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Understanding the impact of genomic secondary findings on clinical care and patient experience: a protocol for a prospective observational study

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ABSTRACT

Introduction Genomic testing allows for the identification of disease-causing genetic variants and may also reveal secondary findings (SF) unrelated to the reason for testing. As the list of medically actionable genes continues to grow, it is important to understand the impact of these findings on clinical care and patient experience, particularly in paediatric settings. This work will generate novel evidence on the clinical, patient, family and system impacts of medically actionable SF generated from genomic testing.

Methods and analysis This mixed-methods, prospective, observational study will describe the impacts of SF on clinical care and the patient and family experience. Participants include probands and/or parents of probands who receive SF (ie, cases), clinicians involved in managing their care and controls matched 2:1 to cases based on age group, phenotype and primary genomic testing result. We aim to enrol 50 cases and 100 controls among those who receive genomic testing through Genome-wide Sequencing Ontario or other local sequencing initiatives in Ontario, Canada. Clinicians involved in follow-up care will complete questionnaires related to risk assessment, medical recommendations and clinical utility of SF post-result disclosure and one year later. Patient questionnaires will record health service use and psychological outcomes (ie, personal utility, empowerment) every 6 months for 2 years. These data will be compared between cases and controls using parametric tests. Cases will be invited to a qualitative interview to learn about their experiences. Data will be analysed using quantitative and qualitative techniques, triangulating datasets to enhance the validity and depth of the findings.

Ethics and dissemination This study is approved by the Clinical Trials Ontario (CTO) Research Ethics Review System (REB# CTO 3655). We plan to present our results to academic, patient, clinician and decision-maker audiences through articles and presentations at provincial, national and international meetings.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Using a mixed-methods approach, this study design will focus on a paediatric population, collecting evidence on the clinical, patient, family, and system impacts of medically actionable secondary findings generated from genomic testing in Canada.
⇒ Using a prospective observational design, this study will follow patients and their clinical care, collecting health service use, and clinical and personal utility outcomes for two years after genomic testing.
⇒ Data collection is supported by medical chart review and a research assistant interviewing participants and guiding them through questionnaires, ensuring a clear understanding and completion.
⇒ Inclusion is limited to patients undergoing genetic testing and using healthcare services in Ontario.

INTRODUCTION

The practice of identifying and reporting secondary and incidental findings generated from exome and genome sequencing (ie, genomic testing) continues to raise important questions around their clinical relevance, as well as patient-centred and system-related outcomes. Secondary and incidental findings (collectively referred to as secondary findings (SF) herein to simplify readability) are genomic variants unrelated to the indication for genetic testing that can provide clinically significant or actionable information, such as knowledge about a predisposition for a hereditary condition, prompting preventive care.[1] While SF are proactively identified based on predefined gene lists, incidental

findings emerge unexpectedly during genomic analysis.[1] The American College of Medical Genetics and Genomics (ACMG) recommends that specific SF in medically actionable genes be sought and returned to patients, with prior consent.[2] In addition to returning variants in genes associated with childhood-onset conditions, the ACMG recommends returning variants associated with conditions occurring in adulthood (eg, cancer risk, cardiovascular conditions) to parents of children, as the results may have immediate implications for family members and future implications for the child.[2 3] In contrast, the Canadian College of Medical Geneticists and the European Society of Human Genetics recommend first seeking evidence of the benefits and risks, as well as the health system impacts, associated with disclosing these findings before establishing firm practice guidelines.[1 3–6]

