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GT4BD (genomic testing for bleeding disorders): a protocol for a randomized controlled trial evaluating the introduction of whole genome sequencing early in the diagnostic pathway for inherited bleeding disorders patients as compared to standard of care

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Note: The following files were submitted by the author for peer review, but cannot be converted to PDF. You must view these files (e.g. movies) online.	
Appendix A- Gene List.xml	

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Title: GT4BD (genomic testing for bleeding disorders): a protocol for a randomized controlled trial evaluating the introduction of whole genome sequencing early in the diagnostic pathway for inherited bleeding disorders patients as compared to standard of care

ABSTRACT

Introduction: The current diagnostic pathway for patients with a suspected inherited bleeding disorder is long, costly, resource intensive, emotionally draining for patients, and often futile as half of patients will remain without a diagnosis and be labelled "Bleeding Disorder of Unknown Cause" (BDUC). Advances in understanding the genetic basis of the inherited bleeding disorders, coupled with both increasing infrastructure for genetic/genomic testing and decreasing costs, have increased the feasibility of introducing genomic testing into the clinical diagnostic pathway as a potential solution to improve the care of these patients. Yet there remain evidence gaps on the optimal integration of genomic analysis into the diagnostic pathway.

Methods and analysis: Using a multicentre randomized-controlled trial design, we will evaluate an early genomic testing strategy for the diagnosis of newly referred patients with a suspected inherited bleeding disorder. Clinical utility will be evaluated via the primary outcome of diagnostic yield, as well as the secondary outcome of time to diagnosis. Additional outcomes will allow for assessment of patient impact via Health-Related Quality of Life (HRQOL) and patient burden measures, as well as evaluation of economic impact through a cost-effectiveness analysis and budget impact analysis.

Ethics and dissemination: This protocol was approved by Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board through Clinical Trials Ontario (CTO-4909). Findings will be disseminated through academic publications.

Registration details: This project is registered at ClinicalTrials.gov under the title "Early Genomic Testing for Inherited Bleeding Disorders (GT4BD)" registration number NCT06736158. It is supported by a Canadian Institute of Health Research (CIHR) Team Grant (RDP-193724).

STRENGTHS AND LIMITATIONS OF THIS STUDY

- A major strength of this study lies in being the first randomized-controlled trial evaluating the introduction of genomic testing into the diagnostic algorithm for inherited bleeding disorders.
- The high-quality evidence generated from this study design carried out in a real-world setting of 3 tertiary care centres will provide invaluable insight into the optimal integration of this technology into hospitals/clinics and healthcare systems.
- The diverse set of secondary outcome measures will allow for thorough assessment of the clinical, patient, and economic impact.
- The multi-disciplinary research team approach brings together experts from many disciplines to provide a thorough evaluation (i.e. hematology, genetics, health economics, statistics, nursing, laboratory testing).
- A major limitation is the high likelihood of finding non-diagnostic variants of uncertain significance (VUS).

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INTRODUCTION

Inherited bleeding disorders are characterized by a defect along the hemostatic response pathway that results in abnormal bleeding symptoms, ranging from mild nuisance bleeding to life threatening hemorrhage. The challenges of diagnosing these rare disorders include issues of symptom dismissal as well as difficulties inherent to current specialized coagulation testing strategy.[1 2] The diagnostic pathway begins with a detailed family history and clinical assessment, including obtaining a comprehensive bleeding history via a standardized bleeding assessment tool (BAT).[3-5] Use of a BAT results in a numeric bleeding score, classifiable as normal or abnormal with score magnitude reflecting bleeding severity. For patients suspected to have an inherited bleeding disorder (i.e., abnormal bleeding history and/or family history of bleeding), the diagnostic pathway then continues to a sequential series of specialized coagulation tests.[6]

First-line testing will effectively diagnose approximately 30% of new referrals, skewed towards identification of von Willebrand Disease (VWD) and Hemophilia A/B as opposed to the other rare inherited bleeding disorders.[7] For the remaining 70% of referrals, subsequent rounds of coagulation and platelet function testing aim to identify platelet function disorders (PFD), rare factor deficiencies, and fibrinolytic disorders, however tests are nonspecific, have low sensitivity, and low overall yield and do not evaluate the vascular component of the hemostatic response.[6] All coagulation testing must be done in specialized coagulation laboratories, only found in large urban areas and not easily accessible by much of the population.[8] Moreover, coagulation tests are variably affected by pre-analytical factors (e.g. transport time, maintenance of the cold chain, physiologic stress, hormones) necessitating repetitive testing for validation of results.[9 10] Other patients will not be able to proceed to further testing due to factors such as medication use or pregnancy which interferes with diagnostic accuracy and validity.[10] For example, antidepressant SSRIs (selective serotonin reuptake-inhibitors) interfere with platelet function, thus patients taking these medications will be unable to complete the full diagnostic work-up which includes platelet function testing, without a prolonged withdrawal of medically necessary therapy.

From the patient's perspective, the burden of this diagnostic delay is significant as it includes multiple hospital visits, repeated venipunctures, days off work/school, travel and childcare costs, worry and uncertainty.[1] It also includes years of living with untreated bleeding symptoms, including mucocutaneous bleeding (e.g., epistaxis and oral cavity bleeding after dental procedures), prolonged bleeding after minor injuries or surgical procedures, and gynecological bleeding (e.g., heavy menstrual bleeding (HMB), postpartum hemorrhage)[11]. The associated negative consequences include diminished health-related quality of life (HRQOL), work/school absenteeism, social isolation, and excessive health-related costs.[11-14] Furthermore, absence of a definitive diagnosis limits the delivery or effective treatment. These negative effects are documented for patients with bleeding disorders across all severities, including bleeding disorder of unknown cause (BDUC).[14 15]

The current reported time from symptom onset to diagnosis of an inherited bleeding disorder ranges from 7-12 years for the 30% of patients that achieve a first-line diagnosis and even longer for patients that need second- and third-line testing.[1] Thus, the resultant diagnostic odyssey ends up being lengthy, costly, resource intensive, emotionally draining for patients and often futile, as up to half of patients will remain without a final diagnosis, despite a clear propensity to bleed.[2 16] Approximately 50% of referrals end up with no definitive diagnosis and are classified as BDUC, defined as those with a positive bleeding score but in whom all current diagnostic test results are repeatedly normal.[16] Managing bleeding complications in BDUC

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patients is challenging as the specific bleeding etiology is not known, and these patients have been shown to continue to experience major bleeding symptoms such as post-partum hemorrhage despite attempts at non-specific hemostatic interventions (e.g., tranexamic acid).[17]

Advances in understanding the genetic basis of the inherited bleeding disorders, coupled with both increasing infrastructure for genetic/genomic testing and decreasing costs, have increased the feasibility of introducing genomic testing into the clinical diagnostic pathway as a remedy for these diagnostic challenges.[18] Yet a major challenge for optimizing integration is the wide variety of diagnostic yields reported, ranging from 10-94% depending on differences in study design (i.e., prospective vs retrospective), inclusion criteria (i.e., single condition studies vs. all bleeding and coagulation disorders), the sequencing method used (panel vs. whole exome sequences (WES) vs. whole genome sequencing (WGS)), the number of genes assessed (i.e. older studies have smaller numbers of genes assessed), and ways of reporting data (i.e., only pathogenic variants vs both pathogenic and likely pathogenic variants). In a recent review paper, overall diagnostic yields were summarized as 95% for patients with clearly defined disorders on laboratory testing, between 50-70% for patients with less well-defined disorders on laboratory testing but well-characterized phenotypically, and between 20-50% for those with poorly defined disorders.[19]

The observed variation in diagnostic yields raises questions of who should receive genetic analysis, which tests should be offered, and at what point in the diagnostic pathway they should be deployed.[20] The integration of genetic/genomic testing into diagnostic pathways for inherited bleeding disorders varies across countries with many outstanding questions of optimization. Real-world clinical studies are needed to produce data to determine the optimal integration of genomic analysis into clinical diagnostic pathways, including evaluations of cost-effectiveness and patient impact.

AIMS AND HYPOTHESES

To evaluate an early genomic testing diagnostic pathway compared with usual care for patients with suspected inherited bleeding disorders along three domains.

1. Clinical Utility: evaluation of the primary outcome diagnostic yield (the proportion of patients who achieve a diagnosis at one year), as well as time to diagnosis (time in days from initial appointment to diagnosis disclosure). ***We hypothesize our intervention group will have a higher diagnostic yield and a shorter time to diagnosis.***
2. Economic Impact: measured by via cost-effectiveness analysis and a budget impact analysis. ***We hypothesize the relatively higher cost of genomic testing will be offset by savings related to fewer medical appointments/diagnostic tests.***
3. Patient impact: evaluation of HRQOL and patient burden outcomes. ***We hypothesize that our intervention group will show a decreased patient burden and improved HRQOL related to less diagnostic uncertainty and improvement in symptom management.***

METHODS

Study design and setting

We will conduct a multi-centre randomized controlled trial (RCT) where patients who do not achieve a first-line diagnosis with standard coagulation test screening will be randomized to Early Genomic Testing Diagnostic Pathway (intervention) or Standard Diagnostic Pathway (control) (Figure 1). Patients in the control group who remain undiagnosed at study end (12-months) will then be offered identical early genomic testing to ensure equitable access to the

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intervention. The study will follow a parallel fixed design with waitlist control group and a 1:1 allocation ratio.

Participants will be recruited from hematology clinics at three tertiary care centres in Ontario with established Inherited Bleeding Disorder Programs: Kingston Health Sciences Centre (KHSC), St. Michael's Hospital (SMH) and The Ottawa Hospital (TOH).

Eligibility criteria

Inclusion: 1) new patient referral for abnormal bleeding*;* 2) age of 12 years and older; 3a) hemostasis expert clinician determined abnormal bleeding history AND family history of bleeding OR 3b) no family history of bleeding but hemostasis expert clinician determined severe bleeding history

Exclusion: 1) prior diagnosis of an inherited bleeding disorder; 2) acquired cause of bleeding (i.e., medication known to cause bleeding, significant renal or hepatic disease).

Recruitment and data collection

At their initial appointment, eligible participants will meet with a Research Assistant at their initial appointment who will provide them with study information and complete the informed consent process. All consenting participants will complete baseline measures prior to randomization via RedCAP including: patient baseline questionnaire, Self-BAT (Self-Administered Bleeding Assessment Tool) and HRQOL measures (Table 1). Participants will proceed to first-line testing as determined by their treating hematologist. Participants who receive a diagnosis with first-line testing will not be eligible for randomization. All remaining patients will be randomized to intervention (early genomic testing) or control (usual care) (Figure 1). A complete, concealed block randomization schedule stratified by site[21] was created by an independent researcher and uploaded to REDCap. Both participants and researchers will be unblinded to randomization result and be made aware of group allocation.

Participants will be followed for 12 months from date of initial consultation and consent. The end of this 12-month period will be the second time point for data collection. Additional items including health resource utilization data will be collected from participant medical records (Table 1). Follow-up information will be collected directly from participants at the 12-month time point via REDCap including: the same HRQOL measures done at baseline and the P-Guide questionnaire about their experience with genetic testing.

Table 1: Summary of study measures with source and data collection time point

Measure	Items	Source	Baseline	12-months
Patient Baseline Questionnaire	Demographics (age, sex, gender, ethnicity, forward sortation index)	Participant	X	
	Bleeding History (duration of symptoms, previous treatment, history of iron deficiency)	Participant	X	
	Patient burden (travel time to appointment, associated travel costs)	Participant	X	
Case Report Form	Reason for referral	Medical chart	X	
	Medications	Medical chart	X	
	Comorbidities	Medical chart	X	

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	Relevant obstetrical history (pregnant, postpartum, breastfeeding/pumping)	Medical chart	X	
	Transfusion history, red cell alloimmunization	Medical chart		X
	Testing timeline (date of initial appointment, date of first-line results, date of genetic results, date of diagnosis etc.)	Medical chart		X
	Diagnostic tests (including type of test, number of times completed, results)	Medical chart		X
	Number of appointments for diagnostic purposes	Medical chart		X
	Number of blood draws for diagnostic purposes	Medical chart		X
	Genomic testing (details, results, implications for medical/surgical management)	Medical chart		X
	Final diagnosis (complete, partial, uncertain, no diagnosis)	Medical chart		X
Bleeding Assessment Tool	Self-BAT (ref)	Participant	X	
HRQOL	PROMIS Profile CAT v1.0-29 (for participants 18+ years)	Participant	X	X
	PROMIS Ped Profile GenPop v3.0- Profile 25 (for participants 12-17 years	Participant	X	X
	Menstrual Bleeding Questionnaire (for participants 18+ years who menstruate)	Participant	X	X
	Adolescent Menstrual Bleeding Questionnaire (for participants 12-17 years who menstruate)	Participant	X	X
Patient Follow-Up Questionnaire	P-Guide: Patient-reported Genetic testing Utility InDEx (ref)	Participant		X

Sample Size

The sample size of 74 per arm was based on the following assumptions. It is anticipated that of the patients who proceed to randomization (no first-line diagnosis), 30% of patients in the control group will receive a diagnosis within 1 year of enrolment.[16] It is predicted that the addition of genomic testing in the intervention pathway will increase the proportion diagnosed within 1 year to 50%.[22] Since the intervention group also receives the same non-genetic laboratory investigations as the control group, it is plausibly inconceivable that a lower diagnostic yield would be seen in the control group. Patients who drop out of the study or are lost to follow-up prior to receiving a diagnosis will be treated as not receiving a diagnosis. Therefore, we are using a one-sided Type I error of 5%. Given these assumptions, in order to achieve 80% power to detect a 20% improvement in diagnostic yield, a sample size of 74 per group is needed.

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The total aim is to recruit 212 patients over 1 year, 148 of whom we predict will not achieve a first-line diagnosis and will proceed to randomization (n=74 for each study arm). Recruiting 212 participants per year is feasible given that approximately 300-350 eligible patients are seen annually at the three sites.

Intervention

The early genomic testing diagnostic pathway (intervention) is outlined in Figure 2.

Optional secondary findings:

All participants will have virtual pre-test genetic counselling with a certified Genetic Counsellor. After reviewing the benefits, limitations, and potential outcomes of testing, participants will declare if they would like their results to be analyzed for variants in the list of medically actionable secondary findings maintained by the American College of Medical Genetics and Genomics (ACMG). Secondary findings are purposely analyzed but unrelated to primary testing indication. The current recommendation of the ACMG is that any time a person is receiving WGS, they should be offered the opportunity to have secondary findings also assessed.[23] At the end of the genetic counselling session, participants who wish to opt-in to secondary findings will complete a separate consent form through REDCap.

Genomic testing approach:

Each sample will undergo WGS as the foundation for analysis. Not all of the data produced will be looked at, as analysis will focus only on identifying genetic variants possibly contributing to a bleeding disorder. A 'virtual gene panel' will be used comprising the most up to date list of genes known to be associated with bleeding, coagulation, platelet, connective and vascular disorders (Appendix A). The virtual panel comprises the International Society of Thrombosis and Haemostasis (ISTH) TIER-1 and TIER-2 gene list, as well as other genes identified in related scientific publications.[24 25] The virtual gene panel will be updated annually, following publication of the updated ISTH gene lists.

