PRECISION MEDICINE IN AUTISM - RESEARCH PROGRAM

GENETIC TESTING QI PROJECT

This interactive document provides links to our website with essential resources for each step, including educational videos, pamphlets, test information, ConnectCare instructions, and referral forms. At PRISMA have included some supplemental materials to assist you in your genetic testing journey. We encourage you to explore these resources and use the checklist to ensure that all key aspects of pre-test counselling are covered.

Our team is available to assist you in ordering genetic testing and to offer counseling for any positive results through our Genomic Psychiatry Consultation service.If you have any questions or would like more information, please don't hesitate to reach out to us by emailing prisma@ualberta.ca.

PRETEST ASD
Genetic Testing Checklist

DIAGNOSTIC CRITERIA

Patient has met criteria for ASD genetic testing

Clinical diagnosis of autism spectrum disorder or global developmental delay, intellectual disability, or speech delay AND Incomplete, outdated or absence of genetic testing

GENETIC TESTING

Understanding Genetic Testing for ASD

1. **ASD is diagnosed clinically**. **A mixture of environment and genetic factors underly the condition.** Over 100 genes, however, are known to play a role. Genetic testing can identify an underlying cause in 40% of individuals. Knowing genetic changes that cause a particular case of ASD could connect patient with organizations and families with the same mutation and guide personal medical management or future planning.
2. **Standard of Care:** Multiple medical professional societies including the Canadian Paediatric Society (CPS), American Academy of Pediatrics (AAP), American College of Medical Genetics (ACMG) and American Academy of Clinical Psychiatrists (AACP) have recommended genetic testing, specifically Fragile X, CMA as the standard of care.
3. Genetic testing is always **a choice.** Genetic counseling remains available should you want to discuss this in more detail.

FAMILY HISTORY

Complete three generation pedigree: **(How To Draw Your Family History Pedigree Video)**

UNDERSTANDING BASIC GENETICS

1. **Share educational video**
   a. **English**
   b. **Spanish**
2. **Provide pamphlet**
3. **Key Points:**
   a. Genetic testing is a blood test to help identify an underlying genetic component to ASD
   b. Genes make us who we are.
   c. Tests: **Chromosomal Microarray** and **Fragile X**
   d. Genetic results may be positive (pathogenic), negative (benign) or uncertain (VUS- variant of uncertain significance).
   e. Genetic testing is protected by the Genetic Non-Discrimination Act (GNDA 2020)

ORDERING TESTING

1. Ordering Via **Connect Care**
2. Ordering Guide: **Chromosomal Microarray (CMA): Information for Ordering**
3. Requisition form for Reference
   a. **Cytogenetics Requisition form (CMA):**
   b. **Molecular Genetics Requisition Form (Fragile X testing, or FMR1 disorders)**

TIMELINE

Genetic test results are usually available in 6-8 weeks after the blood sample is received in the lab

RESULTS DISCLOSURE

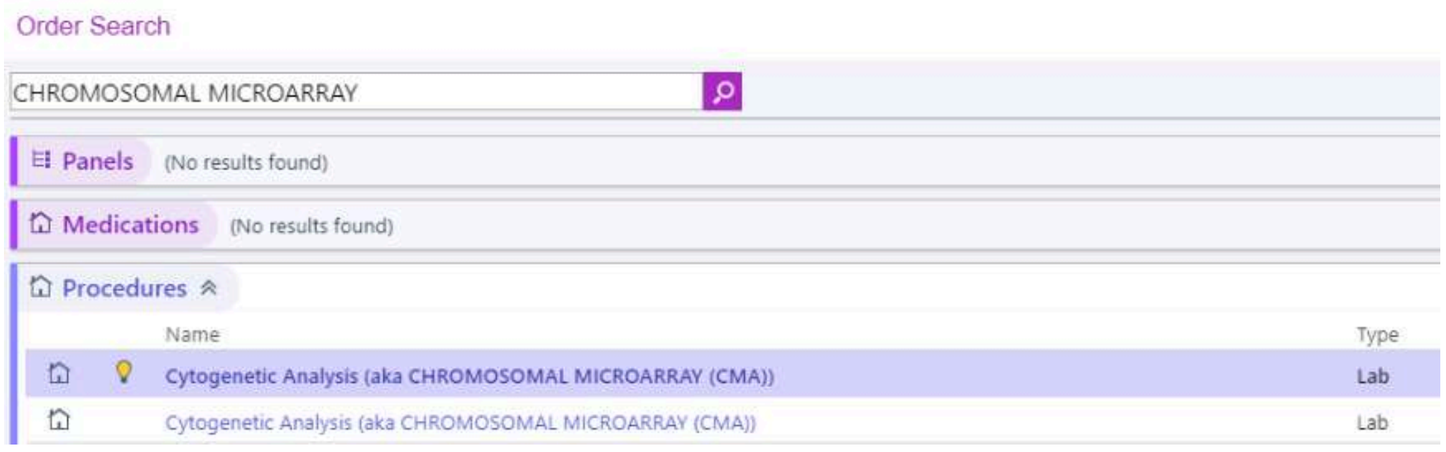
1. **NEGATIVE:** Please discuss results with the patient and assure they received a copy of their results as well as an appropriate handout. Results will live in EHR.
2. **POSITIVE/VUS:** Patients with a pathogenic results or a variant of uncertain significance (VUS) should be referred for an appointment at the Genomic Psychiatry Consultation to ensure that results are reported under the guidance of a genetic professional and management is reviewed. Results will live in EHR. Referrals to the Genomic Psychiatry consult service using ***this form.***

