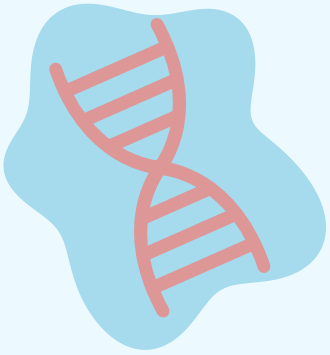
Genetic Support Foundation

A Provider's Guide to

Neurodevelopmental Disorder Genetics



What are neurodevelopmental disorders (NDDs)?

- Neurodevelopmental disorders (NDDs) are conditions that impact a person's **development** in childhood and their ability to **function**. These conditions often exist on a spectrum and co-occur with one another.

1 in 6 children in the US have a developmental disability

- Examples of NDDs include developmental delay (DD), intellectual disability (ID), autism spectrum disorder (ASD), attention deficit/hyperactivity disorder (ADHD), communication disorders, and certain motor disorders.

- **Genetic variation** represents the largest contributor to NDDs. For example, it is estimated that about 50% of those with moderate-to-severe ID and 20-40% of those with ASD have a detectable underlying genetic cause.
- Genetic causes of NDDs include:
  - Single-gene disorders (ex: Fragile X syndrome, Rett syndrome)
  - Copy number variants (ex: Williams syndrome, Smith-Magenis syndrome)
  - Aneuploidies (ex: Down syndrome)

When and why should I refer to genetics?

When to Refer to Genetics

Genetic counseling is recommended for patients with:

- **Developmental delay**
- **Intellectual disability**
- **Autism spectrum disorder**

Red flags which increase the likelihood of a genetic cause include more severe involvement, multiple diagnoses, developmental regression, dysmorphic facial features, congenital anomalies, and a family history of NDDs.

Why Refer to Genetics

Identifying the genetic cause of an NDD can:

- Explain why a child has developmental differences, which may alleviate feelings of guilt or provide other **psychosocial benefits** to the family.
- Provide insight into a child's expected clinical course and **medical management** recommendations.
- Inform **recurrence estimates** and reproductive options.
- Provide **access to support** services and communities of children/families with the same diagnosis.
- **Rule out** specific genetic conditions.

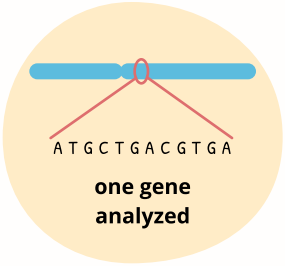
Moreover, genetic counselors are trained to help families understand and adapt to their child's diagnosis, cope with the challenges of NDDs, and make decisions about their child's care.

What genetic tests are performed for NDDs?

Different types of genetic testing may be recommended for a patient depending on their medical and family history. A **genetic counselor** can help determine and coordinate the most appropriate genetic test.

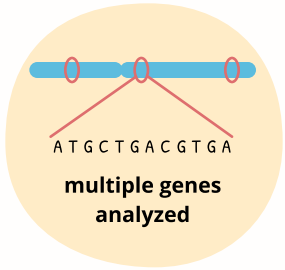
Single Gene Testing

- This test analyzes a **single gene** to detect disease-causing variants.
- This test may be ordered if a specific genetic condition is strongly suspected (such as Fragile X syndrome, the most common genetic cause of ID and ASD).



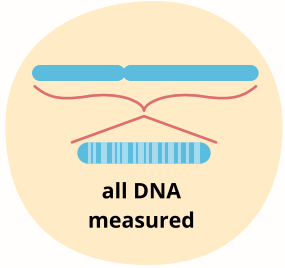
Multi-Gene Panel

- This test analyzes **multiple genes** to detect disease-causing variants.
- This test may be ordered when a patient has symptoms that fit multiple conditions (such as Fragile X and Rett syndrome) or when the suspected condition is associated with many genes.



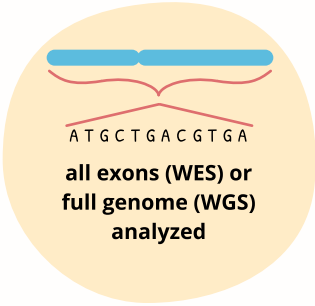
Chromosomal Microarray (CMA)

- This test detects extra (duplicated) or missing (deleted) chromosome material, called **copy number variants** (CNVs).
- This test may be ordered when a patient has features that can be caused by many different CNVs (such as DD/ID).



