

# Medica Coverage Policy



<b>Policy Name:</b>	<b>Genetic and Pharmacogenetic Testing</b>
<b>Effective Date:</b>	<b>6/29/2022</b>

## Important Information – Please Read Before Using This Policy

These services may or may not be covered by all Medica plans. Please refer to the member’s plan document for specific coverage information. If there is a difference between this general information and the member’s plan document, the member’s plan document will be used to determine coverage. With respect to Medicare and Minnesota Health Care Programs, this policy will apply unless those programs require different coverage. Members may contact Medica Customer Service at the phone number listed on their member identification card to discuss their benefits more specifically. Providers with questions about this Medica coverage policy may call the Medica Provider Service Center toll-free at 1-800-458-5512.

Medica coverage policies are not medical advice. Members should consult with appropriate health care providers to obtain needed medical advice, care and treatment.

### This policy addresses the following four types of testing:

- I. Genetic testing for diagnosis and prediction of risk of heritable diseases
- II. Carrier testing for heritable diseases
- III. Molecular and genomic pathology testing
- IV. Pharmacogenetic testing for drug metabolism
- V. Investigative/Not covered services
- VI. MCG Guideline references

Medica has a number of disease- and/or condition-specific criteria for genetic testing, outlined in related coverage and utilization management policies. Please refer to Attachment 1 at the end of this document for a list of those policies. If a separate policy does not exist, the following criteria apply.

Medica has a number of single gene tests for heritable disease that are COVERED. Please refer to examples listed in Attachment 2 at the end of this document. If the single gene test is not listed in Attachment 2, the criteria in Section I below apply.

- I. Single gene and multi-gene panel testing for **diagnosis and/or prediction of risk for heritable diseases not listed above** IS COVERED when documentation in the medical record indicates that the individual meets **either A OR B** below:
  - A. The test is **ordered** by a board-certified medical geneticist or genetic counselor not employed by or contracted with the commercial laboratory performing the testing and medical records document a detailed family history/pedigree and pre- test genetic counseling.
  - B. For tests **ordered** by other than a geneticist or genetic counselor **all of the following** criteria must be met:
    1. Medical records document a detailed family history/pedigree and **pre-test** genetic counseling by **one of the following**:
      - a. A board-certified medical geneticist not employed or contracted with the commercial laboratory performing the testing.
      - b. A board-certified genetic counselor not employed by or contracted with the commercial laboratory performing the testing.
      - c. A board-certified Genetic Clinical Nurse or Advanced Practice Nurse in Genetics (APNG) not employed by or contracted with the commercial laboratory not performing the testing.
      - d. Other qualified healthcare professional (e.g. Physician or Physician Assistant or Nurse Practitioner) with specialized training or certification in medical genetics and not employed by or contracted with the commercial laboratory performing the testing.

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2. The individual has **one of the following**:
  - a. Current signs and/or symptoms suggesting a genetic disease
  - b. Family history indicating that the individual is at high risk for a genetic disease.
3. Medical records document how the test(s) will lead to changes in treatment decisions (e.g., initiate a new course of therapy, alter existing therapy, determine/change level of surveillance, or make reproductive decisions) and/or health outcome for the individual being tested.

II. Single gene testing for **carrier status of heritable diseases** IS COVERED when documentation in the medical records indicates that the individual meets **either A OR B** below:

- A. The test is ordered by a board-certified medical geneticist or genetic counselor not employed by or contracted with the commercial laboratory performing the testing and medical records document a detailed family history/pedigree and pre- test genetic counseling.
- B. For tests **ordered** by other than a geneticist or genetic counselor **all of the following** criteria must be met:
  1. Medical records document a detailed family history/pedigree and **pre-test** genetic counseling by **one of the following**:
    - a. A board-certified medical geneticist not employed by or contracted with the commercial laboratory performing the testing.
    - b. A board-certified genetic counselor not employed by or contracted with the commercial laboratory performing the testing.
    - c. A certified Genetic Clinical Nurse or Advanced Practice Nurse in Genetics (APNG) not employed by or contracted with the commercial laboratory performing the testing.
    - d. Other qualified healthcare professional (e.g. Physician or Physician Assistant or Nurse Practitioner) with specialized training or certification in medical genetics and not employed by or contracted with the commercial laboratory performing the testing.
  2. The individual is currently pregnant or contemplating pregnancy and is at high risk of being a carrier of a specific genetic disorder based on family history. Examples include, but are not limited to:
    - a. One parent is a known carrier of a clinically significant X-linked recessive, or autosomal recessive disease (e.g., hemophilia, cystic fibrosis, Duchenne muscular dystrophy, sickle cell anemia, or Tay Sachs disease).
    - b. A child of the individual(s) has been identified with an autosomal recessive or X-linked disorder.
    - c. One or both parents have a close blood relative (e.g., first or second degree relative) who is affected by a specific genetic disorder or the first-degree relative has an affected child with an autosomal recessive or X-linked disorder.
    - d. There is a maternal history of two or more fetal losses.
  3. The test results will affect reproductive choices.

