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Supplementary File 3 Provider Results Letter

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DATE OF CONSULTATION,

INCIDENTAL GENOMICS STUDY

Dr. XX
Address
Address

Dear Dr. [Doctor's Name]:

RE: [SURNAME], [Name] **DOB: mmm dd, yyyy**

Your patient**, [First Name, Last Name],** is enrolled in the Incidental Genomics Research Study at St. Michael's Hospital which aims to identify the genetic cause of [Patient Name]'s cancer history as well as to evaluate the impact of incidental findings (results unrelated to the reason for undergoing genetic testing) arising from whole exome sequencing (WES). [Patient Name] was informed of these results on [DATE] and given a letter summarizing them. She was invited to participate in this study due to her personal history of cancer and negative genetic testing at [insert recruiting s clinic].

As part of the study, [Patient Name] received genetic counselling, which included a review of the benefits, risks, and limitations of WES and incidental findings. [Patient Name] elected to learn about incidental findings uncovered by WES which are detailed below. Variants of uncertain significance related to incidental findings were not reported. Note that results from the Incidental Genomics Study are research results and therefore have not yet been clinically verified. Please see the results below.

I. RESULTS RELEVANT TO CANCER: XX VARIANTS IDENTIFIED

Given [Patient Name]'s personal history of [type] cancer [and family history of cancer], we tested her for all the currently known variants in 152 genes associated with hereditary cancer syndromes. We did not identify any pathogenic (disease-causing) variants, however we did identify XX variants of uncertain significance in the *XX* and *XX* genes. These genetic variants are not actionable and do not change medical management.

Because a hereditary cause for [Patient Name]'s cancer cannot be ruled out, we recommend that she continue with the follow-up and surveillance that have already been recommended for her based on her medical and family history. She can also contact the [recruiting clinic name] for an update on these variants of uncertain significance to see if they have been reclassified as either cancer-causing or not causative of. Every two-three years is a reasonable timeframe.

II. INCIDENTAL FINDINGS: OTHER VARIANTS OF MEDICAL SIGNIFICANCE

A. SINGLE GENE DISORDERS: 4 VARIANTS IDENTIFIED

Disease	Gene (Variant)	Recommendation(s)	Referral(s)	Action(s) to be taken by GP
Hypertrophic Cardiomyopathy	***MYH7* (c.###; p.###)**	Clinical assessment and confirmatory genetic testing.	[Recruiting clinic] will send referral to the [clinic name]	No action
Early-Onset Familial Alzheimer Disease	***PSEN1* (c.###; p.###)**			
Factor V Leiden	***F5* (c.###; p.###)**			

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Retinitis Pigmentosa	***RHO* (c.###; p###)**			

Hypertrophic Cardiomyopathy

- [Patient Name] carries the c.#### (p.####) pathogenic variant in the *MYH7* gene. This result suggests that [Patient Name] is at an increased risk to develop Hypertrophic Cardiomyopathy (HCM).
- HCM is characterized by the presence of unexplained left ventricular hypertrophy (LVH).
- Symptoms include shortness of breath, chest pain, palpitations, syncope, and can range from asymptomatic to sudden cardiac death.
- Onset of LVH ranges, but typically manifests in adolescence or young adulthood.
- Hypertrophic Cardiomyopathy is a dominant condition where individuals who have single pathogenic variants on their *MYH7* gene, like [Patient name], are prone to develop this condition. Each of [Patient name]'s first degree relatives, such as her children, have a 50% chance in also having this pathogenic variant.
- For more details, please refer to the summary in Genetics Education Canada – Knowledge Organization (GEC-KO): (www.geneticseducation.ca)
- **Recommendation**: The [insert recruiting clinic] will refer [Patient Name] to the [clinic name] for clinical validation of this finding and further assessment.

Early Onset Familial Alzheimer Disease

- [Patient Name] carries the c.#### (p.#### pathogenic variant in the *PSEN1* gene. This result suggests that [Patient Name] is at an increased risk for Early-Onset Familial Alzheimer Disease (EOFAD).
- EOFAD is an inherited form of Alzheimer disease in which onset is typically before the age of 65.
- Symptoms include memory loss, confusion, poor judgment, withdrawal, and increased muscle tone and mutism.
- Early Onset Familial Alzheimer Disease is a dominant condition where individuals who have single pathogenic variants on their *PSEN1* gene, like [Patient name], are prone to develop this condition. Each of [Patient name]'s first degree relatives, such as her children, have a 50% chance in also having this pathogenic variant.
- For more details, please refer to the summary in Genetics Home Reference: https://ghr.nlm.nih.gov/condition/alzheimer-disease
- **Recommendation**: The [insert recruiting clinic] will refer [Patient Name] to the [clinic name] for clinical validation of this finding and further assessment.

