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

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Abstract
Genomic sequencing (GS) can reveal secondary findings (SFs), findings unrelated to the reason for testing, that can be overwhelming to both patients and providers. An effective approach for communicating all clinically significant primary and secondary GS results is needed to effectively manage this large volume of results. The aim of this study was to develop a comprehensive approach to communicate all clinically significant primary and SF results. A genomic test report with accompanying patient and provider letters were developed in three phases: review of current clinical reporting practices, consulting with genetic and non-genetics experts, and iterative refinement through circulation to key stakeholders. The genomic test report and consultation letters present a myriad of clinically relevant GS results in distinct, tabulated sections, including primary (cancer) and secondary findings, with in-depth details of each finding generated from exome sequencing. They provide detailed variant and disease information, personal and familial risk assessments, clinical management details, and additional resources to help support providers and patients with implementing healthcare recommendations related to their GS results. The report and consultation letters represent a comprehensive approach to communicate all clinically significant SFs to patients and providers, facilitating clinical management of GS results.

Introduction
Exome and genome sequencing are increasingly being used in clinical practice to improve diagnosis and guide targeted treatments for patients across many areas of medicine. By 2025, the Global Alliance for Genomics and Health estimates that 60 million people will have their genome sequenced in a healthcare setting (Stark et al. 2019). The costs of genomic sequencing (defined here as including both genome and exome sequencing) have significantly decreased over the past decade and have allowed for more feasible clinical implementation of this technology (Weymann et al. 2017). Furthermore, improvements in analytical benchmarks and reduced sequencing times have made genomic sequencing (GS) superior to standard gene panels and chromosomal microarrays in terms of diagnostic yield across
multiple clinical indications (Suwinski et al. 2019; Shickh et al. 2021). Compared to conventional targeted gene panel testing, the breadth of genetic information generated from GS allows for the simultaneous examination of thousands of genes. This has many clinical and diagnostic advantages including the ability for variant re-analysis as new research emerges, as well as the ability to identify a wide range of genetic variations from a single test, including single nucleotide variants, genomic structural changes and copy number variants. In addition, GS allows for the identification of secondary findings (SFs), defined as findings unrelated to the primary indication for testing.

The identification of SFs allows for early detection, disease prevention, management, and monitoring of certain genetic diseases (Bennette et al. 2015). The current guidelines for communicating SFs provided by the American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) recommend reporting clinically significant findings from a list of 73 medically actionable genes; yet, patients undergoing GS have indicated an interest in receiving a broader range of SFs beyond the recommended standards (Green et al. 2013; Miller et al. 2021; Mighton et al. 2020). The clinical benefits of returning a broad range of SFs from a health system perspective are debated and require evaluation given the potential for overdiagnosis and subsequent unnecessary use of health services (Shickh et al. 2019). However, some evidence is beginning to emerge suggesting that returning SFs can provide health and psychological benefits to patients by facilitating opportunistic screening of diseases (Bennette et al. 2015; Shickh et al. 2019; Facio et al. 2013). Policy models suggest returning SFs are cost-effective and may increase quality-adjusted life-years of cardiomyopathy and cancer patients (Bennette et al. 2015). In addition, learning these results can motivate individuals to take preventative actions, such as alterations to medical management and/or lifestyle changes (Facio et al. 2013). The benefits of learning additional genetic information also extend to asymptomatic family members through cascade genetic testing, which can allow for appropriate disease screening and surveillance (Facio et al. 2013). However, returning a wider range of results to patients and their healthcare providers (HCPs) presents a challenge for clinical diagnostic laboratories utilizing GS as they determine how to effectively communicate these findings.

On average, exome sequencing of all clinically relevant genes can result in over 62,000 variants identified per patient (Reble et al. 2021). Even with stringent variant filtering parameters, the sheer volume of variants returned for primary indications and SFs presents a reporting challenge for diagnostic laboratories. This is further complicated by the majority of variants that are classified as variants of uncertain significance (Reble et al. 2021; Federici and Soddu 2020). In addition, not all SFs fall into the recommended ACMG-AMP classification categories (pathogenic, likely pathogenic, uncertain significance, likely benign, and benign) (Richards et al. 2015). For example, pharmacogenomic variants affecting metabolizer phenotypes and polygenic disease risk variants cannot be accurately classified as pathogenic, and therefore would not fit within the standard clinical reporting structure. Other genomic test reports have been developed to return results from GS, but few have integrated the reporting of a broad range of SFs (Vassy et al. 2014, 2015; McLaughlin et al. 2014; Haga et al. 2014; Dorschner et al. 2014). In addition, as non-genetics HCPs become increasingly involved in managing their patients’ genetic test results, they may face challenges in determining the appropriate clinical management and actionability of these findings without effective guidance (Vassy et al. 2018). Therefore, an effective approach for communicating all clinically significant primary and secondary GS results is needed that addresses these challenges. The aim of this study was to develop a comprehensive genomic test report with accompanying consultation letters for patients and providers to promote the effective communication of all clinically significant sequence variants (including single nucleotide variants (SNVs) and small insertions and deletions) resulting from GS.