NOTE: Multigene panel testing for carrier status is addressed in the following Medica Coverage Policy: *Expanded Carrier Testing for Genetic Diseases in Adults.*

III. Single and multigene **molecular and genomic pathology tissue testing (tumor gene expression profiling)** for cancer management IS COVERED when documentation in the medical record indicates that the individual meets **all of the following** criteria:

- A. The test is ordered by a board-certified pathologist, geneticist, or oncologist/hematologist not employed by or contracted with the commercial laboratory performing the testing.
- B. Medical records document how the test(s) will lead to increased precision in diagnosis and treatment.

IV. **Pharmacogenetic** testing for drug metabolism IS COVERED when documentation in the medical records indicates that the individual meets **either A OR B** below:

- A. Pharmacogenetic testing IS COVERED when testing for a specific gene biomarker **is required** by the U.S. Food and Drug Administration (FDA) prior to initiating drug therapy. A list of FDA required tests can be found here: <https://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools>.

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B. Pharmacogenetic testing for all other indications IS COVERED when documentation in the medical record indicates that **all of the following** criteria are met:

1. The individual is a candidate for a targeted drug therapy associated with a specific gene biomarker or gene mutation.
2. There is reliable evidence that a specific genetic biomarker or mutation is directly linked to a specific therapeutic drug target.
3. Medical records document how the test results will lead to changes in treatment decisions and/or health outcome for the individual being tested.

V. **Investigative and therefore NOT COVERED:**

A. Medica considers the following genetic tests investigative and therefore NOT covered based on MCG 23<sup>rd</sup> Edition Ambulatory Care Guidelines (ACGs):

(NOTE: The following MCG Ambulatory Care Guidelines apply when no specific Medica coverage policy or utilization management policy exists. See Attachment 1, following, for a list of Medica policies that address additional COVERED and NON-COVERED services.)

1. A-0591, Amyotrophic Lateral Sclerosis (ALS) - C9orf72 and SOD1 Genes
2. A-0628, Azathioprine and 6-Mercaptopurine Pharmacogenetics –NUDT15 and TPMT Genes
3. A-0631, Clopidogrel Pharmacogenetics - CYP2C19 Gene
4. A-0647, Tamoxifen Pharmacogenetics - CYP2D6 GeneA-0671, Parkinson Disease – Gene Testing and Gene Panels
5. A-0672, Telomere Analysis
6. A-0705, MicroRNA Detection – Cancer
7. A-0706, Septin 9 (SEPT9) DNA Methylation TestingA-0763, Asthma - ADRB2 Gene
8. A-0764, Attention-Deficit Hyperactivity Disorder Medication Pharmacogenetics - ADRA2A, COMT, CYP2B6, and CYP2D6 Genes
9. A-0768, Autosomal and X-Linked Recessive Disease Carrier Screening - Expanded Gene Panels
10. A-0790, Multiple Cancers, Including Cancer Syndromes (Hereditary) - Gene Panel
11. A-0791, Myelodysplastic Syndromes (Somatic) - Gene Panels
12. A-0800, Post-Transfusion Purpura - Human Platelet Antigen (HPA) Genotyping
13. A-0820, Citalopram Pharmacogenetics - GRIK4 Gene
14. A-0826, Diabetes Mellitus Type 2, Type 2 Diabetes
15. A-0838, MicroRNA Detection – Heart Failure
16. A-0839, MicroRNA Detection – Inflammatory Bowel Disease
17. A-0840, MicroRNA Detection – Ischemic Heart Disease
18. A-0841, MicroRNA Detection – Kidney Disease
19. A-0845, Naltrexone Pharmacogenetics - OPRM1 Gene
20. A-0859, Psychotropic Medication Pharmacogenetics - ABCB1, ADRA2A, BDNF, COMT, DRD, FKBP5, GNB3, HTR, MC4R, OGFRL1, SLC6A4, SPTA1, and TPH1 Genes
21. A-0861, Psychotropic Medication Pharmacogenetics - Gene Panels
22. A-0905, Epilepsies (Hereditary) - Gene Panels
23. A-0906, Familial Frontotemporal Dementia - C9orf72, GRN, and MAPT Genes
24. A-0913, Age-Related Macular Degeneration - Gene Panels
25. A-0914, Autism Spectrum Disorders - Gene Panels
26. A-0923, Intellectual Disability - Gene Panels
27. A-0925, Developmental Delay - Gene Panels
28. A-0992, Opioid Pharmacogenetics - CYP450 Polymorphisms, OPRM1 Gene, and GeneSight Analgesic Panel.
29. A-1005, Narcolepsy – HLA Testing

