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

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Supplementary 3: Example of a provider 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.

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March 28, 2021 **INCIDENTAL GENOMICS STUDY**

Dr. Louise Bernard
30 Bond St
Toronto, ON M5B 1W8

Dear Dr. Bernard:

RE: [insert patient name] DOB: 1975-Jun-18

Your patient**, [insert patient name],** is enrolled in the Incidental Genomics Research Study at St. Michael's Hospital which aims to identify the genetic cause of [insert patient name]'s breast cancer history as well as to evaluate the impact of secondary findings (results unrelated to the reason for undergoing genetic testing) arising from whole exome sequencing (WES). [insert patient name] has been informed of these results on March 28th, 2021 and given a letter summarizing them. She was invited to participate in this study due to her personal and family history of cancer and inconclusive genetic testing at The Cancer Genetics Clinic at Metropolitan Hospital.

As part of the study, [insert patient name] received genetic counselling, which included a review of the benefits, risks, and limitations of WES and secondary findings. [Insert patient name] elected to learn about secondary findings uncovered by WES which are detailed below. Variants of uncertain significance related to secondary 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

Given [insert patient name]'s personal history of breast cancer diagnosed at age 39 and family history of cancer, we tested her for all the currently known variants in 154 genes associated with hereditary cancer and tumour predisposition syndromes. We identified one likely pathogenic (disease-causing) variant in the ***BRCA2* gene (c.67+3A>G)** that likely contributed to [insert patient name]'s breast cancer. Additionally, we identified one variant of uncertain significance in *MSH6* gene that may have an association to [insert patient name]'s family history of cancer. One additional variant of uncertain significance was also identified in a gene that, at this time, has no association to [insert patient name]'s personal and family history of cancer. These variants of uncertain significance are not actionable and do not change medical management.

Single pathogenic variants in the *BRCA2* gene are associated with increased risk for the following cancers following an **autosomal dominant** inheritance pattern: 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. An individual with a single pathogenic variant has a 50% chance of passing the condition on to their offspring. Other first-degree relatives also have a 50% chance of having this variant.

We also discussed that individuals with a single pathogenic *BRCA2* variant are also carriers of **autosomal recessive Fanconi Anemia (FA)**. FA is a multi-system disorder characterized by bone marrow failure and variable presentation of anomalies, including short stature, abnormal skin pigmentation, abnormal thumbs, malformations of the skeletal and central nervous systems, and developmental delay. Risks for leukemia and early onset solid tumors are significantly elevated. FA is inherited in a recessive fashion where an affected individual has pathogenic variants on both copies of their *BRCA2* gene. Carriers for FA, like [insert patient name], do not have any health problems associated with the condition. About 1 in 400 to 1 in 500 individuals in the general population carry a disease-causing variant in their *BRCA2* or *BRCA1* genes.

Recommendation: The Cancer Genetics Clinic will contact [insert patient name] to discuss next steps, including further testing to confirm the *BRCA2* genetic finding to ensure that it is a true finding. [Insert patient name]'s 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.

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For more details, please refer to: https://www.ncbi.nlm.nih.gov/books/NBK1247/

II. SECONDARY FINDINGS (NON-CANCER RELATED RESULTS)

A. Medically Actionable Conditions

Condition(s)	Gene (Variant)	Symptom(s)	Referral(s)	Action(s) to be taken by GP
Hypertrophic cardiomyopathy; Dilated cardiomyopathy; Left ventricular noncompaction	*MYBPC3* (c.26-2A>G)	No symptoms; chest pain, shortness of breath, palpitations, lightheadedness, syncope; arrhythmia	The Cancer Genetics Clinic will refer [insert patient name] to the Adult Genetics Clinic for evaluation and confirmatory genetic testing and to the Hypertrophic Cardiomyopathy clinic.	Please arrange an echo and ECG for [insert patient name] and kindly forward these reports to the Adult Genetics Clinic (Fax: 416-444-4444) and to the HCM clinic (F: 416-222-2222).

- [Insert patient name] carries the c.26-2A>G pathogenic variant in the *MYBPC3* gene which is associated with hyper**trophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM),** and **left ventricular noncompaction (LVNC)**. [Insert patient name]'s c.26-2A>G variant has been reported in individuals with HCM.
- HCM is characterized by hypertrophy of the cardiac muscle. Cardiac 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. Other people may experience chest pain; shortness of breath, especially with physical exertion; palpitations; 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 cardiac muscle becomes thin and weakened in at least one chamber of the heart, causing the open area of the chamber to become dilated. 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, dyspnea, fatigue, syncope, and swelling of the legs and feet. LVNC occurs when the left ventricle does not develop correctly. Some individuals experience no symptoms at all; others have heart problems overlapping with DCM and can include sudden cardiac death.
- HCM, DCM, and LVNC have **dominant inheritance** patterns. In dominant inheritance, individuals who only have one pathogenic variant, like [insert patient name], may present with clinical features of either of HCM, DCM, or LVNC.
- Each of [insert patient name]'s first degree relatives, such as her daughter and brother, has a 50% chance in also carrying this pathogenic variant.
- [Insert patient name] reported she does not have any signs or symptoms of these conditions. Her paternal grandfather died from heart failure, however none of her other relatives have any features of these conditions that [insert patient name] is aware of.
- HCM affects an estimated 1 in 500 people worldwide.
- **Recommendation:** The Cancer Genetics Clinic will refer [insert patient name] to the Adult Genetics Clinic at St. Paul's Hospital for clinical validation of this finding and she will also be referred to the Hypertrophic Cardiomyopathy clinic at St Paul's Hospital for further assessment. [Insert patient name]'s family members may also seek out genetic counselling and testing of this variant. **Please arrange an echocardiogram and electrocardiogram for [insert patient name] and kindly fax these reports to the Adult Genetics Clinic at 416-444-4444 and to the HCM clinic at 416-222-2222.**

B. Carrier Status

Condition	Gene (Variant)	Symptom(s)	Referral(s)	Action(s) to be taken by GP
Leber congenital amaurosis-6	*RPGRIP1* (c.1614_1623del; p.E539Qfs*2)	None; most carriers are not expected to develop symptoms.	No referral has been made. [Insert patient name] may inform family members who are family planning.	No action.