Any variants identified through examination of this panel will be evaluated by variant effect predictor analysis, *in silico* determination of effects on the phenotype, population frequency data, and evidence from previously reported variants. The assignment of pathogenicity likelihood using the five classifications recommended by the ACMG[26] will be determined using Varsome.[27] If a (likely) pathogenic variant is identified, the significance of the variant will be further considered in terms of its pathobiological plausibility and alignment with the bleeding phenotype. Collectively, where a pathogenic variant is found in the virtual gene panel that also meets the additional requirements detailed above, this will be regarded as the cause of the inherited bleeding condition.

When examination of the virtual gene panel proves negative, additional genomic analysis may be done as needed. This may include: (1) Review of additional variants: a review of other variants in the remaining genes; (2) Evaluation of copy number variants through NGS read depth; (3) Family segregation studies: In cases where other affected family members are accessible and permission of the primary participant has been obtained, consistent segregation of the variant with the bleeding phenotype may also be evaluated. Family members will be consented separately and asked to provide a biological sample (e.g., blood, saliva or cheek swab); (4) Epigenetic changes: This analysis allows us to look for changes in the pattern of how genes are turned on and turned off, referred to as “epigenetic regulation”.

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Sequencing and basic analysis will be done at The Centre for Applied Genomics (TCAG) at the Hospital for Sick Children in Toronto, Ontario. Subsequent analysis will be done at Queen's University by Team Members affiliated with the NIBDGL. All patients who undergo genomic testing will be reviewed at a monthly multidisciplinary team meeting, comprising expert Clinicians, Medical and Molecular Geneticists, a Genetic Counsellor, and Laboratory experts. Results of genomic testing will be reviewed along with results of any simultaneously conducted laboratory diagnostic testing, to determine if a confirmed diagnosis can be made. A final genetic report will be issued detailing all genetic findings, primary as well as incidental findings that were opted-in to by the participant. All participants with clinically significant variants or variants of uncertain significance (VUS) will then have an individual appointment with a certified Genetic Counsellor for results disclosure and genetic counselling. Referral to Medical Genetics will also be done for clinical confirmation of research findings and arranging of any necessary clinical management. Disclosure of any bleeding disorder diagnosis and the recommended management will be provided by the treating Clinician.

Control

Participants randomized to the control group will receive usual care as per the standard at each institution as determined by the treating hematologist. Final group classification (i.e. complete/partial diagnosis vs. uncertain/no diagnosis) will be done by the treating Clinician and confirmed by a second independent expert-Clinician. After they have completed the study, patients in the control group will be offered identical early genomic testing, with the same pre-test and post-test counselling as described above.

OUTCOMES AND ANALYSIS

1. Clinical utility

The primary outcome used to power the study is diagnostic yield, defined as the proportion of patients who achieve a complete or partial diagnosis at one year. Patients who drop out of the study or are lost to follow-up prior to receiving a diagnosis will be treated as not receiving a diagnosis. Therefore, there will be no missing data for the primary outcome. A secondary outcome will be the time to diagnosis, defined as the time in days from initial appointment with Hematologist to patient disclosure of final diagnosis disclosure.

The primary outcome will be compared between groups using a one-sided Z-test comparing the proportions receiving diagnoses in each arm. The treatment effect will be reported as the absolute risk difference with a 95% confidence interval. The secondary outcome of time to diagnosis will be analyzed using time-to-event methods. Kaplan-Meier curves will be constructed and a proportional hazards model or suitable parametric model (e.g., if proportional hazard assumption is not reasonable) will be used to estimate the treatment effect.

Additionally, variables such as age, sex, symptoms, and bleeding score will be explored as potential treatment effect modifiers (i.e. sub-group effects) on the primary outcome by modeling the relevant interactions in logistic regression models.

2. Economic impact:

An economic evaluation will be carried out alongside the RCT to evaluate the cost-effectiveness and budget impact analysis of the intervention. We estimate the intervention will be cost-effective due to an increased number of cases detected, and the higher cost of genomic testing offset due to reductions in number of clinic visits and overall diagnostic tests with associated

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cost savings. Budget impact analysis conducted over 5 years will allow for estimation of the cost of implementing the new diagnostic strategy in Ontario.

Cost-effectiveness analysis

The cost-effectiveness analysis will be conducted from both the healthcare system (i.e., the Ontario Ministry of Health) and the societal perspective (i.e. all costs and benefits regardless of who pays and who benefits). Guidelines for economic evaluations of genetic and genomic testing state that the perspective should be defined by who is the decision maker, which in the case of this proposal would be the Ontario Ministry of Health who is the public payer for healthcare in this province.[28] However we also included the societal perspective as the same guidelines acknowledge that a value judgement can be made to consider including costs outside the healthcare sector, such as those borne by patients.[28] As discussed above, coagulation testing can only be completed in specialized laboratories found in large urban areas and not easily accessible by much of the population.[8] Patients are required to travel long distances to reach these specialized medical centers at their own expense, a process that must be repeated with each round of testing. Thus, in order to capture this eventuality, a societal perspective was added which includes all costs and benefits associated with the diagnostic pathway regardless of who pays and benefits.

The time frame of the cost-effectiveness analysis will be January 2025-December 2026 and participants will be followed for the 12-month time period. All costs and benefits will be reported in 2026 CAD using inflation adjustment as per CPI Canada.[29] The primary outcome will be number of cases detected which is the most commonly used outcome in economic evaluations of genomic testing technology as a diagnostic tool.[30-32] The main outcome of this analytic technique will be average cost per case detected of the intervention pathway versus the control pathway, expressed as the mean with 95% confidence interval. Incremental cost per additional case detected will also be calculated and expressed similarly.

Outcome data will be captured through a case report form completed by research staff at each hospital at the end of the 12-month study period for each participant. Costs will be calculated prospectively based on resource utilization related to diagnosis for each participant in the 12-month period. Costs associated with these resources will be accessed from the service provider in the case of genomic testing (TCAG), hospital decision support and financial services at KHSC, and the Ontario Ministry of Health Lab Services Fees. Micro-costing techniques may also be done as needed. Units of resource will be multiplied by price per unit. Indirect costs will be gathered from patient surveys where participants will answer questions about the time spent travelling to their appointment, whether they organized childcare and eldercare (and if yes how much they paid), whether they took paid or unpaid time off work etc. The total patient cost of attending an appointment will be calculated per patient and then multiplied by the number of appointments attended as part of their diagnostic pathway. As this is a diagnostic study, we will not be looking at medical care costs outside of those used for the purpose of diagnosis (i.e., clinic appointments and all testing including lab and genetic)

Uncertainty will be evaluated via one-way sensitivity analyses on key parameters including cost of genomic testing, number of cases detected, and savings due to averted clinic appointments, with additional sub-group analyses also conducted on key parameters.

Budget impact analysis

We will conduct a budget impact analysis from the Ontario Healthcare System perspective over 5 years similar to genomic testing programs for other conditions that have been evaluated by OHTAC (Ontario Health Technology Assessment Committee).[32] Standard budget impact

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analysis techniques will be used[33] to predict the future economic impact of genomic testing over five years from 2025-2030.

In this model-based analysis, the incremental cost of testing for both the control and intervention arm will be determined, which will allow for detailed analysis on the economic impact of inserting genomic testing at different time points along the diagnostic algorithm. This will account for the fact that by the second time point (one-year post initial consultation), some patients in the control arm will not have had sufficient time to complete the full diagnostic work-up and thus the full cost of their diagnostic journey will not be captured. This will provide further evidence of the feasibility and optimal timing of genomic testing. The same methods for prospective cost estimation delineated above will be employed excluding patient incurred costs, with similar sensitivity analyses conducted on key parameters.

3. Patient impact

The impact of the intervention on patients will be evaluated via generic HRQOL measures (i.e. PROMIS), symptom specific HRQOL (i.e. MBQ/aMBQ), and a patient-reported genetic testing utility measure (i.e. P-GUIDE). Additional patient burden indicators related to the diagnostic journey include total number of appointments for diagnosis, total number of blood draws, transfusion information, travel items (distance, mode, associated costs) and productivity loss questions (e.g. time spent away from work, wages lost, child/elder care costs).

The varied nature of these outcomes necessitates a variety of analytic methods for between arm comparisons. Models for count data (e.g., Poisson, negative binomial, etc.) will be used when deemed appropriate (i.e., number of appointments, number of blood draws). Rate ratios and 95% confidence intervals will express the intervention effect. Other analysis will involve simple comparisons of means (e.g., t-test or non-parametric equivalent) as needed. The intervention effect will be expressed as mean difference with 95% confidence interval (or another appropriate difference if t-test assumptions are problematic). HRQOL assessment at one year will be analyzed by linear regression, adjusted for the baseline value and the treatment effect will be the adjusted mean difference with 95% confidence interval.

Data management and monitoring

All data collection activities will be coordinated from KHSC. Participant recruitment, consent and usual care clinical visits will take place at participating hospitals (KHSC, SMH and TOH). Email contact information will be submitted by the participant into REDCap for 12-month follow-up data collection. Data from medical charts will be abstracted on site and entered into REDCap by the local research team. The study REDCap database is hosted by the Centre for Advanced Computing at Queen's University. Long-term storage of data from genome wide sequencing will be stored in the Care4Rare Canada Genomics4RD Research database.[34] The genome-wide sequencing data stored in Genomics4RD will be coded so that no directly identifying information of study participants will be associated with these dataset records.

There will be no interim analyses and no data safety monitoring board as we are conducting a diagnostic clinical trial only, not involving high risks nor diseases with high mortality of morbidity.

ETHICS AND DISEMMINATION:

This protocol was approved by Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board (HSREB) through Clinical Trials Ontario (CTO-

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4909), the provincial platform responsible for approving trials involving two or more academic of healthcare institutions.

Guidelines for incorporating genomic testing into diagnostic algorithms for patients with suspected inherited bleeding disorders, have been published and will be followed with clear recommendations surrounding informed consent, management of incidental findings and clinical interpretation of variants.[35 36] Although full consent for the study will be initially obtained, our study design which delays the opt-in choice until after the pre-test counselling with the certified Genetic Counsellor, serves to ensure full understanding of implications prior to declaring opt-in to secondary findings. Participants will also have post-test counselling and referral to a Medical Geneticist. For pediatric patients under the age of 18 years, families will provide consent with a separate assent collected from the patient. The final protocol has received ethical approval from the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board.

The results of this study will be communicated via traditional methods including conference presentations, published abstracts, and publication of peer-reviewed manuscripts. Additional knowledge translation activities will include presentation of results to key stakeholders including the Ontario Ministry of Health, the Association of Hemophilia Clinic Directors in Canada and the Canadian Association of Nurses in Hemophilia Care, for the incorporation of results into national diagnostic guidelines for the diagnosis of inherited bleeding disorders.

LIMITATIONS:

The major limitation of a genomic diagnostic strategy for inherited bleeding disorders is the high likelihood of finding non-diagnostic VUS. Our genomic testing approach which includes family segregation studies and phenotypic confirmation assays when needed, will partly address this limitation. However, it is important to reiterate that current diagnostic strategies result in non-diagnostic outcomes in up to 70% of the patients who are not diagnosed by first-line testing, thus a fairly high level of diagnostic uncertainty can be accommodated within the new pathway and still find significant improvement in diagnostic yield and time to diagnosis.

AUTHORS' CONTRIBUTIONS: PJ conceived the study. MCh, MB and PJ designed the protocol. MB, JG, AJ, KT, AG, MCo, JL, MS, DL, RK, AP, DG, AM, JC, and RD informed the design of the protocol. MCh drafted the manuscript. All other authors reviewed, revised and approval the final manuscript.

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COMPETING INTERESTS STATEMENT:

PJ receives research funding from Bayer and consultancy fees from Star/Vega Therapeutics, Band/Guardian Therapeutics, Roche and BioMarin. JL has received honoraria from CSL Behring, Novo Nordisk, and Bayer. RK has received honoraria/support from Bayer, Pfizer, Novo Nordisk, Sanofi, Takeda and Roche. MS receives research funding from Pfizer and Octapharma, and honoraria from Octapharma, Sobi, Werfen and Roche. DL receives research funding from Biomarin, CSL-Behring, and Octapharma, and consulting fees from Biomarin, CSL-Behring,

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Novo Nordisk, Pfizer and Sanofi. JC receives research funding from Canadian Blood Services and Octapharma. All other authors have no disclosures.

PATIENT AND PUBLIC INVOLVEMENT:
MCo is a patient representative and involved in the design of the study protocol.

PROVENANCE AND PEER REVIEW:
Not commissioned, peer reviewed for funding approval through CIHR and ethical approval through Queen's University HSREB and CTO prior to journal submission

FIGURE TITLE AND LEGENDS:
Figure 1: Trial Schematic
Legend: *First line coagulation laboratory testing includes: complete blood count; prothrombin; partial thromboplastin time; VWD testing and coagulation factor levels*

Figure 2: Early Genomic Testing Diagnostic Pathway
Legend: *MDT = multidisciplinary team; ACMG= American College of Medical Genetics; (L) PV = likely pathogenic or pathogenic variant (Class 4-5 ACMG); VUS = variant of uncertain significance (Class 3 ACMG); (L) BV = likely benign or benign variant (Class 1-2 ACMG)*

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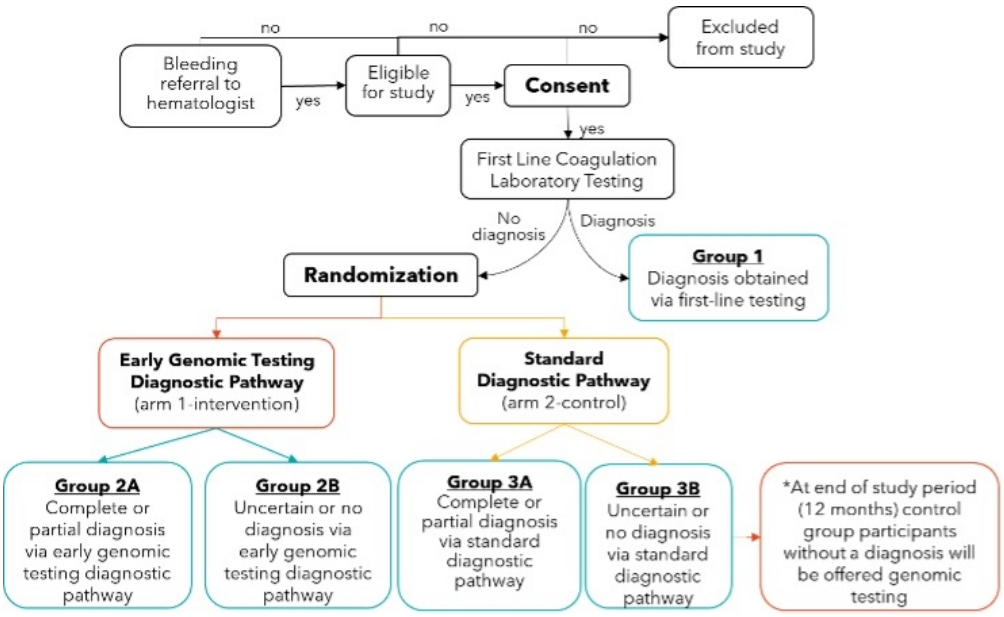