B. Genetic testing is excluded and therefore **NOT COVERED** when:

1. The test is performed in the absence of symptoms or high risk factors for a genetic disease.
2. Knowledge of genetic status will not affect treatment decisions, surveillance, reproductive decisions and/or health

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- outcome of the individual being tested.
3. The test is obtained without an order from a licensed healthcare professional, including direct-to-consumer testing (mailorder, online ordering).
  4. The test is performed as a general screening tool, other than newborn screening performed in accordance with state mandates.
  5. The testing is performed to screen for nonmedical traits (e.g., eye color, hair color).
  6. The testing is performed solely to determine the sex of a child.
  7. The testing is performed solely to determine the paternity of a child.

### VI. MCG Guidelines

- A. Medica may reference MCG Guidelines when no specific Medica Coverage Policy or Utilization Management policy exists.

#### Other Considerations

1. Karyotyping and g-banding are covered standard testing modalities.
2. Most tests, particularly those for inherited disorders, should be accompanied by pre and post-test patient counseling by a board certified genetic counselor, medical geneticist, genetic nurse or other qualified healthcare professional not employed by or contracted with the commercial laboratory performing the testing. Genetic professionals are not excluded if they are employed by or contracted with a laboratory that is part of a health care system that routinely delivers health care services beyond just the laboratory test.
3. Generally, it is not necessary to repeat genetic testing for a heritable disease. However, as science evolves, genetic test results will likely require re-interpretation by a medical geneticist or genetic counselor. Examples in which repeat testing may be necessary include the use of inaccurate methodology with previous testing or discovery of a new mutation relevant to adisease.

### Description

Genetic tests are laboratory tests performed on a sample of blood, saliva, hair, skin, or other tissue that identify changes in chromosomes, genes, or proteins. The results of a genetic test can confirm or rule out a suspected genetic condition or help determine a person's chance of developing or passing on a genetic disorder. Genetic testing utilizes biochemical assays, direct examination of genetic material, or examination of chromosomes or genetic markers. Testing can be performed to identify a single gene or performed as a multi-gene panel. Results of genetic testing are used to:

1. Confirm a diagnosis when an individual has signs or symptoms that suggest a genetic disease (diagnostic testing)
2. Estimate the likelihood of an individual developing a genetic disease (predictive testing)
3. Identify which family members are at risk for a certain genetic condition already known to be present in their family (presymptomatic testing)
4. Determine the likelihood of cancer recurrence (prognostic testing)
5. Determine if an individual has one copy of a gene that, if passed along to a child, may result in a genetic disorder in the child (carrier testing)
6. Determine an individual's response to drugs and susceptibility to drug-induced adverse effects (pharmacogenetic testing)
7. Determine whether an embryo (preimplantation testing) or developing fetus has a genetic mutation (prenatal testing)
8. Identify disorders in newborns that might have long-term health effects (newborn screening)
9. Identify an individual for legal reasons (forensic testing)
10. Learn more about the contributions of genes to health and disease (research testing).

