A comprehensive genomic reporting structure for communicating all clinically significant primary and secondary findings

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Supplementary 2: Example of a patient letter: Breast cancer patient with a LP variant in the *BRCA2* gene, VUS in the *MSH6* gene, and SFs associated with a medically actionable condition, carrier status, pharmacogenomics, and common disease risk variants.

ST. MICHAEL'S
UNITY HEALTH TORONTO

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March 28, 2021 **INCIDENTAL GENOMICS STUDY**

[insert patient name]
123 First Street
Toronto, ON M5R 4J1

Dear [insert patient name]:

It was a pleasure speaking with you on March 28th, 2021 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 history of breast cancer, 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. RESULTS RELEVANT TO CANCER

We analyzed 154 cancer genes and your results showed that you carry a likely disease-causing variant in your ***BRCA2* gene (c.67+3A>G)** that likely contributed to the development of your breast cancers. We discussed that individuals who carry one disease-causing variant in their *BRCA2* gene, like yourself, are at increased risk for the following cancers: breast cancer, up to a 84% risk; second primary breast cancer, up to 62% by age 70; ovarian cancer, up to a 27% risk; pancreatic cancer, 2-7% risk; male breast cancer, up to 8.9% risk; prostate cancer, up to a 20% risk; and an increased risk for melanoma. **Importantly, not everyone who has a disease-causing variant in their *BRCA2* gene will develop cancer**; however, they should be followed more closely. The cancer risks from a *BRCA2* disease-causing variant is inherited in a **dominant manner**. Every person has two copies of most genes, one inherited from each parent. A dominant condition occurs when one copy of a gene has a disease-causing variant. Each child (such as your daughter) of a parent with one *BRCA2* disease-causing variant has a 50% chance of inheriting it. Other first-degree relatives, such as your brother, also have a 50% chance to have inherited this variant.

The result in your *BRCA2* gene also suggests that you are a **carrier** of **Fanconi Anemia (FA)** and are not expected to develop signs and symptoms of this condition. FA is a condition that affects many parts of the body and is usually evident in childhood. Individuals with this condition may have bone marrow failure, physical abnormalities, organ defects including the kidney, and an increased risk of tumors and certain cancers such as acute myeloid leukemia. FA is inherited in a **recessive manner**. A recessive condition occurs when both copies of the same gene have a harmful variant. A carrier is someone like you who has only one copy of a gene with a harmful variant and the other copy of that gene is unaffected. Most people are carriers of at least 8-10 genetic conditions. However, these conditions can be passed unknowingly to a child. When two individuals who are carriers of the same recessive condition have children, 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. About 1 in 400 to 1 in 500 individuals in the general population carry a disease-causing variant in their *BRCA2* or *BRCA1* genes.

We also identified a variant of uncertain significance in the *MSH6* gene which may have some association to your family history of cancer. One additional variant of uncertain significance was identified in a gene that, at this time, has no association to your cancer and family history of cancer. We do not know if these variants are known to cause disease because their roles are not fully understood. This is what we call **variants of uncertain significance**. It is possible that in the future these variants of uncertain significance will be studied and will become reclassified as either cancer-causing or not causative of disease.

Recommendation: The Cancer Genetics Clinic will contact you to discuss next steps, including further testing to confirm the *BRCA2* genetic finding to ensure that it is a true finding. They will also present options for you including high risk

breast screening and risk-reducing surgeries. Your daughter and brother may be referred by their family doctors to their local genetics clinic to have genetic counseling and a discussion on genetic testing for the *BRCA2* variant.

For more information, please refer to: https://medlineplus.gov/genetics/gene/brca2/#conditions

II. SECONDARY FINDINGS (NON-CANCER RELATED RESULTS)

In addition, you elected to receive secondary findings in the following categories: medically actionable conditions, rare genetic conditions, early-onset brain conditions, carrier status, variants affecting response to medications, and risk for common health conditions. No disease-causing variants were identified in the rare genetic conditions and early-onset brain conditions categories. Variants of uncertain significance related to secondary findings were not reported. Please see below results relevant to medically actionable conditions, carrier status, variants affecting response to medications, and risk for common conditions.

