GERMLINE BAP1 ANALYSIS

Background: Germline BAP1 mutations are associated with a predisposition to uveal melanoma and malignant mesothelioma. Uveal melanoma is a rare ocular cancer that affects the uveal tract, comprising the iris, ciliary body, and choroid. Mesothelioma is a cancer that occurs in the tissue that lines internal organs in the chest and abdomen. It is often associated with exposure to asbestos. Other cancer risks that may be associated with a BAP1 germline mutation include cutaneous melanoma, atypical melanocytic tumors, and renal cancers. The full spectrum of cancer types and likeliness of developing those cancers is not currently well defined.

BAP1 testing is recommended for individuals who have a personal/family history of uveal melanoma, malignant mesothelioma, and/or other cancers included in the BAP1 spectrum.

Assay: Sequencing: Sanger sequencing of coding exons of BAP1.

Deletion/Duplication: A custom comparative genomic hybridization and single nucleotide polymorphism (CGH + SNP) array designed using Agilent technologies. This high-density array is designed to detect exonic and intronic copy number changes as small as 400 bp and 1.5kb, respectively, in the targeted gene(s). The analysis of the array hybridization data for targeted gene(s) is performed using Cytogenomics software (Agilent Technologies). These results may be confirmed by qPCR.

Utility: Medical management, identification of at risk family members

Sensitivity: The clinical sensitivity of BAP1 germline mutations in individuals is not currently established.

References:


<table>
<thead>
<tr>
<th>Name of Test</th>
<th>Turnaround Time</th>
<th>Cost</th>
<th>CPT codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAP1: Sequencing with a reflex to deletion/duplication analysis (germline)</td>
<td>4-6 weeks</td>
<td>$1,550*</td>
<td>81479x2</td>
</tr>
<tr>
<td>BAP1: Sequence analysis (germline)</td>
<td>4-6 weeks</td>
<td>$800</td>
<td>81479</td>
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<tr>
<td>BAP1: Deletion/Duplication analysis only (germline)</td>
<td>3-4 weeks</td>
<td>$750</td>
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<tr>
<td>BAP1: Site specific analysis (familial)</td>
<td>2-3 weeks</td>
<td>$360</td>
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*Reflex testing options: Maximum cost is listed, although our lab only bills for the services performed. Final charge may be less than listed price, but cannot be determined until the testing has been completed.
REQUEST FOR GERMLINE BAP1 ANALYSIS

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>BIRTH DATE (MM/DD/YYYY)</th>
<th>GENDER</th>
</tr>
</thead>
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CLINICAL INFORMATION

ICD-10 Codes:*  
- □ C69.30 Malignant neoplasm of unspecified choroid  
- □ C65.9 Malignant neoplasm of unspecified renal pelvis  
- □ C45.0 Malignant mesothelioma of pleura  
- □ C43.9 Malignant melanoma of the skin  
- □ Z85.84 Personal history of malignant neoplasm of eye  
- □ Z85.53 Personal history of malignant neoplasm of renal pelvis  
- □ Z84.81 Family history of carrier of genetic condition  
- □ Other: ____________________________________________

Personal history of cancer? □ No  □ Yes; if yes, describe: ______________________________________________________________

Family history of cancer? □ No  □ Yes; if yes, describe: ______________________________________________________________

CANCER DIAGNOSIS  
- ____________________________________________  
- ____________________________________________  
- ____________________________________________  
- ____________________________________________  

AGE DIAGNOSED  
- ____________________________________________  
- ____________________________________________  
- ____________________________________________  
- ____________________________________________  

If the patient has a diagnosis of ocular melanoma:

Location of tumor (select all that apply)? □ Iris  □ Choroid  □ Ciliary body

Which eye is affected: □ Left  □ Right

What color is the iris? □ Black  □ Brown  □ Blue  □ Green  □ Hazel

If the test request is for site specific 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): ____________________________________________

TEST REQUESTED*  
- □ Sequence analysis of BAP1 gene; if negative, reflex to deletion/duplication analysis  
- □ Sequence analysis of BAP1 gene  
- □ Deletion/duplication analysis of BAP1 gene  
- □ Site specific analysis of BAP1 gene (familial) ________ sequencing * ___________ copy number*

* Required information

9/15/17
**PATIENT REGISTRATION 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>
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### PHYSICIAN INFORMATION*

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<thead>
<tr>
<th>REFERRING PHYSICIAN</th>
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<thead>
<tr>
<th>GENETIC COUNSELOR</th>
<th>PHONE</th>
<th>FAX</th>
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<tr>
<th>EMAIL ADDRESS FOR COUNSELOR</th>
<th>EMAIL ADDRESS FOR PHYSICIAN</th>
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<th>INSTITUTION AND DEPARTMENT</th>
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### 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:

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<th>BILLING ADDRESS</th>
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<tr>
<th>NAME OF INDIVIDUAL AUTHORIZING PAYMENT</th>
<th>PHONE</th>
<th>FAX</th>
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INFORMED CONSENT: BAP1 GENETIC TESTING

**Background:** Germline BAP1 mutations are associated with BAP1 Tumor Predisposition Syndrome which is associated with an increased risk of developing uveal melanoma, malignant mesothelioma, in addition to other cancers. Uveal melanoma is a rare ocular cancer that affects the uveal tract, comprising the iris, ciliary body, and choroid. Mesothelioma is a cancer that occurs in the tissue that lines internal organs in the chest and abdomen. It is often associated with exposure with asbestos. Other cancer risks that may be associated with a BAP1 germline mutation include cutaneous melanoma, atypical melanocytic tumors, renal and lung cancers. The full spectrum of cancer types and likeliness of developing those cancers is not currently well defined.