Figure 1: Trial Schematic
Legend: First line coagulation laboratory testing includes: complete blood count; prothrombin; partial thromboplastin time; VWD testing and coagulation factor levels

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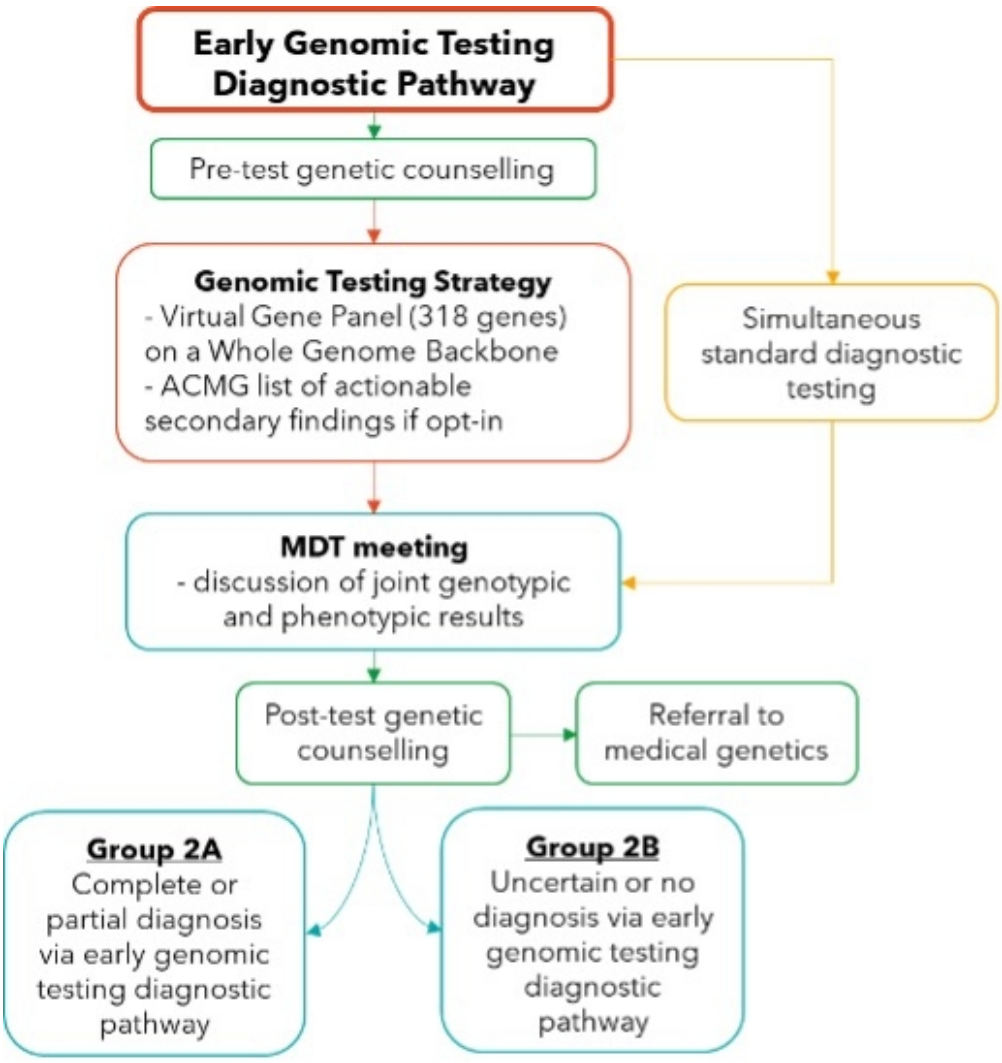

Figure 2: Early Genomic Testing Diagnostic Pathway
Legend: MDT = multidisciplinary team; ACMG= American College of Medical Genetics; (L) PV = likely pathogenic or pathogenic variant (Class 4-5 ACMG); VUS = variant of uncertain significance (Class 3 ACMG); (L) BV = likely benign or benign variant (Class 1-2 ACMG)

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BMJ Open

Genomic testing for bleeding disorders (GT4BD): protocol for a randomized controlled trial evaluating the introduction of whole genome sequencing early in the diagnostic pathway for patients with inherited bleeding disorders as compared to standard of care

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Primary Subject Heading:	Haematology (incl blood transfusion)
Secondary Subject Heading:	Haematology (incl blood transfusion), Genetics and genomics
Keywords:	Bleeding disorders & coagulopathies < HAEMATOLOGY, Genomic Medicine, Clinical Trial

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Appendix A- Gene List.xml

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Manuscripts

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Genomic testing for bleeding disorders (GT4BD): protocol for a randomized controlled trial evaluating the introduction of whole genome sequencing early in the diagnostic pathway for patients with inherited bleeding disorders as compared to standard of care

ABSTRACT

Introduction: The current diagnostic pathway for patients with a suspected inherited bleeding disorder is long, costly, resource intensive, emotionally draining for patients, and often futile as half of patients will remain without a diagnosis and be labelled "Bleeding Disorder of Unknown Cause" (BDUC). Advances in understanding the genetic basis of the inherited bleeding disorders, coupled with both increasing infrastructure for genetic/genomic testing and decreasing costs, have increased the feasibility of introducing genomic testing into the clinical diagnostic pathway as a potential solution to improve the care of these patients. Yet there remain evidence gaps on the optimal integration of genomic analysis into the diagnostic pathway.

Methods and analysis: Using a multicentre randomized-controlled trial design, we will evaluate an early genomic testing strategy for the diagnosis of newly referred patients with a suspected inherited bleeding disorder. Eligible participants will be randomized to Early Genomic Testing Diagnostic Pathway (intervention) or Standard Diagnostic Pathway (control) and will be followed for a 12-month period. Patients in the control group who remain undiagnosed at study end will be offered identical early genomic testing to ensure equitable access to the intervention. The study will follow a parallel fixed design with waitlist control group and a 1:1 allocation ratio. The study will be conducted at three tertiary care centres in Ontario, Canada with a target sample size of 212 participants. Clinical utility will be evaluated via the primary outcome of diagnostic yield, as well as the secondary outcome of time to diagnosis. Additional secondary outcomes will allow for assessment of patient impact via Health-Related Quality of Life (HRQOL) and patient burden measures, as well as evaluation of economic impact through a cost-effectiveness analysis and budget impact analysis.

Ethics and dissemination: This investigator-initiated study was approved by Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board through Clinical Trials Ontario (CTO-4909). Participant informed consent/assent is required. Findings will be disseminated through academic publications.

Trial registration: ClinicalTrials.gov, NCT06736158.

Protocol version: 3.0 (February 7, 2025).

STRENGTHS AND LIMITATIONS OF THIS STUDY

- A major strength of this study lies in the randomized-controlled trial design which will allow for a rigorous evaluating the introduction of genomic testing into the diagnostic algorithm for inherited bleeding disorders.
- The high-quality evidence generated from this study design carried out in a real-world setting of 3 tertiary care centres will provide invaluable insight into the optimal integration of this technology into hospitals/clinics and healthcare systems.
- The diverse set of secondary outcome measures will allow for thorough assessment of the clinical, patient, and economic impact.
- The multi-disciplinary research team approach brings together experts from many disciplines to provide a thorough evaluation (i.e. hematology, genetics, health economics, statistics, nursing, laboratory testing).

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- A major limitation is the high likelihood of finding non-diagnostic variants of uncertain significance (VUS).

INTRODUCTION

Inherited bleeding disorders are characterized by a defect along the hemostatic response pathway that results in abnormal bleeding symptoms, ranging from mild nuisance bleeding to life threatening hemorrhage. The challenges of diagnosing these rare disorders include issues of symptom dismissal as well as difficulties inherent to current specialized coagulation testing strategy.[1 2] The diagnostic pathway begins with a detailed family history and clinical assessment, including obtaining a comprehensive bleeding history via a standardized bleeding assessment tool (BAT).[3-5] Use of a BAT results in a numeric bleeding score, classifiable as normal or abnormal with score magnitude reflecting bleeding severity. For patients suspected to have an inherited bleeding disorder (i.e., abnormal bleeding history and/or family history of bleeding), the diagnostic pathway then continues to a sequential series of specialized coagulation tests.[6]

First-line testing will effectively diagnose approximately 30% of new referrals, skewed towards identification of von Willebrand Disease (VWD) and Hemophilia A/B as opposed to the other rare inherited bleeding disorders.[7] For the remaining 70% of referrals, subsequent rounds of coagulation and platelet function testing aim to identify platelet function disorders (PFD), rare factor deficiencies, and fibrinolytic disorders, however tests are nonspecific, have low sensitivity, and low overall yield and do not evaluate the vascular component of the hemostatic response.[6] All coagulation testing must be done in specialized coagulation laboratories, only found in large urban areas and not easily accessible by much of the population.[8] Moreover, coagulation tests are variably affected by pre-analytical factors (e.g. transport time, maintenance of the cold chain, physiologic stress, hormones) necessitating repetitive testing for validation of results.[9 10] Other patients will not be able to proceed to further testing due to factors such as medication use or pregnancy which interferes with diagnostic accuracy and validity.[10] For example, antidepressant SSRIs (selective serotonin reuptake-inhibitors) interfere with platelet function, thus patients taking these medications will be unable to complete the full diagnostic work-up which includes platelet function testing, without a prolonged withdrawal of medically necessary therapy.

From the patient's perspective, the burden of this diagnostic delay is significant as it includes multiple hospital visits, repeated venipunctures, days off work/school, travel and childcare costs, worry and uncertainty.[1] It also includes years of living with untreated bleeding symptoms, including mucocutaneous bleeding (e.g., epistaxis and oral cavity bleeding after dental procedures), prolonged bleeding after minor injuries or surgical procedures, and gynecological bleeding (e.g., heavy menstrual bleeding (HMB), postpartum hemorrhage)[11]. The associated negative consequences include diminished health-related quality of life (HRQOL), work/school absenteeism, social isolation, and excessive health-related costs.[11-14] Furthermore, absence of a definitive diagnosis limits the delivery or effective treatment. These negative effects are documented for patients with bleeding disorders across all severities, including bleeding disorder of unknown cause (BDUC).[14 15]

The current reported time from symptom onset to diagnosis of an inherited bleeding disorder ranges from 7-12 years for the 30% of patients that achieve a first-line diagnosis and even longer for patients that need second- and third-line testing.[1] Thus, the resultant diagnostic odyssey ends up being lengthy, costly, resource intensive, emotionally draining for patients and

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often futile, as up to half of patients will remain without a final diagnosis, despite a clear propensity to bleed.[2 16] Approximately 50% of referrals end up with no definitive diagnosis and are classified as BDUC, defined as those with a positive bleeding score but in whom all current diagnostic test results are repeatedly normal.[16] Managing bleeding complications in patients with BDUC is challenging as the specific bleeding etiology is not known, and these patients have been shown to continue to experience major bleeding symptoms such as post-partum hemorrhage despite attempts at non-specific hemostatic interventions (e.g., tranexamic acid).[17]

Advances in understanding the genetic basis of the inherited bleeding disorders, coupled with both increasing infrastructure for genetic/genomic testing and decreasing costs, have increased the feasibility of introducing genomic testing into the clinical diagnostic pathway as a remedy for these diagnostic challenges.[18] Yet a major challenge for optimizing integration is the wide variety of diagnostic yields reported, ranging from 10-94% depending on differences in study design (i.e., prospective vs retrospective), inclusion criteria (i.e., single condition studies vs. all bleeding and coagulation disorders), the sequencing method used (panel vs. whole exome sequences (WES) vs. whole genome sequencing (WGS)), the number of genes assessed (i.e. older studies have smaller numbers of genes assessed), and ways of reporting data (i.e., only pathogenic variants vs both pathogenic and likely pathogenic variants). In a recent review paper, overall diagnostic yields were summarized as 95% for patients with clearly defined disorders on laboratory testing, between 50-70% for patients with less well-defined disorders on laboratory testing but well-characterized phenotypically, and between 20-50% for those with poorly defined disorders.[19]

The observed variation in diagnostic yields raises questions of who should receive genetic analysis, which tests should be offered, and at what point in the diagnostic pathway they should be deployed.[20] The integration of genetic/genomic testing into diagnostic pathways for inherited bleeding disorders varies across countries with many outstanding questions of optimization. Real-world clinical studies are needed to produce data to determine the optimal integration of genomic analysis into clinical diagnostic pathways, including evaluations of cost-effectiveness and patient impact.

Aims and hypotheses

To evaluate an early genomic testing diagnostic pathway compared with usual care for patients with suspected inherited bleeding disorders along three domains.

1. Clinical Utility: evaluation of the primary outcome diagnostic yield (the proportion of patients who achieve a diagnosis at one year), as well as time to diagnosis (time in days from initial appointment to diagnosis disclosure). ***We hypothesize our intervention group will have a higher diagnostic yield and a shorter time to diagnosis.***
2. Economic Impact: measured by via cost-effectiveness analysis and a budget impact analysis. ***We hypothesize the relatively higher cost of genomic testing will be offset by savings related to fewer medical appointments/diagnostic tests.***
3. Patient impact: evaluation of HRQOL and patient burden outcomes. ***We hypothesize that our intervention group will show a decreased patient burden and improved HRQOL related to less diagnostic uncertainty and improvement in symptom management.***

METHODS AND ANALYSIS

Study design and setting

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We will conduct a multi-centre randomized controlled trial (RCT) where patients who do not achieve a first-line diagnosis with standard coagulation test screening will be randomized to Early Genomic Testing Diagnostic Pathway (intervention) or Standard Diagnostic Pathway (control) (Figure 1). Patients in the control group who remain undiagnosed at study end (12-months) will then be offered identical early genomic testing to ensure equitable access to the intervention. The study will follow a parallel fixed design with waitlist control group and a 1:1 allocation ratio.

Participants will be recruited from hematology clinics at three tertiary care centres in Ontario with established Inherited Bleeding Disorder Programs: Kingston Health Sciences Centre (KHSC), St. Michael's Hospital (SMH) and The Ottawa Hospital (TOH).

Eligibility criteria

Inclusion: 1) new patient referral for abnormal bleeding*;* 2) age of 12 years and older; 3a) hemostasis expert clinician determined abnormal bleeding history AND family history of bleeding OR 3b) no family history of bleeding but hemostasis expert clinician determined severe bleeding history.

Exclusion: 1) prior diagnosis of an inherited bleeding disorder; 2) acquired cause of bleeding (i.e., medication known to cause bleeding, significant renal or hepatic disease).

Recruitment and data collection

At their initial appointment, eligible participants will meet with a Research Assistant at their initial appointment who will provide them with study information and complete the informed consent process. All consenting participants will complete baseline measures prior to randomization via RedCAP including: patient baseline questionnaire, Self-BAT (Self-Administered Bleeding Assessment Tool) and HRQOL measures (Table 1). Participants will proceed to first-line testing as determined by their treating hematologist. Participants who receive a diagnosis with first-line testing will not be eligible for randomization. All remaining patients will be randomized to intervention (early genomic testing) or control (usual care) (Figure 1). A complete, concealed block randomization schedule stratified by site[21] was created by an independent researcher and uploaded to REDCap. Both participants and researchers will be unblinded to randomization result and be made aware of group allocation.

