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Participant Results Letter

DATE OF CONSULTATION:

INCIDENTAL GENOMICS STUDY

Patient's First Name, Last Name
Address
Address

Dear [First Name]:

It was a pleasure meeting with you on [date] for your genetic counselling session/speaking with you over the phone on [date] to discuss your whole exome sequencing (WES) results from the Incidental Genomics Research Study. You were invited to participate in the study and elected to enroll because of your personal [and family] history of cancer, and uninformative genetic test results thus far. This letter serves as a summary of our discussion. It is important to recognize that these results are from a research study and should not be considered medical-grade until verified through a reputable genetics clinic.

I. SUMMARY OF RESULTS RELEVANT TO CANCER: XX VARIANTS IDENTIFIED

We analyzed 152 cancer genes and your results showed that you carry [insert number] variants of uncertain significance in the *[gene name]* and *[gene name]* genes. At this time, these variants do not explain your history of *[cancer type]* and therefore, your cancer management and your family's cancer management does not change. Please see Section III for a detailed explanation.

II. SUMMARY OF INCIDENTAL FINDINGS: OTHER VARIANTS OF MEDICAL SIGNIFICANCE

In addition, you elected to receive incidental findings in the following categories: medically actionably disorders, rare genetic disorders, early-onset brain disorders, carrier status, variants affecting response to medications, and common disease risks. **No genetic variants associated with medically actionable, rare genetic disorders, early-onset brain disorders or ethnically relevant common disease risks were identified.** Variants of uncertain significance related to incidental findings were not reported. Please see results relevant to variants affecting response to medications, and carrier status below and Section IV for a detailed explanation.

A. GENETIC DISORDERS: 4 VARIANTS IDENTIFIED

Condition	Gene (Variant)	Symptom(s)	Recommendation(s)
Hypertrophic Cardiomyopathy	*MYH7* (c.####; p.####)	Shortness of breath, chest pain, heart palpitations and fainting	Referral to [clinical name] for confirmatory genetic testing.
Early-Onset Familial Alzheimer Disease	*PSEN1* (c.####; p.####)	Memory loss, confusion, poor judgment, withdrawal, speech and muscle abnormalities	Referral to [clinical name] for confirmatory genetic testing.
Factor V Leiden	*F5* (c.####; p.####)	Increased risk for blood clotting	Referral to [clinical name] for confirmatory genetic testing.
Retinitis Pigmentosa	*RHO* (c.###; p.####)	Progressive vision loss that usually begins with a loss of peripheral vision and night blindness followed by loss of central vision	Referral to [clinical name] for confirmatory genetic testing.

B. CARRIER RISK: 1 VARIANT IDENTIFIED

Condition	Gene (Variant)	Symptom(s)	Recommendation(s)
Cystic Fibrosis (carrier)	*CFTR* (c.####; p.####)	None; carriers do not typically develop symptoms	No referral has been made. Please contact your family doctor if you plan to have more children. Family members of childbearing age should be informed of this result.

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For questions and further information please contact the study genetic counsellor directly at [Study GC number] or [Study GC email]

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Supplementary file 2

Participant Results Letter

C. VARIANTS AFFECTING RESPONSE TO MEDICATION: 1 VARIANT IDENTIFIED

Drug	Gene (Metabolizer Type)	Risk and Dosing Information
Warfarin	*CYP2C19* (Rapid metabolizer)	You may experience side effects from warfarin. If your doctor is prescribing you warfarin, it is recommended that your doctor alter your dose, and that you be started on a lower dose.

D. COMMON DISEASE RISKS: 8 VARIANTS IDENTIFIED

Disease	Disease Prevalence in General Population	# Risk Variants Identified
Age-related macular degeneration	8.69%	4
Celiac Disease	0.5-1%	1
Crohn's Disease	0.37%	3
Type I Diabetes	0.45%	2

III. RESULTS RELATED TO YOUR CANCER HISTORY

[insert number] variants of uncertain significance were identified in the *[gene name]* and *[gene name]* genes that are associated with cancer. When a disease-causing variant is identified in these genes, patients may be at risk for a variety of cancers. However, you do not have disease-causing variants, instead you have variants where the roles are not fully understood. We do not know if the changes that have been found in your [gene name] and [gene name] genes are disease-causing or not. This is what we call **variants of uncertain significance**. These results do not confirm or eliminate the possibility of a hereditary form of cancer in you or your family. It is possible that in the future the variants found in you will be studied and will become reclassified as either cancer-causing or not causative of disease.