Genetic variants, also known as mutations, are changes in the genetic code. Variants are classified as benign, disease-causing (pathogenic) or of uncertain significance based on how likely they are to change the way a gene works. Another outcome of genetic testing is that no genetic alteration is found. However, this does not necessarily mean that the individual does not have a variant, only that one was not detected. Furthermore, the absence of known variants does not mean there is no risk of disease, especially with regard to conditions for which not all of the disease-causing genes have been identified.

Limitations of genetic testing include:

1. Testing many genes does not always provide better information.
2. Multigene panels do not include every possible gene that could be related to an individual's medical condition.
3. Panels often include genes that have only a low to moderate risk of causing medical problems, are not well understood or clinically actionable, or are not relevant to the reason for testing, but may have clinical implications for the individual being tested.
4. Variability among multi-gene panels and processes. The vast majority of panels are laboratory developed tests that are proprietary to the lab doing the testing. Each lab may use different sequencing equipment, different testing processes, and different databases and computational systems for identifying genetic variants for the same condition. Therefore, a multigene panel should be carefully selected by a genetics professional based on the individual's medical and family history.

Pharmacogenetics, also known as pharmacogenomics, is a type of genetic testing that uses personal gene-based information to assist in determining the proper drug and dosage for an individual. Pharmacogenetic testing seeks to determine how a drug is absorbed, metabolized or cleared from the body based on an individual's genetic makeup. Test results are intended to allow the clinician to predict the individual's response to pharmacotherapy, assist in making treatment choices, personalize drug dosages in order to maintain a consistent drug level in the body, and avoid adverse reactions from overdose or suboptimal effects from under medication. However, tailoring drug therapy based on genetic variations has a number of limitations, including:

1. The presence of multiple genes affecting a particular drug response and distribution
2. Non-genetic factors affecting response
3. Unclear clinical benefits associated with testing.

### **FDA Approval**

Devices and commercially marketed genetic testing kits are subject to FDA approval. Individual genetic testing laboratories are subject to the regulatory standards of the Clinical Laboratory Improvement Act (CLIA) of 1988. Premarket approval from the FDA is not required as long as the laboratory facility observes CLIA regulations and the test is not marketed for general distribution.

### **Prior Authorization**

Prior authorization is required for testing in accordance with the Utilization Management Policies outlined in Attachment 1. Additionally, services with specific coverage criteria may be reviewed retrospectively to determine if criteria are being met. Retrospective denial may result if criteria are not met.

### **Coding Considerations**

Use the current applicable CPT/HCPCS code(s).

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2/19/2014  
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9/19/2018  
3/20/2019 – Administrative update  
12/18/2019  
9/30/2020 – Administrative update; (MCG 24<sup>th</sup> Edition implemented)  
6/15/2021 – Administrative update; (MCG 25<sup>th</sup> Edition implemented)  
8/25/2021 – Added coverage for hereditary epilepsies (SCN1A) to Attachment 2  
6/29/2022 – Administrative update; (MCG 26<sup>th</sup> Edition implemented)  
07/18/2022 – Administrative updates; (removed MCG ACG A-0869, *Whole Genome/Exome Sequencing – Mitochondrial Disorders*, from Section V.)

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### Attachment 1: Gene/Condition Specific Policies

The following lists are subject to change without notice. Consult [www.medica.com](http://www.medica.com) / Providers / Medical Policies for a complete listing or Medica's Coverage and Utilization Management Policies.

