In medical school there is a saying, “When you hear hoofbeats, think horses not zebras.” Think of common causes of the symptoms first, not the rare. When you encounter a zebra, think GeneDx. We specialize in diagnosing rare genetic disorders.

From Humble Beginnings to Industry Leaders

Sherri Bale and John Compton were working on identifying genetic causes for various rare disorders at the National Institutes of Health (NIH). Families were requesting clinical diagnoses, but they could not provide that service through a research laboratory. Other commercial labs did not want to test for these disorders because of such low volume. To meet that need, Sherri and John decided to open a lab in the year 2000 to offer testing for these rare and ultra-rare disorders. Today, GeneDx provides genetic testing for hundreds of genetic disorders utilizing cutting-edge technologies and offers a broad array of special services such as: carrier screening, targeted testing, prenatal diagnosis, research testing, and exome and genome sequencing.

Sherri and John have been recognized for their great work numerous times. Sherri is a member of various working groups with the American College of Medical Genetics, and works closely with the Association for Molecular Pathology in the projects related to genetic testing.
Sherri Bale, PhD, FACMG, our founder, is a co-author on the 2007 and 2015 guidelines on the interpretation of sequence variants.\(^1\)\(^2\) She is also a co-author on the 2013 ACMG guidelines on next-generation sequencing.\(^3\)


GeneDx offers a comprehensive testing menu which includes clinically relevant genes associated with hereditary cancer and meets the testing needs across clinical indications.

**Our Cancer Panels at a Glance**

GeneDx offers a comprehensive testing menu which includes clinically relevant genes associated with hereditary cancer and meets the testing needs across clinical indications.

**Breast and Gynecologic Cancer Panels (see pages 5 and 6)**
- **BRCA1/BRCA2 Ashkenazi Founder Panel** (TAT 8-10 days)
  - Three Targeted Pathogenic Variants
- **BRCA1/BRCA2 Sequencing and Deletion/Duplication Analysis** (TAT 8-10 days)
- **Breast Cancer Management Panel** (TAT 2 weeks; RUSH surgical cases 8-10 days)
  - 9 genes
- **Breast/Gyn Cancer Panel** (TAT 2 weeks)
  - 23 genes

**Colorectal Cancer Panels (see pages 7 and 8)**
- **Colorectal Cancer Panel** (TAT 2 weeks)
  - 20 genes
- **Lynch/Colorectal High Risk Panel** (TAT 2 weeks)
  - 7 genes

**Panels for Multiple Cancer Types (see page 9)**
- **Comprehensive Common Cancer Panel** (TAT 2 weeks)
  - 46 genes
- **Common Cancer Management Panel** (TAT 2 weeks)
  - 37 genes

**Tumor Specific Panels (see page 9)**
- **Melanoma Panel** (TAT 2 weeks)
  - 9 genes
- **Pancreatic Cancer Panel** (TAT 2 weeks)
  - 15 genes
- **Pediatric Tumor Panel** (TAT 3 weeks)
  - 27 genes
- **PGL/PCC Panel** (TAT 3 weeks)
  - 12 genes
- **Hereditary Prostate Cancer Panel** (TAT 2 weeks)
  - 12 genes
- **Renal Cancer Panel** (TAT 3 weeks)
  - 18 genes

**Custom Panel (see page 10)**
- **OncoGeneDx Custom Panel** (TAT 3 weeks)
  - up to 64 genes
Experience Matters: Over 140,000 Hereditary Cancer Tests Performed

GeneDx Offers a Comprehensive Cancer Program

**Identification**
GeneDx offers tools to assist providers in identifying individuals who may be at risk to develop cancer due to a hereditary cancer syndrome

**Education**
GeneDx provides educational materials to improve the understanding of hereditary cancer and genetic testing

**Selection**
GeneDx offers a comprehensive and flexible testing menu to meet the testing needs of health care providers and their patients

**Support**
GeneDx offers a variety of post-test patient educational and management tools
Hereditary Breast and Gynecologic Cancer Testing

Approximately 5-10% of all breast cancers, 25% of all ovarian cancers, and 5-10% of all endometrial cancers occur because a woman was born with a pathogenic variant in a gene that increased her risk to develop cancer.