A. Medically Actionable Conditions

Condition(s)	Gene (Variant)	Symptom(s)	Recommendation(s)
Hypertrophic cardiomyopathy; Dilated cardiomyopathy; Left ventricular noncompaction	*MYBPC3* (c.26-2A>G)	No symptoms; chest pain, shortness of breath, palpitations, lightheadedness, fainting; abnormal heart rate	The Cancer Genetics Clinic will refer you to the Adult Genetics Clinic for confirmatory genetic testing and to the Hypertrophic Cardiomyopathy clinic for evaluation. Your family doctor will order an echocardiogram (ultrasound of your heart) for you.

- The results show that you carry a disease-causing variant in the *MYBPC3* gene (c.26-2A>G) which is associated with the heart conditions **hypertrophic cardiomyopathy (HCM)**, **dilated cardiomyopathy (DCM)**, and **left ventricular noncompaction (LVNC)**. Your c.26-2A>G variant has been reported so far in individuals with HCM.
- HCM is characterized by thickening (hypertrophy) of the heart muscle which makes it difficult for the heart to pump blood to the rest of the body and may also cause an abnormal heart rhythm (arrhythmia). Hypertrophy often begins in adolescence or young adulthood, although it can develop at any time throughout an individual's lifetime. The symptoms of HCM are variable, even within the same family. **Many affected individuals have no symptoms at all**. Other people may experience chest pain; shortness of breath, especially with exercise; heart palpitations (a sensation of fluttering or pounding in the chest); lightheadedness; dizziness; and fainting. While most people are symptom-free or have only mild symptoms, this condition can have serious consequences such as arrhythmias, increased risk of sudden death and a small number of affected individuals develop potentially fatal heart failure, which may require heart transplantation.
- DCM occurs when the heart muscle becomes thin and weakened. It usually takes many years for symptoms of DCM to cause health problems. They typically begin in mid-adulthood, but can occur at any time from infancy to late adulthood. Signs and symptoms can include arrhythmias, shortness of breath, fatigue, fainting, and swelling of the legs and feet. LVNC occurs when one section of the heart (the left ventricle) does not develop correctly. Some individuals experience no symptoms at all; others have heart problems similar to DCM and can include sudden cardiac death.
- HCM, DCM, and LVNC have dominant inheritance patterns. In dominant inheritance, individuals who only have one disease-causing variant, like you, may present with features of HCM, DCM, or LVNC.
- Each of your first degree relatives, such as your daughter and brother have a 50% chance in also carrying this *MYBPC3* variant.
- You reported that you currently do not have any signs or symptoms of these conditions. Your paternal grandfather died from heart failure, however none of your other family members have any signs or symptoms that you are aware of.
- HCM affects an estimated 1 in 500 people worldwide.

- **Recommendation:** The Cancer Genetics Clinic will refer you to the Adult Genetics Clinic at St. Paul's Hospital for confirmatory genetic testing of this variant and to the Hypertrophic Cardiomyopathy clinic at St Paul's Hospital for further assessment. Your family doctor will order an echocardiogram (ultrasound of your heart) for you. Your family members may also seek out genetic counseling and testing of this variant.
- For more details, please refer to: https://medlineplus.gov/genetics/gene/mybpc3/#conditions

B. Carrier Status

Condition	Gene (Variant)	Symptom(s)	Recommendation(s)
Leber congenital amaurosis-6	*RPGRIP1* (c.1614_1623del; p.E539Qfs*2)	None; carriers are not expected to develop symptoms.	No referral has been made. You may inform family members who are considering starting a family of this result.

- The results shows that you carry a disease-causing variant in the *RPGRIP1* gene (c.1614_1623del; p.E539Qfs*2). This suggests that you are also a **carrier** of **Leber congenital amaurosis-6** and are not expected to develop symptoms.
- At birth, babies present with severe vision loss and other eye issues like involuntary movements of the eyes (nystagmus).
- Your first-degree relatives (daughter and brother) have a 50% chance to also be carriers for this condition. 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: https://medlineplus.gov/genetics/condition/leber-congenital-amaurosis/

C. Variants Affecting Response to Medications

Drug	Gene (Metabolizer Type)	Recommendation(s)
Warfarin	*CYP2C9 & VKORC1* (Intermediate Metabolizer for both)	**You are currently not taking this medication.** You may require a lower starting dose of warfarin if you are prescribed this medication. This should be discussed with your physician or pharmacist.
Amitriptyline, Citalopram, Escitalopram, Voriconazole, Lansoprazole, Omeprazole, Pantoprazole, Clopidogrel	*CYP2C19* (Rapid Metabolizer)	**You are currently not taking any of these medications.** If you require amitriptyline, citalopram, escitalopram, or voriconazole in the future, alternative medications should be discussed with your physician or pharmacist. If you require lansoprazole, omeprazole and pantoprazole, an increased starting dose is recommended. If you require clopidogrel in the future, your physician may prescribe the recommended starting dose.

