OVERGROWTH PANEL

Background: Overgrowth syndromes encompass a variety of different diseases and are associated with both germline and somatic mutations in several different genes. This testing targets 8 genes associated with overgrowth, as well as other overlapping and non-overlapping clinical features.

Somatic mutations in AKT1 (OMIM 164730) are associated with Proteus syndrome. Mutations in AKT2 (OMIM 164731) are associated with hemihypertrophy with pseudohyperinsulinism. Somatic mutations in PIK3CA (OMIM 171834) are associated with CLOVES syndrome and macrodactyly. Mutations in AKT3 (OMIM 611223) and PIK3R2 (OMIM 603157) are associated with megalencephaly. Mutations in CDKN1C (OMIM 600856) are associated with familial cases of Beckwith-Wiedemann syndrome. Somatic, mosaic mutations in GNAQ (OMIM 600998) are associated with non-syndromic port-wine stains, as well as Sturge-Weber syndrome. Mutations in MTOR (OMIM 601231) are associated with hemimegalencephaly.

Most mutations in the genes above that result in the above diagnoses are somatic in their origin. These mutations are often mosaic and typically poorly detected in the blood and better detected in a clearly affected tissue (skin, muscle, adipose, CNS).

Assay: Multiplex PCR and Next Generation Sequencing on IonTorrent PGM platform.

Testing assesses specific regions related to overgrowth in the following 8 genes: AKT1, AKT2, AKT3, CDKN1C, GNAQ, MTOR, PIK3CA, PIK3R2 (Overgrowth version 1.0)

Utility: Confirmation of a clinical diagnosis, prognostic evaluation, clinical management.

Sensitivity: Testing targets specific gene mutations or exons of the genes listed above and does not detect mutations that are outside of the targeted area. Testing does not completely sequence every exon of each one of the 8 genes. The limit of detection is 5% at 500X sequencing coverage and 10% at 200X coverage. This technology cannot reliably detect mutations at coverage below 100X coverage. Confirmation of mutations is performed by repeat sequencing of independent replicate sample.

Turn around: 6-8 weeks

Fee: $2500

CPT codes: 81479
INSTRUCTIONS FOR OVERGROWTH PANEL SAMPLE SUBMISSION

Documentation:
Each sample must be accompanied by:
1. A request form for DNA analysis completed by the physician, nurse or genetic counselor requesting screening. Please note: ICD-9 code is required for billing purposes. If ICD-9 code is unknown, please provide patient’s clinical symptom(s) that prompted testing.
2. A completed registration form with check, money order, credit card authorization or information for billing the referring institution.
3. An informed consent signed by the patient (if under 18 years of age, the parent or guardian should sign) and the professional obtaining the consent. Please have the patient initial at the top of each page and send all pages of the consent.
4. A verification of samples form signed by the patient, parent or guardian. The form should be signed at the time of blood draw or procedure to obtain other tissue.
5. The patient’s pedigree to include three generations, if possible.

IN THE EVENT THAT ALL PROPERLY COMPLETED FORMS DO NOT ACCOMPANY THE SPECIMEN, YOU WILL BE NOTIFIED, AND TESTING WILL BE HELD UNTIL PAPERWORK IS COMPLETE

Sample Requirements:
- Two samples are required for testing.
- One sample must be obtained from affected tissue.
- The second sample should be from unaffected tissue or blood.
- For the blood sample, obtain 1 EDTA tube (lavender top) – approximately 5 mL whole blood
- For skin tissue sample, obtain 50 mg or more of skin tissue (one 3mm punch biopsy) shipped in tissue culture media.
- We accept banked or recently extracted DNA; please include the concentration and source of sample. Please call for requirements.
- Label each sample with the patient’s name and date sample was obtained.

Shipping Sample:
Ship at room temperature via Federal Express or other overnight courier that guarantees AM delivery to arrive Monday-Friday. There is no one in the laboratory evenings and weekends to receive samples. If sample is drawn on a Friday, please refrigerate it until shipment on the following business day.