Retinitis Pigmentosa

- [Patient Name] carries the c.#### (p.####) pathogenic variant in the *RHO* gene. These results suggest that [Patient Name] has or is at risk to develop Retinitis Pigmentosa (RP).
- RP is an inherited eye disorder caused by abnormalities in the photoreceptors and leads to progressive vision loss.
- Symptoms include night vision loss and loss of peripheral vision which progresses to loss of central vision.
- Retinitis Pigmentosa is a dominant condition where individuals who have single pathogenic variants on their *RHO* gene, like [Patient name], are prone to develop this condition. Each of [Patient name]'s first degree relatives, such as her children, have a 50% chance in also having this pathogenic variant.
- For more details, please refer to the summary in Genetics Home Reference: https://ghr.nlm.nih.gov/condition/retinitis-pigmentosa
- **Recommendation**: The [insert recruiting clinic] will refer [Patient Name] to [clinic name] for clinical validation of this finding and further assessment.

Factor V Leiden

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- [Patient Name] carries the c.#### (p.####) pathogenic variant in the F5 gene. These results suggest that [Patient Name] is at an increased risk for blood clotting.
- Individuals who have a Factor V Leiden pathogenic variant are at a 3 to 8-fold increase risk for a venous thromboembolism (VTE).
- Females with a Factor V Leiden pathogenic variant are at an increased risk of pregnancy loss and other obstetric complications.
- The risk of clotting depends on other genetic changes as well as environmental factors (e.g. obesity and oral contraceptives). Therefore, we cannot predict the exact risk for Mrs./Ms./Mr. [Surname] to develop the disease or the risk to her family members.
- Management is generally based on the clinical and family history of the patient.
- Individuals who are heterozygous for Factor V Leiden variant should be tested for other thrombophilic disorders to assess for the risk of thrombosis (DNA testing for F2 thrombophilia, coagulation assays for lupus inhibitor, and serological assays for anticardiolipin antibodies and anti-beta$_2$-glycoprotein 1 antibodies.).
- For patients with a history of recurrent VTE/family history of VTE at a young age, evaluation should also include assays of protein C activity, antithrombin activity, and protein S and free protein S antigen.
- For patients who do not have a history of thrombosis, long-term anticoagulation is not recommended.
- Factor V Leiden is a dominant condition where individuals who have single pathogenic variants on their *F5* gene, like [Patient name], are prone to develop this condition. Each of [Patient name]'s first degree relatives, such as her children, have a 50% chance in also having this pathogenic variant.
- **Recommendation**: The [insert recruiting clinic] will refer [Patient Name] to [clinic name] for clinical validation of this finding and further assessment.
- For more details, please refer to the summary in GEC-KO: (www.geneticseducation.ca)

B. CARRIER RISK: 1 VARIANT IDENTIFIED

Disease	Recommendation(s)	Referral(s)	Action(s) to be taken by family doctor
Cystic Fibrosis (carrier)	None; carriers are not expected to develop symptoms	No referral has been made. Patient has completed her family and may inform family members who are considering starting a family	Refer for genetic counselling if patient is of reproductive age

Cystic Fibrosis Carrier Status

- [Patient Name] carries the c.#### (p.####) pathogenic variant in the *CFTR* gene. This result suggest that [Patient Name] is a carrier for Cystic Fibrosis (CF).
- CF is a recessive condition and [Patient Name] is **not** expected to develop any signs or symptoms.
- CF occurs when both copies of the *CFTR* gene are altered and results in respiratory damage, pancreatic insufficiency, digestive problems, male infertility and additional complications. As [Patient Name] has completed her family, we do not have any specific recommendations for her. If [Patient Name]'s reconsiders starting a family in the future, we recommend that her partner be referred to a genetics clinic for carrier screening of CF.
- We instructed [Patient Name] to inform her family members who are starting a family of this results and to seek genetic counselling if necessary.
  For more details, please refer to Genetics Home Reference: https://ghr.nlm.nih.gov/condition/cystic-fibrosis

C. ASSOCIATIONS AFFECTING DRUG METABOLISM: 1 VARIANT IDENTIFIED

[Patient Name]'s whole exome was genotyped according to Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines (May 2018). [Patient Name] was found to have the following changes related to drug metabolism and dosing. You may seek the advice of a pharmacist or clinical pharmacologist on this finding before prescribing any of the medications mentioned below.

