the test being initiated.
Results are sent to the ordering provider and available in Netcare and Connect Care.

Next Steps
If appropriate, refer the family for genetic assessment and counselling.

Clinical Genetics Referral
Edmonton & North: Medical Genetics Clinic
Phone: 780-407-7333 Fax: 780-407-6845

Calgary & South: R.B. Lowry Genetics Clinic
Phone: 403-955-7373 Fax: 403-955-2701

Requisition forms, contact information and other resources can be found at:
http://ahsweb.ca/lab/if-lab-genetics-and-genomics

Contact Information
Genetic Counsellors, Genetics & Genomics
Edmonton: 780-407-1015
Calgary: 403-955-3097