**Methods**

**Interpreting exome sequencing results**

Exome sequencing, data processing and variant filtration, and curated gene and variant lists for SF categories analyzed were performed as previously reported (Reble et al. 2021). Filtered variants were classified in accordance with the “Standards and Guidelines for the Interpretation of Sequence Variants” developed by the ACMG and AMP (Richards et al. 2015).

**Development of the genomic test report and consultation letters**

The genomic test report and consultation letters were developed to support a randomized controlled clinical trial (RCT) that aimed to evaluate the health outcomes, utility, and costs of returning secondary results to patients undergoing exome sequencing (Shickh et al. 2019). The RCT enrolled 260 patients with cancer who previously received uninformative results from panel testing and were randomized into one of two study arms. In the control arm, patients received exome sequence variant results related to their personal and/or family history of cancer. In the intervention arm, patients received exome sequence variant results related to their personal and/or family history of cancer as well as the option to receive sequence variant SFs from the following categories: medically actionable conditions, pharmacogenomic findings, common disease single nucleotide polymorphisms (SNPs), Mendelian disorders, early-onset
neurodegenerative conditions, and carrier status findings. Genomic test reports and consultation letters outlining findings from exome sequencing were returned to both patients and their primary care providers (PCPs). Reports and letters were developed before the start of the RCT based on feedback from genomic experts and non-genetics HCPs.

(i) Initial reporting structure

The early draft of the report was developed by both the study’s clinical molecular geneticist and genomic laboratory analyst. The report aimed to mimic the same basic format as a clinical genetic test report to maintain consistency with previous genetic test reports that medical geneticists and genetic counselors would be familiar with. The genomic laboratory analyst also performed a review of previously published comprehensive genetic reports in the literature and from multiple clinical laboratories to gain insight into how best to structure a report with such a wide range of genetic findings (Vassy et al. 2014, 2015, 2018; McLaughlin et al. 2014; Haga et al. 2014; Dorschner et al. 2014). The reporting of each type of finding was determined independently for each category of SF. Reporting of primary indication results (cancer, per the RCT protocol (Shickh et al. 2019)), medically actionable findings, Mendelian findings, early-onset neurodegenerative findings and carrier status findings included variants that would be classified according to the ACMG-AMP standards, and therefore followed previous clinical reporting structures. Additional categories of SFs reported in the trial are not typically analyzed or reported by clinical labs, therefore certain specialists with experience in these areas were consulted in this initial phase to advise on specific areas of the report. This included a pharmacogenomics expert to advise on how to appropriately present pharmacogenomic results. For common disease SNPs, both the clinical molecular geneticist and genomic laboratory analyst analyzed the literature and the NHGRI-EBI Catalog of human genome-wide association studies to determine the odds ratio cutoff for common disease SNPs and selection of common diseases.

(ii) Initial consultation letters

In keeping with clinical practice, genetic counseling was provided to the patients for their results. Two consultation letters were developed for both the patient and their primary care providers (PCPs) by the study genetic counselors to aid with comprehension of the report (Supplementary 2—Sample Patient Letter; Supplementary 3—Sample Provider Letter). PCPs were initially consulted to determine the format and content of the letters to provide further support for PCPs when managing their patients’ SFs. The study’s medical geneticist, genetic counselors, genomic analyst, PCPs and pharmacogenomic expert provided feedback on the letters in an advisory capacity before the RCT.

(iii) Circulation to key stakeholders

The preliminary report and letters were distributed to key stakeholders for feedback, including medical and laboratory geneticists, genetic counselors, genetic analysts, pharmacogenomics experts, and PCPs. These experts and non-genetic experts provided recommendations on the report structure, visual esthetics, language, tone, types of genetic findings to report, testing limitations, and the types of supplementary material to include. Feedback was provided in an informal manner and was continually incorporated into the report and letters in an iterative process prior to the RCT.