Whole Exome & Genome Sequencing (WES & WGS)

- These tests are the most **comprehensive** sequencing tests available. These tests may be ordered when a genetic etiology is highly suspected, but there is no clear genetic cause or previous genetic testing has been uninformative.
- WES sequences all **protein-coding DNA** (gene ***exons***) to detect disease-causing variants. Most known genetic causes of health issues are found in exons.
- WGS sequences **all genetic material** (the ***genome***), and can detect disease-causing variants in exons, introns, and regulatory DNA. This test is also better able to detect repeat expansions, CNVs, and structural variants than WES.



Genetic testing typically requires a blood draw, saliva collection, or cheek swab.

What guidelines exist for NDD genetic testing?

- The **American College of Medical Genetics and Genomics** (ACMG) and the **American Academy of Pediatrics** (AAP) have published guidelines on the genetic evaluation of DD, ID, and ASD.
- If a specific diagnosis is suspected, targeted testing (such as single-gene testing) may be ordered for that condition. If no specific diagnosis is suspected, both ACMG and AAP recommend a **tiered approach** to genetic testing.

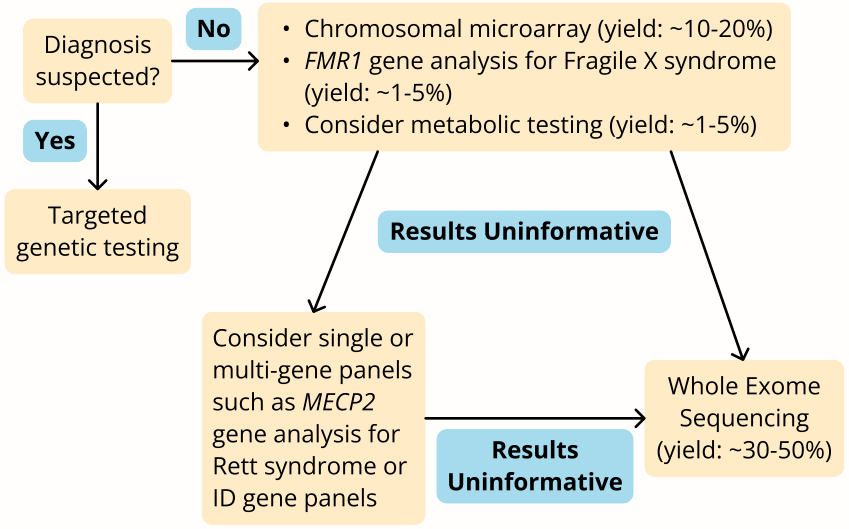
Factors to Consider Prior to Genetic Testing

While genetic testing can provide many potential benefits, genetic counseling is recommended to help patients understand the potential drawbacks as well:

- There is **no guarantee** that genetic testing will identify a genetic cause, and an identified genetic cause may not be well understood or impact medical management.
- Genetic testing may find **variants of unknown significance**, which may take months or years to be re-classified.
- Genetic testing can reveal unexpected **incidental or secondary findings** such as adult-onset conditions, susceptibility to cancer or other diseases, or non-paternity.
- Genetic testing may carry concerns for **genetic discrimination** when seeking life, long-term care, and disability insurance.
- **Prior approval** by insurance is often needed before genetic testing can be performed. Not all insurance companies will cover the recommended genetic testing.

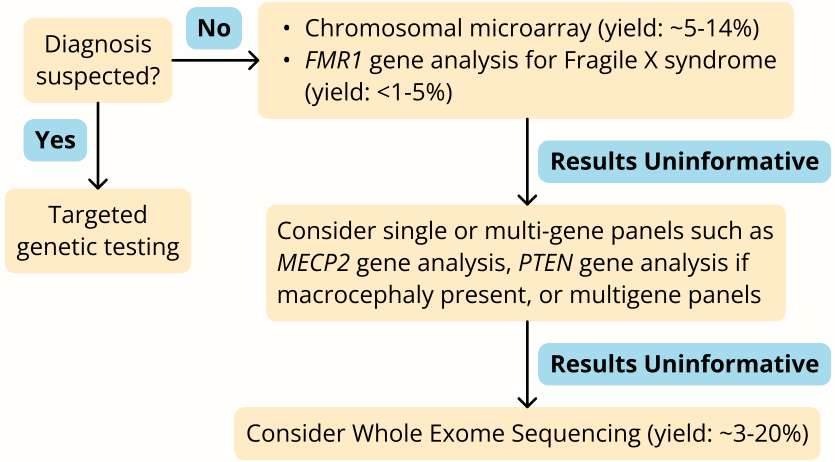
Developmental Delay and Intellectual Disability

- Perform CMA as a first-tier test (AAP, 2014, reaffirmed 2018).
- Consider WES/WGS as a first or second-tier test (ACMG, 2021).