***Billing: To ensure that the time you spent having these discussions and coordinating care with your patients is adequately accounted for, you could consider adding the following billing codes to your encounter: 08.19C (2 units)**

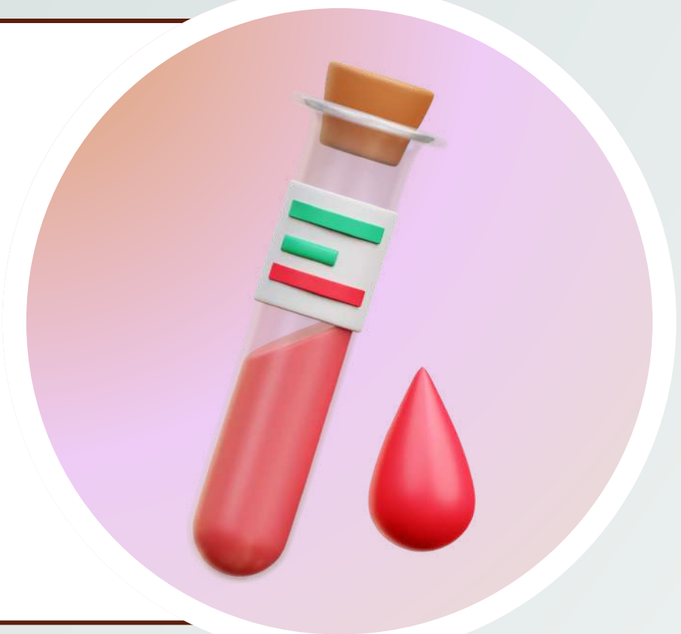
Ordering CMA in Connectcare

Alberta Precision Laboratories | Lab Services (albertahealthservices.ca)

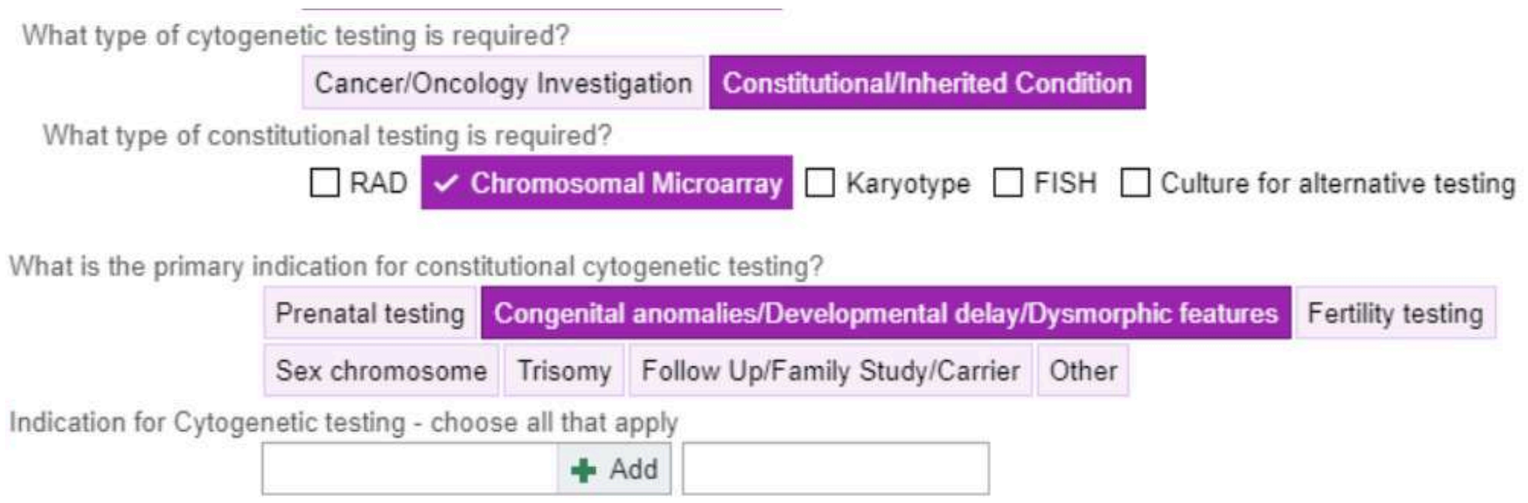
Open the order **“cytogenetic analysis”**This can also be found be searching “chromosomal microarray” or CMA