Participants will be followed for 12 months from date of initial consultation and consent. The end of this 12-month period will be the second time point for data collection. Additional items including health resource utilization data will be collected from participant medical records (Table 1). Follow-up information will be collected directly from participants at the 12-month time point via REDCap including: the same HRQOL measures done at baseline and the P-Guide questionnaire about their experience with genetic testing. Participants will be given a $25 CAD gift card as a thank you for completing the 12-month follow-up questionnaires.

The study is expected to open in April of 2025 with recruitment starting at that time. Participants can withdraw from the study at any time without having to provide a reason, without penalty. The study will only stop early if the sponsor decides or if the research ethics board withdraws permission for the study to continue.

Table 1. Summary of study measures with source and data collection time point

Measure	Items	Source	Baseline	12-months

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Patient Baseline Questionnaire	Demographics (age, sex, gender, ethnicity, forward sortation index)	Participant	X	
	Bleeding History (duration of symptoms, previous treatment, history of iron deficiency)	Participant	X	
	Patient burden (travel time to appointment, associated travel costs)	Participant	X	
Case Report Form	Reason for referral	Medical chart	X	
	Medications	Medical chart	X	
	Comorbidities	Medical chart	X	
	Relevant obstetrical history (pregnant, postpartum, breastfeeding/pumping)	Medical chart	X	
	Transfusion history, red cell alloimmunization	Medical chart		X
	Testing timeline (date of initial appointment, date of first-line results, date of genetic results, date of diagnosis etc.)	Medical chart		X
	Diagnostic tests (including type of test, number of times completed, results)	Medical chart		X
	Number of appointments for diagnostic purposes	Medical chart		X
	Number of blood draws for diagnostic purposes	Medical chart		X
	Genomic testing (details, results, implications for medical/surgical management)	Medical chart		X
	Final diagnosis (complete, partial, uncertain, no diagnosis)	Medical chart		X
Bleeding Assessment Tool	Self-BAT	Participant	X	
HRQOL	PROMIS Profile CAT v1.0-29 (for participants 18+ years)	Participant	X	X
	PROMIS Ped Profile GenPop v3.0- Profile 25 (for participants 12-17 years	Participant	X	X
	Menstrual Bleeding Questionnaire (for participants 18+ years who menstruate)	Participant	X	X
	Adolescent Menstrual Bleeding Questionnaire (for participants 12-17 years who menstruate)	Participant	X	X
Patient Follow-Up Questionnaire	P-Guide: Patient-reported Genetic testing Utility InDEx	Participant		X

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Sample size

The sample size of 74 per arm was based on the following assumptions. It is anticipated that of the patients who proceed to randomization (no first-line diagnosis), 30% of patients in the control group will receive a diagnosis within 1 year of enrolment.[16] It is predicted that the addition of genomic testing in the intervention pathway will increase the proportion diagnosed within 1 year to 50%.[22] Since the intervention group also receives the same non-genetic laboratory investigations as the control group, it is plausibly inconceivable that a lower diagnostic yield would be seen in the control group. Patients who drop out of the study or are lost to follow-up prior to receiving a diagnosis will be treated as not receiving a diagnosis. Therefore, we are using a one-sided Type I error of 5%. Given these assumptions, in order to achieve 80% power to detect a 20% improvement in diagnostic yield, a sample size of 74 per group is needed.

The total aim is to recruit 212 patients over 1 year, 148 of whom we predict will not achieve a first-line diagnosis and will proceed to randomization (n=74 for each study arm). Recruiting 212 participants per year is feasible given that approximately 300-350 eligible patients are seen annually at the three sites.

Intervention

The early genomic testing diagnostic pathway (intervention) is outlined in Figure 2.

Optional secondary findings

All participants will have virtual pre-test genetic counselling with a certified Genetic Counsellor. After reviewing the benefits, limitations, and potential outcomes of testing, participants will declare if they would like their results to be analyzed for variants in the list of medically actionable secondary findings maintained by the American College of Medical Genetics and Genomics (ACMG). Secondary findings are purposely analyzed but unrelated to primary testing indication. The current recommendation of the ACMG is that any time a person is receiving WGS, they should be offered the opportunity to have secondary findings also assessed.[23] At the end of the genetic counselling session, participants who wish to opt-in to secondary findings will complete a separate consent form through REDCap.

Genomic testing approach

Each sample will undergo WGS as the foundation for analysis. Not all of the data produced will be looked at, as analysis will focus only on identifying genetic variants possibly contributing to a bleeding disorder. A 'virtual gene panel' will be used comprising the most up to date list of genes known to be associated with bleeding, coagulation, platelet, connective and vascular disorders (Appendix A). The virtual panel comprises the International Society of Thrombosis and Haemostasis (ISTH) TIER-1 and TIER-2 gene list, as well as other genes identified in related scientific publications.[24 25] The virtual gene panel will be updated annually, following publication of the updated ISTH gene lists.

Any variants identified through examination of this panel will be evaluated by variant effect predictor analysis, *in silico* determination of effects on the phenotype, population frequency data, and evidence from previously reported variants. The assignment of pathogenicity likelihood using the five classifications recommended by the ACMG[26] will be determined using Varsome.[27] If a (likely) pathogenic variant is identified, the significance of the variant will be further considered in terms of its pathobiological plausibility and alignment with the bleeding phenotype. Collectively, where a pathogenic variant is found in the virtual gene panel that also

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meets the additional requirements detailed above, this will be regarded as the cause of the inherited bleeding condition.

When examination of the virtual gene panel proves negative, additional genomic analysis may be done as needed. This may include: (1) Review of additional variants: a review of other variants in the remaining genes; (2) Evaluation of copy number variants through NGS read depth; (3) Family segregation studies: In cases where other affected family members are accessible and permission of the primary participant has been obtained, consistent segregation of the variant with the bleeding phenotype may also be evaluated. Family members will be consented separately and asked to provide a biological sample (e.g., blood, saliva or cheek swab); (4) Epigenetic changes: This analysis allows us to look for changes in the pattern of how genes are turned on and turned off, referred to as "epigenetic regulation".

Sequencing and basic analysis will be done at The Centre for Applied Genomics (TCAG) at the Hospital for Sick Children in Toronto, Ontario. Subsequent analysis will be done at Queen's University by Team Members affiliated with the NIBDGL. All patients who undergo genomic testing will be reviewed at a monthly multidisciplinary team meeting, comprising expert Clinicians, Medical and Molecular Geneticists, a Genetic Counsellor, and Laboratory experts. Results of genomic testing will be reviewed along with results of any simultaneously conducted laboratory diagnostic testing, to determine if a confirmed diagnosis can be made. A final genetic report will be issued detailing all genetic findings, primary as well as incidental findings that were opted-in to by the participant. All participants with clinically significant variants or variants of uncertain significance (VUS) will then have an individual appointment with a certified Genetic Counsellor for results disclosure and genetic counselling. Referral to Medical Genetics will also be done for clinical confirmation of research findings and arranging of any necessary clinical management. Disclosure of any bleeding disorder diagnosis and the recommended management will be provided by the treating Clinician.

Control

Participants randomized to the control group will receive usual care as per the standard at each institution as determined by the treating hematologist. Final group classification (i.e. complete/partial diagnosis vs. uncertain/no diagnosis) will be done by the treating Clinician and confirmed by a second independent expert-Clinician. After they have completed the study, patients in the control group will be offered identical early genomic testing, with the same pre-test and post-test counselling as described above.

Outcomes and analysis

1. Clinical utility (primary and secondary outcomes)

The primary outcome used to power the study is diagnostic yield, defined as the proportion of patients who achieve a complete or partial diagnosis at one year. Patients who drop out of the study or are lost to follow-up prior to receiving a diagnosis will be treated as not receiving a diagnosis. Therefore, there will be no missing data for the primary outcome. A secondary outcome will be the time to diagnosis, defined as the time in days from initial appointment with Hematologist to patient disclosure of final diagnosis disclosure.

The primary outcome will be compared between groups using a one-sided Z-test comparing the proportions receiving diagnoses in each arm. The treatment effect will be reported as the absolute risk difference with a 95% confidence interval. The secondary outcome of time to diagnosis will be analyzed using time-to-event methods. Kaplan-Meier curves will be

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constructed and a proportional hazards model or suitable parametric model (e.g., if proportional hazard assumption is not reasonable) will be used to estimate the treatment effect.

Additionally, variables such as age, sex, symptoms, and bleeding score will be explored as potential treatment effect modifiers (i.e. sub-group effects) on the primary outcome by modeling the relevant interactions in logistic regression models.

2. Economic impact (secondary outcome)

An economic evaluation will be carried out alongside the RCT to evaluate the cost-effectiveness and budget impact analysis of the intervention. We estimate the intervention will be cost-effective due to an increased number of cases detected, and the higher cost of genomic testing offset due to reductions in number of clinic visits and overall diagnostic tests with associated cost savings. Budget impact analysis conducted over 5 years will allow for estimation of the cost of implementing the new diagnostic strategy in Ontario.

Cost-effectiveness analysis

The cost-effectiveness analysis will be conducted from both the healthcare system (i.e., the Ontario Ministry of Health) and the societal perspective (i.e. all costs and benefits regardless of who pays and who benefits). Guidelines for economic evaluations of genetic and genomic testing state that the perspective should be defined by who is the decision maker, which in the case of this proposal would be the Ontario Ministry of Health who is the public payer for healthcare in this province.[28] However we also included the societal perspective as the same guidelines acknowledge that a value judgement can be made to consider including costs outside the healthcare sector, such as those borne by patients.[28] As discussed above, coagulation testing can only be completed in specialized laboratories found in large urban areas and not easily accessible by much of the population.[8] Patients are required to travel long distances to reach these specialized medical centers at their own expense, a process that must be repeated with each round of testing. Thus, in order to capture this eventuality, a societal perspective was added which includes all costs and benefits associated with the diagnostic pathway regardless of who pays and benefits.

The time frame of the cost-effectiveness analysis will be January 2025-December 2026 and participants will be followed for the 12-month time period. All costs and benefits will be reported in 2026 CAD using inflation adjustment as per CPI Canada.[29] The primary outcome will be number of cases detected which is the most commonly used outcome in economic evaluations of genomic testing technology as a diagnostic tool.[30-32] The main outcome of this analytic technique will be average cost per case detected of the intervention pathway versus the control pathway, expressed as the mean with 95% confidence interval. Incremental cost per additional case detected will also be calculated and expressed similarly.

Outcome data will be captured through a case report form completed by research staff at each hospital at the end of the 12-month study period for each participant. Costs will be calculated prospectively based on resource utilization related to diagnosis for each participant in the 12-month period. Costs associated with these resources will be accessed from the service provider in the case of genomic testing (TCAG), hospital decision support and financial services at KHSC, and the Ontario Ministry of Health Lab Services Fees. Micro-costing techniques may also be done as needed. Units of resource will be multiplied by price per unit. Indirect costs will be gathered from patient surveys where participants will answer questions about the time spent travelling to their appointment, whether they organized childcare and eldercare (and if yes how

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much they paid), whether they took paid or unpaid time off work etc. The total patient cost of attending an appointment will be calculated per patient and then multiplied by the number of appointments attended as part of their diagnostic pathway. As this is a diagnostic study, we will not be looking at medical care costs outside of those used for the purpose of diagnosis (i.e., clinic appointments and all testing including lab and genetic)

Uncertainty will be evaluated via one-way sensitivity analyses on key parameters including cost of genomic testing, number of cases detected, and savings due to averted clinic appointments, with additional sub-group analyses also conducted on key parameters.

Budget impact analysis

We will conduct a budget impact analysis from the Ontario Healthcare System perspective over 5 years similar to genomic testing programs for other conditions that have been evaluated by OHTAC (Ontario Health Technology Assessment Committee).[32] Standard budget impact analysis techniques will be used[33] to predict the future economic impact of genomic testing over five years from 2025-2030.

In this model-based analysis, the incremental cost of testing for both the control and intervention arm will be determined, which will allow for detailed analysis on the economic impact of inserting genomic testing at different time points along the diagnostic algorithm. This will account for the fact that by the second time point (one-year post initial consultation), some patients in the control arm will not have had sufficient time to complete the full diagnostic work-up and thus the full cost of their diagnostic journey will not be captured. This will provide further evidence of the feasibility and optimal timing of genomic testing. The same methods for prospective cost estimation delineated above will be employed excluding patient incurred costs, with similar sensitivity analyses conducted on key parameters.

3. Patient impact (secondary outcomes)

The impact of the intervention on patients will be evaluated via generic HRQOL measures (i.e. PROMIS), symptom specific HRQOL (i.e. MBQ/aMBQ), and a patient-reported genetic testing utility measure (i.e. P-GUIDE). Additional patient burden indicators related to the diagnostic journey include total number of appointments for diagnosis, total number of blood draws, transfusion information, travel items (distance, mode, associated costs) and productivity loss questions (e.g. time spent away from work, wages lost, child/elder care costs).

The varied nature of these outcomes necessitates a variety of analytic methods for between arm comparisons. Models for count data (e.g., Poisson, negative binomial, etc.) will be used when deemed appropriate (i.e., number of appointments, number of blood draws). Rate ratios and 95% confidence intervals will express the intervention effect. Other analysis will involve simple comparisons of means (e.g., t-test or non-parametric equivalent) as needed. The intervention effect will be expressed as mean difference with 95% confidence interval (or another appropriate difference if t-test assumptions are problematic). HRQOL assessment at one year will be analyzed by linear regression, adjusted for the baseline value and the treatment effect will be the adjusted mean difference with 95% confidence interval.

Data management and monitoring

All data collection activities will be coordinated from KHSC. Participant recruitment, consent and usual care clinical visits will take place at participating hospitals (KHSC, SMH and TOH). Email contact information will be submitted by the participant into REDCap for 12-month follow-up data collection. Data from medical charts will be abstracted on site and entered into

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REDCap by the local research team. The study REDCap database is hosted by the Centre for Advanced Computing at Queen's University. The final trial dataset will be placed in an open-access, publicly accessible repository.

Long-term storage of data from genome wide sequencing will be stored in the Care4Rare Canada Genomics4RD Research database.[34] The genome-wide sequencing data stored in Genomics4RD will be coded so that no directly identifying information of study participants will be associated with these dataset records.

There will be no interim analyses and no data safety monitoring board as we are conducting a diagnostic clinical trial only, not involving high risks nor diseases with high mortality of morbidity.

Patient and public involvement

MCo is a patient representative and involved in the design of the study protocol.