Identifying Patients at Risk for Hereditary Breast and Gynecologic Cancer

- Breast or endometrial cancer diagnosed under 50 years of age
- Multiple cancers in one person, either of the same origin (such as two separate breast cancers) or of different origins (such as breast and ovarian cancer or endometrial and colon cancer)
- Ovarian cancer or male breast cancer at any age
- Multiple relatives diagnosed with the same or related cancers (including breast, ovarian, endometrial, pancreatic and/or prostate) on the same side of the family and spanning multiple generations
- Ashkenazi Jewish ancestry with a history of breast, ovarian or pancreatic cancer
- A known pathogenic variant in a blood relative

Exploring the Positive Results at GeneDx for Breast Cancer

Pathogenic/likely pathogenic variants have been found in a number of genes in women with a personal history of breast cancer. The pie chart below describes our experience at GeneDx.

Pathogenic and Likely Pathogenic Variants in Women with Breast Cancer

- BRCA1: 16%
- PALB2: 9%
- CHEK2: 26%
- ATM: 12%
- BRCA2: 19%
- Other Moderate-Risk Genes**: 6%
- Other High-Risk Genes*: 5%
- Newer-Risk Genes***: 7%

*Other High-Risk Genes: CDH1, MLH1, MSH2, MSH6, PMS2, PTEN, TP53
**Other Moderate-Risk Genes: BRI1, RAD51C, RAD51D
***Newer-Risk Genes: FANCC, NBN, BARD1
Hereditary Breast and Gynecologic Cancer Panels

Breast and Ovarian Cancer Testing Options

- **BRCA1/BRCA2 Ashkenazi Founder Panel (TAT 8-10 days)**
  Targeted testing for three known founder variants in BRCA1 and BRCA2

- **BRCA1/BRCA2 Sequencing and Deletion/Duplication Analysis (TAT 8-10 days)**
  BRCA1, BRCA2

- **Breast Cancer Management Panel (TAT 2 weeks; RUSH surgical cases 8-10 days)**
  ATM, BRCA1, BRCA2, CDH1, CHEK2, NBN, PALB2, PTEN, TP53

- **Breast/Gyn Cancer Panel (TAT 2 weeks)**
  ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, FANCC, MLH1, MSH2, MSH6, MUTYH, NBN, NF1, PALB2, PMS2, POLD1, PTEN, RAD51C, RAD51D, RECQL, TP53

Endometrial Cancer Testing Options

- **Breast/Gyn Cancer Panel (TAT 2 weeks)**
  ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, FANCC, MLH1, MSH2, MSH6, MUTYH, NBN, NF1, PALB2, PMS2, POLD1, PTEN, RAD51C, RAD51D, RECQL, TP53

- **Lynch/Colorectal High Risk Panel (TAT 2 weeks)**
  APC, EPCAM, MLH1, MSH2, MSH6, MUTYH, PMS2

For patients and families with a history of rare or multiple cancer types, we also offer more comprehensive hereditary cancer testing options. Please see pages 9 and 10 for more details.

Positive Yields for Patients Referred for Hereditary Breast and Gynecologic Cancer Testing

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female Breast</td>
<td>9.6%</td>
</tr>
<tr>
<td>Female Breast, Personal and Family History</td>
<td>9.8%</td>
</tr>
<tr>
<td>Female Breast Cancer Diagnosed &lt;50</td>
<td>10.8%</td>
</tr>
<tr>
<td>Ovarian</td>
<td>13.1%</td>
</tr>
<tr>
<td>Endometrial</td>
<td>9.2%</td>
</tr>
<tr>
<td>Male Breast</td>
<td>15.4%</td>
</tr>
</tbody>
</table>
Hereditary Colorectal Cancer Testing

Pathogenic variants in several genes have been associated with hereditary colorectal cancer, such as Lynch and other cancer syndromes. Individuals with pathogenic variants in these genes may develop colorectal cancer at young ages or may have an increased risk for multiple cancer diagnoses in a lifetime.