Testing is performed on blood.You must also confirm that pre-test counselling has been provided.



Select Constitutional/Inherited Condition and check only “chromosomal microarray”



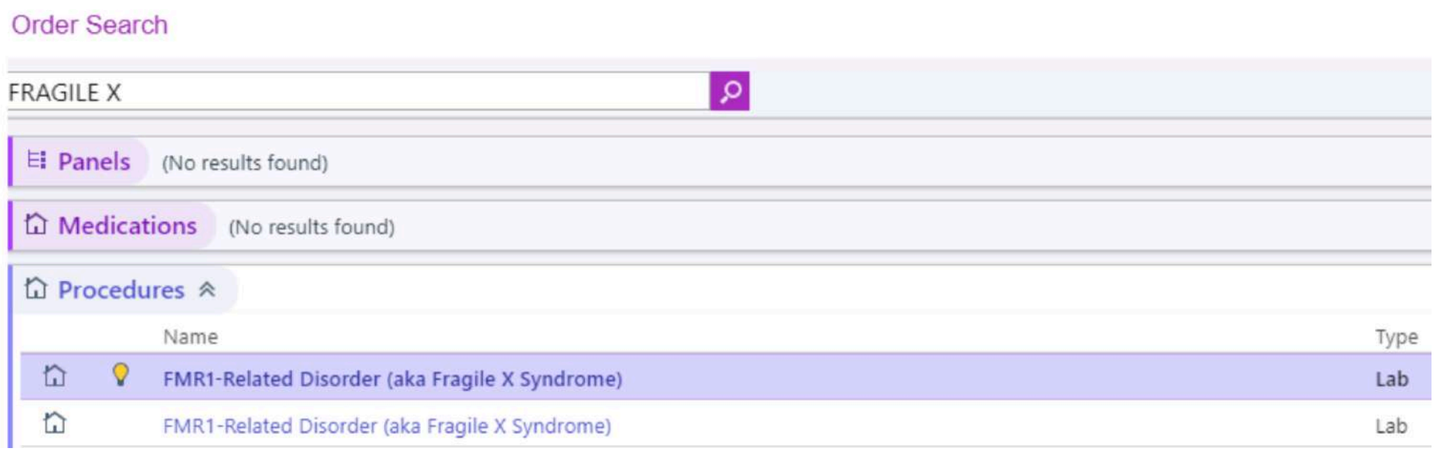
Provide reason for testing and choose from the options provided.

Be sure to specify whether the patient has: autism spectrum disorder, intellectual disability speech delay, global developmental delay from the **“Indication for Cytogenetic testing”** drop down box to ensure testing is accepted by the lab.