Studies have illustrated mixed and diverse views towards SF from patients, families and clinicians. While many clinicians support the identification and reporting of SF, given the anticipated health advantages for patients and their family members, concerns persist related to workload, interpretability of results (ie, penetrance), long-term benefits and appropriate allocation of resources.[7–13] Studies related to the benefits and risks of disclosing SF suggest that adverse psychological impacts are limited and that healthcare costs are modest.[7–11 14–23] In addition, the evidence highlights variation in follow-up care, a need for educational and supportive resources for patients and concerns related to privacy, discrimination, family communication and equity in access to information.[10–12 14–17 19 22] A systematic review of disclosure practices and outcomes associated with SF described existing evidence associated with receiving SF as both limited and weak.[24] Evidence from a Canadian perspective is limited. While a recent Canadian study with 287 adult patients with cancer found that SF were not associated with psychological distress and were associated with higher uptake of preventive medical and lifestyle behaviours compared with controls, no Canadian studies have explored the family, clinical and system impacts of SF in a paediatric setting.[25]

In addition to the concerns highlighted by these studies and critical gaps related to whether morbidity and mortality are reduced through this type of opportunistic screening, the impacts of SF generated in paediatric populations are not well understood.[17 24 26 27] In paediatrics, clear guidance regarding the clinical management of SF is limited, raising clinical and ethical challenges.[18 28] The majority of the literature reporting on SF in paediatric populations is descriptive, reporting on diagnostic yield, types of SF identified and the most commonly associated conditions.[23 24 28–30] However, these conditions differ in the typical age of disease onset, with some beginning in adulthood, creating uncertainty and inconsistency with respect to best practices for returning SF to paediatric patients and managing related care.[24 29] The proposed study will leverage recent local access to clinical-grade genomic testing to characterise the patient, clinician and system impacts of medically actionable SF in both adult and paediatric settings, providing relevant data that can inform national and international clinical practice and policy.[31–33]

AIMS AND OBJECTIVES

In the proposed study, we aim to determine the impacts of SF on clinical care and the patient and family experience. We will assess (1) patients' and family members' healthcare use and perceived utility and (2) clinicians' assessment of risk, medical management recommendations and perceived utility of SF.

METHODS AND ANALYSIS

Study design

Using a mixed-methods prospective case-control study design, we will determine the clinical and patient/family impacts of SF on those who receive these results compared with matched controls who do not receive SF.

Study setting

This study will leverage local sequencing initiatives in Ontario, Canada, that offer genomic testing during which SF could be identified, including Genome-wide Sequencing Ontario (GSO).[31–36] GSO (www.gsontario.ca) is a multi-institutional service developed to deliver and monitor the performance of clinical genomic testing (ie, exome and genome sequencing).[31–33] GSO is co-led by The Hospital for Sick Children (SickKids) in Toronto and the Children's Hospital of Eastern Ontario (CHEO) in Ottawa, Canada. GSO extends its service across the province of Ontario.[31–33]

At the time of consenting to genomic testing, the possibility of identifying SF is explained to patients and/or their parents/substitute decision-makers. It is explained that SF associated with medical actionability in childhood will be disclosed automatically in patients under 18 years of age. Patients and/or their parents are given the ability to opt out of receiving SF associated with medical actionability in adulthood. Biological parents are also given the option to learn about the inheritance of SF identified in their child to inform the management of their own potential health risks. Participants who agree to be recontacted for future research studies through GSO at any of the 14 clinical sites participating in this study or other local sequencing initiatives will be identified and invited to participate in this study.

Sample

This SF Impact Study will include adult patients and parents/caregivers of patients who receive genomic testing for a rare disease diagnostic workup and clinicians involved in disclosing SF results and/or managing SF-related follow-up care.

Eligibility criteria

Patient/parent sample

We will recruit patients and parents/caregivers of patients receiving genomic testing in Ontario who can provide

