XomeDx: Whole Exome Sequencing

A Guide for Patients

GeneDx
an OPKO Health Company

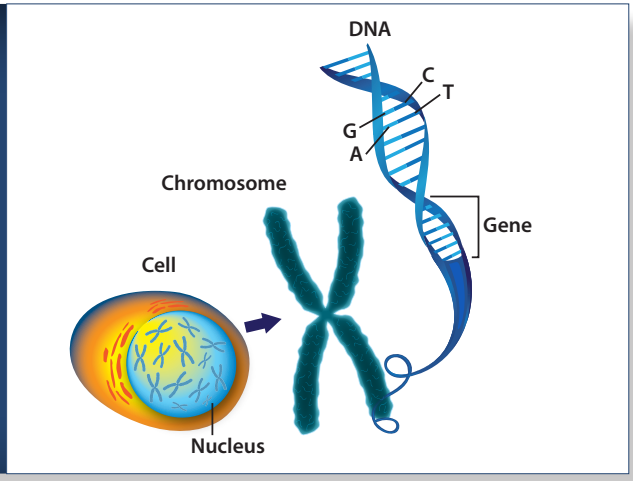
KNOWING WHAT TO LOOK FOR KNOWING WHERE TO LOOK AND KNOWING WHAT IT MEANS

Whole Exome Sequencing

What is an exome?

Our body is made up of cells that contain our chromosomes. Chromosomes are made of DNA, which carries the genetic information in units called genes which are passed down from one generation to the next (Figure 1). Genes provide instructions that are used to develop and maintain each part of the body, allowing each organ to do its job correctly. Approximately 1-2% of our DNA provides instructions for proteins, and that 1-2% is called the exome. When mistakes in our DNA occur in the exome, it can lead to disease.

Figure 1



What is XomeDx and how is it performed?

XomeDx is GeneDx's test to read and check the spelling, or "sequence," of the exome by a method called sequencing. Whole exome sequencing is currently one of the most comprehensive genetic tests available. With current technology, we are able to analyze approximately 96% of the exome, which includes approximately 99% coverage for over 4,500 genes that have previously been associated with disease. XomeDx is performed on a patient's sample that is sent to our laboratory. Once we receive the sample, the lab isolates the DNA and compares the sequence of the affected individual's exome with the sequence of the exome from healthy people. This comparison looks for misspellings, or variants, that could leave a gene unable to do its job correctly and could be the cause of the individual's disease. XomeDx*Plus* is also available; this includes mitochondrial genome sequencing and deletion testing.

Who should undergo whole exome sequencing?

XomeDx is useful for patients:

- With a genetically heterogeneous disease as pathogenic findings could be present in many different genes
- With a long list of differential diagnoses
- With an atypical presentation of a genetic disorder
- Who have exhausted other currently available genetic testing options

Where are the results sent after XomeDx is completed, and how long does it take?

Results are sent directly to the healthcare provider who ordered the test. Please visit our XomeDx test information page for the turn-around-time for this test: www.genedx.com/xomedx.

What type of test results can I expect?

There are four possible types of results we can find while analyzing your exome. Analyzing all of an individual's genetic information is complicated, and the results can be complex. Your test results may contain a table with one or more of the types of changes below:

- A pathogenic or likely pathogenic variant, which is a "misspelling" or variation in DNA that is known or highly likely to cause disease and is in a gene that has been associated with the features and symptoms of the affected individual. This is the most straightforward result and can be used to test other family members to determine their risk for developing that disease or having a child with that disease.

- A variant of uncertain significance (VUS), which means we found a change in a gene, and the *gene* is thought to be associated with the affected individual's disease, but we are not sure if the *specific change* we found in that gene actually causes disease. GeneDx always tries to minimize the number of VUS reported, and this can be done by testing additional family members, usually the biological parents. It is best to send samples from both biological parents at the time the initial patient sample is sent. A VUS is less straightforward, and may require more information by testing additional family members to fully interpret the meaning of the result.

- A VUS in a candidate gene, which are genes that have not been implicated previously with a human disease, but there is good reason to think they might be. However, additional research is needed to confirm a gene's association with disease.

- Negative, which means we did not detect any variants related to the reported clinical features in any area of the exome that was tested. This does not necessarily mean that the cause of the affected individual's disease is not due to an underlying genetic condition. It is still possible that there is a variant in a region of the exome that is not covered by this test, a type of variant that cannot be detected by the exome test, or there is a variant that is observed in a gene not yet known to cause human disease. If the results are negative, your doctor or genetic counselor may discuss the possibility of additional testing.

Is other genetic information included in the report?

The American College of Medical Genetics and Genomics (ACMG) has recommended that secondary findings identified in 56 genes associated with medically actionable inherited disorders be reported for all patients undergoing whole exome sequencing. Secondary findings are defined as known or expected pathogenic variants, identified by whole exome sequencing, in genes that are unrelated to the reported clinical features in the patient. Secondary findings are actionable in some way, such as with increased medical surveillance. All pathogenic variants will be reported for the patient, including the inheritance of those variants if parental samples are submitted, unless the relevant Opt Out checkbox is selected on the consent form.

Can XomeDx detect all possible genetic causes of disease?