#### **Medica has the following Coverage Policies related to genetic tests:**

1. Apolipoprotein E (APOE) Genetic Testing for Prediction and Management of Cardiovascular Disease
2. Bladder Cancer Screening, Diagnosis and Monitoring Using Ancillary Urinary Tests
3. Donor-Derived Cell-Free Testing to Detect Rejection in Kidney Transplantation
4. Expanded Carrier Testing for Genetic Diseases in Adults
5. Gene Expression Profiling Assays for Breast Cancer
6. Gene Expression Profiling Assay for Predicting Coronary Artery Disease
7. Gene Expression Profiling for Assessing Cancers of Unknown Origin
8. Gene Expression Profiling for Melanoma
9. Gene Expression Profiling for Detection of Heart Transplantation Rejection
10. Genetic Testing for Alzheimer Disease
11. Genetic Testing for Cardiac Channelopathies
12. Genetic Testing for Cardiomyopathies
13. Genetic Testing for Colorectal Cancer
14. Genetic Testing for Inherited Susceptibility to Malignant Melanoma
15. Genetic Testing for Thyroid Cancer
16. Genetic Testing: ScolioScore™ Adolescent Idiopathic Scoliosis (AIS) Prognostic Test
17. Genetic Testing: TP53 (p53) Testing for Li-Fraumeni Syndrome
18. KRAS Mutation Analysis for Predicting Response to Drug Therapy
19. Laboratory Tests
20. Liquid Biopsy: Testing of Circulating Tumor Cells or Cell-Free Tumor DNA
21. Cytochrome P450 (CYP450) Variant Genotyping (e.g., CYP2D6, CYP2C9, CYP2C19, CYP1A2, CYP3A4)
22. Maternal Plasma Tests for Detection of Cell-Free Fetal DNA for Analysis of Chromosomal Aneuploidies
23. Methylenetetrahydrofolate Reductase (MTHFR) Gene Mutation Testing
24. Multivariate Biomarker Blood Testing for Predicting Malignancy in Women with Adnexal Mass
25. PancreGEN™ Genotyping for Risk Assessment of Pancreatic Cancer
26. Pharmacogenetic Testing of the VKORC1 Gene for Warfarin Response
27. Pharmacogenetic Testing to Predict Toxicity to 5-Fluorouracil (5-FU)/Capecitabine-Based Chemotherapy
28. Single Nucleotide Polymorphism (SNP) Genetic Testing for Assessment of Cancer Risk
29. VeriStrat Proteomic Testing
30. Whole Genome Testing.

#### **Medica has the following Utilization Management policies related to genetic tests:**

1. Comparative Genomic Hybridization (CGH) Microarray Testing
2. Genetic Testing for Prostate Cancer
3. Genetic Testing for Susceptibility to Colorectal Cancer (CRC) Syndromes
4. Genetic Testing For Susceptibility to Hereditary Breast and Ovarian Cancer
5. Whole Exome Sequencing.

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### Attachment 2: Single Gene Testing for Heritable Disease

The following **single gene** tests are examples of tests that ARE COVERED (not all-inclusive). Note: This list is subject to change without notice.

Alpha-1 antitrypsin disease ( <i>SERPINA1</i> )	Hereditary hemochromatosis (HFE)
Alpha thalassemia ( <i>HBA1/HBA2</i> )	Huntington's disease ( <i>HTT, HD (Huntington)</i> )
Beta thalassemia	Maple syrup urine disease ( <i>BCKDHA, BCKDHB, DBT</i> )
Bloom syndrome ( <i>BLM</i> )	Marfan's syndrome ( <i>TGFBR1, TGFBR2</i> )
Canavan disease ( <i>ASPA (aspartoacylase A)</i> )	Mucopolipidosis type IV ( <i>MCOLN1, mucolipin 1</i> )
Charcot Marie Tooth ( <i>PMP-22</i> )	Muscular dystrophy ( <i>DMD (dystrophin)</i> )
Congenital adrenal hyperplasia/21 hydroxylase deficiency ( <i>CYP21A2</i> )	Neimann-Pick disease, type A ( <i>SMPD1, sphingomyelin phosphodiesterase</i> )
Cystic fibrosis ( <i>CFTR</i> )	Nonsyndromic hearing loss ( <i>GJB2, GJB6</i> )
Factor V Leiden ( <i>F5 (Factor V)</i> ) for coagulopathy	Phenylketonuria ( <i>PAH</i> )
Familial dysautonomia ( <i>IKBKAP</i> )	Prader-Willi-Angelman syndrome ( <i>SNRPN, GABRA5, NIPAI, UBE3A, ANCR, GABRA</i> )
Fanconi anemia ( <i>FANCC, FANCD</i> )	Rett syndrome ( <i>FOXG1, MECP2</i> )
Fragile X syndrome ( <i>FMRI</i> )	Sickle cell disease ( <i>HBB Gene</i> )
Gaucher disease (GBA (acid beta glucosidase) )	Spinal muscular atrophy ( <i>SMNI</i> )
Hemophilia A/Factor 8 deficiency (F8 (Factor VIII))	Tay-Sachs disease (HEXA)
Hereditary epilepsies (SCN1A)	Von Hippel-Lindau syndrome (VHL)