informed consent. Initially, clinical criteria for GSO eligibility included individuals who have had a baseline genetics evaluation (eg, phenotyping, family history, pretest genetic counselling) and a clinical presentation that involved ≥2 of the following: moderate to severe developmental or functional impairment; multisystem involvement; a progressive clinical course unexplained by another cause; a differential diagnosis that includes ≥2 conditions that require evaluation by multiple targeted gene panel tests; and/or a suspected severe genetic syndrome not yet diagnosed for which multiple family members are also affected or where parents are consanguineous. Since the launch of GSO, eligibility for genome testing and this study has expanded to allow clinical geneticists' best judgement and include individuals who fit any of the following categories (1) neurodevelopmental indications (eg, global developmental delay, intellectual disability, etc); (2) medical or congenital indications (eg, two or more congenital anomalies, suspected neuromuscular disease or ataxia, etc) and (3) suspected genetic conditions with multisystem involvement or a broad genetic differential diagnosis requiring two or more genetic investigations.[37 38] Individuals meeting criteria for genomic testing through other local sequencing initiatives will also be eligible. Since most individuals who receive genomic testing in Ontario have a neurodevelopmental phenotype, the capacity for assent is limited. As such, only parents/caregivers of paediatric index cases are eligible to participate.

Clinician sample

The clinician sample will include (1) medical geneticists or specialists who ordered genomic testing and returned SF to the patients/parents and (2) specialists involved in the index patient/parent's circle of care following the disclosure of SF. Clinicians will only be eligible if their patient who received SF consents to participate in this study and their practice location is among the 14 research ethics-approved study sites in Ontario, Canada.

Sample size

Patients/parents

Based on eligibility criteria, GSO anticipates enrolling a total of 1970 patients over two years from clinical genetics centres in Ontario.[31 32] Based on existing literature, it is estimated that 80% of patients receiving genomic testing will agree to receive SF.[28 39] As such, the eligible sample for this study will be 1576 plus individuals receiving genomic testing from other local sequencing initiatives.[34–36] Since early experience at GSO suggests that SF will be identified in ~5.5% of cases, we anticipate that ~86 index cases will receive a positive SF over the study period.[33] These individuals, along with two matched controls, will be invited to participate in the study. Based on related work, we anticipate the response rate to be ~60% for a final total of 50 index cases and ~100 matched controls (n=150).[28 39]

Clinicians

Since up to 50 cases with SF identified are expected to enrol in this study, it is plausible that up to 50 unique ordering clinicians will be eligible to participate. We anticipate that, per patient, 1–2 additional specialists involved in follow-up care may be eligible to participate. To optimise clinician participation, we have engaged geneticists and specialist champions within each of the 14 sites to support clinician participation.

Recruitment

Patients/parents

Starting January 2023, patients (and parents of index patients) who receive SF associated with medical actionability in childhood or adulthood will be invited. In addition, controls who opted to learn SF (but for whom SF were not detected) will be identified through the GSO REDCap database and research databases supporting other local sequencing studies.[32 33] Cases and controls will be matched on index patient age group (eg, <3 years, 3–11 years, 12–17 years and ≥18 years), primary variant result type (ie, diagnostic, non-diagnostic) and primary indication for genetic testing (eg, absence or presence of intellectual disability). Those fulfilling the matching enrolment criteria will be invited consecutively to participate. Recruitment will continue until the target sample size is achieved.

At the time of disclosure of SF, all index cases or parents/caregivers who receive SF will be notified of their eligibility for the study. Matched controls will be identified through the GSO REDCap database and limited to individuals who agreed to be recontacted for research. At SickKids, the study information sheet, with the study coordinators' contact information, will be included in the report that the ordering clinician receives from the laboratory and will be provided to potential participants at the time of disclosure. The information sheet will explain that if they do not opt out within 2 weeks, they will be contacted by the study coordinator to discuss the study procedures in more detail. Three contact attempts per participant will be made by email/phone, 2 weeks apart. For all other sites, the study information sheet will be sent directly to the ordering clinician, and they will be asked to share the study information with eligible participants. Eligible participants from non-GSO sequencing initiatives will be identified by their clinician and invited to the study. Verbal informed consent will be obtained from participants who agree to participate and documented.

To further explore the utility of SF from patients'/parents' perspectives and understand their experiences, we will conduct semistructured interviews 6–9 months following the return of SF with ~20 participants. We aim to interview ~10 index patients and ~10 parents/family members who received SF. Participants will be invited by the study coordinator at the end of their first follow-up data collection session (figure 1).