Results

Genomic test report overview

The final 9–13 page report included primary and secondary findings separated into distinct categories, with details of each finding provided in the main body of the report. Details of the patient’s personal cancer history and other clinical features, as well as their family medical history, were described in the indication for referral. Given the primary indication of cancer, the family history was described with an emphasis on past cancers; however, a full family history was also provided to cover phenotypes relevant to any potential SFs. Based on feedback from genetic and non-genetic experts, a results summary indicating the number of variants detected from sequencing as well as the number of primary cancer and SFs identified in each category were listed on the first page to provide a broad overview of results (Fig. 1). Following the overview of results section, summary tables were included that listed any primary cancer and SFs in a color-coded manner based on the categories of results (Figs. 2, 3, 4, 5).

Primary cancer findings

In keeping with the current standards of practice, findings related to the primary indication of cancer were prioritized and discussed first in the report, prior to the secondary findings (Fig. 2). The primary cancer findings were presented in a table including the disease association and mode of inheritance using Online Mendelian Inheritance in Man® (OMIM) terms, gene name using HGNC terms, RefSeq transcript, cDNA and protein information using Human Genome Variant Society (HGVS) nomenclature, zygosity, variant frequency from the gnomAD v.2.1.1 control population, and ACMG-AMP variant classification (Tweedie et al. 2021; O’Leary et al. 2016; Karczewski et al. 2020; Hamosh et al. 2002). A brief written summary accompanied the table and provided a general discussion of the implications of the findings (e.g., Unknown clinical significance for VUSs or
potential disease association for positive [likely pathogenic and pathogenic] findings). Full variant assessments, associated disease summaries and familial risk information were provided in subsequent pages for any variants reported in the primary cancer findings table.

Variants reported in the primary cancer indication table included all pathogenic and likely pathogenic variants in cancer genes, and variants of uncertain significance (VUS) only in genes with a cancer association directly related to the patient’s personal and/or family history of cancer. The relevance of any given gene or variant to the patient’s personal and/or family history of cancer was ultimately at the discretion of the clinical laboratory director; however, in general, VUSs identified in genes with limited disease associations for a cancer present in the patient’s personal or family history were not included in the main body of the report even if the associated disease phenotype was consistent with a cancer in the personal and/or family history. The study genetic counselors indicated that these types of findings added another layer of uncertainty and complexity when communicating results to patients because heterozygotes would not be expected to develop features of an autosomal recessive condition even if these VUSs were to be upgraded to likely pathogenic or pathogenic.

An additional appendix (Appendix A) was provided at the end of the genomic test report (Supplementary 1, page 10) that included all cancer variants identified, including those not directly related to the personal or family history at the time of return of results. This provided a comprehensive list of cancer variants identified in the patient, and could be useful in the event of a change in gene–disease association or variant classification as new information becomes available. A second appendix, Appendix B, listed all genes analyzed in relation to the primary indication of cancer in an effort to provide transparency to clinicians and patients receiving the report (Supplementary 1, page 11).

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**Fig. 1** Preview of the genomic test report with example findings using patient and clinician pseudonyms. This section of the report displays patient information, clinic information, sample information, test details, reason for referral, and summary of results.
Secondary findings

Reporting of SFs warranted a novel reporting format as these findings have not been typically reported on standard clinical tests, and, therefore, do not have a standard reporting format. Medically actionable SFs, Mendelian SFs, early-onset neurodegenerative SFs, and carrier status SFs were presented in the same format as the primary cancer findings, as each of these findings include variants classified using the ACMG
### Common Disease Variants

Ten of 24 common disease risk variants were identified in this individual and are associated with increased risk for age-related macular degeneration (CFH rs1061170; SKIV2L rs429608; CFB rs641153; C2 rs9332739; NELFE rs522162). Crohn’s disease (IL23R rs11209026, rs11465804), Type 1 diabetes (INS rs689; HLA-DQA1 rs9272346), and Celiac disease (HLA-DQA1 rs2187668).

