GOPATH®
LABORATORIES
Global Pathology Services

GeneticsNow™

The Next Generation of Hereditary Cancer Testing

Why Genetic Testing?

Cancers can appear to run in families. Often this is due to shared environmental or lifestyle patterns, such as tobacco use. However, in some cases certain familial patterns not caused by environmental factors can be traced to the presence of a genetic mutation that is passed down through family blood lines. Having an inherited genetic mutation can increase a person's risk for developing a specific type of cancer. Knowing about this mutation can help patients to make informed decisions about their healthcare, such as having more frequent cancer screenings to catch cancer in its early stages or making other lifestyle changes to reduce the risk of developing cancer.

GoPath's GeneticsNow™ Series

GoPath Laboratories has developed several assays to help determine whether or not a patient has inherited a genetic mutation that may indicate an increased risk for a specific type of cancer. Using state-of-the-art next-generation sequencing technology, our proprietary screening protocols will detect various germline mutations rapidly and with minimal expense. These tests include BRCANow® Basic, BRCANow® Plus HBOC and BRCANow® Extended Comprehensive Risk Panel for mutations associated with breast, ovarian, and prostate cancer, and LynchNow™ Basic, LynchNow™ Plus - HNPCC, and LynchNow™ Extended for the genetic alterations associated with Lynch syndrome/HNPCC such as colon and endometrial cancer, among others. We offer several versions of these tests to give patients more options, flexibility and accurate testing to best meet their individual needs.

Genetic Counseling & Patient Support

To begin the screening process, GoPath's team of genetic counselors will schedule a time to speak with your patient and his/her family members by phone and/or a web-based program to guide them through a series of questions regarding their medical and family history and previous cancer screenings. At the end of the session, the genetic counselor will:

- Share the risk evaluation results and potential for being a genetic mutation carrier
- Recommend genetic testing options
- Walk them through the genetic testing process and results
- Offer information on cancer screening options and cancer risk prevention measures
- Develop a management plan with the patient's physician

If the patient decides to proceed with genetic testing, the genetic counselor will contact his/her physician to obtain the test order and work with GoPath's pre-authorization team to begin the insurance coverage process. GoPath's team of professional support personnel is prepared to make the genetic testing process as convenient and easy to understand as possible.

We also have created an online resource to provide information and guidance to patients who are considering genetic testing. Visit our website at **www.GoPathGenetics.com** to learn more about the genetic testing process and to discover resources such as a self-evaluation form, testing guides, payment options, and links to other cancer websites and helpful mobile apps.

BRCANow® Hereditary Breast and Ovarian Cancer

Approximately one in every 500 women in the United States has a BRCA1 or BRCA2 genetic mutation. BRCA1/2 mutations can be inherited from a mother or a father in an autosomal dominant fashion. This means that having only one copy of a BRCA1/2 mutation can increase a person's chance of developing certain cancers such as breast and ovarian. If a mother or a father carries a BRCA mutation, there is a 50% chance of the child inheriting that same mutation.

While not everyone who inherits the BRCA mutation develops cancer, having the mutation puts them at a higher risk. While the majority of breast and ovarian cancers are not inherited, genetic mutations account for 5-10% of all breast and ovarian cancers, which makes genetic testing an important option for patients at risk. We have recently learned that detecting BRCA mutations in men can also be important. Not only can men pass on the mutation to their children, but men with a BRCA mutation have been shown to be at greater risk for developing prostate, pancreatic and male breast cancer.

Table 1. BRCA Mutation Cancer Risk

Risk of Cancer in Individuals Wth a BRCA1 or BRCA2 Mutation			
Cancer Type	General Population (No Mutation)	Individuals With Mutation	
		BRCA1	BRCA2
Breast	12%	50-80%	40-70%
Ovarian	1-2%	24-40%	11-18%
Male Breast	0.10%	1-2%	5-10%
Prostate	15% (N. Europe Origin)	up to 30%	up to 39%
	18% (African American)		
Pancreatic	0.50%	1-3%	2-7%

GoPath offers several versions of the BRCANow® test to give patients more options to address their specific testing needs. These panels include BRCANow® Basic, BRCANow® Plus HBOC and BRCANow® Extended. We also offer individual testing for BRCA1 and BRCA2 target analysis, Ashkenazi Jewish and BRCA1/2 del/dup analysis.