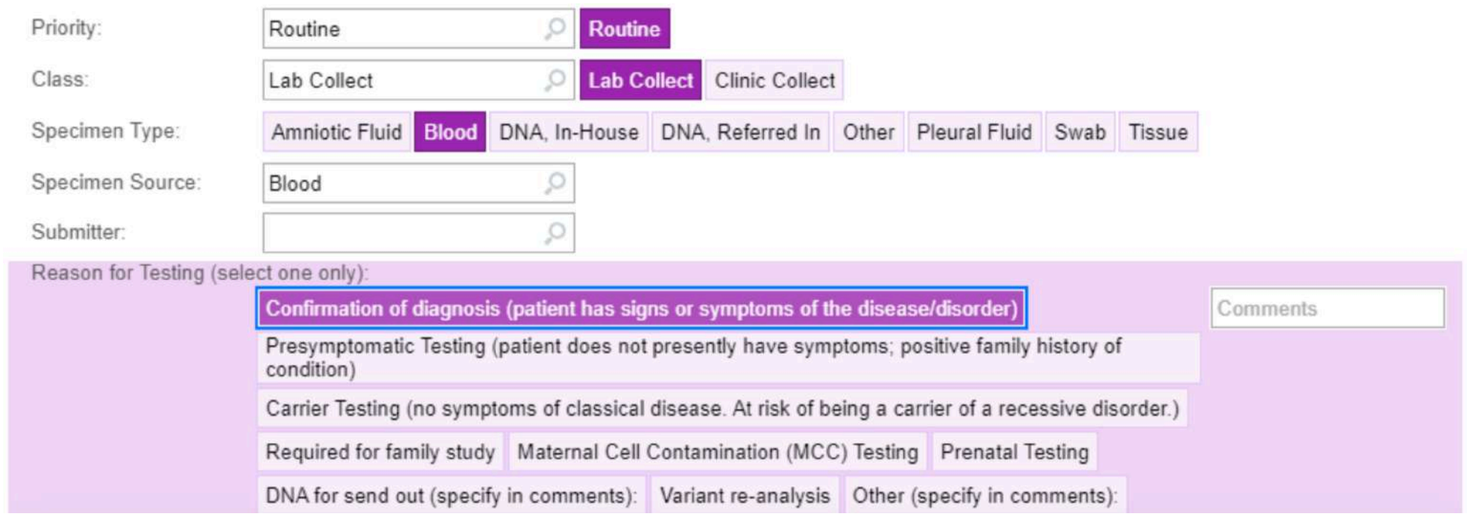
Ordering Fragile X Testing

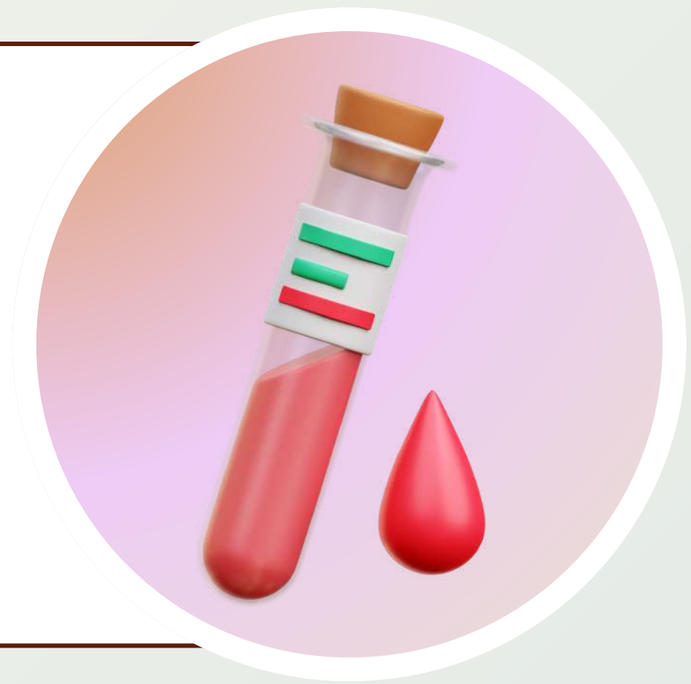
Alberta Precision Laboratories | Lab Services (albertahealthservices.ca)

Open the order “FMR1-Related Disorder”. This can also be found be searching **“Fragile X” Syndrome”.**