A probable genetic cause for your cancer was **not** identified in this study. **This does not mean that your personal and family history of cancer is not hereditary.** There are many possible explanations of these results, including:

- You may have a disease-causing genetic variant in a cancer gene that was not analyzed by our current technology because it has not yet been shown to be associated with cancer.
- You may have a harmful variant in one of the cancer genes that was analyzed, however the variant was not detected because of limitations of technology.
- Your personal and family history of cancer may be due to chance, and not related to an underlying genetic cause.
- The variants of uncertain significance identified in this study may be related to your cancer, but their clinical significance is not known at this time.

Given that we cannot rule out a genetic cause for your cancer history, we recommend that you and your family members continue with the follow-up and surveillance protocols as recommended by your providers.

IV. INCIDENTAL FINDINGS (NON-CANCER RELATED RESULTS)

Hypertrophic Cardiomyopathy

The results show that you have a disease-causing genetic variant in the *MYH7* gene (c.####; p.####). These results suggest that you are at an increased risk to develop Hypertrophic Cardiomyopathy (HCM).

- HCM is a disease that affects your heart and causes the muscles of the heart to be thicker than normal.
- Individuals with HCM may experience shortness of breath, chest pain, heart palpitations and fainting. In some cases, individuals with HCM may not experience any symptoms. In rare cases, HCM may cause sudden death.
- There are medications and surgery that may help to treat the symptoms and reduce complications associated with HCM.
- HCM is inherited in an autosomal dominant manner, meaning that your first-degree relatives are at up to a 50%

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Participant Results Letter

risk to have inherited this variant and be at risk for HCM.
- For more details, please refer to the summary in Genetics Home Reference: [insert link]
- **Recommendation**: The [Recruiting clinic name] will refer you to [clinic name] to clinically confirm the *[insert gene name]* variant and for further assessment. Your relatives can be referred to their local Genetics clinic for genetic counselling and a risk assessment after your finding has been confirmed.

Early Onset Familial Alzheimer Disease

The results show that you have a disease-causing genetic variant in the *PSEN1* gene (c.####; p.####). These results suggest that you are at an increased risk to develop early-onset familial Alzheimer disease (EOFAD).
- Features associated with EOFAD include memory loss, confusion, poor judgment, withdrawal, speech and muscle abnormalities.
- There are no specific medical treatments for EOFAD, however some lifestyle changes may help to manage the symptoms, such as reducing sudden changes in the environment.
- EOFAD is inherited in an autosomal dominant manner, meaning that your first-degree relatives are at up to a 50% risk to have inherited this variant and be at risk for EOFAD.
- For more details, please refer to the summary in Genetics Home Reference: [insert link]
- **Recommendation**: The [Recruiting clinic name] will refer you to [clinic name] clinically confirm the *[insert gene name]* variant and for further assessment. Your relatives can be referred to their local Genetics clinic for genetic counselling and a risk assessment after your finding has been confirmed.

Retinitis Pigmentosa

The results show that you have a disease-causing variant in the *RHO* gene (c.####; p.####). These results suggest that you are at an increased risk to develop Retinitis Pigmentosa (RP).
- RP is characterized by progressive vision loss that usually begins with a loss of peripheral vision and night blindness followed by loss of central vision.
- Individuals with RP should avoid supplements with a high dose of Vitamin E, bright lights, smoking and use of UV-blocking sunglasses. There are treatments and recommended surveillance for individuals with RP.
- RP inherited in an autosomal dominant manner, meaning that your first-degree relatives are at up to a 50% risk to have inherited this variant and be at risk for RP.
- For more details, please refer to the summary in Genetics Home Reference: [insert link]
- **Recommendation**: The [Recruiting clinic name] will refer you to [clinic name] to clinically confirm the *[insert gene name]* variant and for further assessment. Your relatives can be referred to their local Genetics clinic for genetic counselling and a risk assessment after your finding has been confirmed.