Figure 1. BRCA Associated Genes

BRCANow® Basic (BRCA1/2 & BRCA1/2 dup/del analysis):

This is a capture-based NGS assay designed to detect germline mutations of 15 genes which are known to be associated with risks of several common human cancer syndromes including the hereditary breast and ovarian cancer syndrome (HBOC).

BRCANow® Plus - HBOC Panel:

In addition to BRCA 1/2 and BRCA 1/2 dup/del analysis, this panel also examines additional genes associated with increased risk for breast cancer. The genes included in this panel are: ATM, BARD1, BRCA1/2, BRCA1/2 dup/del, BRIP1, CDH1, CHEK2, MRE11A, MUTYH, NBN, NF1, PALB2, PTEN, RAD50, RAD51C, RAD51D, STK11 and TP53.

BRCANow® Extended Comprehensive Risk Panel:

This panel goes even further in-depth by examining a broader range of genes commonly associated with hereditary cancers. These include: APC, ATM, BARD1, BMPR1A, BRCA1/2, BRCA1/2 dup/del, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, MLH1, MSH2, MSH6, MRE11A, MUTYH, NBN, NF1, NF2, PALB2, PMS2, PTEN, RAD50, RAD51C, RAD51D, SMAD4, STK11, TP53, VHL.

The BRCAnow® Basic assay was designed to detect single and multi-nucleotide substitutions, insertions, duplications and small deletions in coding and exon-intron junction of BRCA1/2 genes. The assay provides >1500X average coverage at the targeted genomic regions of BRCA1/2 genes. Sensitivity and specificity of the assay for detection of BRCA1/2 mutations in targeted genomic regions is 96.5% and 100% with a negative predictive value (NPV) and positive predictive value of 96.5% and 100%. Targeted regions with inadequate sequencing read coverage (read depth < 200X) from NGS are sequenced by a Sanger DNA Sequencing method. Variant frequency of ≥10% was defined as the value of limit-of-detection (LOD) of the assay.

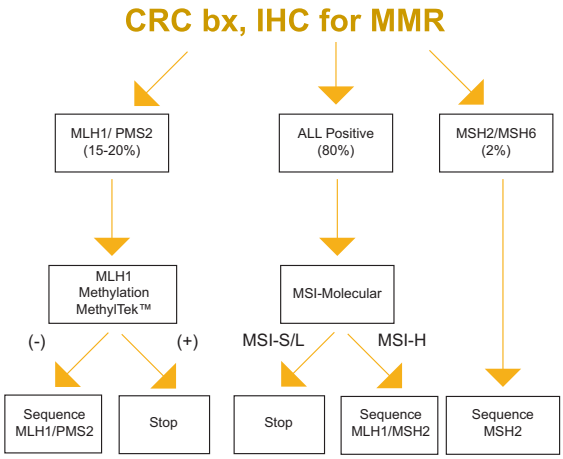
Familial Adenomatous Polyposis (FAP)

We also offer an assay to detect an inherited genetic mutation in which numerous adenomatous polyps form. More than 95% of people with Familial Adenomatous Polyposis (FAP) will have multiple colon polyps by age 35. If FAP is not diagnosed and treated, it is likely that the patient will develop colorectal cancer in his or her lifetime. Patients with FAP also have an increased risk of developing other cancers associated with FAP such as cancer of the stomach or small intestine.

LynchNow™ for Lynch Syndrome (HNPCC) Screening

GoPath also offers testing to detect hereditary nonpolyposis colorectal cancer (HNPCC), commonly called Lynch syndrome. People with Lynch syndrome have an increased risk of developing cancer of the digestive tract, particularly the colon (large intestine) and rectum. Those with Lynch syndrome also have a greater risk for developing cancers associated with this syndrome including stomach, small intestine, liver, gallbladder, upper urinary tract, brain, skin and prostate cancer. Women who have Lynch syndrome have a significantly greater risk of developing endometrial and ovarian cancers.

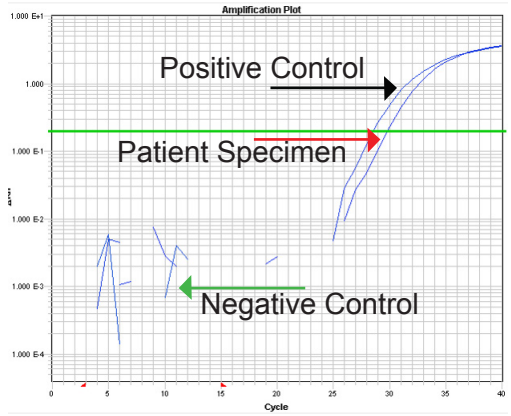
Figure 2. Lynch Algorithm Protocol



Lynch syndrome is associated with approximately 3%-5% of all colorectal cancers and is believed to be caused by mutations in DNA mismatched repair (MMR) genes. Those carrying a mutation have a 50%-80% higher than normal chance of developing colorectal cancer during his or her lifetime and at an earlier age.