Shipping Address:
Genetic Diagnostic Laboratory
University of Pennsylvania
415 Anatomy-Chemistry Building
3620 Hamilton Walk
Philadelphia, PA 19104
OVERGROWTH PANEL REQUEST FORM

Please provide the following information. We cannot perform your test without ALL of this information. PLEASE PRINT ALL ANSWERS

PATIENT INFORMATION

<table>
<thead>
<tr>
<th>FIRST NAME</th>
<th>MI</th>
<th>LAST NAME</th>
<th>MAIDEN NAME</th>
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<th>BIRTH DATE</th>
<th>GENDER</th>
<th>RACE</th>
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CLINICAL INFORMATION

ICD-9 CODE(S):

- 759.89 Hemihypertrophy
- 756.0 Cranial asymmetry
- 757.39 Other specified anomalies of skin
- 251.1 Hyperinsulinism
- 775.6 Neonatal hypoglycemia
- 742.4 Megalencephaly
- 766.1 Large for gestational age
- 757.32 Port-Wine Stain(s)
- 755.57 Macroductyly
- 214.9 Lipoma

ADDITIONAL CLINICAL SYMPTOMS: __________________________________________

If the test request is for FAMILIAL ANALYSIS for a KNOWN MUTATION:

Name of person previously tested and relationship: ____________________________

Was the previous testing performed at the Genetic Diagnostic Laboratory?  
- Yes  
- No

Result (Please include a copy of the result): __________________________________

SAMPLE TYPE

- Venous blood
- FFPE sections/block
- Frozen tissue
- Skin punch biopsy
- Cultured cells
- Other: __________________________________

TEST REQUESTED

- Overgrowth panel (NextGen v.1)

* Please include a copy of genetic result for affected family member for any familial test requests.
PATIENT REGISTRATION FORM

Please provide the following information. We cannot perform your test without ALL of this information. PLEASE PRINT ALL ANSWERS

PATIENT INFORMATION

FIRST NAME  MI  LAST NAME  BIRTH DATE  GENDER

STREET ADDRESS

CITY  STATE  ZIP  PHONE

PHYSICIAN INFORMATION

REFERRING PHYSICIAN  PHONE  FAX

GENETIC COUNSELOR  PHONE  FAX

EMAIL ADDRESS FOR COUNSELOR  EMAIL ADDRESS FOR PHYSICIAN

INSTITUTION AND DEPARTMENT

STREET ADDRESS  CITY  STATE  ZIP

PAYMENT OPTIONS (must choose one) [a receipt will be mailed to the patient for self-pay options]

☐ I have enclosed a check payable to the “Genetic Diagnostic Laboratory” for $ ______________________

☐ Please charge my credit card for the amount of $ ______________________

☒ VISA  ☐ Master Card  ☐ Discover  ☐ American Express

Card Number: ____________________________________________  Exp date: __________

Name of cardholder as it appears on card: ____________________________________________

☐ I have Pennsylvania Medicaid. A copy of my Medicaid card is attached.

☐ INSTITUTIONAL BILLING: The Institution where my testing originated has agreed to pay all charges for the testing.

INCLUDE Billing Address, Person Authorizing Payment, Telephone, and Fax below:

BILLING ADDRESS

BILLING ADDRESS

NAME OF INDIVIDUAL AUTHORIZING PAYMENT  PHONE  FAX
VERIFICATION OF CORRECTLY IDENTIFIED SAMPLES

I am a participant in genetic DNA testing.

I have been shown the tubes containing my tissue or blood for this genetic testing and my name has been correctly placed on each one of these tubes.

I have signed a copy of the consent form regarding this genetic testing to be sent along with my blood samples. I have been given a copy of the consent form to keep.