Gene	Allele	Predicted Effect	Medication	Recommendation(s)

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CYP2C9	*1/*3	Intermediate Metabolizer	Phenytoin Warfarin	Participant carries a variant which indicates **reduced metabolism** of CYP2C9 substrate drugs (e.g. **phenytoin, warfarin**). This may lead to higher blood levels and increased probability of toxicities. If required and per published guidelines, a 25% reduction of recommended starting phenytoin maintenance dose is recommended. Furthermore, per pharmacogenomics calculation and incorporation of CYP2C9, VKORC1 and CYP4F2 genotypes lower warfarin starting dose may be recommended.
VKORC1	*2/*2	Poor Metabolizer	Warfarin	Participant carries a variant which may produce fewer functional copies of the mature VKORC1 protein. This may have implications for initial warfarin dosing, as it may be associated with a lower **warfarin** dose requirement. Please refer to CYP2C9 recommendations for warfarin starting dose.

D. COMMON DISEASE RISK: 8 VARIANTS IDENTIFIED

Disease	Variant ID	Risk Factor (Odds Ratio)[1]	Disease Prevalence[2]	Publication (PubMed ID)[3]
Age-related macular degeneration (choroidal neovascularisation or wet form)	rs10490924	3.67	8.69%	22705344
Age-related macular degeneration (choroidal neovascularisation or wet form)	rs641153	2.22	8.69%	22705344
Age-related macular degeneration (dry and wet forms)	rs1061170	2.41	8.69%	21665990
Age-related macular degeneration (dry and wet forms)	rs121913059	20.28	8.69%	26691988
Age-related macular degeneration (dry and wet forms)	rs141853578	3.64	8.69%	26691988
Age-related macular degeneration (dry and wet forms)	rs147859257	2.86	8.69%	26691988
Age-related macular degeneration (dry and wet forms)	rs35292876	2.42	8.69%	26691988
Age-related macular degeneration (dry and wet forms)	rs429608	2.16	8.69%	20385819
Celiac disease	rs2187668	6.23	0.5-1%	20190752
Crohn's disease	rs11209026	3.18	0.37%	22293688
Crohn's disease	rs11465804	2.5	0.37%	18587394
Crohn's disease	rs2066847	3.99	0.37%	18587394
Crohn's disease	rs6596	3.74	0.37%	28008999
Crohn's disease	rs76418789	2.06	0.37%	23850713
Type 1 diabetes	rs2476601	2.7073	0.45%	25936594
Type 1 diabetes	rs2647044	8.3	0.45%	17632545

[1]The magnitude by which having this variant increases the odds of developing disease.
[2]Prevalence of the disease in the general population.
[3]For more information about the risk associated with these genomic variants, please use the PubMed ID at [https://www.ncbi.nlm.nih.gov/pubmed].

[Patient Name]'s exome was analyzed according to genomic positions associated with several disease categories including: Celiac disease, Crohn's disease, Age-related macular degeneration (both dry and wet forms), and Type I diabetes. [Patient Name] was found to have variants which are associated with risk of the following disorders: age-related macular degeneration (both dry and wet forms) and Crohn's disease. Developing these conditions is also dependent on other genetic and environmental risk factors, therefore the presence of these variants is associated with a small contribution of risk for these diseases.

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It is important to note that these results do not exclude a hereditary risk for any other disease not listed in the common disease risk table. WES results also do not alleviate risk due to family history of any disease. Individuals with a family history of a disease may be at increased risk for that disease and should receive appropriate medical care based on their medical and family history.

III. FOLLOW-UP PLAN:

[Insert recruiting centre] has facilitated a referral for [Patient Name] to the [clinic name] for further assessment of the above findings. **All consultation notes and results will be forwarded to your office.** At this time, there are no recommended referrals for [Patient Name]'s research cancer genetic findings. We recommend that [Patient Name] continue the appropriate follow-up and surveillance as recommended based on her medical and family history. 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 [study GC number] or [study GC email].

No further genetic testing will be performed as part of this study, and we do not provide ongoing updates to [Patient Name]'s test results. We have not planned a follow-up appointment at this time. All of [Patient Name]'s questions were answered to the best of our ability. We are available for any additional questions that may arise in the future. [Patient Name] is aware that any changes to her personal or family health history should be communicated to her clinicians. Further evaluation and/or ongoing care for the health risks identified by this study may be continued by her primary care provider and/or other medical specialists, as required.

Thank you for allowing us to participate in the care of your patient. If you have any questions about these results, the study, actions and recommendations please feel free to contact the **study genetic counsellor, [study GC],** directly at **[study GC number]** or **[GC email]**.

Sincerely,

[study GC], [GC designation]
Genetic Counsellor

Reviewed and signed electronically by:

[Study geneticist name], [Designation]
Medical Geneticist

[Principle Investigator name]
[Designation]

Copy to: Clinic GC

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