Developing these conditions is also dependent on other genetic and environmental risk factors, therefore the presence of these variants accounts for a small contribution of the overall disease risk.

| Disease (\% Prevalence) | Gene; rs #; Zygosity for risk allele | Reported Odds Ratio; Publication ID | Risk Allele Frequency (gnomAD) |
|-------------------------|-------------------------------------|------------------------------------|-----------------------------|
| Age-related macular degeneration (8.69\%) | CFH; rs1061170; heterozygous | 2.41; PMID: 21665990 | 0.3213 |
|                         | SKIV2L; rs429608; heterozygous      | 2.16; PMID: 20385819 | 0.8571 |
|                         | CFB; rs641153; heterozygous         | 2.22; PMID: 22705344 | 0.9042 |
|                         | C2; rs9332739; homozygous           | 2.17; PMID: 21665990 | 0.9647 |
|                         | NELFE; rs522162; homozygous         | 2.33; PMID: 23577725 | 0.8884 |
| Crohn’s disease (0.37\%) | IL23R; rs11209026; homozygous       | 2.66; PMID: 21102463 | 0.9576 |
|                         | IL23R; rs11465804; heterozygous     | 2.5; PMID: 18587394 | 0.9556 |
| Type 1 diabetes (0.90\%) | INS; rs689; heterozygous            | 2.38; PMID: 25751624 | 0.7343 |
|                         | HLA-DQA1; rs9272346; heterozygous   | 5.49; PMID: 17554300 | 0.525 |
| Celiac disease (0.5-1\%) | HLA-DQA1; rs2187668; heterozygous   | 6.23; PMID: 20190752 | 0.0777 |

**Fig. 4** Preview of the genomic test report: summary of example common disease SFs

### Pharmacogenomic Associations

Three of 26 pharmacogenomic variants alter the metabolizer phenotype in this individual: *VKORC1* *1/*2 (rs9923231), *CYP2C9* *1/*2 (rs1799853), and *CYP2C19* *1/*17 (rs12248560). Refer to Appendix C on page 11 for a full list of medications and dosing recommendations.

| Gene & Genotype (SNP ID) | Metabolizer Phenotype | Associated Medication(s) | Dosing Recommendation(s) |
|--------------------------|-----------------------|--------------------------|--------------------------|
| *VKORC1* *1/*2 (rs9923231) | Intermediate Metabolizer | Warfarin (blood thinner) | Warfarin: Based on this individual’s *VKORC1* and *CYP2C9* genotypes, a lower warfarin starting dose is recommended. |
| *CYP2C9* *1/*2 (rs1799853) | Intermediate Metabolizer | Warfarin (blood thinner), Phenytoin & Phosphenytoin (anti-seizure medications), Celecoxib, Flurbiprofen, Ibuprofen, Lornoxicam, Meloxicam, Piroxicam & Tenoxicam (nonsteroidal anti-inflammatory drugs; NSAIDs) | Standard dosing is recommended for phenytoin, fosphenytoin, celecoxib, flurbiprofen, ibuprofen, lornoxicam, meloxicam, piroxicam and tenoxicam. |
| *CYP2C19* *1/*17 (rs12248560) | Rapid Metabolizer | Amitriptyline (anti-depressant & anti-pain medication), Citralopram & Escitalopram (anti-depressants), Voriconazole (anti-fungal medication), Lansoprazole, Omeprazole & Pantoprazole (proton pump inhibitors; stomach and esophageal medications) | Alternative therapy may be recommended for amitriptyline, citralopram, escitalopram and voriconazole due to the potential for therapeutic failure. Increased dosing is recommended for lansoprazole, omeprazole and pantoprazole due to the potential for therapeutic failure. Standard dosing is recommended for clopidogrel. |

**Fig. 5** Preview of the genomic test report: summary of example pharmacogenomics SFs
guidelines (Fig. 3). Pathogenic, likely pathogenic, and VUSs associated with primary cancer findings were included in the genomic test report, while only likely pathogenic and pathogenic variants SFs were included. Unlike primary cancer findings, VUSs from SF categories were not reported because of their lack of relation to the testing indication. Nonetheless, detailed information for all variants (cancer and SFs) that were not included in the main report were made available at the request of referring HCPs.