ETHICS AND DISEMMINATION

This protocol was approved by Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board (HSREB) through Clinical Trials Ontario (CTO-4909), the provincial platform responsible for approving trials involving two or more academic of healthcare institutions. Informed consent will take place at the initial hematology appointment by trained research staff with the full consent form reviewed, questions answered, and the participant given a copy of the consent form for their records (Appendix B). Pediatric participants under the age of 18 who do not have the capacity to consent will provide assent as per ethics regulations with their parent/guardian providing consent (Appendix C). For participants who would like the optional analysis of the ACMG list of actionable secondary findings, after pre-testing counselling with a certified genetic counsellor, a secondary consent/assent form will be reviewed virtually with the participant and informed consent obtained virtually through REDCap (Appendix D and E). Consent form will ask permission to recontact participants for future research studies. All protocol modifications will be communicated to relevant parties as per Queen's HSREB guidelines.

Guidelines for incorporating genomic testing into diagnostic algorithms for patients with suspected inherited bleeding disorders, have been published and will be followed with clear recommendations surrounding informed consent, management of incidental findings and clinical interpretation of variants.[35 36] Although full consent for the study will be initially obtained, our study design which delays the opt-in choice until after the pre-test counselling with the certified Genetic Counsellor, serves to ensure full understanding of implications prior to declaring opt-in to secondary findings. Participants will also have post-test counselling and referral to a Medical Geneticist. For pediatric patients under the age of 18 years, families will provide consent with a separate assent collected from the patient. The final protocol has received ethical approval from the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board.

The results of this study will be communicated via traditional methods including conference presentations, published abstracts, and publication of peer-reviewed manuscripts. Additional knowledge translation activities will include presentation of results to key stakeholders including the Ontario Ministry of Health, the Association of Hemophilia Clinic Directors in Canada and the Canadian Association of Nurses in Hemophilia Care, for the

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incorporation of results into national diagnostic guidelines for the diagnosis of inherited bleeding disorders.

CONTRIBUTORS: PJ conceived the study and is the guarantor. MCh, MB and PJ designed the protocol. MB, JG, AJ, KT, AG, MCo, JL, MS, DL, RK, AP, DG, AM, JC, and RD informed the design of the protocol. MCh drafted the manuscript. All other authors reviewed, revised and approval the final manuscript.

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FIGURE TITLE AND LEGENDS:

Figure 1. Trial schematic
First line coagulation laboratory testing includes: complete blood count; prothrombin; partial thromboplastin time; VWD testing and coagulation factor levels.

Figure 2. Early genomic testing diagnostic pathway
MDT = multidisciplinary team; ACMG= American College of Medical Genetics; (L) PV = likely pathogenic or pathogenic variant (Class 4-5 ACMG); VUS = variant of uncertain significance (Class 3 ACMG); (L) BV = likely benign or benign variant (Class 1-2 ACMG).

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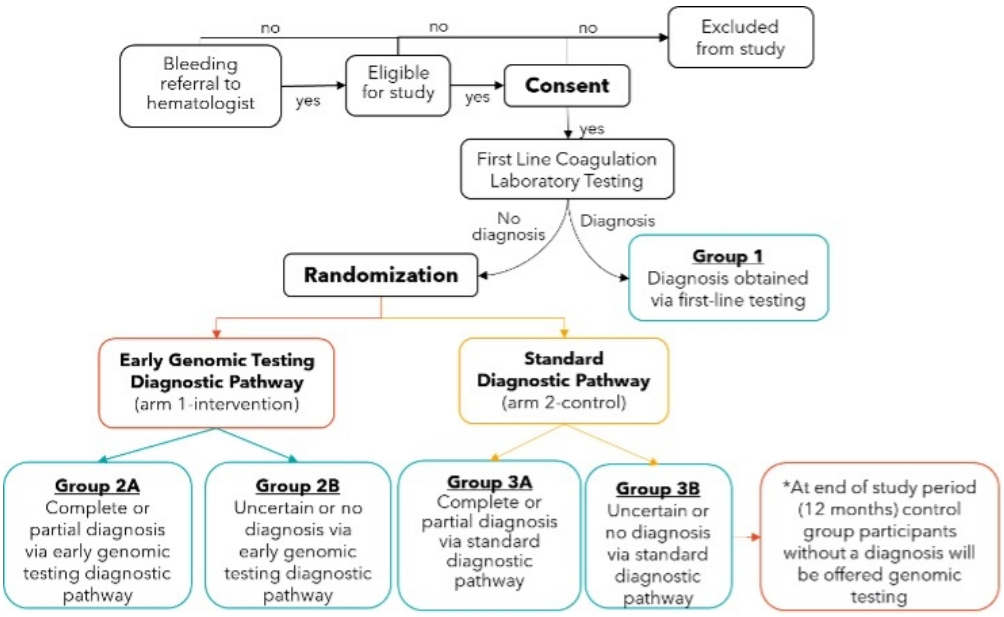

Figure 1: Trial Schematic
Legend: First line coagulation laboratory testing includes: complete blood count; prothrombin; partial thromboplastin time; VWD testing and coagulation factor levels

125x77mm (150 x 150 DPI)

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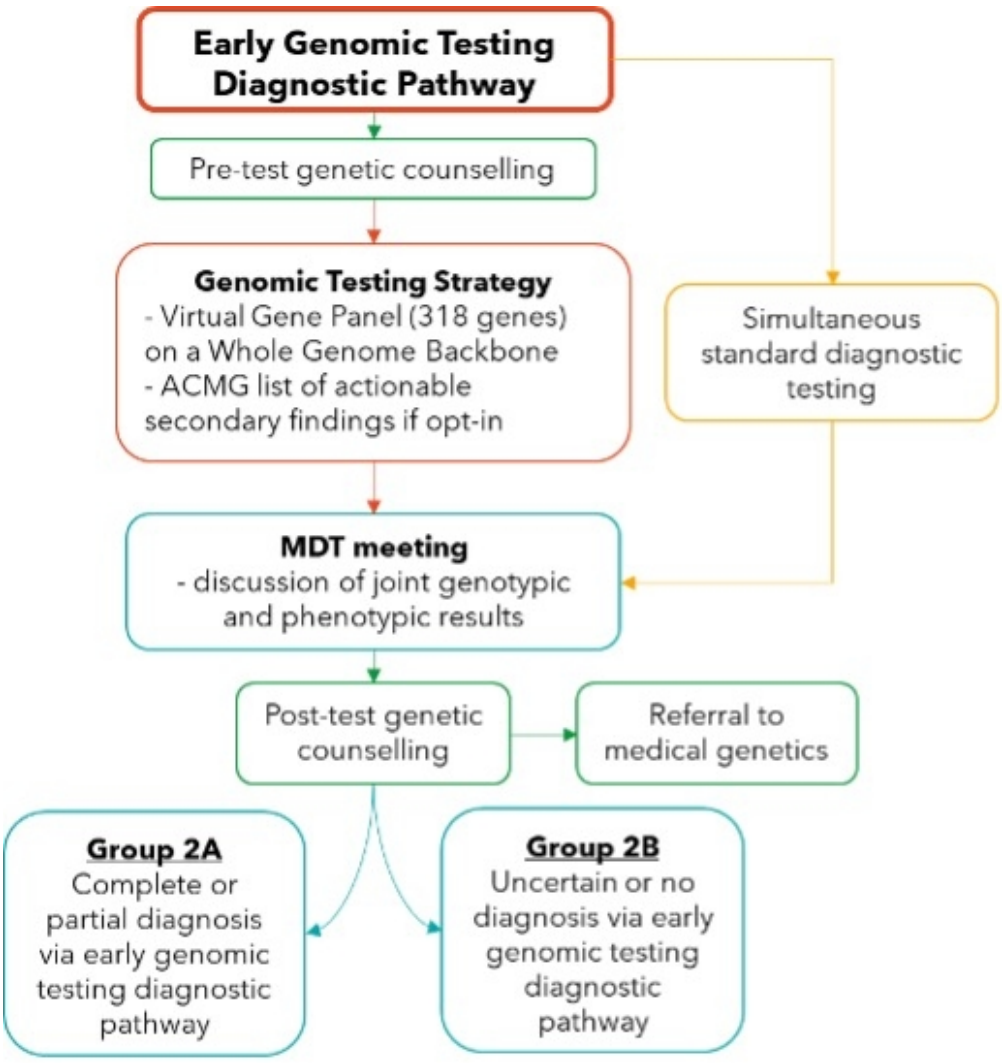

Figure 2: Early Genomic Testing Diagnostic Pathway
Legend: MDT = multidisciplinary team; ACMG= American College of Medical Genetics; (L) PV = likely pathogenic or pathogenic variant (Class 4-5 ACMG); VUS = variant of uncertain significance (Class 3 ACMG); (L) BV = likely benign or benign variant (Class 1-2 ACMG)

87x92mm (150 x 150 DPI)

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PATIENT INFORMATION AND CONSENT FORM

Study Title: Early genomic testing for Inherited Bleeding Disorders in patients without a diagnosis after first line testing: a randomized controlled trial

Below is a summary of information about the study. There is more information in the document called an "informed consent form" that follows this summary. Please read the informed consent form. The research team will also talk to you about the study and you can ask any questions you may have.

Participation in research is voluntary. It is your choice whether you take part in this clinical trial.

STUDY PURPOSE

The purpose of this study is to see if adding genetic testing can improve the diagnosis for inherited bleeding disorders. Currently, up to half of patients with symptoms of a bleeding disorder do not receive a diagnosis despite many rounds of testing. We know that genetics plays a role in the cause of inherited bleeding disorders, so this study will involve adding early genetic testing to the current diagnosis pathway.

DURATION

It is expected that study participation will last 12 months.

STUDY PROCEDURES

This study is looking at the effects of adding early genetic testing for the diagnosis of inherited bleeding disorders. Participants will be randomized to receive standard diagnostic care (control pathway) or standard diagnostic care plus early genetic testing (intervention pathway). You will be informed which pathway you will be receiving and all participants receiving standard diagnostic care only will be offered genetic testing at the end of the study period (12 months) if they have not received a diagnosis. Additionally, you will be asked to complete some questionnaires which will take 15-20 minutes of your time on two different occasions, at your initial appointment and at 12 months.

RISKS.

Participation in this study may involve risks to you. These risks are described in detail in the informed consent form. The risks you are most likely to experience are discomfort from the blood draw.

BENEFITS.

You may or may not benefit directly from participating in this study. Study results may help in identifying the cause of your bleeding symptoms which will be directly beneficial to you. This information may help doctors know what medical concerns to watch out for, change treatment plans, and determine the risk for you and other family members.

We hope that results from the study will improve our understanding of bleeding disorders and may benefit patients and treatments in the future.

ALTERNATIVES.

You do not have to participate in this study to receive medical care.

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Informed Consent Form for Participation in a Research Study

Study Title: Early genomic testing for Inherited Bleeding Disorders in patients without a diagnosis after first line testing: a randomized controlled trial

Study Doctor: insert name, department and telephone or pager number

Study Funder: Canadian Institute of Health Research (CIHR)

INTRODUCTION

As a Substitute Decision Maker, you are being asked to provide informed consent on behalf of a person who is unable to provide consent for him/herself. If the participant gains the capacity to consent for him/herself, your consent for them will end. Throughout this form, "you" means the person you are representing.

You are being invited to participate in a clinical trial (a type of study that involves research). You are invited to participate in this trial because you have been referred to Hematology due to a problem with bleeding or bruising. This consent form provides you with information to help you make an informed choice. Please read this document carefully and ask any questions you may have. All your questions should be answered to your satisfaction before you decide whether to participate in this research study.

Please take your time in making your decision. You may find it helpful to discuss it with your friends and family. The study staff will tell you about the study timelines for making your decision.

Taking part in this study is voluntary. You have the option to not participate at all or you may choose to leave the study at any time. Whatever you choose, it will not affect the usual medical care that you receive outside the study

This study has received ethical approval from the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board

IS THERE A CONFLICT OF INTEREST?

The institution is receiving financial payment from CIHR to cover the cost of conducting this study. The study doctors and research staff are not receiving any direct payment to do the study.

Describe any conflict of interest that exists or may appear to exist as it relates to any of the investigators, study staff or member of their immediate family. A conflict of interest exists if there is a potential benefit to the investigator(s), study staff or member of their immediate family beyond the professional benefit from academic achievement or presentation of the results. Examples include, but are not limited to, speaker's fees, travel assistance, consultant fees, honoraria, gifts, and intellectual property rights such as patents. A declaration of conflict of interest should include the identity of the person with the conflict of interest, the type of incentive or inducement, and its source. See examples below.

WHAT IS THE BACKGROUND INFORMATION FOR THIS STUDY?

Patients with a bleeding tendency often do not receive a diagnosis of an inherited bleeding disorder despite multiple rounds of testing. The standard treatment of care is currently a round of first-line

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screening tests (determined by your hematologist) followed by additional testing rounds when indicated. There are many reasons why the testing may be inconclusive, including the types of medication you are taking or your personal medical situation. Currently, up to half of patients who have symptoms of a bleeding disorder do not receive a diagnosis.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to see if adding genetic testing to the current diagnostic pathway for inherited bleeding disorders can help us diagnose more people. We will also be evaluating if there are effects on the time to diagnosis, the cost of diagnosis, and the patient experience. Each participating site must ensure that the standard or usual treatment described in below matches the standard of care at that site. Site specific differences must be reflected in the Centre Initial Application and the site-specific consent form.

Genetic testing involves isolating your genes from your blood sample(s). Every person has their own unique set of genes, or "genome". Genes are small sections of DNA which provide instructions for how our bodies grow, develop and function. Genes are passed down from parents to children but can sometimes change between generations or because of other factors (e.g., environment). Between people, the DNA sequence of a gene can vary slightly. These differences in DNA sequence are called variants which may or may not be harmful. Currently, there are many variants known to cause different bleeding disorders and lead to a diagnosis. Other variants have yet to be discovered or have uncertain significance.

In this study, we will be looking for "genetic variants" in people with unexplained bleeding that may lead to a diagnosis of an inherited bleeding disorder. This research will allow us to evaluate if adding genetic testing to the current diagnostic process will help us improve the diagnosis of inherited bleeding disorders.

WHAT OTHER CHOICES ARE THERE?

You do not need to participate in this study. All patients will receive the standard diagnostic testing pathway regardless of if they consent. If you choose to participate, genetic testing may be added to your testing pathway, nothing will be removed. If you choose not to participate, you will receive the standard diagnostic testing currently done.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

It is anticipated that about 212 people will take part in this study, from research sites located in Canada. This study should take 3 years to complete and the results should be known in about 4 years.

WHAT WILL HAPPEN DURING THIS STUDY?

ASSIGNMENT TO A GROUP

If you decide to participate then you will be "randomized" into one of the groups described below. Randomization means that you are put into a group by chance (like flipping a coin). There is no way to predict which group you will be assigned to. You will have an equal chance of being placed in either group. Neither you, the study staff, nor the study doctors can choose what group you will be in.

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You will be told which group you are in.

Group 1 (Experimental intervention): Standard diagnostic care plus early genetic testing

If you are randomized to this group you will receive standard diagnostic care plus early genetic testing. During your initial diagnostic bloodwork, a sample will also be taken for genetic testing. If after the first round of standard diagnostic testing you do not receive a diagnosis, your sample will then be sent for genetic testing. You will continue with additions round(s) of standard diagnostic testing as determined by your hematologist, while your genetic testing is underway. Normally, genetic testing would not be routinely done in clinical unless you have a family history of a specific condition or your lab results indicate a specific condition. In this case, single-gene testing for that condition would usually be performed.