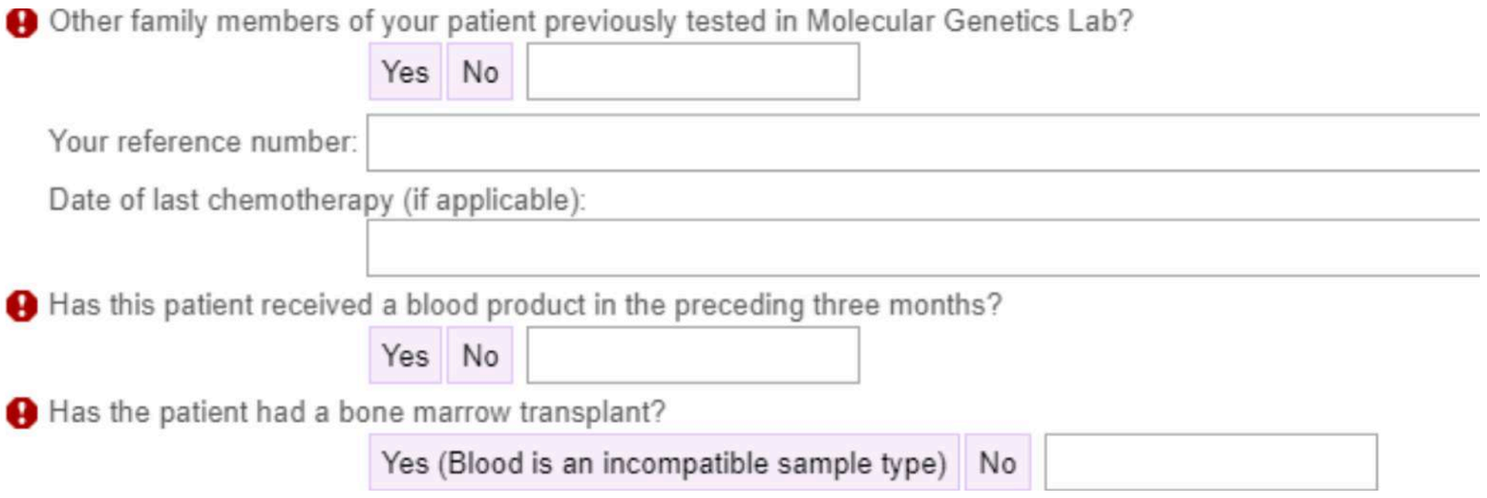


Testing is performed on blood. In Reason for Testing, select “Confirmation of diagnosis”.





Complete mandatory questions as appropriate



Specify in “**Additional Information”** whether patient has diagnosis of autism spectrum disorder.

Non-urgent results will be reported in 6-8 weeks.

Return of Negative Results

- Even when genetic testing is negative, genetics still play a role in most cases of autism and neurodevelopmental disorders. Many cases are multifactorial, resulting from an interaction of several genes with environmental factors. A helpful counselling tool is the “**Jar Model”** of multifactorial inheritance developed by Dr. Jehannine Austin’s team: **Figure - PMC (nih.gov)[1]**
- Discussion with the family should convey that no genetic diagnosis has been made by either test performed, however this can not rule out all possible genetic conditions. For example, most single-gene disorders would not be detected by chromosomal microarray and Fragile X testing.
- Consider referral to genetic services for coordination of further testing if any of the below criteria are met
  - Multisystem involvement (e.g. presence of congenital anomalies or significant physical health concerns)
  - Multiple family members similarly affected
  - Parents of the affected individual are consanguineous (related by blood)
  - Family is highly interested in pursuing further testing (e.g. for reproductive risk assessment for other family members) and patient has moderate to severe functional impact