Factor V Leiden

The results showed that you carry the disease-causing variant in the F5 gene (c.####; p.####). These results suggest that you are at an increased risk for blood clotting.
- Individuals with this variant are at a 3 to 8-fold increased risk above the population to have a type of clot called a venous thromboembolism (VTE). Females with this variant are also at an increased risk of pregnancy loss and other obstetric complications.
- The risk of experiencing a clot depends on other genetic changes as well as environmental factors (e.g. obesity and oral contraceptives). Your family doctor can manage you for the risks associated with this variant.
- The chance of developing a blood clot depends on whether an individual has one or two copies of an abnormal F5 gene. Relatives of individuals with one or two abnormal copies of the F5 gene may be at risk to have the abnormal gene and be at increased risk for clotting.
- For more details, please refer to the summary in Genetics Home Reference: [insert link]

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Supplementary file 2

Participant Results Letter

- **Recommendation**: The [Recruiting clinic name] will refer you to [clinic name] clinically confirm the *[insert gene name]* variant and for further assessment. Your relatives can be referred to their local Genetics clinic for genetic counselling and a risk assessment after your finding has been confirmed.

Cystic Fibrosis Carrier Status

The results show that you carry a disease-causing variant in the *CFTR* gene (c.####; p.####). These results suggest that you are a carrier of cystic fibrosis (CF).

- Cystic fibrosis is an autosomal recessive condition. Every person has two copies of most genes, one inherited from each parent. A recessive disease occurs when both copies of the same gene have a harmful variant. A carrier is someone who has only one gene with a harmful variant and one gene that is unaffected. Carriers typically do not have any health problems and most people are carriers of at least 8-10 genetic conditions. However, these conditions can be passed unknowingly to a child. If both members of a couple are carriers of the same recessive condition, they have a 1 in 4 (25%) chance with each pregnancy to have a child affected with a genetic disease; a 1 in 2 (50%) chance to have unaffected carrier children; and a 25% chance of having unaffected and non-carrier children.
- Cystic fibrosis is characterized by a buildup of thick mucus that results in damage to the respiratory and digestive systems. Individuals affected with cystic fibrosis have chronic infections and poor weight gain and growth. Carriers of cystic fibrosis are generally unaffected and do not experience the symptoms associated with the disease.
- Your first-degree relatives (parents, brother, and children) have a 50% chance to also be carriers for Cystic fibrosis. Other biological relatives may also be carriers. If they are considering starting or expanding their family, they can request a referral to their local genetics clinic for a risk assessment and carrier screening.
- For more details, please refer to Genetics Home Reference: https://ghr.nlm.nih.gov/condition/cystic-fibrosis

Variants Affecting Response to Medication

The results suggest that you have genetic changes in the *CYPD2D6* gene that are **associated with increased risk for side effects from codeine,** a medication used to treat pain. If you need medications to help manage pain, it is important that your health care provider prescribe an alternative medication other than codeine/modify your dose of codeine. First degree relatives and other biological relatives could also be at risk to have a serious adverse reaction to codeine. We advised that you to discuss these results with your family members.

Common Disease Risk–these risk variants are typically not incorporated into the medical management of patients as their effects are small

Your exome sequencing results were assessed for variants associated with risks for the following common disorders: Age-related macular degeneration (AMD), Celiac disease, Crohn's disease and Type I diabetes. These are disorders that are common in the general population that are caused by a combination of genetic and environmental risk factors. No risk variants for Celiac disease and Type 1 diabetes were identified in this study, however the data from exome sequencing studies does not look at all of the possible changes in your genes. Your risk to develop these disorders is affected by other genetic variants that have not been analyzed and by lifestyle factors (e.g. diet and exercise).