Your hematologist will inform you of the results of all testing, both standard and genetic testing, as they become available. At the time of your initial appointment and again at the end of the study period (12-months later), you will be asked to complete a few questionnaires that will take 15-20 minutes of your time.

Group 2 (Non-Experimental Intervention): Standard diagnostic care

If you are randomized to this group you will receive standard diagnostic care. This includes a series of blood tests, determined by your hematologist. Standard diagnostic care does not routinely involve genetic testing, unless indicated by family history or laboratory testing. For example, if you have a family history of a specific bleeding disorder such a hemophilia A or B, you will likely receive targeted genetic testing for that condition as part of your standard care. All standard diagnostic care testing decisions will be made by your Hematologist, the same as if you were not part of the study.

At the time of your initial appointment and again at the end of the study period (12-months later), you will be asked to complete a few questionnaires that will take 15-20 minutes of your time. These are not part of standard care but will allow us to make comparisons between the two groups in regards to the patient experience.

If you are part of Group 2, standard diagnostic care and you have not received a diagnosis at the end of the study period (12 months), you will be offered genetic testing as outlined in the intervention pathway.

WHAT ARE THE STUDY PROCEDURES?

Non-Experimental Procedures

The following tests may be done as part of your standard care, and the results will be used as part of this study.

- Blood Tests – Standard Diagnostic Coagulation Testing which may include: CBC (complete blood count), PT (prothrombin time), PTT (partial thromboplastin time), fibrinogen, thrombin time, von Willebrand factor testing (antigen and activity), PFA-100 (platelet function test), Factor Level testing (ex. Factor II, Factor V, Factor VII, Factor VIII, Factor IX, Factor X, Factor XI, Factor XIII as indicated), additional platelet function testing, and/or other coagulation tests as

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determined by your hematologist

Experimental Procedures:

Questionnaires- You will be provided with 2-3 questionnaires before you begin the study and then again 12-months later. The purpose of the questionnaire is collect information about your health-related quality of life, the burden placed on patients as they go through the diagnostic process for an inherited bleeding disorder, and your experience with having genetic testing done. The questionnaires will take approximately 15-20 minutes of your time.

The information you provide is for research purposes only. Some of the questions are personal and you may experience emotional and/or psychological distress. You can choose not to answer questions if you wish.

Even though you may have provided information on a questionnaire, these responses will not be reviewed by your health care team or study team - if you wish them to know this information please bring it to their attention.

MANDATORY SAMPLE COLLECTION

The researchers doing this study need to do tests on blood samples (described below) to determine if there is a genetic diagnosis for your bleeding symptoms.

The collection of these samples is a necessary part of this study. The samples will not be sold.

Reports about research tests done with your samples will be given to the study doctor(s) who will pass the information to your hematologist. Your hematologist will inform you of the results.

Blood Collection (Required)

Blood samples will be taken by inserting a needle into a vein in your arm. These will be taken at the same time as your standard initial diagnostic testing whenever possible. Only one blood sample is required at the start of the study.

Blood samples will be processed in Dr. Paula James' research lab at Queen's University, and a portion of the DNA extracted from this blood sample will be shipped for whole genome sequencing at The Centre for Applied Genomics (TCAG), Hospital for Sick Children (SickKids). The DNA will then be securely disposed of by the standard operating procedures at TCAG. The remaining portion of this DNA sample will be stored indefinitely under the Study ID at Queen's University and may be used in future tests related to inherited bleeding disorders. These de-identified samples may be sent to other laboratories for research on other genetic conditions.

How will samples be identified?

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To protect your identity, the information that will be on your samples will be limited to a unique Study ID with no reference to your name or other identifiable information (i.e., de-identified). A master log linking the Study ID to your name and medical record number will be kept and stored separately from all study data using the study site's secure network. This will be kept indefinitely. All information that identifies you (i.e. signed consent form) will be kept confidential and stored and locked in a secure place that only the study personnel will be able to access. No information that can directly identify you will be allowed off site in any form. Only study personnel at your study site will have access to the linking log.

Despite protections being in place, there is a risk of unintentional release of information. Due to technological advances in genetics, there may be a risk that the genetic information in the samples could be linked back to you.

Genetic Testing

This study involves genetic testing. Researchers will be looking at your genes (DNA).

Your research sample will undergo whole genome sequencing which will provide researchers with an enormous amount of data. Not all this data will be looked at. Analysis will focus only on identifying genetic variants contributing to a possible bleeding disorder. Additionally, if you choose, your sample can also be analyzed for a number of other known genetic conditions not related to your bleeding. These are called secondary findings and you may select at the end of this form if you would like this additional analysis to be done.

The analysis may include:

1. Gene panel for bleeding: This analysis will be done first and will look at a list of genes known to be associated with rare coagulation, platelet, connective tissue, and bleeding disorders. There are currently 318 genes on the panel however this list may be updated throughout the study.
2. Review of actionable secondary findings: If you choose, a list of actionable secondary findings that is maintained by the American College of Medical Genetics and Genomics can be reviewed. This analysis is optional and will assess for other genetic conditions not related to your bleeding symptoms. If you are interested in this option, you can select at the end of this form to be contacted by a certified genetic counsellor to discuss additional details. If you choose to be contacted, you will have a virtual meeting with the genetic counsellor and then go through a separate consent process for this part of the study.
3. Microarray testing: This analysis may also be done as needed to look for missing or extra sections of DNA, referred to as "copy number variants".
4. Family segregation studies: With your permission only, your biological family members, such as parents and siblings, may be asked to participate by providing a biological sample (e.g., blood, saliva or cheek swab). This will help us understand the importance of variant(s) found in your results. Checking the genetics of family members should help us determine the potential importance of genetic variants we believe may be the cause of your bleeding problem. Your family members would be consented separately.
5. Epigenetic changes: This analysis allows us to look for changes in the pattern of how genes are turned on and turned off, referred to as "epigenetic regulation".

Results of your genetic testing, whether positive or negative, will be reported to you along with all other laboratory testing done for the diagnosis of your bleeding disorder. Any participant with a positive

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genetic finding will be offered a referral to medical genetics for counselling at no cost. This will help you understand the personal and family implications of results. You may also choose not to get genetic counselling.

Your genome-wide sequencing data will be stored in a rare disease database called "Genomics4RD." Storage of your data will allow us to go back and reanalyze your information should new disease-causing mutations be identified. Genomics4RD is an electronic database that is owned and maintained by the Care4Rare Canada Consortium and is under the care of the Children's Hospital of Eastern Ontario Research Institute. It is an online database that uses a secure cloud-based server. The storage and transfer of your data will meet privacy, security and safety standards. The database can only be accessed by people who are involved in approved research studies.

Data stored in Genomics4RD is eligible to be shared with national and international research partners, in order to better understand the nature of genetic diseases. Only research projects approved by an REB and the governing body of Genomics4RD may request access to this data, and this data would not include information that can directly identify you. To facilitate data access while protecting privacy, Genomics4RD has established a policy that subsets of data can be shared using three different levels of access:

- Controlled-access: To have access to the controlled-access database, researchers must submit a research proposal that has been approved by an Ethics Board to be considered by the Genomics4RD Data Access Committee (DAC) (a centralized office that manages data access requests). Researchers having access to this database will have access to your genetic information and will protect it accordingly.
- Registered-access: This type of access enables trusted rare disease researchers to see specific portions of your data, for example, to compare to their data to help find new rare diseases.
- Open-access: General information from the database (such as number of participants, types of diseases, candidate genes and mutations being studied) will be publicly accessible to other researchers but will not contain information that could be used to identify you.

Every person has their own unique set of genes or 'genome'. Sometimes there are differences between individuals, but these differences are very small. The reason this is important is because these results might contain information (for example, an inherited genetic disease) that could impact you or your biological (blood) relatives. When you donate your genetic information or materials you are sharing information about yourself, and it can be used to identify these relatives.

Even with protections in place, there is a risk that your information could be released by accident. Advances in technology could also increase the risk that your genetic samples and results could be linked back to you or your relatives. There is no way to predict what effects such an information loss would have. For example, if an insurer, a current or future employer, or law enforcement were to learn your genetic code it could result in loss of privacy and to possible future discrimination in employment or insurance against you or your relatives. Even though this risk is unlikely, we think you should be aware.

If you are a First Nations or an indigenous person who has contact with Elders, you may want to talk to them before you make a decision about this research study. Elders may have concerns about some research procedures including genetic testing.

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Can I withdraw these samples?

If you no longer want your samples to be used in this research, you should tell
Site Coordinator Name: XXX.XXX.XXXX
Site Coordinator Phone number: XXX.XXX.XXXX
who will ensure the samples are destroyed.

If tests have already been done on your sample(s) it will be possible to withdraw those results. However, we will not be able to withdraw your data following publication.

You can choose to withdraw your study data from the Genomics4RD database at any time without having to provide a reason. If you choose to withdraw, you are encouraged to contact your local study team member or anyone on the research team. If you withdraw your study data from Genomics4RD, all your study data will be removed and destroyed from this central database. However, any data that has already been shared and used by other researchers cannot be withdrawn.

WHAT ARE THE RESPONSIBILITIES OF STUDY PARTICIPANTS?

If you choose to participate in this study, you will be expected to:

- Complete your blood test(s) as prescribed by your hematologist
- Fill out study questionnaires at the two time points (start of study and 12-months later)

HOW LONG WILL PARTICIPANTS BE IN THE STUDY?

The study intervention will last for about 12 months depending on if and when we are able to find a diagnosis for your bleeding symptoms. Regardless of when/if you receive a diagnosis, we will follow the results of your diagnostic journey for 12 months. At the end of the 12 months you will be asked to complete the second set of study questionnaires.

If you were part of the standard diagnostic pathway, did not receive a diagnosis during the 12-month study period, and chose to have the invention genetic testing, you will continue to be followed until the results of the genetic testing are complete.

Your coded health and genetic data will remain in Genomics4RD indefinitely or until you decide to withdraw your participation.

CAN PARTICIPANTS CHOOSE TO LEAVE THE STUDY?

You can choose to end your participation in this research (called withdrawal) at any time without having to provide a reason. If you choose to withdraw from the study, you are encouraged to contact the study doctor or study staff.

You may withdraw your permission to use information that was collected about you for this study at any time by letting the study doctor know. However, this would also mean that you withdraw from the study.

CAN PARTICIPATION IN THIS STUDY END EARLY?

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The study doctor may stop your participation in the study early, and without your consent, for reasons such as:

- The Sponsor decides to stop the study
- The research ethics board withdraws permission for this study to continue

If this happens, it may mean that you would not receive the study intervention for the full period described in this consent form.

If you are removed from this study, the study doctor will discuss the reasons with you and plans will be made for your continued care outside of the study.

WHAT ARE THE RISKS OR HARMS OF PARTICIPATING IN THIS STUDY?

If you are an Indigenous person who has contact with Elders, you may want to talk to them before you make a decision about this research study. Elders may have concerns about some research procedures, including genetic testing.

There may be a small amount of bleeding when blood is taken from a vein and there may be slight discomfort and bruising or redness that will disappear in a few days.

There is an inconvenience of time related to filling out the initial study questionnaires. While filling out the questionnaires, you may experience some anxiety, emotional and/or psychological distress due to the nature of the questions. You can choose to skip or not answer any question.

When you donate your blood or tissue for research, you are sharing genetic information, not only about yourself, but also about biological (blood) relatives - information that could eventually be linked to you. Due to the rapid pace of technological advances, the potential future use (and potential future risks) of genetic information such as loss of privacy and financial, social, emotional or discrimination risks is unknown.

Finding out new genetic knowledge could cause psychological stress to you and your family. It may be upsetting to learn about genetic causes and incidental findings which may result in a new diagnosis or "label" for you. Because parent(s) and children can share genetic variants, the discovery of harmful variants in your genome may lead to identifying the same variants in your family members' genome. It may be upsetting to learn that other members of your family share these genetic variants.

In rare cases, knowing about the presence of a genetic problem might possibly affect your health insurance coverage in the future. Genetic abnormalities found as part of this research study will be kept confidential in your research file. However, if you share information/results from this study with your family doctor or if you choose to have an appointment with a clinical genetics counsellor, this information will become part of your health record. Insurance companies may request access to your health record when determining coverage. We do not know for sure how genetic information could be interpreted now or in the future. You should be aware that genetic information cannot be protected from disclosure by court order.

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WHAT ARE THE BENEFITS OF PARTICIPATING IN THIS STUDY?

You may or may not benefit directly from participating in this study. Study results may help in identifying the cause of your bleeding symptoms which will be directly beneficial to you. This information may help doctors know what medical concerns to watch out for, change treatment plans, and determine the risk for you and other family members.

We hope that results from the study will improve our understanding of bleeding disorders and may benefit patients and treatments in the future.

HOW WILL PARTICIPANT INFORMATION BE KEPT CONFIDENTIAL?

If you decide to participate in this study, the study doctors and study staff will only collect the information they need for this study. Records identifying you at this centre will be kept confidential and, to the extent permitted by the applicable laws, will not be disclosed or made publicly available, except as described in this consent document.

Authorized representatives of the following organizations may look at your original (identifiable) medical/clinical study records at the site where these records are held, to check that the information collected for the study is correct and follows proper laws and guidelines.

- Authorized Representatives of Queen's University, its affiliated hospitals and/or Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board (HSREB)
- This institution and affiliated sites, to oversee the conduct of research at this location

Information that is collected about you for the study (called study data) may also be sent to the organizations listed above. Representatives of Clinical Trials Ontario, a not-for-profit organization, may see study data that is sent to the research ethics board for this study. Your name, address, email, or other information that may directly identify you will not be used. The records received by these organizations may contain your participant code, date of birth (year), age, sex, ethnicity, race, and medical history/information relevant to the study (listed below). Studies involving humans sometimes collect information on race and ethnicity as well as other characteristics of individuals because these characteristics may influence how people respond to different interventions. Providing information on your race or ethnic origin is voluntary.

The following organizations will also receive study data:

- Care4Rare Canada Consortium and its representatives, to oversee research using the Genomics4RD database

All study information, including your personal data and any sensitive personal data, collected will be stored for 10 years after the end of the study by the study doctor.

If the results of this study are published, your identity will remain confidential. It is expected that the information collected during this study will be used in analyses, data could be published in medical journals or shared with other individuals during scientific meetings.

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Even though the likelihood that someone may identify you from the study data is very small, it can never be completely eliminated.

Communication via e-mail is not absolutely secure. We do not recommend that you communicate sensitive personal information via e-mail.

The data for this research study will be collected using the Research Electronic Data Capture (REDCap) system, which is hosted and maintained by the Centre for Advanced Computing at Queen's University. REDCap is a secure, web-based application designed for building and managing online surveys and databases. It is widely used in academic research for its robust data management and security features. The following measures are in place to ensure the security and confidentiality of the data collected:

1. Data Encryption: Data transmitted to and from REDCap is encrypted using industry-standard encryption protocols. This ensures that data is protected during transmission over the internet.
2. Access Control: Access to the REDCap system and the collected data is restricted to authorized personnel only. Users must authenticate through secure login procedures, and access permissions are granted based on role and necessity.
3. Data Storage: Data collected through REDCap is stored on servers maintained by the Centre for Advanced Computing at Queen's University. These servers are housed in secure data centers with physical and network security measures in place to prevent unauthorized access.