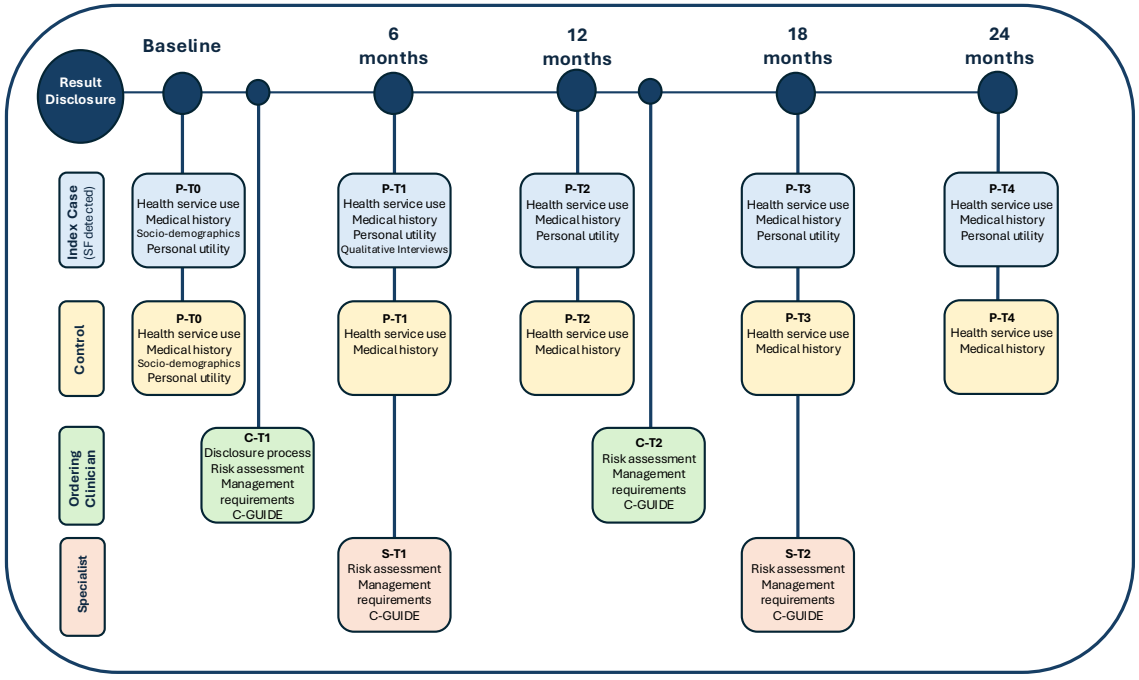

Figure 1 Data collection flow chart. C-TX, clinician timepoint; P-TX, patient timepoint; SF, secondary finding; S-TX, specialist timepoint; C-GUIDE, Clinician-reported Genetic testing Utility InDEx.

Clinicians

After an index case enrols in the study, the ordering clinician will be notified of their own eligibility to participate in this study. The invitation letter will include the study coordinator's contact information and instructions on how to participate or opt out. If the ordering clinician does not respond to the email invitation, one additional email reminder will be sent. Specialists who practise at the 14 study sites and who provide SF-related follow-up care for the index cases or their family members within 12 months of the disclosure of the SF will be identified and invited to participate in the study. To supplement this recruitment strategy, index patients will be asked to notify the study coordinator when an appointment is booked with a new clinician so they can be invited closer to the appointment date.

