VGECGR00003MUL Rapid Aneuploidy Detection (RAD) and Chromosomal Microarray (CMA) of Stillbirth or Fetal Loss: Information for Ordering Physicians

Genetic testing may include:

- Rapid Aneuploidy Detection (RAD)
- Chromosomal Microarray (CMA) when indicated and requested
- Maternal Cell Contamination (MCC)
- Single gene testing when indicated and requested

RAD is used for the rapid detection of aneuploidy of chromosomes 13, 18, 21 and the sex chromosomes, or triploidy.

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

Indications for genetic testing on fetal tissue:

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

RAD is the first line test on all eligible fetal tissue specimens. → If RAD is normal → CMA testing will only be initiated if a signed CMA requisition form is received AND sample has at least one indication.

Sample requirements for CMA:

- Preferred tissue types include: direct fetal tissue (e.g. muscle or thymus) or umbilical cord.
- Do NOT send placenta unless fetal tissue is unavailable.
- 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 (15mL EDTA) using a CMA requisition.

Please note that culturing/karyotyping of perinatal tissue samples in no longer routinely performed.

How do I order RAD and CMA?

- To order RAD ONLY:
  - For Calgary and Southern Alberta, indicate ‘RAD’ when completing the “Constitutional Cytogenetic Requisition” form.
  - For Edmonton and Northern Alberta, complete a “Molecular Diagnostic Laboratory Requisition” form with RAD indicated under ‘Other’.
- To order RAD and CMA, complete a “Chromosomal Microarray (Array CGH) Requisition” form.

- CMA can be requested on a stored or banked DNA sample (where RAD was normal) by faxing a completed CMA requisition form to the appropriate Cytogenetic Laboratory.
- Requisition forms should be accompanied by the fetal sample unless a sample has already been submitted for testing.

How long will the results take?

- RAD results will be available within 3 weeks
- CMA results will be available within 6 weeks of the test being initiated

What are the benefits of CMA?

- Provides a detailed study of the chromosomes which may not have been previously possible
- May help to understand the cause of the pregnancy loss or stillbirth
- May help guide management and care of future pregnancies
- May identify couples at increased risk of pregnancy loss or an abnormal liveborn with a chromosomal imbalance

What are the limitations and unanticipated outcomes of CMA?

- May find an imbalance unrelated to the pregnancy loss, but that indicates risk for other unanticipated health problems for the parents and family members (e.g. cancer, late onset neurological disease).
- Not all genetic conditions are detectable by CMA, as some are caused by mutations within a single gene or are multifactorial in nature.
- Additional descriptions of result classifications can be found in the Chromosomal Microarray information sheet (**http://ahsweb.ca/lab/if-lab-genetics-and-genomics**)
- A normal CMA result does not exclude all genetic causes of disease.
- CMA testing may require testing of parents to help establish pattern of inheritance and clinical implications.
- May detect the absence of heterozygosity (AOH).
    - AOH limited to one chromosome may be suggestive of uniparental disomy (UPD) and follow-up testing may be required.
    - AOH detected on multiple chromosomes suggests these regions are identical by descent.
    - 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.

I have CMA results, now what?

- If an abnormal result or variant of uncertain significance is reported, it is appropriate to refer the family for genetic assessment and counselling.
- If the CMA result is normal, it does not mean that there is not a genetic cause for the pregnancy loss. Other genetic testing may be appropriate, in consultation with Clinical Genetics.

Referrals to Clinical Genetics can be sent to:

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

I have questions about array CMA. Who do I talk to?

Contact the laboratory genetic counsellors:
Edmonton at 780-407-1015

Calgary at 403-955-3097

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.

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