Identifying Patients at Risk for Hereditary Colorectal Cancer

- Colorectal or endometrial cancer under 50 years of age
- Multiple cancers in one person, either of the same origin (such as two separate colon cancers) or of different origins (such as colorectal and endometrial cancer)
- Diagnosis of multiple colon polyps at any age
- Tumor testing which indicates an increased risk for Lynch syndrome
- Multiple relatives diagnosed with the same or related cancers (such as colorectal, endometrial, ovarian, urinary tract, gastric) on the same side of the family and spanning multiple generations
- A known pathogenic variant in a blood relative

Exploring the Results at GeneDx for Colorectal Cancer

Pathogenic/likely pathogenic variants have been found in a number of genes in patients with a personal history of colorectal cancer. The pie chart below describes our experience at GeneDx.

Pathogenic and Likely Pathogenic Variants in Individuals with Colorectal Cancer

*Other Polyp Genes: BMPR1A, POLE, PTEN, STK11
**Other Cancer Genes: AXIN2, BARD1, BRCA1, BRCA2, BRIP1, FANCC, NBN, PALB2, RAD51C, RAD51D, TP53, SDHD
Hereditary Colorectal Cancer Panels

For patients and families with a history of rare or multiple cancer types, we also offer more comprehensive hereditary cancer testing options. Please see pages 9 and 10 for more details.

Positive Yields Among Patients with Lynch-Related Cancers

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td>14.5%</td>
</tr>
<tr>
<td>Endometrial</td>
<td>13.6%</td>
</tr>
<tr>
<td>Ovarian</td>
<td>12.3%</td>
</tr>
<tr>
<td>Gastric</td>
<td>14.1%</td>
</tr>
</tbody>
</table>
Testing for Multiple Cancer Types

In some cases, it may be beneficial to address a broad range of cancer susceptibility genes. Testing using these panels may be appropriate for patients/families with a wide spectrum of cancers or for providers who want to customize their cancer panel.

Panels for Multiple Cancer Types

**Comprehensive Common Cancer Panel (TAT 2 weeks)**
APC, ATM, AXIN2, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, FANCC, FH, FLCN, HOXB13, MET, MITF, MLH1, MSH2, MSH6, MUTYH, NBN, NF1, NTHL1, PALB2, PMS2, POLD1, POLE, POT1, PTEN, RAD51C, RAD51D, RECQL, SCG5/GREM1, SDHB, SDHC, SDHD, SMAD4, STK11, TP53, TSC1, TSC2, VHL

**Common Cancer Management Panel (TAT 2 weeks)**
APC, ATM, AXIN2, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDKN2A, CHEK2, EPCAM, FH, FLCN, MLH1, MSH2, MSH6, MUTYH, NBN, NF1, NTHL1, PALB2, PMS2, POLD1, POLE, PTEN, RAD51C, RAD51D, SCG5/GREM1, SDHB, SDHC, SDHD, SMAD4, STK11, TP53, TSC1, TSC2, VHL

**OncoGeneDx Custom Panel (TAT 3 weeks)**
Create a customized cancer panel from a list of 64 cancer susceptibility genes. Please see page 10 for more details.

GeneDx offers a variety of testing options that may be appropriate for patients with a personal or family history of a rare or specific cancer phenotype(s).

**Tumor Specific Panels**

**Melanoma Panel (TAT 2 weeks)**
BAP1, BRCA2, CDK4, CDKN2A, MITF, POT1, PTEN, RB1, TP53

**Pancreatic Cancer Panel (TAT 2 weeks)**
APC, ATM, BRCA1, BRCA2, CDK4, CDKN2A, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, STK11, TP53, VHL

**Pediatric Tumor Panel (TAT 3 weeks)**
ALK, APC, CDC73, DICER1, EPCAM, MEN1, MLH1, MSH2, MSH6, NF1, NF2, PHOX2B, PMS2, PRKAR1A, PTCH1, PTEN, RB1, RET, SMARCA4, SMARCB1, STK11, SUFU, TP53, TSC1, TSC2, VHL, WT1

**PGL/PCC Panel (TAT 3 weeks)**
FH, MAX, MEN1, NF1, RET, SDHA, SDHAF2, SDHB, SDHC, SDHD, TMEM127, VHL

**Hereditary Prostate Cancer Panel (TAT 2 weeks)**
ATM, BRCA1, BRCA2, CHEK2, EPCAM, HOXB13, MLH1, MSH2, MSH6, NBN, PMS2, TP53

**Renal Cancer Panel (TAT 3 weeks)**
BAP1, EPCAM, FH, FLCN, MET, MITF, MLH1, MSH2, MSH6, PMS2, PTEN, SDHB, SDHC, SDHD, TP53, TSC1, TSC2, VHL
Testing with a Custom Panel

OncoGeneDx Custom Panel

The OncoGeneDx Custom Panel is a flexible testing option that allows providers to customize their test in order to meet the individual needs of their patient. Providers have the option to choose anywhere from a single gene test to a full 64 gene panel. Below is a list of available genes separated into their current risk category.