Outcomes

Objective 1: healthcare use and assessment of personal utility

Index cases or parents/caregivers and matched controls will complete the patient baseline questionnaire (P-T0), which includes five sections: (1) sociodemographics, (2) medical history, (3) health resource use and out-of-pocket costs in the previous 6 months, (4) perceived utility of SF, as measured by the validated Patient Reported Utility (PrU),[40] Lupo *et al*'s items related to patients' perceived utility of their genomic test results,[41 42] and an adapted version of the Multidimensional Impact of Cancer Risk Assessment (MICRA).[43] Sections (1)—(3) apply to both cases and matched controls (table 1). Follow-up questionnaires will be administered every 6 months for 2 years and will follow the same core structure, capturing services used since the previous assessment and perceptions of utility over time. Follow-up questionnaires will also include a section on communication of SF with family members and cascade testing. For cases, the questionnaire will explicitly ask respondents to think about SF, distinguishing them from the genomic findings they may have received related to the primary indication for testing. Participants will also be asked to indicate their confidence level regarding how specific their responses are to SF. Questionnaires were co-designed with patient partners and will be pilot-tested with three adult index patients and three parents of children who have received SF in the past year, and feedback will be collated to inform survey refinements.

Objective 2: clinicians' assessment of risk, medical management plan and utility

To capture the clinical assessment and medical management plan triggered by SF, ordering geneticists will be asked to complete the ordering clinician questionnaire (C-T1). According to Katz *et al*, clinicians should employ an evaluation and management strategy that accounts for both the increased disease risk associated with a SF and the lower positive predictive value of a screening result compared with indication-based diagnostic testing.[44] This approach to clinical evaluation includes five domains: (1) medical history, (2) physical exam, (3) family history, (4) diagnostic phenotypic testing (ie, biochemistry, imaging,

Table 1 Outcome data collection across time points

	Baseline-post-result disclosure		Within 1 month of enrolment		6 months		12 months				18 months		24 months	
	P-T0		C-T1	S-T1	P-T1		P-T2		C-T2	S-T2	P-T3		P-T4	
	Index	MC			Index	MC	Index	MC			Index	MC	Index	MC
Patient reported														
Sociodemographics and medical history	x	x												
Health services use (preceding 6 months)	x	x			x	x	x	x			x	x	x	x
Perceived utility	x	x			x		x				x		x	
Psychosocial impact of genetic test result disclosure	x				x		x				x		x	
Communicating SF results and cascade testing					x		x				x		x	
Clinician reported														
Clinical characteristics of the case (eg, medical history, physical exam, family history)			x	x					x	x				
Diagnostic phenotypic testing indicated (ie, biochemistry, imaging, etc)			x	x					x	x				
Medical management implications (eg, referrals, medication changes)			x	x					x	x				
Variant correlation with phenotype			x	x					x	x				
Longitudinal follow-up			x	x					x	x				
Disclosure process for SF			x	x					x	x				
Clinical utility of SF			x	x					x	x				

C-TX, Clinician Timepoint; Index, index case (SF-detected); MC, matched control (SF-negative); P-TX, patient timepoint; SF, secondary finding; S-TX, specialist timepoint.

electrical activity tests) and (5) variant correlation.[44] The ordering clinician questionnaire will ask about these elements of evaluation and medical management implications (eg, referrals, medication changes, activity restrictions), longitudinal follow-up and the disclosure process for SF. Ordering clinicians will also be asked to complete the SF module of the Clinician-reported Genetic testing Utility InDEx (C-GUIDE™), a validated tool for measuring the clinical utility of genetic testing, developed by our team.[45 46] This C-GUIDE module is designed to capture the clinical utility of SF as it relates to (1) referrals or investigations, (2) informing medical management, (3) awareness and actionability of reproductive and health risks for patients and family members and (4) psychosocial impact on patient and family. Clinicians complete C-GUIDE by reflecting on how specific genetic test results contribute to these dimensions of value after results are returned to patients and families.[45 46]

To capture if/how specialists are involved in follow-up care of patients with SF, specialists will complete the specialist questionnaire (S-T1). This questionnaire includes questions related to clinical evaluation and medical management in particular clinical areas (eg, oncology, cardiology). Ordering and specialist clinicians will also be asked to complete the clinician practice characteristics questionnaire (ie, years in practice, setting and geographic region) immediately after consenting.

Questionnaires will be tested by three ordering clinicians and three specialists for answerability, wording and comprehensiveness. Pilot participants will include clinicians who have managed medically actionable SF within the past year and will be drawn from the GSO clinician network. Pilot feedback will be collated to inform survey refinements.