The manifestation of common diseases, such as age-related macular degeneration and Crohn’s disease, is largely dependent on both genetic and environmental risk factors (Yu et al. 2011; Franke et al. 2010); thus, the 5-tier ACMG-AMP classification standards do not apply to these common disease risk SNPs. Instead, SNPs in this SF category were reported using results from genome-wide association studies (GWAS). Risk SNPs were included on the report only if the patient’s ancestry was consistent with the ancestral population assessed in the GWAS where the risk SNP association was reported, in recognition of the fact the most GWAS to date include predominately individuals of European descent, resulting in the identification of fewer ancestrally relevant risk SNPs in non-European individuals (Popejoy and Fuller-ton 2016; Fatumo et al. 2022). In addition, full drug names and class of medications affected by the variant were listed. Dosing recommendations were provided in accordance with the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines (Fig. 5) (Relling and Klein 2011). For medications where metabolism is known to be influenced by multiple genes, the genes and variants were grouped together with dosing formulas. An example of this includes the medication Warfarin, where the dosing recommendations take into account both VKORC1 and CYP2C9 metabolizer phenotypes (Dean 2012). Pharmacogenomic findings that would not alter the metabolizer phenotype (genotype is homozygous for the reference allele) were not provided in the main report but were provided at the end of the report in Appendix C (Supplementary 1; page 12). This single-page appendix serves as a quick reference for patients and their HCPs, and provides information for all analyzed pharmacogenomic associations, including both normal and alternative metabolizer phenotypes. Providing the genotype for all variants analyzed allows for adjustments

| Table 1 | Publicly available resources for providing detailed variant and disease information |
|---------|----------------------------------------------------------------------------------|
| Resource                                                                 | Benefits                                                                 | Limitations                                                                 |
| GeneReviews (Adam et al. 2022)                                           | Gene–disease association                                                  | Limited number of diseases covered                                          |
|                                                    | Guidelines for diagnosis, management, and genetic counseling                |                                                                             |
|                                                    | Curated and peer-reviewed                                                   |                                                                             |
| MedlinePlus (Miller et al. 2000)                                          | Gene–disease association                                                  | Management information is not provided                                      |
|                                                    | Gene function and disease mechanisms                                         |                                                                             |
|                                                    | Disease characteristics, frequency, inheritance pattern, and causes         |                                                                             |
| ClinGen: Clinical Genome Resource (Rehm et al. 2015)                       | Gene–disease validity                                                     | Limited number of gene–diseases relationships                               |
|                                                    | Dosage sensitivities                                                        |                                                                             |
|                                                    | Clinical actionability                                                     |                                                                             |
| ClinVar (Landrum et al. 2014)                                              | Reports of variants found in patient samples                               | Disease information                                                         |
|                                                    | Variant classification status based on verified submitters                  |                                                                             |
|                                                    | Variant-specific references                                                 |                                                                             |
| Online Mendelian Inheritance in Man (Hamosh et al. 2002)                   | Gene–disease association                                                  | Limited number of gene–disease relationships                               |
|                                                    | Disease characteristics                                                     |                                                                             |
|                                                    | Catalog of variants in affected individuals                                 |                                                                             |
| Clinical Genomic Database (Solomon et al. 2013)                            | Gene–disease association                                                  | Limited number of gene–disease relationships                               |
|                                                    | Description of medical interventions                                       |                                                                             |

The published (PubMed ID) odds ratios were provided for each finding to allow for the assessment of the magnitude of disease risk in relation to the genetic variant. This information allowed patients and HCPs to assess the information in the context of common disease risk.

Pharmacogenomic variants associated with drug metabolism required a unique reporting format. Pharmacogenomic findings that would result in an altered metabolizer phenotype were included in the main body of the report in a summary table that included the gene, variant (using pharmacogenomic star-allele nomenclature when applicable), and the resulting metabolizer phenotype associated with each variant (e.g., rapid metabolizer, intermediate metabolizer, etc.). In addition, full drug names and class of medications affected by the variant were listed. Dosing recommendations were provided in accordance with the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines (Fig. 5) (Relling and Klein 2011). For medications where metabolism is known to be influenced by multiple genes, the genes and variants were grouped together with dosing recommendations adjusted according to dosing formulas. An example of this includes the medication Warfarin, where the dosing recommendations take into account both VKORC1 and CYP2C9 metabolizer phenotypes (Dean 2012). Pharmacogenomic findings that would not alter the metabolizer phenotype (genotype is homozygous for the reference allele) were not provided in the main report but were provided at the end of the report in Appendix C (Supplementary 1; page 12). This single-page appendix serves as a quick reference for patients and their HCPs, and provides information for all analyzed pharmacogenomic associations, including both normal and alternative metabolizer phenotypes. Providing the genotype for all variants analyzed allows for adjustments
to the starting dose in the event dosing recommendations change over time.