### Attachment 3: Glossary

1. An **allele** is an alternative form of a gene that is located at a specific position on a specific chromosome. Humans inherit one allele from their mother and another allele from their father. The physical characteristics (e.g., eye color, hair color, skin color) of an individual depend on both of the alleles. If the alleles are different, the **dominant** allele will be expressed, while the effect of the other allele, called **recessive**, is masked. In the case of a recessive genetic disorder, an individual must inherit two copies of the mutated allele in order for the disease to be present.
2. A **chromosome** is an organized package of DNA found in the nucleus of the cell. Humans have 23 pairs of chromosomes-- 22 pairs of numbered chromosomes, called autosomes, and one pair of sex chromosomes, X and Y. Each parent contributes one chromosome to each pair so that offspring get half of their chromosomes from their mother and half from their father.
3. A **close blood relative** includes first or second degree blood relative. First degree relative is a relative with whom one half of an individual's genes are shared (i.e., parent, sibling, offspring). Second degree relative is a relative with whom one quarter of an individual's genes is shared (i.e., grandparent, grandchild, uncle, aunt, nephew, niece, half-sibling).
4. **Deoxyribonucleic acid (DNA)** is a nucleic acid molecule and is the hereditary material in humans that constitute the 23

pairs of chromosomes in the human genome. A **variant**, also known as a gene mutation, is a permanent alteration in the DNA sequence that makes up a gene, such that the sequence differs from what is found in most people. There are also variants known as benign DNA variants where the alteration in the DNA sequence does not cause a change in the function of the gene. Mutations can vary in size; they can affect a single DNA base pair or be due to small deletions or insertions or rearrangements of DNA base pairs. Larger duplication and/or deletions of varying sizes include segments of a chromosome that can include multiple genes. A **gene** is the basic physical and functional unit of heredity. Genes, which are made up of DNA, act as instructions to make molecules called proteins. Genes are passed from parents to offspring and contain the information needed to specify traits.

5. **Heritable** disorders are conditions that are caused by gene mutations which can be inherited (passed down from parent to child). These typically are life-long mutations that affect multiple family members.
6. **Multigene panel testing** is genetic testing that uses next-generation sequencing to test multiple genes simultaneously, and is also called multiple-gene panel testing and multiple-gene testing.
7. A **mutation** is a permanent alteration in the DNA sequence that makes up a gene, such that the sequence differs from what is found in most people. Mutations are also referred to as variants.
8. **Next-generation sequencing (NGS)**, also known as massively parallel or high through-put sequencing, is an automated method of sequencing DNA that can process many genes at one time. NGS is used to test multiple genes simultaneously. This is known as **multigene panel testing**, also known as multiple-gene panel testing or multiple-gene testing. Using NGS, DNA sequencing is less costly and less time-consuming than traditional manual DNA sequencing of one gene at a time.
9. **Ribonucleic acid (RNA)** is a nucleic acid molecule similar to DNA and is formed using DNA as its template. DNA transcription produces RNA, then RNA translation makes proteins. This process is known as gene expression. If a DNA mutation(s) are present, proper protein synthesis can be affected. Gene expression profiling measures one type of RNA - messenger RNA (mRNA), showing the pattern of genes expressed by a cell at the transcription level. Gene expression profiling is often used as a predictive and/or prognostic tool. If tumor tissue cells express higher or lower levels of certain genes than normal, thus affecting protein formation, this receptor may be involved in the cancer. Results of the profile can then be used to predict chance of tumor recurrence and/or to guide targeted drug therapy.
10. **X-linked** is a trait located on the X chromosome. Humans and other mammals have two sex chromosomes, the X and the Y. In an X-linked or sex linked disease, it is usually males that are affected because they have a single copy of the X chromosome that carries the mutation. In females, the effect of the mutation may be masked by the second healthy copy of the X chromosome.