Methylation Analysis (of chromosomes 14 and 15)

**TEST DESCRIPTION:**
Methylation Analysis (of chromosomes 14 and 15) is performed to detect imprinting abnormalities that can occur on these chromosomes. Imprinting disorders include:

- **Maternal Uniparental Disomy (UPD) 14**
  - Caused by absence of the paternal copy of chromosome region 14q32.2.

- **Paternal Uniparental Disomy (UPD) 14**
  - Caused by absence of the maternal copy of chromosome region 14q32.

- **Paternal Uniparental Disomy (UPD) 15 (Angelman syndrome)**
  - Angelman syndrome (AS) is caused by absence of the paternal copy of chromosome region 15q11-q13.
  - The combination of genetic testing offered at our laboratory, including methylation 15, UBE3A sequencing, UPD Array, and deletion/duplication analysis will detect an abnormality for approximately 89-90% of individuals with AS.
  - Due to clinical overlap with other genetic conditions, also consider our Rett/Atypical Rett/Angelman/Angelman-like Syndrome Gene Panel OR the more comprehensive Autism/Intellectual Disability/Multiple Anomalies Gene Panel which includes the Rett/Atypical Rett/Angelman Syndrome Panel plus additional genes of interest.
  - Approximately 10-11% of individuals with AS will not have an identifiable AS-causing genetic abnormality due to either incorrect clinical diagnosis or limitations of current methods of testing.

- **Maternal Uniparental Disomy (UPD) 15 (Prader-Willi syndrome)**
  - Prader-Willi syndrome (PWS) is caused by absence of the paternal copy of the PWS/Angelman syndrome region of chromosome 15.
  - A combination of methylation, FISH, chromosomes, and/or UPD will detect a genetic abnormality in ~99% of individuals with PWS; our laboratory does not perform sequence analysis on the imprinting center which is the cause for less than 1% of individuals with PWS.

**TEST DETAILS:**
- Methylation analysis is used to detect and identify the parental origin of deletions, uniparental disomy (UPD), and methylation defects occurring in the imprinted promoter regions of chromosomes 14 (MEG3/GTL2) & 15 (SNRPN).

![Diagram of Methylation Analysis]

- DNA methylation analysis at 5’ SNRPN
- Abnormal methylation pattern observed
- Microarray analysis or FISH for 15q11.2q13.1 deletion
- Normal deletion analysis
- DNA polymorphism analysis
- Biparental inheritance observed
- Deletion
- Uniparental disomy
- Imprinting defect

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INDICATIONS FOR TESTING (Maternal Uniparental Disomy 14):
Temple syndrome OMIM http://www.omim.org/entry/616222?search=maternal%20upd14&highlight=maternal%20upd14
- Intra uterine growth retardation
- Low birth weight
- Feeding problems early in life
- Dysmorphic facial features
- Short stature
- Significantly reduced final height
- Hypotonia
- Motor delay
- Early puberty
- Small hands and feet

INDICATIONS FOR TESTING (Paternal Uniparental Disomy 14):
- Dysmorphic facial features
- Congenital heart defect
- Respiratory failure
- Small bell shaped thorax
- "Coat hanger" ribs
- Skeletal Anomalies
- Hypotonia
- Developmental delay
- Feeding difficulty

INDICATIONS FOR TESTING (Paternal Uniparental Disomy 15):
- Delayed attainment of developmental milestones without loss of skills
- Speech impairment, with minimal to no word use
- Movement or balance disorder, ataxic gait
- Behavioral uniqueness, frequent laughter, hand flapping
- Seizures
- Microcephaly

INDICATIONS FOR TESTING (Maternal Uniparental Disomy 15):
- Hypotonia with history of poor suck (infancy)
- Poor feeding early in life
- Global developmental delay
- Excessive eating, with central obesity if uncontrolled
- Small hands and feet
- Hypothalamic hypogonadism

SPECIMEN COLLECTION & TRANSPORT:
Complimentary test kits are available upon request, but are not required.

SAMPLE TYPE and REQUIREMENTS:
- blood: 2-5 ml whole blood in an EDTA tube (purple top)
  - newborn minimum requirement: 1-3 ml
- buccal swab: 5 swabs
- extracted DNA: 70 ng/µg with a total yield of 7-10 µg (in TE) in a DNA microcentrifuge tube
  * When submitting extracted DNA for genetic testing, nucleic isolation must have occurred in a CLIA-certified laboratory or a laboratory meeting equivalent requirements as determined by the CAP and/or CMS.
SHIPPING:
- Maintain and ship samples at room temperature.
- Coordinate transport for sample to be received in our laboratory within 24-48 hours of collection.
  - LOCAL: Call 402-559-5070 (option 1)
  - OUT OF AREA: Prior to shipment, please fax the completed test request form to 402-559-7248, including the FedEx® airbill tracking number.
    - Saturday delivery MUST be checked when sending FedEx® on Friday.
    - Please include Internal Billing Reference # 3155070600 on the FedEx® airbill.
- Ship To: Human Genetics Laboratory – Zip 5440
  UNMC Shipping & Receiving Dock
  601 S. Saddle Creek Road
  Omaha, NE 68106

REQUIRED FORM: The following form can be downloaded via our website.
- Postnatal Test Request Form

OPTIONAL FORM:
- Informed Consent for Genetic Testing

POTENTIAL TEST RESULTS:

NORMAL:
- A normal result indicates no clinically-significant methylation abnormalities were identified using the (MEG3/GTL2) primer set on chromosome 14 and/or the SNRPN primer set on chromosome 15.

ABNORMAL:
- MAT UPD 14
- PAT UPD 14
- MAT UPD 15
- PAT UPD 15

TURN-AROUND-TIMES: Results are typically available in 1-2 weeks for routine studies; 5-7 days for newborn studies.

BILLING: Our laboratory offers patient/self-pay, insurance (including Medicare/Medicaid), and client/institution billing options. Verifying coverage requirements or obtaining preauthorization PRIOR TO OR AT THE TIME OF SPECIMEN COLLECTION is often necessary. We provide preauthorization services upon request by calling 402-559-5070 (option 3); the following form is helpful for obtaining the information required by insurance providers and can be downloaded via our website.
- Insurance Preauthorization Request

In some circumstances, a test may be warranted even though insurance coverage is denied or not guaranteed. For these situations, we request the following form be signed by the patient and submitted with the sample. This helps inform patients of their potential financial responsibility, should the costs of genetic testing not be paid by their insurance provider.
- Advanced Beneficiary Notice of Noncoverage (ABN) – required when billing Medicare

CPT CODES:
- Methylation Analysis of chromosome 14: 81402
- Methylation Analysis of chromosome 15: 81331

PRICING: For current costs contact the laboratory billing staff at 402-559-5070 (option 3).

updated 4/2015