We advise that you discuss these results with your family members. Your healthcare provider may refer you to a pharmacist or clinical pharmacologist for a discussion on the effects of these drugs prior to starting these medications. Other genetic and clinical factors may also influence your response to any of these medications.

Warfarin Metabolism

The results suggest that you carry genetic changes in your *CYP2C9* and *VKORC1* genes causing you to be an intermediate metabolizer for the drug, warfarin (blood thinner to treat blood clots). As an intermediate metabolizer, you have decreased ability to break down warfarin, compared to those who are normal metabolizers, which means you might require a lower dose. If you require this medication, it is important that your healthcare provider lower your starting dose.

Amitriptyline, Citalopram, Escitalopram, Voriconazole, Clopidogrel, Lansoprazole, Omeprazole and Pantoprazole Metabolism

The results show that you have a genetic change in the *CYP2C19* gene causing you to be a rapid metabolizer. As a rapid metabolizer, this means you are able to clear these drugs faster from your body compared to those who don't have this variant (normal metabolizers). This may lead you to not respond effectively to the following drugs: amitriptyline (anti-pain and anti-depressant), citalopram, escitalopram (anti-depressants), and voriconazole (anti-fungal medication). If you need any of these drugs, you may require an alternative medication. If you need lansoprazole, omeprazole and pantoprazole (stomach and esophageal medications for gastroesophageal reflux and stomach ulcers), an increased starting dose is recommended. If you need clopidogrel (blood thinner used to reduce the risk of heart disease and stroke), your physician may prescribe the recommended starting dose.

D. Common Health Conditions

Condition	Condition Prevalence in General Population	# Risk Variants Identified
Age-related macular degeneration	8.69%	5
Celiac disease	0.5-1%	1
Crohn's disease	0.37%	2
Type I diabetes	0.90%	2

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 conditions: age-related macular degeneration (AMD), Celiac disease, Crohn's disease, chronic obstructive pulmonary disease (COPD), stroke, Type I diabetes, Type II diabetes, and ulcerative colitis. These conditions are common in the general population and are caused by a combination of genetic and environmental risk factors. No risk variants for COPD, stroke, Type II diabetes, and ulcerative colitis 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 conditions is affected by other genetic variants that have not been analyzed and by lifestyle factors (e.g. diet and exercise).

Out of the ten risk variants assessed in this study associated with AMD, you were found to have 5 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 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 this risk variant. 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://medlineplus.gov/genetics/condition/celiac-disease/

Out of the four risk variants assessed in this study associated with Crohn's disease, you were found to have 2 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 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://medlineplus.gov/genetics/condition/crohn-disease/; http://crohnsandcolitis.ca/About-Crohn-s-Colitis/What-are-Crohns-and-Colitis

Out of the four risk variants assessed in this study associated with Type I diabetes, you were found to have 2 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 produce insulin, which results in high blood sugar levels. For more details, please refer to: https://medlineplus.gov/genetics/condition/type-1-diabetes/; https://www.diabetes.ca/about-diabetes/types-of-diabetes

III. 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. Your genetic counselor at the Cancer Genetics Clinic will contact you to discuss confirmatory genetic testing of your *BRCA2* variant and further next steps. Furthermore, the Cancer Genetics Clinic will refer you to the Adult Genetics Clinic at St. Paul's Hospital for confirmatory genetic testing of the cardiomyopathy (*MYBPC3*) genetic finding and to the Hypertrophic Cardiomyopathy Clinic at St. Paul's Hospital for further assessment. Your family doctor will also order an echocardiogram (ultrasound of your heart) for you. In addition, you may contact your genetic counselor at the Cancer Genetics Clinic every 2-3 years to see if there is updated information on your cancer 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.

At this time, no further genetic testing will be performed as part of this study. If there are any changes to your personal and/or family health history, please inform your doctor and genetic counsellor at the Cancer Clinic. It was a pleasure speaking with you again and 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 us at **222-333-4444 x555** or **janice.ma@hospital.com.**

Sincerely,

Reviewed and signed electronically by:

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Encl: WES Report