Our next-generation sequencing-based Lynch screening panel detects these common MMR genes (MSH2, MSH6, MLH1, PMS2 and EPCAM) as well as many other genes associated with Lynch syndrome. We use a step-by-step approach in our general Lynch screening program that incorporates MMR-IHC, MSI-PCR and our proprietary MLH-1 promoter methylation test known as MethylTek™ (see Figure 2).

Figure 3. Example of a Positive MethylTek™ Result



Data generated using Applied Biosystems 7900HT Real-Time PCR

LynchNow™ Basic:

MLH1, MSH2, MSH6, PMS2 and EPCAM

LynchNow™ Plus - HNPCC Panel

APC, AXIN2, BMPR1A, BUB1B, CDH1, CHEK2, EPCAM, EXO1, FLCN, GREM1, MLH1, MLH3, MSH2, MSH6, MUYTH, PMS1, PMS2, POLD1, POLE, PTEN, SMAD4, STK11, TGFBR2 and TP53

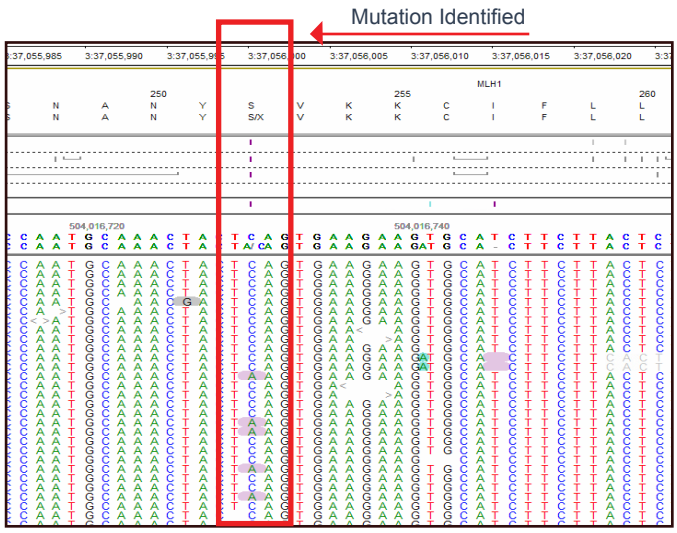
LynchNow™ Extended

APC, AXIN2, BLM, BMPR1A, BRCA1/2, BUB1B, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, EXO1, FLCN, GREM1, MLH1, MLH3, MSH2, MSH6, MUYTH, NF2, PMS1, PMS2, POLD1, POLE, PTEN, SMAD4, STK11, TGFBR2, TP53 and VHL

Methylation of MLH1 promoter (MethylTek™) is determined by the score of Methylation index (Mdex). Samples with a Mdex score of 0 to 1 are recorded as negative, and samples with a Mdex score of 3 or higher are recorded as positive. Negative MLH1 promoter methylation indicates that IHC loss of MLH1 staining in the tested tumor is not caused by somatic hypermethylation. Therefore, Lynch syndrome is suggested. Consultation with a genetic counselor is recommended with possible sequencing of the MLH-1 gene for confirmation.

The assay is designed to detect single and multi-nucleotide substitutions, insertions, duplications and small deletions in coding and exon-intron junction of the genes in this NGS panel. The assay provides >1500X average coverage at the targeted genomic regions of the tested genes. Sensitivity and specificity of the assay for detection of mutations in targeted genomic regions is 96.5% and 100% with a negative predictive value (NPV) and positive predictive value of 96.5% and 100%.