Out of the eight risk variants assessed in this study associated with AMD, you were found to have four of these risk variants. Some studies have suggested up to 52 risk variants associated with this disorder, therefore we cannot provide an accurate estimate for your risk to develop AMD. AMD is the leading cause of blindness in North America in adults over the age of 55. It causes damage to the macula, a small spot near the center of the retina and the part of the eye needed for sharp, central vision, which lets us see objects that are straight ahead. Age is the most common risk factor in developing the disease as well as smoking. Early signs of AMD may be found during

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Supplementary file 2

Participant Results Letter

an eye examination even if no symptoms are noticed. For more details, please refer to: https://opto.ca/health-library/amd%20and%20low%20vision; https://nei.nih.gov/health/maculardegen/armd_facts

We assessed one risk variant for Celiac disease in this study, which you were found to have. Some studies have suggested up to 40 risk variants associated with Celiac disease, therefore we cannot provide an accurate estimate for your risk of developing Celiac disease. Celiac disease is an autoimmune disorder caused by damage to the small intestine from abnormal sensitivity to gluten, a group of proteins found in grains such as wheat, rye and barley. For more details, please refer to: https://www.celiac.ca/gluten-related-disorders/celiac-disease/; https://ghr.nlm.nih.gov/condition/celiac-disease

Out of the five risk variants assessed in this study associated with Crohn's disease, you were found to have three of these risk variants. Some studies have suggested over 200 risk variants associated with Irritable Bowel Syndrome, including Crohn's disease, therefore we cannot provide an accurate estimate for your risk to develop Crohn's disease. Crohn's disease causes inflammation of the lining of the GI (gastrointestinal) tract and disrupts the body's ability to digest food, absorb nutrition, and eliminate waste in a healthy manner. For more details, please refer to: https://ghr.nlm.nih.gov/condition/crohn-disease#inheritance; http://crohnsandcolitis.ca/About-Crohn-s-Colitis/What-are-Crohns-and-Colitis

Out of the two risk variants assessed in this study associated with Type I Diabetes, you were found to have one of these risk variants. Some studies have suggested over 40 risk variants associated with Type I Diabetes, therefore we cannot provide an accurate estimate for your risk of developing Type I Diabetes. Type I Diabetes occurs when the pancreas cannot produces insulin, which results in high blood sugar levels. For more details, please refer to: https://ghr.nlm.nih.gov/condition/type-1-diabetes; https://www.diabetes.ca/about-diabetes/types-of-diabetes

V. FOLLOW-UP PLAN:

All of the results that you have received from the Incidental Genomics Study are research results, and have not been verified by clinical testing. Clinical testing for your research results [insert results] will be coordinated by [insert recruiting clinic] who will refer you to [clinic name] At this time, there are no recommended referrals for your cancer genetic findings, however we recommend that you continue the appropriate follow-up and surveillance based on your medical and family history. In addition, you may contact your genetic counsellor at the [insert recruiting clinic] every 2-3 years to see if there is updated information on the variants of uncertain significance. A copy of your results will be forwarded to your family doctor.

It is important to note that these results do not exclude a hereditary risk for any other disorder. Individuals with a family history of a disease may be at increased risk for that disease regardless of their WES results and should receive appropriate medical care based on their medical and family history. It is recommended that you speak with your healthcare providers before altering medications or lifestyle behaviours based on these results.

No further genetic testing will be performed as part of this study. Your primary care provider will coordinate your follow up care, however we are available for any additional questions that may arise in the future. It was a pleasure meeting with you. Thank you for your participation in the study. If you have any questions about these results, the study, actions and recommendations please feel free to contact the **study genetic counsellor, [study GC name],** directly at **[number] or** [**email].**

Sincerely,

[Study GC name], [Designation]
Genetic Counsellor

Reviewed and signed electronically by:

[Study geneticist name], [Designation]
Medical Geneticist

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For questions and further information please contact the study genetic counsellor directly at [Study GC number] or [Study GC email]

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Participant Results Letter

[Principle Investigator name]
[Designation]

Copy to: Family Doctor
Recruiting clinic genetic counsellor

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For questions and further information please contact the study genetic counsellor directly at [Study GC number] or [Study GC email]

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