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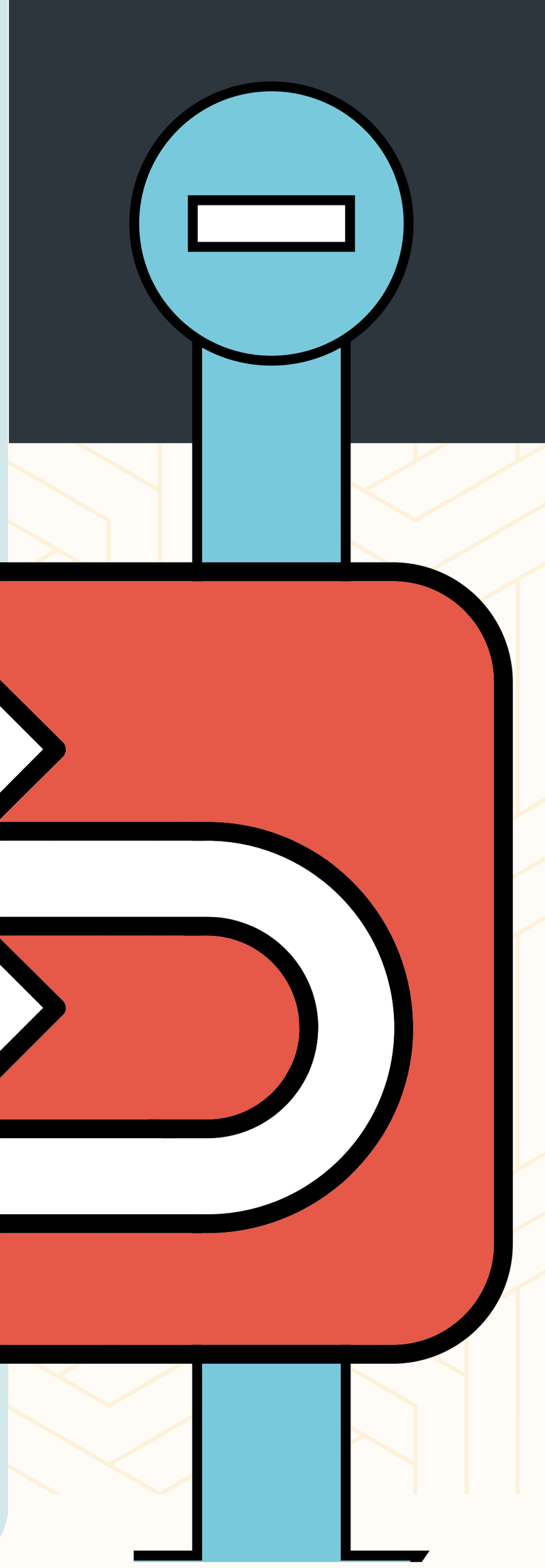

Letter / Consult Note Template for Negative Results Return

Template is written to be saved as a ConnectCare smart phrase. Please feel free to adapt and modify to suit your practice.

This letter is to summarize genetic testing completed to date for @NAME@. Genetic testing was offered due to their diagnosis of *** and these investigations have now been completed. The results of genetic testing completed for @FNAME@ are summarized below:

- Chromosomal Microarray: No clinically significant gains or losses identified.
- Fragile X Syndrome Testing: Negative, no expansion detected within the FMR1 gene.

We discussed that these results greatly reduce the likelihood of a genetic diagnosis for @FNAME@ but cannot rule out a genetic cause beyond the detection limits of available testing. In the absence of a genetic diagnosis, ***(diagnosis) is thought to be of multifactorial etiology. Multifactorial disorders result from an interaction of several genes with environmental factors. Recurrence risks are estimated from empiric evidence as well as the number of affected individuals in the family, and how they are related. Management should continue to be based on @FNAME@'s presenting symptoms.

1] Austin JC. Evidence-Based Genetic Counseling for Psychiatric Disorders: A Road Map. Cold Spring Harb Perspect Med. 2020 Jun 1;10(6):a036608. doi: 10.1101/cshperspect.a036608. PMID: 31501264; PMCID: PMC7263094.

GENETIC COUNSELING & GENOMIC PSYCHIATRY CONSULT SERVICES AUTISM & NEURODEVELOPMENTAL CONDITIONS

Primary Physician

Child/adolescent/adult Psychiatrist; Pediatrician; Developmental Pediatrician; Child/adult Neurologist; Internist; PCP

Continue Longitudinal care

Did my patient have Fragile X testing, Chromosomal microarray (CMA) , and/or Exome/Genome sequencing?

NO

Either offer genetic testing, or refer for Genetic Counseling Service

YES

ABNORMAL

NORMAL

Refer to Genomic Psychiatry Consult Service

- Neuropsychiatric management based on genetics results, detailed discussion, personalized information, support groups
- Close collaboration with Medical Genetics at the University of Alberta and Alberta Health Services

Option to participate in research

Referrals to other medical subspecialties

Additional lab or imaging tests

Education & collaboration with referring provider for ongoing treatment

PRISMA

PRECISION MEDICINE IN AUTISM

Where you'll meet Bo, DiNA, and the rest of their friends!

WATCH NOW

SCAN ME!

We are eager to launch our new video aimed at kids on the autism spectrum and their families, explaining in a clear and engaging way key concepts like autism, genetics and genetic testing.

Our video is now available in English and Spanish! Take a look at the links below.

English: https://youtu.be/iXvd_GEdNCE

Spanish: https://youtu.be/mirvSuo3aS4

Genetic Testing

Although autism cannot be diagnosed with a genetic test, it is very important to look at the genome of people on the autism spectrum after a diagnosis is made, as finding a genetic change can help people understand better the reason for autism in their case, and give doctors important information to help when needed.