Participant Name: ________________________________

Participant/Parent Signature: ________________________________

Date: ________________
Informed Consent for Overgrowth Panel Testing

I, or my child, ____________________________ request molecular genetic testing for the Overgrowth Panel testing as recommended by my health care provider. Genetic testing requires two samples of tissue or a sample of tissue and sample of blood drawn by venipuncture. DNA will be isolated from the sample(s) for molecular genetic testing.

I understand that:
1. There is usually a minimal amount of risk involved in obtaining a tissue or blood sample. These include pain at the blood draw site, bleeding, and bruising.

2. The risk of disclosure of genetic information might include psychosocial concerns and concerns about genetic discrimination. Please discuss these concerns with your health care provider.

3. There are different types of results that may be reported including:
   a. It is disclosed that the tumor, or submitted tissue, carries a clinically significant molecular alteration known to be associated with disease.
   b. The analysis did not detect a molecular alteration associated with disease. I know that the methods currently in use might be unable to detect all mutations in every gene, and the tumor, may still have a DNA mutation that was not detected by the current technology. Not finding a mutation does not eliminate a clinical diagnosis of disease.

4. The majority of samples submitted for analysis will be to identify somatic mutations in a particular tissue. It is possible, however, that the assay will detect unexpected results. Genetic information might be learned that implicate the presence of an inherited genetic condition that could affect you and/or family members.

5. These tests are subject to change periodically to improve or expand the utility of the test. The tests are not considered research but are considered to be the best and newest laboratory service available. This DNA testing is often complex and utilizes specialized materials. While the testing is highly accurate for detection of the majority of disease-causing mutations, a small fraction of mutations may be missed by the current technology. Due to the nature of the testing, there is a small possibility that the test will not work properly or that an error will occur. Occasionally, testing may reveal a variant of unknown significance that is unable to be definitively interpreted as positive or negative for disease-association based on our current knowledge of the variant.

My signature below acknowledges my voluntary participation in this testing, but in no way releases the laboratory and staff from their professional and ethical responsibility to me.

6. Because of the complexity of molecular based testing and the important implications of the test results, results will be reported to me only through the physician who requested the testing. The results are confidential; they will only be released to other medical professionals or other parties with my verbal or written consent.

7. After the specific tests requested have been completed and reported, the Laboratory may dispose of, retain, or preserve these specimens for research or for validation in the development of future genetic tests. I understand that my identity will be protected and that research results will not be provided to me or to any other party. If use of this genetic material results in a scientific publication, it will not contain any identifying information. Indicate consent or denial

Initials _______
below. Your refusal to consent to research will not affect the reporting of your genetic results.

_____ I consent to the use of my DNA sample for research purposes.

_____ I do not consent to the use of my DNA sample for research purposes.

In the event that my sample is used for research purposes, the Laboratory may wish to contact my physician/genetic counselor for additional information regarding my sample. This includes, but is not limited to, information on personal health and family history as it relates to the genetic testing. If there are new developments in the field, my physician/genetic counselor may be contacted by the Genetic Diagnostic Laboratory staff to offer me the opportunity to have additional clinical testing. Indicate consent or denial to the above sentence by initialing below. My refusal to consent to research will not affect the reporting of my genetic results.

_____ I consent to be contacted by the Laboratory in the future for research purposes.

_____ I do not consent to be contacted by the Laboratory in the future for research purposes.

8. I understand that the Genetic Diagnostic Laboratory is not a DNA banking facility and my DNA or tissue sample may not be available for future clinical studies.

**Physician/Counselor Statement:** I have explained the potential clinical utility for the requested molecular test to this individual. I have addressed the limitations outlined above, and I have answered this individual’s questions.

Signature__________________________________________

Print Name________________________________________

Date ______________________

**Patient Statement:** I agree to the genetic analysis, and I have had the opportunity to ask questions about the testing.

Patient’s Name (PRINTED): ________________________________________

Relationship: _____ Self or _____ Child

Patient’s Date of Birth: _______________________

Signature of Patient or Parent: __________________________________________

Date Signed _________________________