Data collection

Questionnaires

Data will be collected prospectively over 2 years, beginning after SF are disclosed (figure 1). Index case participants/their parents will be asked to complete an online questionnaire administered by the study coordinator by phone or videoconferencing at baseline (P-T0), 6 months (P-T1), 12 months (P-T2), 18 months (P-T3) and 24 months (P-T4) following receipt of SF results. Matched negative controls (patients or a parent of a control patient) will be asked to complete the same questionnaire with skip patterns in place to avoid completion of non-applicable sections. Participants will receive reminders 1 month and 1 week prior to the scheduled data collection appointment. With consent, medical chart review will be used to support data collection efforts in cases where participants are unable to complete the questionnaire by phone or videoconferencing.

Ordering clinicians will be prompted by the study coordinator to complete the ordering clinician questionnaire within 1 week of their index patient consenting to the study and within 1 month of disclosing a SF result (C-T1). They will be prompted to complete a modified version of the ordering clinician questionnaire after 1 year (C-T2) if the patient/parent has not been discharged from the ordering clinician's care. Index case participants/their parents will be asked to notify the study coordinator about appointment dates/times with specialists in advance. Specialists will then be prompted by the study coordinator to complete the specialist questionnaire (S-T1) after the first consultation with the index patient or family member has occurred (ie, 3–6 months following the disclosure of a SF). Specialists will be prompted to complete modified versions of the specialist questionnaire 1 year later (S-T2) if the patient/parent has not been discharged from their care. Clinicians will complete questionnaires online via REDCap. Each clinician questionnaire will take ~10 mins to complete.

Interviews

For the qualitative interviews, verbal consent will be obtained prior to participation, and permission will be obtained to audio-record and transcribe the interview. The semistructured interview guide was developed by the study team and informed by the literature, including a scoping review by our team on the personal utility of genetic testing.[47–50] As such, the interview guide includes dimensions related to the cognitive, affective, behavioural, social, ethical and medical management impacts of SF.[49] It will elicit perspectives from participants on controversial questions related to identifying and reporting SF in children and equity in access to SF for those who receive genomic testing for diagnostic purposes and those who do not. The interview guide will be adapted to respondent types (ie, parents of minors, adult patients) and pilot-tested with three eligible participants to ensure clarity and breadth of questions. Interviews will be conducted either by telephone or videoconference, according to the participant's preference.

Since proficiency in English is not a requirement for study inclusion, interpreter services will be used to facilitate informed consent and data collection (ie, questionnaire or qualitative interview) from individuals who are not comfortable completing data collection in English. We anticipate that interpreter services will be required for ~10% of participants enrolled.

Data analysis

Primary and secondary outcomes

Healthcare use

The methods and analysis plan for comparison of health service use between cases and controls and assessment of the cost-effectiveness of returning SF has been previously described by Ungar *et al*.[51]

Personal utility

For index cases and family members who receive SF, we will report personal utility PrU scores. We will examine the relationship between personal utility scores and case characteristics such as patient age, sex at birth and medically actionable gene implicated, using parametric

Box 1 Risk assessment and medical management plan analysis

Data will be analysed to determine:

⇒ Number and proportion of SF and IF disclosed, by which clinician type and modality and the number of encounters required.

⇒ Number and proportion of cases for whom a clinical evaluation of disease risk was performed (ie, including five specific components of evaluation) and the distribution of specialist type.[44]

⇒ Volume and distribution of types of phenotypic investigations indicated and the distribution of clinician types who ordered and/or assessed them.

⇒ Number and proportion of cases for whom clinical evaluation detected the presence of a previously known or new clinical diagnosis or disease risk.

⇒ Number and proportion of cases for whom cascade family testing was ordered and medical management activities were triggered.