CHROMOSOMAL MICROARRAY

This test looks for any missing or extra pieces of DNA throughout the entire genome, and tells us what specific part of the encyclopedia is involved. Because it looks at every single book, it can uncover big and small changes alike, and tell us whether a genetic change is likely causing clinical symptoms or not.

FRAGILE X TESTING

It looks at one single word, or gene, on the X chromosome, as genetic changes in this gene are one of the most frequent causes of autism and cause Fragile X syndrome.

EXOME AND GENOME SEQUENCING

These tests too look at our entire genome, but they are also able to read each of the words in our encyclopedia, our genes, to detect any chan-ges in their spelling. Some of these changes don't lead to clinical symptoms, while others change the function of our genes; in those cases, we call them mutations.

it is important to remember that the decision about testing is entirely up to families, just as any other medical test. Be sure to ask your doctor or team any questions you have as you make this important decision! Check the complete video: www.youtube.com/watch?v=Es8g8u_tp-g

Visti our website for more information: www.precisionmedicineinautism.org

ASK A DOCTOR

I HAVE HEARD ABOUT GENETIC TESTING FOR AUTISM, BUT IT SEEMS UNCLEAR WHAT THE BENEFITS ARE. HOW WOULD THAT INFORMATION BE USEFUL FOR MY CHILD AND THE DOCTORS? IS THIS A DIFFERENT WAY TO DIAGNOSE AUTISM?

This is an excellent question. We know that autism has a strong genetic component, and in fact, a genetic cause for autism can be detected in up to 40% of people; that percentage can be even higher if there are other accompanying diagnoses such as intellectual disability or seizures. There are many reasons why genetic testing is useful for autism, but before we discuss them, we should make to important points:

- Autism is a clinical diagnosis, meaning that it is given based on the observations by the doctors during an office visit, or with additional psychological testing, such as the Autism Diagnostic Observation Scale (ADOS). That means that genetic testing is not used to diagnose autism; it is recommended after the diagnosis of autism has already been made to uncover potential causes.

- The decision about carrying out genetic testing should be a joint process with your medical team, and the decision to proceed is entirely in the hands of each family.

There are multiple different genetic tests, and for autism, the ones recommended are chromosomal microarray testing and Fragile X testing. These two tests are considered the standard of care for autism spectrum disorders and are recommended by multiple medical professional societies, including the American Academy of Child and Adolescent Psychiatry, the American Academy of Pediatrics, and The American College of Medical Genetics and the American Society of Human Genetics jointly, with growing support for exome sequencies as a first-tier test.

Chromosomal microarray testing looks for missing or extra pieces of genetic material across the genome, called deletions and duplications, or also known collectively as copy number variants (CNVs); With that information in mind, here are a few examples of the potential benefits that genetic testing may bring:

- Finding an explanation and underlying cause for the autism in a given family and putting an end to the diagnostic odyssey.

- Identifying risk for other behavioral and medical conditions associated with a given genetic change, such as cardiac or renal abnormalities, which may in turn impact clinical management, including additional workup and medication choice.

- Obtaining genetic counseling and risk assessment for family planning.

- Having a clearer picture of areas of strengths and vulnerabilities based on information from other families with the same genetic abnormality and accessing specific medical resources.

- Connecting with support groups of other families with the same genetic variant.

- Being eligible for clinical trials targeting people with a specific genetic variant. All the examples above encompass what we now call precision medicine - the ability to use precise individualized information for tailored clinical management.

After highlighting the benefits of genetic testing above, it is also worth mentioning that some families elect not to have genetic testing. Some of the reasons they cite include feeling guilty about potentially having passed on a genetic variant to their child, feeling that there is no clinical use for this information and that this test would not change their child's (or their own) clinical management, religious reasons, ethical concerns, or privacy concerns. While many of these reasons are important, some of them are rooted in misinfor-mation or misunderstanding of the process. We would recommend that the best way to move forward, whether you would like to move forward with genetic testing or hold off, is to have an open discussion with your doctor first to make a well-informed decision.

Remember, the decision of getting genetic testing is entirely up to you and your family and should be a joint process with your doctor. Hopefully, the information above can help you and your family decide on what is right for you!

We're happy to open up this section for all the questions you have about autism, genetics, genetic testing, and precision medicine. We have an outstanding network of clinicians available to answer them! Please send an email to prisma@ualberta.ca, and in the next edition, we will choose one question to answer.