XomeDx does not detect all possible causes of genetic disease. Any variant located outside of the exome, and certain types of variants including large deletions or duplications of genetic material, as well as repeat expansion disorders, would not be detected by this test. Additional testing (such as GenomeDx, our whole genome array) may be warranted in addition to XomeDx. Please speak with your doctor about the most appropriate testing options for you and your family.

Why does GeneDx need to test other family members?

XomeDx is ideally performed on the affected family member (the proband) and two or more additional family members to form what is called a trio. Using additional family members' exome data significantly improves the chance of identifying a disease-causing variant, while also decreasing the chance of identifying a VUS.

Why are biological parents' samples important?

Ideally, the additional family members are the proband's biological parents, and one or more affected or unaffected siblings of the affected individual, if available. These individuals are the most informative and provide GeneDx with the most relevant information for analyzing the affected individual's exome. For example, comparing the probands' exome to their parents' exomic data could show that a pathogenic variant was not inherited from a parent and was new in the proband (i.e, "de novo"). This information could be used to inform the parents that the likelihood they would have another child with the same disease is reduced. If the biological parents are not available and there are no other affected individuals in the family, please contact GeneDx to discuss which other family members might be appropriate to include in the test.

If you are testing multiple people, why is there only one report?

The additional family members' exome data will only be used to help us determine which change(s) in the proband's DNA is most likely to cause disease. GeneDx will not interpret any other results found in other family members' exome data and will not issue separate exome reports for unaffected family members. Additional analysis with a report for affected family members can be ordered for an additional fee.

Should I receive genetic counseling before having this test?

It is recommended that genetic counseling be provided in conjunction with genetic testing, both before the test and after the results are available. XomeDx is a comprehensive test that is best suited for a patient/family when they understand all the benefits and limitations of the test. Pre-test genetic counseling will provide you with the information to decide whether XomeDx is the best test for your family. The National Society of Genetic Counselors maintains a list of national and international genetic counselors. Please visit www.nsgc.org to locate a genetic counselor near you.

How will I learn about my test results?

Your healthcare provider will share your results with you and discuss them in the context of your medical care.

What makes the XomeDx test different from exome tests offered by other labs?

- Our patient-friendly billing policy (see next question for more details)
- Thorough and comprehensive reports which focus on returning results that make a difference in your medical care
- We sequence the exomes of the entire trio, not just the affected individual, which gives a more comprehensive analysis and minimizes the number of VUS reported
- Over 16 years of experience testing for more than 400 rare inherited disorders, and over 30,000 exome tests, comprising 12,000 cases that have been performed
- Reliable turn-around-times

Will insurance cover this test?

GeneDx accepts all commercial insurance policies. The patient is only responsible for the co-pay, co-insurance and unmet deductible dictated by his or her insurance carrier. GeneDx will perform a benefit investigation and attempt to contact the patient if the out-of-pocket cost is expected to be greater than $100. If GeneDx is unsuccessful in their attempts to contact the patient, it will be the patient's responsibility to contact GeneDx to determine the out-of-pocket cost. GeneDx will work with patients who have financial difficulties and offer a financial assistance program to those who qualify. GeneDx provides a compassionate care price, as well as a payment plan for patients who are financially challenged. If the patient receives a payment from the insurance company, it is the patient's responsibility to pay GeneDx within 10 days of receipt of that payment. This payment is not eligible for reduction under any financial assistance or compassionate care program. A completed Advance Beneficiary Notice (ABN) is required for Medicare patients. In most cases, Medicaid will not cover genetic testing for these conditions, though Medicaid coverage varies by state. For more information regarding insurance billing at GeneDx, please call us at 301-519-2100.

What if a patient does not have insurance?

For patients who do not have health insurance or cannot afford to pay the full cost of testing, GeneDx provides a financial assistance program to those who qualify. For more information, call us at 301-519-2100.

Does GeneDx test family members?

Yes, GeneDx offers targeted testing for family members of individuals with a pathogenic variant identified by GeneDx. There is an additional fee for each additional family member tested, but it is much less than the cost of the XomeDx test. For more information, please call one of our genetic counselors at 301-519-2100.

Does GeneDx perform prenatal testing?

Yes, GeneDx can provide prenatal testing for a known familial pathogenic variant in any gene, either previously identified at GeneDx or elsewhere. For more information, please call one of our genetic counselors at 301-519-2100.

Can health insurers or employers discriminate based on genetic test results?

No, the Genetic Information Nondiscrimination Act of 2008, also referred to as GINA, is a federal law that protects Americans from discrimination by health insurance companies and employers based on their genetic information. President George W. Bush signed the act into federal law on May 21, 2008. The parts of the law relating to health insurers took effect in May 2009, and those relating to employers took effect in November 2009. However, this law does not cover life insurance, disability insurance, or long-term care insurance. For more information, please visit www.genome.gov/10002328.

Where can patients find more information?

More information is available at the following websites:

- GeneDx's XomeDx page: www.genedx.com/xomedx
- Genetics Home Reference: https://ghr.nlm.nih.gov
- National Society of Genetic Counselors, an organization that can help you find a counselor near you: www.nsgc.org

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 whole exome sequencing 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 30 geneticists and 100 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.

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