Autism Spectrum Disorder

- Perform CMA and Fragile X as first tier test (ACMG, 2013; AAP, 2020).
- WES may be considered upon review of medical and family history.

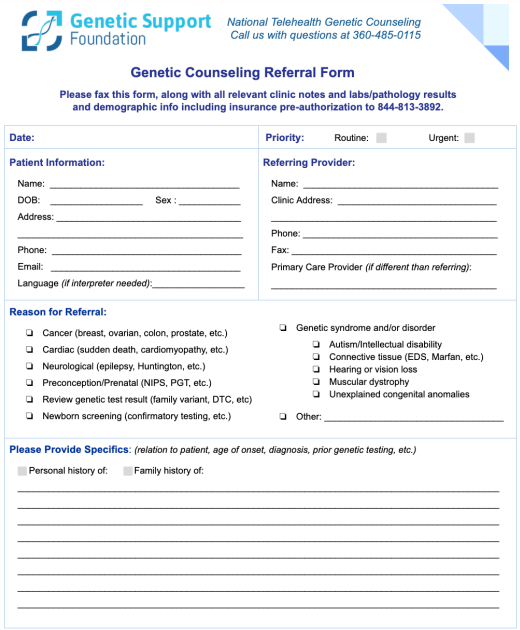


How can I refer my patient to a genetic counselor?

- To refer your patient to a certified genetic counselor, simply download and fill out the GSF referral form.
- Fax this form and relevant medical records and insurance information to:

Fax: 844-813-3892

- We will then contact the patient to schedule an appointment.



Genetic Support Foundation

National Telehealth Genetic Counseling
Call us with questions at 360-485-0115

Genetic Counseling Referral Form

Please fax this form, along with all relevant clinic notes and labs/pathology results and demographic info including insurance pre-authorization to 844-813-3892.

Date:

Priority: Routine: Urgent:

Patient Information:

Name:
DOB: Sex :
Address:
Phone:
Email:
Language *(if interpreter needed)*:

Referring Provider:

Name:
Clinic Address:
Phone:
Fax:
Primary Care Provider *(if different than referring)*:

Reason for Referral:

- Cancer (breast, ovarian, colon, prostate, etc.)
- Cardiac (sudden death, cardiomyopathy, etc.)
- Neurological (epilepsy, Huntington, etc.)
- Preconception/Prenatal (NIPS, PGT, etc.)
- Review genetic test result (family variant, DTC, etc)
- Newborn screening (confirmatory testing, etc.)
- Genetic syndrome and/or disorder
  - Autism/Intellectual disability
  - Connective tissue (EDS, Marfan, etc.)
  - Hearing or vision loss
  - Muscular dystrophy
  - Unexplained congenital anomalies
- Other:

Please Provide Specifics: *(relation to patient, age of onset, diagnosis, prior genetic testing, etc.)*

Personal history of: Family history of:

If genetic testing is recommended, we will ensure that the most appropriate test is ordered. Once the results are back, we will contact the patient to review the information and send your office a summary of the results and recommendations.

Questions?

Connect with a GSF genetic counselor by calling:

Phone: 1-800-364-1641

What should I tell the family about this referral?

Key points to communicate about the referral include:

- Neurodevelopmental differences occur for a variety of reasons, but the largest known cause is **genetic differences**. These differences can occur for the first time in a child and may not be found in other family members.
- A **genetic counselor** can talk to you about your child's medical and family history. Based on this information, they may offer **genetic testing**, which typically involves a blood draw, saliva collection, or cheek swab.
- Identifying a genetic cause of your child's symptoms can provide a number of potential **benefits**. For example, this can:
  - Provide a specific diagnosis for your child and help us better understand what to expect.
  - Increase access to support services and communities of people and families with the same diagnosis.
  - Inform estimates of the chance that future children would experience similar symptoms.