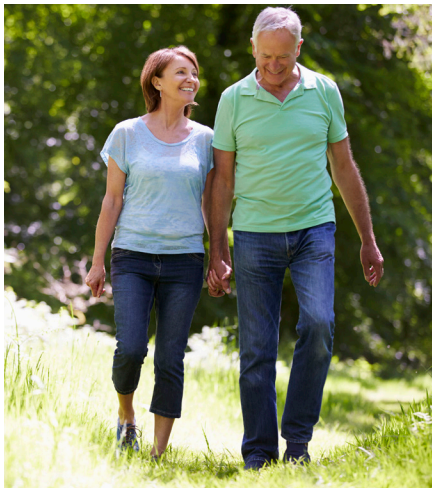
Figure 4. NGS Data For Positive Lynch Patient



Data generated from Illumina MiSeq Sequencer

When to Recommend Genetic Testing to Your Patients

Here are some general guidelines to help you determine whether or not your patient may be a candidate for genetic testing:



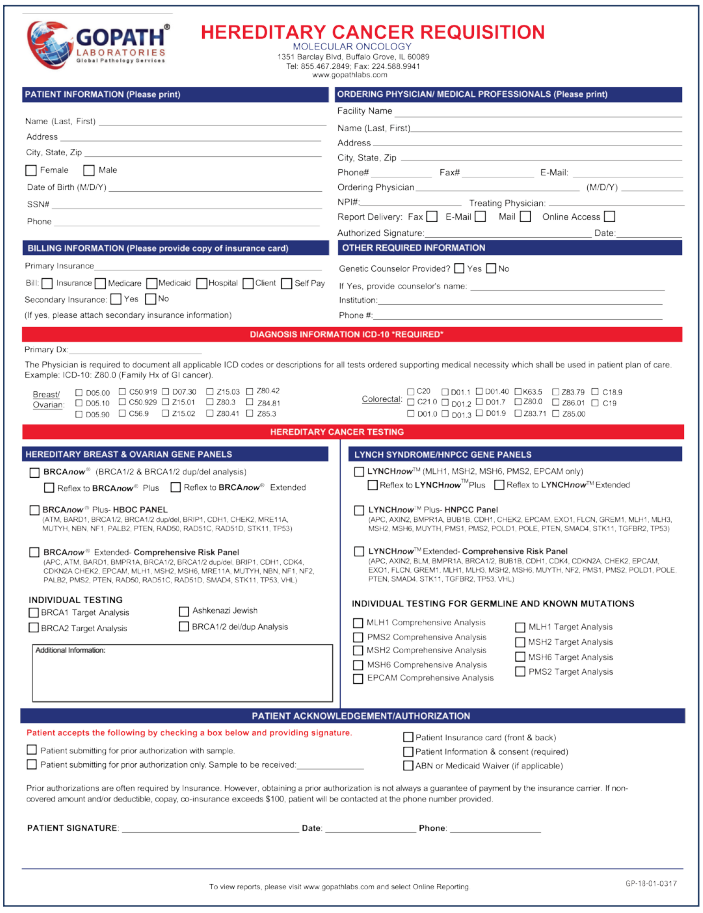
BRCANow® testing may be beneficial if the patient:

- Has had breast cancer before age 50
- Is male and has had breast cancer at any age
- Has had ovarian cancer at any age
- Has had triple negative breast cancer at any age
- Is of Ashkenazi Jewish descent and has a personal or family history of breast, ovarian, prostate or pancreatic cancer
- Has a family member who has had two breast cancers
- Has had two breast cancers on the same side of the family
- Has a family member who has tested positive for the BRCA1, BRCA2, or another related genetic mutation

LynchNow™ testing may be beneficial if the patient:

- Has had colorectal cancer before age 50
- Has had two or more Lynch syndrome cancers at any age
- Has had a Lynch syndrome cancer and has one or more relatives with a Lynch syndrome cancer
- Has a family member who has been identified as having the Lynch syndrome mutation
- Has had two or more family members with a Lynch syndrome cancer, one before the age of 50
- Has had three or more relatives with a Lynch syndrome cancer at any age

GeneticsNow™ Requisition & Sample Report



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HEREDITARY CANCER REQUISITION
MOLECULAR ONCOLOGY
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Tel: 855.467.2849; Fax: 224.588.9941
www.gopathlabs.com

PATIENT INFORMATION (Please print)
Name (Last, First)
Address
City, State, Zip
☐ Female ☐ Male
Date of Birth (M/D/Y)
SSN#
Phone

ORDERING PHYSICIAN/ MEDICAL PROFESSIONALS (Please print)
Facility Name
Name (Last, First)
Address
City, State, Zip
Phone# Fax# E-Mail:
Ordering Physician (M/D/Y)
NPI#: Treating Physician:
Report Delivery: Fax ☐ E-Mail ☐ Mail ☐ Online Access ☐
Authorized Signature: Date:

BILLING INFORMATION (Please provide copy of insurance card)
Primary Insurance
Bill: ☐ Insurance ☐ Medicare ☐ Medicaid ☐ Hospital ☐ Client ☐ Self Pay
Secondary Insurance: ☐ Yes ☐ No
(if yes, please attach secondary insurance information)

OTHER REQUIRED INFORMATION
Genetic Counselor Provided? ☐ Yes ☐ No
If Yes, provide counselor's name:
Institution:
Phone #:

DIAGNOSIS INFORMATION ICD-10 *REQUIRED*
Primary Dx:
The Physician is required to document all applicable ICD codes or descriptions for all tests ordered supporting medical necessity which shall be used in patient plan of care.
Example: ICD-10: Z80.0 (Family Hx of GI cancer).

Breast/ Ovarian: ☐ D05.00 ☐ C50.919 ☐ D07.30 ☐ Z15.03 ☐ Z80.42 ☐ D05.10 ☐ C50.929 ☐ Z15.01 ☐ Z80.3 ☐ Z84.81 ☐ D05.90 ☐ C56.9 ☐ Z15.02 ☐ Z80.41 ☐ Z85.3
Colorectal: ☐ C20 ☐ D01.1 ☐ D01.40 ☐ K63.5 ☐ Z83.79 ☐ C18.9 ☐ C21.0 ☐ D01.2 ☐ D01.7 ☐ Z80.0 ☐ Z86.01 ☐ C19 ☐ D01.0 ☐ D01.3 ☐ D01.9 ☐ Z83.71 ☐ Z85.00

HEREDITARY CANCER TESTING

HEREDITARY BREAST & OVARIAN GENE PANELS
☐ BRCA*now*® (BRCA1/2 & BRCA1/2 dup/del analysis)
☐ Reflex to BRCA*now*® Plus ☐ Reflex to BRCA*now*® Extended
☐ BRCA*now*™ Plus- HBOC PANEL (ATM, BARD1, BRCA1/2, BRCA1/2 dup/del, BRIP1, CDH1, CHEK2, MRE11A, MUTYH, NBN, NF1, PALB2, PTEN, RAD50, RAD51C, RAD51D, STK11, TP53)
☐ BRCA*now*® Extended- Comprehensive Risk Panel (APC, ATM, BARD1, BMPR1A, BRCA1/2, BRCA1/2 dup/del, BRIP1, CDH1, CDK4, CDKN2A CHEK2, EPCAM, MLH1, MSH2, MSH6, MRE11A, MUTYH, NBN, NF1, NF2, PALB2, PMS2, PTEN, RAD50, RAD51C, RAD51D, SMAD4, STK11, TP53, VHL)

INDIVIDUAL TESTING
☐ BRCA1 Target Analysis ☐ Ashkenazi Jewish
☐ BRCA2 Target Analysis ☐ BRCA1/2 del/dup Analysis

Additional Information:

LYNCH SYNDROME/HNPCC GENE PANELS
☐ LYNCH*now*™ (MLH1, MSH2, MSH6, PMS2, EPCAM only)
☐ Reflex to LYNCH*now*™ Plus ☐ Reflex to LYNCH*now*™ Extended
☐ LYNCH*now*™ Plus- HNPCC Panel (APC, AXIN2, BMPR1A, BUB1B, CDH1, CHEK2, EPCAM, EXO1, FLCN, GREM1, MLH1, MLH3, MSH2, MSH6, MUYTH, PMS1, PMS2, POLD1, POLE, PTEN, SMAD4, STK11, TGFBR2, TP53)
☐ LYNCH*now*™ Extended- Comprehensive Risk Panel (APC, AXIN2, BLM, BMPR1A, BRCA1/2, BUB1B, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, EXO1, FLCN, GREM1, MLH1, MLH3, MSH2, MSH6, MUYTH, NF2, PMS1, PMS2, POLD1, POLE, PTEN, SMAD4, STK11, TGFBR2, TP53, VHL)

INDIVIDUAL TESTING FOR GERMLINE AND KNOWN MUTATIONS
☐ MLH1 Comprehensive Analysis ☐ MLH1 Target Analysis
☐ PMS2 Comprehensive Analysis ☐ MSH2 Target Analysis
☐ MSH2 Comprehensive Analysis ☐ MSH6 Target Analysis
☐ MSH6 Comprehensive Analysis ☐ PMS2 Target Analysis
☐ EPCAM Comprehensive Analysis

PATIENT ACKNOWLEDGEMENT/AUTHORIZATION
Patient accepts the following by checking a box below and providing signature.
☐ Patient submitting for prior authorization with sample.
☐ Patient submitting for prior authorization only: Sample to be received:
☐ Patient Insurance card (front & back)
☐ Patient Information & consent (required)
☐ ABN or Medicaid Waiver (if applicable)

Prior authorizations are often required by Insurance. However, obtaining a prior authorization is not always a guarantee of payment by the insurance carrier. If non-covered amount and/or deductible, copay, co-insurance exceeds $100, patient will be contacted at the phone number provided.

