ALBERTA PRECISION LABORATORIES
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# Overgrowth Panel: Information for Ordering Providers

There is significant clinical overlap and phenotypic heterogeneity between the overgrowth disorders. Therefore, making a clinical diagnosis, particularly in infancy, can be challenging. Additionally, pathogenic variants in a single gene may be associated with a broad spectrum of clinical presentations.

Overgrowth disorders are typically *de novo* or inherited in an autosomal dominant fashion. Simpson-Golabi-Behmel syndrome is an X-linked condition; however, female carriers may exhibit some SGBS features[1]. If a pathogenic variant is identified, the patient and/or their family members may be at increased risk for specific cancers. Genetic counselling is recommended for these families.

**Indications for Testing**
Patients presenting with clinical features of a macrocephaly/overgrowth syndrome are eligible for testing in the postnatal or prenatal period.

**Ordering privileges**
This panel may be ordered by Clinical Geneticists.

**Overgrowth NGS panel**

| Gene(s) | Associated cancers and/or clinical features[1,2] | Associated Hereditary Syndrome[1] |
|---|---|---|
| *CDKN1C* | Neonatal hypoglycemia, macrosomia, macroglossia, hemihyperplasia, omphalocele, embryonal tumors, visceromegaly, renal anomalies and ear creases / pits. | Beckwith-Wiedemann syndrome |
| | *Of note: If a patient is suspected to have BWS, the first line test should be assessment for uniparental disomy of 11p15 or abnormal methylation or deletions of this region, with reflex to CDKN1C sanger sequencing. This testing is available through the Calgary Molecular Genetics Lab.* | |
| *DIS3L2* | Macrosomia, visceromegaly, macrocephaly, polyhydramnios, dysmorphic facial features, pancreatic hyperplasia, neurodevelopmental delay, nephroblastomatosis, increased risk of Wilm's tumor. | Perlman syndrome |
| *EZH2* | Tall stature, variable intellect (including normal intellect), characteristic facial appearance. Neuroblastoma occurs at a slightly increased frequency, however, the absolute risk is not known. | *EZH2*-related overgrowth (clinical spectrum ranges from tall stature to Weaver syndrome) |
| *GPC3* | Overgrowth (pre- and post-natal), distinct craniofacial and skeletal findings, variable intellectual disability. Affected individuals are also at increased risk for embryonal tumors. | Simpson-Golabi-Behmel syndrome |
| *NSD1* | Overgrowth, distinctive facial appearance, and mild to severe intellectual disability. Tumors occur in approximately 3% of persons with Sotos syndrome. | Sotos syndrome |
| *PTEN* | Hamartoma tumor syndrome with variable phenotypes; clinical features may include macrocephaly, hamartomatous polyposis, overgrowth, dermatologic features, developmental delay, intellectual disability, and increased risk of benign and malignant tumors. | PTEN hamartoma tumor syndrome (includes Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, PTEN-related Proteus syndrome, and Proteus-like syndrome) |

**Associated Disorders**[1,2]
Some of the genes on this panel are associated with other rare disorders including:

> **Cowden syndrome** is an autosomal dominant multiple hamartoma syndrome caused by germline *PTEN* pathogenic variants. Cowden syndrome is associated with an increased risk of breast cancer, endometrial cancer, and thyroid cancer. Additional clinical features include macrocephaly and dermatologic findings such as trichilemmomas and papillomatous papules.

**When can I expect results?**
Results may take up to 4 months.

**How are results reported?**
Results are sent to the ordering provider and available in Netcare and Connect Care.

**Contact Information**
Genetic Counsellors, Genetics & Genomics
Calgary: 403-955-3097

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

**References**

1. Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018 [cited 2017 Dec]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1116/

2. MedlinePlus [Internet]. Bethesda (MD): National Library of Medicine (US); [cited 2022 Sept 1]. Available from: https://medlineplus.gov/;