**Variant and disease information and resources**

Expanding upon the results summary tables, detailed variant and disease information were provided for each cancer finding and SFs in the medically actionable, Mendelian conditions, early-onset neurodegenerative conditions, and carrier status categories (Supplementary 1; pages 4–6). This included (i) a variant assessment summary and ACMG-AMP evidence used in the final classification, (ii) information about the associated disease(s), such as the clinical characteristics of the disease, age of onset of symptoms, genetic and environmental risk factors, and other information from supporting literature, and (iii) disease inheritance patterns and familial risk for each finding. Detailed variant and disease information was extracted from various curated patient- and provider-friendly resources, such as GeneReviews and MedlinePlus, that the study team identified as helpful resources to include in the report (Table 1) (Adam et al. 2022; Miller et al. 2000).

Transparent communication of testing methodologies and limitations is a standard requirement of genetic test reports from all laboratories (Rehm et al. 2013). The genomic test report provided detailed information about testing and analysis methodologies and limitations (Supplementary 1; pages 7–9). Relevant testing information included bioinformatic pipeline versions, manufacturers, instrument models, capture methodology, sequencing kit, and genome coverage. In addition, filtering and analysis parameters for each category of SF were described along with the sources for each curated gene list with download dates. Despite achieving >95% exome coverage at 10× in most cases, bioinformatic and technological limitations were communicated in the report, such as missed regions due to low coverage, variants outside the region of analysis, and the inability to accurately identify repeat expansions, structural variants, large copy number variants, and non-coding regions (for exome sequencing).

**Consultation letters**

Primary and SF results were returned to patients by the study genetic counselor using the genomic test report, per the trial protocol (Shickh et al. 2019). To aid in comprehension of the genomic test report, a 4–6-page results letter was sent to patients and their HCPs that outlined the results and the discussion with the study genetic counselor (Supplementary 2—Patient Letter; Supplementary 3—Provider Letter). These letters were written for non-genetic expert physicians and patients using lay language to describe or explain medical and genetics terminology, such as inheritance patterns (e.g., autosomal dominant, autosomal recessive, X-linked, Y-linked) and the ACMG classification terms (e.g., VUS). The consultation letters were divided into 3 main sections. First, results relevant to the patient’s personal or family history of cancer were described along with clinical recommendations. Next, SFs were discussed with associations made between the expected phenotypes of the SFs and the clinical characteristics of the patient or family members. Lastly, the follow-up plan discussed in the counseling session was provided, which included any referrals. Unlike the genomic test report, the patient and physician letters did not provide in-depth variant interpretations, but rather focused on the potential health impact (e.g., expected signs and symptoms) and necessary follow-up for each finding (Fig. 6).

**Discussion**

As GS enters clinical practice and reporting guidelines for SFs evolve, communication and documentation of these genomic results must continue to evolve. The sheer volume of results that can be identified through GS can

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**Fig. 6** Preview of the patient results letter: summary of example clinical recommendations for a medically actionable finding
be overwhelming to both patients, providers, and genetic counselors. As such, effective communication of clinically significant GS results to patients and their HCPs represents a critical barrier to implementing GS in clinical practice. In this study, a comprehensive laboratory genomic test report with accompanying patient- and clinician-facing consultation letters were developed, which together represent a comprehensive approach to communicating clinically significant GS results to patients and their providers.

The genomic test report and consultation letters present a myriad of clinically relevant GS results in distinct, tabulated sections, including primary findings (cancer) and SFs in the following categories: medically actionable, pharmacogenomics, common disease risk, rare Mendelian disorders, early-onset neurodegenerative conditions, and carrier status. The genomic test report and consultation letters provide detailed symptoms, personal and familial risk assessments, clinical management details, and additional resources to help support HCPs and patients with implementing healthcare recommendations related to their GS results. To address the burdens of managing all clinically significant SFs, the first 2–3 pages of the genomic test report provide short descriptions of the results for busy clinicians and patients who need a quick summary to guide screening and preventative measures without the need to read the rest of the genomic report in detail. GS results are separated into clearly defined, color-coded sections in an effort to make the results digestible, easy to navigate, and allow clinicians to skip to sections of the report with higher priority or immediate importance. This structure was designed to minimize the information burden to patients and providers, and aid in facilitating the clarity and actioning of GS results in clinical practice. The reports and letters outlined here were designed as part of a RCT (Shickh et al. 2019), and may be modified depending on the types of results offered by any given laboratory.