OTHER FUTURE RESEARCH

Your coded study data and/or coded samples may be used or shared with other researchers (inside and outside of Canada) for future studies. "Coded" means that directly identifying information (such as your name and date of birth) will be replaced by a randomly generated number, which will be applied to the study data and/or samples. This may include storing the coded study data and/or samples in controlled-access databases/biobanks, for which access is limited to researcher(s) who submit a study plan and who sign an agreement to use the coded study data and/or coded samples only for that research. De-identified study data and/or the full coded data set may also be placed in an open access, publicly accessible repository as may be required by scientific journals or funding partners.

The goal of sharing is to make more research possible. However, the code matching your study data and samples with your name and other directly identifying study data will not be shared.

You will not be asked if you agree to take part in future research studies using your study data and/or samples. You or your study doctor will not be told what type of research will be done. You will not be given reports or other information about any research that is done with your study data and/or samples. If you do not want your de-identified data to be available to other researchers for future, similar studies, please indicate that in your consent options.

WILL FAMILY DOCTORS/HEALTH CARE PROVIDERS KNOW WHO IS PARTICIPATING IN THIS STUDY?

Your family doctor/health care provider will not be informed by the study team that you are taking part in the study. You can choose to let your family doctor/health care provider know, if you like.

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WILL INFORMATION ABOUT THIS STUDY BE AVAILABLE ONLINE?

A description of this clinical trial will be available at http://www.clinicaltrials.gov Identifier: NCT06736158. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

WHAT IS THE COST TO PARTICIPANTS?

Participation in this study will not involve any additional costs to you or your private health care insurance.

ARE STUDY PARTICIPANTS PAID TO BE IN THIS STUDY?

If you decide to participate in this study, you will receive a $25 Tim Hortons gift card at the completion of the second study visit.

WHAT ARE THE RIGHTS OF PARTICIPANTS IN A RESEARCH STUDY?

You will be told, in a timely manner, about new information that may be relevant to your willingness to stay in this study.

You have the right to be informed of the results of this study once the entire study is complete. If you would like to be informed of the results of this study, please contact the study doctor.

Your rights to privacy are legally protected by federal and provincial laws that require safeguards to ensure that your privacy is respected.

By signing this form you do not give up any of your legal rights against the study doctor or involved institutions for compensation, nor does this form relieve the study doctor or their agents of their legal and professional responsibilities.

You will be given a copy of this signed and dated consent form prior to participating in this study.

WHAT IF RESEARCHERS DISCOVER SOMETHING ABOUT A RESEARCH PARTICIPANT?

During the study, the researchers may learn something about you that they didn't expect. For example, there is a chance we may find a genetic variant unrelated to your bleeding disorder that has medical implications. This is called an incidental finding and you will be informed of all medically actionable (there is a high chance of a health problem AND treatment and/or screening is available) incidental findings. All incidental findings made through research testing will need to be validated in a clinical laboratory before the information is used for your health care and other important decisions.

WHOM DO PARTICIPANTS CONTACT FOR QUESTIONS?

If you have questions about taking part in this study, or if you suffer a research-related injury, you can talk to your study doctor, or the doctor who is in charge of the study at this institution. That person is:

Study Doctor Name: XXX.XXX.XXXX

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Study Doctor Phone number: XXX.XXX.XXXX

You may also contact the study coordinator at this institution:

Site Coordinator Name: XXX.XXX.XXXX
Site Coordinator Phone number: XXX.XXX.XXXX

If you have questions about your rights as a participant or about ethical issues related to this study, you can talk to someone who is not involved in the study at all. That person is:

- The Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board (HSREB) at 1-844-535-2988 (Toll free in North America) or email researchethics@queensu.ca.

SIGNATURES

- All of my questions have been answered,
- I understand the information within this informed consent form,
- I allow access to medical records and transfer of specimens and related personal health information as explained in this consent form,
- I do not give up any legal rights by signing this consent form,
- I agree, or agree to allow the person I am responsible for, to take part in this study.

You have my consent to store my data for future unspecified research. Yes ☐ No ☐

Signature of Participant/ Substitute Decision-Maker	PRINTED NAME	Date

If consent is provided by Substitute Decision Maker: _____ PRINTED NAME of Participant

Signature of Person Conducting the Consent Discussion	PRINTED NAME & ROLE	Date

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☐ The consent form was read to the participant. The person signing below attests that the study as set out in this form was accurately explained to the participant, and any questions have been answered.

_____ _____ _____

PRINT NAME of witness | Signature | Date

_____

Relationship to Participant

SECONDARY FINDINGS DECLARATION

Please indicate below if you agree to be contacted by a certified genetic counsellor to discuss whether you would like your sample to be analyzed for the list of actionable secondary findings maintained by the American College of Medical Genetics and Genomics.

□ Yes, I agree to be contacted to discuss whether I would like my sample analyzed for actionable secondary findings.

_____ _____

Signature | Date

□ If yes above, I agree that my contact information may be shared with a certified genetic counselor in order to be contacted to discuss whether I would like my sample analyzed for actionable secondary findings.

_____ _____

Signature | Date

□ No, I DO NOT agree to be contacted to discuss whether I would like my sample to be analyzed for actionable secondary findings.

_____ _____

Signature | Date

You will be able to change your mind in the future, just let a member of the research team know.

ADDITIONAL RESEARCH QUESTIONS

By signing this form, you are giving "broad consent". Broad consent means that samples obtained from you may be stored indefinitely. The research team may use this material to continue research into bleeding disorders.

YES **NO** _____ / _____

Initials Date

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We would like permission to collect your email address for communication purposes. There are common risks of using email to communicate including:

- Information travels electronically and is not secure in the way a phone call or regular mail would be.
- If someone sees these emails, they may know that you are a participant in this study or see the health information included in the email.
- Emails may be read or saved by your internet or phone provider (i.e., Rogers, your workplace, "free internet" providers).
- Copies of an email may continue to exist, even after efforts to delete the email have been made.

If you consent, please write your email address below:

_____

FUTURE CONTACT:

You can recontact me to inform me about future research projects about bleeding disorders that I may consider participating in. Your name and email address will be entered into a re-contact database which will be stored on a secure network by the study coordinator at this institution. This database will be retained for 10 years after completion of this study, at which time the information will be securely deleted. You may request to have your information removed from this database by contacting the study coordinator at this institution.

Yes ☐ No ☐

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Study Title: Early genomic testing for Inherited Bleeding Disorders in patients without a diagnosis after first line testing: a randomized controlled trial

Principal Investigator(s): Dr. Paula James, MD, FRCPC, Professor, Department of Medicine
Phone Number: XXX XXX XXXX

Study Coordinator: Julie Grabell **Phone Number:** XXX XXX XXXX

What is a research study?

A research study is a way to test new ideas to see if we can do things better. This research study is a way to learn more about inherited bleeding disorders, a group of diseases that cause bleeding. You do not need to be in a research study if you don't want to.

Why am I being asked to be in this study?

You are being invited to take part in this research study because we are trying to learn more about diseases that cause bleeding and how to diagnose them. We are inviting you to be in the study because you have had problems with bleeding or bruising OR because some of your family members have problems with bleeding or bruising.

We know that some health problems are caused by changes in genes. A gene is something that is in each cell of the human body. Genes carry the information that decides what is passed to you from your parents, like the colour of your eyes and hair. Genes also seem to be important for understanding why bleeding problems occur more in some families than in other families. In our study, we will try to find the gene which causes your problems with bleeding or bruising.

Who will know I am in this study?

This study was explained to your parents/guardians and they said that we could ask you about the study. Your parents/guardians can help you decide if you want to be in this study.

Only the research team and your parents/guardians will know that you are in the study. There may be times where your family doctor will need to know test results performed by this study, for example if you are diagnosed with a bleeding disorder.

If I join this study what do I need to do?

We want to tell you some things about this study. If you agree to take part:

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- You will be in the study for 12 months
- We will use a needle to take some blood from your arm, called blood work. This will be done at the same time as your normal blood work, so it will only be one needle. We will just take one additional tube for the research study, about 1tsp
- We will use your blood sample to do genetic testing. This is how we will try and find the gene which is causing your bleeding or bruising.
- There will be around *20-50* other children in this research study
- We will ask you to answer some questions about your life, your feelings, if you have any pain, and how your bleeding might affect your life. If you have a period, we will ask you some questions about that. You can skip any questions that you don't want to answer.
- We will ask you the questions today, and then one year from today we will ask you to answer the questions a second time.
- We will ask to have access to your medical chart to review your health problems and the results of tests that are done.

Will any part of the study hurt or be scary?

Getting blood work done might hurt or be scary for you. There might be a small bruise where the needle was for a few days after.

You might not like answering some of the questions, they might make you feel uncomfortable. You can skip any questions you don't want to answer.

Will the study help me?

We think that the study might help you by figuring out why you have bleeding or bruising problems.

Will the study help others?

This study might find out things that will help us diagnose other children with the same bleeding or bruising problems as you. If other members of your family also have bleeding or bruising problems, it might help us diagnose them as well.

Can I say no?

Yes of course, you can decide not to be in the study. It's up to you. No one will be upset if you don't want to do this study. You can tell your parents, grandparents, guardians or your doctor if you do not want to be in the study. If you do join the study, you can change your mind and stop being part of it at any time.

What choices do I have if I say no to this study?

If you say no to this study, you will go through the regular steps of seeing if you have an

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inherited bleeding disorder. Your doctor will decide what tests need to be done.

You can ask us for more information about these other choices.

Who will see information about me?

The information collected about you during this study will be kept safe and your name will not be kept with this information. The people doing the research will be able to see the information collected about you. If you receive a diagnosis, this information will be given to your parents/guardians. Your parents/guardians will not see your answers to the questions unless you share it with them. The researchers will not tell your friends or anyone else if you decide to join the study or not. If the researchers think that you might need help then they will need to tell someone.

Other people doing studies in the future would have to ask special permission to look at your information. These researchers would not know your name either.

Do I get anything for being in the study?

You or your parents/guardians will get $25 as a token of appreciation for answering the additional questions.

What if I have questions?

You can ask any questions you want about the study.

What if I have questions later?

If you have any question about this study that you didn't think of now, either you can call or have your parents/guardians call : Dr. Paula James the study doctor, at : 613 533 6329.

You will be given a copy of this paper to keep.

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Would you like to take part in this study?

Yes, I will be in this research study:

_____	_____	_____
Child's name	Signature (if applicable)	Date

□ Assent was obtained orally

I have discussed this research study with using language which is understandable and appropriate for the participant. I believe that I have fully informed him/her of the nature of the study and its possible risks and benefits. I believe the participant understood this explanation and assent to participate in this study.

_____	_____	_____
Person obtaining Assent	Signature	Date

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PATIENT INFORMATION AND CONSENT FORM

Study Title: Early genomic testing for Inherited Bleeding Disorders in patients without a diagnosis after first line testing: a randomized controlled trial: SECONDARY FINDINGS

Below is a summary of information about the study. There is more information in the document called an "informed consent form" that follows this summary. Please read the informed consent form. The research team will also talk to you about the study and you can ask any questions you may have.

Participation in research is voluntary. It is your choice whether you take part in this clinical trial.

STUDY PURPOSE

The purpose of this component of the study for each participant to have the option of receiving additional genetic analysis of medically actionable secondary findings. These are findings that are unrelated to your bleeding issues but may affect other areas of your health.

DURATION

This portion of the study will be done alongside the main component so will last up to 12 months.

STUDY PROCEDURES

This portion of the study involves analysis of the American College of Medical Genetics and Genomics (ACMG) list of medically actionable secondary findings. The current recommendation of the ACMG is that any time a person is receiving whole-genome sequencing (which is being done in the main part of this study), they should be offered the opportunity to have secondary findings also assessed.

These variants are known as *medically actionable secondary findings* because there are clear medical recommendations that can be made to reduce the risk that they will impact a person's health in the future. The laboratory will search for variants in specific disease genes, as defined by the American College of Medical Genetics and Genomics (ACMG) guidelines (detailed list available at gsontario.ca).

RISKS.

Participation in this study may involve risks to you. These risks are described in detail in the informed consent form. The main risk you may experience is emotional distress related to discovery of positive findings.

BENEFITS.

You may or may not benefit directly from participating in this study. A positive finding of a medically actionable result may help doctors know what medical concerns to watch out for, change treatment plans, and determine the risk for you and other family members.

ALTERNATIVES.

You do not have to participate in this portion of the study. It is entirely optional.

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Informed Consent Form for Participation in a Research Study

Study Title: Early genomic testing for Inherited Bleeding Disorders in patients without a diagnosis after first line testing: a randomized controlled trial

Study Doctor: insert name, department and telephone or pager number

Study Funder: Canadian Institute of Health Research (CIHR)

INTRODUCTION

You are being invited to participate in the sub-component of the clinical trial to which you have already consented. The purpose of this component of the study is for each participant to have the option of receiving additional genetic analysis of medically actionable secondary findings. These are findings that are unrelated to your bleeding issues but may affect other areas of your health.

This consent form provides you with information to help you make an informed choice. Please read this document carefully and ask any questions you may have. All your questions should be answered to your satisfaction before you decide whether to participate in this research study.

Please take your time in making your decision. You may find it helpful to discuss it with your friends and family. The study staff will tell you about the study timelines for making your decision.

Taking part in this component of the study is voluntary. You have the option to not participate at all or you may choose to leave the study at any time. Whatever you choose, it will not affect the usual medical care that you receive outside the study or your participation in the main study component.

This study has received ethical approval from the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board.

IS THERE A CONFLICT OF INTEREST?

The institution is receiving financial payment from CIHR to cover the cost of conducting this study. The study doctors and research staff are not receiving any direct payment to do the study.

Describe any conflict of interest that exists or may appear to exist as it relates to any of the investigators, study staff or member of their immediate family. A conflict of interest exists if there is a potential benefit to the investigator(s), study staff or member of their immediate family beyond the professional benefit from academic achievement or presentation of the results. Examples include, but are not limited to, speaker's fees, travel assistance, consultant fees, honoraria, gifts, and intellectual property rights such as patents. A declaration of conflict of interest should include the identity of the person with the conflict of interest, the type of incentive or inducement, and its source. See examples below.

WHAT IS THE BACKGROUND INFORMATION FOR THIS STUDY?

This portion of the study involves analysis of the American College of Medical Genetics and Genomics (ACMG) list of medically actionable secondary findings.

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WHY IS THIS STUDY BEING DONE?

The purpose of this portion of the study is to offer the option for participants to have additional genetic analysis of medically actionable secondary findings. The current recommendation of the ACMG is that any time a person is receiving whole-genome sequencing (which is being done in the main part of this study), they should be offered the opportunity to have secondary findings also assessed.