High-Risk Genes

- Well-studied • Greater than 4-fold risk of developing one or more cancers • Can cause a moderate risk for other cancers • National or expert opinion guidelines for screening and prevention are established

Moderate-Risk Genes

- Well-studied • Approximately 2- to 4-fold risk of developing one or more cancers • May increase risk for other cancers • Limited guidelines for screening and prevention

Newer-Risk Genes

- Not as well-studied • Precise lifetime risks and tumor spectrum not yet determined • Guidelines for screening and prevention are limited or not available

<table>
<thead>
<tr>
<th>High-Risk Genes</th>
<th>Moderate-Risk Genes</th>
<th>Newer-Risk Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALK, APC, BMPR1A, BRCA1, BRCA2, CDC73, CDH1, CDKN2A, EPCAM, FH, FLCN, MEN1, MLH1, MSH2, MSH6, MUTYH, NF1, NF2, PALB2, PHOX2B, PMS2, PRKAR1A, PTCH1, PTEN, RB1, RET, SDHB, SDHD, SMAD4, STK11, TP53, TSC1, TSC2, VHL, WT1</td>
<td>ATM, BRIP1, CHEK2, RAD51C, RAD51D</td>
<td>AXIN2, BAP1, BARD1, CDK4, DICER1, FANCC, HOXB13, MAX, MET, MIF, NBN, NTHL1, POLD1, POLE, POT1, SCG5/GREM1, RECQL, SDHA, SDHAF2, SDHC, SMARCA4, SMARCB1, SUFU, TMEM127</td>
</tr>
</tbody>
</table>
Data Analysis and Variant Classification Process

Every variant identified at GeneDx goes through a comprehensive review process as described below.

**Technical Data Analysis**
- Technical review of raw data
- Confirmation of identified variants by Sanger sequencing, microarray, MLPA or other appropriate method
- Determine nomenclature and technical parameters (e.g. coverage, mosaicism, heteroplasmy)

**Literature and Database Review**
- Comprehensive database and literature review, including Human Gene Mutation Database, ClinVar, as well as gene-specific, population and internal databases
- Review of output from in-silico protein and splicing prediction models, as well as evolutionary conservation data
- Analysis of functional impact, including assessing structural/functional domain and predicted effect on protein
- Performed by PhD-level analysts trained in molecular genetics and/or biochemistry

**Clinical Review**
- In-depth analysis of the variant within clinical context in literature (e.g. segregation, case-control studies, co-occurrence with a known pathogenic variant) and patients’ clinical information
- Consultation and collaboration with recognized scientific experts
- Performed by board-certified/eligible genetic counselors

**Final Review**
- Detailed review of cumulative evidence and final classification of variants in line with 2015 ACMG guidelines: Pathogenic, Likely Pathogenic, Variant of Uncertain Significance (VUS), Likely Benign and Benign
- Performed by board-certified medical and molecular geneticists with specific expertise in the disease area and testing platform

**Reporting**
- Results summarized in clear, concise and thoughtfully written reports customized to the patient tested
- Reports include clinical references, as well as appropriate medical management, patient educational material and other resources, when available
- Written and signed by genetic counselors and board-certified medical and molecular geneticists

We support the community by consistently sharing our data in publicly available variant databases and are the largest commercial laboratory contributor to ClinVar.