In a previous study, primary care providers (PCPs) found the structured provider letters to be an effective solution to managing GS results in practice (Sebastian et al. 2022). The features they found to be effective included concise summaries of results, in-depth disease information for monitoring of symptoms, and clear next steps with follow-up recommendations and resources. PCPs felt these features improved their capacity to act on GS results (including clinical, lifestyle and family planning actions) (Sebastian et al. 2022). With the current shortages of genetic professionals (genetic counselors and medical geneticists), the responsibility to manage a patient’s SFs may ultimately fall to non-genetics HCPs (Sebastian et al. 2021). Effective communication of GS results to PCPs and HCPs across multiple disciplines is critical and can ultimately improve the value of GS in practice.

The GS reporting structure presented here includes a lab report and consultation letters in tandem. Although non-genetics HCPs found this model to be useful (Sebastian et al. 2021), generating both reports and letters may incur a burden to clinical labs as this is not standard practice. Indeed, this may represent an additional responsibility for laboratories to provide effective communication of GS results, especially to non-genetics HCPs. Future GS reporting strategies may combine elements from both genomic test reports and consultation letters, while digitizing and automating certain reporting features to help to ease this burden. In addition, the merger of reports and letters with digital health and education tools can increase and improve access to genetics services and information for HCPs and patients; however, these elements must also be integrated into electronic medical records to improve continuity of care and utility of results (Sebastian et al. 2021; Recchia et al. 2020; Bombard et al. 2020; Bombard and Hayeems 2021). The organization of the genomic test report and consultation letters into clear sections allows it to be easily modified and integrated into future digital platforms and electronic medical records.

There are limitations in the development and design of the reports and consultation letters in this study. The development of the genomic test report and consultation letters lacked a formal evaluation of communication and comprehension efficacy, as well as actionability from patients and non-genetics HCPs. The genomic test report and consultation letters may not be understandable for a patient, especially given the diversity of patients’ attitudes, concerns, and utility of SFs (Mighton et al. 2019). To address comprehension challenges, further work is needed to develop patient-friendly genomic test reports that are delivered in tandem with digital tools, which have been previously shown to improve patients’ knowledge about GS and SFs (Bombard et al. 2020). In addition, the reports and letters were only designed to return sequence variants (SNVs and small insertions/deletions), so its format may not be suitable to return other variant types (e.g., copy number variants and large insertions/deletions) that require a different reporting format. Similarly, the reports and letters were developed with cancer as the primary indication, so it is unknown if this structure is applicable to other specialties beyond oncology. Finally, the genomic test report and consultation letters presented here were intentionally designed to be broad, reflecting the broad range of SFs reported in the RCT (Shickh et al. 2019). While not reflective of current standard practice, the trial will generate data on the clinical utility, costs, and health outcomes of returning all clinically relevant SFs to providers and patients and impacts on the health system to inform future state of genomic practice.

Limitations notwithstanding, the genomic test report and consultation letters presented here provide a comprehensive
approach to optimize the communication and management of GS results, including primary findings and all clinically significant SFs, representing a critical step towards clinical implementation of GS.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s00439-022-02466-5.

**Acknowledgements** This study was supported by a Foundation Grant from the Canadian Institutes of Health Research and a Quality of Life Grant from the Canadian Cancer Society Research Institute awarded to Yvonne Bombard (Grant #s 143310 and 705665, respectively). Yvonne Bombard was supported by a New Investigator Award from the Canadian Institute of Health Research (Grant #136664) during the conduct of this study. Jordan Lerner-Ellis was funded by the McLaughlin Centre (Grant #MC-2012-13 and #MC-2014-11-1) and CIHR-Champions of Genomics: Building the Next Generation Grant (FRN: 135730).

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**Funding** This study was supported by a Foundation Grant from the Canadian Institutes of Health Research and a Quality of Life Grant from the Canadian Cancer Society Research Institute (grant numbers 143310 and 705665, respectively).

**Data availability** The data and findings in this study are available in the manuscript and/or supplemental material.

**Declarations**

**Conflict of interest** On behalf of all the authors, the corresponding author states that there is no conflict of interest.

**Ethical approval** This study was approved by the Research Ethics Board of Unity Health Toronto–St. Michael’s Hospital (CT00819); ClinicalTrial.gov identifier NCT03597165. Informed consent was obtained from all the participants involved in this study. Any individual-level data, including clinical data, found in this manuscript or supplemental files have been de-identified and pseudonyms were used where appropriate.

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