Each participating site must ensure that the standard or usual treatment described in below matches the standard of care at that site. Site specific differences must be reflected in the Centre Initial Application and the site-specific consent form.

In this portion of the study, we will be looking for "genetic variants" in in the list of medically actionable secondary findings as defined by the American College of Medical Genetics and Genomics (ACMG) guidelines (detailed list available at gsontario.ca). These variants are known as *medically actionable secondary findings* because there are clear medical recommendations that can be made to reduce the risk that they will impact a person's health in the future.

- In children, secondary findings that reveal a risk for a condition that is *medically actionable during childhood* will be reported to the parents/caregivers. Parents/caregivers can choose to receive, or not, the analysis of variants in genes that are associated with adult-onset medically actionable conditions for their children. Mature minors, may choose for themselves to receive, or not, the analysis of variants in genes that are associated with adult-onset medically actionable conditions.
- In incompetent adults, secondary findings will be reported to the legal representative, unless the patient expressed wishes to the contrary while still competent.
- **In competent adults**, reporting of secondary findings is optional.
- The patient's choice regarding secondary findings will not impact the results of their test.

WHAT OTHER CHOICES ARE THERE?

You do not need to participate in this portion of the study. All participants will receive the components of the main study, regardless of if they choose to participate in this secondary component. If you choose to participate, actionable secondary findings will be analyzed from your genetic sample. If you choose not to participate, you will receive the standard procedures as outlined in the main study consent.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Everyone in the main study who is receiving whole genome sequencing will be offered this option.

WHAT WILL HAPPEN DURING THIS STUDY?

You will meet virtually with a Certified Genetic Counsellor to have pre-test counselling and review this consent form. You will hear additional details about the specific list of genes and conditions that are part of the list of actionable secondary findings and have the opportunity to ask questions. At the end you will indicate if you would like to opt-in to this sub-component of the study.

WHAT ARE THE STUDY PROCEDURES?

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Pre-Test Genetic Counselling: You will meet virtually with a Certified Genetic Counsellor to have pre-test counselling and review this consent form. You will hear additional details about the specific list of genes and conditions that are part of the list of actionable secondary findings and have the opportunity to ask questions. At the end you will indicate via a secure survey form if you would like to opt-in to the additional analysis of secondary findings. This will take 30-60 minutes of your time, depending on how many questions you may have for the Genetic Counsellor.

Additional Genetic Testing:

This part of the study involves additional analysis of genetic testing results. If you choose to participate, your genetic sequencing results will be analyzed to identify variants in the list of medically actionable secondary findings as defined by the ACMG guidelines (detailed list available at gsontario.ca).

Results of this additional genetic analysis, whether positive or negative, will be reported to you along with all other laboratory testing done for the diagnosis of your bleeding disorder. Any participant with a positive genetic finding will be offered a referral to medical genetics for counselling at no cost. This will help you understand the personal and family implications of results. You may also choose not to get genetic counselling.

WHAT ARE THE RESPONSIBILITIES OF STUDY PARTICIPANTS?

If you choose to participate in this part of the study, you will be expected to:

- Meet with the genetic counsellor for pre-test counselling
- Declare your opt-in decision via a secure electronic form called REDCap

HOW LONG WILL PARTICIPANTS BE IN THE STUDY?

This intervention runs alongside the main study and will last for about 12 months depending on the time needed for pre-test counselling and analysis.

CAN PARTICIPANTS CHOOSE TO LEAVE THE STUDY?

You can choose to end your participation in this portion of the research study (called withdrawal) at any time without having to provide a reason. If you choose to withdraw from this portion, you are encouraged to contact the study doctor or study staff.

You may withdraw from this portion of the study and still remain in the main portion.

CAN PARTICIPATION IN THIS STUDY END EARLY?

The study doctor may stop your participation in the study early, and without your consent, for reasons such as:

- The Sponsor decides to stop the study
- The research ethics board withdraws permission for this study to continue

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If this happens, it may mean that you would not receive the study intervention for the full period described in this consent form.

If you are removed from this study, the study doctor will discuss the reasons with you and plans will be made for your continued care outside of the study.

WHAT ARE THE RISKS OR HARMS OF PARTICIPATING IN THIS STUDY?

If you are an Indigenous person who has contact with Elders, you may want to talk to them before you make a decision about this research study. Elders may have concerns about some research procedures, including genetic testing.

Finding out new genetic knowledge could cause psychological stress to you and your family. It may be upsetting to learn about genetic causes and incidental findings which may result in a new diagnosis or "label" for you. Because parent(s) and children can share genetic variants, the discovery of harmful variants in your genome may lead to identifying the same variants in your family members' genome. It may be upsetting to learn that other members of your family share these genetic variants.

In rare cases, knowing about the presence of a genetic problem might possibly affect your health insurance coverage in the future. Genetic abnormalities found as part of this research study will be kept confidential in your research file. However, if you share information/results from this study with your family doctor or if you choose to have an appointment with a clinical genetics counsellor, this information will become part of your health record. Insurance companies may request access to your health record when determining coverage. We do not know for sure how genetic information could be interpreted now or in the future. You should be aware that genetic information cannot be protected from disclosure by court order.

WHAT ARE THE BENEFITS OF PARTICIPATING IN THIS STUDY?

actionable results may help doctors know what medical concerns to watch out for, change treatment plans, and determine the risk for you and other family members.

HOW WILL PARTICIPANT INFORMATION BE KEPT CONFIDENTIAL?

If you decide to participate in this study, the study doctors and study staff will only collect the information they need for this additional portion of the study. Records identifying you at this centre will be kept confidential and, to the extent permitted by the applicable laws, will not be disclosed or made publicly available, except as described in this consent document.

Authorized representatives of the following organizations may look at your original (identifiable) medical/clinical study records at the site where these records are held, to check that the information collected for the study is correct and follows proper laws and guidelines.

- Authorized Representatives of Queen's University, its affiliated hospitals and/or Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board (HSREB)
- This institution and affiliated sites, to oversee the conduct of research at this location

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Information that is collected about you for the study (called study data) may also be sent to the organizations listed above. Representatives of Clinical Trials Ontario, a not-for-profit organization, may see study data that is sent to the research ethics board for this study. Your name, address, email, or other information that may directly identify you will not be used. The records received by these organizations may contain your participant code, date of birth (year), age, sex, ethnicity, race, and medical history/information relevant to the study (listed below). Studies involving humans sometimes collect information on race and ethnicity as well as other characteristics of individuals because these characteristics may influence how people respond to different interventions. Providing information on your race or ethnic origin is voluntary.

The following organizations will also receive study data:

- Care4Rare Canada Consortium and its representatives, to oversee research using the Genomics4RD database

All study information, including your personal data and any sensitive personal data, collected will be stored for 10 years after the end of the study by the study doctor.

If the results of this study are published, your identity will remain confidential. It is expected that the information collected during this study will be used in analyses, data could be published in medical journals or shared with other individuals during scientific meetings.

Even though the likelihood that someone may identify you from the study data is very small, it can never be completely eliminated.

Communication via e-mail is not absolutely secure. We do not recommend that you communicate sensitive personal information via e-mail.

The data for this research study will be collected using the Research Electronic Data Capture (REDCap) system, which is hosted and maintained by the Centre for Advanced Computing at Queen's University. REDCap is a secure, web-based application designed for building and managing online surveys and databases. It is widely used in academic research for its robust data management and security features. The following measures are in place to ensure the security and confidentiality of the data collected:

1. Data Encryption: Data transmitted to and from REDCap is encrypted using industry-standard encryption protocols. This ensures that data is protected during transmission over the internet.
2. Access Control: Access to the REDCap system and the collected data is restricted to authorized personnel only. Users must authenticate through secure login procedures, and access permissions are granted based on role and necessity.
3. Data Storage: Data collected through REDCap is stored on servers maintained by the Centre for Advanced Computing at Queen's University. These servers are housed in secure data centers with physical and network security measures in place to prevent unauthorized access.

OTHER FUTURE RESEARCH

Your coded study data and/or coded samples may be used or shared with other researchers (inside and outside of Canada) for future studies. "Coded" means that directly identifying information (such as your

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name and date of birth) will be replaced by a randomly generated number, which will be applied to the study data and/or samples. This may include storing the coded study data and/or samples in controlled-access databases/biobanks, for which access is limited to researcher(s) who submit a study plan and who sign an agreement to use the coded study data and/or coded samples only for that research. Very limited coded study data may also be placed in an open access, publicly accessible database. De-identified study data and/or the full coded data set may also be placed in an open access, publicly accessible repository as may be required by scientific journals or funding partners.

The goal of sharing is to make more research possible. However, the code matching your study data and samples with your name and other directly identifying study data will not be shared.

You will not be asked if you agree to take part in future research studies using your study data and/or samples. You or your study doctor will not be told what type of research will be done. You will not be given reports or other information about any research that is done with your study data and/or samples. If you do not want your de-identified data to be available to other researchers for future, similar studies, please indicate that in your consent options.

WILL FAMILY DOCTORS/HEALTH CARE PROVIDERS KNOW WHO IS PARTICIPATING IN THIS STUDY?

Your family doctor/health care provider may or may not be informed by the study team that you are taking part in the study. You can choose to let your family doctor/health care provider know, if you like.

WILL INFORMATION ABOUT THIS STUDY BE AVAILABLE ONLINE?

A description of this clinical trial will be available at http://www.clinicaltrials.gov Identifier: NCT06736158. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

WHAT IS THE COST TO PARTICIPANTS?

Participation in this study will not involve any additional costs to you or your private health care insurance.

ARE STUDY PARTICIPANTS PAID TO BE IN THIS STUDY?

You will not be paid for participating in this part of the study.

WHAT ARE THE RIGHTS OF PARTICIPANTS IN A RESEARCH STUDY?

You will be told, in a timely manner, about new information that may be relevant to your willingness to stay in this study.

You have the right to be informed of the results of this study once the entire study is complete. If you would like to be informed of the results of this study, please contact the study doctor.

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Your rights to privacy are legally protected by federal and provincial laws that require safeguards to ensure that your privacy is respected.

By signing this form you do not give up any of your legal rights against the study doctor or involved institutions for compensation, nor does this form relieve the study doctor or their agents of their legal and professional responsibilities.

You will be given a copy of this consent form prior to participating in this study.

WHOM DO PARTICIPANTS CONTACT FOR QUESTIONS?

If you have questions about taking part in this study, or if you suffer a research-related injury, you can talk to your study doctor, or the doctor who is in charge of the study at this institution. That person is:

Study Doctor Name: XXX.XXX.XXXX
Study Doctor Phone number: XXX.XXX.XXXX

You may also contact the study coordinator at this institution:

Site Coordinator Name: XXX.XXX.XXXX
Site Coordinator Phone number: XXX.XXX.XXXX

If you have questions about your rights as a participant or about ethical issues related to this study, you can talk to someone who is not involved in the study at all. That person is:

- The Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board (HSREB) at 1-844-535-2988 (Toll free in North America) or email researchethics@queensu.ca.

SIGNATURES

- All of my questions have been answered,
- I understand the information within this informed consent form,
- I allow access to medical records and transfer of specimens and related personal health information as explained in this consent form,
- I do not give up any legal rights by signing this consent form,
- I agree, or agree to allow the person I am responsible for, to take part in this study.

You have my consent to store my data for future unspecified research. Yes ☐ No ☐

_____	_____	_____
Signature of Participant/	PRINTED NAME	Date

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Substitute Decision-Maker

If consent is provided by Substitute Decision Maker: _____ PRINTED NAME of Participant

_____ _____ _____

Signature of Person Conducting the Consent Discussion | PRINTED NAME & ROLE | Date

☐ The consent form was read to the participant. The person signing below attests that the study as set out in this form was accurately explained to the participant, and any questions have been answered.

_____ _____ _____

PRINT NAME of witness | Signature | Date

_____

Relationship to Participant

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Study Title: Early genomic testing for Inherited Bleeding Disorders in patients without a diagnosis after first line testing: a randomized controlled trial

Principal Investigator(s): Dr. Paula James, MD, FRCPC, Professor, Department of Medicine
Phone Number: XXX XXX XXXX

Study Coordinator: Julie Grabell **Phone Number:** XXX XXX XXXX

What is a research study?

A research study is a way to test new ideas to see if we can do things better. This research study is a way to learn more about genetic disorders that might affect your health. You do not need to be in a research study if you don't want to.

Why am I being asked to be in this study?

You are being invited to take part in this research study because you are part of a larger research study looking at people with bleeding problems.

We know that some health problems are caused by changes in genes. A gene is something that is in each cell of the human body. Genes carry the information that decides what is passed to you from your parents, like the colour of your eyes and hair. Genes also seem to be important for many different health problems. In the large study, we will try to find the gene which causes your problems with bleeding or bruising. In this part of the study, we will see if you have genes for other health problems.

Who will know I am in this study?

This study was explained to your parents/guardians and they said that we could ask you about the study. Your parents/guardians can help you decide if you want to be in this study.

Only the research team and your parents/guardians will know that you are in the study. There may be times where your family doctor will need to know test results performed by this study, for example if you are diagnosed with a health problem.

If I join this study what do I need to do?

We want to tell you some things about this study. If you agree to take part:

- Talk with someone called a genetic counsellor who will tell you more about the health problems that could be found
- Say if you would like us to look at genes for other health problems

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Will any part of the study hurt or be scary?

It might feel upsetting to learn about new health problems.

Will the study help me?

We think that the study might help you by finding if you have other health problems that can be treated.

Will the study help others?

This study might find out if this type of extra testing is helpful to find other health problems in children. It might also tell us if other members of your family may also have the same health problem.

Can I say no?

Yes of course, you can decide not to be in the study. It's up to you. No one will be upset if you don't want to do this study. You can tell your parents, grandparents, guardians or your doctor if you do not want to be in the study. If you do join the study, you can change your mind and stop being part of it at any time.

What choices do I have if I say no to this study?

If you say no to this study, you will still be part of the larger study about bleeding problems.

You can ask us for more information about these other choices.

Who will see information about me?

The information collected about you during this study will be kept safe and your name will not be kept with this information. The people doing the research will be able to see the information collected about you. If you receive a diagnosis, this information will be given to your parents/guardians. Your parents/guardians will not see your answers to the questions unless you share it with them. The researchers will not tell your friends or anyone else if you decide to join the study or not. If the researchers think that you might need help then they will need to tell someone.

Other people doing studies in the future would have to ask special permission to look at your information. These researchers would not know your name either.

Do I get anything for being in the study?

You will not be paid to be in this part of the study

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What if I have questions?

You can ask any questions you want about the study.

What if I have questions later?

If you have any question about this study that you didn't think of now, either you can call or have your parents/guardians call : Dr. Paula James the study doctor, at : 613 533 6329.

You will be given a copy of this paper to keep.

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Would you like to take part in this study?

Yes, I will be in this research study:

Child's name	Signature (if applicable)	Date

□ Assent was obtained orally

I have discussed this research study with using language which is understandable and appropriate for the participant. I believe that I have fully informed him/her of the nature of the study and its possible risks and benefits. I believe the participant understood this explanation and assent to participate in this study.

Person obtaining Assent	Signature	Date

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