**Variant Follow-Up**
- Complimentary Variant Testing Program available to eligible families to aid in variant classification
- Re-evaluation of variants incorporates literature and database review, segregation and clinical data, when available
- Applies to variants identified in a new patient or upon client request, when it has been more than 6 months since the variant was last vetted or pertinent, new data is available
- Updated results report provided to the ordering healthcare provider for any one-step classification change involving a VUS, Likely Pathogenic Variant or Positive
- Continued communication with clients to discuss cases and results
GeneDx provides unique tools to help identify individuals at risk for hereditary cancer, including:

- MyGeneticsTree.com, a web-based family history tool that identifies individuals who meet criteria for hereditary cancer testing and can be completed prior to a scheduled visit.
- Family History Forms, a questionnaire which can help determine if individuals or other family members are candidates for genetic testing.

A variety of patient educational materials are available through GeneDx, including:

- Patient-friendly guides and panel fact sheets which can be referenced while discussing genetic testing options.
- Patient videos, providing test specific details and information.
- www.genedx.com/oncology, a website discussing hereditary cancer and testing options.

GeneDx strives to make the genetic testing process as smooth as possible for patients and providers, including:

- Local sales representatives can help coordinate testing.
- Genetic counselors are available to support test selection and education.
- Easy to complete requisition and family history forms.

After testing, GeneDx offers numerous tools to assist with patient management, including:

- Patient-friendly Reports that provide an explanation and discussion of individual test results and management options.
- Lifetime risk assessment materials outlining cancer risks based on the test results.
- Post-test genetic counseling is available upon request.

Identification

Materials

Testing

Patient Support
How to Order

Ordering with a Requisition

1. Download the test requisition forms from the GeneDx website:
   www.genedx.com/forms
2. Complete all the forms with the required information
3. Ship completed forms along with appropriate patient sample to the following address:
   Accessions
   GeneDx
   207 Perry Parkway
   Gaithersburg, MD 20877

Ordering Through Our Online Portal

GeneDx is committed to providing an easy to use online platform to order genetic tests. Our online portal makes the ordering process simple and straightforward. Providers can now upload clinical information electronically, track the progress of an order, and receive results instantaneously through the portal. The portal can be accessed from our website www.genedx.com. Additionally, GeneDx forms can also be easily accessed for digital or print use at www.genedx.com/forms.

Specimen Requirements

- Blood in EDTA (5-6 mL in lavender top tube)
- Oral Rinse in a 50 mL centrifuge tube (at least 30 mL of Scope oral rinse)
- DNA (>20 ug)
- Buccal Swab

We provide specimen collection kits to health care providers upon request. To place an order for kits, please visit our website: www.genedx.com/supplies or email us at zebras@genedx.com
Billing Policy

Commercial Insurance

- All commercial insurance is accepted.
- A benefit investigation is performed. We work with insurance carriers and patients to minimize the out-of-pocket cost to patients.

Medicare/Medicaid

- Medicare is accepted but an Advance Beneficiary Notice is required for patients who do not meet Medicare criteria.
- Medicaid coverage varies by state; Medicaid will not cover genetic testing in most cases.

Institutional

- A referring institution is billed directly if a GeneDx Institutional Account has been established.
- A GeneDx Institutional Account allows the referring physician to submit samples through their facility’s send-out laboratory.
- To set up an institutional account, please call us at 301-519-2100.

Self-Pay

- A payment plan is available for patients who are financially challenged or those who do not have insurance.
- For more information, please call us at 301-519-2100.

Notes

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
About GeneDx

GeneDx was founded in 2000 by two scientists from the National Institutes of Health (NIH) to address the needs of patients diagnosed with rare disorders and the clinicians treating these conditions. Today, GeneDx has grown into a global industry leader in genomics, having provided testing to patients and their families in over 55 countries. Led by its world-renowned clinical genomics program, and an unparalleled comprehensive genetic testing menu, GeneDx has a continued expertise in rare and ultra-rare disorders. Additionally, GeneDx also offers a number of other genetic testing services, including: diagnostic testing for hereditary cancers, cardiac, mitochondrial, and neurological disorders, prenatal diagnostics, and targeted variant testing. At GeneDx, our technical services are backed by our unmatched scientific expertise and our superior customer support. Our growing staff includes more than 35 geneticists and 140 genetic counselors specializing in clinical genetics, molecular genetics, metabolic genetics, and cytogenetics who are just a phone call or email away to assist you with your questions and testing needs. We invite you to visit our website: www.genedx.com to learn more about us.