- [Insert patient name] carries the c.1614_1623del (p.E539fs*2) likely pathogenic variant in the *RPGRIP1* gene. This suggests that [insert patient name] is a **carrier** of **Leber congenital amaurosis-6** and we do not expect her to develop any signs or symptoms of this condition.
- Leber congenital amaurosis-6 occurs when both copies of the *RPGRIP1* gene are altered resulting in early-onset childhood vision loss, nystagmus, and severe retinal dysfunction.
- Since [insert patient name] has completed her family, we do not have any specific recommendations for her. We instructed [insert patient name] to inform her family members who are starting a family of this result so they can consider genetic counselling. Each of [insert patient name]'s first degree relatives (daughter and brother) has a 50% chance of also being carriers for these conditions.
- For more details, please refer to: https://medlineplus.gov/genetics/condition/leber-congenital-amaurosis/

C. Variants Affecting Response to Medications

Variants affecting drug metabolism were extracted from the Pharmacogenomics Knowledgebase (PharmGKB, December 2020). [Insert 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 these findings before prescribing any of the medications mentioned below. Other genetic and clinical factors may also influence [insert patient name]'s response to these drugs.

Gene & Genotype (SNP ID)	Predicted Effect	Medication	Recommendation(s)
VKORC1 *1/*2 (rs9923231) *CYP2C9* *1/*2 (rs1799853)	Intermediate Metabolizer	*Warfarin* (blood thinner)	If applicable and per pharmacogenomic warfarin dosing algorithms, a lower warfarin starting dose is recommended for patients with the *CYP2C9* *1/*2 and *VKORC1* *1/*2 genotypes. Other genetic and clinical factors may also influence a patient's warfarin dose requirement. **[Insert patient name] reported she is not taking this drug.**
CYP2C19 *1/*17 (rs12248560)	Rapid Metabolizer	*Amitriptyline* (anti-depressant & anti-pain medication) *Citalopram & Escitalopram* (anti-depressants) *Voriconazole* (anti-fungal medication) *Lansoprazole, Omeprazole & Pantoprazole* (proton pump inhibitors; stomach and esophageal medications) *Clopidogrel* (blood thinner)	[Insert patient name] carries a variant which indicates increased metabolism of *CYP2C19* substrate drugs leading to lower blood levels and a probability of pharmacotherapy failure. Alternative medication therapy may be warranted for amitriptyline, citalopram, mescitalopram and voriconazole. Increased dosing is recommended for lansoprazole, omeprazole and pantoprazole. Therapy may be initiated with recommended starting dose for clopidogrel. **[Insert patient name] reported she is not taking any of these drugs.**

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

Disease (% Prevalence[1])	Variant ID	Risk Factor (Odds Ratio)[2]	Publication (PubMed ID)[3]
Age-related macular degeneration (8.69%)	rs1061170	2.41	21665990
	rs429608	2.16	20385819
	rs641153	2.22	22705344
	rs9332739	2.17	21665990
	rs522162	2.33	23577725
Celiac disease (0.5-1%)	rs2187668	6.23	20190752
Crohn's disease (0.37%)	rs11209026	2.66	21102463
	rs11465804	2.5	18587394
Type I diabetes (0.90%)	rs689	2.38	25751624
	rs9272346	5.49	17554300

[1]Disease prevalence in the general population.
[2]The magnitude by which having this variant increases the odds of developing disease.
[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.

[Insert patient name]'s exome was analyzed according to genomic positions associated with several disease categories including: 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. [Insert patient name] was found to have variants which are associated with risk of the following disorders: AMD, Celiac disease, Crohn's disease and Type I diabetes. 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 conditions.

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

The Cancer Genetics Clinic will contact [insert patient name] to discuss confirmatory genetic testing regarding the likely pathogenic variant identified in her *BRCA2* gene and further next steps. [Insert patient name] will also inform her daughter, brother, and other family members of this finding so that they may seek out genetic counselling. The Cancer Genetics Clinic will refer [insert patient name] to the Adult Genetics Clinic at St. Paul's Hospital for clinical validation of the cardiomyopathy (*MYBPC3*) genetic finding as well as to the Hypertrophic Cardiomyopathy Clinic at St. Paul's Hospital for further assessment. **Please arrange an echocardiogram and electrocardiogram for [insert patient name] and kindly fax these reports to the Adult Genetics Clinic at 416-444-4444 and to the HCM clinic at 416-222-2222**. All consultation notes and results will be forwarded to your office. If you have any questions about these results, the study, actions and recommendations please feel free to contact the study genetic counsellor, Janice Ma, directly at 222-333-4444 x555 or janice.ma@hospital.com.

At this time, no further genetic testing will be performed as part of this study and we do not provide ongoing updates to [insert patient name]'s test results. All of [insert 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. [Insert 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.

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We are grateful that your patient participated in our research study. If you have any questions about these results, the study, actions and recommendations please feel free to contact the **study genetic counsellor, Janice Ma**, directly at **222-333-4444 x555** or **janice.ma@hospital.com**.

Sincerely,

Janice Ma, MSc, CCGC
Study Genetic Counselor

Reviewed and signed electronically by:

Azere Adichie, MD/PhD, FRCPC, FCCMG, FACMG
Study Medical Geneticist

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Encl: WES Report