PATIENT SIGNATURE: Date: Phone:

To view reports, please visit www.gopathlabs.com and select Online Reporting.

GP-18-01-0317

Comprehensive BRCA 1/2 Sequencing Analysis Report

Date: 02/16/2016
Order ID: GM16-4086
Order Date: 02/05/2016

GOPATH® LABORATORIES
Global Pathology Services

Patient Name: **JANE DOE**

Patient Information	Specimen Information	Physician Information
Name: JANE DOE	**Sample Type:** Peripheral blood	**Referring Physician:** DR. JIM LU
DOB: 09/17/1960	**Collected:** 02/04/2016	**Address:** 1351 BARCLAY BOULEVARD,
Gender: Female	**Received:** 02/05/2016	BUFFALO GROVE, IL 60089
Diagnosis: Breast Cancer	**Specimen ID:**	**Phone:** 224-588-9940 **Fax:** 224-588-9941

Report

TEST PERFORMED	RESULT	ZYGOSITY	SIGNIFICANCE
BRAC1 Sequencing	Variant detected c.1067 A>G (p.Q356R)	Heterozygous	Benign
BRCA1 Del/Dup	Negative	N/A	N/A
BRCA2 Sequencing	Negative	N/A	N/A
BRCA2 Del/Dup	Negative	N/A	N/A

Comments

A missense variant was detected at nucleotide 1067 of coding cDNA sequence (c. 1067 T>C). This rare variant causes amino acid change from glutamine to arginine at codon 356 (p. Q356R) at BRCA1 protein. The detected variant has been classified as benign which is not associated with an increased risk for the Hereditary Breast and Ovarian Cancer Syndrome. Interpretation and classification of clinical significance of this variant as benign variant are based on catalogued information from LOVD database (http://databases.lovd.nl/shared/genes/) and NCBI ClinVar database (http://www.ncbi.nlm.nih.gov/clinvar/variation/), as well as the results from a large population follow-up study (see Reference 1 on page 3). No variant was detected in BRCA2 gene.

Comprehensive sequencing analysis was also performed for other genes associated with increased risk of breast and ovarian cancers, including CHEK2, PALB2, PTEN, TP53, BARD1, ATM, CDH1, STK11, BRIP1 and NBN genes. No pathogenic or likely pathogenic variant was detected in any of these genes.

Recommendation

Based on accumulated information from clinical and research sources, the detected BI benign variant which is not associated with an increased risk for the Hereditary Breast Genetic counseling with a health care professional who has training and experience in to discuss cancer risks and other disease risks associated with this genetic test result. If you have any question about this report and wish to speak with the genetic experts i 855-467-2849 (Toll Free).

-2849 FAX: 224-588-9941

GoPath Pathology Associates SC, 1351 Barclay Blvd, Buffalo Grove, IL 60089, Phone: (855)

GoPath Laboratories' Client Services

Let Us Help You Get Started

Providing appropriate information saves valuable time, eliminates confusion, limits phone calls & shortens turnaround time.

- Indicate Billing
- Patient's Legal Name
- Patient's DOB and Gender
- Date of Service / Collection
- Patient's Address and Phone Number
- Ordering Physician's Name, Facility and NPI
- ICD10-CM Codes

Account Set Ups

- Immediate
- Customized Requisitions
- Personalized In-Service and Training
- Convenient Supply Ordering
- Specialized Account Set Up Team

Office Pickup Options

- Local Courier Services
- FedEx Express
- FedEx Same Day City

Billing Capabilities

Billing shouldn't frustrate your patients or distract your staff. We offer the following billing solutions:

- In-Network Lab Accepting All Government Insurances
- Work With Most Insurances & Customized Billing Options Available
- Convenient Client Billing
- Dedicated Billing Support
- Technical and Professional Model Billing Available
- Financial Assistance Plans Available for Patients with Financial Hardships

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- Research Collaborations
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- Test Supply Order Forms
- Information About Our Pathologists, Scientific and Executive Team Members

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