⇒ Number and proportion of cases for whom longer-term management was recommended for risk mitigation and the distribution of clinician type.

or non-parametric statistics as appropriate. If possible, we will explore whether clinically important variables as well as the impact of SF result disclosure (captured via MICRA) are associated with higher or lower PrU scores using multilinear regression.[40 43] We will also explore whether there is a correlation between utility scores provided by clinicians (via C-GUIDE) and patients/parents (via PrU).[40 45 46]

Clinical utility

The C-GUIDE SF module will be scored, and mean standardised scores associated with relevant case characteristics, such as patient age, sex at birth and type of gene implicated (ie, secondary or incidental finding) will be calculated.[45 46] The relationship between case characteristics and C-GUIDE scores will be examined using parametric or non-parametric statistics as appropriate. If possible, we will explore whether specific clinical variables are significantly associated with higher C-GUIDE scores using multilinear regression. For example, we anticipate C-GUIDE scores to be higher when the age of the case is closer to the age for which medical actionability is recommended.

Risk assessment and medical management plan

For index cases and family members who receive a SF result, data will be analysed separately for SF and incidental findings (IF) using descriptive statistics (box 1). Where possible, we will perform subgroup comparisons based on patient age, sex and the medically actionable gene implicated using parametric or non-parametric statistical tests.

Qualitative data

The qualitative interview transcripts will be analysed using a mixed deductive and inductive approach. First, the transcripts will be deductively coded for the presence or absence of each aforementioned domain of personal utility, as defined by Kohler *et al* and Hayeems *et al*.[48–50] Sensitising concepts related to ethical principles of beneficence, best interests and equity will be integrated into the thematic analysis. Salient themes that emerge inductively will be included. Two members of the study team will code all transcripts using NVivo 15.[52] Coding discrepancies will be resolved through discussion between the two primary coders or by consulting a third member of the team. Related codes will be grouped into themes, and relationships among themes will be articulated to convey a rich description of the utility of medically actionable SF from the perspectives of patients and parents.

Data integration

The quantitative and qualitative findings will be integrated to generate a comprehensive understanding of both clinical and experiential outcomes. Integration will occur at the interpretation stage, where findings will be triangulated across data sources to identify areas of convergence and divergence. This approach will allow us to contextualise quantitative trends with narrative insights, enhancing our understanding of how SF influence clinical care and the lived experiences of patients and families.

Data management

With site-specific support, data will be collected and managed centrally by the study coordinator at SickKids. Consenting study participants will be assigned a unique study identification number at baseline. A separate participant log will be maintained that includes participant contact information to schedule repeat assessments. Data will be kept confidential by maintaining questionnaires in a locked location and electronic data on a password-protected cloud-based research electronic database (REDCap). REDCap will be programmed to enhance data quality by preventing illogical entries (eg, fixed date format and fixed allowable ranges). Only team members will have access to data files.

ETHICS AND DISSEMINATION

This study is approved by the Clinical Trials Ontario (CTO) Research Ethics Review System (REB# CTO 3655), a harmonised research ethics board for the province of Ontario, to enable recruitment and data collection from all 14 GSO sites. We will leverage our established research partnerships with (1) investigators and faculty members involved with evaluating and implementing genomic testing in Ontario; (2) knowledge users and decision-makers involved in shaping policy for genomic technologies and (3) patient partners and their respective advocacy networks who are invested in optimising patient access to high-quality genome diagnostics (eg, Canadian Organisation for Rare Disorders, Rare Disease Foundation). Results will be presented to academic, patient, clinician and decision-maker audiences through lay results summaries, peer-reviewed journal articles and

presentations at provincial, national and international academic meetings.

SIGNIFICANCE

We anticipate this study will generate novel evidence related to the patient, family and health system impact of medically actionable SF generated from clinical-grade genomic testing. This study is also novel in its emphasis on the impact of SF in a predominantly Canadian paediatric population. Evidence generated from this work will lead to further refinement of the assessment of clinical and personal utility of SF. Findings from this work can inform policy and practice decisions related to the allocation and responsible use of new genomic technologies in research and clinical care both nationally and internationally.

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