**Purpose:** The diagnostic samples will be used for the purpose of attempting to determine if I (or my child) am/is a carrier of an altered BAP1 gene related to a hereditary predisposition for cancer. This information may help establish appropriate medical management.

**Results:** I understand that there are five possible results to this testing:

- **PATHOGENIC VARIANT:** A clinically significant variant is detected in the BAP1 gene. This may explain my personal or family history of cancer. My or my child's healthcare provider will make medical management recommendations based on this information.
- **LIKELY PATHOGENIC VARIANT:** A variant is detected in the BAP1 gene which is the likely deleterious. This may explain my personal or family history of cancer. My or my child's healthcare provider will make medical management recommendations based on this information.
- **VARIANT OF UNCERTAIN SIGNIFICANCE:** The laboratory may detect an alteration in the BAP1 gene which is currently of unknown significance, called a "variant of unknown significance (VUS)". The laboratory will work with my physician to help determine if the VUS can be further classified as to whether it is disease-causing for a predisposition to cancer.
- **LIKELY BENIGN VARIANT:** A variant is detected the BAP1 gene which is not likely to be clinically significant. This result reduces the likelihood that I, or my child, have a clinically significant variant in the gene(s) tested.
- **NEGATIVE:** No clinically significant mutations were identified in the BAP1 gene. This result reduces the likelihood that I, or my child, have a clinically significant variant in the gene tested. Methods currently in use are unable to detect all mutations and therefore may still carry a variant that was not detected by the current technology.

**Disclosure Policy:** The Genetic Diagnostic Laboratory will release my test results to the ordering healthcare provider or genetic counselor, and otherwise only as permitted by law. The results will be kept confidential to the extent allowed by law. If I provide separate written consent, the lab will release my test results to other medical professionals or third persons I want to receive my results.

**Limitations:** While genetic 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 the current knowledge of the variant. The DNA analysis performed at the University of Pennsylvania Genetic Diagnostic Laboratory is specific only for the gene(s) analyzed and in no way guarantees my health.

There are federal laws in place that prohibit health insurers and employers from discriminating based on genetic information, such as test results. There currently are no federal laws prohibiting discrimination based on genetic information by life insurance, long term care, or disability insurance companies, but state laws may restrict this. I understand I can ask my ordering provider or genetic counselor for more information about how insurers might use genetic information.
Use of Specimens After Clinical Test Performed: I understand my blood or tissue specimen will not be returned to me or the ordering healthcare provider, and becomes the property of the lab upon receipt. The laboratory is not a DNA banking facility; therefore this is no guarantee that samples will be available or usable for additional or future testing. Samples from New York residents will be disposed of 60 days after clinical testing is complete.

After the laboratory completes the ordered clinical test, the lab may retain and preserve the specimen to validate the development of future genetic tests or for future research or education purposes. The laboratory is committed to continuous improvement and therefore I understand my coded sample may be used to validate a new assay. If testing reveals a clinically significant result during the validation process of a new assay related to the original indication for testing, my health provider may be contacted. If the lab uses the specimen for future research or education purposes, the specimen will be de-identified by removing my personally identifying information. My name, address and other personal identifying information will not be linked to the samples, or the results of the research, and I will not be identified in any research results or publications. I will not receive a copy of the research results. I can decline for my sample to be retained at the lab by filling out “Research Opt Out” form found on the following website: http://www.med.upenn.edu/genetics/gdl/.

I understand the lab may wish to contact me, or my ordering healthcare provider, for additional information. The additional information may include, but would not be limited to, information about health and family history that might be relevant to the research. I understand I can decline future contact from the lab by filling out “Research Opt Out” form found on the following website: http://www.med.upenn.edu/genetics/gdl/.

Genetic Counseling provided by a qualified specialist (i.e. genetic counselor/ medical geneticist) is a recommendation for individuals proceeding with genetic testing. This service is available before and after genetic testing. Additionally, other testing or further physician consults may be warranted.

The Genetic Diagnostic Laboratory is also an available resource to ask more questions about this testing. The laboratory genetic counselor can be reached at 215-573-9161 and Arupa Ganguly, PhD, FACMG can be reached at 215-898-3122. I will be given a copy of this consent form to keep.

HEALTHCARE PROVIDER STATEMENT:
I have explained to _________________________________ the purpose of this genetic testing, the procedures required and the possible risks and benefits to the best of my ability.

_______________________________________________________
Printed Name of Professional Obtaining Consent

_______________________________________________________ ______________________
Signature of Professional Obtaining Consent Date

CONSENT OF PATIENT:
I have read and received a copy of this consent form. I agree to have genetic testing performed for myself, child or my fetus, and accept the risks. I understand the information provided in this document and I have had the opportunity to ask questions I have about the testing, the procedure, the associated risks and the alternatives.

Patient’s Printed Name: ___________________________________________ DOB: _________________

Patient’s Signature: ___________________________________________ Date: _________________
(or Parent/Guardian if patient is a minor)

Name and Relationship: ___________________________________________ (Parent/Guardian if patient is a minor)

Initials ________

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